Integrated Review

Table 1. Application Information

Application type	NDA
Application number(s)	220073, 202155/S-039, 202155/S-040
Priority or standard	Priority
Submit date(s)	10/17/2024
Received date(s)	10/17/2024
PDUFA goal date	4/17/2025
Division/office	Division of Nonmalignant Hematology (DNH)
Review completion date	4/17/2025
Established/proper name	Apixaban
(Proposed) proprietary name	ELIQUIS, ELIQUIS SPRINKLE
Pharmacologic class	Factor Xa inhibitors
Other product name(s)	ELIQUIS (apixaban, BMS-562247)
Applicant	Bristol-Myers Squibb Company
Dosage form(s)/formulation(s)	Film-coated tablets for oral suspension, powder in capsule for oral suspension
Dosing regimen	Age and weight-based algorithm twice daily
Applicant-proposed indication(s)/ population(s)	Treatment of venous thromboembolism (VTE) and reduction in the risk of recurrent VTE in pediatric patients from birth and older after at least 5 days of initial anticoagulation treatment.
SNOMED CT code for proposed indication disease term(s)[1]	429098002 Thromboembolism of vein (disorder)
Regulatory action	Approval
Approved dosage (if applicable)	N/A
Approved indication(s)/ population(s) (if applicable)	Treatment of venous thromboembolism (VTE) and reduction in the risk of recurrent VTE in pediatric patients from birth and older after at least 5 days of initial anticoagulation treatment.
SNOMED CT code for approved indication disease term(s)[1]	429098002 Thromboembolism of vein (disorder)

[1] For internal tracking purposes only.
Abbreviations: DNH, Division of Nonmalignant Hematology; N/A, not applicable; PDUFA, Prescription Drug User Fee Act; SNOMED CT, Systematized Nomenclature of Medicine Clinical Terms; VTE, venous thromboembolism

Table of Contents

Table of Tables

Table of Figures

Glossary

AE	adverse event
ALL	acute lymphoblastic leukemia
AR	adverse reaction
AUC	area under the concentration-time curve
AUC_{inf}	area under the concentration-time curve extrapolated to infinity
AUC_{ss}	area under the concentration-time curve at steady state
$AUC_{ss,T}$	area under the concentration-time curve at steady state in one dosing interval
AUC_{T}	area under the concentration-time curve in one dosing interval
AXA	antifactor Xa activity
BID	twice daily
C_{max}	maximum concentration
CRNM	clinically relevant nonmajor
CSVT	cerebral sinus venous thrombosis
C_{trough}	trough concentration
CVC	central venous catheter
CYP	cytochrome p450
DBS	dried blood spot
DILI	drug-induced liver injury
DVT	deep vein thrombosis
eGFR	estimated glomerular filtration rate
EOT	end of treatment
FDA	U.S. Food and Drug Administration
GoF	goodness-of-fit
IIV	interindividual variability
IND	investigational new drug
LC-MS/MS	liquid chromatography tandem mass spectrometry
LL	lymphoblastic leukemia
LMWH	low molecular weight heparin
NDA	new drug application
OPQ	Office of Pharmaceutical Quality
pc-VPC	prediction-corrected visual predictive check
PD	pharmacodynamic
PE	pulmonary embolism
P-gp	P-glycoprotein
PI	prescribing information
PK	pharmacokinetic
PMR	postmarketing requirement
popPK	population pharmacokinetics
PPQ	process performance qualification
PPSR	proposed pediatric study request
PT	preferred term
PTS	post-thrombotic syndrome
PWR	Pediatric Written Request

SAE	serious adverse event
SEE	substantial evidence of effectiveness
SOC	standard of care
sNDA	supplemental new drug application
TEAE	treatment-emergent adverse event
UFH	unfractionated heparin
USPI	United States Prescribing Information
VKA	vitamin K antagonist
VPC	visual predictive check
VTE	venous thromboembolism
WR	Written Request

I. Executive Summary

1. Overview

1.1. Summary of Regulatory Action

The Applicant, Bristol-Myers Squibb, submitted an original drug application NDA 220073 for the registration of ELIQUIS (apixaban) SPRINKLE for oral suspension and two supplemental new drug applications (sNDAs): sNDA 202155/S-039 for 2.5 mg and 5 mg film-coated tablets and sNDA 202155/S-040 for 0.5 mg film-coated tablets for oral suspension to the previously approved NDA 202155 for ELIQUIS (apixaban). The information submitted in the NDA and sNDAs are intended to support the approval of apixaban, a direct factor Xa inhibitor, for the indication of the treatment of venous thromboembolism (VTE) and reduction in the risk of recurrent VTE in pediatric patients from birth and older after at least 5 days of initial anticoagulant treatment. Administration of apixaban for the indicated population is fixed-dosed by weight tier.

The original NDA 202155 for ELIQUIS film coated tablets (2.5 mg, 5 mg) received approval on December 28, 2012 for the indication of reduction of the risk of stroke and systemic embolism in adults with nonvalvular atrial fibrillation. Subsequent sNDA approvals of ELIQUIS included indications for prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE), following knee or hip replacement surgery in adults (approved March 13, 2014), treatment of DVT and PE and reduction in the risk of recurrence of DVT and PE following initial therapy in adults (approved August 21, 2014).

The Applicant submitted results from one adequate and well-controlled study (main treatment phase of Study CV185325/B0661037). This trial, along with extrapolation of efficacy and pharmacokinetic (PK)/pharmacodynamic (PD) data from adult studies, provides substantial evidence of effectiveness (SEE) of apixaban for the proposed indication and supports approval for the treatment of VTE in pediatric population. Apixaban has a warning for serious, potentially fatal bleeding. The safety profile observed in the pediatric population was manageable with low rates of major and clinically relevant nonmajor (CRNM) bleeding.

The submitted NDA was also intended to support fulfillment of postmarketing requirements (PMRs) 3103-1 and 3103-2 and Pediatric Written Request (PWR) requirements related to pediatric exclusivity determination. The submission contains data to fulfill the above PMRs and to make a determination regarding pediatric exclusivity.

A multidisciplinary review team reviewed the applications. Each discipline recommends approval, and the signatory authority concurs that the applications should be approved. The overall benefit-risk profile is favorable as described in the benefit-risk framework (Table 2).

1.2. Conclusions on Substantial Evidence of Effectiveness

Substantial evidence of effectiveness (SEE) was established with evidence that supported SEE from a prior approval.

Evidence of effectiveness for the treatment of VTE and reduction in the risk of recurrent VTE in pediatric patients from birth and older after at least 5 days of initial anticoagulant treatment was based on the results of Study CV185325/B0661037, a phase 3, randomized, open-label, active-controlled trial in which 229 pediatric subjects from birth to <18 years of age with acute VTE who received at least 5 days of parenteral anticoagulation were randomized to apixaban or standard of care (SOC) comparator (2:1) for the treatment and prevention of recurrence of VTE. The recommended apixaban dose was exposure matched to 10 mg twice daily (BID) for the first 7 days and then 5 mg BID thereafter in adults. This was determined using a population PK (popPK) modeling and simulation approach for selection and recommendation of fixed-dose by bodyweight-tiered dosing regimen, in addition to the phase 1 and 2 studies.

Substantial evidence of effectiveness was demonstrated by the incidence of adjudicated, symptomatic, or asymptomatic recurrent VTE and VTE-related mortality. During the main treatment phase, 4 out of 155 subjects (2.6%, 95% CI 0.7%, 6.5%) who received apixaban had a recurrent VTE compared to 2 out of 74 subjects (2.7%, 95% CI 0.3, 9.4) in the SOC group. No subjects experienced VTE-related death. An acceptable benefit-risk profile was demonstrated with no subjects in either treatment arm experiencing an adjudicated major bleeding event, 2 out of 155 subjects (1.3%, 95% CI 0.2, 4.7) in the apixaban arm, and 1 out of 74 subjects (1.4%, 95% CI 0.0, 7.4) in the SOC comparator group experiencing at least one adjudicated CRNM bleeding event. Fifty-three out of 155 subjects (34.2%) subjects who entered the extension phase did not have any adjudicated symptomatic or asymptomatic recurrent VTE and VTE-related mortality events.

Study CV185325 was an adequate and well controlled trial. When considering the rarity of pediatric VTE, Study CV185325 included a sufficient number of pediatric subjects of all age groups, from birth and older and the overall the demographics, baseline characteristics, and risk factors are representative of the pediatric VTE population. Therefore, the study results are applicable to pediatric patients with VTE in clinical practice. The study was not designed to show a difference in effectiveness, as this would not be feasible given the rarity of thromboembolism in pediatric patients and the challenges of enrolling a large number of pediatric subjects in clinical trials.

Apixaban was previously FDA-approved for the following adult indication: treatment of deep vein thrombosis and pulmonary embolism and for the reduction of risk of recurrent DVT and PE following initial therapy. While risk factors and hemostatic differences are important considerations, given that the pathophysiology and clinical outcomes of VTE are similar between pediatric and adult patients, it is reasonable to partially extrapolate efficacy and PK/PD. Therefore, the prior determination of effectiveness of apixaban for the treatment of DVT, PE, and prevention of recurrent DVT and PE in adults is further evidence of effectiveness applicable to pediatric patients. In addition, two phase 3 studies CV185155 and CV185362 that enrolled pediatric subjects also suggest the benefit of apixaban as a clinically meaningful reduction in

incidence of VTE, and an absence of VTE events were observed in each clinical trial, respectively.

In summary, the randomized, active-controlled, multicenter study results of Study CV185325 indicate that apixaban weight-based dosing demonstrates substantial benefit in terms of the incidence of symptomatic or asymptomatic recurrent VTE occurring at a comparable rate to SOC in pediatric patients with acute VTE from birth and older. The safety profile is manageable, as demonstrated by the lack of subjects in the apixaban group experiencing major bleeding event and low incidence of CRNM bleeding. Approval is based on a single adequate and well controlled phase 3 study with 229 pediatric subjects in addition to extrapolation of efficacy and PK/PD from studies that supported approval of the same indication in adult subjects. While the etiology of VTE in pediatric and adult patients differ, the pathophysiology of clot formation and clinical outcomes (i.e., clot progression, risk of PE, post-thrombotic syndrome [PTS] etc.) are the same. Therefore, it is reasonable to extrapolate efficacy from the adult population. This approach has been used with other anticoagulants approved for pediatric patients. The study results support expanding the indication of treatment of VTE to pediatric patients and are further supported by the literature and adult experience with apixaban. This is appropriate given the rarity and seriousness of VTE in pediatric patients, particularly in very young children down to birth.

2. Benefit-Risk Assessment

2.1. Benefit-Risk Framework

Table 2. Benefit-Risk Framework

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of condition	• The incidence of VTE in the pediatric population has been estimated to be between 0.07 to 0.14 per 10,000 children per year. • While overall VTE rates are lower in pediatric patients compared to adults, it is notable that VTE rates have been increasing in hospitalized children. • There are many risk factors that contribute to the development of VTE such as malignancy, infection, immobility, surgery, and thrombophilia. Most risk factors are provoking risk factors, the most common being the presence of a central venous catheter (CVC). • VTE may result in significant morbidity such as extremity pain and/or swelling, postthrombotic syndrome, organ dysfunction, pulmonary embolism, stroke, infection, prolonged hospitalization, loss of catheter function, and death.	VTE in pediatric patients is a rare and serious condition that is associated with significant morbidity and mortality.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current treatment options	• Most treatment guidelines and/or recommendations for the treatment of VTE in children are based off of adult experience. • Common anticoagulants used in children are unfractionated heparin (UFH), low molecular weight heparin (LMWH), fondaparinux and vitamin K antagonists (VKA). All anticoagulants have a risk of bleeding. • The formulation of available anticoagulants may not be suitable for all ages, younger patients may not be able to swallow pills and receiving injections and/or venipuncture for monitoring can be challenging. • There following anticoagulants are FDA approved:. (1) Dalteparin (LMWH) for the treatment of symptomatic venous thromboembolism (VTE) to reduce the recurrence in pediatric patients from birth (≥35 weeks' gestation) and older. (2) Dabigatran (oral direct thrombin inhibitor) for the treatment and reduction of risk of recurrence of VTE in pediatric patients 3 months to <18 years of age. (3) Rivaroxaban (oral Factor Xa inhibitor) for the treatment of VTE and reduction in risk of recurrent VTE in pediatric patients and for thromboprophylaxis in pediatric patients with congenital heart disease after the Fontan procedure.	There is an unmet need for an effective therapy for the treatment and prevention of recurrent VTE in the pediatric population after at least 5 days of initial anticoagulation treatment. Specifically, there is a need for oral anticoagulants in pediatric patients including very young children down to birth.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• During the main treatment phase of Study CV185325, 4 out of 155 (2.6%, 95% CI 0.7, 6.5) subjects who received apixaban had a recurrent VTE compared to 2 out of 74 subjects (2.7%, 95% CI 0.3,9.4) in the SOC comparator group. • No subjects experienced VTE-related death. • Similar rates of index VTE regression and clot resolution between apixaban arm and the SOC comparator group was observed. • Fifty-three out of 155 subjects (34.2%) subjects who entered the extension phase treated for a median duration of 168 days (range 91-176 days) did not have any adjudicated symptomatic or asymptomatic recurrent VTE and VTE-related mortality events. • Apixaban was previously FDA-approved for the following adult indication: treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) and for the reduction of risk of recurrent DVT and PE following initial therapy. • While there may be differences in risk factors and hemostatic differences the underlying pathophysiology and clinical outcomes of VTE are similar between pediatric and adult patients, and it is reasonable to partially extrapolate efficacy and pharmacokinetic and pharmacodynamic (PK/PD) data from adult data.	The benefit of apixiban for the treatment of venous thromboembolism (VTE) and reduction in the risk of recurrent VTE in pediatric patients from birth and older after at least 5 days of initial anticoagulation treatment was demonstrated in Study CV185325. In Study CV185325, a low proportion of subjects in the apixaban group had a symptomatic or asymptomatic recurrent VTE comparable to the rates in the SOC comparator group and there were no VTE related deaths. The reduction in risk of recurrent VTE is a clinical benefit, reducing the morbidity and mortality associated with VTEs. Given that the pathophysiology and clinical outcomes of VTE are similar between pediatric and adult patients, the prior determination of effectiveness of apixaban for the treatment of DVT, PE, and prevention of recurrent DVT and PE in adults is further evidence of effectiveness applicable to pediatric patients. Substantial evidence of effectiveness of apixiban was based on on one adequate and well-controlled study plus extrapolation of efficiacy from adult population for whom there is a previously approved indication of apixiban for the treatment of DVT and PE and for reduction of risk of recurrent DVT and PE following initial therapy.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and risk management	• The most common TEAEs occurring in ≥10% of subjects in the apixaban group include headache, vomiting, and excessive menstrual bleeding. • No major bleeding events occurred in the apixaban group. • CRNM bleeding occurred in similar proportion of subjects in the apixaban group compared to the SOC comparator group (1.3% versus 1.4%, respectively) • Minor bleeding events occurred at a higher proportion of subjects in the apixaban group compared to SOC comparator group (35.5% versus 28.8%, respectively). • Higher proportion of subjects in the apixaban group compared to the SOC comparator group experienced excessive menstrual bleeding (11% versus 4%, respectively)	The safety data submitted were sufficient to characterize the toxicity profile of apixaban. Overall, the safety profile of apixaban is acceptable for pediatric patients from birth to less than 18 years of age for the treatment and reduction in the risk of recurrent VTE in pediatric patients after at least 5 days of initial anticoagulation treatment. The safety profile is consistent with observed toxicities in the adult population with VTE. Risks of apixaban, including bleeding, can be sufficiently addressed in the United States Prescribing Information (USPI).

Abbreviations: CI, confidence interval; CRNM, clinically relevant nonmajor; CVC, central venous catheter; LMWH, low molecular weight heparin; SOC, standard of care, TEAE, treatment-emergent adverse event; UFH, unfractionated heparin; VKA, vitamin K antagonist; VTE, venous thromboembolism

2.2. Conclusions Regarding Benefit-Risk

Overall, the benefit-risk profile is favorable of apixaban for the treatment of VTE and reduction in the risk of recurrent VTE in pediatric patients from birth and older after at least 5 days of initial anticoagulant treatment. Study CV185325 was an adequate and well controlled trial that provided sufficient data to establish weight-based dosing of apixaban (tablets, tablets for oral suspension, capsule for oral suspension) as an effective treatment for VTE and for the reduction in the risk of recurrent VTE, as demonstrated by similar incidences of symptomatic and asymptomatic recurrent VTE in the apixaban group compared to SOC. Furthermore, the rates of VTE regression and resolution were similar between apixaban and the SOC comparator group, which also supports apixaban as an effective treatment for VTE and reduction in risk of recurrent VTE. In addition, given that the pathophysiology and clinical outcomes of VTE are similar between pediatric and adult patients, the prior determination of effectiveness of apixaban for the treatment of DVT, PE, and prevention of recurrent DVT and PE in adults is further evidence of effectiveness applicable to pediatric patients.

The risks associated with apixaban, in particularly bleeding events, are manageable across all age groups and can be adequately described in labeling. The added benefits of apixaban include the availability of both tablets and powder capsules for oral suspension for administration to the youngest age groups and the absence of frequent blood monitoring for levels. The latter is an advantage in the pediatric population, in which frequent venipuncture can be a challenge.

II. Interdisciplinary Assessment

3. Introduction

The Applicant, Bristol-Myers Squibb, seeks approval of ELIQUIS® (apixaban) SPRINKLE for oral suspension 0.15 mg (NDA 220073) and in parallel submitted two sNDAs to the approved ELIQUIS® (apixaban) NDA for film-coated tablets 2.5 mg and 5 mg (NDA 202155/S-039) and for film-coated tablets for oral suspension 0.5 mg (NDA 202155/S-040). The information submitted in the new drug application and supplemental applications are in support of the following indication: Treatment of VTE and reduction in the risk of recurrent VTE in pediatric patients from birth and older.

Apixaban is a factor Xa inhibitor anticoagulant approved for the following indications:

- Reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation
- Prophylaxis of DVT, which may lead to PE in patients who have undergone hip or knee replacement surgery
- Treatment of DVT and PE, and for the reduction in the risk of recurrent DVT and PE following initial therapy

Apixaban is not currently approved for any pediatric indication.

The VTE incidence in pediatric population has been estimated to be between 0.07 to 0.14 per 10,000 children per year (Monagle et al. 2018). VTE rates have been increasing in hospitalized children, from 5.3 events per 10,000 pediatric hospital admissions in the early 1990s to 30 to 58 events per 10,000 hospital admissions currently (Witmer and Raffini 2020). Many more adult patients than pediatric patients developed VTEs; thus, there are many more adult patients who could potentially participate in clinical trials for VTE prophylaxis and treatment.

There are differences in the etiology of VTE in pediatrics compared to the adults, in particular in younger children. Genetic, anatomic, and acquired risk factors may impact the risk of developing VTE. Neonates and adolescents are at the highest risk for VTE (Monagle et al. 2018). Unlike adults, in which a significant number of VTE events are spontaneous, the vast majority of VTEs occurring in children are provoked (Mahajerin and Croteau 2017). The most common provoking risk factor is the presence of a central venous catheter (CVC), which >90% of VTEs in neonates and >60% in older children is attributed to (Monagle et al. 2018). Other risk factors include cancer, sickle cell disease, congenital heart disease, trauma, thrombophilia, nephrotic syndrome, obesity, infection, inflammatory bowel disease, illness, medications, and inflammatory states (Mahajerin and Croteau 2017). Similar to adults, immobility, oral contraceptive use, and surgery are risk factors as well. Unprovoked VTEs do occur but are much less common. Often, pediatric patients have comorbidities such as serious illness.

Similar to adults, VTE can lead to significant morbidity and mortality. VTE may result in post thrombotic syndrome, pain and/or swelling at the affected site, organ dysfunction, PE, stroke,

infection, prolonged hospitalization, loss of catheter function, and even death (Witmer and Raffini 2020).

Treatment guidelines recommend anticoagulation for the initial treatment of symptomatic VTE in both adults and children. The goal of therapy is to prevent clot extension, embolism, and reoccurrence. The benefits of anticoagulation must be carefully weighed against the risk, most importantly the risk of bleeding (Witmer and Raffini 2020). Due to a lack of adequate and well controlled pediatric trials and overall paucity of data from pediatric studies, treatment recommendations are often based on adult experience or observation. There are important considerations unique to pediatric patients which include developmental hemostasis, increased frequency of illness or comorbidities, vascular access issues, and heterogeneity within the pediatric population (i.e., age, weight, and risk factors) (Witmer and Raffini 2020). In addition, the formulation of anticoagulants may not be suitable for all ages, as younger patients will not be able to swallow pills and receiving injections can be challenging. As VTE rates increase, with many patients with complex medical conditions, there is a significant unmet need for safe and effective oral anticoagulant for pediatric patients.

The most commonly used anticoagulants in children are unfractionated heparin (UFH), low molecular weight heparin (LMWH), fondaparinux, and vitamin K antagonists (VKAs) . Currently, there are four FDA-approved anticoagulants in children. First, dalteparin is a LMWH, given subcutaneously, approved in 2019 for the treatment of symptomatic VTE to reduce the recurrence in pediatric patients 1 month of age and older, and in 2023 to extend the indication to neonatal patients down to birth (neonates ≤28 days old, and ≥35 weeks gestation). The second is dabigatran, an oral direct thrombin inhibitor, approved in 2021 for the treatment and reduction of risk of recurrence of VTE in pediatric patients 8 to less than 18 years of age. Third, rivaroxaban is a factor Xa inhibitor approved for the treatment of VTE and reduction in risk of recurrent VTE in pediatric patients from birth to less than 18 years after 5 days of initial parenteral anticoagulant treatment and thromboprophylaxis in pediatric patients aged 2 years and older with congenital heart disease who have undergone the Fontan procedure. While UFH does not have a pediatric indication, pediatric dosing is described in the United States Prescribing Information (USPI). Fourth, fondaparinux is a factor Xa inhibitor approved in 2024 for the treatment of venous thromboembolism in pediatric patients weighing at least 10 kg. A summary of the commonly used anticoagulants in pediatrics is summarized in Table 3.

The American Society of Hematology published guidelines in 2018 for the treatment of pediatric VTE (Monagle et al. 2018). The guidelines recommend <3 months of treatment for provoked DVT or PE, and longer if the causative risk factor persists. For unprovoked DVT or PE, treatment was recommended for 6 to 12 months. Anticoagulation was also recommended for cerebral sinus venous thrombosis (CSVT). A recent study in 2022 concluded that for patients younger than 21 years of age with provoked VTE, anticoagulant therapy for 6 weeks was noninferior to the standard recommendation of 3 months (Goldenberg et al. 2022).

The 2018 American Society of Hematology guidelines suggest using LMWH or VKA for anticoagulation in patients with symptomatic DVT or PE. A recommendation on the use of direct oral anticoagulants were not made in these guidelines due to lack of available data from clinical trials (Monagle et al. 2018). Expert opinion has acknowledged the rapidly increasing use of direct oral anticoagulants in pediatric patients and their convenience over SOC anticoagulants because of their oral route of administration, child-friendly formulations, and significant reduction in monitoring (Bhat et al. 2024). Heparins and LMWHs require frequent monitoring

and injections. VKAs are given orally, but also require frequent monitoring with venipuncture. In addition, there is no approved liquid formulation and international normalized ratio levels are impacted by diet and concomitant medications. There remains an unmet need for additional oral anticoagulants in pediatric patients.

Table 3. Summary of Treatment Armamentarium Relevant to Proposed Indications

Product(s) Name	Relevant Indication	Year of Approval	Route and Frequency of Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments (e.g., Subpopulation not Addressed
FDA-Approved Treatments						
Dabigatran capsules and oral pellets	1) For the treatment of venous thromboembolic events (VTE) in pediatric patients aged 3 months to less than 18 years of age who have been treated with a parenteral anticoagulant for at least 5 days 2) To reduce the risk of recurrence of VTE in pediatric patients aged 3 months to less than 18 years of age who have been previously treated	2021	Oral BID, weight-based	Based on extrapolation from adult trials and pediatric clinical trials	In pediatric trials the major safety issue was bleeding Gastrointestinal adverse reactions Alopecia	Approval does not cover the entire pediatric age range
Rivaroxaban tablets and oral granules	1) Treatment of VTE and reduction in the risk of recurrent VTE in pediatric patients from birth to less than 18 years 2) Thromboprophylaxis in pediatric patients 2 years and older with congenital heart disease after the Fontan procedure	2021	Oral once to three times a day, age and weight-based	Based on extrapolation from adult trials and pediatric clinical trials	In pediatric trials the major safety issue was bleeding Gastrointestinal adverse reactions	

Product(s) Name	Relevant Indication	Year of Approval	Route and Frequency of Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments (e.g., Subpopulation not Addressed
Dalteparin injection (LMWH)	Treatment of symptomatic VTE to reduce the recurrence in pediatric patients from birth (gestational age ≥35 weeks)	2021; 2024, expanded approval from ≥1 month down to birth	Subcutaneous injection BID, based on age	Based on extrapolation from adult trials and pediatric clinical trials	In pediatric trials the major safety issue was bleeding Heparin-induced thrombocytopenia (HIT), or heparin-induced thrombocytopenia and thrombosis (HITT) Hypersensitivity	
Fondaparinux sodium injection	Treatment of venous thromboembolism in pediatric patients weighing at least 10 kg	2024	Subcutaneous injection once daily, based on weight	Based on extrapolation from adult trials and pediatric clinical trials	In pediatric trials, the major safety issue was bleeding	Approval is for ≥10 kg weight

Product(s) Name	Relevant Indication	Year of Approval	Route and Frequency of Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments (e.g., Subpopulation not Addressed
Other treatments – not FDA-approved for pediatric patients						
Heparin (unfractionated heparin)			Initial dose: 75 to 100 units/kg IV bolus over 10 minutes Maintenance dose: Infants: 25-30 units/kg/hour Children: >1 year of age: 18-20 units/kg/hour	Target aPTT of 60-85 sec, assuming this reflects an antifactor Xa level of 0.35 to 0.70	Bleeding risk HIT and HITT Hypersensitivity Antidote – protamine	Dosing for pediatric patients is described in the USPI Use preservative-free heparin sodium injection in neonates and infants
Warfarin			Initial dose: 0.1 mg/kg/day oral	Target INR between 2-3	Bleeding risk HIT Tissue necrosis Antidote: Vitamin K	

Source: FDA Clinical Reviewer
Abbreviations: aPTT, activated prothrombin time; HIT, heparin induced thrombocytopenia; HITT, heparin-induced thrombocytopenia and thrombosis; INR, International Normalized Ratio; IV, intravenous; LMWH, low molecular weight heparin; sec, seconds; USPI, United States Prescribing Information; VTE, venous thromboembolic event

3.1. Review Issue List

3.1.1. Key Efficacy Review Issues

3.1.1.1. Demonstration of Substantial Evidence of Effectiveness From Submitted Clinical Studies

Discussion regarding substantial evidence of effectiveness (SEE) is included in Section 6.3.1.

3.1.2. Key Safety Review Issues

3.1.2.1. Pooling Strategy of Safety Data

Discussion regarding pooling of safety data is included in Section 7.7.1.

3.2. Approach to the Clinical Review

Table 4 provides an overview of the clinical trials submitted to establish the efficacy and safety of apixaban in the pediatric population.

The assessment of benefit was primarily based on Study CV185325, a phase 3, randomized, open-label, active-control safety and descriptive efficacy study comparing apixaban to SOC treatment for anticoagulation in pediatric subjects with image-confirmed VTE requiring anticoagulation. SEE was also established through extrapolation from evidence from the original approval of the same indication in adult patients.

Studies CV185155 and CV185362 were also reviewed to support the efficacy of apixaban in the pediatric population.

The assessment of risk was primarily completed for data derived from Study CV185325, but also included an analysis of the safety sets in pediatric subjects receiving apixaban from Studies CV185079, CV185118, CV185155, and CV185362.

3.3. Approach To Establishing Substantial Evidence of Effectiveness

Select from the options below to indicate how SEE was established (if applicable). If there are multiple indications, repeat items 1–3 for each indication.

1. Verbatim indication (enter approved indication if the application was approved and the Applicant's proposed indication if the application received a complete response [CR]):

   Treatment of venous thromboembolism (VTE) and reduction in the risk of recurrent VTE in pediatric patients from birth and older after at least 5 days of initial anticoagulation treatment.

2. SEE was established with (check **one** of the options for traditional or accelerated approval pathways and CR not due to lack of demonstrating SEE)
   a. Adequate and well-controlled clinical investigation(s):
      i. ☐ Two or more adequate and well-controlled clinical investigations, **OR**
      ii. ☐ One adequate and well-controlled clinical investigation with highly persuasive results that is considered to be the scientific equivalent of two clinical investigations

      OR

   b. ☐ One adequate and well-controlled clinical investigation and confirmatory evidence[1,2,3]

      OR

   c. ☒ Evidence that supported SEE from a prior approval (e.g., 505(b)(2) application relying only on a previous determination of effectiveness; extrapolation; over-the-counter switch)[2]
3. CR, if applicable
   a. ☐ SEE was established
   b. ☐ SEE was not established *(if checked, omit item 2)*

[1] Draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (December 2019)

[2] Guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* (May 1998)

[3] Draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness With One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence* (September 2023)

Table 4. Clinical Studies/Trials Submitted in Support of Efficacy and/or Safety Determinations for Apixaban

Study/Trial Identifier (NCT#)	Study/Trial Population	Study/Trial Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized	Number of Centers and Countries
CV185325/B0661037	Pediatric subjects from birth to <18 years of age with a minimum weight of 2.6 kg at the time of randomization and with the presence of an index VTE confirmed by imaging	Control type: Active-controlled Randomization: Apixaban or SOC (VKA, LMWH, or UFH for subjects aged <2 years) Randomization ratio: 2:1 Blinding: Open-label Biomarkers: None Innovative design features: None	Drug: Apixaban OS, tablet, or capsule for oral suspension administered PO or via an NGT or GT Dosage: Fixed dose, body weight tiered regimen for all ages, i.e., >35 kg: 10 mg BID x7 days followed by 5 mg BID <35 to 25 kg: 8 mg BID x7 days followed by 4 mg BID <25 to 18 kg: 6 mg BID x7 days followed by 3 mg BID <18 to 12 kg: 4 mg BID x7 days followed by 2 mg BID <12 kg to 9 kg: 3 mg BID x7 days followed by 1.5 mg BID <9 to 6 kg: 2 mg BID x7 days followed by 1 mg BID <6 to 5 kg: 1 mg BID x7 days followed by 0.5 mg BID <5 to 4 kg: 0.6 mg BID x7 days followed by 0.3 mg BID <u>Neonatal dosing (<28 days)</u>: ≥2.6 kg: 0.1 mg BID or as determined by PK measurements x7 days followed by 0.1 mg BID <4 to 2.6 kg: 0.2 mg BID x7 days followed by 0.1 mg BID Number treated: Apixaban, n=152; SOC, n=73 Duration: 12 weeks >2 years, 6-12 weeks <2 years	Primary: Adjudicated composite of (1): all image-confirmed and adjudicated symptomatic and asymptomatic recurrent VTE, defined as either contiguous progression or noncontiguous new thrombus and including, but not limited to DVT, PE, and paradoxical embolism and (2) VTE-related mortality Secondary: All-cause death, VTE-related mortality, index VTE status (e.g., unchanged, regression, or resolution), stroke, new or recurrent symptomatic or asymptomatic DVT/PE, VTEs other than DVT or PE (i.e., CSVT, RVT, PVT, catheter-related VTE) Safety: Composite of major and CRNM bleeding	243 planned; 229 randomized	120 centers in 14 countries

Study/Trial Identifier (NCT#)	Study/Trial Population	Study/Trial Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized	Number of Centers and Countries
CV185155	Male and female pediatric subjects with acute lymphoblastic leukemia and lymphoblastic lymphoma undergoing induction chemotherapy with asparaginase	Control type: No treatment control Randomization: Apixaban or no systemic anticoagulant Blinding: Open-label Biomarkers: None Innovative design features: None	Drug: Apixaban OS, tablet, or capsule for oral suspension administered PO or via an NGT or GT Dosage: Fixed dose, body weight tiered regimen for all ages, i.e., ≥35 kg: 2.5 mg BID 25 to <35 kg: 2 mg BID 18 to <25 kg: 1.5 mg BID 10.5 to <18 kg: 1 mg BID 6 to <10.5 kg: 0.5 mg BID Number treated: Apixaban, n=250; SOC, n=256 Duration: ~28-day chemotherapy induction period with asparaginase	Primary: Composite of nonfatal (asymptomatic or symptomatic) DVT, PE, and CSVT; and VTE related death, all objectively confirmed by independent adjudication Secondary: Individual components of the primary endpoint (nonfatal asymptomatic DVT, nonfatal symptomatic DVT, nonfatal PE, CSVT, and VTE-related death)	500 planned; 512 randomized	74 centers in 10 countries
CV185362	Male and female pediatric subjects with congenital or acquired heart disease requiring chronic anticoagulation for thromboembolism prevention	Control type: Active-Controlled Randomization: Apixaban or SOC (VKA or LMWH) Blinding: Open-label Biomarkers: Thrombin generation, factor VIII, d-dimer, protein C and S, fibrinogen Innovative design features: None	Drug: Apixaban OS, tablet, or capsule for oral suspension administered PO or via an NGT or GT Dosage: Fixed dose, body weight tiered regimen for all ages, i.e., ≥35 kg: 5 mg BID <35 to 25 kg: 4 mg BID <25 to 18 kg: 3 mg BID <18 to 12 kg: 2 mg BID <12 to 9 kg: 1.5 mg BID <9 to 6 kg: 1 mg BID <6 to 5 kg: 0.5 mg BID <5 to 4 kg: 0.3 mg BID <4 to 3 kg: 0.2 mg BID Number treated: Apixaban, n=126; SOC, n=62 Duration: ≤12 months or until treatment was no longer needed	Primary: No primary efficacy endpoint Secondary: Composite of adjudicated thromboembolic events and thromboembolic event-related deaths Patient/proxy-reported outcome or QOL measures to assess the effects of apixaban versus VKA/LMWH.	200 planned; 192 randomized	33 centers in 12 countries

Study/Trial Identifier (NCT#)	Study/Trial Population	Study/Trial Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized	Number of Centers and Countries
CV185118	Male and female pediatric subjects at risk for venous or arterial thrombotic events	Control type: None Randomization: None Blinding: Open-label Biomarkers: antifactor Xa activity	Drug: Apixaban OS (0.4 mg/mL), Apixaban sprinkle capsule (0.1 mg) administered PO or via NGT or GT single dose Dosage: Group 1: 0.1 mg Group 2a: 1.08-2.43 mg/m^2 Group 2b: 1.08 mg/m^2 Group 3: 1.17 mg/m^2 Group 4: 1.80 mg/m^2 Group 5: 2.19 mg/m^2 Number treated: 49 Duration: Single-dose study	Primary: Assess PK of a single dose of apixaban in pediatric subjects Secondary: Assess the single-dose safety and tolerability of apixaban in pediatric subjects To assess antifactor Xa activity following a single dose of apixaban in pediatric subjects	63 planned; 49 randomized	27 centers in 4 countries

Source: Applicant's CSR
Abbreviations: BID, twice daily; n, number of subjects; CRNM, clinically relevant nonmajor; CSVT, cerebral sinus venous thrombosis; DVT, deep vein thrombosis; GT, gastric tube; LMWH, low molecular weight heparin; NCT, national clinical trial; NGT, nasogastric tube; OS, oral suspension; PE, pulmonary embolism; PO, by mouth; PK, pharmacokinetic; PVT, portal vein thrombosis; QOL, quality of life; RVT, renal vein thrombosis; SOC, standard of care; UFH, unfractionated heparin; VKA, vitamin K antagonist; VTE, venous thromboembolism

4. Patient Experience Data

Patient/proxy-reported outcome or quality of life measures to assess the effects of apixaban versus VKA/LMWH were conducted in Study CV185362. This data is not discussed as the focus of this review on the pivotal Study CV185325.

Table 5. Patient Experience Data Submitted or Considered

Data Submitted in the Application		
Check if Submitted	**Type of Data**	**Section Where Discussed, if Applicable**
Clinical Outcome Assessment Data Submitted in the Application		Not applicable.
☒	Patient-reported outcome	
☐	Observer-reported outcome	
☐	Clinician-reported outcome	
☐	Performance outcome	
Other Patient Experience Data Submitted in the Application		
☐	Patient-focused drug development meeting summary	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☐	Other: (please specify)	
☐	If no patient experience data were submitted by Applicant, indicate here.	
Data Considered in the Assessment (But Not Submitted by Applicant)		
Check if Considered	**Type of Data**	**Section Where Discussed, if Applicable**
☐	Perspectives shared at patient stakeholder meeting	
☐	Patient-focused drug development meeting summary report	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☐	Other: (please specify)	

5. Pharmacologic Activity, Pharmacokinetics, and Clinical Pharmacology

5.1. Nonclinical Assessment of Potential Effectiveness

Please refer to original nonclinical review of prescription NDA 202155 written by Patricia P. Harlow, PhD and Thomas Papoian, PhD, and finalized for a drug approval package on December 28, 2012. No new assessments were conducted for this NDA.

5.2. Clinical Pharmacology/Pharmacokinetics

Table 6. Summary of Clinical Pharmacology and Pharmacokinetics

Characteristic	Drug Information
	Pharmacologic Activity
Established pharmacologic class (EPC)	Factor Xa inhibitor
Mechanism of action	Apixaban is a selective inhibitor of FXa. By inhibiting FXa, apixaban decreases thrombin generation and thrombus development.
Active moieties	Apixaban
QT prolongation	At a dose of up to 50 mg, apixaban does not prolong the QT interval to any clinically relevant extent.
	General Information
Bioanalysis	Plasma apixaban concentrations were measured using a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) method
Healthy subjects versus VTE subjects	Plasma pharmacokinetics of apixaban are generally similar in healthy subjects and VTE subjects
Drug exposure at steady state following the therapeutic dosing regimen (or single dose, if more relevant for the drug)	**Table 7. Apixaban PK Parameters at Steady State as Estimated by PopPK Model Summarized by Body Weight Tiers, Study CV185325**

Variable	Summary Statistic	2.6 to < 4 kg (n = 9)	4 to < 5 kg (n = 1)	6 to < 9 kg (n = 2)	9 to < 12 kg (n = 6)	12 to < 18 kg (n = 2)	18 to < 25 kg (n = 6)	25 to < 35 kg (n = 14)	≥ 35 kg (n = 95)	Overall (n = 144)
AUCss(TAU)	Geometric mean (%CV)	643 (25.3)	485 (NA)	1200 (59.2)	1080 (31.7)	1240 (6.45)	1530 (34.4)	1400 (28.5)	1080 (38)	1090 (42.1)
Cmaxss (ng/mL)	Geometric mean (%CV)	65.3 (25)	49.3 (NA)	159 (53.1)	156 (25.7)	176 (12.1)	211 (25.6)	180 (26.7)	134 (34.5)	137 (42.7)
Cminss (ng/mL)	Geometric mean (%CV)	40 (26.1)	30.3 (NA)	45.7 (84.1)	34.7 (63.1)	43.8 (6.64)	57.6 (55.8)	59.2 (36.3)	48.6 (52.5)	48.1 (53.3)

Source: Table 5.1.4.2-2 of the Study CV185325 Pharmacometric Report
Note: The approved doses in body weight groups 2.6 to <4 kg and 4 to <5 kg are different than what was studied in Study CV185325
Abbreviations: $AUC_{ss,T}$, area under the concentration-time curve at steady state in one dosing interval; $C_{max,ss}$, maximum concentration at steady state; $C_{min,ss}$, minimum concentration at steady state; CV, coefficient of variation; n, number of subjects; NA, not applicable; PK, pharmacokinetic; popPK, population pharmacokinetic

Characteristic	Drug Information
Range of effective dose(s) or exposure	Dosing in pediatric subjects is based on body weight. Table 8 displays the recommended doses in pediatric subjects from birth to <18 years of age across different body weight tiers.

Table 8. Recommended Apixaban Doses in Pediatric Subjects Across Body Weight Tiers

Presentation	Body Weight (kg)	Dosing Schedule Days 1-7	Maximum Daily Dose Days 1-7	Dosing Schedule Days 8 and Beyond	Maximum Daily Dose Days 8 and Beyond
Powder in capsule, 0.15 mg	2.6 to <4	0.3 mg BID	0.6 mg	0.15 mg BID	0.3 mg
Tablet 0.5 mg	4 to <6	1 mg BID	2 mg	0.5 mg BID	1 mg
	6 to <9	2 mg BID	4 mg	1 mg BID	2 mg
	9 to <12	3 mg BID	6 mg	1.5 mg BID	3 mg
	12 to <18	4 mg BID	8 mg	2 mg BID	4 mg
	18 to <25	6 mg BID	12 mg	3 mg BID	6 mg
	25 to <35	8 mg BID	16 mg	4 mg BID	8 mg
Tablets 2.5 mg and 5 mg	≥35	10 mg BID	20 mg	5 mg BID	10 mg

Source: Table 66 in Appendix 14.5
Note: The recommended doses in body weight groups 2.6 to <4 kg and 4 to <5 kg are different than what was studied in Study CV185325.
Abbreviation: BID, twice daily

Dose proportionality	Apixaban demonstrates linear pharmacokinetics with dose-proportional increases in exposure for oral doses up to 10 mg in adults.
Accumulation	Accumulation index is 1.3 to 1.9 with BID dosing in adults. Similar observation is also expected in pediatric subjects.
Time to achieve steady state	Steady-state was reached by Day 3 in adults. Similar observation is also expected in pediatric subjects.
Bridge between to-be-marketed and clinical trial/study formulations	0.5 mg tablet (to be marketed) and 0.1 mg capsule were used in the pivotal study. The 0.1 mg capsule and 0.15 mg capsule (to be marketed) are (b) (4) similar, but with different fill weight. Likewise, the 0.5 mg tablet and commercial adult tablet (2.5 mg and 5 mg) are (b) (4) similar in composition. A relative bioavailability study comparing the 0.1 mg capsule to the 0.5 mg tablet showed that the capsule had a 28% higher C_{max} and 10% higher AUC compared to the tablet.

<table>
<tr><th>Characteristic</th><th>Drug Information</th></tr>
<tr><td></td><td>Absorption</td></tr>
<tr><td>Bioavailability</td><td>The absolute bioavailability of apixaban is approximately 50% for doses up to 10 mg in adults.</td></tr>
<tr><td>T_{max}</td><td>1.8 h (1.4 h, 2.5 h) represented as median (min, max) in pediatric subjects</td></tr>
<tr><td>Food effect (fed/fasted)
Geometric least square mean and 90% CI</td><td>Table 9. Food Does Not Affect the Bioavailability of Apixaban
<table>
<tr><th rowspan="2">Pharmacokinetic Parameter</th><th colspan="2">Adjusted Geometric Means</th><th>Ratios of Geometric Means (Fed/Fasted)</th></tr>
<tr><th>Apixaban 10 mg Fasted</th><th>Apixaban 10 mg Fed</th><th>Point Estimate (90% CI)</th></tr>
<tr><td>C_{max} (ng/mL)</td><td>150.8</td><td>165.3</td><td>1.10 (1.004, 1.197)</td></tr>
<tr><td>AUC_{inf} (ng·h/mL)</td><td>1789.3</td><td>1868.1</td><td>1.04 (1.004, 1.086)</td></tr>
<tr><td>T_{max}</td><td>3h</td><td>4h</td><td>33%</td></tr>
</table>
Source: Study CV185008 Clinical Study Report
Note: Fed state is after a high-fat, high-calorie meal with 52%, 34%, and 14% of calories from fat, carbohydrates, and proteins, respectively.
Abbreviations: AUC_{inf}, area under the concentration-time curve extrapolated to infinity; CI, confidence interval; C_{max}, maximum concentration; T_{max}, time to maximum concentration</td></tr>
<tr><td></td><td>Distribution</td></tr>
<tr><td>Volume of distribution</td><td>21 liters</td></tr>
<tr><td>Plasma protein binding</td><td>Protein binding for apixaban is ~87%, predominantly bound to albumin</td></tr>
<tr><td>Drug as substrate of transporters</td><td>Apixaban is a substrate for efflux transport proteins, P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP).</td></tr>
<tr><td></td><td>Elimination</td></tr>
<tr><td>Mass balance results</td><td>Following oral administration, ~25% of the administered apixaban dose in humans was recovered as metabolites, with the majority recovered in feces. O-demethylation and hydroxylation at the 3-oxopiperidinyl moiety are the major sites of biotransformation. Renal elimination accounts for ~27% of apixaban total clearance with the remainder ~73% accounted by nonrenal pathways of elimination.</td></tr>
<tr><td>Clearance</td><td>Apparent total clearance is 2.59 L/h in pediatric subjects</td></tr>
<tr><td>Half-life</td><td>~12 hours</td></tr>
<tr><td>Metabolic pathway(s)</td><td>Apixaban is metabolized mainly via CYP3A4/5 with minor contributions from CYP1A2, 2C8, 2C9, 2C19, and 2J2</td></tr>
<tr><td>Primary excretion pathways (% dose)</td><td>Renal elimination accounts for ~27% of apixaban total clearance with the remainder, ~73% accounted by nonrenal pathways of elimination.</td></tr>
</table>

Characteristic	Drug Information
	Intrinsic Factors and Specific Populations
Body weight	Body weight was a significant predictor of both apixaban CL/F and V_c/F. Body weight tiered regimen is recommended in pediatric patients.
Age	CL/F in pediatric subjects was generally consistent across the pediatric age groups after normalizing for body weight, except in the youngest age groups. Since apixaban dosing is determined by body weight categories, which is highly corelated to age, no age-based dose adjustment is necessary.
Renal impairment	In pediatric patients ≥2 years of age, ELIQUIS is not recommended in patients with an estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2 body surface area (BSA). In patients <2 years of age, ELIQUIS is not recommended in patients with inadequate renal function as defined in the pediatric VTE trial by sex and postnatal age. See Section 8.1 for details.
Hepatic impairment	Apixaban has not been studied in pediatric patients with hepatic impairment.
	Drug Interaction Liability (Drug as Perpetrator)
Inhibition/induction of metabolism and transporter systems	Apixaban is a substrate of CYP3A4 and P-gp. Inhibitors of CYP3A4 and P-gp increase exposure to apixaban and increase the risk of bleeding. Inducers of CYP3A4 and P-gp decrease exposure to apixaban and increase the risk of stroke and other thromboembolic events. Concomitant administration of combined P-gp and strong CYP3A4 inhibitors has not been studied in pediatric patients.

Source: Reviewer's evaluation of the pediatric submission and current approved drug label of ELIQUIS
Abbreviations: AUC, area under the concentration-time curve; BCRP, breast cancer resistance protein; BID, twice daily; CL/F, apparent oral clearance; C_{max}, maximum concentration; CYP, cytochrome p450; EPC, established pharmacologic class; LC-MS/MS, liquid chromatography-tandem mass spectrometry; max, maximum; min, minimum; P-gp, P-glycoprotein; USPI, United States Prescribing Information; V_c/F, apparent volume of distribution of the central compartment; VTE, venous thromboembolism

6. Efficacy (Evaluation of Benefit)

6.1. Assessment of Dose and Potential Effectiveness

Applicant's Proposed Dosage

The recommended dose of ELIQUIS is based on the patient's weight; see Table 10. Adjust the dose according to weight tier as treatment progresses. Initiate ELIQUIS treatment for pediatric patients from birth to less than 18 years of age following at least 5 days of initial anticoagulation therapy. Individualize duration of overall therapy after careful assessment of the treatment benefit and the risk for bleeding. ELIQUIS is not recommended for use in pediatric patients less than 2.6 kg because ELIQUIS was not studied in these subjects.

Table 10. Dose Recommendation in Pediatric Patients From Birth to <18 Years of Age for the Treatment of VTE and Reduction in the Risk of Recurrent VTE

Presentation	Body Weight (kg)	Dosing Schedule	Maximum Daily Dose	Dosing Schedule	Maximum Daily Dose
		Days 1-7		Days 8 and Beyond	
Capsule 0.15 mg	2.6 to <4	0.3 mg BID	0.6 mg	0.15 mg BID	0.3 mg
	4 to <5	0.6 mg BID	1.2 mg	0.3 mg BID	0.6 mg
Tablet 0.5 mg	5 to <6	1 mg BID	2 mg	0.5 mg BID	1 mg
	6 to <9	2 mg BID	4 mg	1 mg BID	2 mg
	9 to <12	3 mg BID	6 mg	1.5 mg BID	3 mg
	12 to <18	4 mg BID	8 mg	2 mg BID	4 mg
	18 to <25	6 mg BID	12 mg	3 mg BID	6 mg
	25 to <35	8 mg BID	16 mg	4 mg BID	8 mg
Tablets 2.5 mg and 5 mg	≥35	10 mg BID	20 mg	5 mg BID	10 mg

Source: Module 2.7.2 Summary of Clinical Pharmacology Studies of NDA 220073
Abbreviations: BID, twice daily; VTE, venous thromboembolism

Dose Selection in Pediatric Subjects

An exposure-matching strategy was adopted for pediatric dose selection, aiming to identify doses that achieve exposures comparable to adults receiving safe and effective VTE treatment doses (10 mg twice daily [BID] for 7 days, then 5 mg BID). Adult exposure for VTE treatment is defined by a steady-state median area under the concentration-time curve in one dosing interval at steady-state (AUC_T) estimated via a popPK model.

Pediatric exposure was estimated using a popPK model adapted from adults and updated with data from a single-dose pediatric Study CV185118. Interim analyses from Study CV185118 showed that apixaban's oral clearance increases with age, and achieves adult clearance levels (e.g., ~3.3 L/h) in subjects over 12 years. Body weight was a key covariate for clearance, and when normalized to body weight, clearance remained relatively stable across the 28-day to 18-year age range.

For subjects aged >28 days to <18 years, a bodyweight-based (mg/kg) dosing approach was used in the early versions of study protocols for pivotal Study CV185325. With the availability of

0.5 mg tablets, dosing shifted to a fixed-dose, bodyweight-tiered regimen, using increments of 0.5 mg tailored to specific weight ranges.

For neonates, an initial dose of 0.1 mg BID (via 0.1 mg capsules) was administered, later adjusted based on Day 1 PK data to target a daily AUC at steady state (AUC_{ss}) within 1,293 to 4,807 ng·h/mL (90% prediction interval for adult 5 mg BID). The 0.1 mg dose was chosen to produce slightly lower exposure than the adult 5 mg BID median but within the adult range, as predicted by modeling and simulation. A relatively conservative initial dose was selected to assure safety in neonates.

With the emergence of new data and the introduction of new formulations (0.5 mg tablets and 0.1 mg capsules), the Applicant revised their protocols, proposing the final dose regimen as outlined in Table 11. Neonates, as well as infants aged 28 days to less than 5 years (weighing at least 4 kg and under 35 kg), received either a 0.5 mg film-coated tablet for oral suspension or a 0.1 mg capsule (sprinkle for oral suspension), depending on the assigned drug dose. For pediatric subjects aged 5 to less than 18 years with a weight greater than 35 kg, a 5 mg tablet or oral solution was administered, based on the appropriateness of the assigned dose. Administration of the apixaban oral solution (0.4 mg/ml) via nasogastric tube or gastrostomy tube is acceptable. Studies to assess the relative bioavailability of 0.5 mg tablets compared to 0.1 mg capsules (Study CV185687), and 0.4 mg/mL oral solution compared to 5 mg tablets (Study CV185029) were performed which showed similar exposures between formulations.

Table 11. Apixaban Doses in Study CV185325

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

Source: Table 3 of the Study CV185325 CSR
[a] Age group 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).
[b] Subjects enrolled in age group 3, 28 days to <2 years (a minimum of 4 kg) and <35 kg were administered 0.5 mg film-coated tablet for oral suspension or 0.1 mg capsules based on the assigned apixaban dose.
[c] Neonate PK cohort includes 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 was targeted to achieve an exposure similar to 5 mg BID in adults.
[d] Neonates were defined as infants from birth to ≤27 days of life. For preterm infants born between 34 and <37 weeks gestation, investigators had the option to define the 27-day neonatal period starting from the actual date of birth (postnatal age) or may have chosen to define the 27-day neonatal period starting when the postmenstrual age (gestational age plus the postnatal age) reached 37 weeks and enroll the infant no more than 27 days thereafter into Cohort 4.
[e] Neonatal dose may have been modified during PK-subanalysis period until a fixed-dose was determined.
[f] For the study's neonate postPK cohort, (i.e., those neonates recruited after the PK subanalysis is completed), which may be treated with standard of care therapies for up to 14 days prior to randomization. In this study, no neonates were enrolled under the post PK cohort.
Abbreviations: BID, twice daily; PK, pharmacokinetic

Evaluation of the Proposed Dosage in Pediatric Subjects

In Study CV185325, blood samples for PK and PD assessments were collected in pediatric subjects. Apixaban PK parameters for subjects in Study CV185325 were estimated by popPK modeling and summarized by body weight tiers in Table 12.

Table 12. Summary of Individual Estimated Pharmacokinetic Parameters and Simulated Steady-State Exposures for Subjects by Body Weight Tiers, Study CV185325

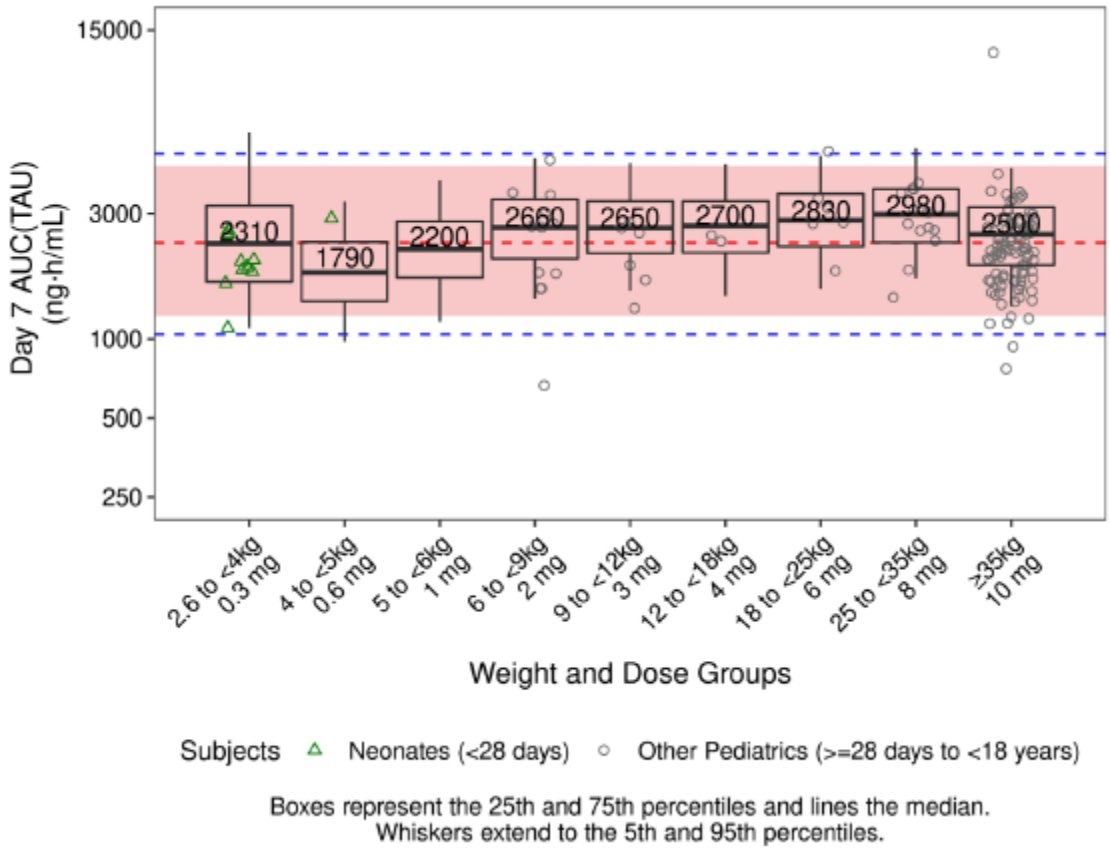
Variable	Summary Statistic	2.6 to < 4 kg (n = 9)	4 to < 5 kg (n = 1)	6 to < 9 kg (n = 2)	9 to < 12 kg (n = 6)	12 to < 18 kg (n = 2)	18 to < 25 kg (n = 6)	25 to < 35 kg (n = 14)	≥ 35 kg (n = 95)	Overall (n = 144)
AUCss(TAU) (ng•h/mL)	Geometric mean (%CV)	643 (25.3)	485 (NA)	1200 (59.2)	1080 (31.7)	1240 (6.45)	1530 (34.4)	1400 (28.5)	1080 (38)	1090 (42.1)
CL/F (L/h)	Geometric mean (%CV)	0.164 (26.1)	0.22 (NA)	0.835 (59.2)	1.38 (31.6)	1.58 (6.42)	1.89 (34.2)	2.68 (28.6)	4.27 (38)	2.59 (126)
Cmaxss (ng/mL)	Geometric mean (%CV)	65.3 (25)	49.3 (NA)	159 (53.1)	156 (25.7)	176 (12.1)	211 (25.6)	180 (26.7)	134 (34.5)	137 (42.7)
Cminss (ng/mL)	Geometric mean (%CV)	40 (26.1)	30.3 (NA)	45.7 (84.1)	34.7 (63.1)	43.8 (6.64)	57.6 (55.8)	59.2 (36.3)	48.6 (52.5)	48.1 (53.3)
Ka (1/h)	Geometric mean (%CV)	1.34 (7.76)	1.48 (NA)	1.23 (16.8)	1.32 (7.66)	1.33 (3.88)	1.29 (3.41)	1.25 (5.73)	1.27 (9.81)	1.27 (9.93)
Q/F (L/h)	Geometric mean (%CV)	0.0129 (17.7)	0.0128 (NA)	0.104 (31)	0.152 (21.4)	0.261 (48.7)	0.451 (15.9)	0.578 (22.6)	0.902 (12.1)	0.476 (182)
Tmax (h)	Median (Min, Max)	1.89 (1.81, 2.11)	1.81 (1.81, 1.81)	1.8 (1.46, 2.28)	1.64 (1.38, 1.86)	1.64 (1.59, 1.68)	1.66 (1.52, 1.78)	1.75 (1.59, 1.96)	1.79 (1.43, 2.45)	1.78 (1.38, 2.45)
Vc/F (L)	Geometric mean (%CV)	3.27 (24.7)	4.44 (NA)	6.24 (41.7)	8.71 (26.8)	10.3 (18.2)	13.1 (16.7)	21.7 (25.3)	39.3 (33.8)	23.6 (105)
Vp/F (L)	Geometric mean (%CV)	18.1 (0)	18.1 (NA)	18.1 (0)	18.1 (0)	18.1 (0)	18.1 (0)	18.1 (0)	18.1 (0)	18.1 (0)

Source: Table 5.1.4.2-2 of the Study CV185325 Pharmacometric Report
Note: As neither IIV in Vp/F nor an effect of body weight or age (as a scaling factor on Vp/F) were estimated in the popPK model, all subjects are predicted to have the same Vp/F estimate of 18.1 L.
Abbreviations: $AUC_{ss,T}$, area under the concentration-time curve at steady state in one dosing interval; CL/F, apparent oral clearance; $C_{max,ss}$, maximum concentration at steady state, $C_{min,ss}$, minimum concentration at steady state; IIV, intraindividual variability; K_a, absorption rate constant; popPK, population pharmacokinetic; Q/F, apparent intercompartmental clearance; T_{max}, time to maximum concentration; Vc/F, apparent volume of distribution of the central compartment; Vp/F, apparent volume of distribution of the peripheral compartment

Individual exposure estimates indicated that apixaban exposure in pediatric subjects across most body weight groups was generally comparable to median exposures (1,223 ng·h/mL) observed in adult VTE subjects following apixaban 5 mg BID. However, for the two lightest body weight groups, the AUC_{ss} was relatively lower compared to other body weight groups. After normalization with body weight, CL/F in pediatric subjects was similar across the pediatric age groups, except in the youngest age group, demonstrating that physiological maturation impacts apixaban exposure in younger pediatric subjects.

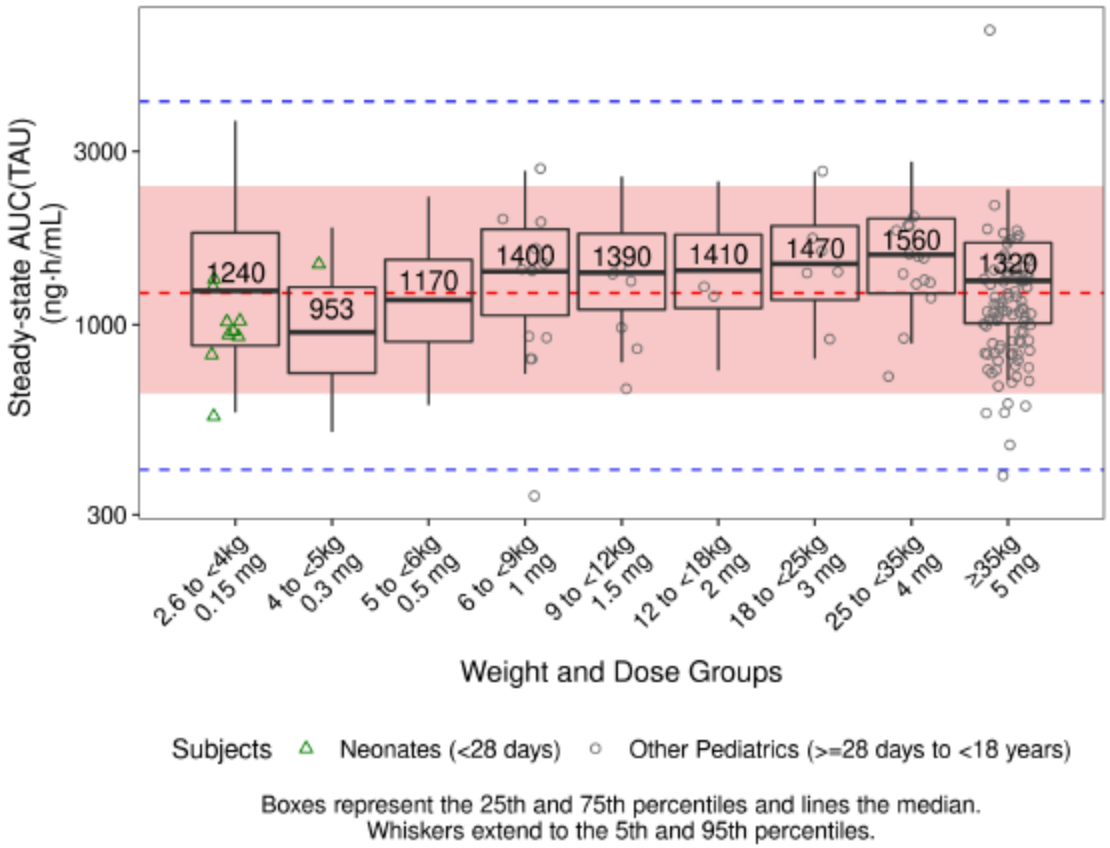
To confirm the dosing, stochastic simulations with virtual pediatric subjects receiving apixaban for VTE treatment were performed with an established popPK model. The Applicant increased the neonatal dose while keeping doses for other groups unchanged. For neonates (2.6 to <4 kg), the dose was revised to 0.3 mg BID for Days 1 to 7 and 0.15 mg BID thereafter, up from the initial 0.1 to 0.2 mg BID and 0.1 mg BID thereafter. Simulation results, expressed as Day 7 AUC_T and area under the concentration-time curve at steady state (beyond Day 7) in one dosing interval ($AUC_{ss,T}$), showed exposure in pediatric subjects largely contained within the adult exposure range following VTE treatment regimens 10 mg BID (Figure 1) and 5 mg BID (Figure 2), respectively.

Figure 1. Simulated Exposures at Day 7 for Virtual Pediatric Subjects From Birth to <18 Years of Age by Body Weight Tiers; Neonate (2.6-4 kg) Starting Dose of 0.3 mg BID and the Adult VTE Treatment Population Starting Dose of 10 mg BID



Source: Figure 5.1.4.2-6 of the Study CV185325 Pharmacometrics Report
Note: Red dashed line and shaded region represent the median and 5th/95th percentiles of exposure, respectively, in the adult VTE treatment population based on simulations (with uncertainty) performed to predict apixaban AUC_T exposure. The 5th, 50th (median), and 95th percentile Day 7 AUC_T were 1,228, 2,325, and 4,568 ng•h/mL, respectively, for the 10 mg BID dose regimen.21 The upper blue dashed line is the maximum adult value for Day 7 AUC_T of 5,076.50 ng•h/mL observed in the adult VTE treatment population in Studies CV185017, CV185056, and CV185057 for the 10 mg BID dose regimen; lower blue dashed line is the minimum adult value of 1,041.70 ng•h/mL
Note: Open symbols in the body weight tier boxplots denote model-predicted exposures for pediatric subjects in Study CV185325; no pediatric subjects were in the 5 to <6 kg body weight tier group. The high exposure value in the body weight tier ≥35 kg was a pediatric subject (ID (b) (6)) in Study CV185325, aged 16.6 years with body weight of 57.2 kg and Day 7 AUC_T of 12, 582 ng•h/mL.
Abbreviations: AUC_T, area under the concentration-time curve in one dosing interval; BID, twice daily; VTE, venous thromboembolism

Figure 2. Simulated Steady-State Exposures for Virtual Pediatric Subjects From Birth to <18 Years of Age by Body Weight Tiers; Neonate (2.6-4 kg) Dose of 0.15 mg BID and the Adult VTE Treatment Population Dose of 5 mg BID



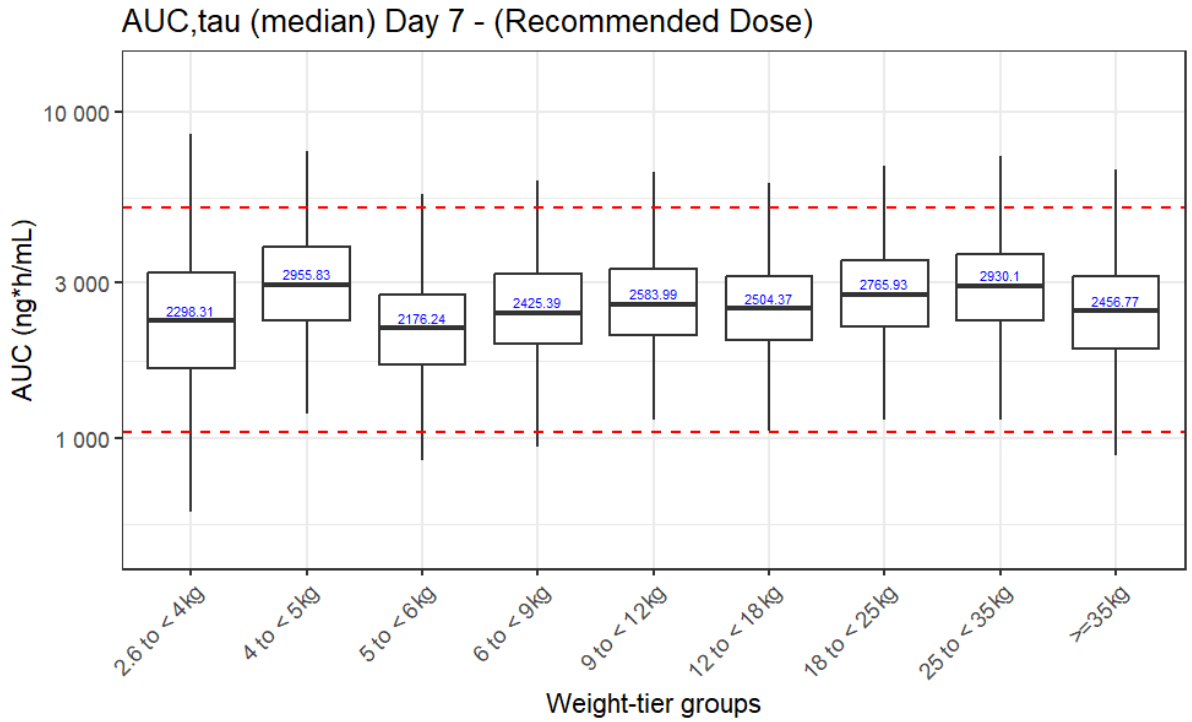
Source: Figure 5.1.4.2-7 of the Study CV185325 Pharmacometrics Report
Note: Red dashed line and shaded region represent the median and 5th/95th percentiles of exposure, respectively, in the adult VTE treatment population based on simulations (with uncertainty) performed to predict apixaban daily AUC_{ss} exposure. The 5th, 50th (median), and 95th percentile $AUC_{ss,T}$ were 647, 1,223, and 2,404 ng•h/mL, respectively, for the 5 mg BID dose regimen.21 The upper blue dashed line is the maximum adult value for $AUC_{ss,T}$ of 4,113.5 ng•h/mL observed in the adult VTE treatment population in Studies CV185017, CV185056, and CV185057 for the 5 mg BID dose regimen; lower blue dashed line is the minimum adult value of 399.5 ng•h/mL.
Note: Open symbols in the body weight tier boxplots denote model-predicted exposures for pediatric subjects in Study CV185325; no pediatric subjects were in the 5 to <6 kg body weight tier group. The high exposure value in the body weight tier ≥35 kg was a pediatric subject (ID (b) (6)) in Study CV185325, aged 16.6 years with body weight of 57.2 kg and $AUC_{ss,T}$ of 6,590.8 ng•h/mL.
Abbreviations: AUC_{ss}, area under the concentration-time curve at steady state; $AUC_{ss,T}$, area under the concentration-time curve at steady state in one dosing interval; BID, twice daily; VTE, venous thromboembolism

The results showed that median exposures across most pediatric body weight tiers were similar to adult median exposures (2,325 ng·h/mL for 10 mg BID and 1,223 ng·h/mL for 5 mg BID), with the exposure distribution largely falling within the minimum and maximum values observed in adults. While the median exposure for the 4 to <5 kg group fell within the adult exposure range, the exposure distribution was relatively lower compared to other body weight groups. Additionally, only one subject was enrolled in this body weight category in the study. Given the narrow 1 kg range and relatively lower exposures in this group, the review team considered combining the 4 to <5 kg group with the 5 to <6 kg body weight group. Merging these groups has advantages:

1. it decreases the number of dosing groups, thereby simplifying the dosing in neonates and young infants, and
2. by raising the initial dose from 0.6 mg to 1 mg BID and the maintenance dose from 0.3 mg to 0.5 mg BID, the predicted exposure for the 4 to <5 kg body weight group increases, bringing the levels comparable to other pediatric body weight groups and adults.

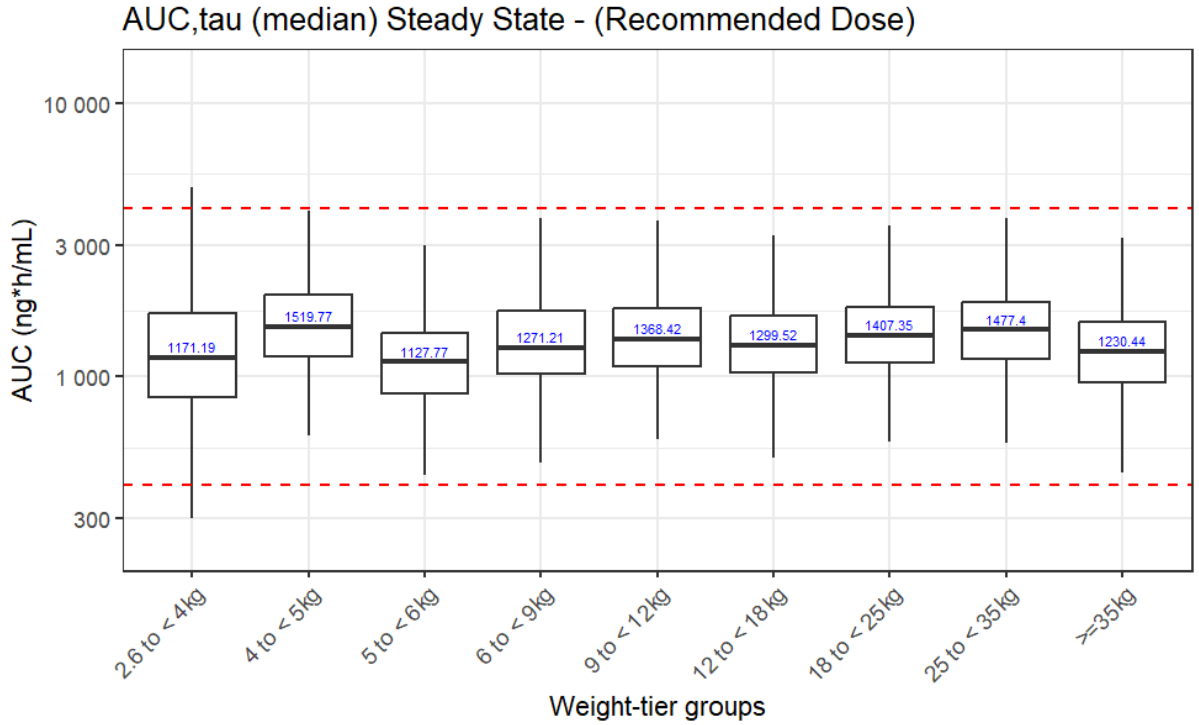
The simulation results employing a combined 4 to <6 kg body weight group receiving 1 mg BID for Days 1 to 7 and 0.5 mg BID thereafter are presented below (Figure 3 and Figure 4).

Figure 3. Simulated Exposures at Day 7 for Virtual Pediatric Subjects From Birth to <18 Years of Age by Body Weight Tiers; 2.6-<4 kg: 0.3 mg BID, 4-<5 kg: 1 mg BID and the Adult VTE Treatment Population Starting Dose of 10 mg BID



Source: Figure 6 of Section 14. 5 Pharmacometrics Review.
Abbreviations: AUC,tau, area under the concentration-time curve in one dosing interval; BID, twice daily; VTE, venous thromboembolism

Figure 4. Simulated Steady-State Exposures for Virtual Pediatric Subjects From Birth to <18 Years of Age by Body Weight Tiers; 2.6-<4 kg: 0.15 mg BID, 4-<5 kg: 0.5 mg BID and the Adult VTE Treatment Population Dose of 5 mg BID



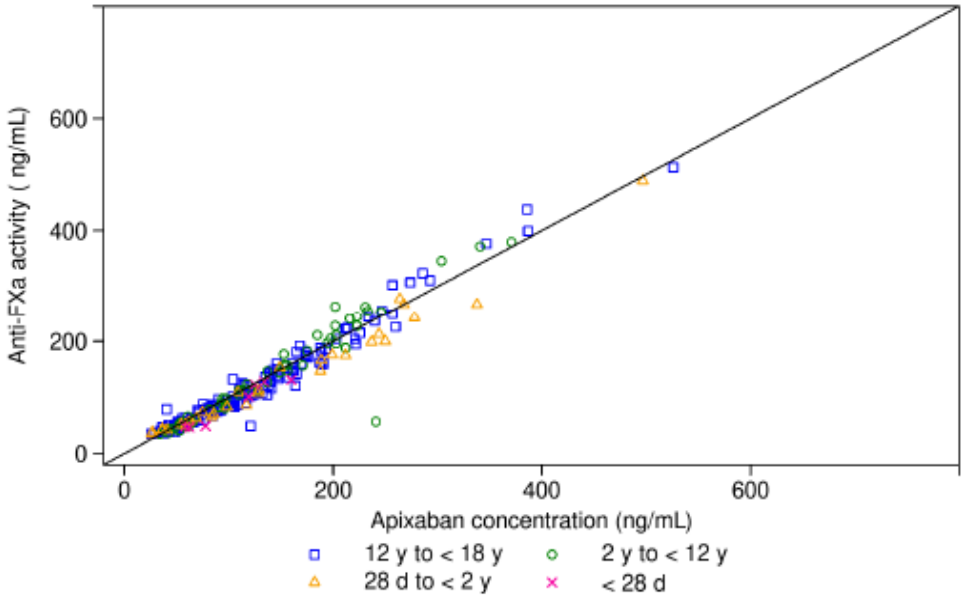
Source: Figure 6 of Section 14.5 Pharmacometrics Review
Abbreviations: AUC,tau, area under the concentration-time curve in one dosing interval; BID, twice daily; VTE, venous thromboembolism

For further information, please refer to Section 14.5.

PK/PD Analysis for Pediatric Subjects in Study CV185325

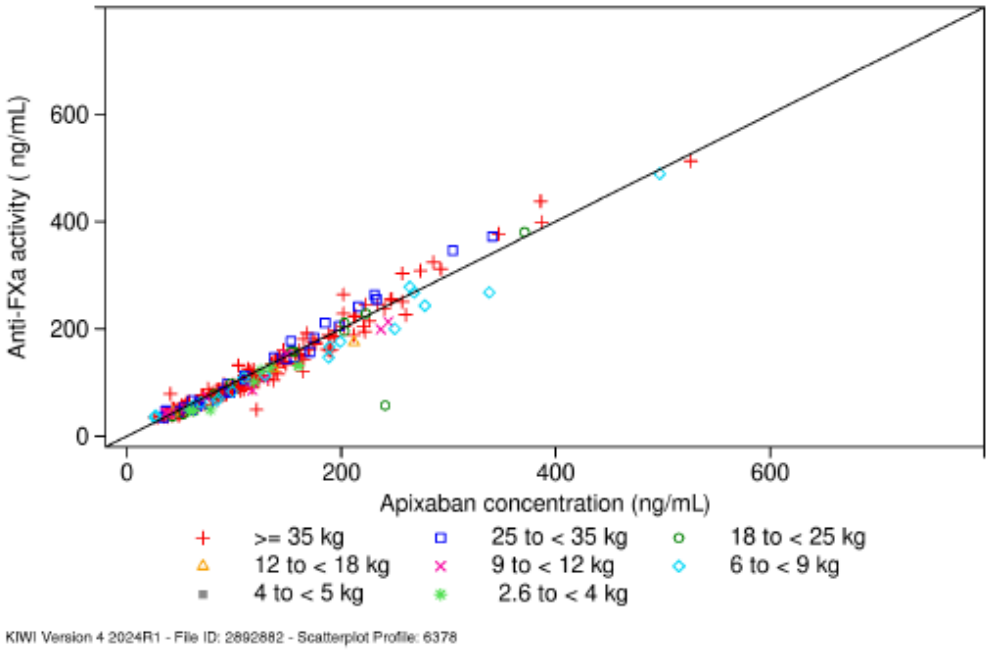
PK/PD analysis exploring the relationship between time-matched antifactor Xa activity (AXA) and apixaban concentration in pediatric subjects from Study CV185325 was conducted (Figure 5 and Figure 6). The findings demonstrate a linear correlation between AXA and apixaban concentration across all age and body weight groups.

Figure 5. Observed AXA vs. Apixaban Concentrations, Stratified by Age Group in Study CV185325



Source: Figure 1 (Appendix 3.3.2.4-1) of the Study CV185325 Pharmacometrics Report
Abbreviations: AXA, antifactor Xa activity; vs., versus

Figure 6. Observed AXA vs. Apixaban Concentrations, Stratified by Body Weight Group in Study CV185325

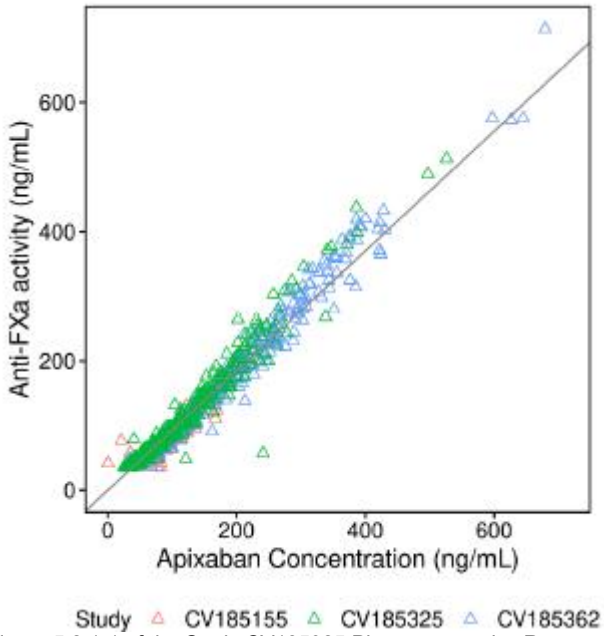


Source: Figure 3.3.2.4-4 of the Study CV185325 Pharmacometrics Report
Abbreviations: AXA, antifactor Xa activity; vs., versus

Furthermore, the PK/PD relationship was compared across pediatric subjects from different studies. Time-matched apixaban concentrations and AXA data from Study CV185325 were combined with data from Studies CV185155 and CV185362 for PK/PD analysis, as the assay for measuring AXA levels was consistent across these three studies. The results showed that a linear mixed effects model, with the intercept fixed at zero and interindividual variability (IIV) in the

slope parameter, effectively characterized the relationship between apixaban concentration and AXA in pediatric subjects (Figure 7).

Figure 7. Goodness-of-Fit Plot for the Final Apixaban Pharmacokinetic/Pharmacodynamic Model, Colored by Study for Antifactor Xa Activity



Source: Figure 5.2.1-1 of the Study CV185325 Pharmacometrics Report
Note: Triangles represent observed data and solid lines represent model predictions.

Comparison of PK/PD Relationship Between Pediatric and Adult Subjects

Direct comparison of the PK/PD relationship from Study CV185325 to adults was not feasible, as Study CV185325 employed a different AXA assay with units distinct from those used in adult studies. In contrast, Study CV185118 utilized an AXA assay identical to the adult assay, enabling a direct comparison.

For pediatric subjects in Study CV185118, the PK-AXA slope estimate was 0.0155 IU/ng, which is similar to the adult slope estimate of 0.0159 IU/ng. A comparison of the slope parameter estimates and their 95% CIs from the final PK/PD model for AXA activity between pediatric subjects of Study CV185118 and adults is provided in Table 13.

Table 13. Slope Parameter Estimates and 95% Confidence Intervals for the Final Pharmacokinetic/Pharmacodynamic Model for Antifactor Xa Activity in Pediatrics and Adults, Study CV185118

Parameter	Pediatric (CV185118) PK/PD Analysis	Adult PK/PD Analysis
Slope (IU/ng)	0.0155	0.0159
95% CI	0.0151, 0.016	0.0157, 0.0161

Source: Summary of Clinical Pharmacology (adults) in NDA 202155, SN0096, October 24, 2013; Section 3.2.2 pediatric (Study CV185118)
Abbreviations: CI, confidence interval; PK/PD, pharmacokinetic/pharmacodynamic

Considering the consistent, linear PK-AXA relationship observed across multiple pediatric studies and the similar slope estimates in both pediatric and adult populations, it is reasonable to conclude that the PK/PD relationship in pediatric patients aligns closely with that in adults.

Consequently, extrapolating efficacy from adults to pediatric patients seems justified based on achieving similar apixaban exposures in children compared to those observed in adults.

6.2. Clinical Studies/Trials Intended To Demonstrate Efficacy

6.2.1. Study CV185325/B0661037

Overall

Study CV185325 was a randomized, open-label, active-controlled, safety and descriptive efficacy study in pediatric subjects requiring anticoagulation treatment for VTE (Figure 8).

Study Objectives

The primary objective was to assess the safety and descriptive efficacy of apixaban in pediatric subjects requiring anticoagulation for the treatment of a VTE.

The secondary objective was to evaluate apixaban PK and AXA in pediatric subjects requiring anticoagulant for a treatment of a VTE.

6.2.1.1. Design, Study CV185325/B0661037

Results from Study CV185325 serve as the primary basis of the benefit evaluation.

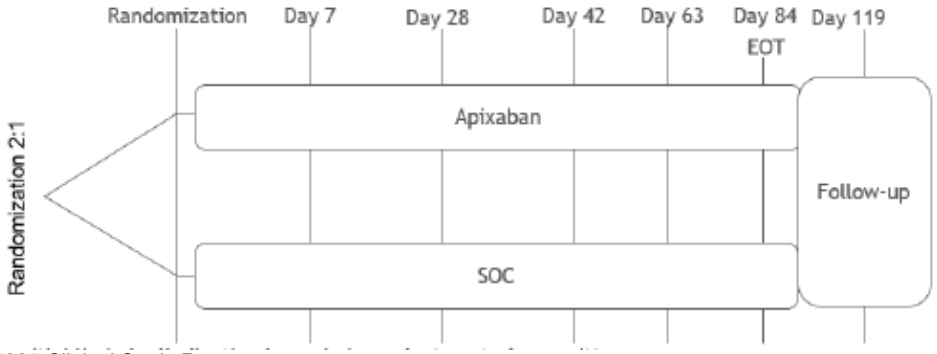
Study CV185325 was a randomized, open-label, active-controlled, safety and descriptive efficacy study in pediatric subjects requiring anticoagulation treatment for VTE. The study schema is shown in Figure 8. Subjects who had an image-confirmed index VTE were randomized into this open-label, active-controlled study using a ratio of 2:1 for apixaban to SOC, respectively. Subjects were randomized into one of four age groups in a tiered scheme beginning with the oldest age group: subjects in the 12 to <18 years age group (age group 1), subjects in the 2 to <12 years age group (age group 2), subjects in the 28 days to <2 years age group (age group 3), and neonatal subjects in the birth up to 27 days age group (age group 4).

Neonatal subjects received at least 5 days and no more than 14 days of SOC anticoagulation treatment prior to randomization. Subjects 28 days or older could receive up to 14 days of SOC anticoagulant treatment prior to randomization. Subjects 2 years or older who were randomized to the apixaban arm received apixaban treatment for 12 weeks, while subjects less than 2 years old received apixaban for 6 to 12 weeks. For subjects <2 years old, SOC was limited to UFH or LMWH, and for subjects >2 years old, SOC was either UFH, LMWH, or a VKA. Concomitant use of apixaban with antithrombotic agents were prohibited in the study. However, subjects could have been dosed on the same day prior to randomization (e.g., morning SOC dose and evening first dose of apixaban).

Radiologic imaging was performed and subsequently adjudicated to confirm the index event (i.e., primary diagnosis of thromboembolic event, which was to be treated with apixaban or SOC in this study). For subjects ≥2 years old, new radiologic images of the clot were obtained at approximately Week 6 and at end of treatment (EOT) visits. For subjects 28 days to <2 years old and neonates (birth to ≤27 days of age), imaging was performed at the EOT. For subjects 28 days to <2 years old, if the treatment duration was <12 weeks, a midpoint image could be omitted at the discretion of the investigator. All of the aforementioned images were adjudicated by an independent adjudication committee to confirm the presence or absence of thrombotic events. Additional imaging assessments may have been performed at any time during the study at the discretion of the investigator. The optional extension phase was defined as study participation beyond the 12-week visit and up to the 24-week EOT visit. Only subjects ≥28 days old who had been assigned to receive apixaban were eligible to continue treatment for 6 or 12 additional weeks, if clinically indicated.

All components of primary efficacy and safety endpoints and all bleeding events were adjudicated by a blinded independent adjudication committee.

Figure 8. Study CV185325 Design Schematic



Source: Study CV185325 Clinical Study Report
Note: This was an open-label study with blinded adjudication by an independent central committee. All neonates enrolled under protocol amendment 8 were assigned to the apixaban treatment arm.
Abbreviations: EOT, end of treatment; SOC, standard of care.

6.2.1.2. Eligibility Criteria, Study CV185325/B0661037

Key eligibility criteria are summarized in this section.

Inclusion Criteria

- Children from birth to <18 years old with a minimum weight of 2.6 kg at the time of randomization.
  - Neonates are defined as infants from birth up to ≤27 days of life. For preterm infants born between 34 and <37 weeks of gestation, investigators have the option to define the 27-day neonatal period as starting from the actual date of birth (postnatal age) or starting from when the postmenstrual age (gestational age plus the postnatal 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 a <34-week

gestation age were excluded from this study until the age of ≥6 months old. Gestational age was only taken into consideration for eligibility up to 6 months old.

- Presence of an index VTE, which is confirmed by imaging. Index VTE include, but are not limited to, DVT, PE, cerebral sinovenous thrombosis, renal vein thrombosis, portal vein thrombosis, catheter-related thrombosis, and splanchnic thrombosis.
- 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 old for 6 to 12 weeks.

Exclusion Criteria

- 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 SOC anticoagulation prior to randomization for a minimum of 5 days and a maximum of 14 days. Neonates that are enrolled into the post-PK cohort may receive SOC anticoagulation for up to 14 days prior to randomization.
- Thrombectomy, thrombolytic therapy, or insertion of a cava filter to treat the index VTE.
- A mechanical heart valve.
- Active bleeding or high risk of bleeding (e.g., central nervous system tumors) at the time of randomization.
- Intracranial bleed, including intraventricular hemorrhage, within 3 months prior to randomization.
- Platelet count of $<50 \times 10^9$ per L at randomization.
- Known inherited or acquired antiphospholipid syndrome.
- Known inherited bleeding disorder or coagulopathy with increased bleeding risk (e.g., hemophilia, von Willebrand disease, etc.).
- Use of prohibited concomitant medications at time of randomization.
  - Systemic treatment with strong inhibitors of both cytochrome P450 (CYP) 3A4 (CYP3A4) and P-glycoprotein (P-gp), such as ketoconazole, itraconazole, posaconazole, telithromycin, and ritonavir.
  - Systemic treatment with strong inducers of both cytochrome CYP3A4 and P-gp, such as phenobarbital, phenytoin, fosphenytoin, rifabutin, rifampin, carbamazepine, and St. John's wort.
  - Aspirin >165 mg per day or other antiplatelet therapies such as thienopyridines (e.g., clopidogrel, ticlopidine).
  - Other antithrombotic agents (e.g., UFH, LMWH, direct thrombin inhibitors, factor Xa inhibitors, fondaparinux).
  - Glycoprotein IIb/IIIa inhibitors (e.g., abciximab, eptifibatide, tirofiban).

6.2.1.3. Statistical Analysis Plan, Study CV185325/B0661037

6.2.1.3.1. Protocol Amendments, Study CV185325/B0661037

Major protocol amendments are summarized below. For added safety, a stepped down approach to enrolling pediatric subjects by age was conducted. Protocol amendments did not impact the integrity of the trial.

Protocol Amendment 1 (July 20, 2015):

- Eligibility limited to children 12 to <18 years old (age group 1)
- Approved amendment protocol to be implemented prior to enrollment of each subsequent age group
- Added "Day 84 (EOT)" and "if not medically necessary" to the 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"

Protocol Amendment 3 (March 1, 2017)

- Apixaban dose selection rationale and dose recommendations for the following age groups were included: subjects between the ages of 2 to <18 years old who are <35 kg
- Eligibility age was updated to allow for enrollment of children 2 to <18 years old (age groups 1 and 2) at the time of consent

Protocol Amendment 4 (October 30, 2017)

- Apixaban dose selection rationale and dose recommendations for subjects ≥3 months old and with ≥6 kg body weight were included
- Eligibility age and weight was updated to allow enrollment of children 3 months to <18 years old with a minimum weight of 6 kg at the time of consent
- Neonates were defined throughout the protocol as ≥34 weeks gestational or ≥37 weeks post conception, but not more than 27 days old

Protocol Amendment 5 (August 31, 2018)

- Apixaban dose selection rationale and dose recommendations for age group 3 (subjects ≥28 days old to <2 years old with ≥4 kg body weight) were included
- Eligibility age and weight were updated to allow enrollment of children 28 days old to <18 years old with a minimum weight of 4 kg
- Schedule of activities updated to include that SOC may be administered up to 14 days prior to randomization
- Added definition of index event and added language stating that midpoint imaging for subjects <2 years old is only required at the discretion of the investigator, but an EOT image should be collected

- Additional inclusion and exclusion criteria added regarding safety
  - Inclusion criteria: able to tolerate oral, nasogastric, or gastric feeding for at least 5 days
  - Exclusion criteria: aggressive life-saving therapies such as ventricular assist devices or extracorporeal membrane oxygenation at time of enrollment, subjects unable to take oral or enteric medication via nasogastric or gastrostomy tube, subjects with known inherited or acquired antiphospholipid syndrome, subjects with a known inherited bleeding disorder or coagulopathy with increased bleeding risk
- Clarification of SOC limited to only heparin (UFH or LMWH) for subjects <2 years old
- Updated sample size from 150 to 250 subjects with rationale

Protocol Amendment 7 (February 12, 2020)

- Apixaban dose selection rationale and dose recommendations for age group 4 (≤27 days old) were included
- Eligibility age and weight were updated to define neonates and clarify that they could be enrolled if they achieved a minimum weight of 2.6 kg
- Clarified that extension phase is only applicable to subjects in age groups 1 through 3
- Clarified that endpoints would not be limited to DVT or 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

Protocol Amendment 8 (February 12, 2020)

- All neonatal subjects enrolled under Amendment 8 were to be assigned to treated with apixaban only
- Clarified that SOC treatment of neonates was to be limited to heparins or direct thrombin inhibitors
- Neonatal group sample size determination updated

6.2.1.3.2. Statistical Analysis Plan, Study CV185325/B0661037

Sample Size Determination

Study CV185325 was a descriptive study with no formal predefined hypothesis testing. Therefore, there was no power calculation for the sample size determination. It was expected that a sample size up to 250, increased from an original sample size of 150, was needed in order to provide a reasonable safety and PK database in pediatric subjects. A target of 30 subjects were to 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 old), the sample size may be adjusted based on a PK subanalysis that would 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 would not exceed 20 subjects.

Endpoints

Primary Efficacy Endpoint

A composite of: (1) all image-confirmed and adjudicated symptomatic and asymptomatic recurrent VTE defined as either contiguous progression or noncontiguous new thrombus including, but not limited to DVT, PE and paradoxical embolism and (2) VTE-related mortality.

Secondary Endpoints

- All cause death
- VTE-related mortality
- Index VTE status (e.g., 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 (i.e., cerebral sinovenous thrombosis, renal vein thrombosis, portal vein thrombosis, catheter-related VTE, and splanchnic thrombosis)
- Major bleeding
- CRNM bleeding
- Minor bleeding
- Apixaban concentrations
- AXA

Table 14 shows the lag time of main phase and extension phase analyses.

Table 14. Definitions for Lag Time of Main Phase and Extension Phase Analyses for VTE, VTE-Related Death, All-Cause Death, Bleeding Event, VTE Status at the End of Main Phase

Endpoint	The Lag Time of Main Phase Analyses
VTE event	• For a subject who enters Extension Phase (EP): includes VTE event (AE/SAE event) that occurs up to last dose in Main Phase (MP), includes VTE event (Interval) that occurs up to latest date of last dose or last image in MP. • For a subject who doesn't enter EP: includes VTE event (AE/SAE event) that occurred up to last dose in MP +2 days if it is AE or up to the last dose in MP +30 days if it is SAE, includes the VTE event (Interval) that occurs up to the last dose in MP +7 days.
VTE related death/All Cause Death	• For a subject who enters Extension Phase (EP): includes VTE related death that occurred up to last dose in Main Phase (MP). • For a subject who doesn't enter EP: includes VTE related death that occurs up to last dose in MP +30 days.
Bleeding	• For a subject who enters Extension Phase, includes bleeding event that occurs from the first dose in the Main Phase up to the last dose in the Main Phase. • For a subject who doesn't enter Extension Phase, includes bleeding event that occurs from the first dose in the Main Phase up to the last dose in Main Phase +2 days if it is AE, or up to the last dose in Main Phase +30 days if it is SAE.
Index VTE status at the end of Main Phase	• For a subject who enters Extension Phase, includes the last image data for this subject up to the latest date of last dose or last image in the Main Phase. • For a subject who doesn't enter Extension Phase, includes the last image data for this subject up to the last dose in the Main Phase +7 days.

Endpoint	The Lag Time of Extension Phase Analyses
VTE event	• Includes VTE event (AE/SAE) that occurs from the first dose in extension phase up to the last dose in extension phase + 2 days if it is AE, or up to the last dose in extension phase + 30 days if it is SAE, includes VTE event (Interval Study) that occurs from the first dose in extension phase up to the last dose in extension phase + 7 days.
VTE related death/All Cause Death	• Includes VTE related death that occurs from the first dose in extension phase up to the last dose in extension phase + 30 days.
Bleeding	• Includes bleeding event from the first dose in extension phase up to the last dose in extension phase + 2 days if it is AE, or up to the last dose in extension phase + 30 days if it is SAE.

Source: Appendix 2 of Applicant's Statistical Analysis Plan Version 6.0, dated April 30, 2024
Abbreviations: AE, adverse event; EP, extension phase; MP, main phase; SAE, serious adverse event; VTE, venous thromboembolism

Analysis Sets

Table 15. Data Analysis Sets Definitions

Population	Description
Enrolled	All subjects with a signed informed consent document
Full analysis set	The Full Analysis Set contains all randomized subjects and those assigned to apixaban postPA8. It will be used under the intent-to-treat principle (subjects will be categorized to the treatment group to which they were assigned, regardless of the treatment actually received).
Per-protocol analysis set	There will be no Per Protocol Analysis Set defined in this protocol. No analysis will be performed for Protocol Analysis Set.
Safety analysis set	The safety data set (as treated) will consist of all randomized subjects who received at least one dose of study drug. For the purpose of safety analyses, subjects will be categorized according to the treatment received.
Extension phase analysis set	The extension phase analysis set will consist of subjects who are randomized to apixaban group and continue treatment beyond Day 84 visit for up to 12 weeks.
PrePA8 analysis set	The PrePA8 Analysis Set includes all subjects who were randomized prior to implementation of protocol amendment 8 and excludes neonates (birth-≤27 days) who were enrolled post-implementation of PA8 and assigned to apixaban without 2:1 randomization. It will be used under the intent to treat principle (subjects will be categorized to the treatment group to which they were assigned, regardless of the treatment actually received).

Population	Description
PrePA8 safety analysis set	The PrePA8 Safety analysis set (as-treated) will consist of all subjects who were randomized prior to implementation of PA8 who received at least one dose of study drug. For the purpose of safety analyses, subjects will be categorized according to the treatment received.
PostPA8 analysis set	The PostPA8 analysis set includes subjects enrolled postPA8 implementation and assigned to apixaban. It will be used under the intent-to-treat principle (subjects will be categorized to the treatment group to which they were assigned, regardless of the treatment actually received).

Source: Section 4 of Applicant's Statistical Analysis Plan (Version 6.0, dated 30 April 2024)
Abbreviation: PA8, protocol amendment 8

General Methods

There are two phases in this study: the main phase and the extension phase. For the main phase, all efficacy and safety analyses were to be performed for the overall study population and each age group. Two sets of analysis tables would be provided: one for overall study population and one for each age group. The overall study population tables and age group tables include all randomized subjects, including those who were enrolled under PA8 without 2:1 ratio randomization.

For the extension phase, the summary table for primary and secondary endpoints would be provided for the apixaban group. Treatment-emergent adverse events (TEAEs) (all causalities), TEAEs by system organ class and preferred term (PT) (all causalities), and duration of treatment will be summarized for the apixaban group.

Analyses for Binary Endpoints

Binary endpoints are summarized using the total number of subjects and number and percent. The corresponding 95% confidence intervals of the percent are provided using Agresti-Coull's method. For the main phase, the percent and corresponding 95% confidence interval are presented by treatment group, and age group by treatment group. For the extension phase, the percent and corresponding 95% confidence interval are presented for subjects in the extension phase analysis set.

Analyses for Continuous Endpoints

Continuous endpoints are summarized using means, standard deviations, median, and range. For the main phase, these are presented by treatment group and age group by treatment group. For the extension phase, these are presented for subjects in the extension phase analysis set.

Analyses for Categorical Endpoints

Categorical endpoints are summarized using the total number of subjects, number, and percent. For the main phase, these statistics are presented by treatment group and age group by treatment group. For the extension phase, these statistics are presented for subjects in the extension phase analysis set.

Missing Data

No imputation will be made for missing efficacy and safety endpoints.

Analysis of the Primary Efficacy Endpoint

This is a descriptive study. No formal inferences were to be performed. The analysis set is the full analysis set during the main phase.

For the overall study population and each age subgroup, the percentage of subjects with the composite primary efficacy endpoint is summarized using the number of subjects having an endpoint event and percentage of subjects having an endpoint event with a 95% exact confidence interval.

Analysis of Secondary Endpoints

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

Interim Analyses

There was an interim analysis (efficacy and safety) planned in this study. The interim analysis was performed when all randomized subjects in age groups 1, 2 and 3 completed the required minimal treatment periods or discontinued from the study. The objective of this interim analysis was to provide an interim clinical study report for age groups 1, 2, and 3 while age group 4 continued to enroll the targeted number of subjects.

6.2.1.4. Results of Analyses, Study CV185325/B0661037

Data Quality and Integrity

Data were provided electronically in standard format with a study data tabulation model and analysis data model. The Applicant's statistical analysis programs used to create key efficacy and safety outputs for the study were submitted along with the data of the NDA.

Subject Disposition

Subject disposition is shown in Table 16.

The proportion of subjects who discontinued from the study during the treatment main phase was comparable between apixaban and SOC arms with a discontinuation rate of approximately 10.5%. Higher rates of adverse events (AEs) leading to study discontinuation were observed in the apixaban versus SOC arm (4.5% versus 0%, respectively).

The most common reason for not completing the main treatment phase was due to AEs. Of the seven subjects in the apixaban arm who discontinued due to an AE, four subjects are explained in Section 7.6.1.4. An information request was submitted to obtain information on the three additional subjects. According to the Applicant, one subject was randomized but withdrawn from the study on the same day, and no further information regarding this AE is available. The second subject was discontinued on study Day -2 prior to study drug treatment due to grade 3 hematuria. The third subject was discontinued on study Day 45 due to grade 3 mucositis in the setting of underlying malignancy. "Other" reasons for study discontinuation include transfer back to SOC therapy to receive procedure listed in exclusion criteria (n=1), medication noncompliance (n=2), and low PK levels in a neonatal subject (n=1).

Table 16. Subject Disposition, Main Phase, Study CV185325/B0661037

Disposition Outcome	Apixaban N=155 n (%)	SOC N=74 n (%)	Risk Difference % (95% CI)
Subjects randomized	155	74	NA
Subjects treated	152	73	NA
Completed	138 (89.0)	65 (87.8)	1.2 (-7.1, 11.4)
Discontinued study	16 (10.3)	8 (10.8)	-0.5 (-10.4, 7.4)
Adverse event	7 (4.5)	0	4.5 (-0.5, 9.0)
Lost to follow-up	3 (1.9)	0	1.9 (-3.1, 5.5)
No longer meets eligibility criteria	0	1 (1.4)	-1.4 (-7.3, 1.1)
Withdrawal by parent/guardian	0	4 (5.4)	-5.4 (-13.1, -2.1)[a]
Withdrawal by subject	1 (0.6)	0	0.6 (-4.3, 3.6)
Other	4 (2.6)	2 (2.7)	-0.1 (-7.0, 4.3)

Source: CDS.xpt and adsl.xpt; Software: R
[a] 95% confidence interval excludes zero
Duration is 84 days
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Abbreviations: CI, confidence interval; n, number of subjects in specified population or group; N, number of subjects in treatment arm; NA, not applicable; SOC, standard of care

Demographics and Baseline Clinical Characteristics

Subject demographics were well-balanced between the apixaban and SOC arms (Table 17). The majority of subjects were adolescents. The youngest age group, neonates up to 27 days, had the smallest proportion of subjects (7.2% in the apixaban group and 5.5% in the comparator group). This is reasonable given the difficulty of enrolling neonates in clinical trials and the rarity of VTE.

Table 17. Baseline Demographic and Clinical Characteristics, Treated Population, Study CV185325/B0661037

Characteristic	Apixaban N=152	SOC N=73
Sex, n (%)		
Female	84 (55.3)	42 (57.5)
Male	68 (44.7)	31 (42.5)
Age, years		
Mean (SD)	12.8 (5.2)	12.6 (4)
Median (min, max)	15 (1, 25)	14 (1, 17)
Age group, n (%)		
Neonates up to 27 days	11 (7.2)	4 (5.5)
28 days to <2 years	21 (13.8)	10 (13.7)
2 years to <12 years	29 (19.1)	14 (19.2)
12 years to <18 years	91 (59.9)	45 (61.6)
Race, n (%)		
American Indian or Alaska Native	1 (0.7)	0
Asian	4 (2.6)	4 (5.5)
Black or African American	22 (14.5)	9 (12.3)
White	118 (77.6)	54 (74.0)
Multiple	1 (0.7)	1 (1.4)
Other	3 (2.0)	1 (1.4)
Missing	3 (2.0)	4 (5.5)
Ethnicity, n (%)		
Hispanic or Latino	12 (7.9)	12 (16.4)
Not Hispanic or Latino	140 (92.1)	61 (83.6)

Characteristic	Apixaban N=152	SOC N=73
Country of participation, n (%)		
Russia	16 (10.5)	8 (11.0)
United States	110 (72.4)	49 (67.1)
Others	26 (17.1)	16 (21.9)
Is in United States, n (%)		
United States	110 (72.4)	49 (67.1)
Non-United States	42 (27.6)	24 (32.9)

Source: CDS. adsl.xpt; Software: R
Abbreviations: max, maximum; min, minimum; n, number of subjects with given characteristic; N, number of subjects in treatment group; SD, standard deviation; SOC, standard of care

Approximately 93% of subjects had significant medical history findings (Table 18). The most common medical histories of these subjects include gastrointestinal disorders (31%), congenital abnormalities (30%), respiratory disorders, metabolism and nutrition disorders (27%), and nervous system disorders (25%).

Table 18. Medical History (>10% of Subjects), Treated Population, Main Phase, Study CV185325/B0661037

Primary System Organ Class	Apixaban N=155 n (%)	SOC N=74 n (%)
Blood and lymphatic disorders	29 (18.7)	16 (21.6)
Cardiac disorders	13 (8.4)	12 (16.2)
Congenital, familial, and genetic disorders	47 (30.3)	17 (23.0)
Ear and labyrinth disorders	1 (0.6)	3 (4.1)
Endocrine disorders	8 (5.2)	6 (8.1)
Eye disorders	10 (6.5)	4 (5.4)
Gastrointestinal disorders	48 (31.0)	19 (25.7)
General disorders and administration site conditions	45 (29.0)	14 (18.9)
Hepatobiliary disorders	6 (3.9)	3 (4.1)
Immune system disorders	27 (17.4)	6 (8.1)
Infections and infestations	37 (23.9)	20 (27.0)
Injury, poisoning and procedural complications	13 (8.4)	6 (8.1)
Investigations	15 (9.7)	10 (13.5)
Metabolism and nutrition disorders	42 (27.1)	19 (25.7)
Musculoskeletal and connective tissue disorders	33 (21.3)	15 (20.3)
Neoplasm	23 (14.8)	11 (14.9)
Nervous system disorders	38 (24.5)	16 (21.6)
Psychiatric disorders	28 (18.1)	17 (23.0)
Renal and urinary disorders	10 (6.5)	7 (9.5)
Respiratory, thoracic and mediastinal disorders	41 (26.5)	21 (28.4)
Skin and subcutaneous tissue disorders	21 (13.5)	13 (17.6)
Surgical and medical procedures	14 (9.0)	2 (2.7)
Vascular disorders	17 (11.0)	9 (12.2)

Source: Adapted from CSR
Abbreviations: CSR, clinical study report; n, number of subjects in specified population or group; N, number of subjects in treatment arm; SOC, standard of care

The most frequently reported index event was DVT in the apixaban and SOC groups (Table 19).

Table 19. Summary of Index VTE Events, Main Phase, Study CV185325/B0661037

VTE Event	Apixaban N=155 n (%)	SOC N=74 n (%)
Deep vein thrombosis	83 (53.5)	32 (43.2)
Upper extremity DVT (incl. SVC)	27 (17.4)	13 (17.6)
Lower extremity DVT (incl. IVC)	56 (36.1)	19 (25.7)
Pulmonary embolus	37(23.9)	16(21.6)
Other VTE	47 (30.3)	27 (36.5)
Cerebral sinovenous thrombosis	12 (7.7)	8 (10.8)
Renal vein thrombosis	3 (1.9)	2 (2.7)
Portal/splanchnic vein thrombosis	3 (1.9)	1(1.4)
Intracardiac thrombus	9 (5.8)	2 (2.7)
Other	20 (12.9)	15 (20.3)
Device-related thrombosis	5 (3.2)	1 (1.4)

Source: Adapted from CSR
Note: VTE data related to central venous access devices were categorized using the primary diagnosis preferred term for the neonatal population only. Subjects could have multiple index events. Each subject was counted only once in an index event category but could be counted in more than one index event category.
Abbreviations: DVT, deep vein thrombosis; incl., including; IVC, inferior vena cava; n, number of subjects in specified population or group; N, number of subjects in treatment arm; SOC, standard of care; SVC, superior vena cava; VTE, venous thromboembolism

Primary Efficacy Endpoint

The primary efficacy endpoint was the composite of all image-confirmed and adjudicated symptomatic and asymptomatic recurrent VTE and VTE-related mortality. No subjects had a VTE-related death in this study. There were four (2.6%) subjects in the apixaban group and two (2.7%) subjects in the SOC group who had at least one adjudicated symptomatic or asymptomatic recurrent VTE event. Details are given in Table 20.

Table 20. Analysis of Adjudicated Primary Efficacy Endpoint – Full Analysis Set

Parameter	Apixaban (N=155)	SOC (N=74)
Number (%) of subjects with event (symptomatic and asymptomatic recurrent VTE[a] and VTE[a]-related mortality)	4 (2.6)	2 (2.7)
95% CI (exact method)	(0.7, 6.5)	(0.3, 9.4)

Source: FDA analysis
[a] Only the events within the lag time of analysis were included. See Table 14 for details.
Abbreviations: CI, confidence interval; N, number of subjects in treatment arm; SOC, standard of care; VTE, venous thromboembolism

The subgroup analysis by age is given in Table 21. In the 12 to <18 years old age group, one (1.1%) subject in the apixaban group and two (4.3%) subjects in the SOC group had at least one adjudicated symptomatic or asymptomatic VTE event. In the 2 to <12 years old age group, three (10.0%) subjects in the apixaban group and none in the SOC group had at least one adjudicated symptomatic or asymptomatic VTE event. In the neonatal and 28 days to <2 years old age groups, none of the subjects in either treatment group had a reported VTE event.

Table 21. Subgroup Analysis of Adjudicated Primary Efficacy Endpoint by Age – Full Analysis Set

	Number (%) of Subjects With Event (Symptomatic and Asymptomatic Recurrent VTE[a] and VTE[a]-Related Mortality)	
Age Group	**Apixaban (N=155)**	**SOC (N=74)**
<28 days	0 (0), n=12	0 (0), n=4
28 days to <2 years	0 (0), n=22	0 (0), n=10
2 to <12 years	3 (10.0), n=30 95% exact CI: (2.1, 26.5)	0 (0), n=14
12 to <18 years	1 (1.1), n=91 95% exact CI: (0.0, 6.0)	2 (4.3), n=46 95% exact CI: (0.5, 14.8)

Source: FDA analysis
[a] Only the events within the lag time of analysis were included. See Table 14 for details.
Abbreviations: CI, confidence interval; N, number of subjects in treatment arm; SOC, standard of care; VTE, venous thromboembolism

Additional Analyses

In the previous analyses, only the events within the lag time of analysis were included. An additional analysis was conducted by including subjects with symptomatic and asymptomatic recurrent VTE and VTE-related mortality reported at any time.

One more subject with event was found in the apixaban group. There were five (3.2%) subjects in the apixaban group and two (2.7%) subjects in the SOC group who had at least one adjudicated symptomatic or asymptomatic recurrent VTE event reported at any time. Details are given in Table 22.

Table 22. Analysis of Adjudicated Primary Efficacy Endpoint (Any Time) – Full Analysis Set

Parameter	**Apixaban (N=155)**	**SOC (N=74)**
Number (%) of subjects with event (symptomatic and asymptomatic recurrent VTE and VTE-related mortality)	5 (3.2)	2 (2.7)
95% CI (exact method)	(1.1, 7.4)	(0.3, 9.4)

Source: FDA analysis
Abbreviations: CI, confidence interval; N, number of subjects in treatment arm; SOC, standard of care; VTE, venous thromboembolism

In addition, the modified efficacy endpoint was defined as a composite of symptomatic and asymptomatic recurrent VTE and all-cause mortality reported at any time. All-cause mortality occurred in three (1.9%) subjects in the apixaban group and one (1.35%) subject in the control group. The analysis of the modified efficacy endpoint is given in Table 23.

Table 23. Analysis of Modified Efficacy Endpoint (Any Time) – Full Analysis Set

Parameter	**Apixaban (N=155)**	**SOC (N=74)**
Number (%) of subjects with event (symptomatic and asymptomatic recurrent VTE and all-cause mortality)	8 (5.2)	3 (4.1)
95% CI (exact method)	(2.3, 9.9)	(0.8, 11.4)

Source: FDA analysis
Abbreviations: CI, confidence interval; N, number of subjects in treatment arm; SOC, standard of care; VTE, venous thromboembolism

Secondary Efficacy Endpoints

Four (2.6%) subjects in the apixaban group experienced at least one VTE event, three (1.9%) of which were adjudicated as other symptomatic or asymptomatic VTE, while one (0.6%) was adjudicated as new symptomatic or asymptomatic DVT. Two (2.7%) subjects in the SOC group experienced at least one VTE event that was adjudicated as a new symptomatic or asymptomatic DVT (one [1.4%] subject) and other symptomatic or asymptomatic VTE (one [1.4%] subject) respectively. There were two (1.3%) subjects in the apixaban group and one (1.4%) subject in the SOC group who experienced all-cause death. There was a third apixaban treated subject whose death occurred outside of the 35-day follow-up period. No subjects in either treatment group had VTE-related mortality or stroke events. None of the subjects in the apixaban group had any symptomatic and asymptomatic recurrent VTE events during the extension phase of the study. The analysis of adjudicated secondary efficacy endpoints is given in Table 24.

Table 24. Analysis of Adjudicated Secondary Efficacy Endpoints – Full Analysis Set

Parameter	Apixaban (N=155)	SOC (N=74)
Symptomatic and asymptomatic recurrent VTE[a]		
Number (%) of subjects with event	4 (2.6)	2 (2.7)
95% CI	(0.7, 6.5)	(0.3, 9.4)
Symptomatic or asymptomatic DVT		
Number (%) of subjects with event	1 (0.6)	1 (1.4)
95% CI	(0.0, 3.5)	(0.0, 7.3)
New symptomatic or asymptomatic DVT		
Number (%) of subjects with event	1 (0.6)	1 (1.4)
95% CI	(0.0, 3.5)	(0.0, 7.3)
Symptomatic or asymptomatic PE		
Number (%) of subjects with event	0	0
95% CI		
New symptomatic or asymptomatic PE		
Number (%) of subjects with event	0	0
95% CI		
Other symptomatic or asymptomatic VTE[b]		
Number (%) of subjects with event	3 (1.9)	1 (1.4)
95% CI	(0.4, 5.6)	(0.0, 7.3)
New other symptomatic or asymptomatic VTE[b]		
Number (%) of subjects with event	0	0
95% CI		
VTE*-related mortality		
Number (%) of subjects with event	0	0
95% CI		
All cause death[c]		
Number (%) of subjects with event	2 (1.3)	1 (1.4)
95% CI	(0.2, 4.6)	(0.0, 7.3)

Parameter	Apixaban (N=155)	SOC (N=74)
Stroke		
Number (%) of subjects with event	0	0
95% CI		

Source: Adapted from Table 15 of Applicant's Clinical Study Report
Note: 95% CI was calculated using the exact method.
[a] Recurrent VTE, defined as either contiguous progression or non-contiguous new thrombus and including, but not limited to, DVT, PE and paradoxical embolism.
[b] Other VTE, defined as including, but not limited to, cerebral sinovenous thrombosis, renal vein thrombosis, portal vein thrombosis, catheter-related VTE, and splanchnic thrombosis. If VTE event type is blank, it will be included in the "Other VTE" category. Only the events within the lag time of analysis were included. See Table 14 for details.
[c] Reviewer's note: There were 3 deaths in the apixaban group. Two of them occurred within the lag time defined in Table 14. One of them occurred outside the lag time and hence was not counted in accordance with the statistical analysis plan.
Abbreviations: CI, confidence interval; DVT, deep vein thrombosis; N, number of subjects in treatment arm; PE, pulmonary embolism; SOC, standard of care; VTE, venous thromboembolism

Index VTE status was defined as the last image obtained during the main treatment phase for each subject's comparison to baseline imaging. According to Section 5.1.2.2 of the Applicant's clinical study report, index VTE status results for all subjects with both positive and negative index events (entire study population) were as follows: (Note: subjects could have multiple concomitant index events such as the presence of DVT and PE at baseline.)

- Resolution: 77 (49.7%) subjects in the apixaban group and 36 (48.6%) subjects in the SOC group
- Regression (i.e., unequivocal decrease [>50%] of the total volume/mass of the thrombus compared to the index event): 25 (16.1%) subjects in the apixaban group and 11 (14.9%) subjects in the SOC group
- Unchanged: 23 (14.8%) subjects in the apixaban group and 12 (16.2%) subjects in the SOC group
- Contiguous recurrence: 2 (1.3%) subjects in the apixaban group and no subjects in the SOC group
- New recurrence: no subjects in either treatment group

Efficacy Narratives

Main Phase

Subject (b) (6)

Subject (b) (6) was a 6-year-old male with T-cell lymphoma diagnosed with subclavian vein thrombosis on Day -3 and randomized to the apixaban arm. The subject had the study drug held on multiple days between study Days 15 through 79 (approximately 10 days) due to lumbar puncture procedures for chemotherapy administration. On Day 80, the independent adjudication committee classified the subject's thrombus status as recurrence-contiguous with a new DVT in the upper extremity including superior vena cava.

The reviewer agrees with the assessment and acknowledges that multiple interruptions to the study drug may have contributed to recurrence of DVT.

Subject (b) (6)

Subject (b) (6) was a 14-year-old male with history of nephrotic syndrome diagnosed with PE on Day -1. The subject was found to have a superficial vein thrombosis on Day 1, and per protocol should have been discontinued due to the development of a thromboembolic event but was continued in error and reported as a protocol deviation. The blinded independent adjudication committee confirmed the superficial vein thrombosis as a new upper extremity DVT.

The reviewer agrees with the committee's assessment, however, acknowledges that the presence of this thrombosis was present at the time of index VTE diagnosis.

Subject (b) (6)

Subject (b) (6) was a 9-year-old female diagnosed with left subclavian vein thrombosis on Day -5 and randomized to the apixaban arm. An ultrasound scan showed ongoing DVT of the left subclavian vein and left axillary vein on study Day 116. The blinded independent adjudication committee assessed the event as recurrence-contiguous progression of index event.

The reviewer agrees with this assessment and acknowledges that multiple interruptions of the study drug may have contributed to recurrence of event.

Subject (b) (6)

Subject (b) (6) was a 3-year-old male with history of acute lymphoblastic leukemia (ALL) diagnosed with CSVT on Day -7 and randomized to the apixaban arm. The subject received a lumbar puncture on study Day 17 and was found to have a headache and was vomiting on Day 18 with imaging demonstrating extension of thrombosis. The subject had multiple days prior to the extension event of drug interruptions for lumbar puncture procedures. The blinded independent adjudication committee assessed the event as recurrence-contiguous of index event.

The reviewer agrees with this assessment and acknowledges that multiple interruptions of the study drug may have contributed to recurrence of event.

Extension Phase

Subject (b) (6)

Subject (b) (6) was a 15-year-old female diagnosed with left leg DVT on Day -2 randomized to the apixaban arm and treated from Days 1 through 171 (main phase and extension phase). On Day 203, the subject was found to have swelling of the left lower extremity, revealing DVT. The event was classified by the blinded independent adjudication committee as recurrence-contiguous related to index event of DVT.

The reviewer finds it appropriate that this case was not included in the primary efficacy analysis as it follows the extension phase while subject was off study drug. Details surrounding recurrence were not provided in the available narrative.

6.2.2. Study CV185155

Study CV185155 was a phase 3, randomized, open-label, multicenter study of the safety and efficacy of apixaban for VTE prevention versus no systemic anticoagulant prophylaxis during induction chemotherapy in children with newly diagnosed ALL or lymphoblastic lymphoma (T or B cell) treated with asparaginase.

The primary objectives were:

1. to compare the effect of prophylactic oral or enteric apixaban versus no systemic anticoagulant during ~28 days of induction chemotherapy, including asparaginase, on the composite endpoint of adjudicated nonfatal DVT (including symptomatic and asymptomatic), PE, and CSVT; and VTE-related death; and
2. to assess the effect of prophylactic oral or enteric apixaban versus no systemic anticoagulant.

Subjects aged ≥1 to <18 years old, with the consent of their legal guardian(s), who were diagnosed with de novo ALL or B or T cell lymphoblastic leukemia (LL) and were to undergo treatment with induction chemotherapy, including asparaginase, via a central venous access device were included. Enrolled subjects were randomized to either the apixaban arm or the SOC arm (that received no systemic anticoagulation) in a 1:1 ratio. In the study, 537 subjects were enrolled and 512 were randomized.

The primary efficacy endpoint was a composite of adjudicated events of nonfatal symptomatic DVT, nonfatal asymptomatic DVT, PE, CSVT, and VTE-related death. The primary efficacy analyses were performed based on the intent-to-treat population, which was defined as all randomized subjects. To compare apixaban versus SOC on the primary efficacy endpoint, a Mantel-Haenszel test stratified by age group (<10 years old or ≥10 to <18 years old) was used to test for superiority at the one-sided $\alpha = 0.025$ level. The result of this test did not reach statistical significance, with a one-sided p-value of 0.04, which is equivalent to a two-sided p-value of 0.08. Details are given in Table 25.

Table 25. Analysis of Primary Efficacy Endpoint – All Randomized Population

Primary Composite Efficacy Endpoint	Apixaban N=256	SOC N=256
Event rate, n (%)	31 (12.11%)	45 (17.58%)
(95% CI lower bound, upper bound)	(8.63%, 16.71%)	(13.38%, 22.73%)
Relative risk (apixaban/SOC)		0.69
95% CI for the relative risk (lower, upper)		(0.45, 1.05)
One-sided p-value for superiority test		0.0403

Source: Table 7.1-1 of Applicant's Clinical Study Report for Study CV185155
Abbreviations: CI, confidence interval; N, number of subjects in treatment arm; SOC, standard of care

The study failed to show significance, although it was planned to have more than 80% power to demonstrate superiority at a one-sided 0.025 level. In the sample size planning, it was assumed that the rates of the primary efficacy endpoint in the apixaban and SOC arm were 8.5% and 17%, respectively. However, the actual event rate in the apixaban arm (12.11%) was somewhat higher than the assumed rate, which might be the reason for the failure of the study.

6.2.3. Study CV185362

Study CV185362 was a prospective, randomized, open-label, multicenter study of the safety and PK of apixaban versus VKAs or LMWH in pediatric subjects with congenital or acquired heart disease requiring chronic anticoagulation for thromboembolism prevention.

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

Pediatric subjects with congenital or acquired heart disease requiring chronic prophylactic anticoagulation were randomized 2:1 to apixaban or SOC, which was either VKA or LMWH. Randomization was stratified by three age groups: 28 days to <2 years old, 2 to <12 years old, or 12 to <18 years old. Randomization was also stratified by clinical diagnosis of single ventricle physiology versus other types of congenital or acquired heart disease. Subjects were treated for up to 12 months or until anticoagulation was no longer needed, whichever was first. Approximately 200 subjects were planned to be randomized. One hundred and ninety-eight subjects were enrolled, 192 of whom were randomized.

There was no primary efficacy endpoint in the study. The secondary efficacy endpoints included any adjudicated thromboembolic events detected by imaging or clinical diagnosis and thromboembolic event-related deaths (composite of adjudicated thromboembolic events and thromboembolic event-related deaths).

There were no adjudicated thromboembolic events or thromboembolic event-related deaths reported with an onset during the intended treatment period in either treatment arm.

6.3. Key Efficacy Review Issues

6.3.1. Demonstration of Substantial Evidence of Effectiveness From Submitted Clinical Studies

Issue

Demonstration of SEE from the submitted clinical studies.

Background

The Applicant submitted this pediatric supplement for the proposed indication for the treatment of VTE and reduction in the risk of recurrent VTE in pediatric patients from birth to less than 18 years of age. Study CV185325, was descriptive and primary efficacy endpoint (a composite of VTE or VTE related death) was generally comparable between apixaban and SOC; however, the CIs were considered wider than expected in the apixaban arm compared to the control arm. Additionally, in the 2 to <12 year old subgroup, apixaban had higher rates of VTE events (10%) than the control (0%).

In Study CV185155, apixaban treatment was associated with a 31% risk reduction in the incidence of VTE versus SOC in pediatric subjects with ALL/LL receiving induction

chemotherapy. While the result did not reach statistical significance, it is considered clinically meaningful.

Assessment

An information request was sent to the Applicant to provide additional information regarding the primary efficacy endpoint for Study CV185325, where there were four (2.6%) subjects with events in the apixaban arm with a95% CI (0.7, 6.5) compared with two (2.7%) subjects with events in the control arm, with 95% CI of(0.3, 9.4). The CI of the apixaban arm was entirely contained within that of the control arm. Additionally, the Applicant was asked to address why in the subgroup of subjects aged 2 to <12 years old, there were three (10%) subjects with events in the apixaban arm with a 95% CI of (2.1, 26.5) compared to the control arm, where no subjects had events within this subgroup.

The Applicant acknowledged that Study CV185325 was designed as a descriptive study without predefined hypothesis testing, therefore the study is not formally powered to demonstrate efficacy of apixaban compared to SOC overall or within subgroups. Overall, due to a 2:1 randomization, there were twice as many subjects with a primary efficacy event in the apixaban group compared to SOC, however, the proportions of the primary efficacy events were similar between groups. The Applicant also acknowledged wider CIs in the apixaban arm were attributed to a relatively small sample size for the descriptive study. Particularly, the 95% CI for the SOC treatment group is wider than the 95% CI for the control group, resulting in the exact 95% CI for the apixaban arm falling entirely within the exact 95% CI for the control group. The review team concluded that descriptive efficacy results support the finding that the efficacy is comparable between the two treatment groups and there appears to be no notable differences for efficacy.

The two additional studies, Studies CV185325 and CV185155, had limitations that precluded the ability to use them to provide evidence of efficacy. In terms of the 2 to <12 age subgroup group cohort findings for Study CV185325, due to small sample sizes within each cohort and a low number of events observed, a change of one event could have a large impact on the results within an age subgroup, particularly with 2:1 randomization. This further supports a lack of difference between the two treatment groups in relation to the primary endpoint.

In Study CV185155, although the results were considered clinically meaningful, the results were not considered statistically significant with a p-value of 0.0403. Therefore, the efficacy data from this study was not used in support of effectiveness, given the lack of statistically significant findings.

Both the efficacy data and PK/PD data from the adult studies, including the AMPLIFY study used to support approval of the same indication of for the treatment of DVT and PE, and for the reduction in the risk of recurrent DVT and PE following initial therapy in adult patients, was extrapolated to support the efficacy for the pediatric population. The PK/PD data from adult apixaban studies was also used provide further evidence of effectiveness for the proposed pediatric indication. While there are some differences in etiology and development of VTEs in pediatric and adult patients, the pathophysiology of clot formation and clinical outcomes (i.e., clot progression, risk of PE, PTS etc.) are the same. Therefore, it is reasonable to extrapolate efficacy from the adult population.

Conclusion

Study CV185325, although descriptive in nature, demonstrated comparable efficacy between the apixaban and SOC treatment arms with the 95% CI for apixaban falling within the exact 95% CI for the control group. The totality of the data from this study suggests comparable efficacy between the apixaban and SOC arms. Additionally, PK/PD data can be extrapolated from the adult studies used for approval of apixaban in the adult population for the same indication.

Therefore, SEE was determined to be based on a single adequate and well controlled phase 3 study with 229 pediatric subjects, in addition to extrapolation of efficacy and PK/PD from studies that supported approval of the same indication in adult patients. The review team determined this to be appropriate given the rarity and seriousness of VTE in pediatric patients and the continued unmet need for new oral anticoagulants in pediatric patients, particularly in very young children down to birth. While the etiology of VTE in pediatric and adult patients differ, the pathophysiology of clot formation and clinical outcomes (i.e., clot progression, risk of PE, PTS etc.) are the same. Therefore, it is reasonable to extrapolate efficacy from the adult population. This approach has been used with other anticoagulants approved for pediatric patients. In summary, the study results support expanding the indication of treatment of VTE to pediatric patients and are further supported by the literature and adult experience with apixaban.

7. Safety (Risk and Risk Management)

7.1. Potential Risks or Safety Concerns Based on Nonclinical Data

The nonclinical review for NDA 202155[4] that supported the original approval of apixaban for the treatment or prevention DVT in adults included discussion of juvenile rat study data with relevance to the current sNDA for pediatric patients of any age. The review authors noted findings of moderate to marked testicular seminiferous tubular degeneration (unilateral and bilateral) and hypospermia in the epididymis of a few animals given the highest dose of apixaban. Drug exposures in those animals corresponded to approximately three times the clinical exposure at the maximum recommended human dose of 10 mg/day. At the time of the original review, there was no proposal for including pediatric patients in the apixaban indication. However, given the numerical imbalance in histologic findings that slightly exceeded the historical control, the low clinical exposure margins, and unknown etiology, the authors suggested that the issue be revisited, should the Applicant ever propose to indicate the use of apixaban in pediatric patients.

To address the concern, we reevaluated the histological findings in male reproductive tissues in the context of all relevant nonclinical information. Reassuringly, the histological finding appeared to be reversible, and males exposed to the highest dose of apixaban that were allowed to mature to adulthood successfully impregnated naïve females at the same rate as control males. This indicated that there was ultimately no impact of the findings on overall fertility. We noted decreased body weight gain in affected males, which may indicate that a developmental delay

[4] The original nonclinical review for NDA 202155 was conducted by Patricia P. Harlow, PhD and Thomas Papoian, PhD, and was finalized on November 1, 2011.

(rather than toxicity) in that group may have contributed to the initial imbalance in the histological data. Furthermore, no correlative findings were observed in a pre and postnatal developmental toxicity study, or in a chronic toxicity study in adult rats.

Given the aforementioned, we conclude that the observed imbalance in histological findings in reproductive organs of juvenile male rats given the highest dose of apixaban are unlikely to translate to a significant fertility risk in the pediatric population. No additional juvenile animal studies or additions to labeling are warranted to address this issue, and we have no objections to approval of apixaban for the proposed pediatric population.

7.2. Potential Risks or Safety Concerns Based on Drug Class or Other Drug-Specific Factors

Potential safety concerns were identified based on known information from apixaban approved for other indications and other approved factor Xa inhibitors.

All factor Xa inhibitors carry a boxed warning for premature discontinuation increasing the risk of thrombotic/ischemic events and spinal/epidural hematoma.

Apixaban has a boxed warning for the following:

1. Premature discontinuation of ELIQUIS increases the risk of thrombotic events: Premature discontinuation of any oral anticoagulant, including ELIQUIS, increases the risk of thrombotic events. To reduce the risk, consider coverage with another anticoagulant if ELIQUIS is discontinued for a reason other than pathological bleeding or completion of a course of therapy.
2. Spinal/epidural hematoma: Epidural or spinal hematomas may occur in patients treated with ELIQUIS who are receiving neuraxial anesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis. Consider these risks when scheduling patients for spinal procedures.

7.3. Potential Risks or Safety Concerns Identified Through Postmarket Experience

Apixaban is commercially available and approved for pediatric use in the European Union for the treatment of VTE and prevention of recurrent VTE in pediatric patients from 28 days to less than 18 years of age.

Apixaban is authorized for marketing in 105 countries worldwide for one or more of the following three indications:

- Prevention of VTE in adult patients who have undergone elective hip or knee replacement surgery.
- Prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation, with one or more risk factors such as prior stroke or transient ischemic attack, age ≥75 years, hypertension, diabetes mellitus, or symptomatic heart failure (New York Heart Association Class ≥ II).
- Treatment of DVT and PE, and prevention of recurrent DVT and PE in adults.

7.3.1. Adverse Events Identified in Postmarket Experiences

Current USPI labeling for apixaban does not identify any new potential risks or safety concerns through postmarketing experience.

A 120-day safety update was submitted by the Applicant, reporting no new safety information detected for ELIQUIS either in postmarketing setting or from review of the published literature, up to January 31, 2025, that might reasonably affect the information in the draft drug labeling and medication guide submitted with the current application. The Applicant stated in this update that no pediatric subjects have been dosed in any company sponsored clinical trials since the date of the submission of this application, and no spontaneous reports have been submitted to the Applicant that alter the current safety profile for ELIQUIS. An information request was submitted to the Applicant to obtain detailed information on postmarketing cases involving apixaban use in pediatric patients.

The Applicant stated that a cumulative search for postmarketing reports of pediatric use from the international birth date of apixaban on May 18, 2011 to the first approval in the European Union on January 31, 2025 identified a total of 143 postmarketing cases, 7 of which were reported as a fetal outcome. All cases with fatal outcomes were reported before the current NDA and sNDA submission. Between the current NDA and sNDA submission and January 31, 2025, five postmarketing cases were received. Of these, there was one serious event indicating “liver function test abnormal.” The Applicant reports that the report provided for the one serious event had limited information regarding indication, concurrent and medical history, and clinical course, precluding a meaningful clinical assessment of the case other than that the subject recovered. The remaining cases were nonserious events.

The cause of the fatal cases included unknown (n=4), COVID-19 complications (n=1), subdural hematoma (n=1), and cerebrovascular hemorrhage (n=1).

Bleeding-related events in ELIQUIS pediatric postmarketing cases include a subdural hematoma (n=1), cerebrovascular hemorrhage (n=1), epistaxis (n=3), hematuria (n=2), hematochezia (n=1), hemoptysis (n=1), hemorrhoidal hemorrhage (n=1), postprocedural hematoma (n=1), traumatic hemorrhage (n=1), wound hemorrhage (n=1), uterine hemorrhage (n=1), and contusion (n=1).

The reviewer agrees with the Applicant’s assessment that the reports submitted do not alter the current safety profile of ELIQUIS.

7.3.2. Expectations on Safety

Safety in the postmarket setting is expected to be similar to that observed in the clinical studies reviewed in this application and what is known from adult postmarketing safety data.

7.3.3. Additional Safety Issues From Other Disciplines

No additional safety issues were identified from other disciplines.

7.4. FDA Approach to the Safety Review

The focus of the safety review was based on the phase 3 Study CV185325/B0661037. For Study CV185325, the safety review focused on the main treatment period (randomization and first dose of study drug to 12 weeks of treatment for subjects ≥2 years old, or 6 to 12 weeks for neonates and subjects <2 years old). For further details on the design for Study CV185325, see Section 6.2.1.

The following additional studies were submitted by the Applicant to support safety findings and were reviewed as part of our assessment.

Study CV185118

Open-label phase 1 study of a single oral dose of apixaban to evaluate PK, PD, safety, and tolerability in pediatric subjects at risk for venous or arterial thrombotic events.

Study CV185155

Open-label, 1:1 randomized, multicenter, phase 3 study to evaluate the safety and efficacy of apixaban for VTE prevention versus no systemic anticoagulant prophylaxis during induction chemotherapy in pediatric subjects with newly diagnosed ALL or LL (T or B cell) treated with asparaginase.

Study CV185362

Prospective, 2:1 randomized, open-label, multicenter, phase 2 study to evaluate the safety and PK of apixaban versus VKA or subcutaneous LMWH in pediatric subjects with congenital or acquired heart disease requiring chronic anticoagulation for thromboembolism prevention.

Study CV185079

Open-label, sequential, ascending, multiple-dose study to evaluate the PK, PD, safety profile, and tolerability following multiple oral doses of apixaban in pediatric subjects with an indwelling CVC.

Review of safety was based upon:

- Clinical Study Reports for studies
- Study protocols
- Data sets for the populations described above in studies

- Summary of clinical safety
- Patient narratives
- Case report forms

Case report forms and narratives were provided and reviewed for AEs of interest, serious AEs (SAEs), and deaths that occurred in safety populations.

Particular emphasis was focused on bleeding AEs. The TEAEs of special interest (identified by the Applicant) in Study CV185325 consisted of bleeding AEs, drug-induced liver injury (DILI), overdose, and VTE.

Analysis by the clinical data scientist support team were performed using JMP 17 (SAS, Inc. Cary, N.C.). No major issues were identified with respect to recording, coding, and categorizing AEs. AEs were analyzed by the medical dictionary for regulatory activities PTs. Similar PTs were grouped by standardized groupings of related PTs through FDA's Office of New Drugs custom medical queries.

The clinical review and clinical data scientist support teams did not identify any major data quality or integrity issues that precluded performing a safety review.

The primary safety endpoint was a composite of adjudicated major and CRNM bleeding using the International Society on Thrombosis and Hemostasis recommendations (Mitchell et al. 2011).

Major bleeding is defined as bleeding that satisfies one or more of the following criteria: (1) fatal bleeding; (2) clinically overt bleeding associated with a decrease in Hgb of at least 20 g/L (2 g/dL) in a 24-hour period; (3) bleeding that is retroperitoneal, pulmonary, intracranial, or otherwise involves the central nervous system; and (4) bleeding that requires surgical intervention in an operating suite (including interventional radiology).

CRNM bleeding is defined as bleeding that satisfies one or both of the following: (1) overt bleeding for which a blood product is administered, and which is not directly attributable to the subject's underlying medical condition; and (2) bleeding that requires medical or surgical intervention to restore hemostasis, other than in an operating suite.

Minor bleeding is defined as any overt or macroscopic evidence of bleeding that does not fulfill the above criteria for either major bleeding or CRNM. Menstrual bleeding resulting in a medical consultation and/or intervention was classified as a minor bleeding event.

7.5. Adequacy of the Clinical Safety Database

In Study CV185325, 225 subjects were exposed to either apixaban (152 subjects) or a comparator (73 subjects) for a main treatment phase of 12 weeks (6 to 12 weeks for neonates and subjects <2 years old) with the option of extending treatment for apixaban treated subjects 28 days and older who completed 12 weeks of treatment.

During the main treatment phase, the mean duration of apixaban exposure was 77 days, which was similar to the comparator group of 75 days (Table 26). The duration of exposure was similar between the apixaban and comparator groups.

Fifty-three subjects (34.8%) entered the extension phase of the study and were treated with apixaban. The mean duration of apixaban exposure for the combined main and extension phases was 103 days (Table 27)

There is adequate exposure to apixaban to inform safety in Study CV185325.

Table 26. Duration of Exposure, Safety Population, Study CV185325/B0661037, Main Phase

Parameter	Apixaban N=152 n (%)	SOC N=73 n (%)
Duration of treatment, days		
Mean (SD)	77.4 (21.5)	74.8 (22.4)
Median (Q1, Q3)	83 (78, 90)	83 (77, 86)
Min, max	1, 114	2, 96
Total exposure (person-years)	32	15
Subjects treated, by duration, n (%)		
<14 days	6 (3.9)	4 (5.5)
≥14 to <42 days	9 (5.9)	5 (6.8)
≥42 to <84 days	62 (40.8)	31 (42.5)
≥84 to <91 days	46 (30.3)	26 (35.6)
≥91 to <98 days	26 (17.1)	7 (9.6)
≥98 days	3 (2.0)	0

Source: adex.xpt and adsl.xpt; Software: R
Note: Duration is 84 days.
Abbreviations: max, maximum; min, minimum; n, number of subjects with given treatment duration; N, number of subjects in treatment arm; Q1, first quartile; Q3, third quartile; SD, standard deviation; SOC, standard of care

Table 27. Duration of Exposure, Safety Population, Study CV185325/B0661037, Combined Main Phase and Extension Phase

Variable	Apixaban N=152 n (%)	SOC N=73 n (%)
Duration of treatment, days		
Mean (SD)	102.7 (47.8)	76.9 (26.4)
Median (Q1, Q3)	87 (80,163)	83 (77,86)
Min, Max	1,176	2,175
Total exposure (person years)	43	15
Subjects treated, by duration, n (%)		
<42 days	15 (9.9)	9 (12.3)
≥42 to <84 days	43 (28.3)	29 (39.7)
≥84 to <98 days	42 (27.6)	33 (45.2)
≥98 to <126 days	5 (3.3)	0
≥126 to <150 days	5 (3.3)	1 (1.4)
≥150 to <174 days	34 (22.4)	0
≥174 to <198 days	8 (5.3)	1 (1.4)
≥198 days	0	0

Source: Adapted from Applicant's response to Information Request
Abbreviations: n, number of subjects with given treatment duration; N, number of subjects in treatment arm; Q1, first quartile; Q3, third quartile; SD, standard deviation; SOC, standard of care

7.6. Safety Results

7.6.1. Safety Results, Main Phase, Study CV185325

Overall, apixaban was well tolerated in the pediatric population with a safety profile comparable to that observed among adults who receive apixaban.

Deaths

Four deaths occurred during the main treatment phase of Study CV185325. The causes of death in the apixaban arm were meningitis with sepsis, progression of embryonal rhabdomyosarcoma, and pseudomonas bacteremia. The cause of death in the comparator arm was a gunshot wound. Additional details are provided under Section 7.6.1.2.

Serious Adverse Events

Overall, the rates of SAEs were similar between the apixaban and comparator arms in the main treatment phase of Study CV185325 (23.7% versus 23.3%, respectively). Serious AEs occurring in the apixaban arm included hematochezia, mucosal inflammation, increase in alanine aminotransferase, and cerebral venous sinus thrombosis. Additional details are provided under Section 7.6.1.3.

AEs Leading to Drug Discontinuation

In the main treatment phase of Study CV185325, there was a higher proportion of AEs leading to treatment discontinuation in the apixaban arm compared to the comparator arm (3.3% versus 0%). AEs leading to study drug discontinuation included mucosal inflammation, progression of embryonal rhabdomyosarcoma, cerebral venous sinus thrombosis, pseudomonas bacteremia, and hematochezia. Additional details are provided under Section 7.6.1.4.

7.6.1.1. Overview of Treatment-Emergent Adverse Events Summary, Study CV185325

Table 28 provides a summary of TEAEs reported in the main phase of Study CV185325. Four subjects with five AEs discontinued study drug in the apixaban arm. One subject discontinued study intervention due to TEAEs of cardiac arrest and cardiogenic shock. Subsequently, the same subject experienced the TEAE of pseudomonal bacteremia.

Table 28. Overview of Treatment-Emergent Adverse Events, Safety Population, Study CV185325/B0661037, Main Phase

Event Category	Apixaban N=152 n (%)	SOC N=73 n (%)	Risk Difference % (95% CI)
SAE	36 (23.7)	17 (23.3)	0.4 (-12.1, 11.6)
SAEs with fatal outcome	3 (2.0)	1 (1.4)	0.6 (-5.5, 4.5)
Life-threatening SAEs	2 (1.3)	2 (2.7)	-1.4 (-8.3, 2.4)
AE leading to permanent discontinuation of study drug	5 (3.3)	0	3.3 (-1.8, 7.5)

Event Category	Apixaban N=152 n (%)	SOC N=73 n (%)	Risk Difference % (95% CI)
AE leading to dose modification of study drug	18 (11.8)	12 (16.4)	-4.6 (-15.7, 4.6)
AE leading to interruption of study drug	18 (11.8)	10 (13.7)	-1.9 (-12.5, 6.9)
AE leading to reduction of study drug	0	2 (2.7)	-2.7 (-9.5, -0.2)[a]
AE leading to dose delay of study drug	0	0	0.0 (-5.0, 2.5)
Any AE	131 (86.2)	61 (83.6)	2.6 (-6.8, 13.8)
Severe and worse	33 (21.7)	19 (26.0)	-4.3 (-17.0, 7.1)
Moderate	33 (21.7)	20 (27.4)	-5.7 (-18.4, 5.9)
Mild	65 (42.8)	22 (30.1)	12.6 (-1.0, 25.1)

Source: adae.xpt; Software: R
[a] 95% confidence interval excludes zero.
Note: TEAEs defined as all events that start on or after the first dosing day and time/start time, if collected, but before the last dose will be flagged as treatment-emergent. The algorithm will not consider any events that started prior to the first dose date. If an AE starts on the same day as the first dose date, it will be considered treatment-emergent unless the CRF data indicates otherwise via explicitly recording time for AE onset and treatment dosing. Additional treatment-emergent definitions applied for adverse events summarized for the Main Phase and for the Extension Phase includes data up to end of treatment (Day 84) for subjects entering Extension Phase, or up to 35 days post-end of treatment (Day 84) for subjects not entering Extension Phase.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Severity as assessed by the investigator.
Abbreviations: AE, adverse event; CI, confidence interval; CRF, case report form; n, number of subjects with at least one event; N, number of subjects in treatment arm; ; SAE, serious adverse event; SOC, standard of care; TEAE, treatment-emergent AE

7.6.1.2. Deaths, Study CV185325

Table 29 provides a summary of deaths reported in the main phase of Study CV185325.

Table 29. Deaths, Safety Population, Study CV185325/B0661037, Main Phase

Preferred Term	Apixaban N=152 n (%)	SOC N=73 n (%)	Risk Difference % (95% CI)
Any AE leading to death	3 (2.0)	1 (1.4)	0.6 (-5.5, 4.5)
Death	1 (0.7)	0	0.7 (-4.4, 3.6)
Meningitis bacterial	1 (0.7)	0	0.7 (-4.4, 3.6)
Multiple organ dysfunction syndrome	1 (0.7)	0	0.7 (-4.4, 3.6)
Pseudomonal bacteremia	1 (0.7)	0	0.7 (-4.4, 3.6)
Sepsis	1 (0.7)	0	0.7 (-4.4, 3.6)
Gunshot wound	0	1 (1.4)	-1.4 (-7.4, 1.1)

Source: adae.xpt; Software: R
Note: Treatment-emergent adverse events defined as all events that start on or after the first dosing day and time/start time, if collected, but before the last dose will be flagged as treatment-emergent. The algorithm will not consider any events that started prior to the first dose date. If an AE starts on the same day as the first dose date, it will be considered treatment-emergent unless the CRF data indicates otherwise via explicitly recording time for AE onset and treatment dosing. Additional treatment-emergent definitions applied for adverse events summarized for the Main Phase and for the Extension Phase includes data up to end of treatment (Day 84) for subjects entering Extension Phase, or up to 35 days post-end of treatment (Day 84) for subjects not entering Extension Phase.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Abbreviations: AE, adverse event; CI, confidence interval; CRF, case report form; n, number of subjects with adverse event; N, number of subjects in treatment arm; SOC, standard of care

Subject Narratives for Deaths in Study CV 185325, Main Phase (Apixaban Arm Only)

Subject (b) (6)

Subject (b) (6) was a 12-year-old male with a present medical history of relapsed ALL randomized to the apixaban arm for upper extremity vein thrombosis diagnosed on Day -2. The subject developed epistaxis on Day 45 and received multiple antifibrinolytic agents for

prevention of hemorrhage. The AE was assessed by the blinded independent adjudication committee as CRNM bleeding. The study drug was temporarily interrupted 2 days prior to the epistaxis event due to the subject developing worsening thrombocytopenia (moderate to severe), requiring platelet transfusion. Other SAEs during the main phase included bacterial and fungal pneumonia, DILI, coagulopathy, anemia requiring red blood cell transfusion, mucosal inflammation, bone marrow failure, and febrile neutropenia. Concomitant medications while on the study drug included broad spectrum antibiotics and antifungals, oral and systemic chemotherapy, antifibrinolytics, and immunoglobulin. All events were assessed as not related to study intervention and related to chemotherapy and/or leukemia, per the Applicant. On Day 46, the subject experienced the SAE of multiple organ dysfunction, and on Day 49 experienced SAEs of sepsis and bacterial meningitis. The subject died on Day 49 after failed resuscitation measures. The Applicant assessed all events after the onset of SAE multiple organ dysfunction as unrelated to study intervention and related to chemotherapy and/or leukemia.

The clinical reviewer agrees with the assessment that the SAE of multiple organ dysfunction, sepsis, and bacterial meningitis are unlikely to be related to study drug. However, thrombocytopenia and liver enzyme abnormalities have been reported in apixaban-treated subjects, therefore there is a reasonable possibility that the study drug may have contributed to the SAEs of thrombocytopenia and DILI in the context of the subject's underlying chemotherapy use and leukemia.

Subject (b) (6)

Subject (b) (6) was a 5-year-old male with a present medical history of embryonal rhabdomyosarcoma diagnosed with an atrial thrombosis diagnosed on Day -4. On study Day 31, the subject was brought into the emergency room due to abdominal pain, headaches, and altered mentation, and started on broad spectrum antibiotics and antivirals for suspected meningitis with magnetic resonance imaging of the brain showing progression of cancer to neoplastic meningitis. The study drug was interrupted for a planned procedure of lumbar puncture to rule out meningitis and tumor progression. The subject had worsening vision problems and high intracranial pressure after the planned procedure and was withdrawn from the study due to progression of disease and the family's desire to discontinue therapy. The subject died in the setting of cardiorespiratory failure.

The Applicant assessed all events as unrelated to study intervention and related to malignancy. The clinical reviewer agrees with the assessment.

Subject (b) (6)

Subject (b) (6) was a 9-month-old premature (28 weeks) female with a history of atrial septal defect, bronchopulmonary dysplasia, tracheostomy, mechanical ventilation dependence, and pulmonary hypertension. Prior to receiving study drug, the subject was on enoxaparin for the treatment of a right upper extremity thrombosis diagnosed on Day -8. On study Day 2, the subject experienced SAEs of cardiac arrest requiring epinephrine and chest compression. The study intervention was discontinued the same day after three doses of apixaban. The subject was placed on venoarterial extracorporeal membrane oxygenation support and found to have chest films demonstrating pneumonia. Culture tests showed *pseudomonas aeruginosa.* Brain ultrasound did not show evidence of intracranial hemorrhage. The subject developed seizure activity, worsening lactic acidosis, and died after withdrawal of support.

The Applicant assessed all events as unrelated to study intervention and related to bacteremia. The clinical reviewer agrees with the assessment.

7.6.1.3. Serious Treatment-Emergent Adverse Events, Study CV185325

In the main treatment phase of Study CV185325, the frequency of SAEs was similar between the apixaban and comparator arms (24% versus 23%, respectively). All treatment-emergent SAEs are shown in Table 30. The most commonly affected system organ class based on PT in the apixaban group were "infections and infestations" (8.6% versus 2.7% in the comparator group) and "general disorders and administration site conditions" (4.6% versus 5.5% in the comparator group). The breakdown of SAEs based on the Office of New Drugs custom medical query analysis is described in Table 31. The most common SAEs occurring in over 1% of subjects in the apixaban arm that were not bleeding related were sickle cell anemia with crisis (1.3% versus 0% in the comparator group), pyrexia (2.0% versus 1.4% in the comparator group), mucosal inflammation, alanine aminotransferase increase (2.0% versus 0% in the comparator group), cerebral venous sinus thrombosis (1.3% versus 0% in the comparator group).

In the main treatment phase, three (2.0%) subjects in the apixaban arm had an SAE related to bleeding, compared to zero subjects in the comparator arm. Bleeding SAEs in the apixaban group included hematochezia, hematemesis, and heavy menstrual bleeding.

While there were some differences in AE patterns and frequency between treatment groups (i.e., "gastrointestinal disorders" and "infections and infestations"), subjects had other concurrent illnesses (e.g., sickle cell anemia, congenital heart disease, malignancy), which may confounders impacting the ability to make a definite attribution, and in some cases were the more likely cause of the AE.

Subject Narratives for Bleeding-Related and Thrombosis SAEs

Subject (b) (6)

Subject (b) (6) was a 16-year-old female with a history of obesity and dysfunctional uterine bleeding diagnosed with left upper extremity thrombosis on Day -1 and randomized to the apixaban arm. The subject developed the SAE of heavy menstrual bleeding on study Day 6, requiring red blood transfusion. No action was taken with the study drug in response to heavy menstrual bleeding. The bleeding resolved without further sequelae. The Applicant considered the SAE of heavy menstrual bleeding to be related to the study intervention.

The clinical reviewer agrees with this assessment; there is a possibility that the underlying pre-existing condition of dysfunctional uterine bleeding may have also contributed to the SAE.

Subject (b) (6)

Subject (b) (6) was a 4-year-old female with Ewing's sarcoma diagnosed with DVT on Day -5 and randomized to the apixaban arm. On study Day 30, the subject experienced the SAE of hematemesis. The subject also required platelet transfusion for thrombocytopenia (platelet count 50 K/µL. The subject was also concurrently diagnosed with colitis and ileus. No action was taken with the study drug in response to hematemesis. The investigator considered the SAE

to be unrelated to study intervention but most likely due to underlying colitis in the setting of malignancy.

The clinical reviewer partially agrees with this assessment as the SAE may have been related to study drug intervention in the context of the subject's comorbidities.

Subject (b) (6)

Subject (b) (6) was a 21-day-old male with congenital heart disease diagnosed with catheter-related thrombosis of the upper extremity on Day -1 and randomized to apixaban arm. The subject had three episodes of hematochezia between study Days 4 through 9. The subject was on concomitant aspirin that was reduced by 50% on the first episode of hematochezia. The study drug was permanently discontinued on study Day 10 in response to the event of hematochezia as well as repeat ultrasound which showed resolution of thrombus. The investigator stated that there was a reasonable possibility that the SAE of hematochezia was related to study intervention.

The clinical reviewer agrees with this assessment.

Subject (b) (6)

Subject (b) (6) was a 3-year-old female with ALL diagnosed with cerebral venous sinus thrombosis on Day -7 and randomized to the apixaban arm. The study drug had been interrupted three times prior to the onset of SAE cerebral venous sinus thrombosis on study Day 18 due to lumbar puncture procedures for chemotherapy administration. The subject developed extension of the thrombosis on imaging leading to drug discontinuation on the same day. The investigator stated that there was a reasonable possibility that the SAE was related to study intervention.

The clinical reviewer agrees with this assessment and also suspects that the multiple drug interruptions prior to SAE in the setting of underlying malignancy contributed to the SAE.

Subject (b) (6)

Subject (b) (6) was a 17-year-old female with Factor V Leiden, May-Thurner syndrome, diagnosed with bilateral PE and left lower extremity DVT on Day -6 and randomized to the apixaban arm. On study Day 2, the subject experienced an SAE of cerebral venous sinus thrombosis after additional medical history revealed a several week history of headaches. No action was taken with the study drug. According to the investigator, the SAE of cerebral venous sinus thrombosis was deemed unrelated to apixaban therapy.

The clinical reviewer agrees with this assessment, as the SAE likely predated the index event.

Table 30. Subjects With Serious Adverse Events by System Organ Class and Preferred Term, Safety Population, Study CV185325/B0661037, Main Phase

System Organ Class Preferred Term	Apixaban N=152 n (%)	SOC N=73 n (%)	Risk Difference % (95% CI)
Any SAE	36 (23.7)	17 (23.3)	0.4 (-12.1, 11.6)
Blood and lymphatic system disorders	6 (3.9)	2 (2.7)	1.2 (-5.8, 6.2)
Sickle cell anemia with crisis	2 (1.3)	0	1.3 (-3.7, 4.7)
Cold type hemolytic anemia	1 (0.7)	0	0.7 (-4.4, 3.6)
Myelosuppression	1 (0.7)	0	0.7 (-4.4, 3.6)
Neutropenia	1 (0.7)	0	0.7 (-4.4, 3.6)
Pancytopenia	1 (0.7)	0	0.7 (-4.4, 3.6)
Thrombocytopenia	1 (0.7)	0	0.7 (-4.4, 3.6)
Febrile neutropenia	1 (0.7)	2 (2.7)	-2.1 (-8.9, 1.3)
Cardiac disorders	1 (0.7)	1 (1.4)	-0.7 (-6.8, 2.5)
Cardiac arrest	1 (0.7)	0	0.7 (-4.4, 3.6)
Cardiogenic shock	1 (0.7)	0	0.7 (-4.4, 3.6)
Cardiorespiratory arrest	0	1 (1.4)	-1.4 (-7.4, 1.1)
Eye disorders	1 (0.7)	0	0.7 (-4.4, 3.6)
Eye movement disorder	1 (0.7)	0	0.7 (-4.4, 3.6)
Gastrointestinal disorders	6 (3.9)	0	3.9 (-1.1, 8.4)
Hematochezia	2 (1.3)	0	1.3 (-3.7, 4.7)
Abdominal pain	1 (0.7)	0	0.7 (-4.4, 3.6)
Colitis	1 (0.7)	0	0.7 (-4.4, 3.6)
Constipation	1 (0.7)	0	0.7 (-4.4, 3.6)
Gastrointestinal pain	1 (0.7)	0	0.7 (-4.4, 3.6)
Gastroesophageal reflux disease	1 (0.7)	0	0.7 (-4.4, 3.6)
Hematemesis	1 (0.7)	0	0.7 (-4.4, 3.6)
Ileus paralytic	1 (0.7)	0	0.7 (-4.4, 3.6)
Esophagitis	1 (0.7)	0	0.7 (-4.4, 3.6)
Small intestinal obstruction	1 (0.7)	0	0.7 (-4.4, 3.6)
Stomatitis	1 (0.7)	0	0.7 (-4.4, 3.6)
General disorders and administration site conditions	7 (4.6)	4 (5.5)	-0.9 (-9.1, 4.9)
Mucosal inflammation	2 (1.3)	0	1.3 (-3.7, 4.7)
Death	1 (0.7)	0	0.7 (-4.4, 3.6)
Multiple organ dysfunction syndrome	1 (0.7)	0	0.7 (-4.4, 3.6)
Pyrexia	3 (2.0)	1 (1.4)	0.6 (-5.5, 4.5)
Noncardiac chest pain	1 (0.7)	1 (1.4)	-0.7 (-6.8, 2.5)
Chest pain	0	1 (1.4)	-1.4 (-7.4, 1.1)
Peripheral swelling	0	1 (1.4)	-1.4 (-7.4, 1.1)
Hepatobiliary disorders	1 (0.7)	0	0.7 (-4.4, 3.6)
Drug-induced liver injury	1 (0.7)	0	0.7 (-4.4, 3.6)
Immune system disorders	1 (0.7)	0	0.7 (-4.4, 3.6)
Transplant rejection	1 (0.7)	0	0.7 (-4.4, 3.6)

System Organ Class Preferred Term	Apixaban N=152 n (%)	SOC N=73 n (%)	Risk Difference % (95% CI)
Infections and infestations	13 (8.6)	2 (2.7)	5.8 (-1.6, 11.9)
Cellulitis	1 (0.7)	0	0.7 (-4.4, 3.6)
Device related bacteremia	1 (0.7)	0	0.7 (-4.4, 3.6)
Escherichia urinary tract infection	1 (0.7)	0	0.7 (-4.4, 3.6)
Gastroenteritis rotavirus	1 (0.7)	0	0.7 (-4.4, 3.6)
Infective pulmonary exacerbation of cystic fibrosis	1 (0.7)	0	0.7 (-4.4, 3.6)
Meningitis bacterial	1 (0.7)	0	0.7 (-4.4, 3.6)
Mycoplasma infection	1 (0.7)	0	0.7 (-4.4, 3.6)
Osteomyelitis	1 (0.7)	0	0.7 (-4.4, 3.6)
Pneumonia viral	1 (0.7)	0	0.7 (-4.4, 3.6)
Pseudomonal bacteremia	1 (0.7)	0	0.7 (-4.4, 3.6)
Rhinovirus infection	1 (0.7)	0	0.7 (-4.4, 3.6)
Sepsis	1 (0.7)	0	0.7 (-4.4, 3.6)
Toxic shock syndrome	1 (0.7)	0	0.7 (-4.4, 3.6)
Upper respiratory tract infection	1 (0.7)	0	0.7 (-4.4, 3.6)
Urinary tract infection bacterial	1 (0.7)	0	0.7 (-4.4, 3.6)
Escherichia pyelonephritis	0	1 (1.4)	-1.4 (-7.4, 1.1)
Pyomyositis	0	1 (1.4)	-1.4 (-7.4, 1.1)
Varicella	0	1 (1.4)	-1.4 (-7.4, 1.1)
Injury, poisoning and procedural complications	1 (0.7)	2 (2.7)	-2.1 (-8.9, 1.3)
Lower limb fracture	1 (0.7)	0	0.7 (-4.4, 3.6)
Gunshot wound	0	1 (1.4)	-1.4 (-7.4, 1.1)
Incisional hernia	0	1 (1.4)	-1.4 (-7.4, 1.1)
Suture rupture	0	1 (1.4)	-1.4 (-7.4, 1.1)
Investigations	4 (2.6)	1 (1.4)	1.3 (-4.9, 5.5)
Alanine aminotransferase increased	2 (1.3)	0	1.3 (-3.7, 4.7)
Medical observation	1 (0.7)	0	0.7 (-4.4, 3.6)
Weight increased	1 (0.7)	0	0.7 (-4.4, 3.6)
Blood urea increased	0	1 (1.4)	-1.4 (-7.4, 1.1)
Musculoskeletal and connective tissue disorders	1 (0.7)	0	0.7 (-4.4, 3.6)
Cytarabine syndrome	1 (0.7)	0	0.7 (-4.4, 3.6)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	1 (0.7)	0	0.7 (-4.4, 3.6)
Embryonal rhabdomyosarcoma	1 (0.7)	0	0.7 (-4.4, 3.6)
Nervous system disorders	2 (1.3)	5 (6.8)	-5.5 (-13.9, -0.7) [a]
Cerebral venous sinus thrombosis	2 (1.3)	0	1.3 (-3.7, 4.7)
Intracranial pressure increased	1 (0.7)	0	0.7 (-4.4, 3.6)
Complex regional pain syndrome	0	1 (1.4)	-1.4 (-7.4, 1.1)
Headache	0	1 (1.4)	-1.4 (-7.4, 1.1)
Hypoxic-ischemic encephalopathy	0	1 (1.4)	-1.4 (-7.4, 1.1)
Seizure	0	1 (1.4)	-1.4 (-7.4, 1.1)
Transient ischemic attack	0	1 (1.4)	-1.4 (-7.4, 1.1)
Psychiatric disorders	1 (0.7)	2 (2.7)	-2.1 (-8.9, 1.3)
Selective eating disorder	1 (0.7)	0	0.7 (-4.4, 3.6)
Depression	0	1 (1.4)	-1.4 (-7.4, 1.1)
Munchausen's syndrome	0	1 (1.4)	-1.4 (-7.4, 1.1)
Renal and urinary disorders	2 (1.3)	0	1.3 (-3.7, 4.7)
Acute kidney injury	1 (0.7)	0	0.7 (-4.4, 3.6)
Nephrotic syndrome	1 (0.7)	0	0.7 (-4.4, 3.6)
Polyuria	1 (0.7)	0	0.7 (-4.4, 3.6)
Reproductive system and breast disorders	1 (0.7)	0	0.7 (-4.4, 3.6)
Heavy menstrual bleeding	1 (0.7)	0	0.7 (-4.4, 3.6)

System Organ Class Preferred Term	Apixaban N=152 n (%)	SOC N=73 n (%)	Risk Difference % (95% CI)
Respiratory, thoracic and mediastinal disorders	5 (3.3)	2 (2.7)	0.5 (-6.4, 5.3)
Acute chest syndrome	1 (0.7)	0	0.7 (-4.4, 3.6)
Acute respiratory distress syndrome	1 (0.7)	0	0.7 (-4.4, 3.6)
Dyspnea	1 (0.7)	0	0.7 (-4.4, 3.6)
Hyperventilation	1 (0.7)	0	0.7 (-4.4, 3.6)
Pneumomediastinum	1 (0.7)	0	0.7 (-4.4, 3.6)
Pleural effusion	0	1 (1.4)	-1.4 (-7.4, 1.1)
Respiratory failure	0	1 (1.4)	-1.4 (-7.4, 1.1)
Vascular disorders	3 (2.0)	0	2.0 (-3.1, 5.7)
Axillary vein thrombosis	1 (0.7)	0	0.7 (-4.4, 3.6)
Post thrombotic syndrome	1 (0.7)	0	0.7 (-4.4, 3.6)
Subclavian vein thrombosis	1 (0.7)	0	0.7 (-4.4, 3.6)
Superficial vein thrombosis	1 (0.7)	0	0.7 (-4.4, 3.6)

Source: adae.xpt; Software: R
[a] 95% confidence interval excludes zero
Note: Treatment-emergent AEs defined as all events that start on or after the first dosing day and time/start time, if collected, but before the last dose will be flagged as treatment-emergent. The algorithm will not consider any events that started prior to the first dose date. If an AE starts on the same day as the first dose date, it will be considered treatment-emergent unless the CRF data indicates otherwise via explicitly recording time for AE onset and treatment dosing. Additional treatment-emergent definitions applied for AEs summarized for the Main Phase and for the Extension Phase includes data up to end of treatment (Day 84) for subjects entering Extension Phase, or up to 35 days post-end of treatment (Day 84) for subjects not entering Extension Phase.
SAEs defined as any untoward medical occurrence that at any dose results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Abbreviations: AE, adverse event; CI, confidence interval; CRF, case report form; incl., including; n, number of subjects with AE; N, number of subjects in treatment arm; SAE, serious AE; SOC, standard of care

Table 31. Subjects With Serious Adverse Events by System Organ Class, OND Custom Medical Query (Narrow) and Preferred Term, Safety Population, Study CV185325/B0661037, Main Phase

System Organ Class OND Custom Medical Query (Narrow) Preferred Term	Apixaban N=152 n (%)	SOC N=73 n (%)	Risk Difference % (95% CI)
Blood and lymphatic system disorders			
Anemia	4 (2.6)	0	2.6 (-2.4, 6.6)
Sickle cell anemia with crisis	2 (1.3)	0	1.3 (-3.7, 4.7)
Cold type hemolytic anemia	1 (0.7)	0	0.7 (-4.4, 3.6)
Pancytopenia	1 (0.7)	0	0.7 (-4.4, 3.6)
Leukopenia	1 (0.7)	0	0.7 (-4.4, 3.6)
Pancytopenia	1 (0.7)	0	0.7 (-4.4, 3.6)
Thrombocytopenia	1 (0.7)	0	0.7 (-4.4, 3.6)
Pancytopenia	1 (0.7)	0	0.7 (-4.4, 3.6)
Thrombocytopenia	1 (0.7)	0	0.7 (-4.4, 3.6)
Cardiac disorders			
Heart failure	1 (0.7)	0	0.7 (-4.4, 3.6)
Cardiogenic shock	1 (0.7)	0	0.7 (-4.4, 3.6)
Gastrointestinal disorders			
Abdominal pain	2 (1.3)	0	1.3 (-3.7, 4.7)
Abdominal pain	1 (0.7)	0	0.7 (-4.4, 3.6)
Gastrointestinal pain	1 (0.7)	0	0.7 (-4.4, 3.6)
Constipation	1 (0.7)	0	0.7 (-4.4, 3.6)
Constipation	1 (0.7)	0	0.7 (-4.4, 3.6)
Vomiting	1 (0.7)	0	0.7 (-4.4, 3.6)
Hematemesis	1 (0.7)	0	0.7 (-4.4, 3.6)

System Organ Class OND Custom Medical Query (Narrow) Preferred Term	Apixaban N=152 n (%)	SOC N=73 n (%)	Risk Difference % (95% CI)
General disorders and administration site conditions			
Pyrexia	4 (2.6)	2 (2.7)	-0.1 (-7.0, 4.4)
Pyrexia	3 (2.0)	1 (1.4)	0.6 (-5.5, 4.5)
Febrile neutropenia	1 (0.7)	2 (2.7)	-2.1 (-8.9, 1.3)
Peripheral edema	0	1 (1.4)	-1.4 (-7.4, 1.1)
Peripheral swelling	0	1 (1.4)	-1.4 (-7.4, 1.1)
Hepatobiliary disorders			
Hepatic injury	3 (2.0)	0	2.0 (-3.1, 5.7)
Alanine aminotransferase increased	2 (1.3)	0	1.3 (-3.7, 4.7)
Drug-induced liver injury	1 (0.7)	0	0.7 (-4.4, 3.6)
Infections and infestations			
Bacterial infection	7 (4.6)	2 (2.7)	1.9 (-5.2, 7.0)
Cellulitis	1 (0.7)	0	0.7 (-4.4, 3.6)
Device related bacteremia	1 (0.7)	0	0.7 (-4.4, 3.6)
Escherichia urinary tract infection	1 (0.7)	0	0.7 (-4.4, 3.6)
Meningitis bacterial	1 (0.7)	0	0.7 (-4.4, 3.6)
Mycoplasma infection	1 (0.7)	0	0.7 (-4.4, 3.6)
Pseudomonal bacteremia	1 (0.7)	0	0.7 (-4.4, 3.6)
Sepsis	1 (0.7)	0	0.7 (-4.4, 3.6)
Toxic shock syndrome	1 (0.7)	0	0.7 (-4.4, 3.6)
Urinary tract infection bacterial	1 (0.7)	0	0.7 (-4.4, 3.6)
Escherichia pyelonephritis	0	1 (1.4)	-1.4 (-7.4, 1.1)
Pyomyositis	0	1 (1.4)	-1.4 (-7.4, 1.1)
Pneumonia	2 (1.3)	0	1.3 (-3.7, 4.7)
Infective pulmonary exacerbation of cystic fibrosis	1 (0.7)	0	0.7 (-4.4, 3.6)
Pneumonia viral	1 (0.7)	0	0.7 (-4.4, 3.6)
Nasopharyngitis	1 (0.7)	0	0.7 (-4.4, 3.6)
Upper respiratory tract infection	1 (0.7)	0	0.7 (-4.4, 3.6)
Viral infection	3 (2.0)	1 (1.4)	0.6 (-5.5, 4.5)
Gastroenteritis rotavirus	1 (0.7)	0	0.7 (-4.4, 3.6)
Pneumonia viral	1 (0.7)	0	0.7 (-4.4, 3.6)
Rhinovirus infection	1 (0.7)	0	0.7 (-4.4, 3.6)
Varicella	0	1 (1.4)	-1.4 (-7.4, 1.1)
Purulent material	0	1 (1.4)	-1.4 (-7.4, 1.1)
Pyomyositis	0	1 (1.4)	-1.4 (-7.4, 1.1)
Metabolism and nutrition disorders			
Cachexia	1 (0.7)	0	0.7 (-4.4, 3.6)
Selective eating disorder	1 (0.7)	0	0.7 (-4.4, 3.6)
Musculoskeletal and connective tissue disorders			
Fracture	1 (0.7)	0	0.7 (-4.4, 3.6)
Lower limb fracture	1 (0.7)	0	0.7 (-4.4, 3.6)
Nervous system disorders			
Stroke and TIA	2 (1.3)	1 (1.4)	-0.1 (-6.1, 3.5)
Cerebral venous sinus thrombosis	2 (1.3)	0	1.3 (-3.7, 4.7)
Transient ischemic attack	0	1 (1.4)	-1.4 (-7.4, 1.1)
Headache	0	1 (1.4)	-1.4 (-7.4, 1.1)
Headache	0	1 (1.4)	-1.4 (-7.4, 1.1)
Seizure	0	1 (1.4)	-1.4 (-7.4, 1.1)
Seizure	0	1 (1.4)	-1.4 (-7.4, 1.1)
Psychiatric disorders			
Depression	0	1 (1.4)	-1.4 (-7.4, 1.1)
Depression	0	1 (1.4)	-1.4 (-7.4, 1.1)

System Organ Class OND Custom Medical Query (Narrow) Preferred Term	Apixaban N=152 n (%)	SOC N=73 n (%)	Risk Difference % (95% CI)
Renal and urinary disorders			
Acute kidney injury	1 (0.7)	0	0.7 (-4.4, 3.6)
Acute kidney injury	1 (0.7)	0	0.7 (-4.4, 3.6)
Renal & urinary tract infection	1 (0.7)	1 (1.4)	-0.7 (-6.8, 2.5)
Escherichia urinary tract infection	1 (0.7)	0	0.7 (-4.4, 3.6)
Urinary tract infection bacterial	1 (0.7)	0	0.7 (-4.4, 3.6)
Escherichia pyelonephritis	0	1 (1.4)	-1.4 (-7.4, 1.1)
Reproductive system and breast disorders			
Abnormal uterine bleeding	1 (0.7)	0	0.7 (-4.4, 3.6)
Heavy menstrual bleeding	1 (0.7)	0	0.7 (-4.4, 3.6)
Excessive menstrual bleeding	1 (0.7)	0	0.7 (-4.4, 3.6)
Heavy menstrual bleeding	1 (0.7)	0	0.7 (-4.4, 3.6)
Respiratory, thoracic and mediastinal disorders			
Dyspnea	1 (0.7)	0	0.7 (-4.4, 3.6)
Dyspnea	1 (0.7)	0	0.7 (-4.4, 3.6)
Respiratory failure	1 (0.7)	1 (1.4)	-0.7 (-6.8, 2.5)
Acute respiratory distress syndrome	1 (0.7)	0	0.7 (-4.4, 3.6)
Cardio-respiratory arrest	0	1 (1.4)	-1.4 (-7.4, 1.1)
Hypoxic-ischemic encephalopathy	0	1 (1.4)	-1.4 (-7.4, 1.1)
Respiratory failure	0	1 (1.4)	-1.4 (-7.4, 1.1)
Vascular disorders			
Thrombosis venous	4 (2.6)	0	2.6 (-2.4, 6.6)
Cerebral venous sinus thrombosis	2 (1.3)	0	1.3 (-3.7, 4.7)
Axillary vein thrombosis	1 (0.7)	0	0.7 (-4.4, 3.6)
Post thrombotic syndrome	1 (0.7)	0	0.7 (-4.4, 3.6)
Subclavian vein thrombosis	1 (0.7)	0	0.7 (-4.4, 3.6)
Hemorrhage	3 (2.0)	0	2.0 (-3.1, 5.7)
Hematochezia	2 (1.3)	0	1.3 (-3.7, 4.7)
Hematemesis	1 (0.7)	0	0.7 (-4.4, 3.6)
Thrombosis	4 (2.6)	1 (1.4)	1.3 (-4.9, 5.5)
Cerebral venous sinus thrombosis	2 (1.3)	0	1.3 (-3.7, 4.7)
Axillary vein thrombosis	1 (0.7)	0	0.7 (-4.4, 3.6)
Post thrombotic syndrome	1 (0.7)	0	0.7 (-4.4, 3.6)
Subclavian vein thrombosis	1 (0.7)	0	0.7 (-4.4, 3.6)
Transient ischemic attack	0	1 (1.4)	-1.4 (-7.4, 1.1)
Thrombosis arterial	0	1 (1.4)	-1.4 (-7.4, 1.1)
Transient ischemic attack	0	1 (1.4)	-1.4 (-7.4, 1.1)

Source: adae.xpt; Software: R
Note: Treatment-emergent AEs defined as all events that start on or after the first dosing day and time/start time, if collected, but before the last dose will be flagged as treatment-emergent. The algorithm will not consider any events that started prior to the first dose date. If an AE starts on the same day as the first dose date, it will be considered treatment-emergent unless the CRF data indicates otherwise via explicitly recording time for AE onset and treatment dosing. Additional treatment-emergent definitions applied for AEs summarized for the Main Phase and for the Extension Phase includes data up to end of treatment (Day 84) for subjects entering Extension Phase, or up to 35 days post-end of treatment (Day 84) for subjects not entering Extension Phase.
Serious AEs defined as any untoward medical occurrence that at any dose results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Each OCMQ is aligned to a single system organ class based on clinical judgment. However, please be aware that some OCMQs may contain PTs from more than one system organ class.
Abbreviations: AE, adverse event; CI, confidence interval; CRF, case report form; n, number of subjects with AE; N, number of subjects in treatment arm; OCMQ, Office of New Drugs custom medical query; PT, preferred term; SOC, system organ class; TIA, transient ischemic attack

7.6.1.4. Adverse Events Leading to Treatment Discontinuation, Study CV185325

In the main treatment phase, 4 out 152 subjects (2.6%) in the apixaban group and 0 subjects in the comparator group discontinued the study drug due to an AE. One subject discontinued study intervention due to two TEAEs of cardiac arrest and cardiogenic shock. A list of all TEAEs leading to drug discontinuation is shown in Table 32 and Table 33. The overall low rates of discontinuation support the tolerability of apixaban in pediatric patients.

Table 32. Subjects With Adverse Events Leading to Treatment Discontinuation by System Organ Class and Preferred Term, Safety Population, Study CV185325/B0661037, Main Phase

System Organ Class Preferred Term	Apixaban N=152 n (%)	SOC N=73 n (%)	Risk Difference %(95% CI)
Any AE leading to discontinuation	5 (3.3)	0	3.3 (-1.8, 7.5)
Cardiac disorders	1 (0.7)	0	0.7 (-4.4, 3.6)
Cardiac arrest	1 (0.7)	0	0.7 (-4.4, 3.6)
Cardiogenic shock	1 (0.7)	0	0.7 (-4.4, 3.6)
Gastrointestinal disorders	1 (0.7)	0	0.7 (-4.4, 3.6)
Hematochezia	1 (0.7)	0	0.7 (-4.4, 3.6)
General disorders and administration site conditions	1 (0.7)	0	0.7 (-4.4, 3.6)
Mucosal inflammation	1 (0.7)	0	0.7 (-4.4, 3.6)
Infections and infestations	1 (0.7)	0	0.7 (-4.4, 3.6)
Pseudomonal bacteremia	1 (0.7)	0	0.7 (-4.4, 3.6)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	1 (0.7)	0	0.7 (-4.4, 3.6)
Embryonal rhabdomyosarcoma	1 (0.7)	0	0.7 (-4.4, 3.6)
Nervous system disorders	1 (0.7)	0	0.7 (-4.4, 3.6)
Cerebral venous sinus thrombosis	1 (0.7)	0	0.7 (-4.4, 3.6)

Source: adae.xpt; Software: R
Note: Treatment-emergent AEs defined as all events that start on or after the first dosing day and time/start time, if collected, but before the last dose will be flagged as treatment-emergent. The algorithm will not consider any events that started prior to the first dose date. If an AE starts on the same day as the first dose date, it will be considered treatment-emergent unless the CRF data indicates otherwise via explicitly recording time for AE onset and treatment dosing. Additional treatment-emergent definitions applied for AEs summarized for the Main Phase and for the Extension Phase includes data up to end of treatment (Day 84) for subjects entering Extension Phase, or up to 35 days post-end of treatment (Day 84) for subjects not entering Extension Phase.
Risk difference (with 95% CI) is shown between total treatment and comparator.
Abbreviations: AE, adverse event; CI, confidence interval; CRF, case report form; incl., including; n, number of subjects with AE; N, number of subjects in treatment arm; SOC, standard of care

Table 33. Subjects With Adverse Events Leading to Treatment Discontinuation by System Organ Class, OND Custom Medical Query (Narrow) and Preferred Term, Safety Population, Study CV185325/B0661037, Main Phase

System Organ Class OCMQ (Narrow) Preferred Term	Apixaban N=152 n (%)	SOC N=73 n (%)	Risk Difference % (95% CI)
Cardiac disorders			
Heart failure	1 (0.7)	0	0.7 (-4.4, 3.6)
Cardiogenic shock	1 (0.7)	0	0.7 (-4.4, 3.6)
Infections and infestations			
Bacterial infection	1 (0.7)	0	0.7 (-4.4, 3.6)
Pseudomonal bacteremia	1 (0.7)	0	0.7 (-4.4, 3.6)
Nervous system disorders			
Stroke and TIA	1 (0.7)	0	0.7 (-4.4, 3.6)
Cerebral venous sinus thrombosis	1 (0.7)	0	0.7 (-4.4, 3.6)

System Organ Class OCMQ (Narrow) Preferred Term	Apixaban N=152 n (%)	SOC N=73 n (%)	Risk Difference % (95% CI)
Vascular disorders			
Hemorrhage	1 (0.7)	0	0.7 (-4.4, 3.6)
Hematochezia	1 (0.7)	0	0.7 (-4.4, 3.6)
Thrombosis	1 (0.7)	0	0.7 (-4.4, 3.6)
Cerebral venous sinus thrombosis	1 (0.7)	0	0.7 (-4.4, 3.6)
Thrombosis venous	1 (0.7)	0	0.7 (-4.4, 3.6)
Cerebral venous sinus thrombosis	1 (0.7)	0	0.7 (-4.4, 3.6)

Source: adae.xpt; Software: R
Note: Treatment-emergent AEs defined as all events that start on or after the first dosing day and time/start time, if collected, but before the last dose will be flagged as treatment-emergent. The algorithm will not consider any events that started prior to the first dose date. If an AE starts on the same day as the first dose date, it will be considered treatment-emergent unless the CRF data indicates otherwise via explicitly recording time for AE onset and treatment dosing. Additional treatment-emergent definitions applied for AEs summarized for the Main Phase and for the Extension Phase includes data up to end of treatment (Day 84) for subjects entering Extension Phase, or up to 35 days post-end of treatment (Day 84) for subjects not entering Extension Phase.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Each OCMQ is aligned to a single system organ class based on clinical judgment. However, please be aware that some OCMQs may contain PTs from more than one SOC.
Abbreviations: AE, adverse event; CI, confidence interval; CRF, case report form; n, number of subjects with AE; N, number of subjects in treatment arm; OCMQ, FDA's Office of New Drugs custom medical query; PT, preferred term; SOC, standard of care; TIA, transient ischemic attack

7.6.1.5. Treatment-Emergent Adverse Events and Adverse Reactions, Study CV185325

Table 34 describes the TEAEs occurring at ≥5% frequency in the safety population during the main treatment phase.

Table 34. Subjects With Common Adverse Events Occurring at ≥5% Frequency, Safety Population, Study CV185325/B0661037, Main Phase

Preferred Term	Apixaban N=152 n (%)	SOC N=73 n (%)	Risk Difference % (95% CI)
Any AE	131 (86.2)	61 (83.6)	2.6 (-6.8, 13.8)
Vomiting	20 (13.2)	4 (5.5)	7.7 (-1.2, 15.1)
Heavy menstrual bleeding	17 (11.2)	3 (4.1)	7.1 (-1.1, 13.9)
Cough	11 (7.2)	1 (1.4)	5.9 (-0.6, 11.4)
Nasal congestion	8 (5.3)	2 (2.7)	2.5 (-4.6, 7.9)
Upper respiratory tract infection	8 (5.3)	2 (2.7)	2.5 (-4.6, 7.9)
Constipation	10 (6.6)	3 (4.1)	2.5 (-5.4, 8.4)
Headache	25 (16.4)	11 (15.1)	1.4 (-9.8, 10.8)
Arthralgia	8 (5.3)	3 (4.1)	1.2 (-6.6, 6.8)
Diarrhea	13 (8.6)	6 (8.2)	0.3 (-9.0, 7.5)
Pain in extremity	13 (8.6)	6 (8.2)	0.3 (-9.0, 7.5)
Abdominal pain	10 (6.6)	5 (6.8)	-0.3 (-9.0, 6.3)
Nausea	10 (6.6)	5 (6.8)	-0.3 (-9.0, 6.3)
Abdominal pain upper	7 (4.6)	4 (5.5)	-0.9 (-9.1, 4.9)
Pyrexia	13 (8.6)	7 (9.6)	-1.0 (-10.7, 6.4)
Noncardiac chest pain	10 (6.6)	6 (8.2)	-1.6 (-10.8, 5.2)
Fatigue	5 (3.3)	4 (5.5)	-2.2 (-10.3, 3.2)
Thrombocytopenia	5 (3.3)	4 (5.5)	-2.2 (-10.3, 3.2)
Oropharyngeal pain	8 (5.3)	6 (8.2)	-3.0 (-12.0, 3.6)
Epistaxis	24 (15.8)	14 (19.2)	-3.4 (-15.1, 6.6)
Hypokalemia	3 (2.0)	4 (5.5)	-3.5 (-11.5, 1.3)

Preferred Term	Apixaban N=152 n (%)	SOC N=73 n (%)	Risk Difference % (95% CI)
Leukopenia	3 (2.0)	4 (5.5)	-3.5 (-11.5, 1.3)
Dyspnea	7 (4.6)	6 (8.2)	-3.6 (-12.6, 2.7)
Febrile neutropenia	2 (1.3)	4 (5.5)	-4.2 (-12.1, 0.3)
Abdominal discomfort	0	4 (5.5)	-5.5 (-13.3, -2.1)[a]
Injection site hemorrhage	0	4 (5.5)	-5.5 (-13.3, -2.1)[a]
Contusion	11 (7.2)	10 (13.7)	-6.5 (-16.8, 1.6)
Anemia	5 (3.3)	8 (11.0)	-7.7 (-17.2, -1.1)[a]
Injection site bruising	0	12 (16.4)	-16.4 (-26.6, -9.6)[a]

Source: adae.xpt; Software: R
[a] 95% confidence interval excludes zero
Note: Treatment-emergent AEs defined as all events that start on or after the first dosing day and time/start time, if collected, but before the last dose will be flagged as treatment-emergent. The algorithm will not consider any events that started prior to the first dose date. If an AE starts on the same day as the first dose date, it will be considered treatment-emergent unless the CRF data indicates otherwise via explicitly recording time for AE onset and treatment dosing. Additional treatment-emergent definitions applied for AEs summarized for the Main Phase and for the Extension Phase includes data up to end of treatment (Day 84) for subjects entering Extension Phase, or up to 35 days post-end of treatment (Day 84) for subjects not entering Extension Phase.
Coded as MedDRA preferred terms.
Risk difference (with 95% CI) is shown between total treatment and comparator.
Abbreviations: AE, adverse event; CI, confidence interval; CRF, case report form; MedDRA, Medical Dictionary for Regulatory Activities; n, number of subjects with AE; N, number of subjects in treatment arm; SOC, standard of care

Table 35. Subjects With Adverse Events by System Organ Class and OND Custom Medical Query (Narrow), Safety Population, Study CV185325/B0661037, Main Phase

System Organ Class OCMQ (Narrow)	Apixaban N=152 n (%)	SOC N=73 n (%)	Risk Difference % (95% CI)
Blood and lymphatic system disorders			
Thrombocytopenia	5 (3.3)	7 (9.6)	-6.3 (-15.5, -0.0)[a]
Anemia	11 (7.2)	10 (13.7)	-6.5 (-16.8, 1.6)
Leukopenia	4 (2.6)	7 (9.6)	-7.0 (-16.1, -0.9)[a]
Cardiac disorders			
Heart failure	2 (1.3)	0	1.3 (-3.7, 4.7)
Tachycardia	7 (4.6)	3 (4.1)	0.5 (-7.2, 5.9)
Arrhythmia	8 (5.3)	4 (5.5)	-0.2 (-8.4, 5.7)
Palpitations	1 (0.7)	1 (1.4)	-0.7 (-6.8, 2.5)
Myocardial ischemia	0	1 (1.4)	-1.4 (-7.4, 1.1)
Systemic hypertension	2 (1.3)	3 (4.1)	-2.8 (-10.2, 1.4)
Gastrointestinal disorders			
Vomiting	21 (13.8)	5 (6.8)	7.0 (-2.3, 14.7)
Constipation	10 (6.6)	3 (4.1)	2.5 (-5.4, 8.4)
Dyspepsia	11 (7.2)	4 (5.5)	1.8 (-6.6, 8.1)
Diarrhea	14 (9.2)	6 (8.2)	1.0 (-8.4, 8.3)
Nausea	10 (6.6)	5 (6.8)	-0.3 (-9.0, 6.3)
Dry mouth	0	1 (1.4)	-1.4 (-7.4, 1.1)
Abdominal pain	19 (12.5)	11 (15.1)	-2.6 (-13.5, 6.5)
General disorders and administration site conditions			
Fall	5 (3.3)	2 (2.7)	0.5 (-6.4, 5.3)
Fatigue	8 (5.3)	4 (5.5)	-0.2 (-8.4, 5.7)
Pyrexia	17 (11.2)	9 (12.3)	-1.1 (-11.5, 7.3)
Volume depletion	0	1 (1.4)	-1.4 (-7.4, 1.1)
Dizziness	6 (3.9)	4 (5.5)	-1.5 (-9.7, 4.0)
Decreased appetite	1 (0.7)	2 (2.7)	-2.1 (-8.9, 1.3)
Peripheral edema	3 (2.0)	3 (4.1)	-2.1 (-9.6, 2.4)
Local administration reaction	5 (3.3)	16 (21.9)	-18.6 (-29.7, -9.9)[a]

System Organ Class OCMQ (Narrow)	Apixaban N=152 n (%)	SOC N=73 n (%)	Risk Difference % (95% CI)
Hepatobiliary disorders			
Hepatic injury	6 (3.9)	3 (4.1)	-0.2 (-7.8, 5.1)
Immune system disorders			
Anaphylactic reaction	1 (0.7)	0	0.7 (-4.4, 3.6)
Hypersensitivity	3 (2.0)	1 (1.4)	0.6 (-5.5, 4.5)
Infections and infestations			
Nasopharyngitis	16 (10.5)	5 (6.8)	3.7 (-5.4, 10.9)
Viral infection	14 (9.2)	5 (6.8)	2.4 (-6.6, 9.4)
Pneumonia	3 (2.0)	2 (2.7)	-0.8 (-7.6, 3.4)
Bacterial infection	17 (11.2)	9 (12.3)	-1.1 (-11.5, 7.3)
Opportunistic infection	0	1 (1.4)	-1.4 (-7.4, 1.1)
Fungal infection	3 (2.0)	3 (4.1)	-2.1 (-9.6, 2.4)
Purulent material	1 (0.7)	3 (4.1)	-3.5 (-10.8, 0.3)
Metabolism and nutrition disorders			
Cachexia	1 (0.7)	0	0.7 (-4.4, 3.6)
Lipid disorder	3 (2.0)	2 (2.7)	-0.8 (-7.6, 3.4)
Musculoskeletal and connective tissue disorders			
Fracture	2 (1.3)	0	1.3 (-3.7, 4.7)
Arthralgia	8 (5.3)	3 (4.1)	1.2 (-6.6, 6.8)
Back pain	6 (3.9)	3 (4.1)	-0.2 (-7.8, 5.1)
Myalgia	1 (0.7)	1 (1.4)	-0.7 (-6.8, 2.5)
Arthritis	0	1 (1.4)	-1.4 (-7.4, 1.1)
Tendinopathy	0	1 (1.4)	-1.4 (-7.4, 1.1)
Nervous system disorders			
Headache	25 (16.4)	11 (15.1)	1.4 (-9.8, 10.8)
Somnolence	2 (1.3)	0	1.3 (-3.7, 4.7)
Syncope	2 (1.3)	0	1.3 (-3.7, 4.7)
Tremor	2 (1.3)	0	1.3 (-3.7, 4.7)
Confusional state	1 (0.7)	0	0.7 (-4.4, 3.6)
Stroke and TIA	2 (1.3)	1 (1.4)	-0.1 (-6.1, 3.5)
Seizure	1 (0.7)	1 (1.4)	-0.7 (-6.8, 2.5)
Paresthesia	5 (3.3)	4 (5.5)	-2.2 (-10.3, 3.2)
Psychiatric disorders			
Irritability	3 (2.0)	0	2.0 (-3.1, 5.7)
Study agent abuse potential	1 (0.7)	0	0.7 (-4.4, 3.6)
Insomnia	3 (2.0)	1 (1.4)	0.6 (-5.5, 4.5)
Depression	3 (2.0)	2 (2.7)	-0.8 (-7.6, 3.4)
Psychosis	0	1 (1.4)	-1.4 (-7.4, 1.1)
Anxiety	0	2 (2.7)	-2.7 (-9.5, -0.2)[a]
Renal and urinary disorders			
Renal & urinary tract infection	5 (3.3)	1 (1.4)	1.9 (-4.3, 6.4)
Acute kidney injury	2 (1.3)	0	1.3 (-3.7, 4.7)
Urinary retention	0	1 (1.4)	-1.4 (-7.4, 1.1)
Reproductive system and breast disorders			
Abnormal uterine bleeding	20 (13.2)	3 (4.1)	9.0 (0.7, 16.2) *
Excessive menstrual bleeding	17 (11.2)	3 (4.1)	7.1 (-1.1, 13.9)
Amenorrhea	1 (0.7)	0	0.7 (-4.4, 3.6)
Decreased menstrual bleeding	1 (0.7)	0	0.7 (-4.4, 3.6)
Respiratory, thoracic and mediastinal disorders			
Cough	11 (7.2)	2 (2.7)	4.5 (-2.8, 10.3)
Respiratory failure	4 (2.6)	2 (2.7)	-0.1 (-7.0, 4.4)
Dyspnea	8 (5.3)	6 (8.2)	-3.0 (-12.0, 3.6)

System Organ Class OCMQ (Narrow)	Apixaban N=152 n (%)	SOC N=73 n (%)	Risk Difference % (95% CI)
Skin and subcutaneous tissue disorders			
Rash	15 (9.9)	2 (2.7)	7.1 (-0.3, 13.5)
Alopecia	5 (3.3)	1 (1.4)	1.9 (-4.3, 6.4)
Urticaria	1 (0.7)	1 (1.4)	-0.7 (-6.8, 2.5)
Pruritus	3 (2.0)	2 (2.7)	-0.8 (-7.6, 3.4)
Erythema	2 (1.3)	3 (4.1)	-2.8 (-10.2, 1.4)
Vascular disorders			
Thrombosis arterial	0	1 (1.4)	-1.4 (-7.4, 1.1)
Hypotension	2 (1.3)	2 (2.7)	-1.4 (-8.3, 2.4)
Thrombosis	7 (4.6)	5 (6.8)	-2.2 (-10.9, 3.8)
Thrombosis venous	6 (3.9)	5 (6.8)	-2.9 (-11.5, 3.0)
Hemorrhage	51 (33.6)	31 (42.5)	-8.9 (-22.5, 4.4)

Source: adae.xpt; Software: R
[a] 95% confidence interval excludes zero.
Note: Treatment-emergent AEs defined as all events that start on or after the first dosing day and time/start time, if collected, but before the last dose will be flagged as treatment-emergent. The algorithm will not consider any events that started prior to the first dose date. If an AE starts on the same day as the first dose date, it will be considered treatment-emergent unless the CRF data indicates otherwise via explicitly recording time for AE onset and treatment dosing. Additional treatment-emergent definitions applied for AEs summarized for the Main Phase and for the Extension Phase includes data up to end of treatment (Day 84) for subjects entering Extension Phase, or up to 35 days post-end of treatment (Day 84) for subjects not entering Extension Phase.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Each OCMQ is aligned to a single system organ class based on clinical judgment. However, please be aware that some OCMQs may contain PTs from more than one system organ class.
Some preferred terms are not included in any OCMQ. Those preferred terms are not shown or counted in this table.
Abbreviations: AE, adverse event; CI, confidence interval; CRF, case report form; n, number of subjects with AE; N, number of subjects in treatment arm; OCMQ, FDA's Office of New Drugs custom medical query; PT, preferred term; SOC, standard of care; TIA, transient ischemic attack

The most common TEAEs (occurring in >10% of subjects in the apixaban arm and occurring more frequently in the apixaban arm compared with SOC arm) were headaches, epistaxis, vomiting, and excessive menstrual bleeding. The clinical review team analyzed the TEAEs in the safety population and the causality of the majority of TEAEs was difficult to determine, given the complexity and comorbid conditions of the enrolled subject population. The Applicant proposed to include the adverse reaction (AR) of heavy menstrual bleeding in the USPI. The clinical review team recommended that the bleeding profile and all common nonbleeding ARs that occurred in >10% of subjects be included in the USPI. Nasopharyngitis occurred in >10% of subjects in the apixaban arm compared with SOC arm. The review team determined that this adverse event was unlikely to be an AR related to apixaban and therefore was not including in the USPI. Table 36 will be included in the USPI.

Table 36. Other Adverse Reactions Occurring in ≥10% of Subjects in Study CV185325

Adverse Reaction	Apixaban N=152 n (%)	SOC N=73 n (%)
Headache	25 (16.4)	11 (15.1)
Vomiting	21 (13.8)	5 (6.8)

Source: Apixaban USPI
Abbreviations: n, number of subjects with AE; N, number of subjects in treatment arm; SOC, standard of care; USPI, United Stated Prescribing Information

7.6.1.6. Laboratory Findings, Study CV185325

This section presents a frequency-based analysis of the objective laboratory assessments.

Assessment of AE reporting based on laboratory assessments is included in the analysis of AEs in the sections above. Overall, no clinically relevant laboratory findings were identified, except for elevated creatinine levels.

Table 37 shows a higher percentage of subjects with one or more elevated creatinine values during the main treatment phase. The medical complexity of the enrolled subject population and a higher percentage of subjects with AEs in the renal and urinary disorders system organ class in the apixaban versus SOC arm (4.6% versus 2.8%) may have contributed to the observed observations of elevated creatinine during the main treatment phase in the apixaban arm. To evaluate a potential safety signal, a review of the analyses for mean change from baseline for serum creatinine was performed (shown in Figure 9) and the changes were minimal.

Table 37. Subjects With One or More Hematology Analyte Values Exceeding Specified Levels, Safety Population, Study CV185325/B0661037, Main Phase

Laboratory Parameter	Apixaban N=152 n/N_w (%)	SOC N=73 n/N_w (%)	Risk Difference % (95% CI)
Complete blood count			
WBC, low (10^3 cells/μL)			
Level 1 (<3.5)	16/138 (11.6)	8/66 (12.1)	-0.5 (-11.5, 8.3)
Level 2 (<3)	10/138 (7.2)	4/66 (6.1)	1.2 (-7.9, 8.0)
Level 3 (<1)	4/138 (2.9)	4/138 (2.9)	2.9 (-2.7, 7.2)
WBC, high (10^3 cells/μL)			
Level 1 (>10.8)	15/138 (10.9)	9/66 (13.6)	-2.8 (-14.0, 6.2)
Level 2 (>13)	10/138 (7.2)	3/66 (4.5)	2.7 (-5.9, 9.2)
Level 3 (>15)	4/138 (2.9)	3/66 (4.5)	-1.6 (-9.9, 3.6)
Hemoglobin, low (g/dL)			
Level 2 (>1.5 g/dL dec. from baseline)	8/123 (6.5)	8/58 (13.8)	-7.3 (-19.0, 1.5)
Level 3 (>2 g/dL dec. from baseline)	4/123 (3.3)	7/58 (12.1)	-8.8 (-19.9, -1.3)[a]
Hemoglobin, high (g/dL)			
Level 2 (>2 g/dL inc. from baseline)	15/123 (12.2)	3/58 (5.2)	7.0 (-3.0, 15.1)
Level 3 (>3 g/dL inc. from baseline)	8/123 (6.5)	2/58 (3.4)	3.1 (-5.8, 9.6)
Platelets, low (10^3 cells/μL)			
Level 1 (<140)	8/136 (5.9)	3/64 (4.7)	1.2 (-7.5, 7.5)
Level 2 (<125)	7/136 (5.1)	3/64 (4.7)	0.5 (-8.2, 6.6)
Level 3 (<100)	6/136 (4.4)	1/64 (1.6)	2.8 (-4.2, 8.1)
WBC differential			
Neutrophils, low (10^3 cells/μL)			
Level 1 (<2)	29/136 (21.3)	16/64 (25.0)	-3.7 (-17.1, 8.2)
Level 2 (<1)	10/136 (7.4)	4/64 (6.2)	1.1 (-8.3, 8.1)
Level 3 (<0.5)	6/136 (4.4)	2/64 (3.1)	1.3 (-6.6, 6.8)
Coagulation studies			
PT, high (sec)			
Level 1 (>1.1X ULN)	2/8 (25.0)	6/12 (50.0)	-25.0 (-59.5, 19.8)
Level 2 (>1.3X ULN)	1/8 (12.5)	6/12 (50.0)	-37.5 (-67.6, 6.8)
Level 3 (>1.5X ULN)	0/8 (0)	4/12 (33.3)	-33.3 (-61.6, 4.9)

Laboratory Parameter	Apixaban N=152 n/N_w (%)	SOC N=73 n/N_w (%)	Risk Difference % (95% CI)
PTT, high (sec)			
Level 1 (>1X ULN)	0/8 (0)	3/7 (42.9)	-42.9 (-75.7, -1.2)[a]
Level 2 (>1.21X ULN)	0/8 (0)	3/7 (42.9)	-42.9 (-75.7, -1.2)[a]
Level 3 (>1.41X ULN)	0/8 (0)	1/7 (14.3)	-14.3 (-52.6, 22.6)

Source: adlb.xpt; Software: R
[a] 95% confidence interval excludes zero
Threshold levels 1, 2, and 3 as defined by the Standard Safety Tables & Figures Integrated Guide
Risk difference (with 95% CI) is shown between total treatment and comparator.
Abbreviations: CI, confidence interval; dec., decrease; inc., increase; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data; PT, prothrombin time; PTT, partial thromboplastin time; SOC, standard of care; ULN, upper limit of normal; WBC, white blood cells

Table 38. Subjects With One or More Chemistry Analyte Values With Elevated or Low Values Meeting Specified Levels, Safety Population, Study CV185325/B0661037, Main Phase

Laboratory Parameter	Apixaban N=152 n/N_w (%)	SOC N=73 n/N_w (%)	Risk Difference %(95% CI)
Sodium, low (mEq/L)			
Level 1 (<132)	0/139 (0)	0/63 (0)	0.0 (-5.8, 2.7)
Level 2 (<130)	0/139 (0)	0/63 (0)	0.0 (-5.8, 2.7)
Level 3 (<125)	0/139 (0)	0/63 (0)	0.0 (-5.8, 2.7)
Sodium, high (mEq/L)			
Level 1 (>150)	0/139 (0)	0/63 (0)	0.0 (-5.8, 2.7)
Level 2 (>155)	0/139 (0)	0/63 (0)	0.0 (-5.8, 2.7)
Level 3 (>160)	0/139 (0)	0/63 (0)	0.0 (-5.8, 2.7)
Potassium, low (mEq/L)			
Level 1 (<3.6)	4/137 (2.9)	1/65 (1.5)	1.4 (-5.5, 6.0)
Level 2 (<3.4)	2/137 (1.5)	1/65 (1.5)	-0.1 (-6.9, 3.9)
Level 3 (<3)	0/137 (0)	1/65 (1.5)	-1.5 (-8.2, 1.2)
Potassium, high (mEq/L)			
Level 1 (>5.5)	0/137 (0)	2/65 (3.1)	-3.1 (-10.6, -0.3)[a]
Level 2 (>6)	0/137 (0)	0/65 (0)	0.0 (-5.6, 2.7)
Level 3 (>6.5)	0/137 (0)	0/65 (0)	0.0 (-5.6, 2.7)
Chloride, low (mEq/L)			
Level 1 (<95)	0/139 (0)	0/63 (0)	0.0 (-5.8, 2.7)
Level 2 (<88)	0/139 (0)	0/63 (0)	0.0 (-5.8, 2.7)
Level 3 (<80)	0/139 (0)	0/63 (0)	0.0 (-5.8, 2.7)
Chloride, high (mEq/L)			
Level 1 (>108)	1/139 (0.7)	2/63 (3.2)	-2.5 (-10.2, 1.3)
Level 2 (>112)	0/139 (0)	0/63 (0)	0.0 (-5.8, 2.7)
Level 3 (>115)	0/139 (0)	0/63 (0)	0.0 (-5.8, 2.7)
Bicarbonate, low (mEq/L)			
Level 1 (<20)	0/138 (0)	1/61 (1.6)	-1.6 (-8.7, 1.1)
Level 2 (<18)	0/138 (0)	0/61 (0)	0.0 (-6.0, 2.7)
Level 3 (<15)	0/138 (0)	0/61 (0)	0.0 (-6.0, 2.7)
Bicarbonate, high (mEq/L)			
Level 3 (>30)	3/138 (2.2)	2/61 (3.3)	-1.1 (-9.2, 3.6)
Glucose, low (mg/dL)			
Level 1 (<70)	7/138 (5.1)	1/63 (1.6)	3.5 (-3.7, 8.9)
Level 2 (<54)	0/138 (0)	0/63 (0)	0.0 (-5.8, 2.7)
Level 3 (<40)	0/138 (0)	0/63 (0)	0.0 (-5.8, 2.7)

Laboratory Parameter	Apixaban N=152 n/N_w (%)	SOC N=73 n/N_w (%)	Risk Difference %(95% CI)
Glucose, random, high (mg/dL)			
Level 2 (≥200)	2/138 (1.4)	0/63 (0)	1.4 (-4.4, 5.1)
Level 3 (>250)	2/138 (1.4)	0/63 (0)	1.4 (-4.4, 5.1)
Calcium, low (mg/dL)			
Level 1 (<8.4)	4/139 (2.9)	4/62 (6.5)	-3.6 (-12.8, 2.2)
Level 2 (<8)	1/139 (0.7)	2/62 (3.2)	-2.5 (-10.4, 1.3)
Level 3 (<7.5)	0/139 (0)	1/62 (1.6)	-1.6 (-8.6, 1.1)
Calcium, high (mg/dL)			
Level 1 (>10.5)	12/139 (8.6)	3/62 (4.8)	3.8 (-5.3, 10.7)
Level 2 (>11)	1/139 (0.7)	1/62 (1.6)	-0.9 (-7.9, 2.6)
Level 3 (>12)	1/139 (0.7)	0/62 (0)	0.7 (-5.2, 4.0)
Phosphate, low (mg/dL)			
Level 1 (<2.5)	7/138 (5.1)	2/59 (3.4)	1.7 (-6.9, 7.5)
Level 2 (<2)	3/138 (2.2)	0/59 (0)	2.2 (-4.0, 6.2)
Level 3 (<1.4)	0/138 (0)	0/59 (0)	0.0 (-6.1, 2.7)
Protein, total, low (g/dL)			
Level 1 (<6)	11/138 (8.0)	3/61 (4.9)	3.1 (-6.2, 9.9)
Level 2 (<5.4)	1/138 (0.7)	1/61 (1.6)	-0.9 (-8.1, 2.6)
Level 3 (<5)	1/138 (0.7)	1/61 (1.6)	-0.9 (-8.1, 2.6)
Albumin, low (g/dL)			
Level 1 (<3.1)	0/140 (0)	0/60 (0)	0.0 (-6.0, 2.7)
Level 2 (<2.5)	0/140 (0)	0/60 (0)	0.0 (-6.0, 2.7)
Level 3 (<2)	0/140 (0)	0/60 (0)	0.0 (-6.0, 2.7)
CPK, high (U/L)			
Level 1 (>3X ULN)	0/133 (0)	2/57 (3.5)	-3.5 (-12.0, -0.6)[a]
Level 2 (>5X ULN)	0/133 (0)	1/57 (1.8)	-1.8 (-9.3, 1.1)
Level 3 (>10X ULN)	0/133 (0)	0/57 (0)	0.0 (-6.3, 2.8)
Blood urea nitrogen, high (mg/dL)			
Level 1 (>23)	128/136 (94.1)	54/64 (84.4)	9.7 (1.1, 21.1)[a]
Level 2 (>27)	84/136 (61.8)	40/64 (62.5)	-0.7 (-14.6, 13.9)
Level 3 (>31)	40/136 (29.4)	26/64 (40.6)	-11.2 (-25.5, 2.7)

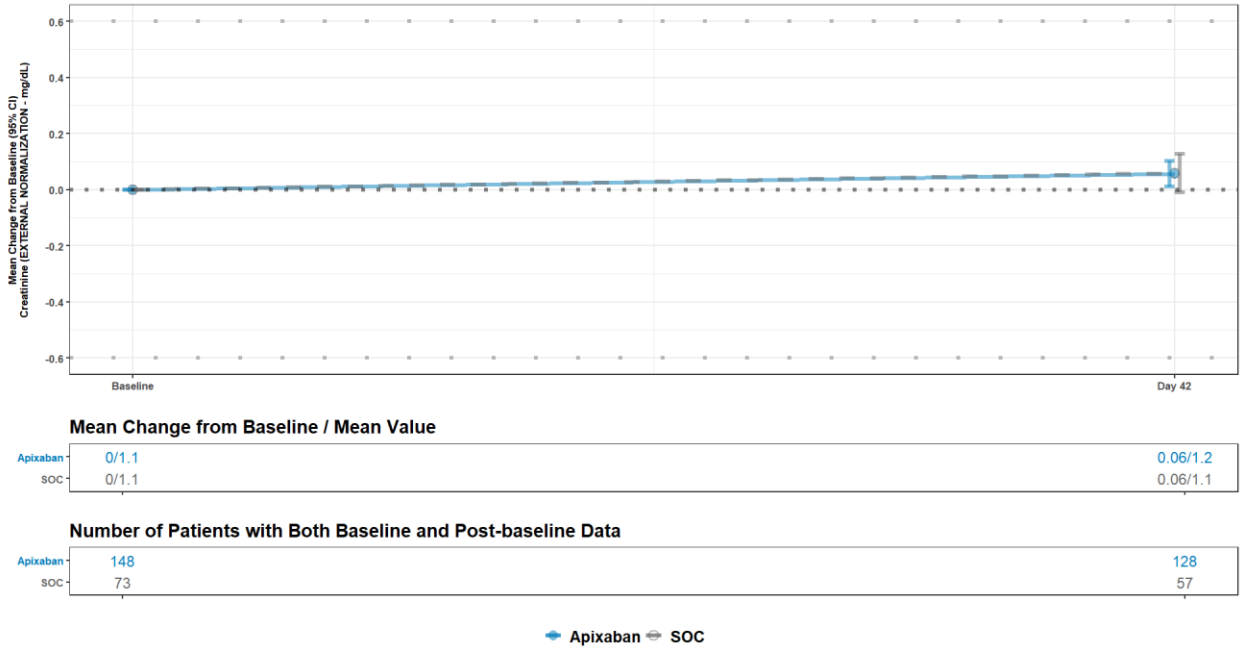
Source: adlb.xpt; Software: R
[a] 95% confidence interval excludes zero
Note: glucose values for hyperglycemia do not follow a nested format like the other labs. Level 1 corresponds to the diagnosis of prediabetes and is not inclusive of Level 2 and 3. Level 2 corresponds to the diagnosis of diabetes. Level 3 represents significant hyperglycemia that may indicate need for insulin or increased risk for diabetic ketoacidosis or other complications.
Threshold levels 1, 2, and 3 as defined by the Standard Safety Tables & Figures Integrated Guide
Risk difference (with 95% CI) is shown between total treatment and comparator.
Abbreviations: CI, confidence interval; CPK, creatine phosphokinase; n, number of subjects meeting criteria; N, number of subjects in treatment arm; N_w, number of subjects with data; SOC, standard of care; ULN, upper limit of normal

Table 39. Subjects With One or More Kidney Function Analyte Values Exceeding Specified Levels, Safety Population, Study CV185325/B0661037, Main Phase

Laboratory Parameter	Apixaban N=152 n/N_w (%)	SOC N=73 n/N_w (%)	Risk Difference % (95% CI)
Creatinine, high (mg/dL)			
Level 1 (≥1.5X baseline)	11/137 (8.0)	1/64 (1.6)	6.5 (-0.9, 12.6)
Level 2 (≥2X baseline)	6/137 (4.4)	0/64 (0)	4.4 (-1.4, 9.2)
Level 3 (≥3X baseline)	1/137 (0.7)	0/64 (0)	0.7 (-5.0, 4.0)

Source: adlb.xpt; Software: R
Note: Threshold levels 1, 2, and 3 as defined by the Standard Safety Tables & Figures Integrated Guide
Risk difference (with 95% CI) is shown between total treatment and comparator.
In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.
eGFR values are calculated from serum creatinine using CKD-EPI equation.
Abbreviations: CI, confidence interval; CKD-EPI; Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; n, number of subjects meeting criteria; N, number of subjects in treatment arm; N_w, number of subjects with data; SOC, standard of care

Figure 9. Mean Laboratory (Kidney Function) Data Change From Baseline Over Time, Safety Population, Study CV185325/B0661037, Main Phase



Source: adlb.xpt; Software: R.
Note: eGFR values are calculated from serum creatinine using CKD-EPI equation.
Abbreviations: CI, confidence interval; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; SOC, standard of care

Table 40. Subjects With One or More Liver Biochemistry Analyte Value(s) Exceeding Specified Levels, Safety Population, Study CV185325/B0661037, Main Phase

Laboratory Parameter	Apixaban N=152 n/N_w (%)	SOC N=73 n/N_w (%)	Risk Difference % (95% CI)
Alkaline phosphatase, high (U/L)			
Level 1 (>1.5X ULN)	2/137 (1.5)	0/62 (0)	1.5 (-4.4, 5.2)
Level 2 (>2X ULN)	1/137 (0.7)	0/62 (0)	0.7 (-5.1, 4.0)
Level 3 (>3X ULN)	0/137 (0)	0/62 (0)	0.0 (-5.9, 2.7)

Laboratory Parameter	Apixaban N=152 n/N_w (%)	SOC N=73 n/N_w (%)	Risk Difference % (95% CI)
Alanine aminotransferase, high (U/L)			
Level 1 (>3X ULN)	8/127 (6.3)	5/57 (8.8)	-2.5 (-13.2, 5.1)
Level 2 (>5X ULN)	2/127 (1.6)	1/57 (1.8)	-0.2 (-7.8, 4.1)
Level 3 (>10X ULN)	0/127 (0)	0/57 (0)	0.0 (-6.3, 3.0)
Aspartate aminotransferase, high (U/L)			
Level 1 (>3X ULN)	4/132 (3.0)	0/62 (0)	3.0 (-2.9, 7.5)
Level 2 (>5X ULN)	1/132 (0.8)	0/62 (0)	0.8 (-5.1, 4.2)
Level 3 (>10X ULN)	0/132 (0)	0/62 (0)	0.0 (-5.9, 2.8)
Bilirubin, total, high (mg/dL)			
Level 1 (>1.5X ULN)	2/136 (1.5)	1/63 (1.6)	-0.1 (-7.1, 3.9)
Level 2 (>2X ULN)	0/136 (0)	1/63 (1.6)	-1.6 (-8.5, 1.2)
Level 3 (>3X ULN)	0/136 (0)	0/63 (0)	0.0 (-5.8, 2.8)

Source: adlb.xpt; Software: R
Note: Threshold levels 1, 2, and 3 as defined by the Standard Safety Tables & Figures Integrated Guide
Risk difference (with 95% CI) is shown between total treatment and comparator.
Abbreviations: CI, confidence interval; n, number of subjects meeting criteria; N, number of subjects in treatment arm; N_w, number of subjects with data; SOC, standard of care; ULN, upper limit of normal

Table 41. Subjects With One or More Lipids Analyte Value(s) Exceeding Specified Levels, Safety Population, Study CV185325/B0661037, Main Phase

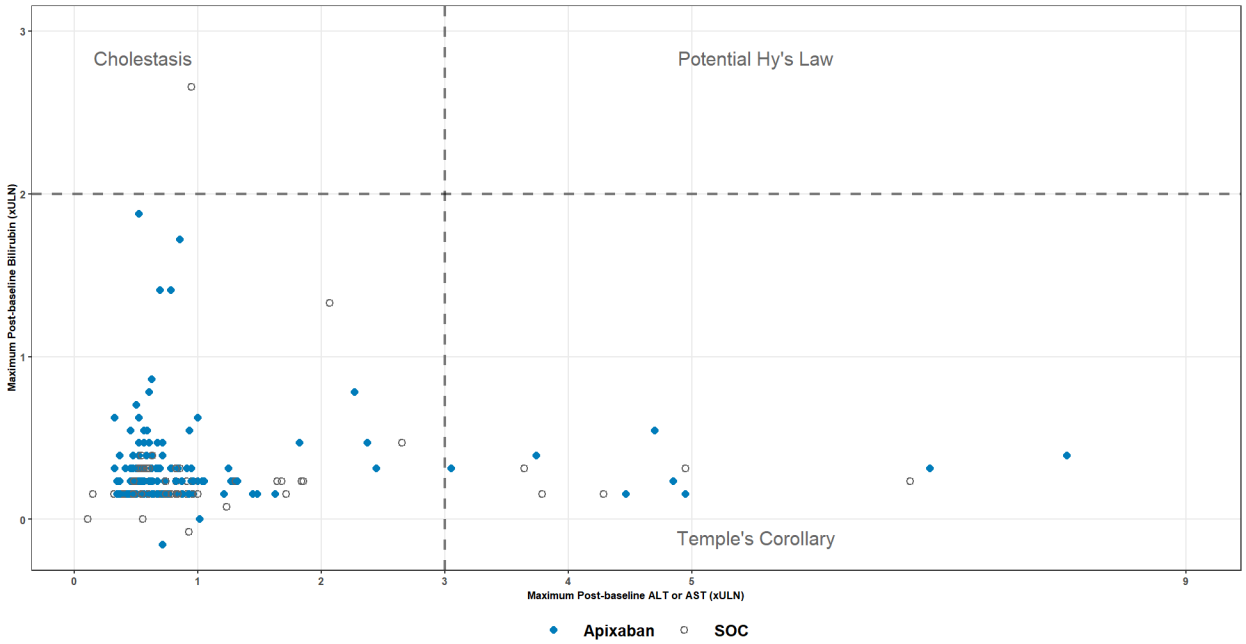
Laboratory Parameter	Apixaban N=152 n/N_w (%)	SOC N=73 n/N_w (%)	Risk Difference % (95% CI)
Cholesterol, total, high (mg/dL)			
Level 1 (>200)	5/134 (3.7)	4/57 (7.0)	-3.3 (-13.3, 3.0)
Level 2 (>210)	4/134 (3.0)	4/57 (7.0)	-4.0 (-14.0, 2.0)
Level 3 (>225)	2/134 (1.5)	2/57 (3.5)	-2.0 (-10.6, 2.5)
HDL, males, low (mg/dL)			
Level 1 (<40)	3/49 (6.1)	1/19 (5.3)	0.9 (-19.3, 12.6)
Level 2 (<30)	0/49 (0)	0/19 (0)	0.0 (-17.0, 7.4)
Level 3 (<20)	0/49 (0)	0/19 (0)	0.0 (-17.0, 7.4)
HDL, females, low (mg/dL)			
Level 1 (<50)	25/65 (38.5)	13/29 (44.8)	-6.4 (-27.6, 14.5)
Level 2 (<40)	8/65 (12.3)	8/29 (27.6)	-15.3 (-34.8, 1.2)
Level 3 (<20)	1/65 (1.5)	1/29 (3.4)	-1.9 (-15.9, 5.4)
LDL, high (mg/dL)			
Missing	NA	NA	NA
Triglycerides, high (mg/dL)			
Level 1 (>150)	46/134 (34.3)	28/57 (49.1)	-14.8 (-29.7, 0.3)
Level 2 (>300)	10/134 (7.5)	7/57 (12.3)	-4.8 (-16.4, 3.7)
Level 3 (>500)	0/134 (0)	2/57 (3.5)	-3.5 (-12.0, -0.6)[a]

Source: adlb.xpt; Software: R
[a] 95% confidence interval excludes zero
Threshold levels 1, 2, and 3 as defined by the Standard Safety Tables & Figures Integrated Guide.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Abbreviations: CI, confidence interval; HDL, high-density lipoprotein; LDL, low-density lipoprotein; n, number of subjects meeting criteria; N, number of subjects in treatment arm; NA, not applicable; N_w, number of subjects with data; SOC, standard of care

7.6.1.7. Assessment of Drug-Induced Liver Injury, Study CV185325

Figure 10 and Table 42 show a screening assessment for potential cases of serious DILI. There were no potential Hy's law cases. There were three subjects who experienced a grade 3 TEAE of alanine aminotransferase increase in the apixaban arm. All three subjects had underlying acute leukocytic leukemia and received chemotherapeutic agents that cause liver enzyme elevations, which may have contributed to the SAEs observed. Liver enzyme elevations are a known AR and are listed in the USPI.

Figure 10. Hepatocellular Drug-Induced Liver Injury Screening Plot, Safety Population, Study CV185325/B0661037, Main Phase



Source: adlb.xpt; Software: R
Note: Each data point represents a subject plotted by their maximum ALT or AST versus their maximum total bilirubin values in the postbaseline period.
A potential Hy's Law case was defined as having any postbaseline total bilirubin equal to or exceeding 2X ULN after a postbaseline ALT or AST equal to or exceeding 3X ULN. Those subjects who meet total bilirubin equal to or exceeding 2X ULN criteria within 30 days of the ALT or AST equal to or exceeding 3X ULN criteria are circled in red.
The within 30 days analysis window rule does not apply to cholestasis and temple's corollary cases.
All subjects with at least one postbaseline ALT or AST, bilirubin and ULN are plotted.
In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.
For number of subjects in each quadrant, see the table "Subjects in Each Quadrant for Potential Hepatocellular Drug-Induced Liver Injury Screening Plot …" and the listing "Listing of Subjects in Hepatocellular Drug-Induced Liver Injury Screening…."
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; SOC, standard of care; ULN, upper limit of normal

Table 42. Subjects in Each Quadrant for Potential Hepatocellular DILI Screening Plot, Safety Population, Study CV185325/B0661037, Main Phase

Quadrant	Apixaban N=152 n/N_w (%)	SOC N=73 n/N_w (%)
Potential Hy's law (right upper)	0/132 (0)	0/62 (0)
Cholestasis (left upper)	0/132 (0)	1/62 (1.6)
Temple's corollary (right lower)	8/132 (6.1)	5/62 (8.1)
Total	8/132 (6.1)	6/62 (9.7)

Source: adlb.xpt; Software: R
A potential Hy's Law case was defined as having any postbaseline total bilirubin equal to or exceeding 2X ULN after a postbaseline ALT or AST equal to or exceeding 3X ULN.
The within 30 days analysis window rule does not apply to cholestasis and Temple's corollary cases.
In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; DILI, drug-induced liver injury; n, number of subjects meeting criteria; N, number of subjects in treatment arm; N_w, number of subjects with data; SOC, standard of care; ULN, upper limit of normal

7.6.1.8. Vital Signs, Study CV185325

Baseline data collected for blood pressure, pulse, and respiratory rate did not demonstrate any significant, clinically meaningful differences between treatment groups.

7.6.1.9. Subgroup Analyses, Study CV185325

An overview of TEAEs by demographic subgroup is presented in Table 43. Overall, no significant differences in rate of AEs were observed by subgroups.

Table 43. Overview of Adverse Events by Demographic Subgroup, Safety Population, Study CV185325/B0661037, Main Phase

Characteristic	Apixaban N=152 n/N_s (%)	SOC N=73 n/N_s (%)	Risk Difference % (95% CI)
Sex			
Female	72/84 (85.7)	37/42 (88.1)	-2.4 (-14.0, 12.1)
Male	59/68 (86.8)	24/31 (77.4)	9.3 (-5.9, 28.0)
Age group			
Neonates up to 27 days	8/11 (72.7)	4/4 (100)	-27.3 (-57.5, 28.4)
28 days to <2 years	14/21 (66.7)	7/10 (70.0)	-3.3 (-34.3, 33.0)
2 years to <12 years	27/29 (93.1)	11/14 (78.6)	14.5 (-6.0, 42.1)
12 years to <18 years	82/91 (90.1)	39/45 (86.7)	3.4 (-7.3, 17.3)
Race			
American Indian or Alaska Native	1/1 (100)	0/0 (NA)	NA
Asian	4/4 (100)	4/4 (100)	0.0 (-52.3, 52.3)
Black or African American	17/22 (77.3)	7/9 (77.8)	-0.5 (-28.6, 36.2)
White	102/118 (86.4)	44/54 (81.5)	5.0 (-6.1, 18.4)
Multiple	1/1 (100)	1/1 (100)	0.0 (-88.5, 88.5)
Other	3/3 (100)	1/1 (100)	0.0 (-63.1, 83.7)
Missing	3/3 (100)	4/4 (100)	0.0 (-59.9, 52.8)
Ethnicity			
Hispanic or Latino	12/12 (100)	10/12 (83.3)	16.7 (-10.6, 45.4)
Not Hispanic or Latino	119/140 (85.0)	51/61 (83.6)	1.4 (-8.7, 13.8)

Characteristic	Apixaban N=152 n/N_s (%)	SOC N=73 n/N_s (%)	Risk Difference % (95% CI)
Is in United States			
United States	99/110 (90.0)	42/49 (85.7)	4.3 (-5.9, 17.6)
Non-United States	32/42 (76.2)	19/24 (79.2)	-3.0 (-22.5, 19.8)

Source: adae.xpt; Software: R
Note: Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Abbreviations: CI, confidence interval; n, number of subjects with AE; N, number of subjects in treatment arm; NA, not applicable; N_s, total number of subjects for each specific subgroup and were assigned to that specific arm; SOC, standard of care

7.6.1.10. Adverse Events of Special Interest, Study CV185325

7.6.1.10.1. Bleeding, Study CV185325

The primary safety endpoint was a composite of adjudicated major and CRNM bleeding per International Society on Thrombosis and Hemostasis criteria. See Section 7.4 for the definitions of major, CRNM, and minor bleeding. Descriptive statistics for the composite endpoint included the number and percentage of subjects having an endpoint event with a 95% exact CI. As this was a descriptive study, no formal inferences were performed.

For subjects who did not enter the extension phase, bleeding events that occurred from the first dose in the main phase up to the last dose in the main phase plus 2 days were included in the analysis if they were considered an AE. Bleeding events were included up to the last dose in the main phase plus 30 days if they were considered an SAE.

Secondary safety endpoints included adjudicated major bleeding, CRNM bleeding (both components of the primary composite endpoint), and minor bleeding.

All components of the primary and secondary endpoints, including all bleeding events, were adjudicated by a blinded, independent adjudication committee.

Main Phase

In the main treatment phase, no subjects in either treatment arm had an adjudicated major bleeding event (Table 44). There were two (1.3%) subjects in the apixaban arm and one (1.4%) subject in the SOC arm who had at least one adjudicated CRNM bleeding event. Rates of subjects with at least one adjudicated minor bleeding event were similar between the apixaban and SOC arms (36% versus 29%, respectively).

Epistaxis was the most common form of bleeding. Of note, heavy menstrual bleeding was observed in greater than 10% of subjects receiving apixaban and at a higher rate compared to SOC. This will be included in the USPI and will be an important consideration for providers.

Table 44. Bleeding Adverse Events by System Organ Class and Preferred Term, Safety Population, Study CV185325/B0661037, Main Phase

System Organ Class Preferred Term	Apixaban N=152 n (%)	SOC N=73 n (%)	Risk Difference % (95% CI)
Subjects with at least one of the composites of adjudicated major or CRNM bleeding events (primary safety endpoint)	2 (1.3)	1 (1.4)	-0.05 (-6.1,3.5)
Cardiac disorders			
Pericardial hemorrhage	1 (0.7)	0	0.7 (-4.4, 3.6)
Respiratory, thoracic, and mediastinal disorders			
Epistaxis	1 (0.7)	0	0.7 (-4.4, 3.6)
Vascular disorders			
Hematoma	0	1 (1.4)	-1.4 (-7.4, 1.1)
Subjects with at least one of the adjudicated major bleeding events (secondary safety endpoint)	0	0	
Subjects with at least one of the adjudicated CRNM events (secondary safety endpoint)	2 (1.3)	1 (1.4)	-0.05 (-6.1,3.5)
Cardiac disorders			
Pericardial hemorrhage	1 (0.7)	0	0.7 (-4.4, 3.6)
Respiratory, thoracic, and mediastinal disorders			
Epistaxis	1 (0.7)	0	0.7 (-4.4, 3.6)
Vascular disorders			
Hematoma	0	1 (1.4)	-1.4 (-7.4, 1.1)
Subject with at least one of the adjudicated minor bleeding events (secondary safety endpoint)	54 (35.5)	21 (28.8)	6.8 (-6.6, 19.0)
Blood and lymphatic system disorders			
Increased tendency to bruise	2 (1.3)	0	1.3 (-3.7, 4.7)
Gastrointestinal disorders			
Hematochezia	6 (3.9)	0	3.9 (-1.1, 8.4)
Hematemesis	1 (0.7)	0	0.7 (-4.3, 3.6)
Rectal hemorrhage	3 (2.0)	2 (2.7)	-0.8 (-7.6, 3.4)
Gingival bleeding	5 (3.3)	3 (4.1)	-0.8 (-8.3, 4.2)
General disorders and administration site conditions			
Vessel puncture site bruise	1 (0.7)	0	0.7 (-4.3, 3.6)
Puncture site hemorrhage	1 (0.7)	1 (1.4)	-0.7 (-6.8, 2.5)
Injection site hemorrhage	0	2 (2.7)	-2.7 (-9.5, -0.2)
Injury, poisoning, and procedural complications			
Scratch	1 (0.7)	0	0.7 (-4.4, 3.6)
Wound hemorrhage	1 (0.7	0	0.7 (-4.4, 3.6)
Skin laceration	3 (2.0)	1 (1.4)	0.6 (-5.5, 4.5)
Postprocedural hemorrhage	0	1 (1.4)	-1.4(-7.4, 1.1)
Traumatic hematoma	0	1 (1.4)	-1.4 (-7.4, 1.1)
Contusion	7 (4.6)	5 (6.8)	-2.2 (-10.9, 3.8)
Renal and urinary disorders			
Hematuria	4 (2.6)	0	2.6 (-2.4, 6.6)
Reproductive system and breast disorders			
Heavy menstrual bleeding	17 (11.2)	3 (4.1)	7.1 (-1.1, 13.9)
Intermenstrual bleeding	2 (1.3)	0	1.3 (-3.7, 4.7)
Vaginal hemorrhage	2 (1.3)	0	1.3 (-3.7, 4.7)
Respiratory, thoracic, and mediastinal disorders			
Epistaxis	22 (14.5)	12 (16.4)	-2.0 (-13.2, 7.5)
Skin and subcutaneous tissue disorders			
Petechiae	2 (1.3)	0	1.3 (-3.7, 4.7)
Ecchymosis	1 (0.7)	0	0.7 (-4.3, 3.6)

System Organ Class Preferred Term	Apixaban N=152 n (%)	SOC N=73 n (%)	Risk Difference % (95% CI)
Vascular disorders			
Hematoma	1 (0.7)	0	0.7 (-4.3, 3.6)

Source: Adapted from applicant's response to information request
Note: Treatment-emergent AEs defined as AEs starting on or after day of first dose.
Risk difference (with 95% CI) is shown between total treatment and comparator.
The confidence interval of risk difference is estimated by the Miettinen and Nurminen method.
The preferred terms in the table are ordered by the descending risk difference.
Abbreviations: CI, confidence interval; CRNM, clinically relevant non-major; n, number of subjects with bleeding AE; N, number of subjects in treatment arm; SOC, system organ class

Narratives for Adjudicated CRNM Bleeding Events (Apixaban Arm Only)

Subject (b) (6)

This subject's narrative is located under Section 7.6.1.2. The event was reported by the investigator as a grade 1 AE unrelated to the study intervention and related to antitumor chemotherapy. The event was classified as a CRNM bleeding event by the adjudication committee.

Subject (b) (6)

Subject (b) (6) was a 7-month-old male with congenital heart disease diagnosed with upper DVT on study Day -4 and randomized to the apixaban arm. The study drug was discontinued on study Day 3 for pericardiocentesis on Day 4. On Day 4, the subject experienced a pericardial hemorrhage that required pericardial drainage. The event was reported by the investigator as a grade 2 AE unrelated to the study intervention and related to post cardiotomy syndrome. The AE of pericardial hemorrhage was classified as a CRNM bleeding event by the blinded independent adjudication committee.

The clinical reviewer partially agrees with the investigator assessments. Bleeding is a well-established AR with apixaban use. Use of the drug in the context of other risk factors for bleeding likely contributed to the clinical presentations described above.

Bleeding Events by Age Group

Table 45 shows bleeding events by age group. There were higher rates of minor bleeding in the apixaban treatment arm compared to SOC (38% versus 21%, respectively) in the 2 to <12 years old group. Given the seriousness of VTE in the younger age groups and the need for additional oral anticoagulants, the benefit continues to outweigh the risk. Bleeding is highlighted as a common AR in the pediatric population in the USPI. Providers can weigh the risk of bleeding for their individual patients.

Table 45. Bleeding Events by Age Group, Safety Population, Study CV185325/B0661037, Main Phase

Bleeding Classification by Age Group	Apixaban N=152 n (%)	(95% CI)	SOC N=73 n (%)	(95% CI)
Ages 28 days to <2 years				
Major bleeding	0		0	
Clinically relevant nonmajor bleeding	1 (4.8)	0.0, 24.4	0	0.0, 32.1
Minor bleeding	1 (4.8)	0.0, 24.4	0	0.0, 32.1
Ages 2 years to <12 years				
Major bleeding	0		0	
Clinically relevant nonmajor bleeding	0		0	
Minor bleeding	11 (37.9)	22.6, 56.1	3 (21.4)	6.8, 48.3
Ages 12 years to 18 years				
Major bleeding	0		0	
Clinically relevant nonmajor bleeding	1 (1.1)	0.0, 6.6	1 (2.2)	0.00, 12.6
Minor bleeding	39 (42.9)	33.2, 53.1	18 (40.0)	27.0, 54.0

Source: Adapted from CSR
Note: 95% CI was calculated using the Agresti-Coull method.
Abbreviations: CI, confidence interval; n, number of subjects with bleeding event; N, number of subjects in treatment arm; SOC, standard of care

Extension Phase

No subjects experienced an adjudicated major or CRNM bleeding event in the extension phase. Adjudicated minor bleeding events in the extension phase were experienced by 8/53 (15%) of subjects.

7.6.2. Safety Results, Study CV185118

Study CV185155 was an open-label phase 1 study of a single oral dose of apixaban to evaluate PK, PD, safety, and tolerability in pediatric subjects at risk for venous or arterial thrombotic events. Forty-nine subjects were treated with apixaban.

There were no deaths. No AEs led to early study discontinuation. Fifteen out of 49 (30.6%) treated subjects had TEAEs. TEAEs considered related to the study drug included prolonged activated prothrombin time, headache and vomiting, diaphoresis, and gingival bleeding. There were no major bleeding events. Three out of 49 (6.1%) subjects had mild to moderate bleeding events including gingival bleeding, contusion, and postprocedural hemorrhage.

7.6.3. Safety Results, Study CV185155

Study CV185155 was a 1:1 randomized, open-label, multicenter, phase 3 study to evaluate the safety and efficacy of apixaban for VTE prevention versus SOC (no systemic anticoagulant) prophylaxis during induction chemotherapy in pediatric subjects with newly diagnosed ALL or LL (T or B cell) treated with asparaginase. Apixaban was administered to 256 subjects.

Four subject deaths occurred during the main phase or within 30 days after the end of the treatment period. Death occurred in one and three subjects (0.4% versus 1.2%) in the apixaban and SOC treatment arms, respectively. The cause of death in the apixaban arm was reported as cardiac arrest with disseminated intravascular coagulation, acute coronary syndrome, and retroperitoneal hemorrhage.

Study CV185155 Narrative of Death (Apixaban Arm Only)

Subject (b) (6)

Subject (b) (6) was a 9-year-old male with ALL who experienced the SAE of cardiac arrest on study Day 18. On the same day, the subject experienced the SAE of coagulopathy with noted oozing from multiple sites of procedures including CVC and chest tube placement sites and a retroperitoneal hemorrhage. The subject died on study Day 19 after failed resuscitative measures. The adjudication committee classified the retroperitoneal hematoma as a major bleeding event.

The primary safety endpoint was adjudicated major bleeding events which occurred in two subjects and at similar rates between the apixaban and SOC arms (0.8% in each arm). The first case was Subject (b) (6), described above with retroperitoneal hemorrhage. The second case was of a 10-year-old female subject with ALL who was diagnosed with bilateral retinal hemorrhages on study Day 1 after enrollment but prior to first dose of apixaban. The retinal hemorrhages were adjudicated as major bleeding events as the location of the bleeds involved the central nervous system. The study drug was discontinued prior to administration of the first dose.

The secondary safety endpoint was a composite of adjudicated major and CRNM bleeding events which occurred at a higher rate in the apixaban arm (5.1% versus 2.0%).

Minor bleeding events were also observed at a higher rate in the apixaban arm compared to the SOC arm (14.5% versus 7.8%). The most common bleeding events included epistaxis, contusion, hematochezia, and hematuria.

The overall rates of AEs and SAEs in subjects in the apixaban and SOC arms were similar. Most common AEs (i.e., anemia, constipation, thrombocytopenia) and SAEs (i.e., febrile neutropenia, pyrexia, sepsis) were likely related to the subject's underlying malignancy and chemotherapy use. Higher rates of TEAEs were reported in the apixaban arm compared to the SOC arm (14.8% versus 1.2%). TEAEs included epistaxis and an increase in alanine aminotransferase, aspartate aminotransferase, and blood bilirubin.

The observed death and higher rates of CRNM and minor bleeding in the apixaban arm highlight the bleeding risk with apixaban use and potential increased bleeding risk in subjects at-risk for bleeding (i.e., subjects with leukemia). Serious, potentially fatal bleeding is an established warning and precaution in the USPI. Liver enzyme elevation is reported as an AR in the USPI and is not unexpected in this patient population that receives treatments (i.e., chemotherapeutic agents) that are also known to cause liver enzyme elevation. Overall rates of liver enzyme elevation were low in the apixaban arm, and the identified potential Hy's law cases were similar between treatment arms. There were no unexpected new safety signals with a safety profile comparable to that observed among adults.

7.6.4. Safety Results, Study CV185362

Study CV185362 was a prospective, 2:1 randomized, open-label, multicenter, phase 2 study to evaluate the safety and PK of apixaban versus VKA or subcutaneous LMWH in pediatric subjects with congenital or acquired heart disease requiring chronic anticoagulation for thromboembolism prevention. Apixaban was administered to 107 subjects.

There were no deaths.

The primary safety endpoint of the composite of adjudicated major or CRNM bleeding showed a lower rate in the apixaban compared to SOC arm (0.8% versus 4.8%, respectively). The only subject in the apixaban arm that met the primary safety endpoint had CRNM and major bleeding events 283 and 286 days after start of dosing, respectively. The CRNM event was classified as a complication of cannulation and embolization of a supradiaphragmatic thoracic duct. The major bleeding event was a gastrointestinal hemorrhage requiring paracentesis and blood transfusions. The study drug was discontinued after the major bleeding event.

Rates of all adjudicated bleeding events were comparable across treatment arms (37% in each arm). The most frequently reported AEs with higher rates observed in the apixaban arm compared to SOC included epistaxis (14.3% versus 6.5%), hematoma (6.3% versus 1.6%), and headache (15.1% versus 4.8%).

TEAEs were reported at a higher frequency in the apixaban arm compared to the SOC arm (32.5% versus 25.8%, respectively). The most frequently reported TEAE in the apixaban arm was epistaxis.

The above safety findings are consistent with the known safety profile of apixaban.

7.6.5. Safety Results, Study CV185079

Study CV185079 was an open-label, sequential, ascending, multiple-dose study to evaluate the PK, PD, safety profile, and tolerability following multiple oral doses of apixaban in pediatric subjects with an indwelling CVC. Eight subjects were treated with apixaban.

There were no deaths or bleeding related safety events.

7.7. Key Safety Review Issues

7.7.1. Pooling Strategy of Safety Data

There was discussion amongst the clinical team to perform an analysis of the pooled safety set in subjects receiving apixaban in Studies CV185325, CV185118, CV185362, and CV185079. The Applicant highlighted challenges of pooling the safety data due to differences in study design, dosing, treatment duration, and population characteristics from each individual study. After review of the safety set between the clinical and clinical data scientist team, the Agency agreed with the above rationale to not conduct a pooled analysis of the safety data. The focus of the safety review was based on the adequate and well-controlled phase 3 Study CV185325/B0661037. Individual safety analyses were performed for the other studies to support the safety assessment of apixaban in the pediatric population. This approach was appropriate, as SEE was established by adequate and well-controlled Study CV185325 and extrapolation of safety from the adult data to support approval of the indication in adults.

8. Therapeutic Individualization

8.1. Intrinsic Factors

Hepatic Impairment

Apixaban should not be used in adult patients with severe hepatic impairment (Child-Pugh Class C). Dosing recommendations cannot be provided for adult patients with moderate hepatic impairment (Child-Pugh B). There is no clinical experience for apixaban in pediatric patients with hepatic impairment. Consistent with the text added to similar products such as XARELTO (rivaroxaban) USPI, ELIQUIS label will state that apixaban has not been studied in pediatric patients with hepatic impairment.

Renal Impairment

Based on the mass balance study in adults, renal excretion accounts for approximately 27% of total clearance. In a dedicated renal impairment study in adults, the impact of moderate renal impairment to end stage renal disease ranges from a 30 to 45% increase in apixaban total systemic exposures compared to subjects with normal renal function.

Due to the modest impact of renal impairment on apixaban exposures, the Applicant opened enrollment for pediatric subjects with renal impairment in Study CV185325. Only pediatric patients with poor or inadequate renal function were excluded from the trial; defined as estimated glomerular filtration rate (eGFR) <30 mL/min/1.73m^2 body surface area (BSA) in subjects 2 years of age and older. In subjects less than 2 years old, inadequate renal function as used in Study CV185325 was defined by sex and postnatal age as shown in Table 46. These threshold eGFRs in patients <2 years was defined as <30% of 1 standard deviation below normal GFR for age and size (Warady and Chadha 2007). Each value corresponds to an eGFR <30 mL/min for subjects equal to or greater than 2 years of age.

Estimated glomerular filtration rate in Study CV185325 was determined by the updated Schwartz formula (eGFR [mL/min/1.73m^2] = [0.413 * height in cm]/serum creatinine in mg/dL) for serum creatinine measured by an enzymatic creatinine method calibrated to be traceable to isotope dilution mass spectrometry.

Table 46. Inadequate Renal Function by Sex and Postnatal Age in Pediatric Subjects <2 Years of Age as Defined in the Pediatric VTE Study CV185325

Postnatal Age (Sex)	Threshold eGFR Used to Define Inadequate Renal Function (mL/min/1.73 m^2)
1 week (males and females)	<8
2-8 weeks (males and females)	<12
>8 weeks to <2 years (males and females)	<22

Source: Revised from the Applicant proposed draft labeling (Module 1.14.1.2)
Abbreviations: eGFR, estimated glomerular filtration rate; VTE, venous thromboembolism

Study CV185325 did not enroll pediatric patients down to the threshold eGFRs allowed in the study. However, given the modest impact of renal impairment on apixaban exposures and the

expectation that apixaban exposures will remain within adult reference range (Figure 3 and Figure 4), the review team agrees with the Applicant's proposal to allow dosing in pediatric patients with renal impairment as defined in Study CV185325.

8.2. Extrinsic Factors

Apixaban is a substrate of both CYP3A4 and P-gp. Concomitant use with drugs that are combined P-gp and strong CYP3A4 inhibitors increases exposure to apixaban which increases the risk for bleeding. Concomitant use with drugs that are combined P-gp and strong CYP3A4 inducers decreases exposure to apixaban which increases the risk for thromboembolic events.

For adult patients receiving apixaban at doses of 5 or 10 mg, the recommendation is to reduce the dose by 50% when coadministered with drugs that are combined P-gp and strong CYP3A4 inhibitors. In the pediatric trials for apixaban, there was no clinical experience with concomitant administration of combined P-gp and strong CYP3A4 inhibitors. Based on the current understanding of CYP3A4 and P-gp ontogeny, there may be uncertainty in extrapolating the adult recommendation or to derive appropriate dosing instructions in pediatric patients for concomitant use with drugs that are combined P-gp and strong CYP3A4 inhibitors. Therefore, ELIQUIS USPI will state that concomitant administration of combined P-gp and strong CYP3A4 inhibitors has not been studied in pediatric patients.

8.3. Plans for Pediatric Drug Development

After approval of NDA 202155/S-006, the following Pediatric Research Equity Act postmarketing requirements (PMRs) were issued to NDA 202155:

- PMR 3103-1: Assess apixaban PK and PD in approximately 50 pediatric subjects aged 0 to less than 18 years who are at risk for a venous or arterial thrombotic disorder, to determine dosing requirements for subsequent studies in children. Completion and submission of results of Study CV185118 and available data from Study CV185079 may be used to fulfill this requirement.
- PMR 3103-2: Conduct a randomized, open-label, active-controlled, safety and descriptive efficacy study to assess apixaban treatment in 150 pediatric subjects aged 0 to less than 18 years old requiring anticoagulation for treatment of VTE. This trial will also evaluate apixaban PK, AXA, and imaging assessment of clot status at the end of treatment in pediatric subjects requiring anticoagulation for the treatment of VTE.

Under the Best Pharmaceuticals for Children Act, a Pediatric Written Request (PWR) for ELIQUIS was first issued on March 24, 2017 and subsequently amended on January 25, 2018 (Amendment 1), September 23, 2020 (Amendment 2) and November 17, 2023 (Amendment 3).

According to the Applicant, this NDA submission is intended to support the following:

1. Approval for the age-appropriate new dosage form of ELIQUIS® (apixaban) 0.15 mg capsules for oral suspension for use of apixaban in pediatric patients in support of the following proposed pediatric indication in the USPI: "Treatment of VTE and reduction in the risk of recurrent VTE in pediatric patients from birth to less than 18 years of age after at least 5 days of initial anticoagulant treatment"
2. Fulfillment of the pediatric assessment of PMR 3103-2
3. Request for a pediatric exclusivity determination, in response to the most recent amended PWR provided by the Agency on November 17, 2023

The review team determined that the Applicant fulfilled the PMRs 3103-1 and 3103-2.

A general advice letter was issued to the Applicant regarding pediatric exclusivity determination on April 15, 2025.

8.4. Pregnancy, Lactation, and Females/Males of Reproductive Potential

Please refer to the original nonclinical review of prescription for NDA 202155 written by Patricia P. Harlow, PhD, and Thomas Papoian, PhD, and finalized for drug approval package on December 28, 2012. No new assessments were conducted for this NDA.

9. Product Quality

Approval With a Post-Marketing Commitment

The Office of Pharmaceutical Quality (OPQ) review team has assessed NDA 220073 with respect to chemistry, manufacturing, and controls and has determined that it meets all applicable standards to support the identity, strength, quality, and purity that it purports. As such, OPQ recommends approval of this NDA from a quality perspective. Please refer to the review in DARRTs by Theodore Carver dated April 10, 2025. The chemistry, manufacturing, and controls post-marketing commitment and between OPQ and the Applicant are listed below in Section 24 should be included in the action letter.

9.1. Device or Combination Product Considerations

Not applicable.

10. Human Subjects Protections/Clinical Site and Other Good Clinical Practice Inspections/Financial Disclosure Review

Study CV185325 was conducted under International Council on Harmonization good clinical practice guidelines. A signed written informed consent form was required to enroll in any of the studies.

The studies were reviewed and monitored by an institutional review board, research ethics board, or an independent ethics committee, depending on the country in which the study site was located.

The results of the clinical site inspections and Applicant inspection support the conclusion that the studies were conducted adequately, and that the data generated support the proposed indication.

Review of the financial disclosures did not raise any concerns about the validity or reliability of the data. Please see Section 22 for a summary of inspection findings and Section 25 for financial disclosures.

11. Advisory Committee Summary

An Advisory Committee meeting was not convened to discuss this application. No issues were identified that would have benefited from a public discussion with external experts.

III. Additional Analyses and Information

12. Summary of Regulatory History

Apixaban was initially approved on December 28, 2012 to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation. Apixaban is now approved for multiple indications in adult patients including the following:

1. Prophylaxis of DVT, which may lead to PE (in patients who have undergone hip or knee replacement surgery (Approved under NDA 202155/S-003)
2. Treatment of DVT and PE, and for the reduction in the risk of recurrent DVT and PE following initial therapy (Approved under NDA 202155/S-006)

After approval of NDA 202155/S-006, the following Pediatric Research Equity Act PMRs were issued to NDA 202155:

1. PMR 3103-1: Assess apixaban PK and PD in approximately 50 pediatric subjects aged 0 to less than 18 years who are at risk for a venous or arterial thrombotic disorder, to determine dosing requirements for subsequent studies in children. Completion and submission of results of Study CV185118 and available data from Study CV185079 may be used to fulfill this requirement.
2. PMR 3103-2: Conduct a randomized, open-label, active-controlled, safety and descriptive efficacy study to assess apixaban treatment in 150 pediatric subjects evaluable for efficacy and safety, aged 0 to less than 18 years, requiring anticoagulation for the treatment of a VTE. This trial will also evaluate apixaban PK, AXA, and imaging assessment of clot status at the end of treatment in pediatric subjects requiring anticoagulation for the treatment of a VTE. Completion and submission of results of Study CV185325 may be used to fulfill this requirement.

The submission of NDA 220073 as well as the sNDAs 202155/S-039 and S-040 are intended to support the following:

1. Approval for the age-appropriate new dosage form of ELIQUIS (apixaban) 0.15 mg capsules for oral suspension for use of apixaban in pediatric patients in support of the following proposed pediatric indication in the USPI: “Treatment of VTE and reduction in the risk of recurrent VTE in pediatric patients from birth and older after at least 5 days of initial anticoagulant treatment”
2. Fulfillment of the pediatric assessment of PMR 3103-2
3. Request for Pediatric Exclusivity Determination, in response to Amendment 3 of the Written Request (WR) that was issued on November 17, 2023

Key regulatory history milestones in the development of apixaban in pediatrics are summarized below.

On November 21, 2013, the Applicant submitted an agreed initial pediatric study plan to IND 066106, and the Agency issued the agreed initial pediatric study plan letter on November 25, 2023.

The Applicant submitted proposed pediatric study request (PPSR) for apixaban to IND 066106 on August 20, 2009, January 28, 2014, and July 11, 2016, and these PPSR submissions were deemed inadequate by the Agency. The PPSR submitted on January 12, 2017 was deemed adequate and the Agency issued a WR letter on March 24, 2017. The WR was subsequently amended on January 25, 2018 (Amendment 1), September 23, 2020 (Amendment 2), and November 17, 2023 (Amendment 3).

Multiple Type B and C meetings were held between 2017 and 2024 to gain alignment between the Agency and the Applicant regarding pivotal Study CV185325.

On May 23, 2024, a type B pre-sNDA meeting request was submitted to gain feedback from the Agency and seek agreement on (1) fulfillment of PMR 3103-2 with the data from pediatric subjects treated in Study CV185325; (2) adequacy of the proposed submission to support the Agency's review of the request for the pediatric exclusivity determination and fulfillment of the Pediatric Written Request (PWR) requirement; and (3) the proposed format and content of the sNDA filing, and review of the submission dossier to support addition of the proposed pediatric indication. The Applicant requested to cancel this meeting after preliminary comments were issued on July 18, 2024.

13. Pharmacology Toxicology

13.1. Summary Review of Studies Submitted With the Investigational New Drug Application

Please refer to original nonclinical review of prescription for NDA 202155 written by Patricia P. Harlow, PhD, and Thomas Papoian, PhD, and finalized for drug approval package on December 28, 2012. No new assessments were conducted for this NDA.

13.2. Individual Reviews of Studies Submitted With the New Drug Application

No new studies were conducted for this NDA.

14. Clinical Pharmacology

14.1. In Vitro Studies

Not applicable.

14.2. In Vivo Studies

Study CV185118

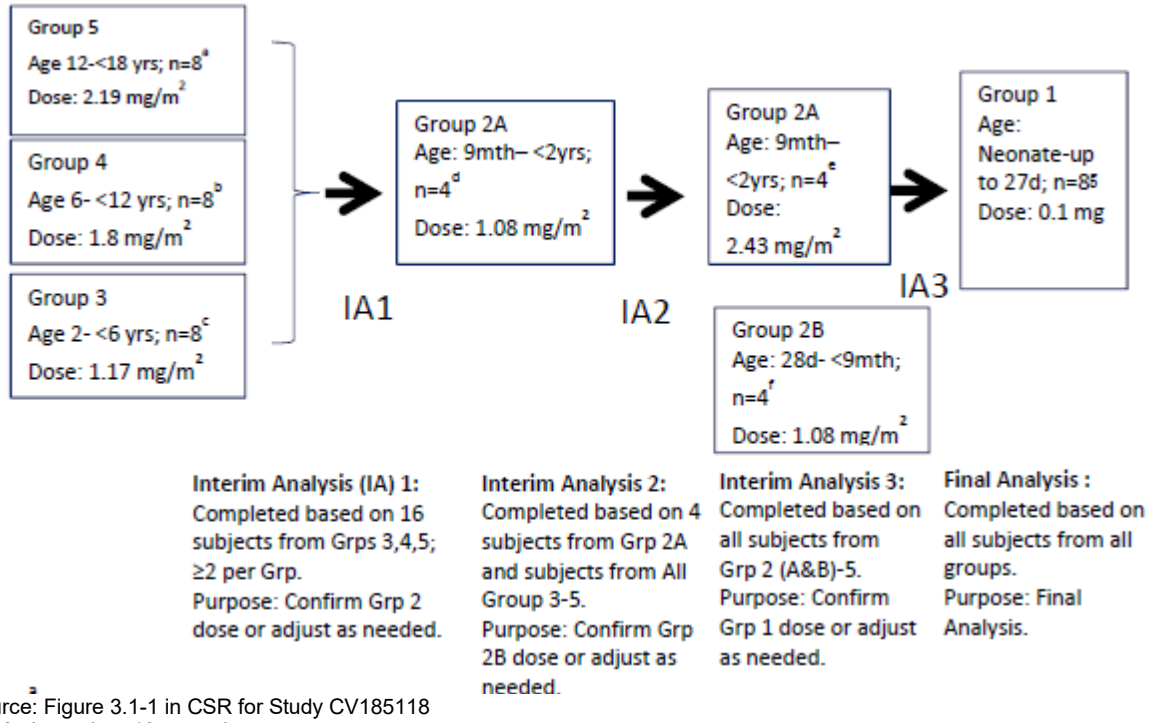
Title

Single-dose study to evaluate the PK, PD, safety, and tolerability of apixaban in pediatric patients at risk for a venous or arterial thrombotic disorder.

Objectives

- To assess the PK of a single dose of apixaban in pediatric subjects
- To assess the AXA following a single dose of apixaban in pediatric subjects

Figure 11. Design Scheme of Study CV186118



Source: Figure 3.1-1 in CSR for Study CV185118
[a] n=8 planned; n=10 treated
[b] n=8 planned; n=10 treated
[c] n=8 planned; n=8 treated
[d] n=4 planned; n=5 treated
[e] n=4 planned; n=4 treated
[f] n=4 planned; n=11 treated
[g] n=8 planned; n=1 treated, before study termination
Abbreviations: grp, group; IA, interim analysis

PK Results

A popPK model was developed with PK data from pediatric Studies CV185079 and CV185118 and adult phase 1 data. The summary of estimated exposures and PK parameters by age group from the final popPK model are shown in Table 47.

Table 47. Summary of Individual Estimated Exposure and PK Parameters for Subjects in Study CV185118 by Age Groups

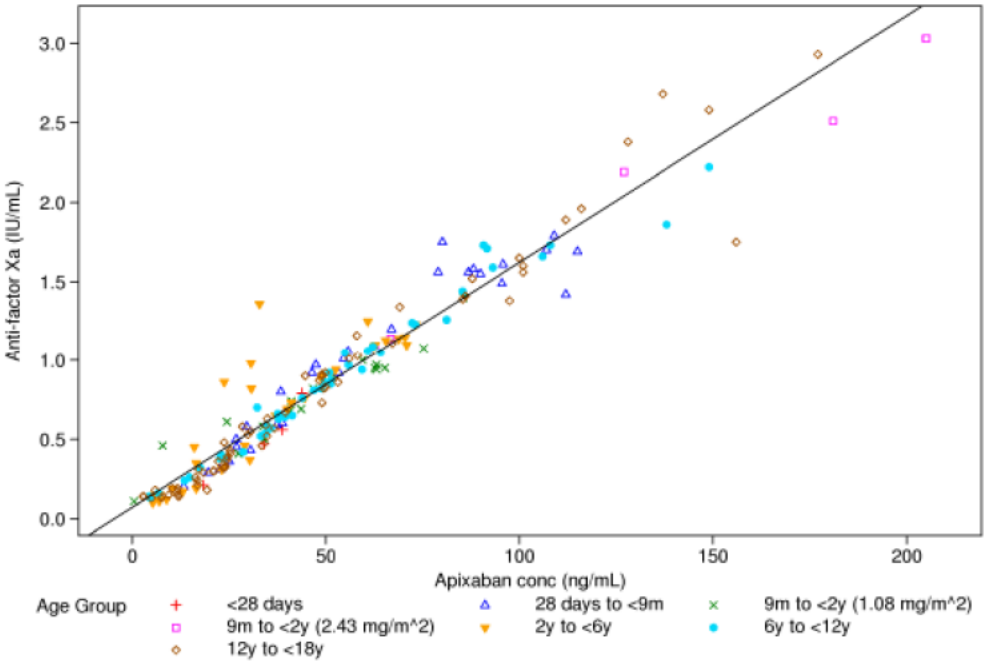
	Statistics	Ka (1/h)	CL/F (L/h)	Vc/F (L)	Cmax (ng/mL)	AUC(INF) (ng•h/mL)
Group 1 (< 28 Days) 0.1 mg	Geometric Mean	0.545	0.0979	1.82	45.9	1120
	%CV	NA	NA	NA	NA	NA
	N	1	1	1	1	1
Group 2B (28 Days to < 9 Months) 1.08 mg/m^2	Geometric Mean	0.717	0.347	2.69	64	806
	%CV	135	41.3	27.9	59.5	31.1
	N	11	11	11	11	11
Group 2A (9 Months to < 2 Years) 2.43 mg/m^2	Geometric Mean	1.31	0.775	4.71	148	1260
	%CV	55	98.8	57.3	35.1	68.7
	N	3	3	3	3	3
Group 2A (9 Months to < 2 Years) 1.08 mg/m^2	Geometric Mean	1.36	0.757	4.55	59.1	501
	%CV	52.5	55.4	36.8	37.8	43.8
	N	6	6	6	6	6
Group 3 (2 to < 6 Years) 1.17 mg/m^2	Geometric Mean	1.03	1.62	8.97	49.9	423
	%CV	50	60.6	36.5	54	67.7
	N	8	8	8	8	8
Group 4 (6 to < 12 Years) 1.80 mg/m^2	Geometric Mean	1.15	2.69	15.4	80	662
	%CV	54.9	38.4	39.5	28	21.7
	N	9	9	9	9	9
Group 5 (12 to < 18 Years) 2.19 mg/m^2	Geometric Mean	1.14	3.85	23.6	96.5	815
	%CV	64.3	66	46.5	29.6	48.4
	N	10	10	10	10	10
Overall	Geometric Mean	1.03	1.23	7.86	72.3	682
	%CV	76.4	151	115	52	53.7
	N	48	48	48	48	48

Source: Table 9.2.4-1 of CSR of Study CV185118
Note: A total of 8 pediatric subjects were enrolled in Study CV185079 and no formal PK assessments were performed due to sparse PK sampling. Due to the low number of subjects recruited in this study, data from Study CV185079 was pooled into Study CV185118 analyses.
Abbreviations: AUC_{inf}, area under the concentration-time curve extrapolated to infinity; CL/F, apparent oral clearance; C_{max}, maximum concentration; CV, coefficient of variation; N, number of subjects in group; V_c/F, apparent volume of distribution of the central compartment

PK/PD Results

AXA samples were collected and assayed in all age groups. AXA was found to be linearly correlated to apixaban concentration with no apparent age-related differences in slope among the pediatric age groups (overall slope estimate of 0.0155 IU/ng, Figure 12).

Figure 12. Observed Plasma AXA Level vs. Apixaban Concentration Stratified by Age Group in Pediatric Subjects



Source: Figure 3.3.2.4-4 of Study CV185325 Pharmacometrics Report

Table 48. Linear Regression Analyses of Plasma AXA vs. Apixaban Concentration, by Age Group, in Pediatric Subjects

Age Group	Number of Subjects	Number of Observations	Slope (IU/ng)	SE (Slope)	95% CI for Slope
Group 1 (Birth to < 28 Days)	1	4	0.0211	0.00373	0.015-0.0272
Group 2B (28 Days to < 9 Months)	9	28	0.0158	0.000927	0.0143-0.0173
Group 2A (9 Months to < 2 Years) 1.08 mg/m^2	6	19	0.0129	0.000943	0.0114-0.0145
Group 2A (9 Months to < 2 Years) 2.43 mg/m^{2a}	2	5	0.0131	0.00128	0.011-0.0152
Group 3 (2 to < 6 Years)	8	33	0.0163	0.00153	0.0138-0.0188
Group 4 (6 to < 12 Years)	11	44	0.0153	0.000428	0.0146-0.016
Group 5 (12 to < 18 Years)	15	66	0.0163	0.000426	0.0156-0.017
All Age Groups	52	201	0.0155	0.000277	0.0151-0.016

Source: Table 5.2-1 of Study CV185118 Pharmacometrics Analysis Report
Abbreviations: AXA, antifactor Xa activity; CI, confidence interval; SE, standard error; vs., versus

Summary

1. CL/F values are generally similar in adolescents 12 years and older compared to adults. Once normalized by body weight, apparent clearances in these pediatric subjects were generally similar across the pediatric age range, except in the youngest group. This assessment demonstrates that in addition to body size, maturation plays a role in the clearance of apixaban in the youngest pediatric subjects <9 months of age.
2. AXA was found to be linearly correlated to apixaban concentration with no apparent age-related differences in slope among the pediatric age groups. The slope of the PK-AXA relationship in pediatric subjects was comparable to that in adults.

Study CV185155

Title

A phase 3 randomized, open-label, multicenter study of the safety and efficacy of apixaban for VTE prevention versus no systemic anticoagulant prophylaxis during induction chemotherapy in children with newly diagnosed ALL or lymphoblastic lymphoma (T or B cell) treated with asparaginase.

Study CV185155 was designed to evaluate the hypothesis that prophylaxis with apixaban during induction of chemotherapy in pediatric subjects with newly diagnosed ALL or LL would reduce the risk of VTE.

Study Design

Table 49. Apixaban Doses by Body Weight for Ages 1 to 18 Years

Weight range	Dose
≥ 35 kg	2.5 mg twice daily
25 to < 35 kg	2 mg twice daily
18 to < 25 kg	1.5 mg twice daily
10.5 to < 18 kg	1 mg twice daily
6 to < 10.5 kg	0.5 mg twice daily

Source: Table 3.4.5-1 in CSR for Study CV185155

See Section 6.2 for details of study design.

PK Results

The popPK analysis was performed utilizing the popPK model updated with data from pediatric Studies CV185118, CV185079, and CV185155. Individual PK parameters and estimated steady-state exposures for subjects in Study CV185155 are summarized by age groups (Table 50) and by weight tiers (Table 51).

Table 50. Summary of Individual Estimated Pharmacokinetic Parameters and Simulated Steady-State Exposures for Subjects in Study CV185155 by Age Groups

		Overall				
Variable		9 m to < 2 y (n = 1)	2 y to < 6 y (n = 105)	6 y to < 12 y (n = 72)	12 y to < 18 y (n = 46)	Overall (n = 224)
AUCss(TAU) (ng•h/mL)	Geometric Mean (%CV)	726 (NA)	604 (47.4)	662 (46.8)	660 (35.9)	634 (45)
CL/F (L/h)	Geometric Mean (%CV)	1.46 (NA)	1.73 (52.5)	2.92 (40.8)	3.98 (45.1)	2.43 (61)
Cmaxss (ng/mL)	Geometric Mean (%CV)	69.5 (NA)	67.7 (39.5)	72.6 (35.1)	65.7 (33.1)	68.8 (36.8)
Cminss (ng/mL)	Geometric Mean (%CV)	24.5 (NA)	14.8 (122)	16.8 (118)	20.4 (58.4)	16.5 (109)
Ka (1/h)	Geometric Mean (%CV)	0.194 (NA)	0.25 (45.4)	0.263 (48)	0.261 (29.5)	0.256 (43.2)
Q/F (L/h)	Geometric Mean (%CV)	0.242 (NA)	0.418 (88)	0.72 (73.9)	1.11 (39.9)	0.607 (89.7)
Tmax (h)	Geometric Mean (%CV)	3.23 (NA)	2.83 (24.9)	2.91 (24.6)	3.2 (12.9)	2.93 (23.2)
Vc/F (L)	Geometric Mean (%CV)	4.76 (NA)	5.91 (35.1)	10.4 (35.4)	16.5 (37.4)	8.75 (57.5)
Vp/F (L)	Geometric Mean (%CV)	22.2 (NA)	23.3 (110)	23.3 (96.2)	23.8 (51.5)	23.4 (93.3)

Source: Table 5.1.3.1-1 of the Study CV185155 Pharmacometrics Analysis Report
Abbreviations: $AUC_{ss,T}$, area under the concentration-time curve at steady-state in one dosing interval; CL/F, apparent oral clearance; $C_{max,ss}$, maximum concentration at steady state; $C_{min,ss}$, minimum concentration at steady state; Ka, absorption rate constant; n, number of subjects in group; Q/F, apparent intercompartmental clearance; T_{max}, time to maximum concentration; V_c/F, apparent volume of distribution of the central compartment; V_p/F, apparent volume of distribution of the peripheral compartment

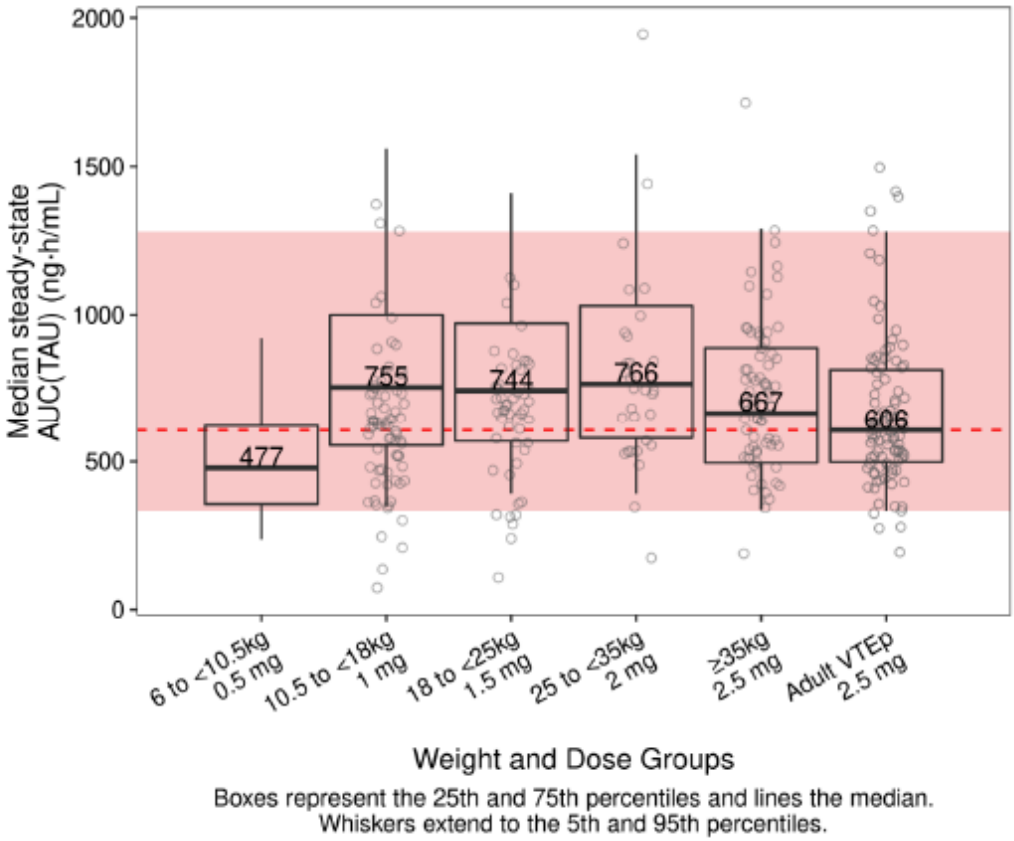
Table 51. Summary of Individual Estimated Pharmacokinetic Parameters and Simulated Steady-State Exposures for Subjects in Study CV185155 by Weight Tiers

		Overall				
Variable		10.5 to < 18 kg (n = 73)	18 to < 25 kg (n = 50)	25 to < 35 kg (n = 30)	≥ 35 kg (n = 71)	Overall (n = 224)
AUCss(TAU) (ng•h/mL)	Geometric Mean (%CV)	572 (49)	611 (45)	723 (46.5)	684 (37.4)	634 (45)
CL/F (L/h)	Geometric Mean (%CV)	1.61 (50.7)	2.16 (47.1)	2.7 (38)	3.85 (43.3)	2.43 (61)
Cmaxss (ng/mL)	Geometric Mean (%CV)	64 (40.9)	72 (34.6)	76.4 (34.6)	68.7 (33.9)	68.8 (36.8)
Cminss (ng/mL)	Geometric Mean (%CV)	14.2 (119)	13.2 (151)	20 (102)	20.9 (61.5)	16.5 (109)
Ka (1/h)	Geometric Mean (%CV)	0.248 (45.9)	0.27 (54.8)	0.242 (35.9)	0.261 (33.9)	0.256 (43.2)
Q/F (L/h)	Geometric Mean (%CV)	0.386 (86.1)	0.568 (89.8)	0.621 (89.4)	1 (44.7)	0.607 (89.7)
Tmax (h)	Geometric Mean (%CV)	2.82 (25.1)	2.71 (28.3)	3.01 (21.1)	3.17 (14)	2.93 (23.2)
Vc/F (L)	Geometric Mean (%CV)	5.43 (31.8)	7.28 (30.8)	9.58 (23.9)	15.6 (35.3)	8.75 (57.5)
Vp/F (L)	Geometric Mean (%CV)	23.4 (106)	25 (128)	20.5 (108)	23.5 (48.7)	23.4 (93.3)

Source: Table 5.1.3.1-2 of the Study CV185155 Pharmacometrics Analysis Report
Abbreviations: $AUC_{ss,T}$, area under the concentration-time curve at steady state in one dosing interval; CL/F, apparent oral clearance; $C_{max,ss}$, maximum concentration at steady state; $C_{min,ss}$, minimum concentration at steady state; Ka, absorption rate constant; n, number of subjects in group; Q/F, apparent intercompartmental clearance; T_{max}, time to maximum concentration; V_c/F, apparent volume of distribution of the central compartment; V_p/F, apparent volume of distribution of the peripheral compartment

Stochastic simulation was performed using the final model and body weight tiered dosing regimen (2.5, 2, 1.5, 1, and 0.5 mg BID regimens for ≥35 kg, 25 to <35 kg, 18 to <25 kg, 10.5 to <18 kg, and 6 to <10.5 kg body weight tiers, respectively) to generate $AUC_{ss,T}$. The simulated steady-state AUC_T values from the virtual pediatric subjects by weight tiers were compared to exposures observed in the adult venous thromboembolism prevention population from the AMPLIFY EXT study receiving 2.5 mg BID apixaban (Figure 13).

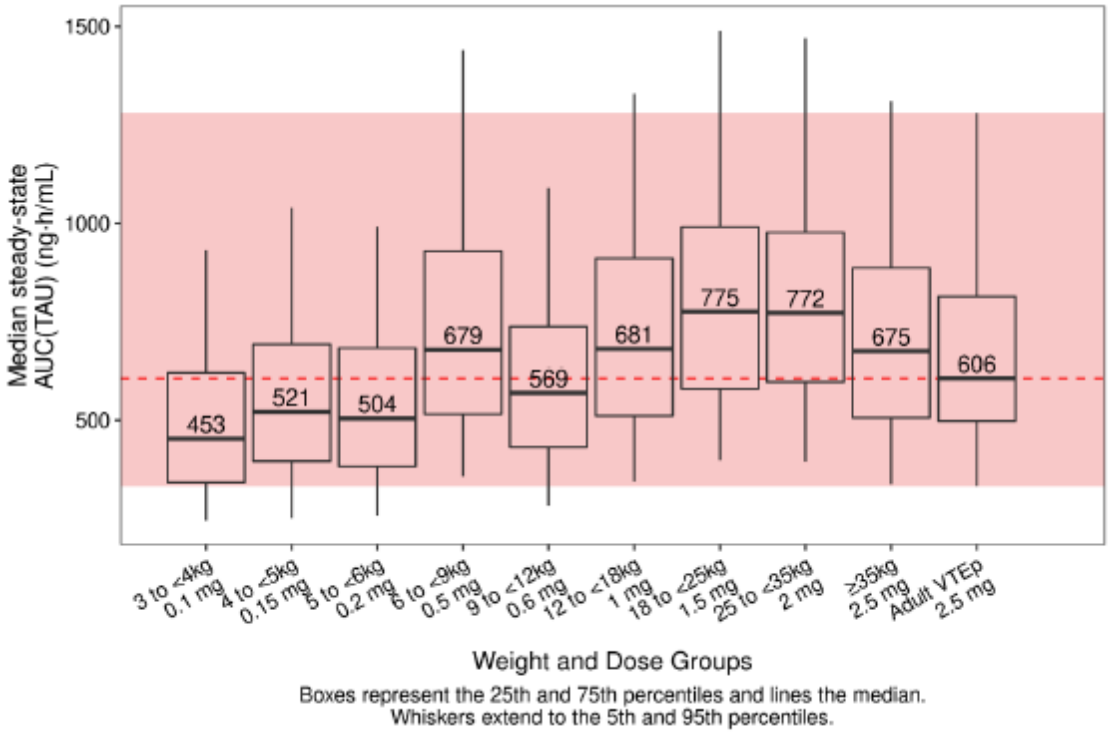
Figure 13. Simulated Median Steady-State AUC_T Exposure in Pediatric Subjects Aged 1 to <18 Years by Weight Tiers and Adult Venous Thromboembolism Prevention Population From AMPLIFY EXT Study



Source: Figure 5.1.3.2-1 of the Study CV185155 Pharmacometrics Analysis Report
Note: Red dashed line and shaded region represent the median, 5th percentile, and 95th percentiles of exposure in the adult population.
Note: Simulated exposures for pediatric subjects with ALL or lymphoblastic lymphoma at risk of VTE treated with asparaginase in Study CV185155 were overlaid on the boxplots.
Abbreviations: AUC_T, area under the concentration-time curve in one dosing interval; VTE, venous thromboembolism; VTE_P, venous thromboembolism prevention

Stochastic simulation was also performed using the final model with the following body weight tiered dosing regimen (2.5, 2, 1.5, 1, 0.6, 0.5, 0.2, 0.15, and 0.1 mg BID regimens for ≥35 kg, 25 to <35 kg, 18 to <25 kg, 12 to <18 kg, 9 to <12 kg, 6 to <9 kg, 5 to <6 kg, 4 to <5 kg, and 3 to <4 kg body weight tiers, respectively) to generate steady-state AUC_T for each virtual subject (Figure 14). This fixed-dose weigh-tiered scheme was used in both Studies CV185325 and CV185362.

Figure 14. Simulated Median Steady-State AUC_T Exposure in Pediatric Subjects Aged 28 Days to <18 Years by Weight Tiers and Adult Venous Thromboembolism Prevention Population From AMPLIFY EXT Study



Source: Figure 5.1.3.3-1 of the Study CV185155 Pharmacometrics Analysis Report
Note: Red dashed line and shaded region represent the median, 5th percentile, and 95th percentile of exposure in the adult population.
Abbreviations: AUC_T, area under the concentration-time curve in one dosing interval; VTE_p, venous thromboembolism prevention

PK/PD Results

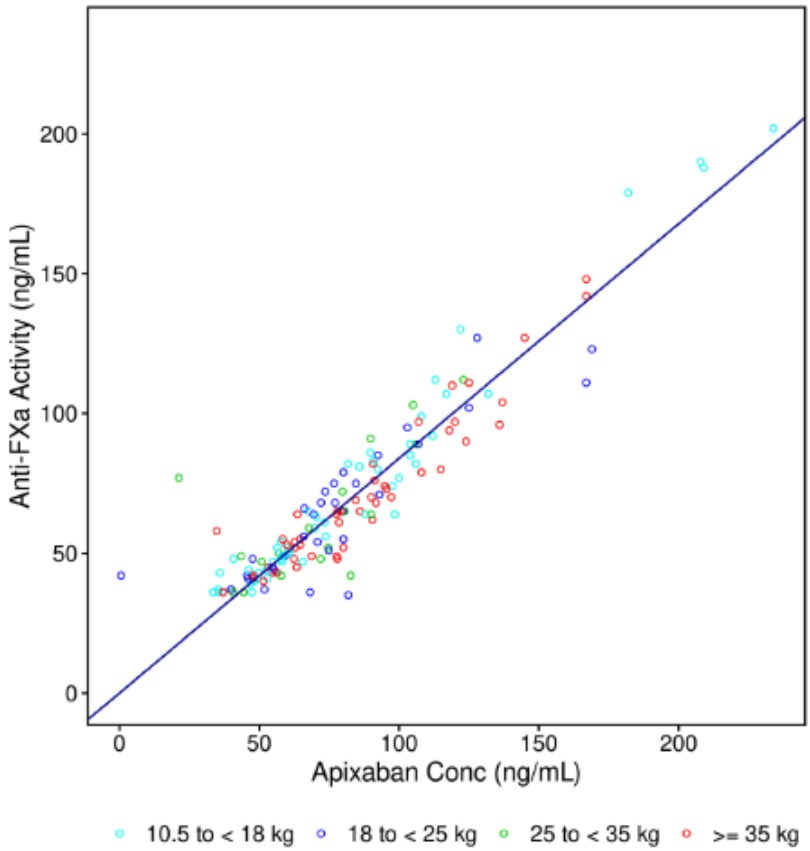
The final PK/PD model for Study CV185155 was a simple linear regression with an estimated slope (standard error) of 0.839 (0.0105) with bootstrap derived 95% CI of 0.817 to 0.861 for the overall data to describe the relationship between apixaban concentration and AXA (Table 55, Table 53). A goodness-of-fit (GoF)plot showing the model fitting to the observed PK/PD data is presented in Figure 15.

Table 52. Parameter Estimate and Standard Error for the Final Pharmacokinetic/ Pharmacodynamic Model for Study CV185155

Parameter	Estimate	Standard Error	Bootstrap Derived 95% CI
Slope	0.839	0.0105	0.817 - 0.861

Source: Table 5.2.1-1 of the Study CV185155 Pharmacometrics Analysis Report

Figure 15. Goodness-of-Fit Plot for the Final Apixaban Pharmacokinetic/Pharmacodynamic Model, by Weight Tier



Source: Figure 5.2.1-1 of the Study CV185155 Pharmacometrics Analysis Report
Abbreviation: conc, concentration

Table 53. Summary of Maximum AXA Values in Pediatric Subjects From Study CV185155

Overall		
	Statistics	AXAmax (ng/mL)
10.5 to < 18 kg	Geometric Mean (%CV)	62.4 (28.1)
	n	41
18 to < 25 kg	Geometric Mean (%CV)	63.7 (24.6)
	n	31
25 to < 35 kg	Geometric Mean (%CV)	65.2 (14.8)
	n	16
≥ 35 kg	Geometric Mean (%CV)	66.7 (25.3)
	n	42
Overall	Geometric Mean (%CV)	64.4 (24.9)
	n	130

Source: Table 5.2.3-1 of the Study CV185155 Pharmacometrics Analysis Report
Abbreviations: AXA, antifactor Xa activity; AXA_{max}, maximum antifactor Xa activity; CV, coefficient of variation

Summary

- The following fixed-dose regimens by body weight tiers explored in Study CV185155 (2.5 mg BID for ≥35 kg, 2 mg BID for 25 to <35 kg, 1.5 mg BID for 18 to <25 kg, 1 mg for 10.5 to <18 kg, and 0.5 mg for 6 to <10.5 kg) were confirmed to provide predicted median steady-state exposures in pediatric subjects aged 1 to <18 years old that were consistent with that in adults receiving 2.5 mg BID apixaban for prophylaxis of DVT following hip or knee replacement surgery.
- In pediatric subjects aged 28 days to <18 years old, the following body weight tiered doses are predicted to achieve steady-state exposures similar to that of adults receiving apixaban 2.5 mg BID for VTE prevention: 2.5 mg BID for ≥35 kg, 2 mg BID for 25 to <35 kg, 1.5 mg BID for 18 to <25 kg, 1 mg for 12 to <18 kg, 0.6 mg for 9 to <12 kg, 0.5 mg for to <9 kg, 0.2 mg for 5 to <6 kg, 0.15 mg for 4 to <5 kg, and 0.1 mg for 3 to <4 kg.
- A simple linear regression model with an intercept at zero and a slope parameter of 0.839 described the relationship between apixaban concentration and AXA in pediatric subjects with ALL or lymphoblastic lymphoma at risk of VTE treated with asparaginase.

Study CV185362

Title

A prospective, randomized, open-label, multicenter study of the safety and pharmacokinetics of apixaban versus VKA or LMWH in pediatric subjects with congenital or acquired heart disease requiring chronic anticoagulation for thromboembolism prevention.

Objectives

- To characterize the PK of apixaban in pediatric subjects with CAHD and evaluate the effect of covariates on apixaban PK.
- To assess whether the current fixed-dose by weight tiered regimen for apixaban in pediatric patients aged 28 days to <18 years achieves target exposures.
- To characterize the PK/PD relationship between AXA and apixaban concentration in pediatric subjects with CAHD.
- To perform exploratory PK/PD analysis of endogenous factor X levels at baseline and inhibition of factor X by apixaban, stratified by age group.
- To assess the timing of apixaban dose changes in response to growth of pediatric subjects and changes in age and weight.

Study CV185362 was designed to evaluate the safety and PK of apixaban versus VKA or LMWH in pediatric subjects with congenital or acquired heart disease requiring chronic anticoagulation for thromboembolism prevention.

Study Design

See Section 6.2 for study design.

PK Results

The popPK model-estimated apixaban PK parameters and simulated exposure measures were obtained using the empirical Bayesian estimates of the PK parameters from the final popPK model. Individual estimated exposures for subjects in Study CV185362 are summarized by age groups and by body weight tiers in Table 54 and Table 55, respectively.

Table 54. Summary of Geometric Mean (%CV) of Individual Estimated Pharmacokinetic Parameters and Simulated Steady-State Exposures for Subjects in Study CV185362 by Age Groups

Variable	28 d to < 9 m (n = 2)	9 m to < 2 y (n = 6)	2 y to < 6 y (n = 37)	6 y to < 12 y (n = 48)	12 y to < 18 y (n = 31)	Overall (n = 124)
AUCss(TAU) (ng•h/mL)	1990 (40.4)	1420 (56.6)	1590 (46.4)	1840 (38.5)	1630 (40)	1690 (42.3)
CL/F (L/h)	0.496 (39.7)	0.804 (51.9)	1.44 (54.9)	1.9 (42.5)	2.88 (43.4)	1.82 (61.8)
Cmaxss (ng/mL)	230 (33.5)	182 (46.4)	220 (38.1)	248 (32.3)	204 (38.5)	224 (37)
Cminss (ng/mL)	89.4 (55.8)	56.4 (83.1)	61.1 (65.3)	72.9 (56.9)	74.5 (52.3)	68.9 (59.6)
Ka (1/h)	0.606 (6.77)	0.904 (42.7)	1.13 (39.3)	1.2 (35.2)	1.07 (28)	1.12 (36.1)
Q/F (L/h)	0.053 (39.9)	0.145 (32.6)	0.439 (76.3)	0.556 (42)	1.09 (49.9)	0.553 (87.1)
Tmaxss (h)	2.7 (6.66)	2.07 (24.9)	1.71 (26.3)	1.71 (21.6)	1.85 (18.2)	1.77 (23.3)
Vc/F (L)	3.91 (21.6)	5.74 (32.6)	9.44 (38.9)	13.5 (33.3)	23.8 (37.4)	13.1 (58.8)
Vp/F (L)	15.3 (75)	21.8 (22.2)	24.6 (88.6)	18.2 (46.6)	23.7 (51.5)	21.4 (62.3)

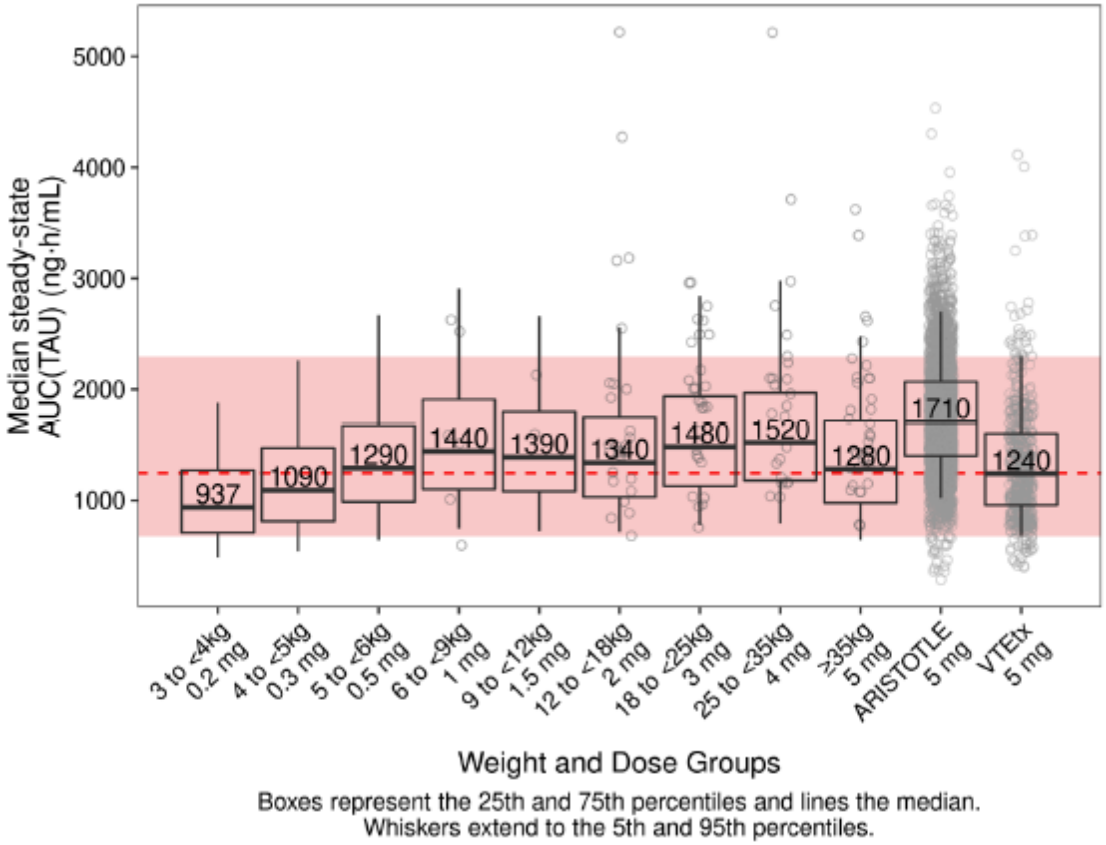
Source: Table 5.1.3.1-1 of the Study CV185362 Pharmacometrics Analysis Report
Abbreviations: $AUC_{ss,T}$, area under the concentration-time curve at steady state in one dosing interval; CL/F, apparent oral clearance; $C_{max,ss}$, maximum concentration at steady state; $C_{min,ss}$, minimum concentration at steady state; Ka, absorption rate constant; n, number of subjects in group; Q/F, apparent intercompartmental clearance; $T_{max,ss}$, time to maximum concentration at steady state; V_c/F, apparent volume of distribution of the central compartment; V_p/F, apparent volume of distribution of the peripheral compartment

Table 55. Summary of Geometric Mean (%CV) of Individual Estimated Pharmacokinetic Parameters and Simulated Steady-State Exposures for Subjects in Study CV185362 by Body Weight Tiers

Variable	6 to < 9 kg (n = 6)	9 to < 12 kg (n = 2)	12 to < 18 kg (n = 28)	18 to < 25 kg (n = 29)	25 to < 35 kg (n = 24)	≥ 35 kg (n = 35)	Overall (n = 124)
AUCss(TAU) (ng•h/mL)	1460 (61.2)	1840 (20.7)	1610 (49.6)	1760 (38.3)	1840 (43.3)	1630 (37.3)	1690 (42.3)
CL/F (L/h)	0.682 (61.4)	0.812 (20.6)	1.25 (51.4)	1.64 (36)	2.12 (40.3)	2.99 (37.3)	1.82 (61.8)
Cmaxss (ng/mL)	185 (48.8)	218 (23.4)	222 (39.6)	244 (30.7)	249 (37.7)	203 (35.9)	224 (37)
Cminss (ng/mL)	57.9 (90.3)	82.7 (21.5)	64.3 (69.5)	67.4 (58.9)	73.1 (64.7)	72.7 (46.8)	68.9 (59.6)
Ka (1/h)	0.868 (45)	0.684 (27.7)	1.1 (47.2)	1.25 (32.4)	1.21 (26.9)	1.06 (29)	1.12 (36.1)
Q/F (L/h)	0.095 (58.2)	0.189 (5.84)	0.449 (92.2)	0.482 (34.9)	0.632 (52.8)	0.964 (53.8)	0.553 (87.1)
Tmaxss (h)	2.14 (27.4)	2.46 (14)	1.72 (30.6)	1.65 (21.5)	1.69 (17.4)	1.89 (16.8)	1.77 (23.3)
Vc/F (L)	4.91 (37.9)	6.22 (12.8)	8.27 (32.6)	11.2 (20.7)	15 (24)	24.5 (30.8)	13.1 (58.8)
Vp/F (L)	18.9 (40.7)	23.5 (18.4)	26.3 (107)	19.2 (35.4)	18.4 (50.8)	22.3 (52.2)	21.4 (62.3)

Source: Table 5.1.3.1-2 of the Study CV185362 Pharmacometrics Analysis Report
Abbreviations: $AUC_{ss,T}$, area under the concentration-time curve at steady state in one dosing interval; CL/F, apparent oral clearance; $C_{max,ss}$, maximum concentration at steady state; $C_{min,ss}$, minimum concentration at steady state; K_a, absorption rate constant; n, number of subjects in group; Q/F, apparent intercompartmental clearance; $T_{max,ss}$, time to maximum concentration at steady state; V_c/F, apparent volume of distribution of the central compartment; V_p/F, apparent volume of distribution of the peripheral compartment

Figure 16. Simulated Exposures of Virtual Pediatric Subjects Aged 28 Days to <18 Years by Weight Tiers and the Adult VTE Treatment Population and ARISTOTLE Study



Source: Figure 5.1.3.2-1 of the Study CV185162 Pharmacometrics Analysis Report
Note: Red dashed line and shaded region represent the median, 5th percentile, and 95th percentile of exposure in the adult population.
Abbreviations: AUC_T, area under the concentration-time curve in one dosing interval; VTE, venous thromboembolism

PK/PD Results

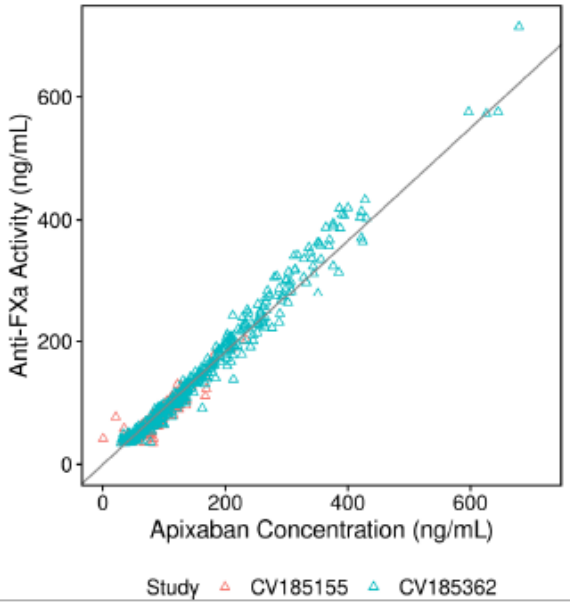
The PK/PD analysis was performed using observed apixaban concentrations and AXA data collected in pediatric Studies CV185362 and CV185155. The final PK/PD model was a linear mixed effect regression model with intercept fixed to zero. The parameter estimates and standard errors for the final PK/PD model are summarized in Table 56 and the GoF plot showing the model fitting to the observed PK/PD data is presented in Figure 17.

Table 56. Parameter Estimates and Standard Errors for the Final Pharmacokinetic/ Pharmacodynamic Model for AXA

Fixed Effect			
Parameter	**Value**	**Standard Error**	**Bootstrap Derived 95% CI**
Slope	0.916	0.00571	0.893 - 0.916
Random Effects			
Parameter	**Value**	**Residual**	
Standard Deviation	0.0528	12.8	

Source: Table 5.2.1-1 of the Study CV185362 Pharmacometrics Analysis Report
Abbreviations: AXA, antifactor Xa activity; CI, confidence interval

Figure 17. Goodness-of-Fit Plot for the Final Apixaban Pharmacokinetic/Pharmacodynamic Model for AXA



Source: Figure 5.2.1-1 of the Study CV185362 Pharmacometrics Analysis Report
Abbreviation: AXA, antifactor Xa activity

Table 57. Summary of Geometric Mean (%CV) of Predicted Maximum AXA Values in Pediatric Subjects From Studies CV185155 and CV185362

Study CV185155	
Weight Tier	**AXAmax (ng/mL) Geometric Mean (%CV)**
9 to < 12 kg (n = 2)	65.5 (12.4)
12 to < 18 kg (n = 39)	74.7 (27.4)
18 to < 25 kg (n = 31)	76.4 (17)
25 to < 35 kg (n = 16)	74.1 (17.9)
≥ 35 kg (n = 42)	72.9 (28.6)
Overall (n = 130)	74.3 (24.3)
Study CV185362	
Weight Tier	**AXAmax (ng/mL) Geometric Mean (%CV)**
6 to < 9 kg (n = 6)	170 (50.4)
9 to < 12 kg (n = 2)	195 (22)
12 to < 18 kg (n = 27)	207 (42.3)
18 to < 25 kg (n = 29)	224 (31.7)
25 to < 35 kg (n = 24)	232 (38.7)
≥ 35 kg (n = 35)	187 (38.5)
Overall (n = 123)	208 (38.8)

Source: Table 5.2.3-1 of the Study CV185362 Pharmacometrics Analysis Report
Abbreviations: AXA, antifactor Xa activity; AXA_{max}, maximum antifactor Xa activity; CV, coefficient of variation; n, number of subjects in group

Summary

- PopPK model demonstrates body weight as a predictor of apixaban CL/F and Vc/F. Apixaban CL/F and Vc/F increased with increase in body weight.
- The proposed fixed-dose regimens by weight tiers (0.2 mg BID for 3 to <4 kg, 0.3 mg BID for 4 to <5 kg, 0.5 mg BID for 5 to <6 kg, 1 mg BID for 6 to <9 kg, 1.5 mg BID for 9 to <12 kg, 2 mg BID for 12 to <18 kg, 3 mg BID for 18 to <25 kg, 4 mg BID for 25 to <35 kg, and 5 mg BID for ≥35 kg) in pediatric subjects aged 28 days to <18 years produced median steady-state exposures comparable to that in adults for VTE treatment in the ARISTOTLE study receiving apixaban 5 mg BID, with relatively lower steady-state AUC_T for the 3 to <4 kg group compared to other weight tiers.
- A linear mixed effect regression model with intercept at zero, slope parameter of 0.916 and IIV on the slope parameter described the relationship between apixaban concentration and AXA in with CAHD at risk of VTE.

Study CV185325

Title

A randomized, open-label, active-controlled, safety and descriptive efficacy study in pediatric subjects requiring anticoagulation for the treatment of a VTE event.

Objective

To evaluate apixaban PK and AXA in pediatric subjects requiring anticoagulation for the treatment of a VTE.

Study Design

See Section 6.2 for study design.

PK Results

Table 58. Summary of Individual Estimated Pharmacokinetic Parameters and Simulated Steady-State Exposures for Subjects in Study CV185325 by Age Groups

Variable	Summary Statistic	< 28 d (n = 10)	28 d to < 2 y (n = 19)	2 y to < 12 y (n = 28)	12 y to < 18 y (n = 87)	Overall (n = 144)
AUCss(TAU) (ng•h/mL)	Geometric mean (%CV)	625 (25.5)	1160 (48.8)	1420 (26.2)	1060 (38.5)	1090 (42.1)
Cmaxss (ng/mL)	Geometric mean (%CV)	63.5 (25.2)	160 (43.3)	187 (22.1)	130 (34.6)	137 (42.7)
Cminss (ng/mL)	Geometric mean (%CV)	38.9 (26.2)	41.7 (74)	57.3 (42.5)	48.1 (52.7)	48.1 (53.3)
CL/F (L/h)	Geometric mean (%CV)	0.169 (26.4)	1.01 (56.4)	2.59 (35.9)	4.35 (38.3)	2.59 (126)
Ka (1/h)	Geometric mean (%CV)	1.35 (7.96)	1.26 (14.2)	1.26 (5.58)	1.27 (10)	1.27 (9.93)
Q/F (L/h)	Geometric mean (%CV)	0.0129 (16.6)	0.121 (34.3)	0.553 (22.9)	0.927 (7.44)	0.476 (182)
Tmax (h)	Median (Min, Max)	1.87 (1.81, 2.11)	1.69 (1.38, 2.28)	1.72 (1.48, 1.96)	1.79 (1.43, 2.45)	1.78 (1.38, 2.45)
Vc/F (L)	Geometric mean (%CV)	3.37 (25.3)	7.07 (39.6)	20 (35.3)	40.6 (32.5)	23.6 (105)
Vp/F (L)	Geometric mean (%CV)	18.1 (0)	18.1 (0)	18.1 (0)	18.1 (0)	18.1 (0)

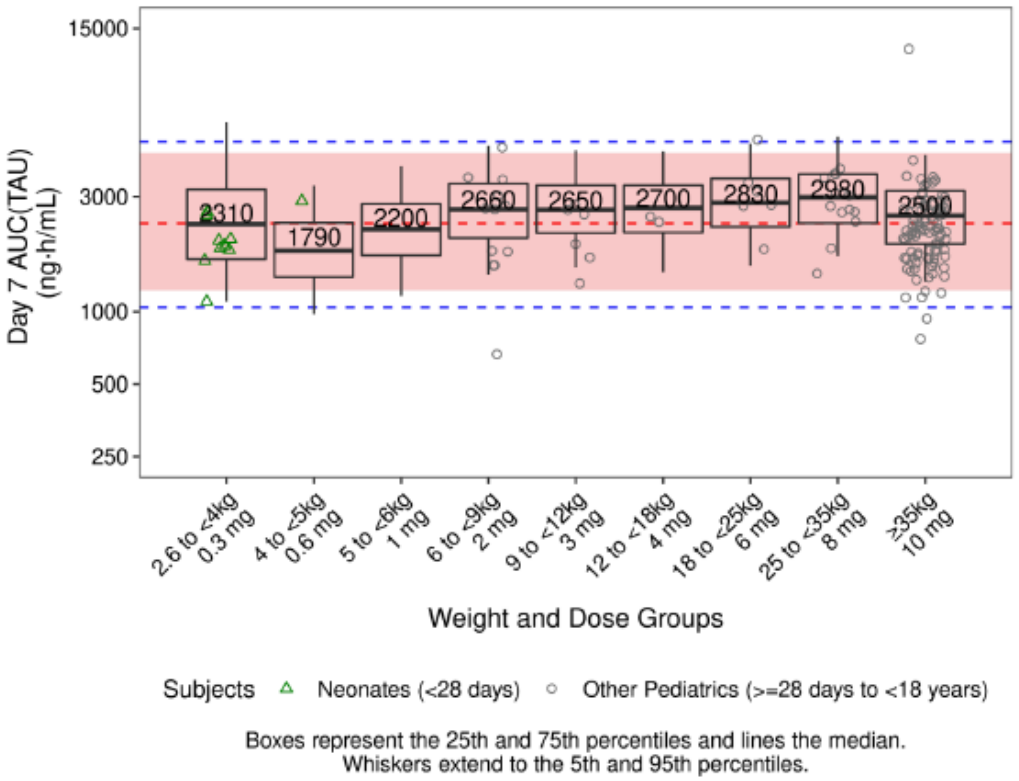
Source: Table 5.1.4.2-1 of the Study CV185325 Pharmacometrics Analysis Report
Abbreviations: $AUC_{ss,T}$ (AUC_{ss}[TAU])area under the concentration-time curve at steady state in one dosing interval; CL/F, apparent oral clearance; $C_{max,ss}$, maximum concentration at steady state; $C_{min,ss}$, minimum concentration at steady state; CV, coefficient of variation; K_a, absorption rate constant; n, number of subjects in group; Q/F, apparent intercompartmental clearance; $T_{max,ss}$, time to maximum concentration at steady state; V_c/F, apparent volume of distribution of the central compartment; V_p/F, apparent volume of distribution of the peripheral compartment

Table 59. Summary of Individual Estimated Pharmacokinetic Parameters and Simulated Steady-State Exposures for Subjects in Study CV185325 by Body Weight Tiers

Variable	Summary Statistic	2.6 to < 4 kg (n = 9)	4 to < 5 kg (n = 1)	6 to < 9 kg (n = 2)	9 to < 12 kg (n = 6)	12 to < 18 kg (n = 2)	18 to < 25 kg (n = 6)	25 to < 35 kg (n = 14)	≥ 35 kg (n = 95)	Overall (n = 144)
AUCss(TAU) (ng•h/mL)	Geometric mean (%CV)	643 (25.3)	485 (NA)	1200 (59.2)	1080 (31.7)	1240 (6.45)	1530 (34.4)	1400 (28.5)	1080 (38)	1090 (42.1)
CL/F (L/h)	Geometric mean (%CV)	0.164 (26.1)	0.22 (NA)	0.835 (59.2)	1.38 (31.6)	1.58 (6.42)	1.89 (34.2)	2.68 (28.6)	4.27 (38)	2.59 (126)
Cmaxss (ng/mL)	Geometric mean (%CV)	65.3 (25)	49.3 (NA)	159 (53.1)	156 (25.7)	176 (12.1)	211 (25.6)	180 (26.7)	134 (34.5)	137 (42.7)
Cminss (ng/mL)	Geometric mean (%CV)	40 (26.1)	30.3 (NA)	45.7 (84.1)	34.7 (63.1)	43.8 (6.64)	57.6 (55.8)	59.2 (36.3)	48.6 (52.5)	48.1 (53.3)
Ka (1/h)	Geometric mean (%CV)	1.34 (7.76)	1.48 (NA)	1.23 (16.8)	1.32 (7.66)	1.33 (3.88)	1.29 (3.41)	1.25 (5.73)	1.27 (9.81)	1.27 (9.93)
Q/F (L/h)	Geometric mean (%CV)	0.0129 (17.7)	0.0128 (NA)	0.104 (31)	0.152 (21.4)	0.261 (48.7)	0.451 (15.9)	0.578 (22.6)	0.902 (12.1)	0.476 (182)
Tmax (h)	Median (Min, Max)	1.89 (1.81, 2.11)	1.81 (1.81, 1.81)	1.8 (1.46, 2.28)	1.64 (1.38, 1.86)	1.64 (1.59, 1.68)	1.66 (1.52, 1.78)	1.75 (1.59, 1.96)	1.79 (1.43, 2.45)	1.78 (1.38, 2.45)
Vc/F (L)	Geometric mean (%CV)	3.27 (24.7)	4.44 (NA)	6.24 (41.7)	8.71 (26.8)	10.3 (18.2)	13.1 (16.7)	21.7 (25.3)	39.3 (33.8)	23.6 (105)
Vp/F (L)	Geometric mean (%CV)	18.1 (0)	18.1 (NA)	18.1 (0)	18.1 (0)	18.1 (0)	18.1 (0)	18.1 (0)	18.1 (0)	18.1 (0)

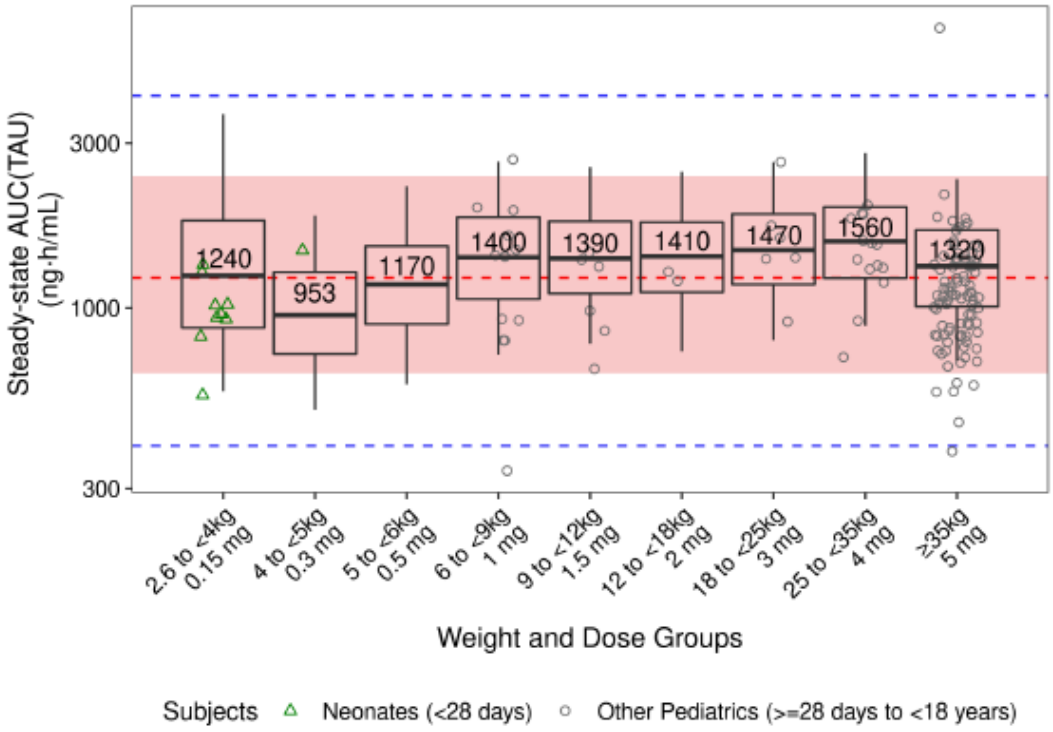
Source: Table 5.1.4.2-2 of the Study CV185325 Pharmacometrics Analysis Report
Abbreviations: $AUC_{ss,T}$ (AUC_{ss}[TAU]), area under the concentration-time curve at steady state in one dosing interval; CL/F, apparent oral clearance; $C_{max,ss}$, maximum concentration at steady state; $C_{min,ss}$, minimum concentration at steady state; CV, coefficient of variation; K_a, absorption rate constant; n, number of subjects in group; Q/F, apparent intercompartmental clearance; $T_{max,}$, time to maximum concentration; V_c/F, apparent volume of distribution of the central compartment; V_p/F, apparent volume of distribution of the peripheral compartment

Figure 18. Simulated Exposures at Day 7 for Virtual Pediatric Subjects From Birth to <18 Years of Age by Body Weight Tiers; Neonate Starting Dose of 0.3 mg BID and the Adult VTE Treatment Population Starting Dose of 10 mg BID



Source: Figure 5.1.4.2-5 of the Study CV185325 Pharmacometrics Report
Note: Model-based simulation of exposures was performed using baseline values for body weight and age.
AUC_T values shown on each boxplot are presented as 3 significant digits.
Red dashed line and shaded region represent the median and 5th/95th percentiles of exposure, respectively, in the adult VTE treatment population based on simulations (with uncertainty) performed to predict apixaban AUC_T exposure. The 5th, 50th (median), and 95th percentile Day 7 AUC_T were 1,228, 2,325, and 4,568 ng·h/mL, respectively, for the 10 mg BID dose regimen.21 The upper blue dashed line is the maximum adult value for Day 7 AUC_T of 5,076.50 ng·h/mL observed in the adult VTE treatment population in Studies CV185017, CV185056, and CV185057 for the 10 mg BID dose regimen; lower blue dashed line is the minimum adult value of 1,041.70 ng·h/mL.
Open symbols in the body weight tier boxplots denote model-predicted exposures for pediatric subjects in Study CV185325; no pediatric subjects were in the 5 to <6 kg body weight tier group. The high exposure value in the body weight tier ≥35 kg was a pediatric subject (ID (b) (6)) in Study CV185325, aged 16.6 years with body weight of 57.2 kg and Day 7 AUC_T of 12, 582 ng·h/mL.
Abbreviations: AUC_T (AUC[TAU]), area under the concentration-time curve in one dosing interval, BID, twice daily; VTE, venous thromboembolism

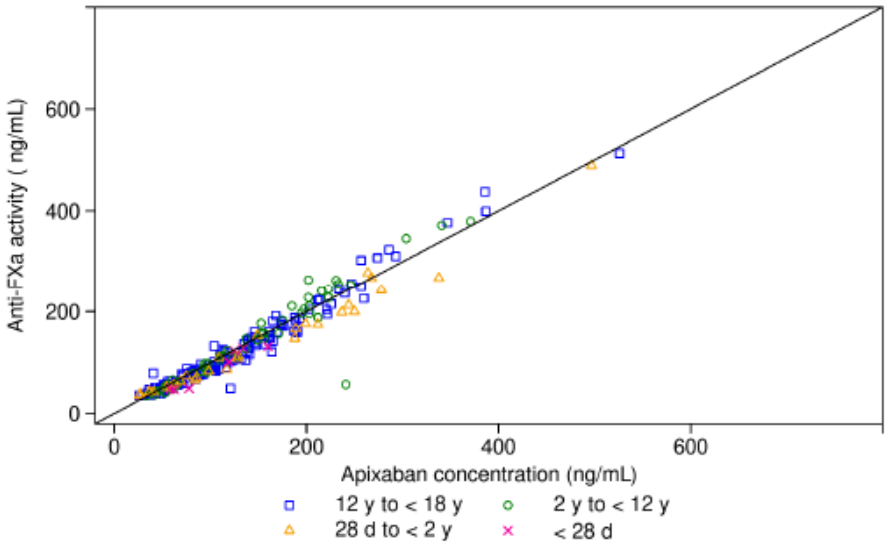
Figure 19. Simulated Steady-State Exposures for Virtual Pediatric Subjects From Birth to <18 Years of Age by Body Weight Tiers; Neonate Dose of 0.15 mg BID and the Adult VTE Treatment Population Dose of 5 mg BID



Source: Figure 5.1.4.2-7 of the Study CV185325 Pharmacometrics Report
Note: Model-based simulation of exposures was performed using baseline values for body weight and age.
$AUC_{ss,T}$ values shown on each boxplot are presented as 3 significant digits.
Red dashed line and shaded region represent the median and 5th/95th percentiles of exposure, respectively, in the adult VTE treatment population based on simulations (with uncertainty) performed to predict apixaban daily AUC_{ss} exposure. The 5th, 50th (median), and 95th percentile $AUC_{ss,T}$ were 647, 1,223, and 2,404 ng•h/mL, respectively, for the 5 mg BID dose regimen.21 The upper blue dashed line is the maximum adult value for AUC_{ss} T of 4,113.5 ng·h/mL observed in the adult VTE treatment population in Studies CV185017, CV185056, and CV185057 for the 5 mg BID dose regimen; lower blue dashed line is the minimum adult value of 399.5 ng·h/mL.
Open symbols in the body weight tier boxplots denote model-predicted exposures for pediatric subjects in Study CV185325; no pediatric subjects were in the 5 to <6 kg body weight tier group. The high exposure value in the body weight tier ≥35 kg was a pediatric subject (ID (b) (6)) in Study CV185325, aged 16.6 years with body weight of 57.2 kg and AUCss T of 6,590.8 ng·h/mL.
Abbreviations: AUC_{ss}, area under the concentration-time curve at steady state; AUC_T (AUC[TAU]), area under the concentration-time curve in one dosing interval, BID, twice daily; VTE, venous thromboembolism

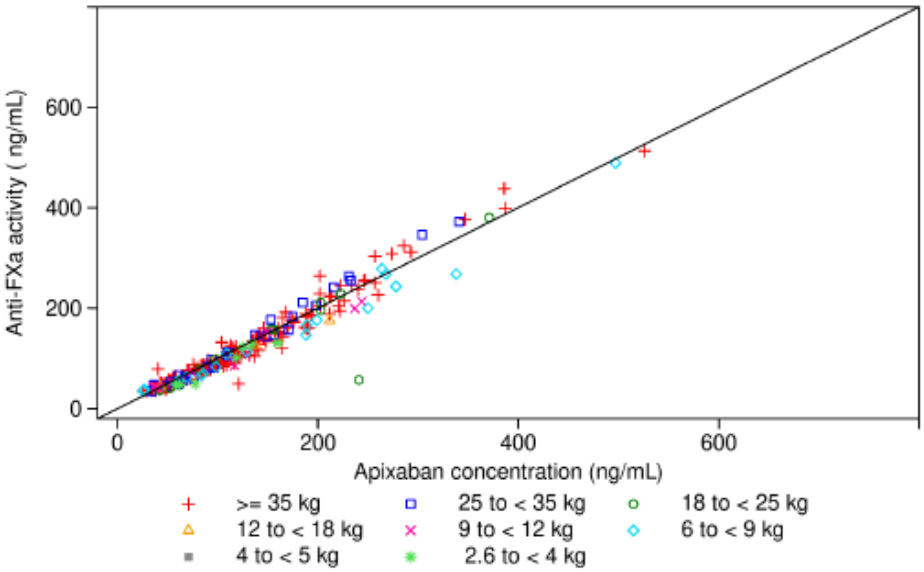
PK/PD Results

Figure 20. Observed Anti-FXa Activity vs. Apixaban Concentrations, Stratified by Age Category/Group in Studies CV185155, CV185362, and CV185325



Source: Figure 1 (Appendix 3.3.2.4-1) of the Study CV185325 Pharmacometrics Report

Figure 21. Observed Anti-FXa Activity vs. Apixaban Concentrations, Stratified by Body Weight Group in Study CV185325



Source: Figure 3.3.2.4-4 of the Study CV185325 Pharmacometrics Report

The final PK/PD model for Studies CV185325, CV185155, and CV185362 was a linear mixed effects model with an estimated slope (standard error) of 0.926 (0.00577) with bootstrap derived 95% CI of 0.91 to 0.93 for the overall data to describe the relationship between apixaban concentration and AXA (Table 60). A GoF plot showing the model fitting to the observed PK/PD data is presented in Figure 22. These results are consistent with the prior AXA evaluation

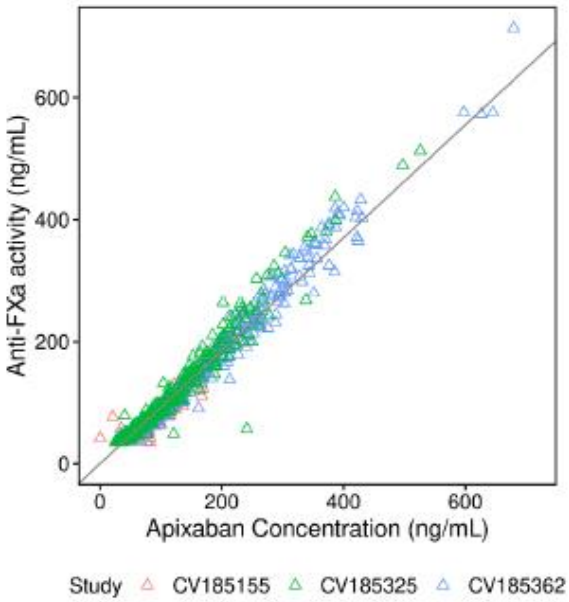
using data from Studies CV185155 and CV185362, where the linear mixed effects model with the IIV parameter for the slope was selected.

Table 60. Parameter Estimates and Standard Errors for the Final Pharmacokinetic/ Pharmacodynamic Model for Anti-FXa Activity

Fixed Effect				
Parameter	Value	Standard Error	Bootstrap Derived 95% CI	Bootstrap Derived Median
Slope	0.926	0.00577	0.91 - 0.93	0.92
Random Effects				
Parameter	**Value**		**Residual**	
Standard Deviation	0.079		12.7	

Source: Table 5.2.1-1 of the Study CV185325 Pharmacometrics Report
Abbreviation: CI, confidence interval

Figure 22. Goodness-of-Fit Plot for the Final Apixaban Pharmacokinetic/Pharmacodynamic Model for Anti-FXa Activity



Source: Figure 5.2.1-1 of the Study CV185325 Pharmacometrics Report

Summary

- Consistent with results from previous analyses, body weight was a significant predictor of both apixaban CL/F and Vc/F, where CL/F and Vc/F increased in a less-than-proportional manner with increase in body weight.
- Consistent with results from previous analyses, age was a significant predictor of apixaban Q/F, where Q/F was predicted to increase in a less-than-proportional manner with increasing age.

- The predicted Day 7 AUC_T median and $AUC_{ss,T}$ median values for each of the pediatric body weight groups were generally similar to that observed in the adult VTE treatment population receiving apixaban 10 mg BID and 5 mg BID, respectively.
- The AXA levels were linearly correlated to apixaban concentrations across the entire pediatric age range, as well as body weight tiers.
- The final PK/PD model that described the relationship between apixaban concentration and AXA concentration in pediatric subjects from Studies CV185155, CV185362, and CV185325 was a linear mixed effect regression model with a slope parameter of 0.926.

Study CV185029

Title

Study of bioavailability of apixaban solution formulation relative to apixaban tablets in healthy subjects.

Objectives

- To assess the oral bioavailability of apixaban solution formulation (Treatment B, 10 mg as 25 mL x 0.4 mg/mL) relative to apixaban phase 3 tablets (Treatment A, 10 mg as 2 x 5 mg tablets) in healthy subjects.
- To assess the PK of a single dose of apixaban as a solution formulation.
- To assess the safety and tolerability of single-dose apixaban.

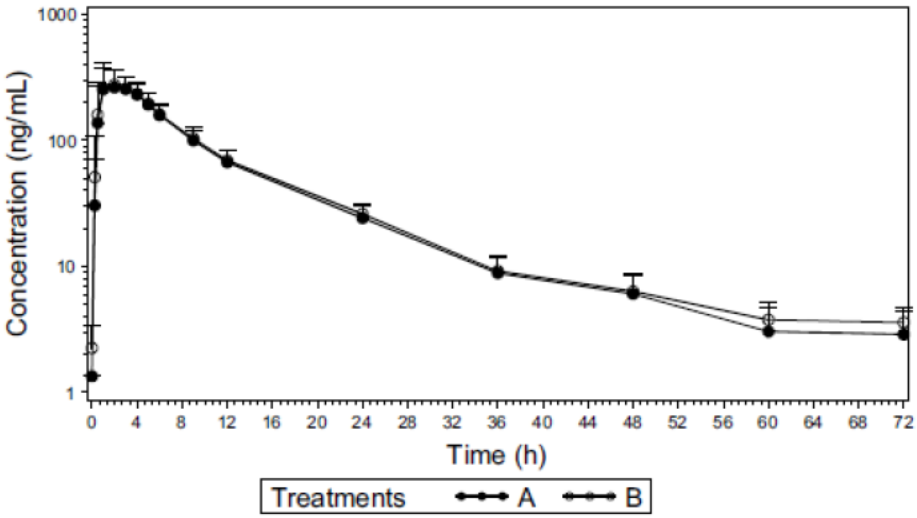
Design

This was an open-label, two-period, two-treatment, crossover study in 14 healthy subjects randomized to receive either:

- Treatment A: apixaban phase 3 tablets (2 x 5 mg, reference treatment).
- Treatment B: apixaban oral solution (10 mg as 25 mL x 0.4 mg/mL).

PK Results

Figure 23. Mean(+SD) Apixaban Plasma Concentration vs. Time Profiles by Treatment in Study CV185029



Source: Figure 9.2 of Study CV185029 Clinical Study Report
Note: N=13 except for Treatment A 0-12 hours where N=14
A=apixaban 2x5 mg Phase 3 tablets
B=apixaban 25 mLx0.4 mg/mL solution
Abbreviations: N, number of subjects in group; SD, standard deviation

Table 61. Summary Statistics for Apixaban Pharmacokinetic Parameters in Study CV185029

Treatment	Cmax (ng•h/mL) Geo.Mean (CV)	Tmax (h) Median (Min-Max)	AUC(0-T) (ng•h/mL) Geom. Mean (CV)	AUC(INF) (ng•h/mL) Geom. Mean (CV)	T-HALF (h) Mean (SD)	Frel (%)
A (N = 13)*	294	2.00	2663	2707	12.3	B vs A
	(37)	(0.50-4.05)	(22)	(21)	(4.53)	105
B (N = 13)	287	2.00	2790	2855	13.8	
	(30)	(1.00-4.00)	(21)	(21)	(6.09)	

Source: Table 9.2 A of Study CV185029 Clinical Study Report
*N=14 for Treatment A: C_{max} and T_{max}
A=apixaban 2x5 mg Phase 3 tablets
B=apixaban 25 mLx0.4 mg/mL solution
Abbreviations: AUC_{0-t}, area under the concentration-time curve from time 0 extrapolated to time t; AUC_{inf}, area under the concentration-time curve extrapolated to infinity; C_{max}, maximum concentration; CV, coefficient of variation; F_{rel}, relative bioavailability; geo. mean, geometric mean; max, maximum; min, minimum; N, number of subjects in group; SD, standard deviation; $t_{1/2}$, elimination half-life; T_{max}, time to maximum concentration

Table 62. Results of Statistical Analyses for Apixaban C_{max}, $AUC_{(0-t)}$, and AUC_{inf} in Study CV185029

TREATMENT AND COMPARISON	Cmax (ng/mL) Adjusted Geom. Mean	AUC(INF) (ng•h/mL) Adjusted Geom. Mean	AUC(0-T) (ng•h/mL) Adjusted Geom. Mean
A	293.99	2712.48	2668.31
B	287.43	2848.97	2784.37
	Ratio of AGM(90% CI)	Ratio of AGM(90% CI)	Ratio of AGM(90% CI)
B vs A	0.977(0.756,1.261)	1.050(0.938,1.176)	1.043(0.933,1.167)

Source: Table 9.2 B of Study CV185029 Clinical Study Report
Note: A=apixaban 2x5 mg Phase 3 tablets; B=apixaban 25 mLx0.4 mg/mL solution
Abbreviations: AGM, adjusted geometric mean; AUC_{0-t}, area under the concentration-time curve from time 0 extrapolated to time t; AUC_{inf}, area under the concentration-time curve extrapolated to infinity; C_{max}, maximum concentration; CI, confidence interval; geom. mean, geometric mean; vs., versus

Summary

- The results showed that the 90% confidence intervals for AUC_T and area under the concentration-time curve extrapolated to infinity (AUC_{inf}) fell within the standard equivalence criteria of 80 to 125%, indicating comparable absorption between the tablet and solution formulations.
- The maximum concentration (C_{max}) 90% confidence interval marginally exceeded the equivalence range (75 to 126%), yet the point estimate was very close to 1.00, suggesting similar absorption rates between the two formulations.

Study CV185687

Title

An open-label, phase 1, randomized study to evaluate the bioavailability of apixaban (BMS-562247) 0.1 mg sprinkle capsules relative to reference 0.5 mg tablets in healthy subjects

Objectives

- To assess the bioavailability of apixaban 0.1 mg sprinkle capsules relative to apixaban 0.5 mg tablets, both administered orally in healthy subjects
- To assess the safety and tolerability of apixaban
- To assess the PK of apixaban 0.1 mg sprinkle capsules
- To assess the PK of apixaban 0.5 mg tablets

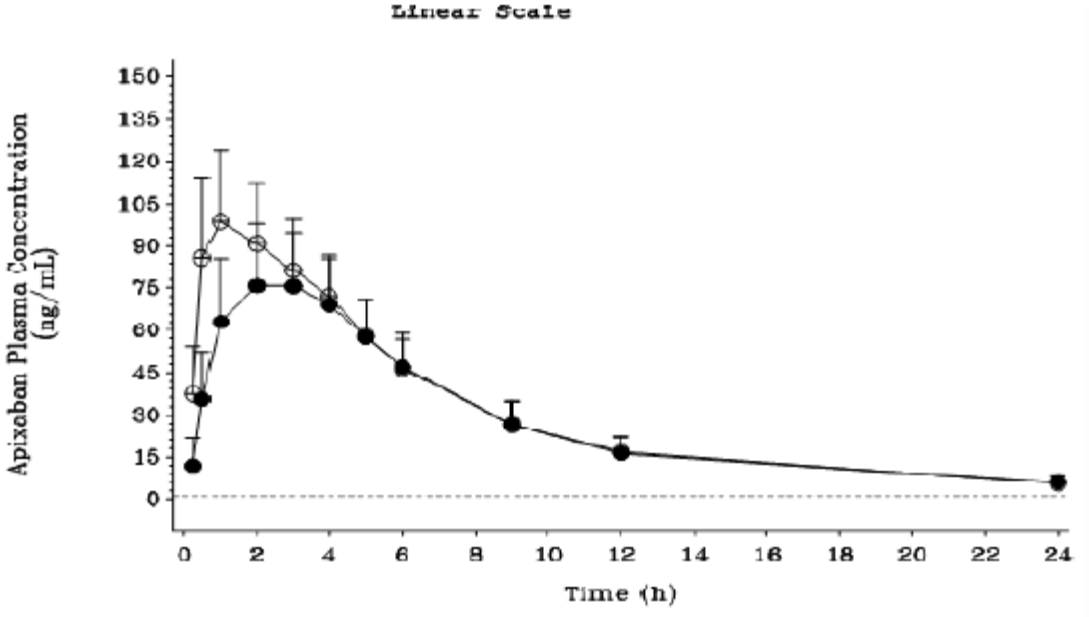
Design

This was a phase 1, open-label, randomized, two-period, two-treatment, crossover study in healthy adult subjects to evaluate the bioavailability of apixaban when administered as 0.1 mg sprinkle capsules compared to 0.5 mg tablets.

PK Results

The summary statistics and statistical analysis of PK parameters for the apixaban 0.1 mg sprinkle capsules and apixaban 0.5 mg tablets are presented in Table 63.

Figure 24. Mean (+SD) Apixaban Plasma Concentration Profile vs. Time



Source: Figure 9.2-1 of Study CV185687 Clinical Study Report
Abbreviation: SD, standard deviation

Table 63. Summary Statistics and Statistical Analysis of Apixaban Pharmacokinetic Parameters

	Adjusted Geometric Mean and Ratios [N] (90% CI)		
Pharmacokinetic Parameter (Unit)	Treatment A	Treatment B	Treatment B vs Treatment A
Cmax (ng/mL)	77.4 [30]	99.3 [30]	1.283 [30]
	(71.3, 84.1)	(92.1, 107)	(1.222, 1.346)
AUC(0-T) (ng·h/mL)	696 [30]	769 [30]	1.105 [30]
	(639, 758)	(714, 829)	(1.074, 1.138)
AUC(INF) (ng·h/mL)	715 [30]	788 [30]	1.102 [30]
	(657, 778)	(733, 847)	(1.071, 1.135)
Tmax (h)	2.09 [30] (1.00, 4.05)	1.00 [30] (0.50, 2.00)	–
T-HALF (h)	9.34 [30] (3.66)	8.23 [30] (2.69)	–
Frel (%)	–	110 [30]	–
		(9.3)	

Source: Table 9.2-1 and Table 9.2-2 of Study CV185687 Clinical Study Report
Note: T_{max} presented as median (N) (min, max); $t_{1/2}$ presented as mean (N) (SD); F_{rel} presented as geometric mean (N) (CV)
Treatments: A=apixaban 2x5 mg Phase 3 tablets; B=apixaban 25 mLx0.4 mg/mL solution
Abbreviations: AUC_{0-t}, area under the concentration-time curve from time 0 extrapolated to time t; AUC_{inf}, area under the concentration-time curve extrapolated to infinity; C_{max}, maximum concentration; CI, confidence interval; F_{rel}, relative bioavailability; N, number of subjects in group; SD, standard deviation; $t_{1/2}$, elimination half-life; T_{max}, time to maximum concentration, vs., versus

Summary

- Following administration of a single dose of apixaban 2.5 mg as 25 x 0.1 mg sprinkle capsules, C_{max} was 28% higher than after administration as 5 x 0.5 mg tablets; however, AUC_T and AUC_{inf} were similar for both formulations.
- Median time to maximum concentration was approximately 1 hour earlier after administration of the sprinkle capsules compared to the 0.5 mg tablets.
- Mean relative bioavailability of the sprinkle capsules compared to 0.5 mg tablets was 110%.
- Oral administration of a single dose of apixaban 2.5 mg (as 25 x 0.1 mg sprinkle capsules and 5 x 0.5 mg tablets) was safe and generally well tolerated by the healthy subjects in this study.

14.3. Bioanalytical Method Validation and Performance

14.3.1. PK Assays

Except for the neonate subjects, the apixaban plasma concentrations in Study CV185325 were determined by using a validated liquid chromatography tandem mass spectrometry (LC-MS/MS) method. There were no changes to this analysis method since the regulatory submissions for indications in adults, except that the method was transferred from (b) (4) to (b) (4). Addendums including a cross-validation report and extended sample stability information were reviewed and the method was cross-validated.

In neonates, apixaban concentrations were measured using a validated dried blood spot (DBS) LC-MS/MS method in whole blood. A method validation report for the DBS LC-MS/MS method in whole blood was provided to support apixaban quantification in the neonate population for Study CV185325 (Table 64).

Table 64. Method Validation Summary of DBS LC-MS/MS Method in Whole Blood

(b) (4) **Project Code**	RNUW2		
Method ID	LCMSD 733.1		
Analyte	BMS-562247		
Matrix	Human Whole Blood [From Dried Blood Spots (DBS)]		
Anticoagulant	Dipotassium EDTA		
Method Description	Liquid-liquid extraction		
Sample Volume (µL)	3-mm diameter punch from the center of a 15-µL dried blood spot		
Sample Storage Condition	Room Temperature / Low Humidity Enviroment		
Hematocrit Values for CALs and QCs	29% ± 2 and 70% ± 2		
Hematocrit Target and Acceptable Low and High Ranges Evaluated	36 ± 2 (CALs and QCs); LBIA 29 ± 2 and HBIA 44 ± 2 50 ± 2 (CALs and QCs); LBIA 44 ± 2 and HBIA 60 ± 2 65 ± 2 (CALs and QCs); LBIA 60 ± 2 and HBIA 70 ± 2		
Internal Standard (IS)	BMS-562247-03		
Regression, Weighting	Linear, 1/concentration^2		
DBS Average Recovery of Drug (%)	73.2%		
LLE Average Recovery of Drug (%)	105%		
LLE Average Recovery of IS (%)	94.1%		
Standard Curve Concentrations	0.500 to 500 ng/mL		
QC Concentrations	0.500, 1.50, 20.0, 250, and 375 ng/mL		
QC Intra-assay Statistics (%)	Conc. (ng/mL)	Precision	Accuracy
	0.500	3.90 to 9.64%	-7.81 to 12.9%
	1.50	3.52 to 6.51%	-6.32 to 6.15%
	20.0	2.39 to 6.22%	-3.36 to 6.28%
	250	3.64 to 7.71%	-8.04 to 3.25%
	375	1.31 to 7.00%	-4.21 to -1.04%
QC Inter-assay Statistics Hct 29 and 70 +/- 2 (%)	Conc. (ng/mL)	Precision	Accuracy
	0.500	9.75%	-0.310%
	1.50	6.58%	-0.218%
	20.0	5.12%	1.78%
	250	7.29%	-2.27%
	375	4.17%	-2.89%
Alternative Anti-Coagulant	Sodium citrate whole blood was an acceptable alternative anti-coagulant.		
Low and High Blood Volume	10-µL to 20-µL blood volume spot sizes are acceptable.		
Dilutional Linearity	1000 ng/mL diluted four-fold		
Freeze-thaw Stability (cycles)	Two cycles stored and cycled at -25 °C		
Elevated Temperature Stability (hrs)	24 and 72 hours at 50 °C		
Swing Storage Stability (hrs)	48 hours at -25 °C then transferred to room temperature storage prior to extraction		
Room Temperature Stability (hrs)	24 hours at room temperature without dessicant		
Extract Stability (hrs)	321 hours at 2 to 8 °C		
Analyte Stability (days)	30 days at room temperature		

Whole Blood Stability	Up to one hour at 37 °C followed by four hours at room temperature
BMS-562247 Solution Stability (days)	1.00 mg/mL in methanol for 50 days at -25 °C
BMS-562247 Solution Stress Stability (hours)	1.00 mg/mL in methanol for 6.00 hours at room temperature
Reinjection Reproducibility	Runs stored at 2 to 8 °C may be reinjected for BMS-562247
Hemolysis	Experiment was not performed for BMS-562247
Lipemia	Experiment was not performed for BMS-562247
Selectivity	No significant interfering peaks noted in blank human whole blood samples
Matrix Factor	Lot-to-lot response consistency was demonstrated for BMS-562247.
Cross-analyte Interference	No significant chromatographic peaks detected at the mass transitions or expected retention times.
SOP Deviations	No SOP deviations occurred during the course of this study.

Source: NDA 220073, 5.3.1.4, Method validation report 930167214 1.0
Abbreviations: CAL, clinical assay laboratory; conc., concentration; DBS, dried blood spots; EDTA, ethylenediaminetetra-acetic acid; HBIA, hand-to-hand bioelectrical impedance analyzer; Hct, hematocrit; ID, identifier; IS, internal standard; LBIA, leg-to-leg bioelectrical impedance analysis; LC-MS/MS, liquid chromatography-tandem mass spectrometry; LLE, liquid-liquid extraction; (b) (4) (b) (4); QC, quality control; SOP, standard operating procedure

The selectivity, specificity, matrix effect, calibration curve (response function), range (lower limit of quantification to upper limit of quantification), accuracy, precision, carryover, dilution integrity, stability, and reinjection reproducibility of this method met the ICH M10 requirements, and the method is validated (November 2022).

Bioanalytical Method Performance

The in-study performance of the DBS LC-MS/MS method in whole blood and LC-MS/MS in human plasma in pivotal pediatric clinical study sample analysis are summarized in Table 65, Table 66, and Table 67.

Table 65. Summary of Apixaban Assay Performance in Human Whole Blood Using the Dried Blood Spot LC-MS/MS Method in the Pivotal Study

Analyte Name	Apixaban (BMS-562247)	
Assay Run Performance* Refer to Table 1 for run assignments	No. of Acceptable Runs 12	No. of Failed Runs 4 (1 run was re-injected acceptably.)
	Run Passing Rate (%) 75.0%	
Standard Curve performance*	**Precision (%CV)**	**Accuracy (%RE)**
Overall (Mean) Inter-Assay Refer to Table 2 and Table 3 for calibration standard (CS) performance	≤5.8%	-5.4% to 3.3%
QC performance*	**Precision (%CV)**	**Accuracy (%RE)**
Overall (Mean) Inter-Assay Performance QC Samples (QCL, QCGM, QCM, QCH) Table 4	≤7.9%	-0.7% to 6.1%
Incurred Sample Reanalysis (ISR) Assessment Refer to Table 5 for ISR data		
Total number of samples analyzed		32
Total number of ISR samples analyzed		11
Percentage of ISR samples analyzed of total number of analyzed samples		34.4%
Total number of ISR samples analyzed within ±20% difference		11
Percentage within ±20.0% difference		100.0%

Source: \\CDSESUB1\EVSPROD\nda202155\0290\m5\53-clin-stud-rep\535-rep-effic-safety-stud\pediatric-venous-thromboembolism\5351-stud-rep-contr\b0661037\b0661037-analytical-reports.pdf
Abbreviations: CS, calibration standard; CV, coefficient of variation; ISR, incurred sample reanalysis; LC-MS/MS, liquid chromatography-tandem mass spectrometry; no., number; QC, quality control; QCGM, quantum continuous gradient model; QCH, quality control high sample; QCL, quality control low sample; QCM, quality control medium sample; RE, relative error

Human plasma samples were analyzed using the LC/MS/MS method. Samples from age groups 1, 2 and most of age group 3 were analyzed at (b) (4), while part of cohort 3 and plasma samples from age group 4 were analyzed at (b) (4). The in-study performance during bioanalysis of the pivotal pediatric clinical study samples is summarized in Table 66 and Table 67.

Table 66. Assay Performance Summary of Apixaban In Human Plasma Using LC-MS/MS in Pivotal Study (b) (4)

Analyte Name	Apixaban (BMS-562247)	
Assay Run Performance* Refer to Table 1 for run assignments	No. of Acceptable Runs 16	No. of Failed Runs 3 (3 runs were re-injected acceptably)
	Run Passing Rate (%) 81.3%	
Standard Curve performance*	**Precision (%CV)**	**Accuracy (%RE)**
Overall (Mean) Inter-Assay Refer to Table 2 and Table 3 for calibration standard (CS) performance	≤6.6%	-2.8% to 2.7%
QC performance*	**Precision (%CV)**	**Accuracy (%RE)**
Overall (Mean) Inter-Assay Performance QC Samples (QCL, QCM, QCH) Table 4	≤5.9%	5.6% to 7.6%
Incurred Sample Reanalysis (ISR) Assessment Refer to Table 5 for ISR data		
Total number of samples analyzed		32
Total number of ISR samples analyzed		16
Percentage of ISR samples analyzed of total number of analyzed samples		50.0%
Total number of ISR samples analyzed within ±20% difference		16
Percentage within ±20.0% difference		100.0%

Source: \\CDSESUB1\EVSPROD\nda202155\0290\m5\53-clin-stud-rep\535-rep-effic-safety-stud\pediatric-venous-thromboembolism\5351-stud-rep-contr\b0661037\b0661037-analytical-reports.pdf
Note: Samples analyzed at (b) (4)
Abbreviations: CV, coefficient of variation; ISR, incurred sample reanalysis; LC-MS/MS, liquid chromatography-tandem mass spectrometry; no., number; QC, quality control; QCH, quality control high sample; QCL, quality control low sample; QCM, quality control medium sample; RE, relative error

Table 67. Assay Performance Summary of Apixaban In Human Plasma Using LC-MS/MS in Pivotal Study (b) (4)

Analyte Name	Apixaban (BMS-562247)	
Assay Run Performance* Refer to Table 1 for run assignments	No. of Acceptable Runs 12	No. of Failed Runs 4 (1 run was re-injected acceptably.)
	Run Passing Rate (%) 75.0%	
Standard Curve performance*	**Precision (%CV)**	**Accuracy (%RE)**
Overall (Mean) Inter-Assay Refer to Table 2 and Table 3 for calibration standard (CS) performance	≤5.8%	-5.4% to 3.3%
QC performance*	**Precision (%CV)**	**Accuracy (%RE)**
Overall (Mean) Inter-Assay Performance QC Samples (QCL, QCGM, QCM, QCH) Table 4	≤7.9%	-0.7% to 6.1%
Incurred Sample Reanalysis (ISR) Assessment Refer to Table 5 for ISR data		
Total number of samples analyzed		32
Total number of ISR samples analyzed		11
Percentage of ISR samples analyzed of total number of analyzed samples		34.4%
Total number of ISR samples analyzed within ±20% difference		11
Percentage within ±20.0% difference		100.0%

Source: \\CDSESUB1\EVSPROD\nda202155\0290\m5\53-clin-stud-rep\535-rep-effic-safety-stud\pediatric-venous-thromboembolism\5351-stud-rep-contr\b0661037\b0661037-analytical-reports.pdf
Note: Samples analyzed at (b) (4)
Abbreviations: CS, calibration standard; CV, coefficient of variation; ISR, incurred sample reanalysis; LC-MS/MS, liquid chromatography-tandem mass spectrometry; no., number; (b) (4); QC, quality control; QCGM, quantum continuous gradient model; QCH, quality control high sample; QCL, quality control low sample; QCM, quality control medium sample; RE, relative error

14.3.2. PD Assays

Antifactor Xa Activity

The factor Xa activity was determined ex vivo using a commercial STA® Liquid Anti-Xa kit (Diagnostica Stago, Inc.). The kit measures the ability of apixaban in a subject's sample to inhibit a known amount of factor Xa in the presence of antithrombin. The residual factor Xa activity is then quantified using a colorimetric reaction, where the color intensity is inversely proportional to the anticoagulant concentration. The summary of anti-Xa assay in-study performance is shown in Table 68.

Table 68. Assay Performance Summary of Liquid Anti-Xa Assay in Pivotal Study

Analyte Name	Liquid Anti-Xa Assay to Quantitate Apixaban (Eliquis®), APIX	
Assay Run Performance Refer to Table 1 for run assignments.	No. of Acceptable Runs 16	No. of Failed Runs 0
	Run Passing Rate (%) 100.0%	
Standard Curve performance **Overall (Mean) Inter-Assay** Refer to Table 2, Table 3, Table 4, Table 5, Table 6, Table 7, and Table 8 for calibration standard (CS) performance.	**Precision (%CV)** ≤1.8%	**Accuracy (%RE)** -8.2% to 1.4%
QC performance **Overall (Mean) Inter-Assay Performance** QC Samples (APIX1, APIX2) and HEPNEG[A], Table 9.	**Precision (%CV)** ≤10.9%	**Accuracy (%RE)** -19.7% to 9.4%
Dilution QC performance **Overall (Mean) Inter-Assay Performance** QCDIL Samples, Table 9	**Precision (%CV)** NA	**Accuracy (%RE)** -12.0% to 5.3%

Source: Appendix16.2.5.10, B0661037 Analytical Report - APIXABAN ANTI-XA ACTIVITY IN 3.2% SODIUM CITRATE HUMAN PLASMA, June 28, 2024
Abbreviations: APIX, chromogenic anti-Xa assay; CS, calibration standard; CV, coefficient of variation; HEPNEG, hepatitis negative; no., number; QCDIL, dilution quality control sample; RE, relative error

The performance of these bioanalytical methods in the pivotal clinical study was reviewed and deemed acceptable for sample analysis.

14.4. Immunogenicity Assessment—Impact of PK/PD, Efficacy, and Safety

Not applicable.

14.5. Pharmacometrics Assessment

14.5.1. Review Summary

This review aimed to assess if the proposed dosing regimen for pediatric patients from birth to less than 18 years of age is appropriate for the treatment of VTE and reduction in the risk of recurrent VTE.

The FDA's Office of Clinical Pharmacology review team agrees with the proposed dosage plan in pediatric subjects from birth to less than 18 years of age except for the 4 to <5 kg body weight category for the treatment of VTE and reduction in risk of recurrent VTE. The pediatric dosage proposed by the Applicant and OCP review team is presented in Table 69. The rationale for recommending an alternative pediatric dosage is described below.

The Applicant proposes a body weight tiered dosing regimen for pediatric subjects that was derived with an objective to achieve similar exposures as observed in adults.

In the current submission, the Applicant updated the previously available adult popPK model with data from studies evaluating pediatric subjects. PK simulations were performed to derive exposures (area under the concentration-time curve [AUC], C_{max}, and trough concentration [C_{trough}]) at Day 7 and at steady state beyond Day 7 in 1,000 virtual pediatric subjects who received the proposed body weight tiered dosing regimen (Table 69). The derived PK exposures of each body weight tier (mainly $AUC_{ss,T}$) were compared with the reference PK exposure range in adults receiving 10 mg BID (for comparison at Day 7) and 5 mg BID (for comparison beyond Day 7).

Furthermore, the OCP review team conducted additional simulations combining body weight groups 4 to <5 kg and 5 to <6 kg to receive apixaban 1 mg BID for the first 7 days and 0.5 mg BID from Day 8 onwards (Table 69). This was done to simplify dosing in neonates by merging two narrow 1 kg body weight bands and because the Applicant's proposed dosage in body weight group 4 to <5 kg resulted in relatively lower exposures compared to other pediatric weight groups.

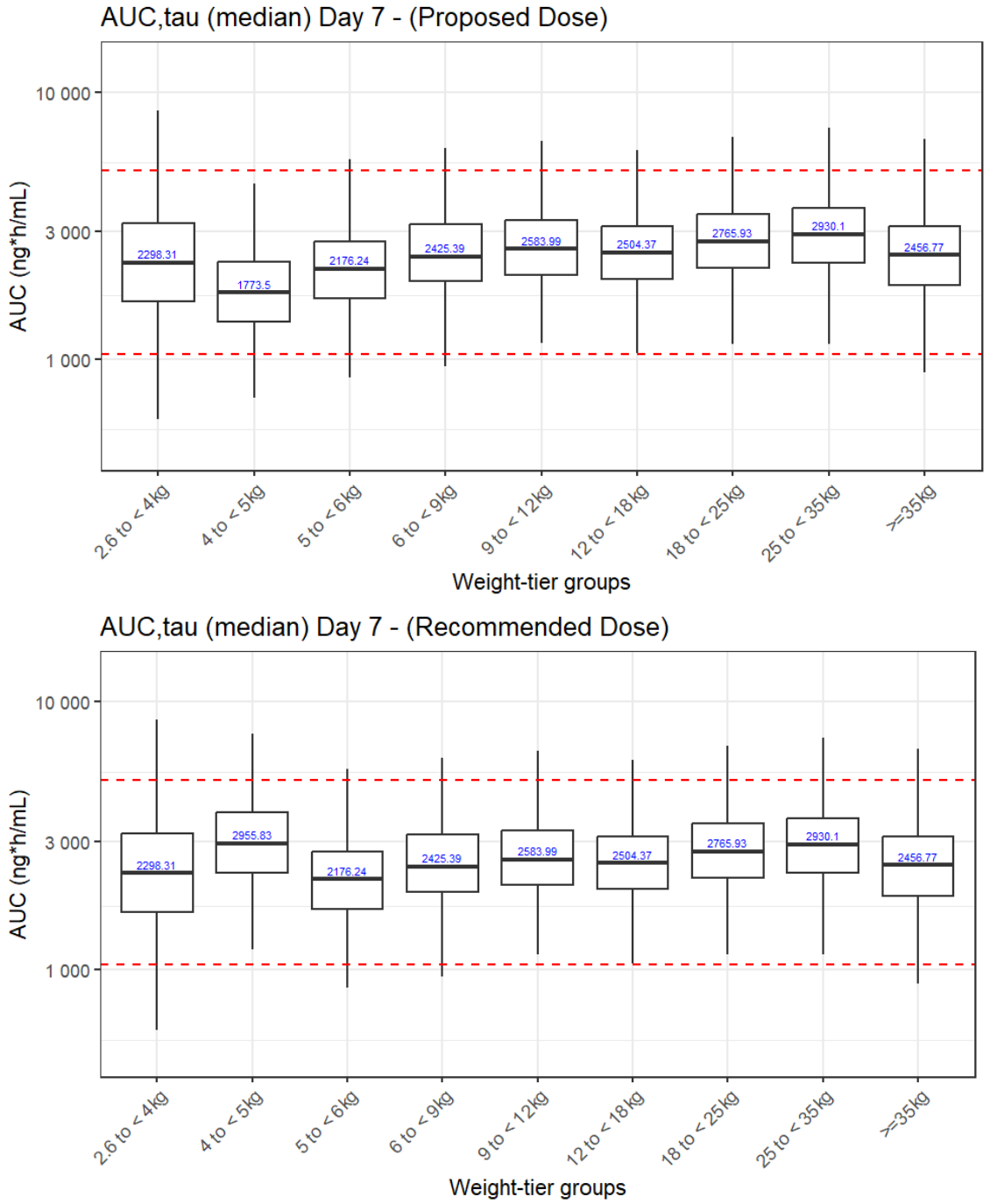
Table 69. Body Weight-Based Dose Regimen Comparing the Applicant's Proposal and OCP Team's Recommendation

Proposed by the Applicant			Recommended by the OCP Team		
Body Weight Tier	Day 1 to 7	Day 8 Onwards	Body Weight Tier	Day 1 to 7	Day 8 Onwards
2.6 to <4 kg	0.3 mg BID	0.15 mg BID	2.6 to <4 kg	0.3 mg BID	0.15 mg BID
4 to <5 kg	0.6 mg BID	0.3 mg BID	4 to <6 kg	1 mg BID	0.5 mg BID
5 to <6 kg	1 mg BID	0.5 mg BID			
6 to <9 kg	2 mg BID	1 mg BID	6 to <9 kg	2 mg BID	1 mg BID
9 to <12 kg	3 mg BID	1.5 mg BID	9 to <12 kg	3 mg BID	1.5 mg BID
12 to <18 kg	4 mg BID	2 mg BID	12 to <18 kg	4 mg BID	2 mg BID
18 to <25 kg	6 mg BID	3 mg BID	18 to <25 kg	6 mg BID	3 mg BID
25 to <35 kg	8 mg BID	4 mg BID	25 to <35 kg	8 mg BID	4 mg BID
≥35 kg	10 mg BID	5 mg BID	≥35 kg	10 mg BID	5 mg BID

Source: Reviewer's analysis
Abbreviations: BID, twice daily; OCP, FDA's Office of Clinical Pharmacology

The AUC comparison at Day 7 for the Applicant's proposed dosage as well as review team's recommended dosage is shown in Figure 25. The review team agrees with the Applicant's proposed dosages for all pediatric body weight tiers. Additionally, when the new recommended dosage for 4 to <5 kg was implemented, the range of PK exposures largely remained within the adult reference range (the red-dashed lines) and therefore, the originally proposed body weight tiers can be simplified by merging the 4 to <5 kg and 5 to <6 kg tier together.

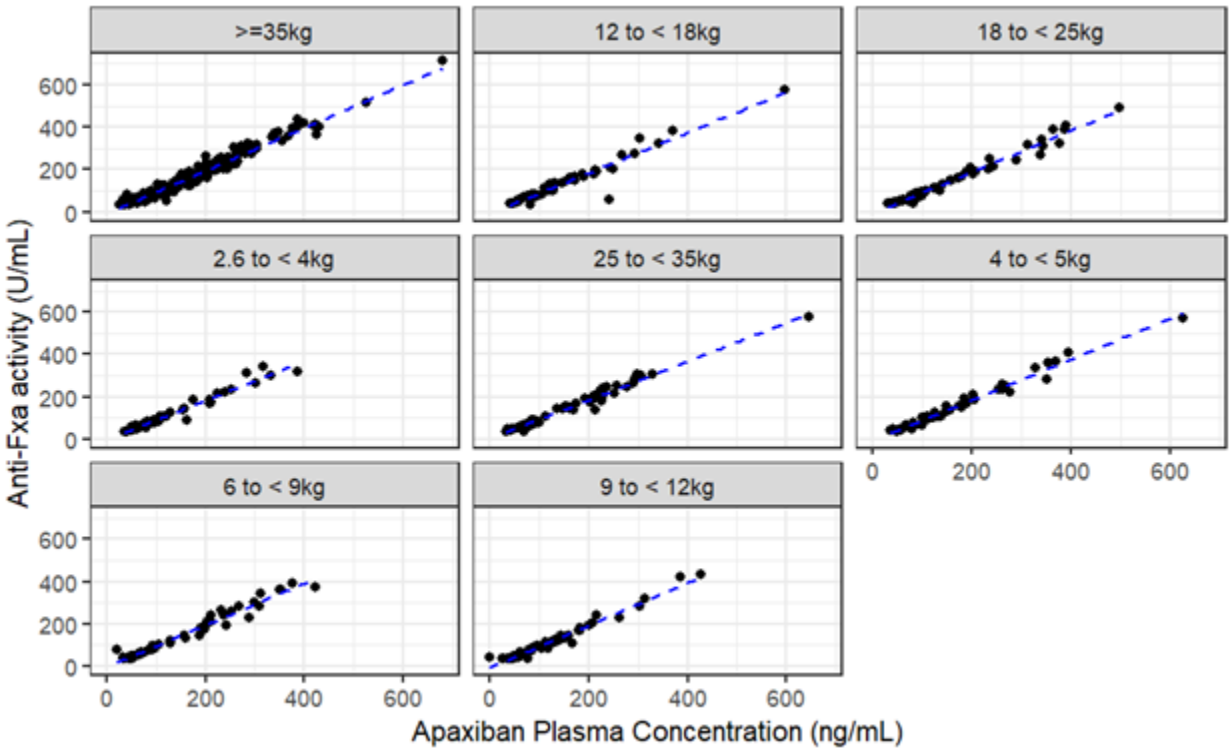
Figure 25. Comparing Exposures Between the Applicant's Proposed (Top Panel) vs. OCP Team's Recommended (Bottom Panel) Doses for the Body Weight Tier 4 to <6 kg



Source: Reviewer's Analysis
Abbreviations: AUC_T (AUC,tau), area under the concentration-time curve in one dosing interval; OCP, FDA's Office of Clinical Pharmacology; vs., versus

Previously, a PK/PD model was developed using data from healthy adults and adult patients treated for VTE. The relationship between apixaban concentration and AXA in adults was described using a linear model. A similar linear relationship (slope =0.926) was identified between apixaban concentration and AXA in the pediatric population (Figure 26).

Figure 26. Relationship Between Antifactor Xa Activity and Plasma Concentrations of Apixaban Stratified by Body Weight Group



Source: Reviewer's analysis

14.5.2. Review of Applicant's PopPK Model

Objective

- Characterize apixaban PK in pediatric subjects from birth to <18 years of age requiring anticoagulation for prevention and/or treatment of VTE and reassess covariate effects including the maturation function.
- Perform model-based simulations to support selection of a fixed-dose body weight tiered regimen of apixaban that achieves the target median apixaban $AUC_{ss,T}$ observed, following the approved dosage in adults.

Data

The final popPK analysis of pediatric subjects from birth to <18 years of age was performed by combining the apixaban concentration data collected in Study CV185325 with data collected in the previously completed adult and pediatric studies listed in Table 70. A summary of demographic characteristics and covariate statistics of the pivotal study stratified by body weight is presented in Table 71.

Model

A base model was developed by reestimating the previously developed final popPK model for Study CV185362 with the following features. Two-compartment model with first-order

absorption, dose-dependent bioavailability that included maturation function on apixaban CL/F based upon literature on CYP ontogeny and relevant covariate effects such as age group and patient type on K_a, dose and sprinkle capsule formulation on F1, body weight on CL/F, and V/F and age on Q/F. These covariate effects included in the base model were reevaluated as data became available to assess if apixaban PK was appropriately described in the younger subjects over the entire treatment duration in the pediatric studies. Following reestimation, delta plots were examined to confirm the adequacy of the covariate-parameter relationships described in the base model to ensure no other covariate effects remained unaccounted (Table 72).

Table 70. Summary of Clinical Studies Included in the Pharmacokinetic Analysis of Apixaban

Study Population (n)[a]	Study Design	Study Drug Dosage Regimens	Nominal PK Assessments	Analysis Type
Adult Studies				
CV185002A[18] Healthy adult male subjects 19 to 44 years of age (n = 36)	Phase 1, double-blind, randomized, placebo-controlled, escalating oral multiple-dose study to evaluate the safety, tolerability, PD, and PK	Apixaban 10, 25 mg QD and 2.5, 5, 10, 25 mg BID tablets or matching placebo / Oral / 7 days	Days 1, 4, 7: Predose (0 h); Post dose (h), BID and QD: 1, 2, 3, 4, 6, 9, 12, and 24; BID only: 13, 14, 15, 16, 18, and 21 Day 3, BID and QD: Predose (72 h) Day 7, BID and QD: 48 and 72 h Days 9 and 10 post dose	popPK
CV185013[19] Healthy adult male Japanese and Caucasian subjects 20 to 42 years of age (n = 22)	Phase 1, double-blind, randomized, placebo-controlled, sequential, 4-period, 4-treatment, ascending single-dose study to assess apixaban PK, PD, safety, and tolerability	Apixaban 2.5, 10, 25, and 50 mg tablets, or matching placebo / Oral / 4 ascending single doses	Predose (0 h); Post dose Day 1 (h): 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 18, 24, 36, 48, and 72	popPK
CV185018[20] Healthy and renally impaired adult male and female subjects 35 to 85 years of age (n = 2)	Phase 1, open-label, single-dose cohort study to assess the effect of stable renal impairment on single dose apixaban PK, PD, safety, and tolerability	Apixaban 10 mg tablets / Oral / single dose	Predose (0 h); Post dose Day 1 (h): 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 18, 24, 36, 48, 72, and 96	popPK
CV185022[21] Healthy adult male and female subjects ≤ 45 years of age and ≥ 65 years of age (n = 40)	Phase 1, open-label, 2 x 2 factorial designed, single-dose study to assess the effect of age and gender on apixaban single dose PK, PD, safety, and tolerability	Apixaban 20 mg tablets / Oral / single dose	Predose (0 h); Post dose Day 1 (h): 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 18, 24, 36, 48, 72, and 96	popPK
CV185046[22] Healthy adult male Japanese subjects 20 to 33 years of age (n = 18)	Phase 1, randomized, placebo-controlled, double-blinded, sequential, ascending multiple-dose study to assess apixaban PK, PD, safety, and tolerability	Apixaban 2.5, 5, and 10 mg tablets or matching placebo BID / Oral / 7 days	Days 1 and 7: Predose (0 h); Post dose (h): 1, 2, 3, 4, 5, 6, 8, 12, 13, 14, 15, 16, and 17 Days 2, 3, 5, 6, 8, and 9: Predose (0 h) or corresponding time Day 4: Predose (0 h), 12 h	popPK
Study Population (n)[a]	**Study Design**	**Study Drug Dosage Regimens**	**Nominal PK Assessments**	**Analysis Type**
Adult Studies (Continued)				
CV185058[23] Healthy adult male and female Chinese subjects (n = 12)	Phase 1, randomized, double-blind, placebo-controlled, single sequence, single- and multiple-dose study to assess apixaban PK, PD, safety, and tolerability	Apixaban 10 mg tablet BID / Oral / single dose, followed by 10 mg tablet / Oral / 6 days	Day 1: Predose (0 h); Post dose (h): 0.5, 1, 2, 3, 4, 6, 9, 12, 18, 24, 36, 48, 60, and 72 Days 7 and 8: Predose (0 h) Day 9: Predose (0 h); Post dose (h): 0.5, 1, 2, 3, 4, 6, 9, 12, 18, 24, 36, and 48	popPK
CV185059[24] Healthy adult male and female subjects ages 18 to 43 years old, weighing ≤ 50 kg, 65 kg to 85 kg, or ≥ 120 kg (n = 54)	Phase 1, open-label, single-dose cohort study to assess apixaban PK and PD	Apixaban 10 mg tablets / Oral / single dose	Day 1: Predose (0 h); Post dose (h): 0.5, 1, 2, 3, 4, 6, 9, 12, 18, 24, 36, 48, 60, and 72	popPK
CV185074[25] Healthy male and female subjects 20 years to 43 years of age (n = 14)	Phase 1, randomized, open-label, 2-period, 2-treatment, crossover study to assess the multiple-dose PK, PD, safety, and tolerability of apixaban and rivaroxaban	Apixaban 2.5 mg / Oral / 4 days Rivaroxaban 10 mg BID / Oral / QD for 4 days	(Apixaban only) Day 1: Predose (0 h) Day 4: Predose (0 h) Post dose (h): 0.5, 1, 2, 3, 4, 6, 8, 12, 12.5, 13, 14, 15, 16, 18, 20, 24, 36, 48, and 60	popPK
Pediatric Studies				
CV185079[4] Pediatric subjects (aged 6 to 18 years) with an indwelling central venous catheter (CVC) (n = 8)	Phase 1, open-label, sequential, ascending, multiple-dose study to evaluate the PK, PD, safety, and tolerability of apixaban in pediatric subjects	Apixaban oral solution, 0.4 mg/mL, administered by mouth or via an NGT or GT BID for 10 days 6 to < 12 years - 0.6 mg/m^2 BID 12 to < 18 years - 0.66 or 1.32 mg/m^2 BID	Day 1: Post dose (h): 0.5, 2 Day 2: Post dose (h): 0.5, 2 Days 5, 6, or 7: Predose (0 h); Post dose (h): 3	popPK
CV185118[5] Pediatric subjects at risk for VTE or ATE (n = 48)	Phase 1, single-dose cohort study to assess apixaban PK and PD. Interim analysis of 6 age groups: Age Group 1 (Neonates) - birth to < 28 days Age Group 2a: 9 m to < 2 y Age Group 2b: 28 days to < 9 m Age Group 3: 2 to < 6 y Age Group 4: 6 to < 12 y Age Group 5: 12 to < 18 y	Apixaban solution (0.4 mg/mL) or 0.1 mg capsule / administered by mouth or via an NGT or GT single dose Age Group 1: 0.1 mg Age Group 2a: 1.08 - 2.43 mg/m^2 Age Group 2b: 1.08 mg/m^2 Age Group 3: 1.17 mg/m^2 Age Group 4: 1.80 mg/m^2 Age Group 5: 2.19 mg/m^2	Age Group 1: Post dose (h): 2, 4, 12, and 24 Age Group 2a: Post dose (h): 0.5, 2, 4, 12, and 24 Age Group 2b: Post dose (h): 0.5, 2, 4, and 12 Age Groups 3-5: Post dose (h): 1, 2, 4, 6, 24, and 26	popPK

Study Population (n)[a]	Study Design	Study Drug Dosage Regimens	Nominal PK Assessments	Analysis Type
Pediatric Studies (Continued)				
CV185155[26] Pediatric patients with newly diagnosed ALL or LL treated with asparaginase (n = 224)	Phase 3 randomized, open label, multi-center study of the safety and efficacy of apixaban for thromboembolism prevention versus no systemic anticoagulant prophylaxis during induction chemotherapy	Apixaban solution (0.4 mg/mL), 2.5 mg tablet, or 0.5 mg tablet administered by mouth or via an NGT or GT as fixed-dose by body weight-tier below. ≥ 35 kg: 2.5 mg BID < 35 to 25 kg: 2 mg BID < 25 to 18 kg: 1.5 mg BID < 18 to 10.5 kg: 1 mg BID < 10.5 to 6 kg: 0.5 mg BID	Inpatient: 1 day prior to LP (eg, Day 7 if LP on Day 8) - Prior to AM dose and 1-4 h post dose. Outpatient: On the day of LP (eg, Day 8) - random pre-dose sample prior to LP Outpatient: Day 15 ± 5 - random post-dose sample collected 0.5 to 12 h after the AM dose and prior to the PM dose of apixaban	popPK and PK/PD (AXA)
CV185362[10] Pediatric subjects with congenital or acquired heart disease requiring chronic anticoagulation (n = 124)	Phase 2 randomized, open label, multi-center study of the safety and pharmacokinetics of apixaban versus vitamin K antagonist or LMWH	Apixaban solution (0.4 mg/mL), 5 mg tablet, 0.5 mg tablet, or 0.1 mg capsule administered by mouth or via an NGT or GT as fixed-dose by body weight-tier below. ≥ 35 kg: 5 mg BID < 35 to 25 kg: 4 mg BID < 25 to 18 kg: 3 mg BID < 18 to 12 kg: 2 mg BID < 12 to 9 kg: 1.5 mg BID < 9 to 6 kg: 1 mg BID < 6 to 5 kg: 0.5 mg BID < 5 to 4 kg: 0.3 mg BID < 4 to 3 kg: 0.2 mg BID	Day 1: Predose (Chromogenic FX), 4 h (3-8 h) (PK, AXA, Chromogenic FX) Week 2 ± 3 days: Predose (PK, AXA) Month 3 ± 2 weeks: 2 ± 1 Post dose (PK, AXA, Chromogenic FX) Month 6 ± 2 weeks: Predose (PK, AXA, Chromogenic FX)	popPK and PK/PD (AXA and FX)

Study Population (n)[a]	Study Design	Study Drug Dosage Regimens	Nominal PK Assessments	Analysis Type
Pediatric Studies (Continued)				
CV185325[b,27] Pediatric subjects requiring anticoagulation for the treatment of a venous thromboembolic event (n = 144)	Phase 4 randomized, open label, active-controlled, multi-center study of the safety, descriptive efficacy, and pharmacokinetics of apixaban versus SoC	Apixaban solution (0.4 mg/mL), 5 mg tablet, 0.5 mg tablet, or 0.1 mg sprinkle capsule administered by mouth as fixed-dose by body weight-tier as shown below. Subjects aged 28 days and older:[c] ≥ 35 kg: 5 mg BID < 35 to 25 kg: 4 mg BID < 25 to 18 kg: 3 mg BID < 18 to 12 kg: 2 mg BID < 12 to 9 kg: 1.5 mg BID < 9 to 6 kg: 1 mg BID < 6 to 5 kg: 0.5 mg BID < 5 to 4 kg: 0.3 mg BID Neonate subject aged ≤ 27 days (PK cohort): ≥ 2.6 kg: 0.1 mg BID	Age Groups 1 to 4: Day 14: Predose (PK, AXA) and 2-4 h post dose (PK, AXA) Day 42 (if sample not collected on Day 14): Predose (PK, AXA) and 2-4 h post dose (PK, AXA) Age Group 4 (Neonate PK cohort) only: Day 1: 2-4 h post-first dose and 12 ± 1 h post-first dose sampling but prior to 2nd dose Day 2: 24 ± 1 h post-first Day 1 dose (but sampling prior to the first dose of apixaban on Day 2)	popPK and PK/PD (AXA)

Source: Applicant's Study CV185325 Pharmacometric Report (BMS-562247), Table 3.1-1, Page 45-8
[a] Number of subjects with evaluable apixaban PK concentration
[b] Study CV 185325 is a new study included in the popPK and PK/PD analyses reported herein. Pediatric studies other than Study CV 185325 (Studies CV185079, CV185118, CV185155, and CV185362) were included in previous popPK analytes. The two previous PK/PD analyses using these pediatric studies were performed separately using Studies CV185079/CV185118 and Studies CV185155/CV185362
[c] Dose regimens are described for Day 8 of treatment and thereafter. Dose regimens during Days 1-7 of treatment were double the amount described.
Abbreviations: AM, ante meridien, morning; ALL, acute lymphoblastic leukemia; ATE, arterial thromboembolism; AXA, antifactor Xa activity; BID, twice daily; CVC, central venous catheter; FX, factor X; GT, gastric tube; LL, lymphoblastic leukemia; LMWH, low molecular weight heparin; LP, lumbar puncture; n, planned number of subjects; NGT, nasal gastric tube; PD, pharmacodynamics; PK, pharmacokinetics; popPK, population pharmacokinetics; QD, once daily

Table 71. Summary Statistics Of Baseline Characteristics in the Pharmacokinetic Analysis of Apixaban

Variable		2.6 to < 4 kg (n = 9)	4 to < 5 kg (n = 1)	6 to < 9 kg (n = 12)	9 to < 12 kg (n = 6)	12 to < 18 kg (n = 2)	18 to < 25 kg (n = 6)	25 to < 35 kg (n = 14)	≥ 35 kg (n = 94)	Overall (n = 144)
Age (years)	Mean (SD)	0.0558 (0.0117)	0.054 (NA)	0.951 (0.42)	1.49 (0.395)	3.25 (1.87)	6.24 (1.41)	8.86 (2.58)	15.5 (2.18)	11.5 (6.33)
	Median	0.054	0.054	0.762	1.53	3.25	5.96	8.59	16.2	14.4
	Min, Max	0.033, 0.071	0.054, 0.054	0.591, 1.74	0.958, 1.85	1.92, 4.57	4.94, 8.79	5.39, 14.3	7.79, 18	0.033, 18
Estimated GFR (mL/min/1.73 m²)[a]	Mean (SD)	98.6 (58.8)	NA (NA)	121 (45.1)	196 (125)	193 (65.4)	236 (80.7)	183 (80.3)	157 (39.2)	158 (59.2)
	Median	78	NA	120	145	193	254	191	151	149
	Min, Max	42.3, 238	NA, NA	66.6, 204	111, 434	147, 239	128, 322	0.111, 374	65.6, 315	0.111, 434
	Missing	0	1	0	0	0	0	0	1	2
Capped eGFR (mL/min/1.73 m²)[b]	Mean (SD)	85.5 (29.5)	NA (NA)	101 (22.2)	117 (4.23)	120 (0)	120 (0)	111 (32)	118 (7.05)	114 (17.2)
	Median	78	NA	110	120	120	120	120	120	120
	Min, Max	42.3, 120	NA, NA	66.6, 120	111, 120	120, 120	120, 120	0.111, 120	65.6, 120	0.111, 120
	Missing	0	1	0	0	0	0	0	1	2
Baseline Body Weight (kg)	Mean (SD)	3.28 (0.489)	4.6 (NA)	7.49 (0.896)	10.5 (1.03)	14.1 (1.13)	19.5 (1.35)	29.8 (3.07)	73.9 (25.9)	53.5 (35.6)
	Median	3.2	4.6	7.65	10.6	14.1	19.1	29	66.8	54.7
	Min, Max	2.6, 3.9	4.6, 4.6	6, 8.8	9.3, 11.8	13.3, 14.9	18.2, 22.1	25.7, 34.9	37.2, 148	2.6, 148
Age Group N (%)	< 28 d	9 (100)	1 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	10 (6.94)
	28 d to < 2 y	0 (0)	0 (0)	12 (100)	6 (100)	1 (50)	0 (0)	0 (0)	0 (0)	19 (13.2)
	2 y to < 12 y	0 (0)	0 (0)	0 (0)	0 (0)	1 (50)	6 (100)	13 (92.9)	8 (8.51)	28 (19.4)
	12 y to < 18 y	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (7.14)	86 (91.5)	87 (60.4)
Race, N (%)	White	8 (88.9)	1 (100)	12 (100)	6 (100)	1 (50)	6 (100)	7 (50)	71 (75.5)	112 (77.8)
	Black	1 (11.1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	4 (28.6)	15 (16)	20 (13.9)
	AI/AN	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (7.14)	0 (0)	1 (0.694)
	Asian	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (7.14)	3 (3.19)	4 (2.78)
	Others	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	4 (4.26)	4 (2.78)
	Missing	0 (0)	0 (0)	0 (0)	0 (0)	1 (50)	0 (0)	1 (7.14)	1 (1.06)	3 (2.08)

Source: Applicant's Study CV185325 Pharmacometric Report (BMS-562247), Table 3.3.1.6-4, Page 64
[a] Calculated using Schwartz method
[b] Estimates of GFR above a physiologically plausible value of 120 mL/min/1.73 m^2 were truncated to that value.
Abbreviations: AI/AN, American Indian/Alaskan native; eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; max, maximum; min, minimum; n, number of subjects; N, number of records; NA, not applicable; SD, standard deviation

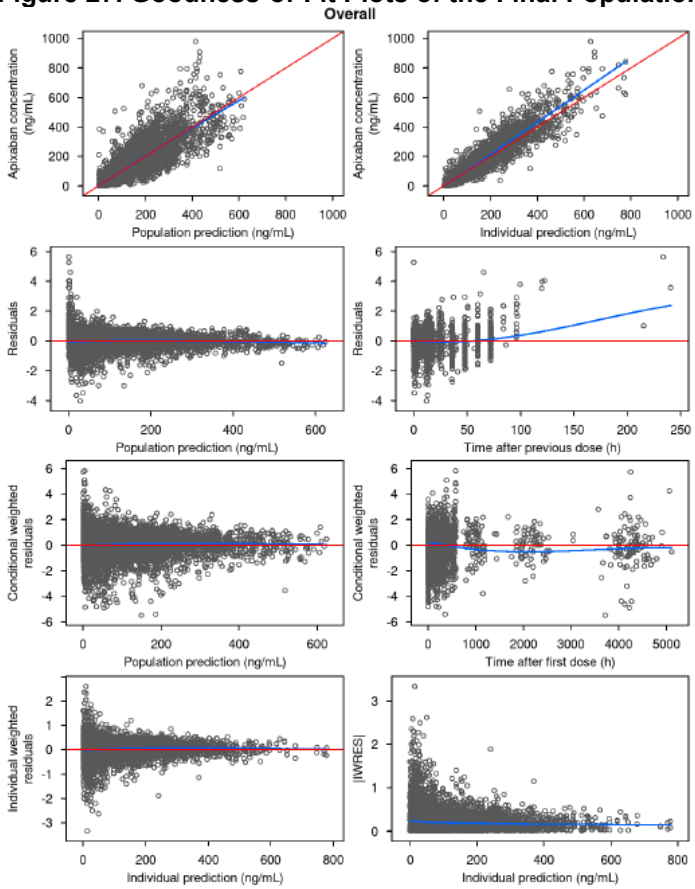
Results

The final popPK model was consistent with the structure of the base popPK model of a two-compartment model with first-order absorption, dose-dependent F1, and first-order elimination that also included the covariate effects added to the base model described in the pediatric data. The final parameter estimates for the model with corresponding precision estimates (% relative standard error) are provided in Table 72. The GoF plots for the overall population are shown in Figure 27.

The relationships between body weight and apixaban CL/F and V_c/F were described using power functions, indicating that both parameters would increase less than proportionally with increasing body weight. The effect of age on Q/F was also described by a power function, indicating that Q/F would increase less than proportionally with increasing age. The estimated K_a in pediatric subjects aged birth to 18 years (1.28 1/h) was 2.5-fold higher than in adult subjects (0.519 1/h).

The prediction-corrected visual predictive check (pc-VPC) was performed by a Monte Carlo simulation in which 1,000 replicates of the analysis dataset were simulated. The 5th, median, and 95th percentiles of the distributions of simulated and observed concentrations, as well as the 95% CI around the simulated median and percentiles, were calculated from both the simulated and observed data for comparison. The pc-VPC is plotted based on the observed data overlaid to visually assess the agreement between the model-based simulated data and the observed data as shown in Figure 28.

Figure 27. Goodness-of-Fit Plots of the Final Population Pharmacokinetic Model for Apixaban



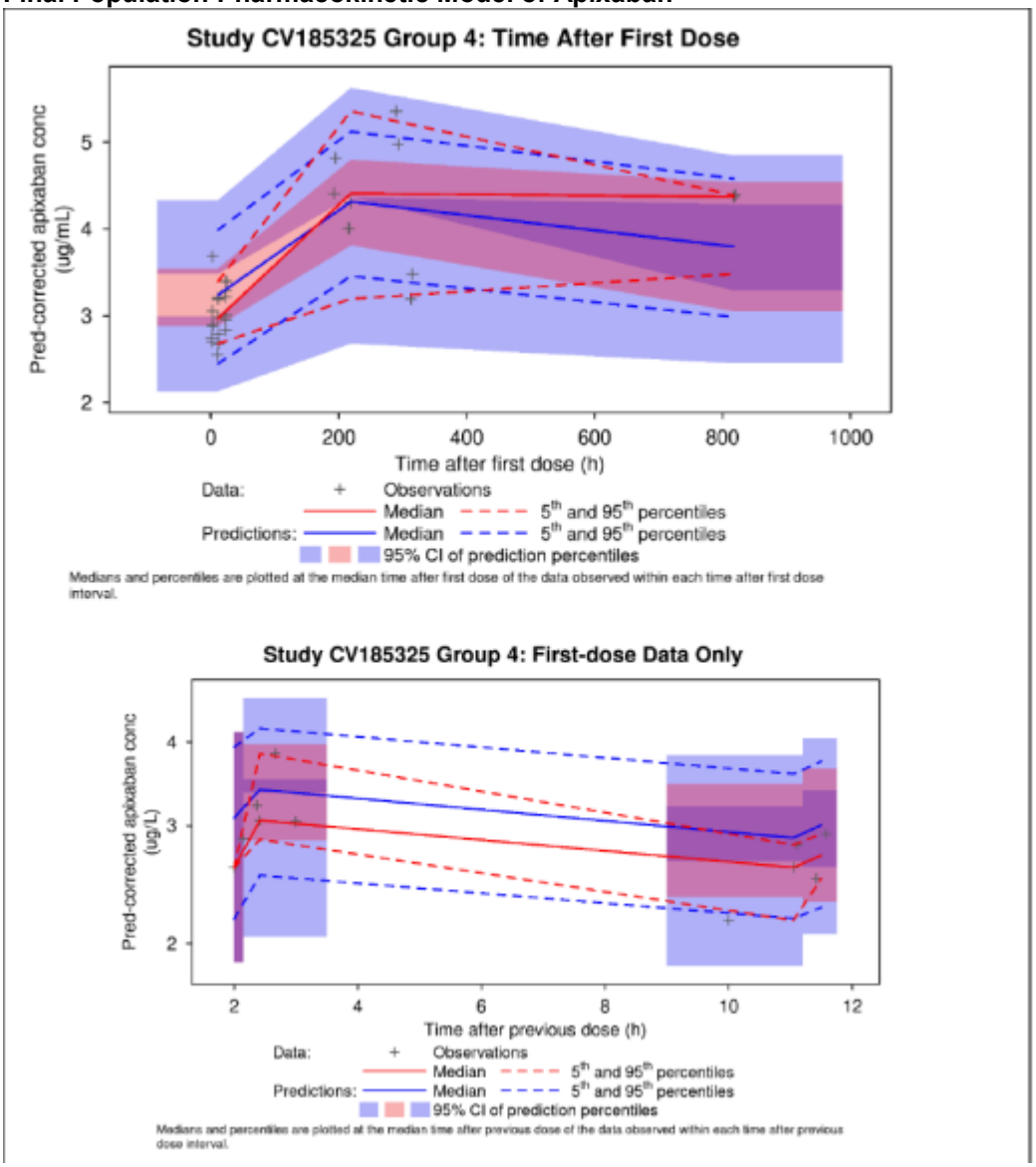
Source: Applicant's Study CV185325 Pharmacometric Report (BMS-562247), Figure 5.1.2-1, Page 126

Table 72. Parameter Estimates of the Final Population Pharmacokinetic Model of Apixaban

Parameter Label	Parameter	Estimate[a]	Standard Error (%RSE)[b]	Bootstrap Derived 95% Confidence Interval[c]
F1: LOGIT Max Reduction in F1 at Dose > 2.5 mg [-]	θ_7	-0.39	0.0339 (8.7)	(-0.632) - (-0.163)
Vc/F: Exponent of (WT/36.1) for Vc/F [-]	θ_8	0.822	0.0311 (3.78)	0.768 - 0.886
CL/F: Exponent of (WT/36.1) for CL/F [-]	θ_9	0.66	0.0205 (3.11)	0.615 - 0.706
Q/F: Exponent of (AGE/10.9) for Q/F [-]	θ_{10}	0.79	0.0453 (5.73)	0.632 - 0.956
Ka: Effect of Age Birth to 18 Years on Ka [-]	θ_{11}	1.48	0.262 (17.6)	1.01 - 2.19
CL/F: Non-Renal Ontogeny Function - Shape Parameter [-]	θ_{12}	0.83 FIXED	NA	NA
CL/F: Non-Renal Ontogeny Function - AGE50 [years]	θ_{13}	0.244 FIXED	NA	NA
F1: Relative F1 for Neonatal Formulation [-]	θ_{14}	1.1 FIXED	NA	NA
CL/F: Non-Renal Ontogeny Function F_{Birth} [-]	θ_{15}	0.05 FIXED	NA	NA
Ka: Effect of Cancer Subject on Ka [-]	θ_{16}	-0.972	0.217 (22.3)	(-1.37) - (-0.548)
CL/F: Effect of CAHD Subject on CL/F [-]	θ_{17}	-0.204	0.0336 (16.5)	(-0.284) - (-0.126)
Vc/F: Effect of VTE Treated Subject on Vc/F [-]	θ_{18}	0.228	0.0597 (26.2)	0.12 - 0.35
Random Effects				
ZKA	$\omega_{1,1}$	0.306 (0.554)	0.0395 (12.9)	0.21 - 0.414
ZCL	$\omega_{2,2}$	0.129 (0.359)	0.0061 (4.73)	0.1 - 0.162
ZVC	$\omega_{3,3}$	0.161 (0.401)	0.0178 (11)	0.12 - 0.21
ZVC:ZCL	$\omega_{3,2}$	0.0852 (0.292)	0.0102 (12)	0.0592 - 0.113
Residual Error[d]				
Additive RV on Log Conc for Study CV185155 [-]	$\sigma_{1,1}$	0.731 (0.855)	0.0374 (5.11)	0.525 - 0.979
Additive RV on Log Conc for Other Studies [-]	$\sigma_{2,2}$	0.114 (0.337)	0.00123 (1.08)	0.104 - 0.125

Source: Applicant's Study CV185325 Pharmacometric Report (BMS-562247), Table 5.1.2-1, Page 124
[a] Random effect and residual error parameter estimates are shown as variance (standard deviation) for diagonal and off-diagonal elements.
[b] %RSE is the relative standard error (standard error as a percentage of estimate).
[c] Confidence interval values are taken from bootstrap calculations (999 successful out of a total of 1,000). Confidence intervals of random effects and residual error parameters are for variance or covariance.
[d] The calculated correlation coefficient (r) of the off-diagonal omega was as follows: 0.591 for ZCL:ZVC.
Abbreviations: CL/F, apparent oral clearance; conc, concentration; F1, bioavailability; K_a, absorption rate constant; LOGIT, a logistic regression model function; max, maximum; RSE, relative standard error; RV, random variable; Vc/F, apparent volume of distribution of the central compartment; WT, weight; ZCL, interindividual variability in CL; ZKA, interindividual variability in K_a; ZVC, interindividual variability in Vc

Figure 28. Prediction-Corrected Visual Predictive Check by Group Within Study CV185325 for the Final Population Pharmacokinetic Model of Apixaban



Source: Applicant's Study CV185325 Pharmacometric Report (BMS-562247), Figure 5.1.2-1, Page 126
Abbreviations: CI, confidence interval; conc, concentration; pred, predicted

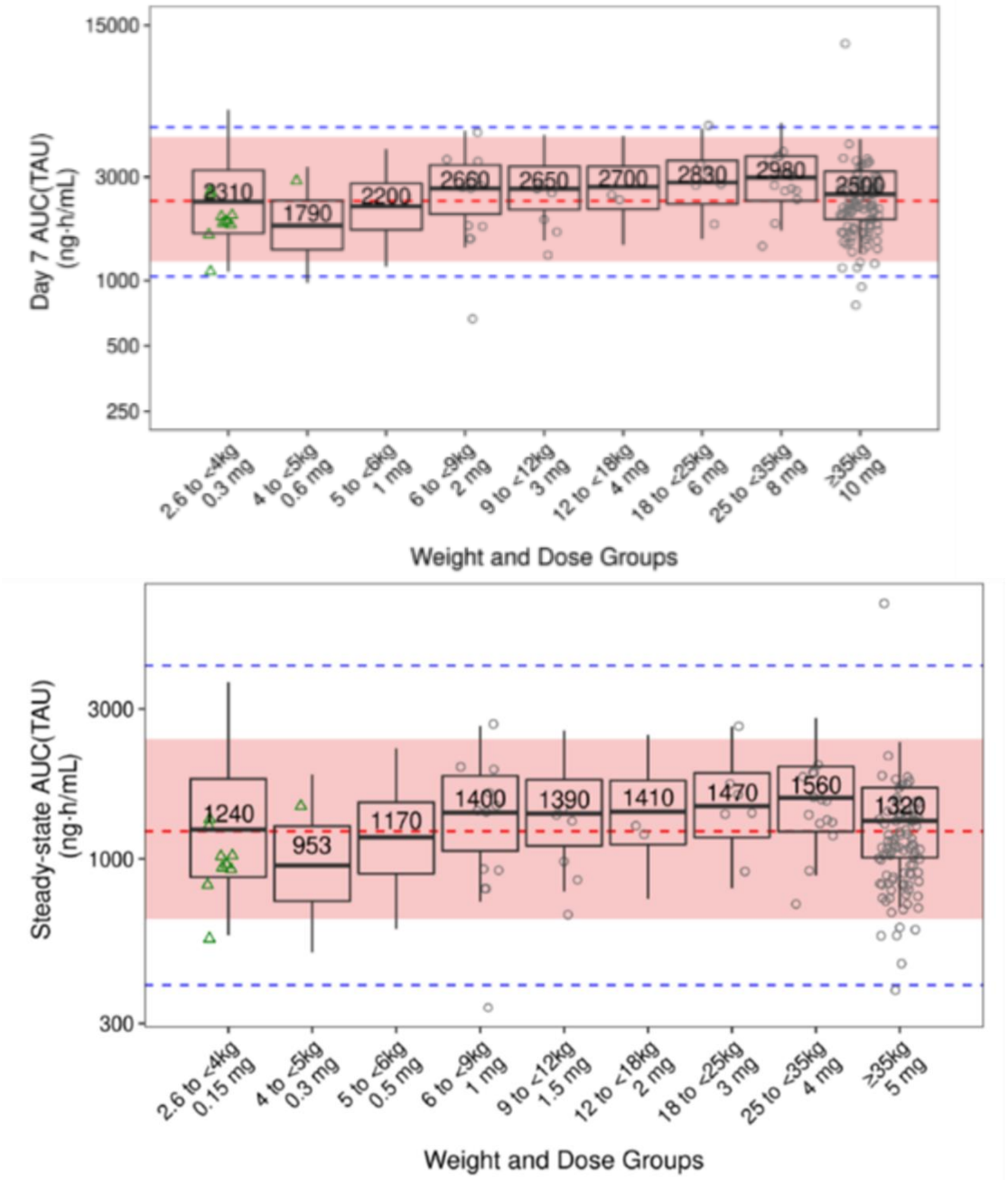
PK simulations were performed to assess whether exposures resulting from the proposed body weight tiered dosing regimen in pediatric subjects (as outlined in Table 73) matched the reference adult exposures. The exposure targets were based on the median daily $AUC_{ss,T}$ observed in the AMPLIFY study in adults receiving apixaban 10 mg BID for the first 7 days, and then 5 mg BID thereafter. A total of 1,000 virtual pediatric subjects per body weight tier were used for the stochastic simulation. Age, body weight, and sex were sampled by body weight tier from the CDC dataset as a vector of covariates. Model-predicted Day 7 AUC_T and $AUC_{ss,T}$ exposures from the pediatric subjects in Study CV185325 were overlaid onto the body weight tier simulated exposure boxplots (Figure 29).

Table 73. Dosing Regimens by Body Weight Tier Used in Simulations

Body Weight-Tier	Days 1 to 7 (Loading Dose)	Dosing Regimen From Day 8 Onward (Maintenance Dose)
≥ 35 kg	**10 mg BID**	**5 mg BID**
25 to < 35 kg	8 mg BID	4 mg BID
18 to < 25 kg	6 mg BID	3 mg BID
12 to < 18 kg	4 mg BID	2 mg BID
9 to < 12 kg	3 mg BID	1.5 mg BID
6 to < 9 kg	2 mg BID	1 mg BID
5 to < 6 kg	1 mg BID	0.5 mg BID
4 to < 5 kg	0.6 mg BID	0.3 mg BID
2.6 to < 4 kg	0.3 mg BID	0.15 mg BID

Source: Applicant's Study CV185325 Pharmacometric Report (BMS-562247), Table 6.3-1, Page 187
Abbreviation: BID, twice daily

Figure 29. Simulated Exposures at Day 7 (Top-Panel) and Steady-State (Bottom-Panel) for Virtual Pediatric Subjects by Body Weight Tiers



Source: Applicant's Study CV185325 Pharmacometric Report (BMS-562247), Figures 5.1.4.2-5 & 5.1.4.2-6, Page 176-7
Abbreviation: AUC_T (AUC[TAU]) area under the concentration-time curve in one dosing interval

Based on the dosing regimen simulations as outlined in Table 73, the median and 5th to 95th percentile of predicted Day 7 AUC_T and steady-state $AUC_{ss,T}$ values for most pediatric body weight groups generally matched the median adult AUC and lied within the adult range for receiving apixaban 10 mg BID and 5 mg BID, respectively. The proposed body weight tier dosing regimen as shown in Table 73 is largely acceptable for pediatric patients from birth to less than 18 years old. See Section 14.5.3 for the proposal to combine weight groups 4 to <5 kg and 5 to <6 kg.

The GoF plots (Figure 27) generally indicate that there is a concurrence between the observed and predicted concentration, as shown by the alignment of blue loess lines with the lines of identity on observed versus population as well as individual predicted concentrations. In addition, the data appear to be distributed nearly equally along the lines of identity, all suggesting that the selected final model describes the observed data. Further, the pc-VPC (Figure 28) plots also indicate that the median, 5^{th} and 95^{th} percentiles of the observed and predicted concentrations appear in alignment, which solidifies further that the model captures both the central tendency (median) and the magnitude of the variability (5^{th} and 95^{th} percentiles) of the observed data. Besides, the performance of the final model was ascertained when the model was used to simulate exposures that generally aligned with the observed exposures (Figure 29). Overall, the model is considered acceptable to describe the observed data and can be used for simulations.

14.5.3. Reviewer's Analysis To Refine the Proposed Body Weight Tiered Dosing Regimen

Background

In the pediatric body weight group 4 to <5 kg, with the proposed dose of 0.6 mg BID for the first 7 days and 0.3 mg BID from Day 8 onwards, the Day 7 AUC_T and $AUC_{ss,T}$ were relatively lower compared to other pediatric body weight groups. Therefore, the aim of the pharmacometrics analysis was to simplify the proposed dosing in neonates and young infants by merging the 4 to <5 kg and 5 to <6 kg body weight groups to receive apixaban doses of 1 mg BID for first 7 days and 0.5 mg BID from Day 8 onwards. PK simulations were done using the Applicant's popPK model.

Objective

- Simulate Day 7 and steady-state exposures (C_{max}, minimum concentration, and AUC) based on the proposed body weight tiered dosing regimens in virtual pediatric subjects
- Match the simulated Day 7 and steady-state AUC_T of each body weight band in the pediatric virtual subject population with that of adults
- Simulate an alternative dosing regimen for body weight group 4 to <5 kg

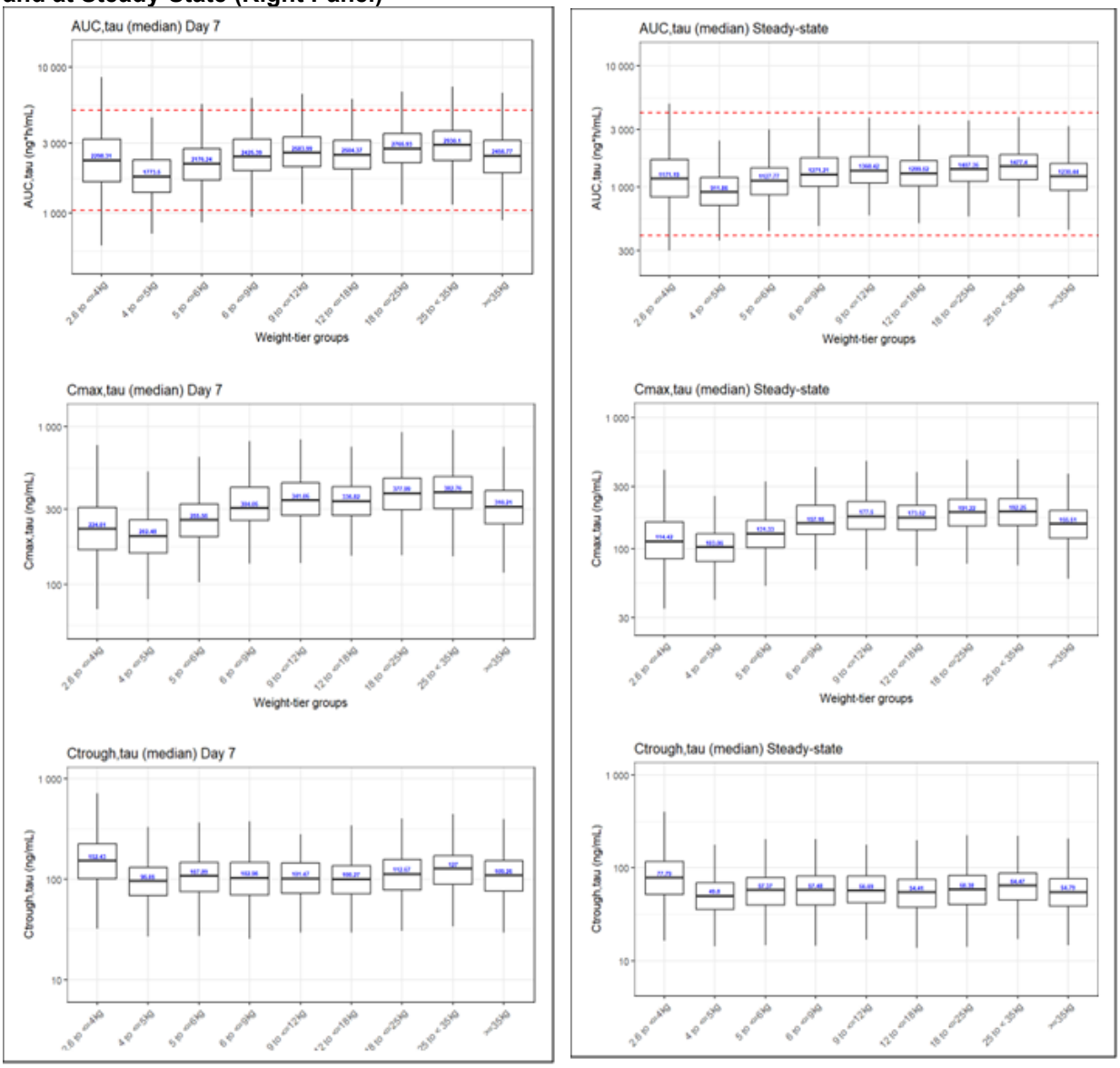
Methods

Initially, the Applicant-supplied, NONMEM-based, model file was rerun to verify model appropriateness. The GoF plots were plotted in R version 4.3.3 and inspected. Once the final model was established, it was used for stochastic simulations based on the proposed dosing regimen for 1,000 virtual pediatric subjects in each body weight category as performed by the Applicant. The simulated exposures were visualized as box-plots. Besides, to explore alternative dosing for the body weight group 4 to <5 kg, additional simulation was done using apixaban doses of 1 mg BID for 7 days, followed by 0.5 mg BID at steady state, the next higher dosing regimen, aiming to simplify the proposed dosing in neonates and young infants.

Results and Conclusion

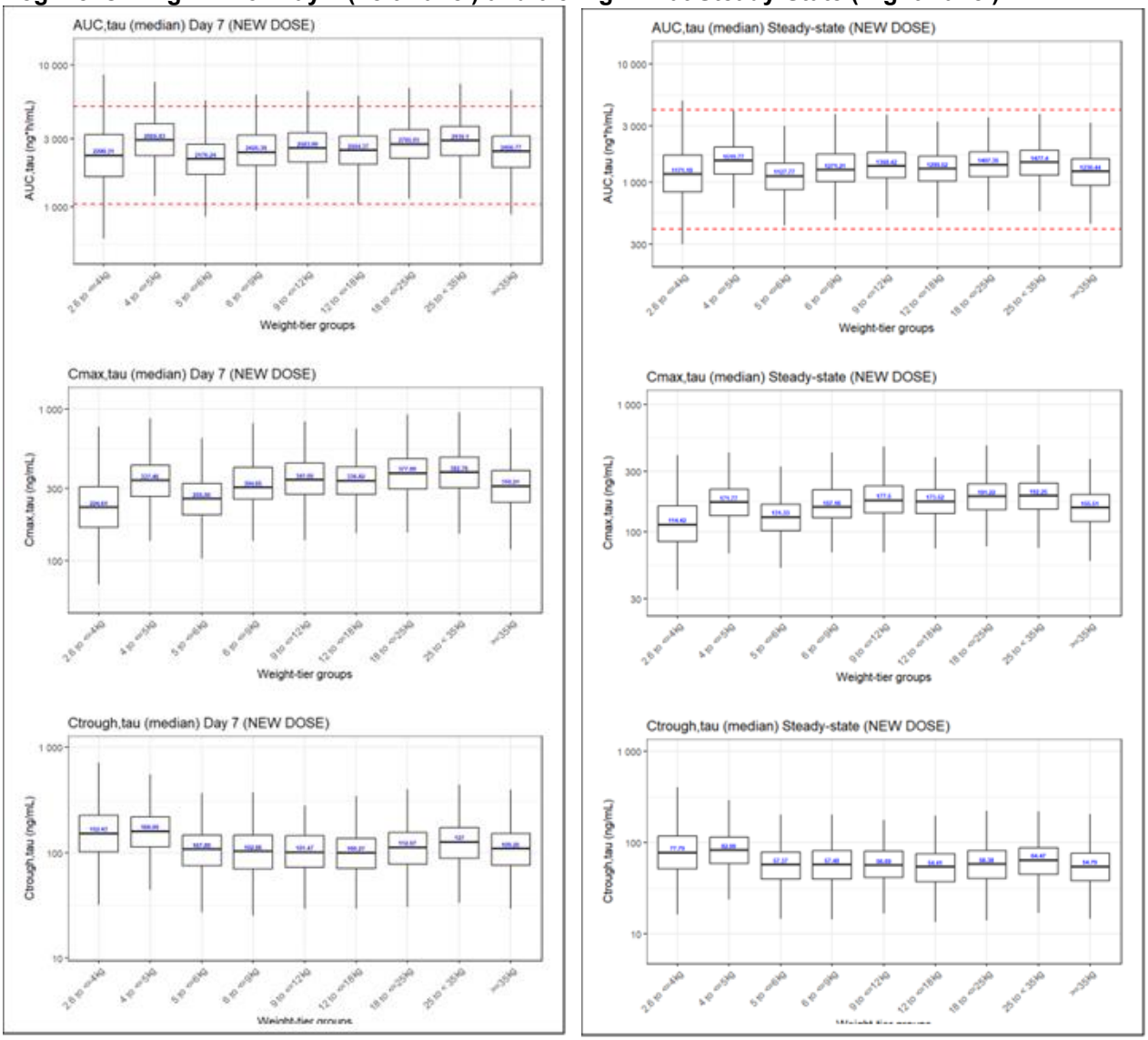
Simulated exposures (C_{max}, C_{trough}, and AUC_T) derived based on the proposed body weight tiered dosing regimens for pediatric subjects fall within the ranges of those observed in the adults (Figure 30), confirming that the proposed dosing regimens are appropriate. Further, in an effort to combine the body weight group 4 to <5 kg with those in the group 5 to <6 kg, the additional simulation conducted by the review team using 1 mg BID for 7 days followed by 0.5 mg BID in group 4 to <5 kg led to comparable exposures with other pediatric body weight groups. This suggests that the 4 to <5 kg and 5 to <6 kg body weight groups can be combined.

Figure 30. Simulated Exposures Based on the Proposed Dosing Regimens on Day 7 (Left Panel) and at Steady-State (Right Panel)



Source: Reviewer's analysis
Abbreviations: AUC_T (AUC,tau), area under the concentration-time curve in a dosing cycle; $C_{max,T}$, maximum concentration in a dosing interval; $C_{trough,T}$, trough concentration in a dosing interval

Figure 31. Simulated Exposures for Body Weight Tier 4 – 5 kg After the Alternative Dosing Regimens 1 mg BID for Day 7 (Left Panel) and 0.5 mg BID at Steady-State (Right Panel)



Source: Reviewer's analysis
Abbreviations: AUC_T (AUC,tau), area under the concentration-time curve in a dosing cycle; BID, twice daily; $C_{max,tau}$, maximum concentration in a dosing interval; $C_{trough,tau}$, trough concentration in a dosing interval

14.5.4. Applicant's PK/PD Analysis

Review Summary

Previously, a PK/PD model was developed using data from healthy adults and adult subjects treated for VTE. The relationship between apixaban concentration and AXA in adults was described using a linear model with a fixed intercept of zero. In the current submission, the Applicant conducted a PK/PD analysis primarily to explore the relationships between apixaban and AXA concentrations in pediatric subjects to compare it qualitatively to adults.

Consistent with the previous observation in adults, the Applicant concluded that a linear mixed effect regression model described the relationship between apixaban concentration and AXA concentration in the current pediatric population with a slope. Further, this relationship was consistent across all body weight tiers.

The review team reproduced the Applicant's PK/PD model and overall confirmed that the relationship between apixaban and AXA concentrations is described by a linear mixed effect regression model. Further, the review team also agrees with the proposed subsection 12.2 of the USPI labeling statement claiming that in pediatric subjects treated with apixaban, the relationship between AXA and plasma concentration is linear.

Objective

This review aimed to assess the PK/PD relationship between apixaban concentration and AXA in pediatric subjects requiring anticoagulation for prevention and/or treatment of VTE. The PK/PD analyses were performed using the apixaban concentrations and AXA concentrations collected from Studies CV185155, CV185362, and CV185325. Details of the studies, including dosing, are presented in Table 70.

Methods

Although it was expected that a linear function would adequately describe the pooled dataset, several approaches such as simple linear regression with an intercept fixed at zero, linear mixed effects model with an intercept fixed at zero, and IIV estimated on the slope parameter and nonlinear models (simple E_{max} and sigmoidal E_{max}) were initially used to assess the relationship between AXA concentration and apixaban concentration. The predictive performance of the selected final PK/PD model was evaluated via visual predictive check (VPC) diagnostic plots.

Results

Model Selection

Both simple linear regression and linear mixed effect models generally described the data well. Based on the objective function value, the linear mixed effect model showed significantly lower value (p value <0.0001). The model parameter estimates of the final PK/PD model are presented in Table 74. Further, to estimate a separate slope parameter for each body weight tier, the linear mixed effects model was evaluated by each stratum, which did not result in a significant decrease in the objective function (p value =0.0118). Visual inspection was coupled with Akaike information criterion values to show that the linear mixed effects model resulted in a better fit to the data than the nonlinear model. Therefore, the linear mixed effects model with a single overall slope parameter was selected as the final PK/PD model to describe the relationship between apixaban concentration and AXA concentration **(**Figure 32**)**.

Table 74. Summary of Model Parameters and Standard Errors for the Final PK/PD Model of Apixaban for Antifactor Xa Activity in Pediatric Population

Fixed Effect				
Parameter	Value	Standard Error	Bootstrap Derived 95% CI	Bootstrap Derived Median
Slope	0.926	0.00577	0.910 - 0.930	0.920
Random Effects				
Parameter	Value		Residual	
Standard Deviation	0.079		12.7	

Source: Applicant's Study CV185325 Pharmacometric Report (BMS-562247), Table 5.2.1-1, Page 179
Abbreviations: CI, confidence interval; PD, pharmacodynamic; PK, pharmacokinetic

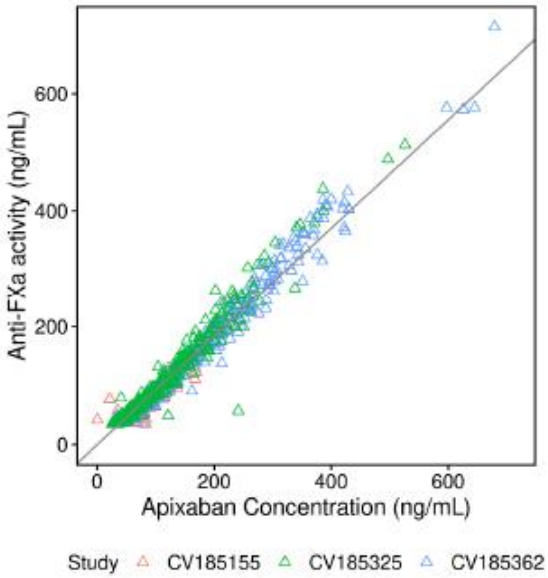
Model Evaluation

The final PK/PD model was evaluated by performing a VPC. One thousand replicates of the analysis dataset were simulated using the final PK/PD model. The median, 5th, and 95th percentiles of the prediction interval were overlaid onto the observed data. As shown in Figure 33, the final model captured the variability and the relationship between AXA concentration and apixaban concentration in the analysis dataset reasonably well.

Conclusion

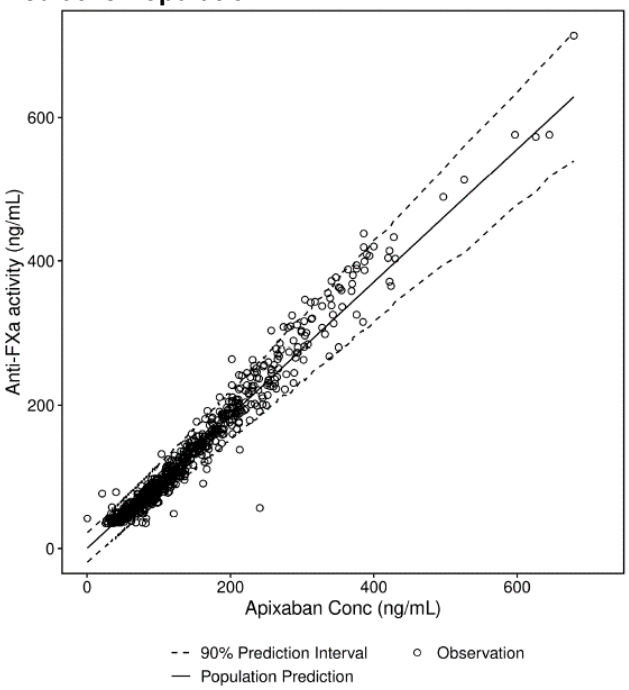
The final PK/PD model that described the relationship between apixaban concentration and AXA concentration in pediatric subjects was a linear mixed effect regression model with a slope parameter of 0.926.

Figure 32. Linear Relationship Between Antifactor Xa Activity and Apixaban Concentrations in Pediatric Population



Source: Applicant's Study CV185325 Pharmacometric Report (BMS-562247), Figure 5.2.1-1, Page 180
Abbreviation: FXa, factor Xa

Figure 33. Visual Predictive Check of the Final Apixaban PK/PD Model for Antifactor Xa Activity in Pediatric Population



Source: Applicant's Study CV185325 Pharmacometric Report (BMS-562247), Figure 5.2.2-1, Page 181
Abbreviation: FXa, factor Xa

The GoF plot (Figure 32) indicates that there is a linear relationship between the AXA (PD) and plasma concentrations of apixaban, suggesting that the selected linear regression PK/PD model appropriately describes the relationship. Further, based on the VPC (Figure 33) plot, the median, 5th and 95th percentiles of the observed data are largely contained within the prediction intervals. Overall, the model is acceptable to describe the relationship between the AXA and plasma concentrations of apixaban, and the conclusions drawn based on the analysis appear accurate.

14.5.5. Reviewer's PK/PD Analysis

Background

Based on the current pediatric data, the Applicant developed a PK/PD model and updated the labeling statement in subsection 12.2. claiming that the relationship between AXA and plasma concentration is linear with a slope close to 1. Therefore, the review team focused to verify this labeling statement.

Objectives

Analysis objectives were to:

- Verify the PK/PD model
- Confirm the linear relationship between AXA and plasma concentration
- Evaluate whether the slope (parameter estimate) is similar for each body weight tier

Methods

Initially, the Applicant-supplied final PK/PD mixed effect linear regression model file was applied to the scatterplots of AXA versus plasma concentrations data to verify the model appropriateness through the GoF plot using R version 4.3.3. The fitted linear regression model slope was also determined. Once the PK/PD model was established, the GoF plot was stratified by the proposed body weight group.

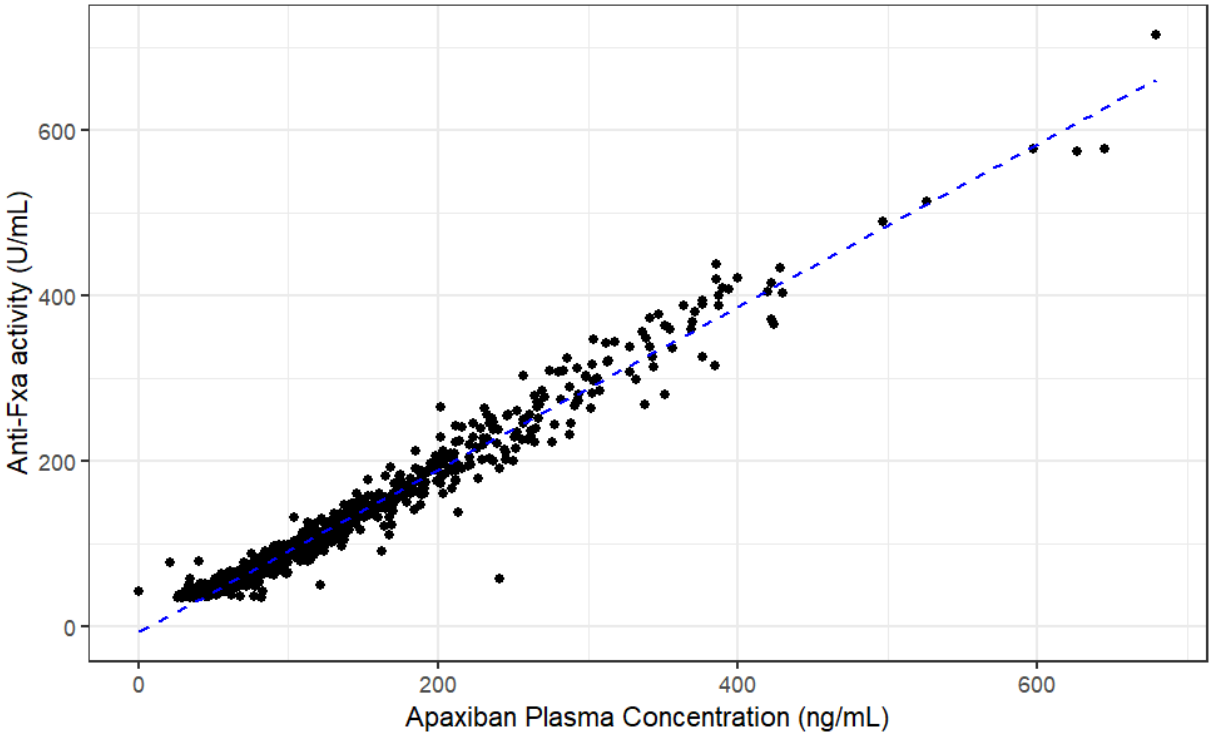
Results

Figure 34 shows the GoF plot of the linear mixed effect PK/PD model. The review team assessed and verified the final PK/PD model based on visual inspection of the GoF diagnostic scatterplot. The plot indicates that the model adequately describes the observed data and confirms the linear relationship illustrated between the AXA versus plasma concentrations with the 0.926 slope estimate. Further, differences did not result in the relationships between AXA versus plasma concentrations among body weight group, as slope estimates remained similar across all body weight groups (Figure 26).

Conclusions

According to the GoF plot, the review team accepted the final PK/PD model that a linear regression model describes the observed relationship between AXA and plasma concentrations of apixaban with a slope of 0.926. The PK/PD relationship remains similar across different weight groups as well.

Figure 34. Relationship Between Anti Factor Xa Activity and Plasma Concentrations



Source: Reviewer's analysis
Abbreviation: FXa, factor Xa

14.6. Pharmacogenetics

Not applicable.

15. Study/Trial Design

15.1. Protocol Synopsis, Version 8 (April 28, 2022), Study CV185325/B0661037

Table 75. 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).

Source: Sponsor protocol

16. Efficacy

See Section 6 for discussion of efficacy.

17. Clinical Safety

See Section 7 for clinical safety review.

18. Clinical Virology

Not applicable.

19. Clinical Microbiology

Not applicable.

20. Mechanism of Action/Drug Resistance

Refer to Section 5 of the review for a description of the mechanism of action of apixaban. There is no established concern for drug resistance with this class of medications for the proposed indication.

21. Other Drug Development Considerations

None.

22. Data Integrity–Related Consults (Office of Scientific Investigations, Other Inspections)

Not applicable.

23. Labeling: Key Changes

This Prescribing Information (PI) review includes a high-level summary of the rationale for major changes to the finalized PI as compared to the currently approved PI and the Applicant's draft PI (Table 76). The PI was reviewed to ensure that it meets regulatory/statutory requirements, is consistent (if appropriate) with labeling guidance, conveys clinically meaningful and scientifically accurate information needed for the safe and effective use of the drug, and provides clear and concise information for the healthcare practitioner.

Table 76. Key Labeling Changes and Considerations

Full PI Sections[1]	Rationale for Major Changes to Finalized PI[2] Compared to Currently Approved PI and Applicant's Draft PI)
BOXED WARNING	No changes.
1 INDICATIONS AND USAGE	Added "in adults" or "in adult patients" to all adult only indications. Updated indications to reflect expanded pediatric indication. Revised "to less than 18 years of age" to "and older" as CDER defines pediatric patients as <17 years of age. Defined conditions in all indications prior to using abbreviation (i.e., DVT, PE, VTE).
2 DOSAGE AND ADMINISTRATION	Updated the pediatric dosage information to avoid passive voice. Removed Table 1 columns to remove (b) (4) for clarity. Updated sections with the new dosage forms and added a description of the new capsules.
4 CONTRAINDICATIONS	No change.
5 WARNINGS AND PRECAUTIONS	Revised "apixaban" to "ELIQUIS" when describing safety risks to avoid distancing the risk from the product.
6 ADVERSE REACTIONS	Updated this section to include a description of the pediatric study and safety data from this study.
7 DRUG INTERACTIONS	Relocated the text that was placed between section 7 and 7.1 to within numbered subsections.
8 USE IN SPECIFIC POPULATIONS (e.g., Pregnancy, Lactation, Females and Males of Reproductive Potential, Pediatric Use, Geriatric Use, Renal Impairment, Hepatic Impairment)	8.4 Pediatric Use: Revised the basis of approval to reflect the small sample size of the pediatric patients and reflect reliance on the adult data to support it. 8.6 Removed (b) (4) to just provide the guidance for dosing in renal impairment. Table 12 was revised to provide eGFR thresholds for patients under 2 years with severe renal impairment. Thresholds for those over 2 years are covered above and omitted here. Normal eGFR ranges are not required in the table
9 DRUG ABUSE AND DEPENDENCE	n/a
10 OVERDOSAGE	Deleted (b) (4) The Overdosage section should not include information about an unapproved dosage (e.g., dosage greater than the maximum recommended dosage in the D&A section) that is not associated with an overdosage because this information may imply or suggest an unapproved dosage regimen. Per 201.57(c)(3)(ii): "Dosing regimens must not be implied or suggested in other sections of the labeling if not included in this section." Added "Consider contacting the Poison Help line (1-800-222-1222) or a medical toxicologist for additional overdose management recommendations" Given that overdose management recommendations may change.
12 CLINICAL PHARMACOLOGY	12.2 Removed reference to the (b) (4) assay being used to measure the effect of apixaban on anti-FXa activity, as it is not FDA cleared for this use. Instead, the relationship between apixaban exposures and anti-FXa activity is described without referencing the assay. 12.3 Removed (b) (4) to avoid use of vague descriptors of time.

Full PI Sections[1]	Rationale for Major Changes to Finalized PI[2] Compared to Currently Approved PI and Applicant's Draft PI)
13 NONCLINICAL TOXICOLOGY	No changes.
14 CLINICAL STUDIES	Section 14.4 revised to describe the pediatric trial, the demographic characteristics of the patients, and efficacy findings.
17 PATIENT COUNSELING INFORMATION	No changes.
Product Quality Sections (i.e., DOSAGE FORMS AND STRENGTHS, DESCRIPTION, HOW SUPPLIED/STORAGE AND HANDLING)	All sections updated to reflect the final dosage forms and revise (b) (4) to "packet".

Source: Comparison of Applicant's submitted draft PI and near-final PI.
[1] Product quality sections (Sections 3, 11, and 16) are pooled under the last row in this table; Section 15 (REFERENCES) is not included in this table.
[2] For the purposes of this document, the finalized PI is the PI that will be approved or is close to being approved.
Abbreviation(s): PI, Prescribing Information

23.1. Approved Labeling Types

Upon approval of this efficacy supplement, the following labeling documents will be FDA -approved:

- United States Prescribing Information
- Medication Guide
- Instructions for Use (tablets for oral suspension)
- Instructions for Use (capsules for oral suspension)

24. Postmarketing Requirements and Commitments

In the submission of the NDA, the primary stability batches were manually packaged and labeled at Bristol Myers Squibb Co. (FEI:2211101). The firm is intended to conduct the commercial packaging and labeling at (b) (4). For commercial batches, apixaban capsules will be packaged and labeled through a (b) (4) process. (b) (4) (b) (4) (b) (4). Based on the response the firm submitted on January 15, 2025, the process performance qualification (PPQ) batches were (b) (4) capped, sealed, and labeled at the commercial packaging site, (b) (4). This process differs from the proposed commercial (b) (4) capping and labeling process. This practice deviated from the 2011 FDA guidance for industry Process Validation: General Principles and Practices that PPQ batches should be manufactured using the actual facility, utilities, and equipment (each now qualified) with the commercial manufacturing process, control procedures, and components; and PPQ is to confirm the process design and demonstrate that the commercial manufacturing process performs as expected. This issue was consulted with the OPMA policy group. Following the OPMA policy suggestion, a post-approval commitment is aimed to monitor the primary

packing operation, e.g., capping and labeling steps with enhanced process controls or tests during the first few commercial batches to mitigate any residual risk.

PMC 4809-01: For manufacturing the first few commercial batches of apixaban capsules for oral suspension, implement enhanced process controls to demonstrate the manufacturability and robustness of the commercial primary packing operation, e.g., capping and labeling steps, to ensure product quality. Demonstrate that the commercial manufacturing process performs as per FDA Guidance for Industry Process Validation: General Principles and Practices (2011).

Final report submission date: February 28, 2028.

25. Financial Disclosure

Table 77. Covered Clinical Studies: B0661037/CV185325

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 657		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c), and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 1 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator: 0 Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 1		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

Abbreviation: FDA, Food and Drug Administration

26. References

Journal Articles

Bhat, RV, G Young, and AA Sharathkumar, 2024, How I treat pediatric venous thromboembolism in the DOAC era, Blood, 143(5):389-403.

Goldenberg, NA, JM Kittelson, TC Abshire, M Bonaca, JF Casella, RA Dale, JL Halperin, F Hamblin, CM Kessler, MJ Manco-Johnson, RF Sidonio, AC Spyropoulos, PG Steg, AGG Turpie, and S Schulman, 2022, Effect of anticoagulant therapy for 6 weeks vs 3 months on recurrence and bleeding events in patients younger than 21 years of age with provoked venous thromboembolism: the Kids-DOTT randomized clinical trial, JAMA, 327(2):129-137.

Mahajerin, A and SE Croteau, 2017, Epidemiology and risk assessment of pediatric venous thromboembolism, Front Pediatr, 5:68.

Mitchell, LG, NA Goldenberg, C Male, G Kenet, P Monagle, and U Nowak-Gottl, 2011, Definition of clinical efficacy and safety outcomes for clinical trials in deep venous thrombosis and pulmonary embolism in children, J Thromb Haemost, 9(9):1856-1858.

Monagle, P, CA Cuello, C Augustine, M Bonduel, LR Brandão, T Capman, AKC Chan, S Hanson, C Male, J Meerpohl, F Newall, SH O'Brien, L Raffini, H van Ommen, J Wiernikowski, S Williams, M Bhatt, JJ Riva, Y Roldan, N Schwab, RA Mustafa, and SK Vesely, 2018, American Society of Hematology 2018 Guidelines for management of venous thromboembolism: treatment of pediatric venous thromboembolism, Blood Advances, 2(22):3292-3316.

Warady, BA and V Chadha, 2007, Chronic kidney disease in children: the global perspective, Pediatr Nephrol, 22(12):1999-2009.

Witmer, C and L Raffini, 2020, Treatment of venous thromboembolism in pediatric patients, Blood, 135(5):335-343.

Guidances

Draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (December 2019)

Guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* (May 1998)

Guidance for industry *M10 Bioanalytical Method Validation and Study Sample Analysis* (November 2022)

Draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness With One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence* (September 2023)

27. Review Team

Table 78. Reviewers of Integrated Assessment

Role	Name(s)
Regulatory project manager	Carleveva Thompson
Nonclinical reviewer	Vanesa Sanchez
Nonclinical team leader	Bo Lee
OCP reviewer(s)	Yaning Sun, Abiy Eyakem
OCP team leader(s)	Sudharshan Hariharan, Vishnu Sharma
Clinical reviewer	Roma Rajput
Clinical team leader	Julie Weisman
Biometrics reviewer	Fei Wu
Biometrics team leader	Lola Luo
Cross-discipline team leader	Julie Weisman
Division director (P/T)	Todd Bourcier
Division director (OCP)	NA

Role	Name(s)
Division director (OB)	NA
Deputy Division director (clinical)	Tanya Wroblewski
Office director (or designated signatory authority)	Tanya Wroblewski

Abbreviations: NA, not applicable; OCP, Office of Clinical Pharmacology; OB, Office of Biostatistics; P/T, Pharmacology and Toxicology

Table 79. Additional Reviewers of Application

Office or Discipline	Name(s)
OPQ	Theodore Carver, Rao Kambhampati, Sureshbabu Dadiboyena, Parvin Akther, Joyce Crich, Zhouxi Wang, Feiyan Jin, Parnali Chatterjee, Haritha Mandula
Microbiology	NA
OPDP	Melissa Khashei
DMPP	Ruth Mayrosh, Barbara Fuller
OSI	Anthony Orencia
OSE/DEPI	NA
OSE/DMEPA	Shabana Rauf, Millie Shah
OSE/DRISK	Carla Darling, Jacqueline Sheppard
DNH Associate Director for Labeling	Virginia Kwitkowski

Abbreviations: DEPI, Division of Epidemiology; DMEPA, Division of Medication Error Prevention and Analysis; DMPP, Division of Medical Policy Programs; DNH, Division of Nonmalignant Hematology; DRISK, Division of Risk Management; NA, not applicable; OPDP, Office of Prescription Drug Promotion; OPQ, Office of Pharmaceutical Quality; OSE, Office of Surveillance and Epidemiology; OSI, Office of Scientific Investigations

27.1. Reviewer Signatures

Table 27-80 Signatures of Reviewers

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Biostatistics Discipline Tertiary Reviewer	Yeh Fong Chen OB DBIX	Sections: 6, 15-16, 23-26	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Signature: Yeh Fong Chen			**Digitally signed by Yeh Fong Chen** **Date: 4/17/2025 11:51 AM EDT** **GUID: 2025417155136**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Associate Director for Labeling Discipline Primary Reviewer	Virginia Kwitkowski OCHEN DNH	Sections: 23	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Virginia Kwitkowski			**Digitally signed by Virginia Kwitkowski** **Date: 4/17/2025 11:51 AM EDT** **GUID: 2025417155159**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Regulatory Project Manager Discipline Primary Reviewer	Carleveva Thompson ORO DROCHEN	Sections: 12	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Signature: Carleveva Thompson			**Digitally signed by Carleveva Thompson** **Date: 4/17/2025 11:54 AM EDT** **GUID: 202541715546**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Biostatistics Discipline Secondary Reviewer	Lola Luo OB DBIX	Sections: 6, 15-16, 23-26	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Lola Luo			**Digitally signed by Lola Luo** **Date: 4/17/2025 11:54 AM EDT** **GUID: 2025417155449**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Primary Reviewer	Yaning Sun OCP DCEP	Sections: 5, 6, 8, 14	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Signature: Yaning Sun			**Digitally signed by Yaning Sun** **Date: 4/17/2025 11:56 AM EDT** **GUID: 2025417155659**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharmacometrics Reviewer Discipline Secondary Reviewer	Vishnu Sharma OCP DPM	Sections: 14.5	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Vishnu Sharma			**Digitally signed by Vishnu Sharma** **Date: 4/17/2025 11:58 AM EDT** **GUID: 2025417155852**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharm-tox/Non-clinical Discipline Primary Reviewer	Vanesa Sanchez OCHEN DPTCHEN	Sections: 5.1, 7.1, 8.4, 13.1; 13.2	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Signature: Vanesa Sanchez			**Digitally signed by Vanesa Sanchez** **Date: 4/17/2025 11:59 AM EDT** **GUID: 2025417155937**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Biostatistics Discipline Primary Reviewer	Lola Luo OB DBIX	Sections: 6, 15-16, 23-26	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Lola Luo			**Digitally signed by Lola Luo** **Sign on behalf of** **Date: 4/17/2025 12:04 PM EDT** **GUID: 202541716459**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Regulatory Project Manager Discipline Secondary Reviewer	Julie Van Der Waag ORO DROCHEN	Sections: 12	Based on my assessment of the application: ☐ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ✓ Not applicable.	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Signature: Julie Van Der Waag			**Digitally signed by Julie Van Der Waag Sign on behalf of J. Van der Waag signing on behalf of S. Kiani Date: 4/17/2025 12:06 PM EDT GUID: 202541716633**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Secondary Reviewer	Doanh Tran OCP DCEP	Sections: 5, 6, 8, 14	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Doanh Tran			**Digitally signed by Doanh Tran Sign on behalf of Signing for Sudharshan Hariharan. Date: 4/17/2025 12:07 PM EDT GUID: 20254171671**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharm-tox/Non-clinical Discipline Secondary Reviewer	Bo Yeon Lee OCHEN DPTCHEN	Sections: 5.1, 7.1, 8.4, 13.1; 13.2	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Signature: Bo Yeon Lee			**Digitally signed by Bo Yeon Lee** **Date: 4/17/2025 12:11 PM EDT** **GUID: 2025417161155**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Discipline Secondary Reviewer	Tanya Wroblewski OCHEN DNH	Sections: ALL Sections	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Tanya Wroblewski			**Digitally signed by Tanya Wroblewski** **Sign on behalf of Signing for Julie Weisman** **Date: 4/17/2025 2:06 PM EDT** **GUID: 202541718634**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Discipline Tertiary Reviewer	Tanya Wroblewski OCHEN DNH	Sections: All	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Signature: **Tanya Wroblewski**			**Digitally signed by Tanya Wroblewski** **Date: 4/17/2025 2:10 PM EDT** **GUID: 2025417181058**	

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

TANYA M WROBLEWSKI
04/17/2025 02:13:18 PM