30 May 2024
EMA/281735/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Eliquis

International non-proprietary name: apixaban

Procedure No. EMEA/H/C/002148/X/0089/G

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Table of contents

List of abbreviations

Term	Definition
AE	adverse event
ALL	acute lymphoblastic leukemia
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AT	Transaminases
BA	bioavailability
BID	twice daily
BMI	body mass index
CBC	complete blood count
CFU	Colony Forming Units
CI	confidence interval
CNS	central nervous system
CRNM	clinically relevant non-major
CSR	clinical study report
CVC	central venous catheter
CVAD	central venous access device
CVST	Cerebral venous sinus thrombosis
CYP	cytochrome P450
DILI	Drug-induced liver injury
DMC	data monitoring committee
DVT	deep venous thrombosis
DXA	dual energy X-ray absorptiometry
EAC	Event adjudication committee
EOT	End of treatment
EMA	European Medicines Agency
ERA	environmental risk assessment
FAS	full analysis set
FDA	Food and Drug Administration
FXa	factor Xa

Term	Definition
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
HDPE	High Density Polyethylene
HPLC	High performance liquid chromatography
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICH	intracranial haemorrhage
iCSR	Interim Clinical Study Report
INR	international normalized ratio
IR	Infrared
ISTH	International Society on Thrombosis and Haemostasis
KIDCLOT	Kids Informed Decrease Complications Learning on Thrombosis
LDPE	Low density polyethylene
LL	lymphoblastic lymphoma
LMWH	low molecular weight heparin
NSAID	nonsteroidal anti-inflammatory drugs
NVAF	non valvular atrial fibrillation
pcVPC	prediction-corrected visual predictive checks
PD	pharmacodynamic(s)
PDA	Photo diode array
PDCO	EMA Paediatric Committee
PE	pulmonary embolism
PedsQL	Pediatric Quality of Life Inventory
P-gp	P-glycoprotein
Ph. Eur.	European Pharmacopoeia
PK	pharmacokinetic(s)
PND	post-natal development
PPK	population pharmacokinetic
PT	preferred term
PVC	Polyvinyl chloride
PVDC	Polyvinylidene chloride
QC	Quality control

Term	Definition
QOL	quality of life
QTPP	Quality target product profile
RH	Relative Humidity
RP	Reversed Phase
SAE	Serious adverse event
SCS	Summary of Clinical Safety
SD	standard deviation
SmPC	Summary of Product Characteristics
SOC	standard of care
SNRI	Serotonin and norepinephrine reuptake inhibitor
SSRI	Selective serotonin reuptake inhibitor
SVP	single ventricle physiology
TEAE	treatment emergent adverse event
UFH	unfractionated heparin
ULN	upper limit of normal
USP	United States Pharmacopoeia
USP/NF	United States Pharmacopoeia/National Formulary
UV	Ultraviolet
VKA	Vitamin K antagonist
VTE	venous thromboembolism
VTEp	venous thromboembolism prevention
VTEt	venous thromboembolism treatment
wk	Week

1. Background information on the procedure

1.1. Submission of the dossier

Bristol-Myers Squibb / Pfizer EEIG submitted on 31 July 2023 a group of variation(s) consisting of extensions of the marketing authorisation and the following variation(s):

Variation(s) requested		Type
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

Extension application to:
1) Introduce a new pharmaceutical form (granules in single-dose container) associated with a new strength (0.15 mg).
2) Introduce a new pharmaceutical form (coated granules in sachet) associated with 3 new strengths (0.5 mg, 1.5 mg and 2 mg)

The above two line extensions are grouped with a type II - C.I.6.a variation:
Extension of indication to include the treatment of venous thromboembolism (VTE) and prevention of recurrent VTE in paediatric patients from 28 days to less than 18 years of age for Eliquis (all strengths), based on a pre-specified interim analysis from Study CV185325; this is an open-label, multi-centre, randomized, active controlled trial to provide PK data and data on anti-Xa activity to support the extrapolation of efficacy to children, to evaluate safety and efficacy of apixaban in children who require anticoagulation for a venous thromboembolism; As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 4.9, 5.1 and 5.2 of the SmPCs are updated. The Package Leaflet and Annex II are updated in accordance. Version 21.0 of the RMP has also been submitted.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 7.2 of Commission Regulation (EC) No 1234/2008 – Group of variations

1.3. Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included EMA Decisions P/0198/2020 and P/0199/2020 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0199/2020 was not yet completed as some measures were deferred.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.5. Scientific advice

The MAH did not seek Scientific advice at the CHMP.

1.6. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Patrick Vrijlandt Co-Rapporteur: Christophe Focke

The Rapporteur appointed by the PRAC was:

The application was received by the EMA on	31 July 2023
The procedure started on	17 August 2023
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	2 November 2023
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	2 November 2023
The CHMP Co-Rapporteur's critique Assessment Report was circulated to all CHMP and PRAC members on	20 November 2023
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	30 November 2023
The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on	14 December 2023
The MAH submitted the responses to the CHMP consolidated List of Questions on	25 March 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	2 May 2024
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	16 May 2024
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Eliquis on	30 May 2024

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The current application concerns extension of indication to include the treatment of venous thromboembolism (VTE) and prevention of recurrent VTE in paediatric patients from 28 days to less than 18 years of age for Eliquis.

Apixaban (Eliquis) was first approved in the EU on 18 May 2011 for the indication of prevention of venous thromboembolism (VTE) following knee or hip replacement surgery in adults. Subsequent approvals in the EU included the indications for prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation (NVAF) with one or more risk factors (19-Nov-2012), treatment of deep venous thrombosis (DVT) or pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults (28-Jul-2014).

2.1.2. Epidemiology

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

2.1.3. Aetiology and pathogenesis

In adults, risk factors include prolonged immobilization, the presence of a central venous line, surgery, trauma, malignancy, pregnancy and puerperium, treatment with oral contraceptives, hormone replacement therapy, presence of antiphospholipid antibodies, and inherited disorders of coagulation. The pathophysiology of VTE in children is similar, but the contribution of each factor differs among age groups [Albisetti et al, 2012].

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

interventions. The most common precipitating factor is the presence of a central venous access device (CVAD), which is related to almost 90% of VTE in neonates and 60% in older children".

2.1.4. Clinical presentation, diagnosis and prognosis

The typical location of VTE in neonates and infants differs from that in adults and adolescents. In neonates and young children, VTE occurs more often (60%) in the upper extremity venous system (vs. only 2% in adults). This reflects the common placement of CVC (the most frequent precipitating factor of VTE in children) via the internal jugular or subclavian veins. The location of the clots results in fewer classic VTE symptoms and also may impair the effective/precise diagnosis with standard measures, i.e. compression ultrasound (CUS) cannot be performed in these locations.

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

2.1.5. Management

In the ASH guidelines (2018) and ACCP guidelines (2012), recommended options for treatment of VTE in children include use of UFH, LMWH, and/or a VKA. These three classes of anticoagulants used for the treatment of VTE, which are well established and approved in adults, are adapted but yet not approved for use in children: VKA (eg, warfarin), UFH, and LMWH, with the exception of one LMWH, FRAGMIN® (dalteparin sodium) injection.

At the time of establishing the ASH 2018 guideline, no results of clinical studies on DOACs in paediatric patients were available. Since then, several direct FXa inhibitors (dabigatran and rivaroxaban) have been approved for treatment of VTE and prevention of recurrence of VTE in paediatric patients.

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

Apixaban has potent, predictable and lasting anticoagulant activity and a predictable PK profile. Distinct features of apixaban include direct binding to the active site of FXa without requiring antithrombin III, a paediatric oral dosing formulation with consistent absorption and no food effect, limited potential for clinically significant drug-drug interaction with other medications, no need for therapeutic monitoring, and a low risk of bleeding. These features may make it superior to currently available antithrombotic agents for thromboprophylaxis in children with a venous thromboembolism, thus addressing an unmet clinical need.

2.2. About the product

Apixaban (BMS-562247) is a potent, oral, reversible, direct, and highly selective inhibitor of FXa. It does not require antithrombin III for antithrombotic activity. Apixaban inhibits free and clot bound FXa along with prothrombinase activity. Activation of factor X to FXa via the intrinsic and extrinsic pathways plays a central role in the cascade of blood coagulation. By inhibiting FXa, apixaban prevents thrombin generation and thrombus development. Apixaban has no direct effects on platelet aggregation, but indirectly inhibits platelet aggregation induced by thrombin.

Apixaban is indicated in adults for:

- Prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective hip or knee replacement surgery.
- Prevention of stroke and systemic embolism in adult patients with non valvular atrial fibrillation (NVAF), with one or more risk factors, such as prior stroke or transient ischaemic attack (TIA); age $\geqslant$ 75 years; hypertension; diabetes mellitus; symptomatic heart failure (NYHA Class $\geqslant$ II).
- Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults (see section 4.4 for haemodynamically unstable PE patients).

The current application concerns extension of indication to paediatric patients as follows:

- Treatment of venous thromboembolism (VTE) and prevention of recurrent VTE in paediatric patients from 28 days to less than 18 years of age.

The proposed extension of the original indication in adults to include the use of apixaban for treatment of VTE and prevention of recurrent VTE in paediatric patients from 28 days to less than 18 years of age is based on a pre-specified interim analysis of main PIP02 Study CV185325. Enrollment in this study for age group 4 (neonates from birth to 27 days of age) is ongoing. The MAH is not seeking an approval for use in neonates at this time. The MAH will assess the possibility to submit an Extension Application grouped with an extension of indication to extend the treatment of VTE and prevention of recurrent VTE indication to neonates once a final CSR for Study CV185325 is issued and upon completion of the final compliance check for PIP02.

Apixaban is commercially available as 2.5-mg and 5-mg film-coated tablets. Both the PIP and Written Request (WR) include the requirement to develop age-appropriate formulations. To address this requirement, two age-appropriate formulations were developed. The proposed commercial formulations for paediatric patient are as follows:

- 2.5 mg film-coated tablet (same as the currently commercialized 2.5 mg film-coated tablet for adults)
- 5 mg film-coated tablet (same as the currently commercialized 5 mg film-coated tablet for adults)
- 0.15 mg granules in capsules for opening
- 0.5, 1.5, and 2.0 mg coated granules in sachets (0.5 mg film-coated tablets will be provided in sachets containing unit doses of 0.5 [1 tablet], 1.5 [3 tablets], and 2.0 [4 tablets] mg)

As the Sponsor is not seeking an indication for neonates in this application; only information on the age-appropriate formulations i.e., 0.15 mg granules in capsules for opening and 0.5 mg coated granules in sachet, is included in dossier.

2.3. Type of Application and aspects on development

The present dossier is a grouped application consisting of two Extensions Applications (introduction of two new paediatric pharmaceutical forms i.e.
granules in capsules for opening (0.15 mg) and coated granules in sachet (0.5 mg, 1.5 mg and 2 mg) and a Type II variation (extension of indication to the paediatric population) as follows:

Type II Variation, category C.I.6.a (Extension of indication): extension of indication to include the treatment of venous thromboembolism (VTE) and prevention of recurrent VTE in paediatric patients from 28 days to less than 18 years of age for Eliquis (all strengths), based on a pre-specified interim CSR from Study CV185325. This is a randomized, open-label, active controlled, safety and descriptive efficacy study in paediatric subjects requiring anticoagulation for the treatment of a venous thromboembolic event. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 4.9, 5.1 and 5.2 of the SmPC are updated. The Package Leaflets are updated in accordance. Version 21.3 of the RMP has also been submitted.

Extension Application to introduce a new pharmaceutical form: granules in capsules for opening (0.15 mg)

Extension Application to introduce a new pharmaceutical form: coated granules in sachet (0.5 mg, 1.5 mg and 2 mg)

2.4. Quality aspects

2.4.1. Introduction

This line extension application covers the introduction of two new pharmaceutical forms for the paediatric population.

1. *Granules in capsules for opening*

The finished product is presented as granules in capsules for opening containing 0.15 mg of apixaban as active substance.

Other ingredients are:

Granules content: hypromellose (E464) and sugar spheres (composed of sugar syrup, maize starch (E1450) and sucrose).

(The granules are filled into a pre-printed gelatine sprinkling capsule which is not ingested.)

Capsule shell: gelatin (E441), titanium dioxide (E171) and iron oxide yellow (E172).

Black printing ink on capsule: shellac (E904), propylene glycol (E1520) and iron oxide black.

The product is available in a high-density polyethylene (HDPE) bottle with a foil induction seal and a child-resistant polypropylene cap as described in section 6.5 of the SmPC.

2. Coated granule(s) in sachet

The finished product is presented as coated granule(s) in sachet containing 0.5 mg, 1.5 mg, or 2.0 mg of apixaban as active substance. Each 0.5 mg sachet contains one coated granule containing 0.5 mg apixaban. Each 1.5 mg sachet contains three coated granules. Each 2.0 mg sachet contains four coated granules.

Other ingredients are:

Granules content: lactose, microcrystalline cellulose (E460), croscarmellose sodium (E468), sodium laurilsulfate (E487) and magnesium stearate (E470b).

Film coat: lactose monohydrate, hypromellose (E464), titanium dioxide (E171), triacetin (E1518) and iron oxide red (E172).

The product is available in a child-resistant aluminium foil sachet as described in section 6.5 of the SmPC.

2.4.2. Active Substance

No new information on the active substance apixaban has been provided with this line extension application. The new presentations use active substance of the same quality as used in the approved presentations (2.5 mg and 5 mg film-coated tablets) and the active substance is manufactured by the approved manufacturing sites. The approved specification of the active substance is suitable for the new presentations and no additional tests are required.

2.4.3. Finished Medicinal Product

1. Granules in capsules for opening

2.4.3.1. Description of the product and pharmaceutical development

The finished product Eliquis granules in capsules for opening is presented as a size #0 hard gelatin capsule comprised of a clear body and a yellow opaque cap that is partially filled with a white to off-white powder. On the capsule cap, "0.15" with "989" underneath is printed radially with black ink. The capsules are filled with an appropriate amount of granules to provide the required strength (0.15 mg apixaban). The granules visually appear as a powder. The closed capsule length is 21.7 mm. For administration, the capsule is opened, and the content is dispersed in a liquid vehicle to form a suspension. The suspension is administered orally, while the capsule shell is not ingested.

The aim of pharmaceutical development was to develop a presentation suitable for the paediatric population. The quality target product profile (QTPP) (Table 4) was defined and information on the identified critical quality attributes was provided (CQAs: identification, assay, uniformity of dosage units, impurities, dissolution, and microbial limits).

Table 1: Finished product QTPP

QTPP Element	Target
Route of Administration	Oral
Dosage Form	Capsule for Oral Suspension
Dosage Strengths	0.1 mg, 0.15 mg
Dose Administration	Method of dose administration must be suitable for caregivers to appropriately administer the dose
Excipient Selection	Common excipients with established safety in pediatrics and meets compendial status where available
Patient Population Targeted	Infants: Body weight of < 5 kg
Container Closure System	High-density polyethylene bottles
Stability	≥ 2 years shelf life at room temperature in all climate zones
Drug Product Quality	
Appearance (Description)	Color, shape, size, and markings to comply with product description
Assay	95.0% to 105.0% of label claim at release
Content Uniformity (CU)	Complies with harmonized compendial requirements
Impurities/Degradants	Meets ICH Q3B(R2) guidelines
Dissolution	Immediate release dissolution of apixaban from the beads to facilitate rapid absorption from the gastrointestinal tract
Microbial Quality	Meets harmonized pharmacopoeial monograph acceptance criteria for microbial limits

The pharmaceutical development of the finished product has been adequately performed and described. The selected formulation, packaging and manufacturing process are justified.

The key development challenges were dosage uniformity at the low dosage strength and ease of use by the caregiver. To maximize content uniformity, it was decided to spray-layer a solution of the active substance onto the granules during manufacturing and to control the capsule fill during encapsulation. Human factor (HF) studies were conducted to establish instructions for dispersing the capsule content in a liquid vehicle. The aim was to ensure caregiver compliance with administering the desired dose to the paediatric patient and to reduce the risk of medication errors. Multiple root cause analyses were conducted to identify the underlying causes for errors and opportunities for improvement after each HF study. Based on the results, the instruction for use were optimised. The resulting instructions for use are clear and easy to follow (see Product Information).

The same quality of active substance is used for the granules in capsules for opening as for the approved 2.5 and 5 mg film-coated tablets. Polymorphic form and particle size of the active substance are not critical since the active substance is completely dissolved in water and ethanol during manufacture of the finished product. Assay of the active substance is also not critical as the amount of granules filled into the capsule is adjusted based on the in-process assay value of the granules.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. Standards, with the exception of the colourant which complies with the NF. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report. The proposed excipient sugar spheres and hypromellose are acceptable because they are well known in the manufacture of oral pharmaceutical forms. No direct safety issues are foreseen with regards to the excipients and their quantities in the

finished product when used in children. The capsule shell is not intended to be ingested. However, no direct safety issues are foreseen if the capsule in ingested accidentally.

No compatibility studies were conducted to demonstrate that the chosen excipients are compatible with the active substance. This is acceptable based on the overall experience with the chosen excipients in oral pharmaceutical forms and the results of the presented stability studies (see chapter on stability below).

Formulation development is described in sufficient detail. A capsule formulation approach was selected for the finished product, whereby the capsules, which contain the sugar spheres coated with the active substance and binder are intended for opening. The provided justification for the formulation choices made is satisfactory. Development batches were manufactured to choose the binder for the formulation and to demonstrate the suitability of the particle size grade and specification of the sugar spheres. The capsule shell material was chosen based on low capsule shell weight variability and ease of opening for the caregiver. The sugar spheres are composed of sugar syrup, maize starch and sucrose. The use of these excipient sugar spheres has been adequately justified for the paediatric population in line with the *Guideline on pharmaceutical development of medicines for paediatric use*. The maximum intake of sucrose in the developed finished product is 0.988 g/day which is well below the acceptable intake (AI) for 0 to 3-month old infants (AI = 25 g per single dose as indicated in the *Safety and Toxicity of Excipients for Paediatrics database by the European Paediatric Formulation Initiative*). In addition, the annex of the guideline on excipients in the labelling and package leaflet does not require a warning for diabetes mellitus because the threshold of 5 g sucrose per dose is not reached. A cariogenic risk is not applicable as the intended population is infants who likely do not have teeth.

The proposed QC method for dissolution testing (paddle apparatus at 50 rpm and a 500 mL dissolution medium of pH 6.8 at 37±0.5°C) is in line with the *Reflection paper on the dissolution specification for generic solid oral immediate release products with systemic action*. The provided solubility data show that sink conditions are achieved. The applicant was not able to demonstrate the discriminatory power of the method, but this is expected due to the high solubility of the active substance. Rotation speed, medium and medium volume were selected to reach the highest possible discriminatory power. The parameters are justified and the method is acceptable.

The finished product formulation granules in capsules for opening was developed in a strength of 0.1 mg and 0.15 mg. Both had the same qualitative and quantitative composition. Only the 0.1 mg apixaban capsule was used in clinical trials. Based on dosing requirements, only the 0.15 mg apixaban capsule is proposed for marketing. Batches of 0.1 mg capsules were used in the pivotal study CV185-325. The granules in the 0.1 mg strength finished product used in the clinical studies are similar to the granules in the 0.15 mg strength finished product. The finished product is administrated by dispersing the granules in a liquid vehicle. 3 capsules of 0.1 mg result in the same oral suspension as 2 capsules of 0.15 mg. Therefore, the 0.1 mg strength used in clinical studies is considered representative of the 0.15 mg strength proposed for marketing.

The granules in capsules for opening are developed to enable administration of the finished product to the paediatric population. Dosing instructions based on body weight are indicated in the SmPC.

The palatability of the granules in the 0.1 mg capsule has been demonstrated in healthy adult subjects as part of the relative bioavailability study CV185-687 and in children (neonates up to 27 days, n=2) in study CV185-325. The palatability study is representative for the applied 0.15 mg strength.

Manufacturing process development is described in sufficient detail. Process risk assessments were conducted for the development of the manufacturing process to identify risks to the quality attributes

of the finished product. The process parameters that were identified from the risk assessment were studied to determine parameter criticality and to establish proven acceptable ranges.

The primary packaging is a high-density polyethylene (HDPE) bottle with a foil induction seal and a child-resistant polypropylene cap. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

2.4.3.2. Manufacture of the product and process controls

The finished product is manufactured by one manufacturing site.

The manufacturing process consists of five main steps: solution preparation, spray layer coating, screening through a sieve, filling, and weight sorting of the filled capsules. The process is considered to be a standard manufacturing process.

The manufacturing process is described in sufficient detail. Equipment type(s) for each unit operation, equipment working capacity (where appropriate) and process parameters along with their target values or ranges and sieve size are included. Critical steps have been presented and the process parameters were defined as critical or non-critical. Sufficient information on the in-process controls has been provided and the acceptance criteria are justified. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

The spray solution, composed of apixaban active substance, hypromellose, water and ethanol may be held prior to the next step of the commercial manufacturing process (spray layer coating onto sugar spheres). The maximum hold time is justified based on results for assay and related substances from one laboratory-scale batch and from one process performance qualification batch (PPQ) manufactured by the commercial process and at commercial scale by the proposed commercial manufacturer.

The proposed hold time for the capsules packed in bulk is acceptable and based on a hold time study. The results of the hold time study support the hold time for the bulk capsules packed in LDPE bags.

Major steps of the manufacturing process have been validated by a number of studies. The manufacturing process has been validated on three commercial scale batches of granules and capsule batches. Considering that the manufacturing process is considered a standard process, this is deemed sufficient. Since assay, content uniformity and dissolution were tested in samples taken from different stages of the encapsulation process it was demonstrated that the granules are encapsulated uniformly throughout the encapsulation process. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.

2.4.3.3. Product specification

The finished product release specifications, include appropriate tests for this kind of dosage form: appearance (visual). identification (LC, UV/PDA), uniformity of dosage units (Ph. Eur.), assay (RP HPLC), impurities (RP HPLC), dissolution (Ph. Eur.) and microbial limits (Ph. Eur.).

The release and shelf-life specifications of the finished product are acceptable. Acceptance criteria are similar at release and shelf-life except for a specified impurity, allowing a potential increase during shelf-life. In response to a major objection raised during the procedure, the dissolution limit was tightened as requested. The major objection was thus resolved.

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for elemental Impurities. The total potential intake for each elemental impurity is well below 30% of their respective PDE. Based on the risk assessment it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification. The information on the control of elemental impurities is satisfactory.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided, it is accepted that there is no risk of nitrosamine impurities in the active

substance or the related finished product. Therefore, no specific control measures are deemed necessary.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for several full-scale and pilot-scale batches including batches of 0.15 mg and clinical batches of 0.1 mg batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The finished product is released on the market based on the above release specifications, through traditional final product release testing.

2.4.3.4. Stability of the product

Stability data from three production-scale batches of finished product stored for up to 24 months under long term conditions (25 ºC / 60% RH) and for up to six months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. In addition, stability data from these three batches stored for 24 months under intermediate conditions (30 ºC / 75% RH) was also provided. The batches of medicinal product are representative to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for: appearance, assay, impurities, water content (KF), dissolution and microbial limits. It is accepted that identification and uniformity of dosage units are not tested during shelf life as these parameters are not stability indicating. The analytical procedures used are stability indicating. The stability indicating nature of the analytical method used for assay and impurities testing was confirmed by a forced degradation study.

Except for a consistent increase in water content, no clear trends or changes were observed in any of the tested parameters at all three storage conditions. All test results remained within the specification limits.

In addition, one batch of finished product was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. Results demonstrate that the finished product is stable under light exposure.

Stability studies were performed on finished product dispersed in baby formula or water in a dosing cup or syringe at room temperature in the presence of ambient light. Samples were stored for 4 hours. No significant changes in assay and impurities were observed. The instruction stated in the SmPC (section 6.3) ”This medicine, once mixed with water or baby formula must be used within 2 hours.” is justified. The feasibility to administer the product through a nasogastric tube and gastric feeding tube when following the instructions in the SmPC has been adequately demonstrated. The study was conducted using a nasogastric tube and included the maximum dose of 8 capsules dispersed in 5 mL liquid representing a worst-case scenario. All samples confirmed a recovery of apixaban of greater than 96%.

Based on available stability data, the proposed shelf-life of 3 years without any special storage conditions as stated in the SmPC (section 6.3 and 6.4) is acceptable. This medicine, once mixed with water or baby formula must be used within 2 hours.

2.4.3.5. Adventitious agents

No excipients derived from animal or human origin have been used.

2.4.4. Finished Medicinal Product

2. Coated granule(s) in sachet

2.4.4.1. Description of the product and pharmaceutical development

The finished product Eliquis coated granule(s) in sachet is presented as very small pink, plain, round shallow biconvex film-coated tablets with a nominal diameter of 3 mm. The granules are packaged in sachets. Each granule delivers 0.5 mg of active substance. To deliver the unit dose of 0.5 mg apixaban, a sachet if filled with one granule. To deliver the unit dose of 1.5 mg apixaban, a sachet is filled with three granules. To deliver the unit dose of 2 mg apixaban, a sachet if filled with four granules.

The aim of pharmaceutical development was to develop a presentation suitable for the paediatric population. The quality target product profile (QTPP) (Table 8) was defined and information on the identified critical quality attributes was provided (CQAs: identification, assay, uniformity of dosage units, impurities, dissolution and microbial limits).

Table 2: Finished product QTPP

QTPP Element	Target
Route of Administration	Oral
Dosage Form	Tablet for Oral Suspension
Dosage Strengths	0.5 mg, 1.5 mg, and 2 mg
Dose Administration	Method of dose administration must be suitable for caregivers to appropriately administer the dose
Excipient Selection	Common excipients with established safety in pediatrics and meeting compendial status where appropriate
Patient Population Targeted	Patients weighing 5 kg to < 35 kg
Container Closure System	The 0.5-mg apixaban tablet will be packaged in 3 unit-dose sachets of 1 tablet, 3 tablets, and 4 tablets to provide unit doses of 0.5 mg, 1.5 mg, and 2 mg, respectively.
Stability	≥ 2 years shelf life at room temperature at all climate zones
Drug Product Quality	
Appearance (description)	Color and shape to comply with product description
Assay	95.0% to 105.0% of label claim at release
CU	Complies with harmonized compendial requirements
Impurities/Degradants	Meets ICH Q3B(R2) guidelines
Dissolution	Immediate release dissolution to facilitate rapid absorption from the gastrointestinal tract
Microbial Limits	Meets harmonized pharmacopoeial monograph acceptance criteria for microbial limits

The pharmaceutical development of the finished product has been adequately performed and described. The selected formulation, packaging and manufacturing process are justified.

The key development challenges were content uniformity and accuracy of the granule count in the sachet. To ensure content uniformity, process parameters and in-process controls were established which ensure acceptable compression performance and thereby acceptable content uniformity. Accurate granule count in the sachet is ensured by the performance of the packaging technology.

The granules are intended to be dispersed in a liquid vehicle and the resulting suspension is then to be administered orally. Human factor studies were conducted to establish instructions for dispersing the sachet content in a liquid vehicle. (see also above for the granules in capsules for opening). Compatibility studies with prescribed liquids/soft foods have been performed.

The formulation development was based on the preferred dosage form outlined in the EMA reflection paper on *Formulations of Choice for the Paediatric Population and Guideline on Pharmaceutical Development of Medicines for Paediatric Use*.

The same quality of active substance is used for the proposed granule(s) in sachet as for the authorised 2.5 mg and 5 mg film-coated tablets and for the new granules in capsules for opening (see above). The N-1 polymorphic form of apixaban is consistently produced. It has been adequately justified that a test for the polymorphic form is not required for the film-coated granules. The suitability of the particle size of the active substance has been demonstrated.

The same excipients in the same quality are used for the new granule formulation as in the authorised 5 mg film-coated tablet. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards, with the exception of the colourant which complies with the NF.

There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report. The coated granule(s) in sachets were developed to enable administration of the finished product to the paediatric population of children weighing 5 kg to < 35 kg. No direct safety issues are foreseen with regards to the excipients and their quantities in the formulation for use in children.

Compatibility studies were not conducted, and this is acceptable considering the same excipients are uses as in the approved 5 mg film-coated tablets. Compatibility is further confirmed by the results of stability studies (see below).

The same QC method as used for release testing of the 2.5 mg and 5 mg film-coated tablets is used. An acceptable justification for the use of surfactant and a rotation speed has been provided in the context of the application for the film-coated tablets. The discriminatory power of the proposed QC method for the new formulation has been demonstrated by testing a 0.5 mg granule batch made using active substance with particle size greater than the specification limit. It has been adequately demonstrated and justified that the QC method is adequate for the new formulation. The information provided is satisfactory.

The same granule core ingredients and film-coating is used as for the authorised 5 mg film-coated tablets. The final blend used in the manufacture of the authorised 2.5 mg and 5 mg tablets was demonstrated to be suitable for the manufacture of the proposed 0.5 mg film coated granules. The impact of particle size of the diluents lactose and microcrystalline cellulose was evaluated, and it was concluded that this was not a critical material attribute for the proposed finished product.

The 0.5 mg granules are manufactured using the same granulation and process that is used for the 2.5 mg and 5 mg film-coated tablets, at the same manufacturing site. Process risk assessments were conducted for the development of the manufacturing process to identify risks to the quality attributes of the finished product. The process parameters that were identified per the risk assessment were studied. For the compression and film-coating step, proven acceptable ranges were established and appropriate in-process controls were developed.The coating formulation used for the coated granules is the same as used for the 5 mg tablets.

Four batches of 0.5 mg coated granules were used in the clinical studies. It has been demonstrated that the difference in coating does not impact the dissolution profile of the finished product. The batches used in the clinical studies are therefore representative of the proposed commercial finished product.

The palatability of the 0.5 mg granules has been demonstrated in healthy adult subjects as part of relative bioavailability study CV185-687 and on children from 28 days to 18 years in clinical efficiency study CV185-325. Acceptability/palatability of the formulation in children is sufficiently confirmed.

2.4.4.2. Manufacture of the product and process controls

The finished product is manufactured by one manufacturing site (Pfizer Ireland Pharmaceuticals, Ireland).

The manufacturing process consists of four main steps: preparation of a final blend, compression, coating, and packaging. The process is considered to be a standard manufacturing process.

The manufacture and control of the final blend is similar to the process used for the approved 2.5 mg and 5 mg film coated tablets. The process flow diagram from the final blend is shown in the scheme below:

The manufacturing process steps to the finished product from the final blend are described in sufficient detail. Critical steps have been presented. The process parameters are in line with the proven acceptable ranges established during development.

Sufficient information on the in-process controls has been provided and the acceptance criteria are justified. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

The control strategy, process parameters and in-process controls are adequate in view of the available development data and in view of the standard nature of the manufacturing process.

A detailed description of the packaging process is provided. Accurate tablet count in each sachet is ensured by 100% in-line weight checking verification. The packaging system includes an auxiliary vision system which verifies the proper opening of sachets before they are filled and confirms that there are no product tablets present on the surface of the pucks. In addition, two in-process controls are performed during the packaging step (sachet printing and sachet filling). Based on the provided description of the packaging technology and the additional two in-process controls, it is considered sufficiently ensured that the correct amount of granules are packed into the sachets.

The proposed hold time for bulk coated granules is acceptable and based on a hold time study. The results of the hold time study support the hold time for the bulk coated granules packed in LDPE bags with desiccant in between.

The manufacturing process, including the packaging process (coated granules in the unit dose sachets to provide the final dose of the finished product), has been validated on three minimum commercial scale batches of coated granules. Considering that the manufacturing process is considered a standard process, this is sufficient. Since assay, content uniformity and dissolution were tested in samples taken from different stages of the compression process it was demonstrated that the core tablets are compressed uniformly throughout the compression process. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.

2.4.4.3. Product specification

The finished product release specifications shown in Table 9 include appropriate tests for this kind of dosage form: appearance (visual). identification (IR, LC), uniformity of dosage units (Ph. Eur.), assay (HPLC), impurities (HPLC), dissolution (Ph. Eur.) and microbial limits (Ph. Eur.).

The release and shelf-life specification of the finished product are acceptable. Acceptance criteria are similar at release and at shelf-life for all parameters. In response to a major objection raised during the procedure, the dissolution limit was tightened as requested. The major objection was resolved.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for elemental Impurities. The total potential intake for each elemental impurity is well below 30% of their respective PDE. Based on the risk assessment it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification. The information on the control of elemental impurities is satisfactory.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided, it is accepted that there is no risk of nitrosamine impurities in the active substance or the related finished product. Therefore, no specific control measures are deemed necessary.

Batch analysis results are provided for six batches (3 stability batches and 3 clinical batches), one clinical batch (batch), four development batches (batches) and one clinical batch (batch) confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The finished product is released on the market based on the above release specifications, through traditional final product release testing.

2.4.4.4. Stability of the product

Stability data from three production-scale batches of finished product stored for up to 24 months under long term conditions (25 ºC / 60% RH) and for up to six months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. In addition, stability data from these three batches stored for 24 months under intermediate conditions (30 ºC / 75% RH) was also provided. The batches of medicinal product are representative to those proposed for marketing and were packed in the primary packaging proposed for marketing. The sachets were tested at a fill of 1 and 8 granules, covering the commercial fill of 1, 3 and 4 coated granules per sachet.

Samples were tested for: appearance, assay, impurities, water content (KF), dissolution and microbial limits. It is accepted that identification and uniformity of dosage units are not tested during shelf life as these parameters are not stability indicating. The analytical procedures used are stability indicating. The stability indicating nature of the analytical method used for assay and impurities testing was confirmed by a forced degradation study.

Except for a consistent increase in water content, no clear trends or changes were observed in any of the tested parameters at all three storage conditions. All test results remained within the specification limits.

In addition, one batch of finished product was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. Results demonstrate that the finished product is stable under light exposure.

Microbial testing is not included in the post-approval stability protocol in line with the already approved 2.5 mg and 5 mg film-coated tablets based on the low water activity and the microbial limits results through 36 months that demonstrated acceptable microbial quality over product shelf life when packaged in PVC/PVDC blisters.

Stability studies were performed with finished product dispersed in baby formula, water or apple juice and samples were stored for 2 hours in a dosing cup followed by two hours in a syringe. No increase of impurities was observed. All assay results were above 93% and the provided justification for the variability in assay is acceptable. The instruction stated in the SmPC "This medicine mixed with water, baby formula or apple juice must be used within 2 hours. This medicine mixed with apple puree must be used immediately." is justified.

The feasibility to administer the product through a nasogastric tube and gastric feeding tube when following the instructions in the SmPC has been adequately demonstrated. The study was conducted using nasogastric tubes of typical sizes.

Based on available stability data, the proposed shelf-life of 3 years without any special storage conditions as stated in the SmPC (section 6.3 and 6.4) is acceptable. This medicine mixed with water, baby formula or apple juice liquid must be used within 2 hours. This medicine mixed with apple puree must be used immediately.

2.4.4.5. Adventitious agents

It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

2.4.5. Discussion on chemical, pharmaceutical and biological aspects

In this extension application no new information was presented for the active substance. The new presentations use active substance of the same quality as used in the approved presentations (2.5 mg and 5 mg film-coated tablets). Information on development, manufacture and control of the finished product has been presented in a satisfactory manner. During the procedure, the QC limit for dissolution testing was tightened for both formulations in response to two respective major objections. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.4.6. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.4.7. Recommendations for future quality development

Not applicable.

2.5. Non-clinical aspects

2.5.1. Introduction

No new non-clinical data was submitted to support the use of Eliquis in children 28 days – 18 years of age. However, two non-clinical studies in juvenile rats were performed previously; an exploratory study at the time of initial marketing authorization (2010) and a definitive juvenile toxicity study was performed within a few months after approval (2011). Both studies were assessed during previous procedures and no adverse outcomes on juvenile animals were identified in those studies at ample

margins of exposure. Dosing in the pivotal juvenile toxicity study was from post-natal development (PND) 4 to PND 90, which is considered sufficient for the requested indication from 28 days of age in humans.

2.5.2. Ecotoxicity/environmental risk assessment (ERA)

The Applicant did not perform a new ERA for the proposed variations. A new pharmaceutical form is introduced (granules) which will be a substitution of tablets in a part of the patient population. Therefore no increased use is foreseen and no new ERA would be necessary. This is accepted.

A new indication in the paediatric population will lead to an increase in use of apixaban and therefore environmental exposure. However, the Applicant justifies that this increase is already covered by the previously submitted and approved ERA, since the PEC refinement in that ERA was based on the whole patient population, including children. This justification is accepted and no new ERA is warranted.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- **Tabular overview of clinical studies**

The applicant provided data on clinical pharmacology from the pivotal PIP02 Study CV185325 for treatment of VTE and prevention of recurrent VTE, supplemented with the PIP01 Studies CV185118 (pharmacokinetics [PK]/ pharmacodynamics [PD] study), and CV185155 and CV185362 in VTE primary prophylaxis (Table 10).

The PK and PD of apixaban have been characterized in healthy adults and adult patients. PD and PK/PD relationship in paediatric patients treated with apixaban were investigated in the global paediatric development program, that has enrolled 970 patients. Clinical and extrapolation studies included in paediatric investigation plan (PIP)01 covered the conditions of prevention of venous and arterial thromboembolism and the clinical study in PIP02 covered conditions requiring treatment of an existing VTE.

Table 3. Clinical and Extrapolation Studies for PIP01 and PIP02

Study	Study Type	Study Identifier
CV185029	Comparative bioavailability study for oral solution vs tablets in adults	Study 3
CV185687	Comparative bioavailability study for oral sprinkle capsules vs 0.5 mg tablets in adults	N/A[a]
CV185118	Single doses in paediatric subjects at risk for venous or arterial thrombotic disorder	Study 4
CV185155	Multiple doses in paediatric subjects with newly diagnosed acute lymphocytic leukemia (ALL) or lymphoblastic lymphoma (LL)	Study 5
CV185362	Multiple doses in paediatric subjects with congenital or acquired heart disease requiring chronic prophylactic anticoagulation	Study 6
Population PK Study	Pharmacometric analysis of PK data accrued from studies 4 (CV185118) and 5 (CV185155)	Study 7
CV185325[3]	Multiple doses in paediatric subjects requiring anticoagulation for the treatment of a venous thromboembolic event	Study 1

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

Pharmacokinetic evaluation

The rationale of the dose regimen in study CV185325 was based on an exposure-matching strategy to adult exposures in the AMPLIFY study where apixaban was investigated for treatment of VTE.

The applicant has developed a POPPK and a PK/PD model to inform dose selection in paediatric patients.

Analysis results were used to assess the fixed-dose by weight-tiered regimen in this paediatric patient population. Stochastic simulations based on the developed final PPK model were performed to confirm the suitability of the current fixed-dose by weight-tiered regimen for subjects 28 days to < 18 years of age.

The exposure targets were based on the median daily AUCss observed in the adult VTE prevention population from the AMPLIFY EXT study, in subjects receiving apixaban 2.5 mg twice daily (BID); therein, daily exposure was ~1,200 ng • h/mL.

This assumes that efficacy was observed over the whole range of exposure reached by the 2.5 mg dose in adults.

A 2-compartment model with first-order absorption, dose-dependent F1, and first-order elimination described the plasma PK of apixaban in paediatric subjects treated for VTE (CV185325). Based on the full PPK model for apixaban:

-Apixaban Ka was higher (by 2.77-fold) in paediatric subjects aged 28 days to < 18 years compared to adults.

-Body weight was a predictor of apixaban CL/F where CL/F increased with increasing body weight.

-Apixaban CL/F was minimally lower in paediatric subjects treated for VTE (~8%) as compared to adults.

-Apixaban Vc/F was related to body weight where Vc/F increased with increasing body weight.

-For Vc/F, the effect of paediatric subjects treated for VTE was a small increase (11% higher) as compared to adults.

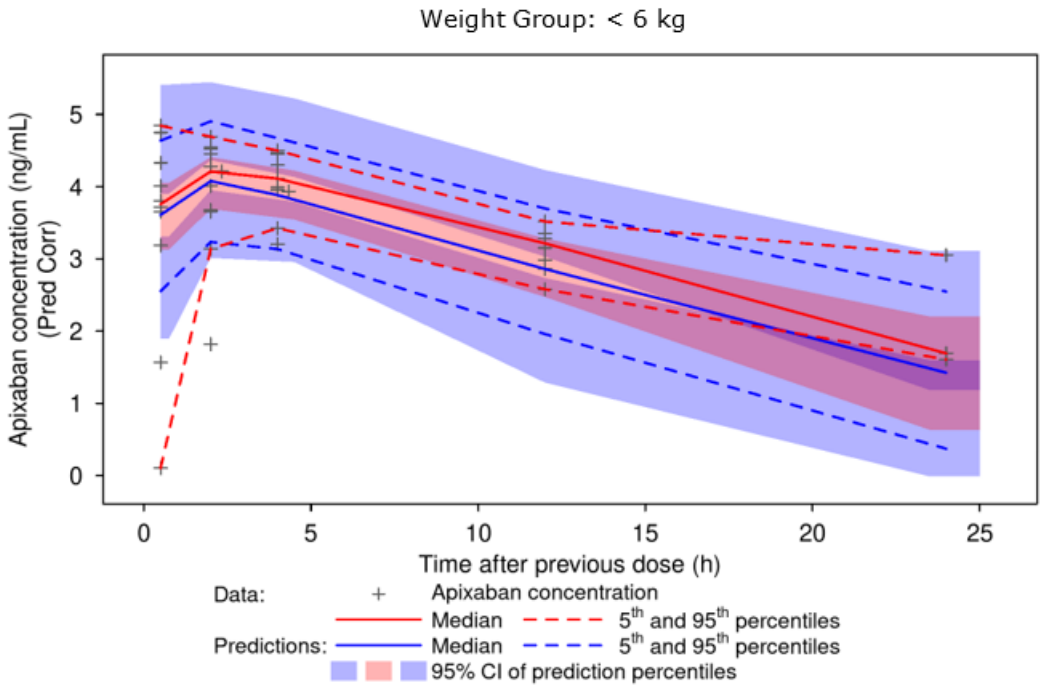
The parameters of the final Study CV185325 PPK model were well estimated and included paediatric subject effect of paediatric venous thromboembolism treatment (VTEt) subjects on Vc/F (26% increase), paediatric subjects with ALL or LL at risk of VTE treated with asparaginase on Ka (61.7% reduction), and paediatric subjects with CAHD on CL/F (18.5% reduction).

The scatterplot of apixaban CL/F versus age, coloured by age group and weight tier, for the subjects in the final analysis (Figure 2) shows that apixaban CL/F increased with increasing age until it reached the adult clearance. The scatterplot of CL/F normalized to body weight effect versus age for paediatric and adult subjects in the analysis dataset, coloured by age group (Figure below) shows that once normalized by body weight effect, CL/F in paediatric subjects was generally consistent across the paediatric age groups, except in the youngest age groups, demonstrating that maturation also plays a role in apixaban exposure in paediatric subjects < 9 months of age.

The individual estimated PK parameters and steady state exposure for subjects in Study CV185325 show a higher degree of variability in subject from 28 days to < 2 years; considering the estimated PK parameters by weight, higher variability is more evident in subjects weighting between 6 to < 9 kg.

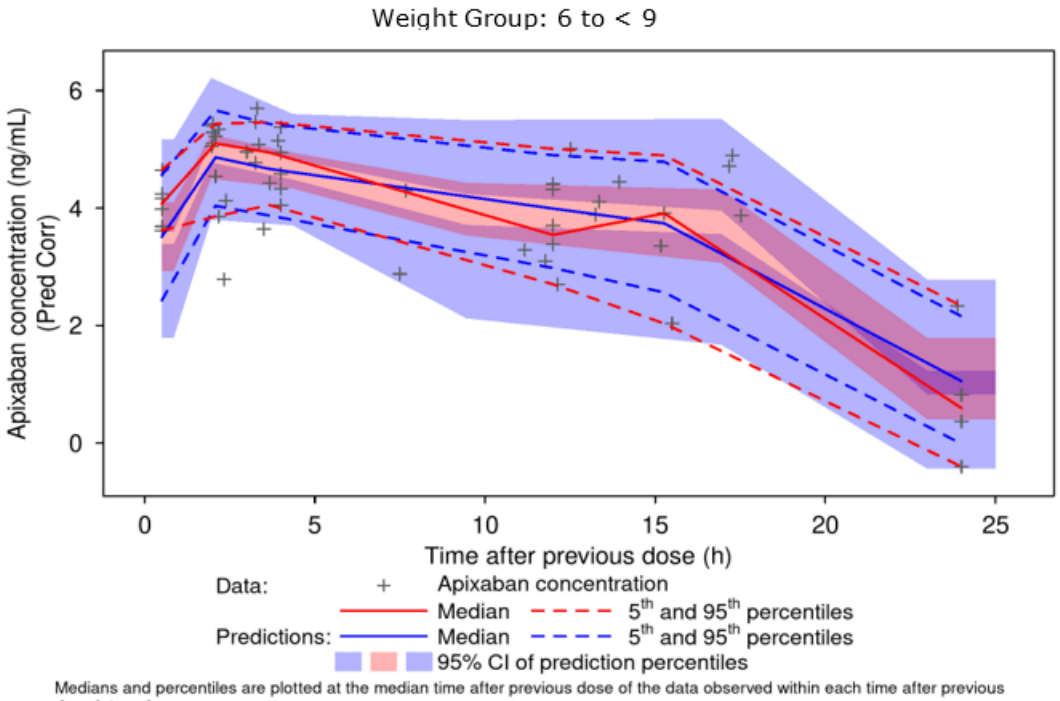
In Study CV185325, subjects of 28 days < 2 years were enrolled. Stochastic simulations were performed to assess whether exposures resulting from the current fixed-dose by weight-tiered regimen in paediatric subjects aged 28 days to < 18 years receiving apixaban for VTEt matched intended adult exposures. When comparing the predicted AUCss(TAU) values from the virtual paediatric subjects by weight tiers to the AUCss(TAU) observed in the adult VTE prevention population receiving 2.5 mg BID apixaban in the AMPLIFY EXT study, the median exposures by weight tiers were similar to those in the adult population, although with relatively higher variability among paediatric subjects compared to adults.

Figure 1. Prediction-corrected Visual Predictive Checks by Body Weight Groups



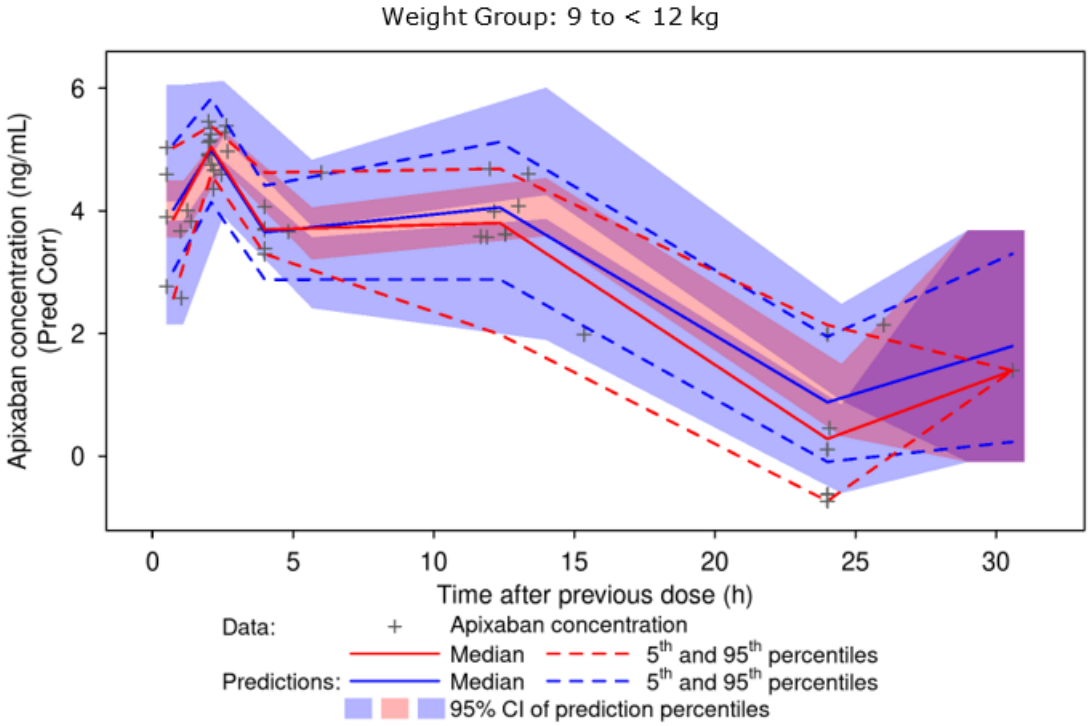
Medians and percentiles are plotted at the median time after previous dose of the data observed within each time after previous dose interval.

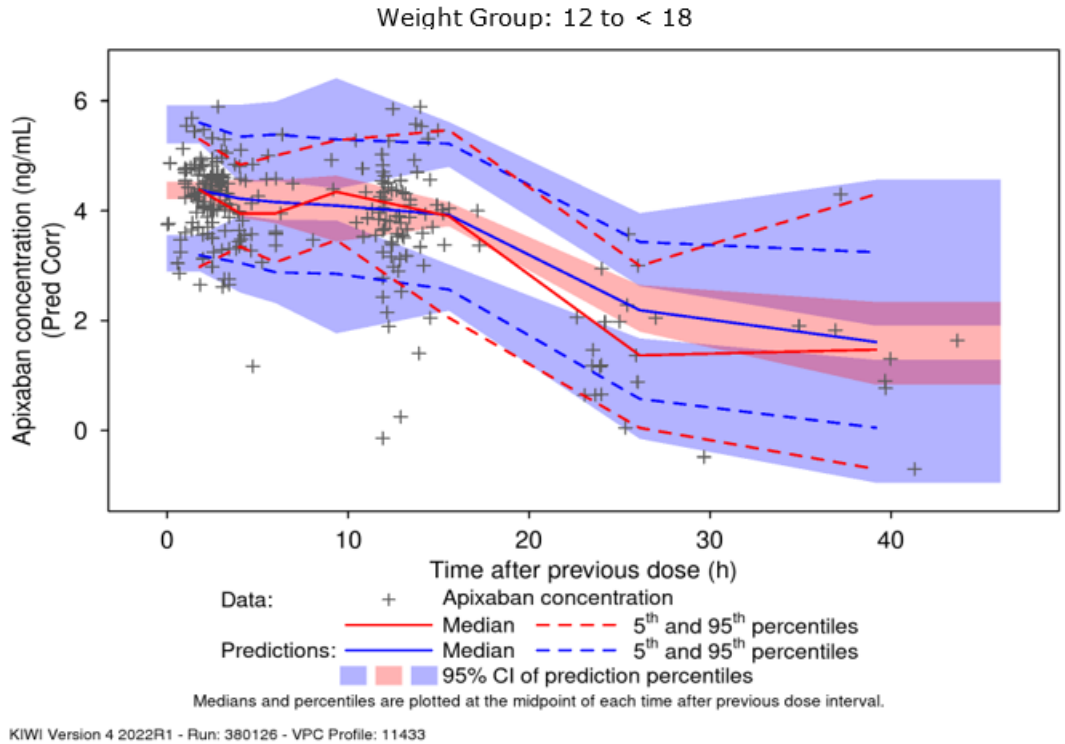
KIWI Version 4 2022R1 - Run: 380056 - VPC Profile: 11430

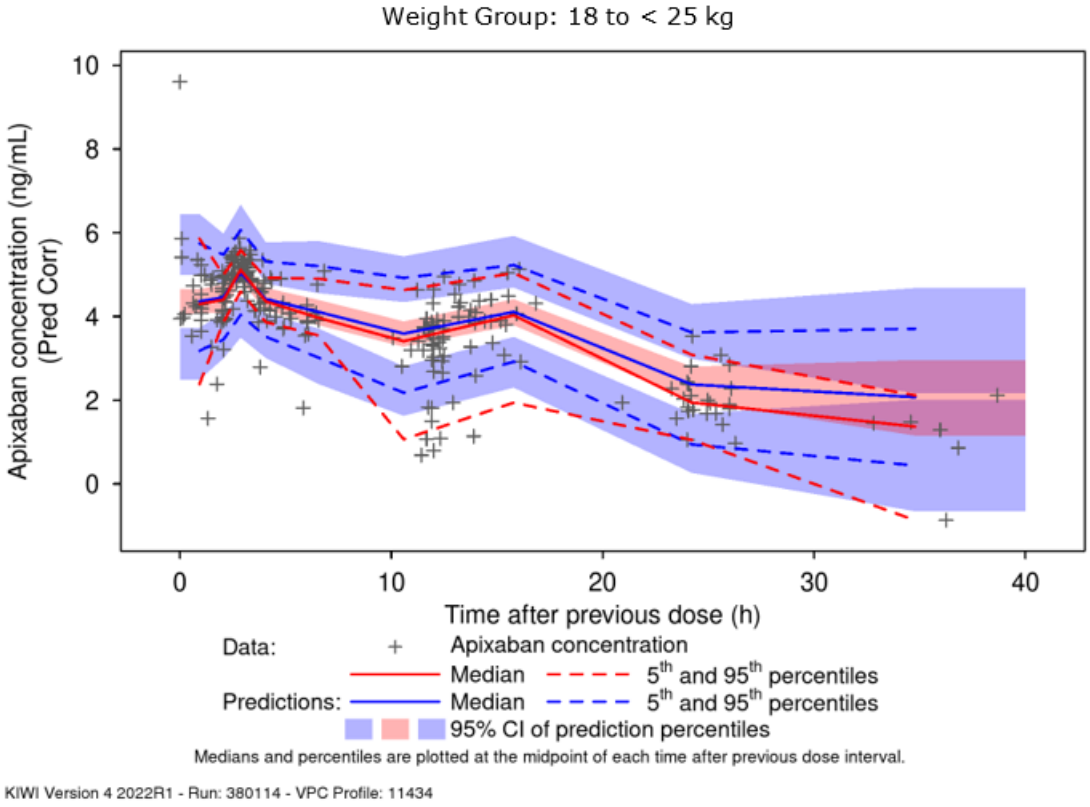


Medians and percentiles are plotted at the median time after previous dose of the data observed within each time after previous dose interval.

KIWI Version 4 2022R1 - Run: 380059 - VPC Profile: 11431

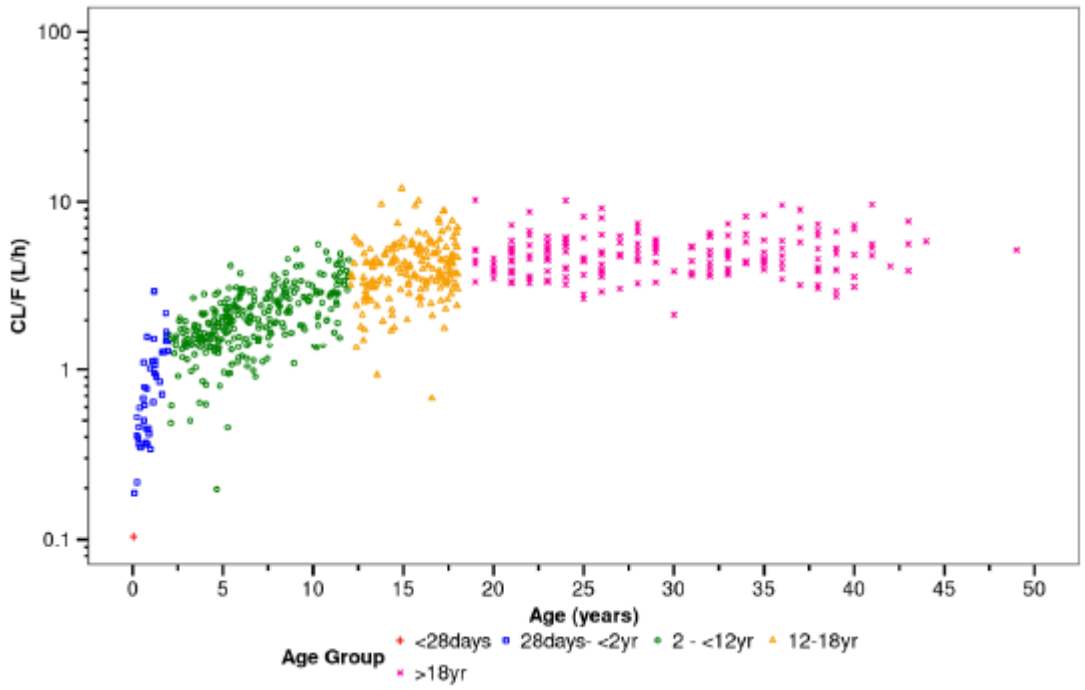

Weight Group: 9 to < 12 kg
Apixaban concentration (ng/mL) (Pred Corr)
Time after previous dose (h)
Data:
Apixaban concentration
Predictions:
Median
5th and 95th percentiles
95% CI of prediction percentiles
Medians and percentiles are plotted at the median time after previous dose of the data observed within each time after previous dose interval.
KIWI Version 4 2022R1 - Run: 380868 - VPC Profile: 11432


Weight Group: 12 to < 18
Apixaban concentration (ng/mL) (Pred Corr)
Time after previous dose (h)
Data:
Apixaban concentration
Predictions:
Median
5th and 95th percentiles
95% CI of prediction percentiles
Medians and percentiles are plotted at the midpoint of each time after previous dose interval.
KIWI Version 4 2022R1 - Run: 380126 - VPC Profile: 11433



The applicant provided pcVPCs broken by bodyweight groups. Overall, the pcVPC results stratified by body weight groups support that the PPK model structure, adequately describe the observed apixaban data across the entire body weight distribution in the analysis population. It should be noted that no separate pcVPCs for the weight group 4-5 and 5-6 kilo were provided, however, the simulation data showed sufficiently comparable exposures in these group.

Figure 2. Scatterplots of Estimated Individual Apparent Clearance Versus Age, Coloured by Age Group and Weight Tier for Adult and Paediatric Subjects in the Analysis Dataset Using the Final Population Pharmacokinetic Model - Semi-Log Scale



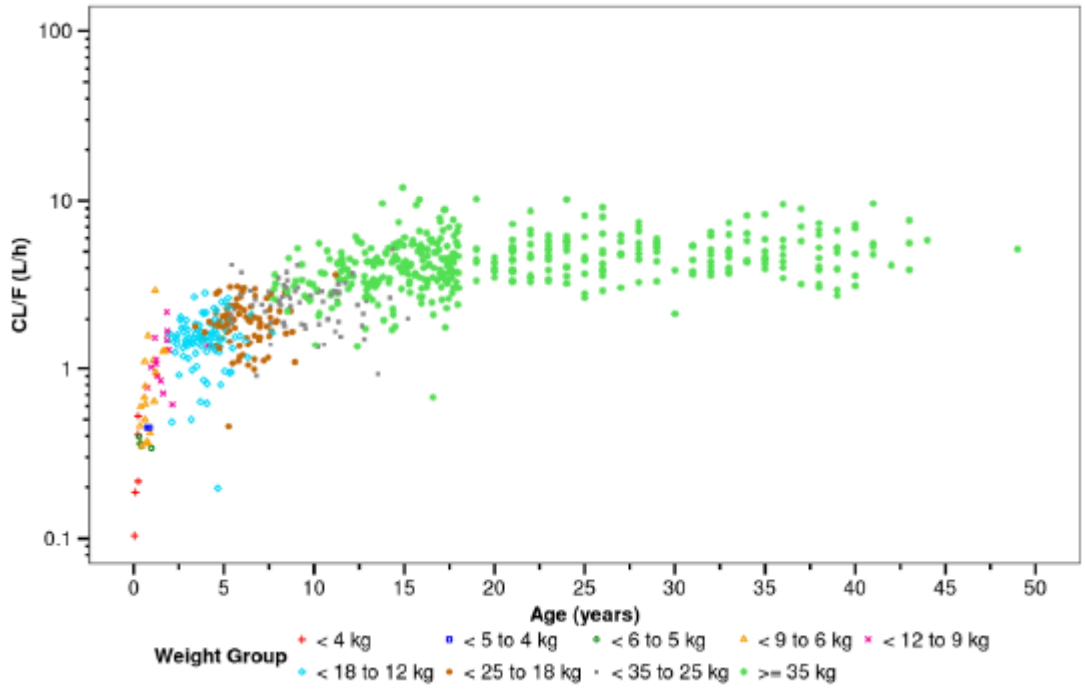
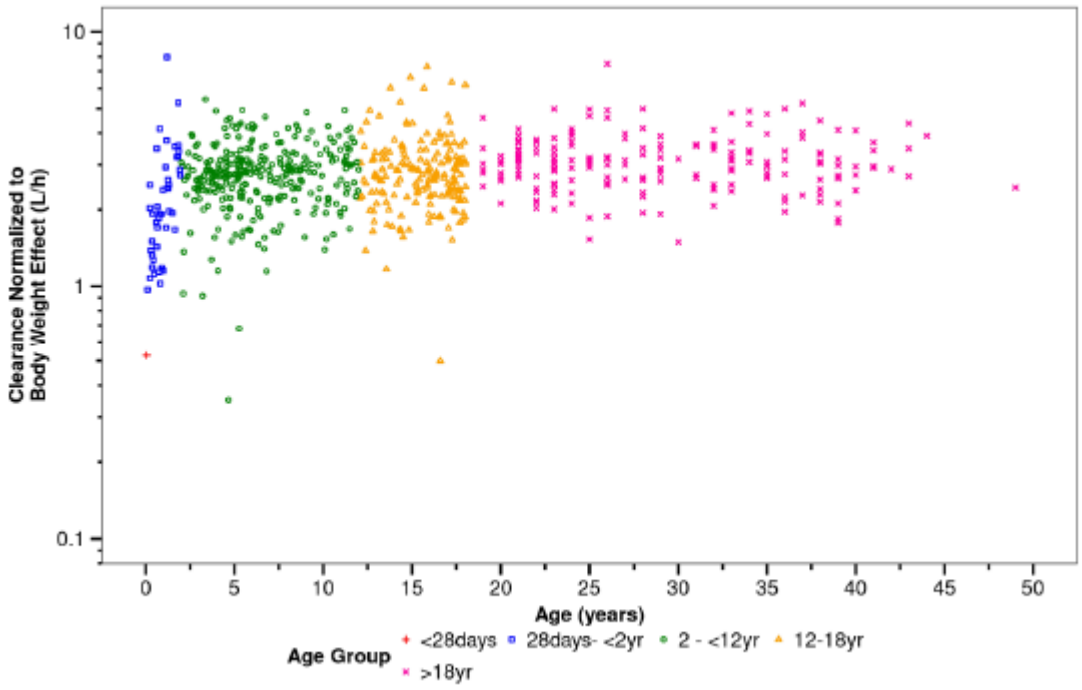
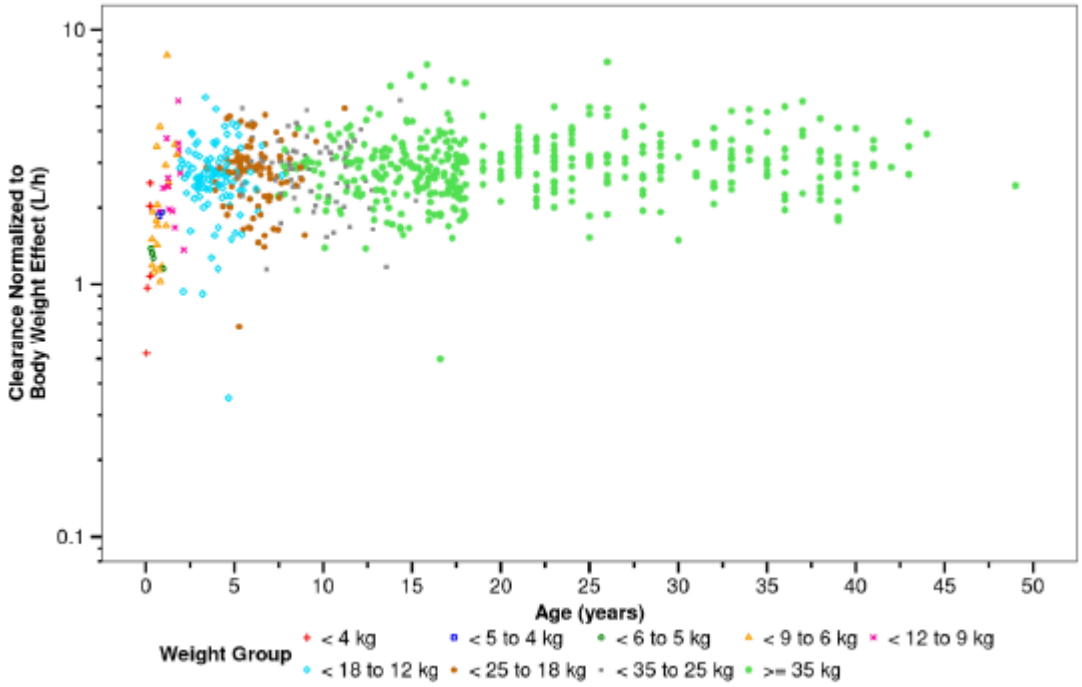


Figure 3. Scatterplots of Estimated Individual Apparent Clearance Normalized to Body Weight Effect Versus Age, Coloured by Age Group and Weight Tier, for Adult and Paediatric Subjects in the Analysis Dataset Using the Final Population Pharmacokinetic Model - Semi-Log Scale



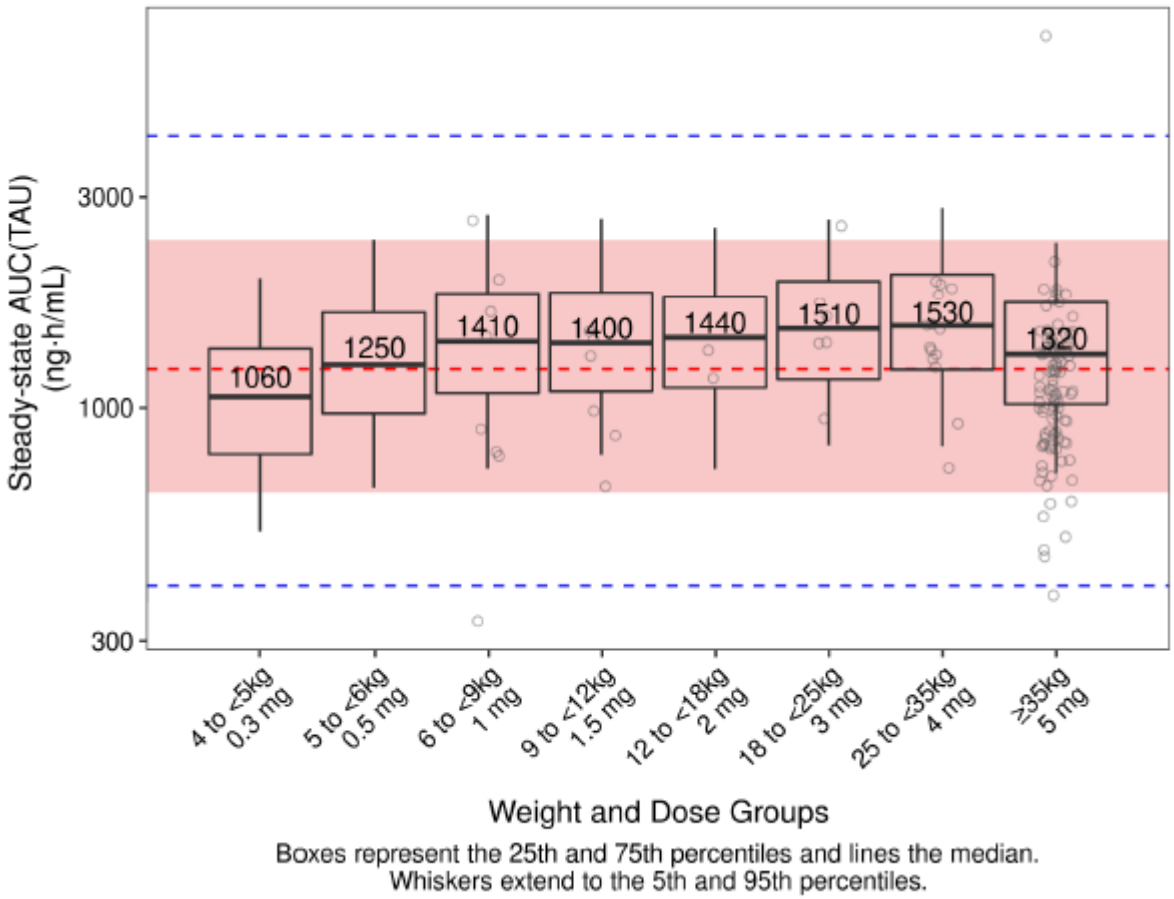


Stochastic Simulation for Dose Confirmation in Paediatric Subjects Aged 28 Days to Less Than 18 Years of Age

Stochastic simulations were performed using the final model parameters and weight-tiered dosing regimens (5, 4, 3, 2, 1.5, 1, 0.5, and 0.3 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, and 4 to < 5 kg weight tiers, respectively) to generate predictions of AUCss(TAU). The simulated AUCss(TAU) values from the virtual paediatric subjects by weight tier were compared with exposures in the adult VTEt population based on simulations with uncertainty performed to predict apixaban daily AUCss exposure. The results shown in Figure 4 are based on AUCss(TAU) exposure-matching to the apixaban 5 mg BID dose regimen in the

adult VTEt population. Model-predicted AUCss(TAU) exposures from the paediatric subjects in Study CV185325 were overlaid on the weight tier boxplots. The results show that the median exposures across the weight tiers were similar to the median exposure (1,223 ng • h/mL) in the adult VTEt population.

Figure 4. Simulated Steady State Exposures for Virtual Paediatric Subjects Aged 28 Days to < 18 Years by Weight Tiers and the Adult VTEt Population



As was demonstrated with the previously established linear relationship between apixaban concentration and AXA concentration in paediatric subjects, the final PK/PD model for Study CV185155 was a simple linear regression with an estimated slope (standard error) of 0.839 (0.0105) and a bootstrap derived 95% confidence interval (CI) of 0.817 to 0.861 for the overall data set, to describe the relationship between apixaban concentration and AXA concentration in paediatric subjects with ALL or LL treated with asparaginase via a central venous access device and at risk for VTE. Data from Studies CV185079 and CV185118 were not included in the PK/PD analysis because the assay used in these studies differed from the one used in Study CV185155. According to the MAH, due to differences in the assay methods used for the PK/PD analysis of Studies CV185079 and CV185118 versus the PK/PD analysis of Study CV185155, the estimated slope values from these analyses are not directly comparable.

The PK-AXA relationship in paediatrics was evaluated to understand if it is similar to the relationship observed in adults. A comparison of paediatric and adult apixaban PK-AXA data has been presented by the Applicant. Anti-Xa activity was measured with two different versions of assays, AXA heparin assay with LMWH as calibrators earlier in the apixaban development program and AXA apixaban assay with

apixaban as calibrators that was utilized in Studies CV185155, CV185362 and CV185325. A linear PK-AXA relationship was observed in both paediatrics and adults with either assay format. For instance, the slope estimate in paediatrics was 0.0155 IU/ng using AXA heparin assay (refer to Section 1.2.3 of the SCP [paediatrics]) compared to an estimate of 0.0159 IU/ng in adults using the AXA heparin assay (refer to Section 2.7.2.3.5.3.1 of the SCP [adults]). In addition, the slope estimate was 0.934 in paediatrics (refer to Section 3.2.4.1 of the SCP [paediatrics],) compared to 0.932 in adults (refer to the Extrapolation Study to Evaluate the Use of Apixaban in Paediatrics) using the AXA apixaban assay. Therefore, the relationship between apixaban PK and AXA in paediatrics is similar to that observed in adults regardless of the AXA assay used. Due to the linear relationship observed between PK and AXA and the estimated slope being close to 1 when the units were the same, the AXA levels closely reflect the apixaban concentrations observed and this may explain the range of AXA levels. According to the Applicant, overall, the structure of the final paediatric PPK model selected upon incorporation of data from Studies CV185155 and CV185362 was generally consistent with the PPK model selected based on adult data: a 2-compartment model with first-order absorption, dose-dependent F1, and first order elimination. Covariate analysis was implemented using the paediatric data. Most of the parameters related to covariate effects were estimated but the ones maturation function were taken from the literature:

The maturation function was represented by the equation below:

$$MF = F_{Birth} + \frac{(1 - F_{Birth}) \bullet AGE_i^{\theta_{12}}}{AGE_i^{\theta_{12}} + AGE_{50}^{\theta_{12}}}$$

Four age appropriate formulations were used in the paediatric development program, including a 0.4 mg/mL oral solution, a 0.1 mg sprinkle capsule, a 0.5 mg mini-tablet and the film coated 2.5 and 5 mg tablet approved for use in adults. The daily intake of propylene glycol for the oral solution exceeded the threshold for paediatric patients < 5 years of age, as specified in the EMA guideline, and therefore the use of oral solution was ended. At the moment, apixaban is commercially available as 2.5 and 5.0 mg film-coated tablets.

Oral administration of apixaban (tablets, mini-tablets, sprinkle capsules, or solution) to paediatric subjects based on fixed-dose by weight-tier dosing resulted in median steady-state exposures and AXA seems to be comparable to that observed in adults.

In general sufficient PK data were submitted and no additional clinical PK studies are judged needed to support this application.

Given that the use of the apixaban oral solution was discontinued based on the risks related to the maximum daily intake of propylene glycol, its bioequivalence with the other formulations is not of concern and study CV185029 should not be evaluated as part of this line extension application. Moreover, this study and the comparison of the exposures was already addressed during a previous PIP submission.

Concerning the sprinkle capsules, comparable bioavailability between the 0.1 mg sprinkle capsule and the 0.5 mg mini-tablet was established in the adult BA study CV185687. Batches of 0.1 mg capsules are used in the pivotal study CV185325. The Apixaban beads in the 0.1 mg strength drug product used in the clinical studies are similar to the Apixaban beads in the applied 0.15 mg drug product. Of note, the MAH is not seeking an approval for use of the 0.1 mg capsule in neonates at this time.

Food effect has not been studied in children. In adults, there was no substantive effect of food intake on apixaban. According to the applicant, these results can be translated to the paediatric population. Dissolution studies were conducted to compare dissolution of 0.1 mg apixaban capsule contents dispersed in baby formula (Similac Advanced, Ready to Use) in a dosing cup as per administration procedure versus a reference without baby formula. Apixaban capsules dispersed in baby formula

demonstrated similar dissolution profiles when compared to apixaban capsules tested without premixing with baby formula. Apixaban capsules contents dissolved rapidly (> 95% at 10 min) in the presence of baby formula, as well as in the control samples in the absence of baby formula. As the dissolution of apixaban is very fast regardless of method of administration no impact on bioequivalence is expected.

Concerning the 0.5 mg mini-tablets, qualitative composition and manufacturing process are identical to that of the 2.5 and 5 mg commercial tablets except for the quantity of the components per tablet. The quantitative compositions are proportional. In addition, it is known that apixaban demonstrates linear pharmacokinetics with dose proportional increases in exposure for oral doses up to 10 mg. Eliquis mini-tablets should be mixed with water, baby formula, apple juice, or apple puree. Administration of a drug product with food or soft food may change the BA by affecting either the drug substance or the drug product. In this case, the administration of soft food vehicles is already mentioned in the current SmPC for Eliquis film-coated tablets for adults and the method of administration is therefore accepted for the mini-tablets without any additional comparative bioavailability study.

Study CV185079 was prematurely stopped and replaced by study CV185118. Study CV185118 has already been submitted in a type II variation to update sections 4.2 and 5.1 of the SmPC to include efficacy and safety information in the paediatric population (EMEA/H/C/002148/II/0088). The paediatric clinical studies CV185118, CV185155 and CV185362 were previously assessed by the CHMP in the context of Article 46 procedures (EMEA/H/C/002148/P46/037, EMEA/H/C/002148/P46/038, EMEA/H/C/002148/P46/039).

2.6.2.2. Pharmacodynamics

Mechanism of action

Apixaban (BMS-562247) is a potent, oral, reversible, direct, and highly selective inhibitor of FXa. It does not require antithrombin III for antithrombotic activity. Apixaban inhibits free and clot bound FXa along with prothrombinase activity. Activation of factor X to FXa via the intrinsic and extrinsic pathways plays a central role in the cascade of blood coagulation. By inhibiting FXa, apixaban prevents thrombin generation and thrombus development. Apixaban has no direct effects on platelet aggregation, but indirectly inhibits platelet aggregation induced by thrombin.

Primary pharmacology

In PIP01-study CV185362 the chromogenic FX assay showed a decrease from baseline in apparent FX levels after treatment with apixaban at Day 1, Week 2, Month 3, and Month 6, consistent with the mechanism of action of apixaban as a direct FXa inhibitor. The magnitude of decrease represented by the percent change from baseline appeared to be greater at 2 to 4 hours post dose (near apixaban peak plasma concentrations) compared with that at pre-dose (near apixaban trough plasma concentrations) (Table 11).

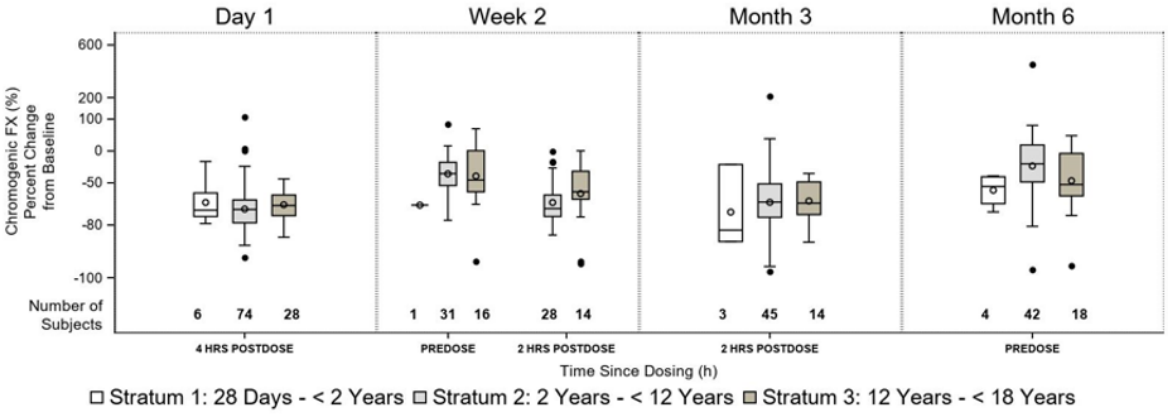
Table 4. Summary Statistics for Chromogenic FX Assay (%) in Subjects Treated with Apixaban – PD Population- Study CV185362

Visit	Time (h)	N	Mean (SE)	Median (Min - Max)
DAY 1	PREDOSE	115	58.87 (2.37)	53.00 (5.5 - 124.0)
	4 HRS POSTDOSE	117	18.90 (1.21)	17.00 (5.5 - 96.0)
WEEK 2	PREDOSE	52	35.88 (1.97)	34.50 (5.5 - 77.0)
	2 HRS POSTDOSE	45	21.26 (1.68)	19.00 (5.5 - 70.0)
MONTH 3	2 HRS POSTDOSE	67	18.25 (0.97)	17.00 (5.5 - 52.0)
MONTH 6	PREDOSE	69	36.57 (1.94)	35.00 (5.5 - 85.0)

population included subjects who received at least one dose of apixaban and had chromogenic FX assay and/or anti-FXa samples collected. Chromogenic FX<LLOQ (11%) pre-dose and post-dose was analyzed as ½ LLOQ (5.5%).

Results for percent change from baseline of chromogenic FX assay across age groups (Figure 5) are consistent with those in the overall PD population.

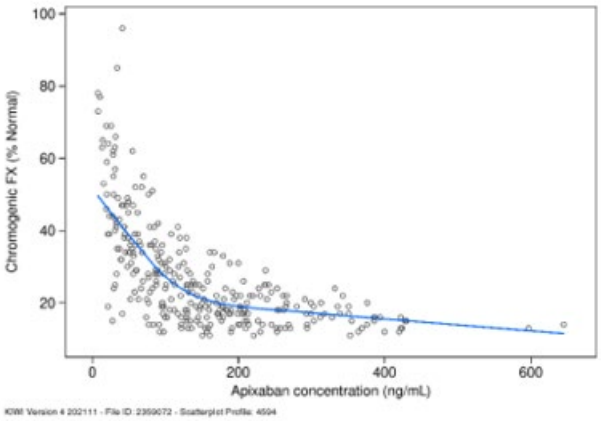
Figure 5. Box and Whisker Plot of Chromogenic FX Assay (%) Percent Change from Baseline in subjects Treated with Apixaban by Age – PD Population (CV185362)



population included subjects who received at least one dose of apixaban and had chromogenic FX assay and/or anti-FXa samples collected. Chromogenic FX<LLOQ (11%) pre-dose and post-dose was analyzed as ½ LLOQ (5.5%). Symbols: open cirle=mean; solid circle=outlier; horizontal bar=median; vertical bar=range.

A graphical assessment of the relationship between apixaban concentration and FX and is shown in Figure 6. With increasing apixaban concentration, FX decreases as shown by the pattern of the blue smoother line. This relationship suggests inhibition of FXa with administration of apixaban dose regimens in paediatric subjects with congenital or acquired heart disease that achieve exposures similar to those observed in adults treated for VTE.

Figure 6. Scatterplot of the Relationship Between Apixaban Concentration and Chromogenic FX (%) Overall, Linear Scale



Abbreviation: FX = factor X.

Secondary pharmacology

PIP01-study CV185362 included an objective to evaluate exploratory biomarkers that may inform anticoagulant efficacy or risk of thrombosis, including FVIII, fibrinogen, protein C, protein S, D-dimer,

and thrombin generation. Exploratory biomarker samples were obtained from 123 subjects in the apixaban arm and 59 subjects in the SOC arm.

Biomarkers. D-dimer is a marker for fibrin clot turnover in vivo. Proteins C and S are anticoagulant proteins, while FVIII and fibrinogen directly participate in the coagulation cascade leading to thrombus formation. The Thrombin Generation Assay (TGA) is an ex vivo assay that measures thrombin generation upon activation of the extrinsic coagulation pathway. This assay is independent of fibrin formation and provides valuable information on capacity to generate thrombin, which is the key step in the activation of coagulation. FXa is the key enzyme required to convert prothrombin to thrombin; as a direct FXa inhibitor, apixaban is expected to have inhibitory effects in the TGA assay. TGA assay parameters include lag-time (time needed for the first amounts of thrombin to be generated), Peak-thrombin (the highest thrombin concentration that can be obtained under the experimental conditions), Time to peak (time needed to reach peak thrombin concentration), Velocity index (the rate of thrombin generation), and ETP (area under the thrombin generation curve, representing the net amount of thrombin that the test plasma can generate).

VKA is known to decrease the production of vitamin K dependent proteins, including FII (prothrombin), FVII, FIX, FX, protein C and protein S; when a patient was switched to apixaban from VKA upon randomization, their subsequent biomarker changes would reflect both the effects of the addition of apixaban and the discontinuation of VKA. Therefore, analysis of biomarker data was stratified by whether the patient received VKA prior to randomization to study treatment. Eighty-six (70%) patients randomized to apixaban were treated with VKA prior to study entry.

In both SOC and apixaban treatment subgroups without prior VKA, raw D-dimer levels were significantly decreased at Month 6 from baseline, while the CFB in the previously VKA-treated apixaban subgroup did not reach statistical significance; the latter was likely due to the lower D-dimer levels present in this group at baseline as a result of prior VKA treatment. A similar observation was made in the ARISTOTLE biomarker sub-study, wherein D-dimer levels at baseline were lower in patients with prior VKA treatment.

Proteins C and S decreased from baseline in the SOC subgroups. Protein C and S levels increased in the apixaban subgroup with prior VKA treatment; however, there was no evident change from baseline (CFB) in the apixaban subgroup without prior exposure to VKA. Mechanistically apixaban is not expected to affect protein C or S blood levels. This absence of an impact of apixaban treatment on the levels of these factors is substantiated by results from the apixaban subgroup with no prior VKA exposure, in which no changes in levels of protein C or S were observed post-randomization to apixaban. Therefore, the increase of protein C and S observed post-randomization in the apixaban subgroup with prior VKA exposure can be reasonably explained as representing a recovery of the hepatic synthesis of these vitamin K dependent factors following VKA withdrawal.

Thrombin generation profiles differed between the apixaban and SOC treatment groups. TGA lag time and time to peak were significantly prolonged in the apixaban subgroups compared to the SOC subgroups at Week 2 and Month 6. Peak thrombin and endogenous thrombin potential (ETP) were reduced in the SOC subgroup with prior VKA. In the apixaban subgroup with prior VKA, paradoxical increases in ETP and peak thrombin were observed, probably due to the carryover effects from prior VKA treatment that resulted in lower baseline values. In patients with no prior VKA treatment, ETP and peak thrombin levels were significantly reduced from baseline in both SOC and apixaban subgroups.

By inhibiting **FXa**, the key enzyme that directly activates thrombin, apixaban is expected to inhibit the rate and magnitude of thrombin generation. This was demonstrated by the apixaban subgroup with no

prior VKA exposure, in which apixaban prolonged lag time and time to peak, reduced the rate of thrombin generation, peak thrombin level, and ETP. These pharmacodynamic changes in TGA parameters were also directly correlated with apixaban concentrations.

Fibrinogen and FVIII levels decreased at Month 6 in the apixaban subgroup with no prior VKA treatment.

The relationship between apixaban concentration and biomarker levels was explored. No correlation was found between apixaban concentration and D-dimer, protein C, protein S, FVIII or fibrinogen levels. Positive correlation was observed between apixaban concentration and TGA lag time and time to peak, and negative correlation was observed between apixaban concentration and TGA ETP, peak thrombin and velocity index.

Overall, these observations were generally consistent with the mechanism of action of apixaban as a direct factor Xa (FXa) inhibitor.

Relationship between plasma concentration and effect

The PK/PD model of anti FXa activity (AXA) for paediatric subjects has been developed using data from healthy adults and adult subjects treated for VTE. During the clinical development programme, AXA activities were assessed with two different versions of assays with units of either IU/mL (LMWH as calibrator, used earlier in the program including most adult studies) or ng/mL (apixaban as calibrator). The relationship between apixaban concentration and AXA in adult subjects was described using a linear model with a fixed intercept of zero. The slope of the linear relationship was estimated to be 0.0159 IU/ng with the AXA heparin assay or 0.932 with the AXA apixaban assay, with negligible between-subject variability.

In single-dose **PIP01 study CV185118** AXA was found to be linearly related to apixaban concentration with no apparent age-related differences in slope in the paediatric age groups (slope estimate of 0.0155 IU/ng). The slope in paediatrics was comparable to that in adults.

In **PIP01-Study CV185155**, apixaban was administered according to a fixed-dose, body weight-tiered regimen designed to produce exposures comparable to those seen in adults who received 2.5 mg twice daily in the AMPLIFY-EXT trial, with steady-state median area under the concentration-time curve in one dosing interval (AUC[TAU]) of 620 ng•hr/mL. The final PK/PD model for study CV185155 (based on 151 AXA values from 130 subjects) was a simple linear regression with an estimated slope (standard error) of 0.839 (0.0105) with bootstrap derived 95% CI of 0.817-0.861 for the overall data to describe the relationship between apixaban concentration and AXA. Generally, AXA showed a linear relationship with apixaban concentrations across different age and weight groups.

In **PIP01-Study CV185362,** apixaban was administered according to a fixed-dose, body weight-tiered regimen designed to produce exposures comparable to those seen in adults who received a dose of 5 mg twice daily (AMPLIFY, AMPLIFY-EXT, and ARISTOTLE-trial). In these trials in adults, the steady-state median area under the concentration-time curve in one dosing interval (AUC[TAU]) was 1200 ng•hr/mL. The pre-dose AXA levels were similar at Week 2 and Month 6, with mean values of 86.24 and 66.93 ng/mL, respectively. Two hours post-dose, mean values for AXA were increased at day 1, week 2 and month 3, with similar values at Week 2 and Month 3 at 242.34 and 228.88 ng/mL, respectively. Results for AXA were consistent across age groups.

In **PIP02-study CV185325,** a PK/PD interim analysis was performed to assess the relationship between AXA and apixaban concentration in paediatric subjects treated for VTE in age Groups 1 to 3. Only AXA values greater than the lowest reportable range (35 ng/mL) were included. Time-matched apixaban concentrations and AXA data from study CV185325 was pooled with data from study CV185155 and study CV185362 for PK/PD analysis since the assay used to measure AXA levels in these three studies was similar. The dataset for the PK/PD analysis included 772 measurable AXA concentrations from 382 subjects.

The final PK/PD model for studies CV185325, CV185155, and CV185362 was a linear mixed effects model with an estimated slope (standard error) of 0.934 (0.00523) with the AXA apixaban assay with bootstrap derived 95% CI of 0.917 – 0.933 for the overall data to describe the relationship between apixaban concentration and AXA (Table 12). These results are consistent with the prior AXA evaluation using data from studies CV185155 and CV185362.

Table 5. 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	0.934	0.00523	0.917 - 0.933	0.925
Random Effects				
Parameter	**Value**		**Residual**	
Standard Deviation	0.065		12.8	

The maximum and minimum AXA activity (AXAmax, AXAmin) for each paediatric subject in the analysis dataset was calculated using the slope parameter and individual Cmaxss and Cminss. Table 13 summarizes the AXAmax and AXAmin for paediatric subjects in Study CV185325 by weight tiers.

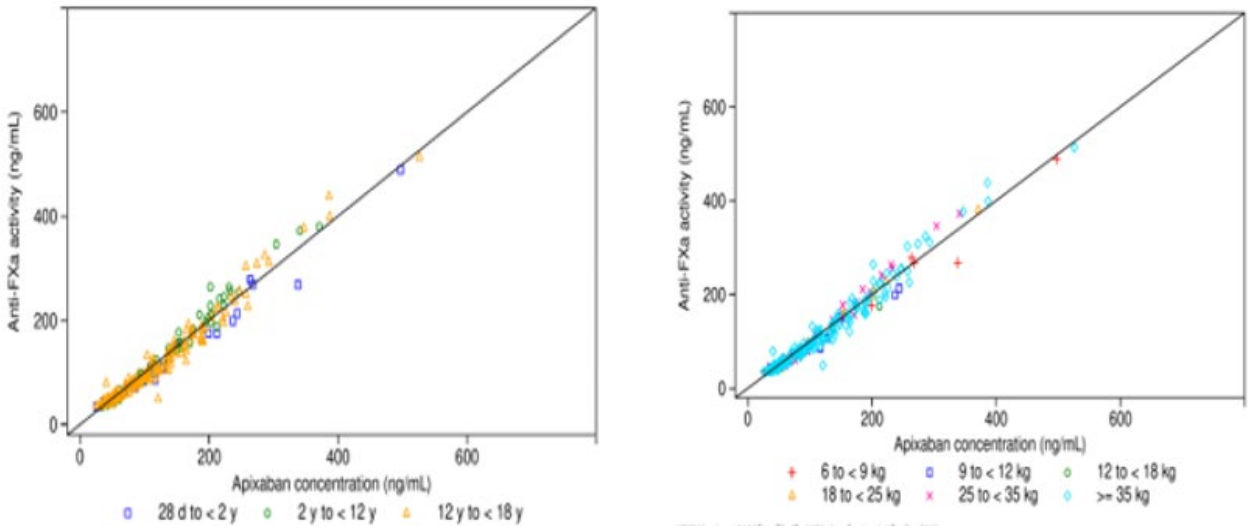
Table 6. Summary of Geometric Mean (%CV) of Predicted Maximum and Minimum AXA values of paediatric subjects in Study CV185325

Weight Tier	AXAmax (ng/mL) Geometric Mean (%CV)	AXAmin (ng/mL) Geometric Mean (%CV)
6 to < 9 kg (n = 7)	170 (42.8)	50.4 (84)
9 to < 12 kg (n = 6)	151 (26.3)	31.7 (63.5)
12 to < 18 kg (n = 2)	171 (7.11)	40.3 (8.58)
18 to < 25 kg (n = 6)	218 (28.3)	55.6 (57.3)
25 to < 35 kg (n = 14)	190 (32)	58.8 (38.8)
≥ 35 kg (n = 94)	135 (39.4)	46.2 (57.1)
Overall (n = 129)	146 (40.2)	47.1 (57.2)

Abbreviations: n, number of individuals.

Observed AXA versus apixaban plasma concentration for paediatric subjects stratified by age group and weight group are shown in Figure 7. In general, AXA showed a linear correlation with apixaban concentrations across age and weight groups.

Figure 7. Observed AXA vs. Apixaban concentrations, stratified by Age(left) and weight (right) Group – Study f185325



Extrapolation exercise based on the criterium of pharmacology

The pathophysiology of intravascular thrombus formation and embolization are similar in adults and paediatric subjects particularly after the first 6-12 months of life. In both adults and children, stasis of blood flow, vascular endothelial injury, and altered circulatory hemodynamics may contribute to activation of the coagulation cascade and an increased risk of thrombosis. The balance between pro- and anti-thrombotic components of the coagulation cascade are known to undergo a maturational process, in which blood concentrations of individual clotting factors change progressively over time. In studies by Andrew et al. in subjects aged from birth upto 18 years, different patterns of maturation was seen with lower concentrations for fII, V, VII, IX, X and Xii, antiplasmin, prekallikerein, protein C and S, and higher concentrations for TPA and PAI-I. However, general assessment of the coagulation system by standard tests, e.g. prothrombin time (from neonatal period), aPTT (from 3 months post-partem) and bleeding time (from neonatal period), is suggestive of a comparable function of the coagulation cascade across age-groups.

Pharmacodynamic effects. FXa is the key enzyme in the prothrombinase complex required for conversion of prothrombin to thrombin. As a direct FXa inhibitor, apixaban is expected to have inhibitory effects for FXa activity, thrombin generation, and D-dimer formation.

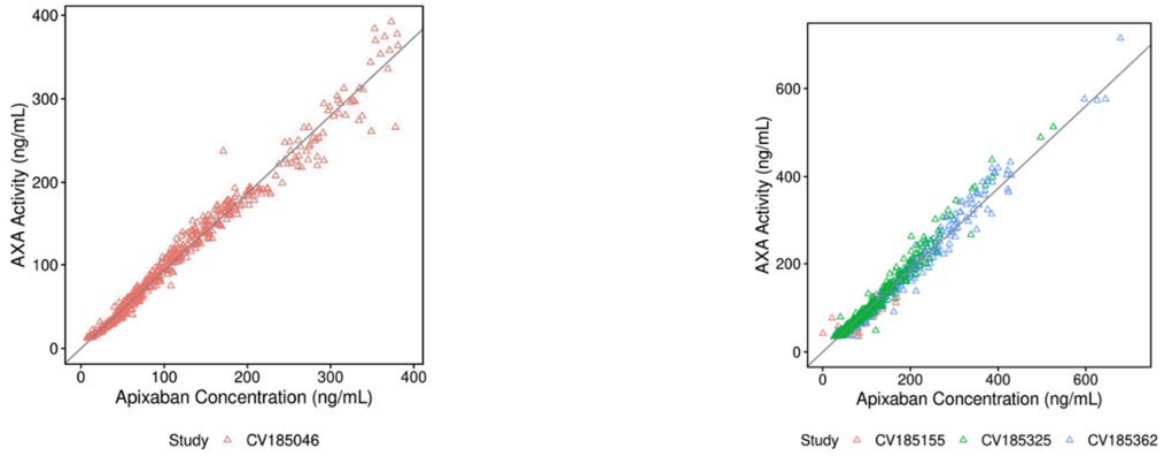
In adult study CV185030, after 2 months of apixaban treatment, **plasma D-dimer** was reduced in the sub-group of patients who had not received prior therapy with a Vitamin K antagonist (VKA), with a geometric mean ratio (GMR) of post-treatment levels relative to baseline (95% CI) of 0.77 (0.74 to 0.80). In the paediatric Study CV185362 (SAXOPHONE), similar trends were observed. In the no-prior VKA sub-group at Month 6, apixaban treatment was associated with fold-change in D-dimer relative to baseline (95% CI) of 0.51 (0.27-0.96) (P=0.0013). Thus, apixaban treatment reduced D-dimer levels in both adult and paediatric patients in a similar fashion.

The **thrombin generation assay (TGA)** is an ex vivo assay that measures the dynamics of thrombin generation under experimental conditions. TGA parameters include endogenous thrombin potential (ETP), defined as the area under the thrombin generation curve, which represents the net amount of

thrombin that the test plasma can generate under the experimental conditions. In the no-prior VKA apixaban treatment sub-group of Study CV185362, the ETP fold change relative to baseline (95% CI) at Month 6 was 0.86 (0.68-1.08), representing a 14% decrease at a mean apixaban concentration of 74.6 ng/mL (data on file). In healthy Caucasian adult participants in Study CV185013 (mean apixaban concentration of 71.7 ng/mL) a similar decrease of 9.1 (12.4)% [mean (SD)] ETP decrease from baseline was seen.

The assessment of **AXA level** is relevant to the direct inhibitory effect of apixaban on coagulation FXa. In adults, anti-FXa exhibited a direct linear relationship with apixaban plasma concentration, reaching maximum values at the time of apixaban peak plasma concentrations as expected. For the PK-AXA analysis in paediatric Studies CV185118 and CV185079, the AXA heparin assay was used and AXA was measured in UI/mL. A linear PK-AXA relationship was observed with the slope estimate being 0.0155 IU/ng with no apparent age-dependent differences in slope. This is consistent with the slope estimate of 0.0159 IU/ng that was previously determined in adults. In addition, PK-AXA analysis was also performed with time-matched apixaban PK and AXA data collected from paediatric Studies CV185155, CV185362 and CV185325. The AXA apixaban assay was used in these studies and AXA was measured in ng/mL. A linear mixed effects model with a single overall slope parameter was considered as a more parsimonious model and was selected as the final PK/PD model to describe the relationship between apixaban concentration and AXA concentration in Study CV185325. The slope estimate for the CV185325 analysis was 0.934. This estimate was similar compared to the slope estimate of 0.932 in adult Study CV185046 in healthy Japanese male participants who received apixaban at doses of 2.5 mg, 5 mg, and 10 mg twice daily for 7 days. The median, 5th, and 95th percentiles of the prediction interval were overlaid on the observed data. As shown in Figure 8, the final models captured the variability and the relationship between AXA concentration and apixaban concentration in the analysis dataset reasonably well.

Figure 8. Goodness-of-fit plot comparison between adult Study CV185046 (Left Figure) and Paediatric Studies, CV185155, CV185325, and CV185362 (Right Figure)



There is no established target exposure range for AXA because AXA is a pharmacodynamic marker reflective of apixaban's mechanism of action. Therefore, rather than aiming for a particular target AXA, evaluation of AXA was based primarily on assessing whether the PK-AXA relationship was consistent between paediatrics and adults. Since the PK-AXA relationship was observed to be similar in paediatrics and adults, the link between AXA levels and drug efficacy can be established using extrapolation based on PK matching. Achieving PK exposures in paediatrics similar to those associated with efficacy in adults should ensure that similar AXA levels are achieved in paediatrics as those associated with efficacy in adults.

Effects of apixaban on **FVIII**, **fibrinogen**, and **Protein C and Protein S** in general were consistent for adults and paediatric subjects.

2.6.3. Discussion on clinical pharmacology

Apixaban (BMS-562247) is a potent, oral, reversible, direct, and highly selective inhibitor of FXa. The **Mechanism-of-Action** is considered well established. In adults PD effects of apixaban that were established include inhibitory effects on FXa activity, prolongation of clotting tests such as PT/INR, aPTT, and mPT, as well as ex vivo thrombin generation. The effect of apixaban on anti-Xa activity was assessed in multiple clinical trials, covering a dose-range of 2.5 to 20 mg.

In PIP01-study CV185362, a dose-dependent decrease in FX levels after treatment with apixaban, determined by the chromogenic FX assay, was demonstrated to a similar extent for the different age-groups. Findings on **pharmacodynamic biomarkers** (chromogenic FX level, D-dimer, thrombin generation, FVIII, fibrinogen, protein C, protein S) were consistent with the previously characterized mechanism of action of apixaban as a direct FXa inhibitor, and in general consistent with findings in adults.

In adult subjects, based on a dose range of 2.5 mg to 20 mg, a linear **PK-PD relationship** between apixaban concentration and AXA was reported, with an estimated slope of 0.0159 IU/ng with the AXA heparin assay (0.932 with the AXA apixaban assay), with negligible between-subject variability. For paediatric subjects, PK/PD relationship has been investigated in the paediatric development programme, including PIP01 studies CV185118, CV185155 and CV185362, and PIP02 study CV185325, and covered a dose range of 2.5 to 5 mg. In study CV185118 a different assay to determine AXA was used, therefore, the PK/PD analysis results from studies CV185155, 185362 and 185325 were used for the PK/PD model analysis. The dosage investigated in Study CV185155 was aimed at achieving similar exposure as adults dosed 2.5 mg BID (dose for the prevention of venous thromboembolism (VTEp) in adults), and the dosage in Studies CV185362 and CV185325 were aimed at achieving similar exposures as adults dosed 5 mg BID (maintenance dose for the treatment of VTE in adults).

AXA measurements < LLOQ (35 ng/ml) and AXA values without time-matched apixaban concentrations were removed. BLQ AXA measurements were mostly seen at a longer time interval postdose (>10 hours) and were mostly associated with lower apixaban concentrations (< 30 ng/ml). Therefore, the BLQ values for AXA are likely not a reflection of an attenuated PD response within a subset of individuals, but rather a consequence of the AXA sampling being performed at late time points postdose and/or at times of low apixaban concentrations. The dataset consisted of 772 measurable AXA concentrations from 382 subjects.

The final PK/PD model was a linear mixed effects model with estimated slope (standard error) of 0.934 (0.00523) with the AXA apixaban assay, similar to the linear PK-AXA relationship that was established in adults. Comparable results were seen across age and weight (ranging from 6 to >= 35 kg).

2.6.4. Conclusions on clinical pharmacology

With regard to PK, no additional clinical PK studies are judged needed to support this application. The POPPK model predictions are overall acceptable.

The Mechanism-of-Action and the pattern of effects on pharmacodynamic biomarkers of apixaban in paediatric patients has been demonstrated to be consistent with results in adults, also including demonstration of a linear PK-PD relationship for apixaban concentration and AXA.

2.6.5. Clinical efficacy

The proposed extension of indication of treatment of VTE and prevention of recurrent VTE from adults to paediatric patients from 28 days to less than 18 years of age is based on a pre-specified interim analysis of pivotal PIP02 Study CV185325 (Table 14). Enrolment for age group 4 (neonates from birth to 27 days of age) is ongoing; data available at the time of the data cut-off for the interim analysis have been included; however, the MAH is not seeking an approval for use in neonates at this time.

Supportive studies are PIP01 Studies CV185155 and CV185362 in VTE primary prophylaxis in 921 paediatric subjects, 519 of whom received apixaban. Results from study CV185118 are not included, since efficacy was not a defined endpoint in this single-dose pharmacokinetics (PK), safety and tolerability Study.

Table 7. Apixaban Paediatric Studies Conducted under PIP01 and PIP02 Providing Efficacy Data

Protocol No.	Study Design	Primary Objective(s)	Study Population (Planned/Analyzed)	Dose/Schedule
CV185155	A Phase 3, randomized, open-label, multi-center study of the safety and efficacy of apixaban for thromboembolism prevention vs no systemic anticoagulant prophylaxis; randomized 1:1; stratified by age group	(1) To compare the effect of apixaban vs SOC on the composite endpoint of VTE and VTE-related-death (2) To assess the effect of apixaban vs SOC on major bleeding events	Subjects (1 to < 18 years) with newly diagnosed ALL/LL with a CVAD who were undergoing induction chemotherapy including asparaginase (~500/512)	Apixaban group: fixed-dose by weight tier regimen PO or via a NGT or GT BID for 29±5 days; SOC group: No systemic anticoagulant
CV185362	A Phase 2, prospective, randomized, open-label, multi-center study of the safety of apixaban vs VKA/LMWH and PK of apixaban; randomized 2:1; stratified by age group and clinical diagnosis	(1) To assess the safety of apixaban compared to VKA/LMWH (2) to evaluate apixaban PK	Subjects (28 days to < 18 years) and weighing ≥ 3 kg, with congenital or acquired heart disease requiring chronic anticoagulation for thromboprophylaxis (~200/192)	Apixaban group: fixed-dose by weight tier regimen PO or via a NGT or GT BID for up to 12 months; VKA/LMWH group: per local SOC
CV185325	A randomized, open-label, active controlled, safety and descriptive efficacy study in paediatric subjects requiring anticoagulation for the treatment of a VTE	(1) To assess the safety and descriptive efficacy of apixaban in paediatric subjects requiring anticoagulation for the treatment of a VTE.	Paediatric 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 (~250/217)	Apixaban group: fixed-dose by weight tier regimen PO or via a NGT or GT BID for up to 12 weeks SOC group: UFH, LMWH or VKA per local SOC for subjects aged > 2 years; Heparins only (ie, UFH or LMWH) for subjects aged < 2 years

Abbreviations: ALL = acute lymphoblastic leukemia; BID = twice daily; CVAD = central venous access device; GT = gastric tube; LL = lymphoblastic lymphoma; LMWH = low molecular weight heparin; NGT = nasogastric tube; PK = pharmacokinetics; PO = by mouth; SOC = standard of care; UFH = unfractionated heparin; VKA = vitamin K antagonist; VTE = venous thromboembolism.

2.6.5.1. Dose response study(ies)

Dose Selection for Paediatric Clinical Studies

Apixaban, 2.5 mg twice daily (BID), was shown to be safe and effective in adults for the prevention of venous thromboembolism (VTEp) following elective knee and hip surgery (ADVANCE 2 and 3) and the

prevention of recurrent DVT and PE (AMPLIFY-EXT). In addition, apixaban, 5 mg BID was shown to be safe and effective for VTE treatment (AMPLIFY, AMPLIFY-EXT) or prevention of VTE associated with NVAF (ARISTOTLE).

Dose-selection in paediatric patients was based on exposure-matching strategy to reference adult exposures (median area under the concentration vs. time curve at steady state) that were deemed to be safe and efficacious, using PPK modeling. Key assumptions were that apixaban exposures proven to be safe and effective in the adult VTEt studies would be similarly safe and effective in the targeted paediatric VTEt population. An iterative model-based approach was employed to guide the conduct of this development program. As such, the PPK and PK/PD model was updated based on studies CV185155, CV185362 and CV185325 to further refine dose selection for the respective age groups in these subsequent studies.

Study CV185118 was an open-label, multi-site, single-dose phase 1 study of apixaban with the purpose of evaluating the Pharmacokinetics, Pharmacodynamics, safety, and tolerability following single oral doses of apixaban in paediatric subjects at risk for venous or arterial thrombotic disorder.

Study Participants. Male and female paediatric subjects, with or without a central venous catheter or arterial line and at risk for a venous or arterial thrombotic disorder, from birth to <18 years of age were eligible for participation (post-neonate waiver: 28 days to <18 years of age). Overall, 8 subjects were planned to be recruited in each of 5 age groups, neonates up to 28 days, 28 days to < 9 months, 9 months to < 2 years, 2 to < 6 years, 6 to < 12 years and 12 to < 18 years. Exclusion criteria included a history or evidence of abnormal bleeding treatment with a potent inhibitor or inducer of CYP3A4 of P-gp, liver dysfunction (ALT>3ULN or AST>3ULN or direct bilirubin >2ULN), renal function < 50% of normal for age and size (Schwartz formula) or platelet count < 50.000/mm3.

Study treatment. Apixaban oral solution (OS) formulation (0.4 mg/mL) for subjects from 28 days to <18 years of age was used. Each group received a single oral dose of apixaban (oral solution or sprinkle capsule for neonate) that was expected to result in a median AUC(INF) equivalent to the median steady state AUC(TAU) achieved in adult VTE prevention after hip or knee replacement surgery treated with apixaban 2.5 mg BID (~800 ng*hr/mL).

PK and PD endpoints. Model-derived population and individual PK parameters (apparent plasma clearance, apparent volume of distribution, rate of absorption) were used to estimate Cmax, AUC(INF) and Tmax in each subject. A population PK-PD (PopPKPD) model was developed using both the plasma concentration and the measured anti-Xa activity vs. time data.

Dose selection for **Study CV185155** was based on the PK simulations performed using the paediatric PPK model and data from Study CV185118 (1 to <18 years) with predefined criteria to achieve median steady state AUC(TAU) following BID administration of apixaban. The target exposure for the Study CV185155, 620 ng•hr/mL, was based on the median AUC(TAU) in adult patients treated with apixaban 2.5 mg for the prevention of recurrent VTE in adult patients in the AMPLIFY-EXT. Using the apixaban paediatric PPK model the program shifted to a tiered body weight-based dosing strategy at the beginning of the study and subsequently a fixed-dose, body weight-tiered dosing approach during the study was instituted.

Similarly, dose selection for the **CV186362 study** was based on the PK simulations performed using the paediatric PPK model and data from Study CV185118. The target AUC(TAU) for the CV185362 study, 1,200 ng • h/mL, was based on the model-estimated median daily steady state apixaban AUC(TAU) from subjects treated with apixaban 5 mg BID for VTE treatment (AMPLIFY, AMPLIFY-EXT) or prevention of VTE associated with NVAF (ARISTOTLE trial). Using the paediatric PK model, a fixed-dose by weight tier dosing approach was used in the CV185362 study.

In **Study CV185325**, dose selection was based on achievement of matching exposures in children from birth to less than 18 years of age similar to the exposures in the AMPLIFY adult study regimen of 10 mg twice daily for the first 7 days and then 5 mg twice daily thereafter. The target AUC(TAU) was 1,200 ng•hr/mL. Population PK modeling and simulation approach was used for selection and subsequent recommendation of fixed-dose by body weight-tiered dosing regimen for paediatric subjects from 28 days to less than 18 years of age.

Dose Selection for study CV185325

In study CV185325 apixaban was administered orally BID based on age and body weight (Table 15). Subjects aged ⩾ 2 years to <18 years (age groups 1 and 2) received apixaban for 12 weeks while subjects aged 28 days to < 2 years and neonates (birth to ⩽ 27 days) (age groups 3 and 4, respectively) received apixaban for 6 to 12 weeks.

Apixaban 5 mg tablets were dispensed for subjects ⩾ 35 kg, 0.5 mg tablets were dispensed for subjects ⩾ 5 kg to < 35 kg, and 0.1 mg sprinkle capsules for subjects < 5 kg. Apixaban oral solution 0.4 mg/ml could only be used in children ⩾ 5 years of age.

Table 8. Apixaban Doses for Age Groups 1, 2, 3, and 4 – 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	Neonates [c]	≥ 2.6 kg	0.1 mg BID or as determined by PK measurements	0.1 mg BID[d]
4 Post-PK Cohort subjects	Neonates	< 4 to 2.6 kg	0.2 mg BID	0.1 mg BID

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 mini-tablets or 0.1 mg sprinkle capsules based on the assigned apixaban dose.
c. Neonates were defined as infants from birth to ≤ 27 days of life. For pre-term 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 (post-natal age) or may have chosen to define the 27-day neonatal period starting when the postmenstrual age (gestational age plus the post-natal age) reached 37 weeks and enroll the infant no more than 27 days thereafter into Cohort 4.
d. Neonatal dose may have been modified during PK-sub-analysis period until a fixed-dose was determined.

Apixaban Formulations for Paediatric subjects

Apixaban has been studied in the paediatric development program using 4 age-appropriate formulations: a 0.4 mg/mL oral solution, a 0.1 mg sprinkle capsule, a 0.5 mg mini-tablet and the 2.5 mg and 5 mg film-coated tablets, the last two approved for use in adults.

Comparable exposure between the apixaban oral solution and the approved film coated tablet was established in Study CV185029 and addressed during a previous PIP submission. In April 2017, the Sponsor suspended use of the apixaban oral solution in children <5 years of age in paediatric studies, because the daily intake of propylene glycol, one of the key solubilizing agents in the apixaban oral solution formulation, would exceed the threshold specified in the EMA guideline Background review for the excipient propylene glycol for children <5 years of age. The apixaban 0.5 mg mini-tablet that was proportionally identical in composition and had identical pharmaceutical characteristics to the approved 2.5 mg and 5 mg adult formulation was developed to support dosing in paediatric patients < 5 years of age, and the dosing regimen for apixaban in Study CV185325 changed from body weight based (mg/kg) BID dosing in Study CV185118 to a fixed-dose, body weight tiered BID dosing regimen in Studies CV185155, CV185362 and CV185325 with implementation of Protocol Amendment 4 (30-Oct-2017).

The 0.1 mg sprinkle capsule was developed as a more suitable formulation for administration of apixaban to neonates. Comparable bioavailability between the 0.1 mg apixaban sprinkle capsule and the 0.5 mg mini-tablet was established in Study CV185687. The sprinkle capsules were available for use in the CV185362 study, but no subjects received them. In Study CV185118 one neonate subject received the sprinkle capsules. Additionally, a 0.15 mg granules in capsules for opening (also referred to as capsules/sprinkle capsules/capsules for oral suspension) has been developed for commercialization which is the same formulation as the 0.1 mg capsule but with a higher fill weight. This formulation will support apixaban 0.3 mg and 0.6 mg doses in paediatric patients with body weight 4 to <5 kg.

2.6.5.2. Main study CV185325

Methods

Methods

Study CV185325 is a randomized (2:1), multicenter, open-label, active-controlled, safety and descriptive efficacy study in paediatric subjects requiring anticoagulation treatment for VTE and prevention of recurrent VTE.

Study design

The study included 4 study periods (Figure 9):

Screening/Randomization Period. Day -14 to Day 1 (=date of randomization).

Main Treatment Phase (Main Phase). Day 1 to Day 42 (for neonates and subjects aged < 2 years) or Day 1 to Day 84 (for subjects aged ⩾ 2 years). Subjects meeting inclusion/exclusion criteria were randomized either to apixaban or SOC in the main phase. On-site visits were scheduled on Days 14 and 42, and on-site or telephone visits on Days 28 and 63. End of treatment (EOT) activities were conducted at visits on Day 42 (neonates and subjects aged < 2 years) or Day 84 (subjects aged ⩾ 2 years). Radiologic reassessment of the index event was conducted at Day 42 and again at EOT for subjects ⩾ 2 years.

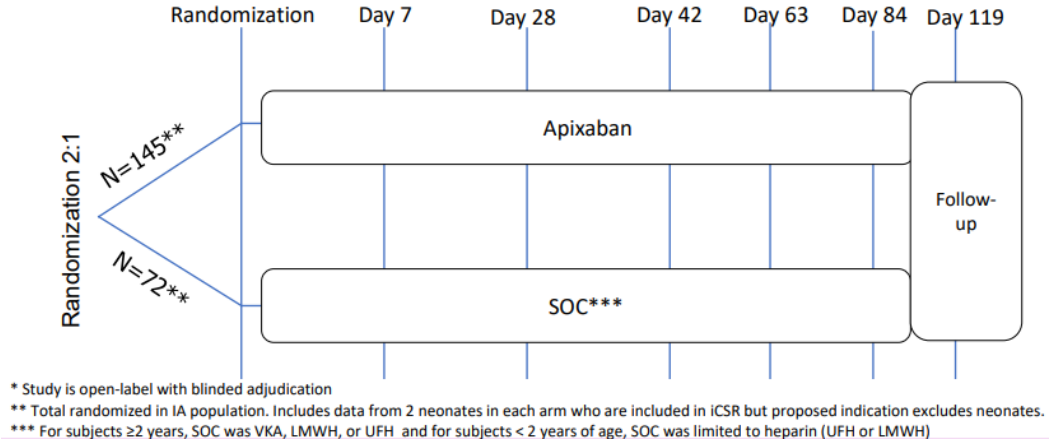
Follow-up Period. Until 35 days post EOT. Conducted after the Main Phase or after the Extension Phase if applicable. The last visit (telephone or office) was to confirm and document contraceptive use and to collect adverse event data.

Extension Phase. Defined as beyond Day 84 visit up to Day168 EOT visit. Subjects from age groups 1, 2, or 3 who were randomized to receive apixaban had the option to continue apixaban treatment

beyond the Day 84 visit for 6 to 12 additional weeks in the Extension Phase. On site visits were scheduled on Days 126 and 168, and on-site or telephone visits on Days 105 and 147. EOT activities were conducted at visits on Day 126 (6 week extension) or 168 (12 week extension).

Radiologic reassessment of the index event was conducted at Day 126 and end of treatment.

Figure 9. Study design - CV185325



- **Study Participants**

Paediatric patients with an index VTE confirmed by imaging, who were in need of anticoagulation for at least 12 weeks for children aged 2 to <18 years or 6-12 weeks for children from birth to <2 years.

Key inclusion criteria:

- Neonates to <18 years of age with a minimum weight of 2.6 kg at the time of consent
- Presence of an index VTE, confirmed by imaging. Index VTE include, but are not limited to, deep vein thrombosis, pulmonary embolus, cerebral sinovenous thrombosis, renal vein thrombosis, portal vein thrombosis, and splanchnic thrombosis
- Intention to manage the index VTE with anticoagulation treatment for at least 12 weeks at age >= 2 years, or at least 6 weeks in subjects aged < 2 years

Key exclusion criteria:

- Anticoagulant treatment for the index VTE for greater than 7 days prior to randomization
- Thrombectomy, thrombolytic therapy, or insertion of a caval filter to treat the index VTE
- A mechanical heart valve.
- Active bleeding or high risk of bleeding (eg, central nervous system (CNS) tumors) at the time of randomization.
- Intracranial bleed, including intraventricular hemorrhage, within 3 months prior to randomization.
- Abnormal baseline liver function (ALT >3 x upper limit of normal (ULN) or conjugated bilirubin >2 x ULN) at randomization; Inadequate renal function, defined as <30% of 1 standard deviation (SD) below normal GFR for age and size as determined by the Schwartz formula [eGFR (ml/min/1.73m2) = 0.413 * (height (cms)/serum creatinine (mg/dL) for ages

up to 2 years. Beyond 2 years of age, the qualifying GFR for this study is >=30 mL/min/1.73m2; Platelet count <50×109 per L,

- Uncontrolled severe hypertension at randomization, defined as a systolic or diastolic BP >=99th percentile plus 5 mmHg as defined by the National High Blood Pressure Education Program Working Group (NHBPEP 1987, updated in 2004).
- Use of prohibited concomitant medication at randomization:
    - Concomitant systemic treatment with strong inhibitors of both cytochrome P450 3A4 (CYP3A4) and P-glycoprotein (P-gp), such as ketoconazole, itraconazole, posaconazole, telithromycin, and ritonavir (fluconazole, topical azole antifungal agents, trimethoprim-sulfamethoxazole, H2-antagonists, and proton pump inhibitors are acceptable and permitted)
    - Concomitant systemic treatment with strong inducers of both cytochrome CYP3A4 and P-gp, such as phenobarbital, phenytoin, rifabutin, rifampicin, St. John's wort
    - Aspirin >165 mg per day and other antiplatelet therapy such as thienopyridines (eg, clopidogrel, ticlopidine)
    - Other antithrombotic agents (eg, UFH, LMWH, direct thrombin inhibitors, factor Xa inhibitors, fondaparinux). Heparin flushes to maintain central venous access device (CVAD) patency and local tissue plasminogen activator to restore CVAD patency are permitted.
    - GP IIb/IIIa inhibitors (eg, abciximab, eptifibatide, tirofiban).
    - Known allergy to apixaban, Female subjects who are either pregnant or breastfeeding a child, Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results

- **Treatments**

Screening/Randomization Period:

Subjects aged ⩾ 28 days received up to 14 days of SOC anticoagulant treatment (UFH, LMWH or VKA) prior to randomization. Neonatal subjects received at least 5 days and no more than 14 days of SOC anticoagulation treatment prior to randomization.

It is recommended that prior to the administration of the first dose of apixaban: ⩾2 hours have passed since the last dose of UFH; ⩾6 hours have passed since the last dose of LMWH labeled for twice daily administration; ⩾12 hours have passed since the last dose of fondaparinux or LMWH labeled for once daily administration; or the INR ⩽2 for subjects receiving a VKA.

Main treatment phase:

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

The duration of treatment is consistent with the recommendation of 2012 American College of Chest Physicians (ACCP) pediatric guidelines, 2018 American Society of Haematology (ASH) pediatric guidelines, and clinical experience and recommendation.

Apixaban (arm 1):

Initial protocol, 15th October 2014. Based on the modelling and simulation results, the following doses were used for subjects between the ages of 12 and <18 years (Table 16).

Table 9. Apixaban Doses for Age Group 1†

Age Group	Age	Body Weight	Days 1- 7	Day 8 and Thereafter
1	12 to <18 years	>40 kg	Two 5 mg tablets taken twice daily OR 10 mg of apixaban using the oral liquid formulation taken twice daily	One 5 mg tablet taken twice daily OR 5 mg of apixaban using the oral liquid formulation taken twice daily
		≤40 kg	0.2 mg/kg twice daily using the oral liquid formulation taken twice daily‡	0.1 mg/kg twice daily using the oral liquid formulation taken twice daily‡
2	2 to <12 years		TBD	TBD
3	29 days to <2 years		TBD	TBD
4	neonates		TBD	TBD

TBD: to be determined

† An updated and Pfizer and EDMC approved dosing Table will be provided in writing to the sites for IRB/EC documented approval prior to enrollment of each subsequent age group.

‡ The actual dose and volume will be provided by the central randomization and drug assignment system. Rounding rules will be employed based on the graduation of each dosing device.

Protocol amendment 4, 30th October 2017. In April 2017, use of the apixaban oral solution in children <5 years of age in studies was discontinued because the amount of propylene glycol, a key solubilizing excipient in the formulation, was found to exceed the recommended maximum daily intake for children <5 years of age, as specified in a 2014 draft EMA guideline. Apixaban 0.5 mg tablets were developed as an alternative to the 0.4 mg/mL oral solution. The dosing paradigm of apixaban changed from mg/kg dosing to a fixed dose, body weight tiered regimen, as outlined in Table 17.

Table 10. Apixaban Doses for Age Groups 1, 2, 3, and 4 – 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	Neonates [c]	≥ 2.6 kg	0.1 mg BID or as determined by PK measurements	0.1 mg BID [d]
4 Post-PK Cohort subjects	Neonates	< 4 to 2.6 kg	0.2 mg BID	0.1 mg BID

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 mini-tablets or 0.1 mg sprinkle capsules based on the assigned apixaban dose.
c. Neonates are defined as infants from birth to ≤ 27 days of life. For pre-term 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 (post-natal age) or may have chosen to define the 27-day neonatal period starting when the postmenstrual age (gestational age plus the post-natal age) reached 37 weeks and enroll the infant no more than 27 days thereafter into Cohort 4.
d. Neonatal dose may have been modified during PK-sub-analysis period until a fixed-dose is determined.
BID = twice daily; PK = pharmacokinetics

Participants who were randomized prior to Protocol Amendment 4 implementation were continued on the weight-based (mg/kg) regimen. Participants randomized to receive apixaban after implementation of Protocol Amendment 4 followed the fixed-dose, body weight tiered regimen for all age groups as outlined in Table 17.

Apixaban 5 mg tablets were dispensed for subjects ≥ 35 kg, 0.5 mg tablets were dispensed for subjects ≥ 5 kg to < 35 kg, and 0.1 mg sprinkle capsules for subjects < 5 kg. Apixaban oral solution 0.4 mg/ml could only be used in children ≥ 5 years of age. Apixaban was to be administered enterally through swallowing or enteral tubes.

Standard-of-Care (Arm 2):

Subjects randomized to SOC received a dose and dosing regimen of anticoagulation treatment (VKA, LMWH, or unfractionated heparin [UFH]) for 6 to 12 weeks based on usual and customary care per local practices. For subjects < 2 years of age, SOC was limited to heparin (UFH or LMWH).

The recommended therapeutic INR ranges for VKA in children are directly extrapolated from recommendations for adult patients because there are no clinical trials that have assessed the optimal INR range for children. Thus, for most indications, the therapeutic target INR is 2.5 (range, 2.0-3.0). The UFH dose is selected based on activated partial thromboplastin time (aPTT) therapeutic ranges: aPTT by protamine titration of 0.2 to 0.4 units/mL or an anti-FXa level of 0.35 to 0.7 units/mL. Therapeutic ranges for LMWH are extrapolated from adults and based on anti-FXa levels. The guideline for therapeutic LMWHs being given subcutaneously twice daily (bid) is an anti-FXa level of 0.50 to 1.0 units/mL in a sample taken 4 to 6 hours following a subcutaneous injection.

Extension phase:

Subjects from age groups 1, 2, or 3 who were randomized to receive apixaban had the option to continue apixaban treatment beyond the Day 84 visit for 6 to 12 additional weeks.

- **Objectives**

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

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

- **Outcomes/endpoints**

Primary endpoints:

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

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

Secondary endpoints:

- All cause death.
- VTE related mortality.
- Index VTE status (eg, unchanged, regression, or resolution).
- Stroke.
- New or recurrent symptomatic or asymptomatic DVT.
- New or recurrent symptomatic or asymptomatic PE.
- VTEs, other than DVT or PE (ie, cerebral sinovenous thrombosis, renal vein thrombosis, portal vein thrombosis, catheter-related VTE, and splanchnic thrombosis).
- Major bleeding.
- Clinically relevant non-major bleeding.
- Minor bleeding.
- Apixaban concentrations (the descriptive summaries were not included in the interim analysis CSR, however population PK and PK-AXA analyses were performed and submitted. Descriptive summaries are planned to be included in the final CSR).
- Anti-FXa activity (the descriptive summaries were not included in the interim analysis CSR, however population PK and PK-AXA analyses were performed and submitted. Descriptive summaries are planned to be included in the final CSR).

Other endpoint(s):

- Palatability Assessment

The primary efficacy endpoint is consistent with that recommended by the ISTH for paediatric clinical trials in venous thromboembolism. Subjects were assessed for signs or symptoms of VTE throughout the course of the study. If signs or symptoms were present, then subjects underwent a diagnostic examination to confirm recurrence of VTE. Adjudication of disease-related efficacy and safety endpoints was performed by an independent Endpoint Adjudication Committee (EAC).

Radiologic imaging of VTE:

- Radiologic imaging was performed, and adjudicated, to confirm the index event (ie, primary diagnosis of thromboembolic event which will be treated with apixaban or SOC in this study).
- For subjects 2 years of age or older, in addition to the radiologic images to confirm the index event, new radiologic images of the clot were planned at approximately mid-point and end of treatment (EOT) visits. For subjects 28 days to <2 years of age and neonates (birth to ⩽27 days of age) imaging should be performed at the EOT. Radiologic images that require sedation and/or radiation at the Day 42 or Day 84 (EOT) visits are not required and may be omitted, if not medically necessary.
- Additional imaging assessments could be performed at the discretion of the Investigator, at any time during the study. In addition, when medically appropriate, new radiologic images will be obtained if recurrent VTE is suspected.

All of the aforementioned imaging were adjudicated. Adjudication of disease-related efficacy and safety endpoints was performed by an independent Endpoint Adjudication Committee.

- **Sample size**

CV185325 is a descriptive study, and there was no formal pre-defined hypothesis testing. Therefore, there was no power calculation for the sample size determination. Approximately 150 subjects were planned to be randomized into the trial using a ratio of 2 to 1 to apixaban or SOC, respectively. A target of 30 subjects were planned to be randomized into each of the 4 age groups.

Throughout the trial, the study team, in conjunction with regulators (ie, Food and Drug Administration [FDA]), evaluated exposure duration, imaging results, and other aspects of the trial to determine if the data from the subjects in the trial are sufficient to address the objectives of the trial. It was expected that a sample size of 250, increased from an original sample size of 150, was needed in order to provide a reasonable safety and pharmacokinetic database in pediatric subjects (as reflected in Protocol amendment 6, 06 September 2019).

- **Randomisation and Blinding (masking)**

Subjects were randomized using a ratio of 2 to 1 to apixaban or SOC, respectively. Randomization was stratified by age group. Enrollment was 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).

Randomization was performed on Day 1, using the central randomization and drug assignment system interactive response technology.

This was an open-label study, treatment assignment was not blinded.

- **Statistical methods**

As this was a descriptive study, there is no formal pre-defined hypothesis testing. In Protocol amendment 7 (5th October 2020) an interim analysis of efficacy and safety was added to the SAP, performed for age groups 1,2 and 3, while age group 4 is still recruiting.

Populations for analysis

For analyses of efficacy, the Full Analysis Set (all randomized subjects) was used for the Main Phase (Day 1 to Day 84), using the intent to treat principle. The safety analysis set consists of all randomized subjects who received at least one dose of study drug (Table 18). For extension phase, these will be presented for subjects in the Extension Phase Analysis Set. The full analysis set will be used to summarize demographic data.

Table 11. Analysis Sets- Study CV185325

Population	Description
Enrolled	All participants who sign the informed consent document.
Full Analysis Set	The Full Analysis Set contains all randomized subjects. 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	NA 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 will consist of subjects who are randomized to apixaban group and continue treatment beyond Day 84 visit for up to 12 weeks.
PK Analysis Set	The PK analysis population is defined as all subjects randomized to and treated with apixaban who have at least 1 concentration of apixaban. The detailed analysed of PK/PD data will be specified in a separate document
PD Analysis Set	The PD analysis population is defined as all subjects randomized to and treated with apixaban who have at least 1 apixaban concentration and 1 corresponding anti-FXa activity measure.

General methods

For main phase, all efficacy and safety analyses described in this document will be performed for the overall study population and each age group.

For extension phase, the summary table for primary and secondary endpoints will be provided for apixaban group. Treatment-Emergent Adverse Events (All Causalities), Treatment-Emergent Adverse Events by System Organ Class and Prefer Term (All Causalities), and duration of treatment will be summarized for apixaban group.

Binary endpoints will be summarized using the total number of subjects and number and percent. The corresponding 95% confidence intervals of the percent will be provided using Agresti-Coull's method. For main phase, the percent and corresponding 95% confidence interval will be presented by treatment group, and age group x treatment group. For extension phase, the percent and corresponding 95% confidence interval will be presented for subjects in the Extension Phase Analysis Set. Continuous endpoints will be summarized using: means, standard deviations, median, and range. Categorical endpoints will be summarized using the total number of subjects and number and percent.

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

Primary Efficacy Endpoint. For overall study population(and for each age group), the percentage of subjects with the composite primary efficacy endpoint will be summarized using the number and percent of subjects having endpoint event with an 95% exact confidence interval. The relative risk of apixaban versus SOC and two-sided 95% confidence interval will be provided based on Cochran-Mantel-Haenszel (CMH) test stratified by age group. The nominal p-value from CMH test stratified by age group will also be provided.

Sensitivity/Supplementary Analysis. For the primary efficacy endpoint, the percentage of subjects with the composite primary efficacy endpoint will be summarized only for subjects that either experienced a primary endpoint, or had at least one radiological evaluation (image assessment) of the index event post treatment during the main phase.

Secondary Efficacy Endpoint.

- Part 1. The component of composite primary efficacy endpoint (symptomatic and asymptomatic recurrent VTE) will be analyzed using the same methods as for primary efficacy endpoints. The symptomatic and asymptomatic recurrent VTE includes new or recurrent symptomatic or asymptomatic DVT, new or recurrent symptomatic or asymptomatic PE, and new or recurrent symptomatic or asymptomatic Other VTEs. Other VTEs includes, not but limited to cerebral sinovenous thrombosis, renal vein thrombosis, portal vein thrombosis, catheter-related VTE, and splanchnic thrombosis. No sensitivity/supplementary analysis is planned.
- Part 2. Index VTE status. The index VTE status at the end of main phase compared to baseline will be summarised using counts and percentage. The VTE status will be classified as recurrence-contiguous, recurrence-new, unchanged, regression, resolution, or indeterminate/non-diagnostic based on image data.

Primary Safety Endpoint. For overall study population (and for each age group), the percentage of subjects with the composite endpoint of major and/or CRNM bleeding will be summarized similar to the primary efficacy endpoint.

Secondary Safety Endpoint. For overall study population (and for each age group), the percentage of subjects with each secondary safety endpoint will be summarized similar to the primary efficacy endpoint.

Other Endpoint(s): Palatability Assessment. For subjects receiving apixaban, palatability will be assessed at the Day 14 study visit. The assessment will be administered to the subject and/or legal guardian in the form of a questionnaire: Which choice most adequately reflects the subject`s response to taste? The outcome of the questionnaire (dislike very much, dislike a little, not sure, like a little, like very much) will be summarized for apixaban group by formulation.

INTERIM ANALYSIS. The interim analysis will be performed when all randomized subjects in age Groups 1, 2 and 3 have completed the required minimal treatment periods or have discontinued from the study. The objective of this interim analysis is to provide an interim clinical study report for age Groups 1, 2, and 3 while age Group 4 continues to enrol the targeted number of subjects. The interim analysis will include all efficacy and Safety analysis tables/listings planned for this study. The PK/PD data will not be included in the interim analysis.

Results

Recruitment

Study initiation date was 22th November 2015 (first patient first visit (FPFV)). At interim data cutoff date 25th March 2022), 3 of the 4 age groups (12 to < 18 years, 2 to < 12 years, and 28 days to < 2 years) fully completed the study.

A total of 228 subjects were screened in 118 study centers in 14 countries, 217 (95.2%) were randomized (145 in the apixaban group and 72 in the SOC group). Subjects were recruited globally, including Australia, North- and South-America, Europe, Israel, Russian Federation.

Participant flow

Of the 228 subjects screened, 217 (95.2%) were randomized (145 in the apixaban group and 72 in the SOC group). At least 30 subjects were randomized in each of the age groups 1, 2, and 3 but only 4 subjects in age group 4 (birth to < 28 days) had been randomized and completed the study.

Of the total of 217 subjects who were assigned to treatment, 214 (98.6%) were treated and 194 (89.4%) completed the Main Phase (Table 19).

Of the 214 participants treated with apixaban or SOC during the Main Phase of the study, 136 (n=91 vs n=45 for apixaban vs SOC) were randomized to age-group 1, 43 (n=29 vs n=14) to age-group 2, 31 (n=21 vs n=10) to age-grouop 3, and 4 (n=2 vs n=2) to age-group 4.

A total of 23 participants discontinued from the study (Table 19): 12(8.8%) participants in the 12 to <18 years age group, 7(15.9%) participants in the 2 to <12 years age group, 3(9.4%) participants in the 28 days to <2 years age group, and 1(25.0%) participant in the neonatal (birth up to 27 days) age group. The proportion of subjects who discontinued from the study during the Main Phase was comparable in the apixaban group (9.7%) and the SOC group (12.5%). The most common reason for not completing the Main Phase was AEs (4.1% and 0% in the apixaban and SOC groups, respectively), withdrawal by parent/guardian (0% and 5.6% in the apixaban and SOC groups, respectively), and other reasons (2.1% and 2.8% in the apixaban and SOC groups, respectively). No subjects in either group discontinued due to insufficient clinical response.

Table 12. Disposition Events Summary (Main Phase) - Full Analysis Set – CV185325

	Apixaban (N=145) n (%)	SOC (N=72) n (%)	Total (N=217) n (%)
Disposition Phase: Main Study Treatment Phase[1]			
Subjects Treated:	143 (98.6)	71 (98.6)	214 (98.6)
Discontinued From the Study [2]	14 (9.7)	9 (12.5)	23 (10.6)
Adverse Event	6 (4.1)	0	6 (2.8)
Death	1 (0.7)	1 (1.4)	2 (0.9)
Protocol Violation	0	0	0
Lost to Follow-Up	3 (2.1)	0	3 (1.4)
Withdrawal by Parent/Guardian	0	4 (5.6)	4 (1.8)
No Longer Meets Eligibility Criteria	0	1 (1.4)	1 (0.5)
Other	3 (2.1)	2 (2.8)	5 (2.3)
Entrance Criteria	1 (0.7)	1 (1.4)	2 (0.9)
Medication Error Without Associated Adverse Event	0	0	0
Completed	131 (90.3)	63 (87.5)	194 (89.4)

Abbreviations: SOC = standard of care

[1] Main Phase was defined as from Day 1 to Day 84 end of treatment.

[2] 'Discontinued from the Study' includes all subjects who discontinued (ie, did not complete) the Main Study Treatment Phase

Fifty five subjects (25.3%) entered the Extension Phase of the study and were treated (53 with apixaban and 2 with SOC, n=43, 10, and 2 for age-groups 1, 2 and 3, respectively; Table 20).

Table 13. Disposition Events Summary (Extension Phase), by Age Group – Full Analysis Set- CV185325

	Apixaban (N=53)
	n (%)
Disposition Phase: Extension treatment Phase	
Subjects Treated:	53 (100.0)
Discontinued	3 (5.7)
Adverse Event	1 (1.9)
Death	0
Protocol Violation	0
Lost to Follow-Up	0
Withdrawal by Parent/Guardian	1 (1.9)
No Longer Meets Eligibility Criteria	0
Other	1 (1.9)
Entrance Criteria	0
Medication Error Without Associated Adverse Event	0
Completed	50 (94.3)

Conduct of the study

Substantial changes in the conduct of the study are described below:

Protocol Amendment 4, 30 October 2017: In April 2017, use of the apixaban oral solution in children <5 years of age in studies was discontinued because the amount of propylene glycol, a key solubilizing excipient in the formulation, was found to exceed the recommended maximum daily intake for children <5 years of age. Apixaban 0.5 mg tablets were developed as an alternative to the 0.4 mg/mL oral solution for pediatric patients weighing ⩾5 kg participating in clinical studies. With the introduction of 0.5 mg tablets, the dosing paradigm of apixaban changed from mg/kg dosing to a fixed dose, body weight tiered regimen. The fixed-dose, body weight-tiered regimen uses apixaban doses in increments of 0.5 mg according to the appropriate weight range, regardless of apixaban formulations. Participants who were randomized prior to the final dosing amendment in October 2017 were continued on their weight-based regimen.

Protocol Amendment 6, 06 September 2019: Eligibility criteria were changed, allowing for duration of SOC anticoagulation treatment for the index VTE prior to randomization of 14 instead of 7 days. Further, sample size was updated from 150 to 250 with rationale.

Protocol Amendment 7, 12t Feb 2020: Updated to include interim analysis of efficacy and safety for Age Groups 1 through 3, while Age Group 4 is still recruiting. The PK/PD data will not be included in the interim analysis (Updated SAP-5th October 2020).

Important Protocol Deviations

The incidence of having at least 1 important protocol deviation was comparable between the apixaban and SOC groups (62.8% and 56.9%, respectively). Most frequently reported for both treatment groups were: Procedure/Test not performed per protocol (12.0% total), Subject not randomized and dosed on the same day (10.1% total), Visit schedule/procedures not completed per protocol (8.3% total), Subject did not return IP (8.3% total).

A total of 6 (2.8%) participants were randomized into the study even though they did not satisfy the exclusion/inclusion criteria as defined by the protocol. Two of these participants, 1 in the apixaban group and 1 in the SOC group, were discontinued prior to receiving treatment.

Four (1.8%) participants met a discontinuation or withdrawal criterion during the study but were not discontinued or withdrawn. This concerned 2 participants in the apixaban-group (1 participant aged 12 to <18 years with CVST based on imaging on the day after randomization, and 1 participant aged 2 to <12 years with a DVT in the left subclavian and left axillary veins on Day 42) and 2 participants in the SOC group (1 participant aged 12 to <18 years underwent 2 procedures (left lower extremity DVT thrombolysis therapy and thrombectomy for DVT), and 1 participant aged 12 to <18 years with an AE of Thrombosis of right vein subclavian with onset on Day 42).

Protocol deviations related to the impact of the COVID-19 pandemic were reported for 3 participants: 2 in the apixaban group and 1 in the SOC group, in all cases being unable to visit the site and perform tests. No impact on participant safety or the interpretability of study results was detected.

Baseline data

Demographics. The overall demographic characteristics were balanced across apixaban and SOC groups (Table 21). The largest age group was 12 to < 18 years (137 [63.1%] subjects randomized). Within each age group, demographic characteristics for gender and race were generally similar to those of the overall study population.

Table 14. Demographic Characteristics – Full Analysis Set – CV185325

	Apixaban (N=145) n (%)	SOC (N=72) n (%)	Total (N=217) n (%)
Age:			
12 Years - < 18 years	91 (62.8)	46 (63.9)	137 (63.1)
2 Years - < 12 years	30 (20.7)	14 (19.4)	44 (20.3)
28 Days - < 2 years	22 (15.2)	10 (13.9)	32 (14.7)
Birth to <= 27 Days	2 (1.4)	2 (2.8)	4 (1.8)
Median (years)	14.49	14.46	14.49
Mean (years)	11.87	12.00	11.91
SD (years)	6.03	5.78	5.93
Range (years)	(0.06, 17.98)	(0.04, 17.92)	(0.04, 17.98)
Gender			
Male	62 (42.8)	30 (41.7)	92 (42.4)
Female	83 (57.2)	42 (58.3)	125 (57.6)
Race			
White	111 (76.6)	54 (75.0)	165 (76.0)
Black	21 (14.5)	8 (11.1)	29 (13.4)
Asian	5 (3.4)	3 (4.2)	8 (3.7)
Other	8 (5.5)	7 (9.7)	15 (6.9)
Ethnicity			
Hispanic or Latino	10 (6.9)	13 (18.1)	23 (10.6)
Not Hispanic or Latino	135 (93.1)	59 (81.9)	194 (89.4)
Racial Designation			
African American	22 (15.2)	9 (12.5)	31 (14.3)
North American Indian	3 (2.1)	0	3 (1.4)
Pacific Islander	1 (0.7)	0	1 (0.5)
Weight (kg)			
N	143	71	214
Median	56.50	57.60	56.90
Mean	55.70	53.74	55.05
SD	34.26	32.24	33.54
Range	(2.90, 147.5)	(2.70, 141.0)	(2.70, 147.5)
Height (cm)\Body Length (cm)			
N	142	69	211
Median	161.6	157.0	160.0
Mean	144.7	142.4	144.0
SD	37.49	38.56	37.77
Range	(49.50, 188.0)	(47.50, 188.0)	(47.50, 188.0)
Body Mass Index (Kg/m**2)			
N	139	66	205
Median	21.52	20.52	21.46
Mean	23.27	23.36	23.30
SD	8.40	8.66	8.46
Range	(11.39, 52.89)	(11.73, 49.96)	(11.39, 52.89)

Abbreviations: SD = standard deviation; SOC = standard of care
Baseline is defined as the latest available value on or before Day 1.
Body Mass Index (kg/m**2) = weight (kg) / [height (cm)]**2.

Baseline Characteristics. The most frequently reported adjudicated index event was DVT in the apixaban and SOC groups (Table 22), and in each of the groups (1-3). No data are available on presence of a CVAD at the location of the DVT. The event adjudication committee determined that 26 (12.0%) subjects were negative for an index event (ie, did not have an index event), and 10 (4.6%) subjects had an indeterminate/non-diagnostic index event (ie, thrombus present, but it could not be determined if presence was due to poor image quality or incomplete imaging).

Table 15. Summary of Adjudicated Index Events – Full Analysis Set – CV185325

	Apixaban (N=145) n (%)	SOC (N=72) n (%)	Total (N=217) n (%)
Deep Vein Thrombosis	76 (52.4)	41 (56.9)	117 (53.9)
Upper extremity DVT (including SVC)	33 (22.8)	25 (34.7)	58 (26.7)
Lower extremity DVT (including IVC)	43 (29.7)	16 (22.2)	59 (27.2)
Pulmonary Embolus	30 (20.7)	13 (18.1)	43 (19.8)
Other VTE	23 (15.9)	11 (15.3)	34 (15.7)
Cerebral Sinovenous Thrombosis	9 (6.2)	7 (9.7)	16 (7.4)
Renal Vein Thrombosis	0	1 (1.4)	1 (0.5)
Portal/Splanchnic Vein Thrombosis	2 (1.4)	0	2 (0.9)
Intracardiac Thrombus	9 (6.2)	2 (2.8)	11 (5.1)
Other	3 (2.1)	1 (1.4)	4 (1.8)
Negative	20 (13.8)	6 (8.3)	26 (12.0)
Indeterminate / Non-diagnostic	9 (6.2)	1 (1.4)	10 (4.6)

Abbreviations: DVT = deep vein thrombosis; IVC = inferior vena cava; SOC = standard of care; SVC = superior vena cava; VTE = venous thromboembolism

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.

Significant Medical History. In the Full Analysis Set, the incidence of participants with at least 1 prior or ongoing disease/syndrome at screening was similar in both treatment groups. Past and ongoing diseases were reported in 97 (66.9%) and 138 (95.2%) participants, respectively, in the apixaban group versus 55 (76.4%) and 67 (93.1%) participants, respectively, in the SOC group. Most frequently encountered concomitant conditions were infectious diseases (19.3% vs 29.2%), obesity (17.9% vs 16.7%), malignancy (15.2% vs 12.5%), congenital cardiovascular disease or cardiac condition (24.8% vs 22.2%), trauma/fracture (9.7% vs 6.9%), surgery (8.3% vs 1.4%), and sex hormone use (17.9% vs 18.1%) (Table 23).

Table 16. Summary by Unique Participant per Grouping Category in Study CV185325

Grouping Category [a]	Apixaban (N = 145)	Standard of Care (N = 72)
Central Nervous System	0 (0%)	3 (4.16%)
Compartment Syndrome	1 (0.68%)	0 (0%)
Congenital CV	22 (15.17%)	8 (11.11%)
Diabetes Mellitus	2 (1.37%)	2 (2.77%)
Embolism	1 (0.68%)	0 (0%)
Infectious Disease	28 (19.31.0%)	21 (29.16%)
Immobilization	3 (2.06%)	1 (1.38%)
Malignancy	22 (15.17%)	9 (12.5%)
Obesity	26 (17.93%)	12 (16.66%)
Orthopedic or Other Surgery	12 (8.27%)	1 (1.38%)
Parenteral Nutrition	0 (0%)	1 (1.38%)
Polycythemia	1 (0.68%)	0 (0%)
Significant Cardiac Condition	14 (9.65%)	8 (11.11%)
Thrombocytosis	2 (1.37%)	2 (2.77%)
Thrombophlebitis	1 (068%)	2 (2.77%)
Thrombophilia	11 (7.58%)	4 (5.55%)
Thrombosis	9 (6.20%)	4 (5.55%)
Trauma/Fracture	14 (9.65%)	5 (6.94%)
Vascular	12 (8.27%)	3 (4.16%)
Sex hormone use	26 (17.93%)	13 (18.05%)
Immunoglobulins infusion	3 (2.06%)	2 (2.77%)

[a] Each participant was listed only once in the specific Grouping Category, but could be counted in more than 1 Grouping Category.

Numbers analysed

Of the total of 217 subjects who were assigned to treatment, 214 (98.6%) were treated and 194 (89.4%) completed the Main Phase (Table 24).

For analyses of efficacy, the Full Analysis Set (all randomized subjects) was used for the Main Phase (Day 1 to Day 84).

Table 17. Subject Evaluation Groups – Full Analysis Set - study CV185325

	Apixaban (N=145) n (%)	Standard Of Care (N=72) n (%)	Total (N=217) n (%)
Screened: 228 Screened Failure: 11 Not Screen Failure but not Randomized: 0			
Assigned to Treatment	145 (100.0)	72 (100.0)	217 (100.0)
Treated	143 (98.6)	71 (98.6)	214 (98.6)
Not Treated	2 (1.4)	1 (1.4)	3 (1.4)
Entered Extension Phase and Treated	53 (36.6)	2 (2.8)	55 (25.3)

Exposure and concomitant therapy

Study therapy. The mean (SD) duration of treatment during the Main Phase of the study was similar in the apixaban (79.59 days [19.32]) and SOC (75.17 days [22.24]) groups. Most subjects (91.6%) were in the study ⩾ 43 days. The extent of exposure for the apixaban group was consistent with the assigned age specific treatment duration.

Concomitant therapy. In total, 211 (98.6%) subjects took at least 1 concomitant medication: 140 (97.9%) subjects in the apixaban group and 71 (100.0%) in the SOC group. The most frequently

administered concomitant medications included enoxaparin or enoxaparin sodium (107 [74.8%] subjects in the apixaban group and 59 [83.1%] subjects in the SOC group).

Outcomes and estimation

Primary efficacy endpoint

The primary efficacy endpoint was the adjudicated composite of (i) all image-confirmed and adjudicated symptomatic and asymptomatic recurrent VTE defined as either contiguous progression or non-contiguous new thrombus and including, but not limited to, DVT, PE and paradoxical embolism and (ii) VTE-related mortality.

There were 4 (2.8%) subjects in the apixaban group and 2 (2.8%) subjects in the SOC group who had at least 1 adjudicated, symptomatic, or asymptomatic recurrent VTE event, Relative Risk of 0.99 (95% CI 0.2,5.3 ; p=0.994.

- In the 12 to <18 years age group, 1 (1.1%) participant in the apixaban group and 2 (4.3%) participants in the SOC group had at least 1 adjudicated symptomatic or asymptomatic VTE event.
- In the 2 to <12 years age group, 3 (10.0%) participants in the apixaban group and none (0.0%) in the SOC group had at least 1 adjudicated symptomatic or asymptomatic VTE event.
- In the age groups of 28 days to <2 years and neonatal (birth up to 27 days), no participants in either treatment group had VTE events.

Note: For 1 of the 4 participants in the apixaban group with an adjudicated symptomatic or asymptomatic recurrent VTE event (age group 12 to <18 years), the event occurred prior to dosing. The event was included in the full analysis set for the main phase as prespecified in the SAP.

No subjects experienced VTE related death.

The prespecified **sensitivity analysis** of the primary efficacy endpoint included participants who either experienced the primary efficacy endpoint or had at least 1 radiological evaluation (image assessment) of the index event post treatment during the Main Phase of the study. There were 4 out of 137 (2.9%) participants in the apixaban group and 2 out of 64 (3.1%) participants in the SOC group who had at least 1 VTE event. The results are consistent with the primary analysis.

Secondary efficacy endpoints

All-Cause Death, VTE-Related Mortality, New or Recurrent Symptomatic or Asymptomatic DVT, New or Recurrent Symptomatic or Asymptomatic PE, VTEs (Other than DVT or PE), Stroke *(*Table 25*)*

VTE. There were 4 (2.8%) participants in the apixaban group who had at least 1 VTE, 3 of which were adjudicated as other symptomatic or asymptomatic VTE, and 1 was adjudicated as new symptomatic or asymptomatic DVT.

There were 2 (2.8%) participants in the SOC group who had at least 1 VTE, which were adjudicated as new symptomatic or asymptomatic DVT (1 [1.4%] participant) and other symptomatic or asymptomatic VTE (1 [1.4%] participant) respectively.

Death***.*** There were 2 (1.4%) participants in the apixaban group and 1 (1.4%) participant in the SOC group who had all cause death. No participants in either treatment group had VTE-related mortality or stroke event.

Table 18. Analysis of Adjudicated Secondary Efficacy Endpoints – FAS - Study CV185325

	Apixaban (N=145)	Standard Of care (N=72)
Symptomatic and Asymptomatic Recurrent VTE*		
Number (%) of Subjects With Event	4 (2.8)	2 (2.8)
95% Confidence Interval [1]	(0.8, 7.1)	(0.2, 10.2)
Relative Risk (Apixaban vs. Standard of Care)	0.99	
95% Confidence Interval [2]	(0.2, 5.3)	
p-value [2]	0.9935	
Symptomatic or Asymptomatic DVT		
Number (%) of Subjects With Event	1 (0.7)	1 (1.4)
95% Confidence Interval [1]	(0.0, 4.2)	(0.0, 8.2)
Relative Risk (Apixaban vs. Standard of Care)	0.50	
95% Confidence Interval [2]	(0.0, 7.8)	
p-value [2]	NE	
New Symptomatic or Asymptomatic DVT		
Number (%) of Subjects With Event	1 (0.7)	1 (1.4)
95% Confidence Interval [1]	(0.0, 4.2)	(0.0, 8.2)
Relative Risk (Apixaban vs. Standard of Care)	0.50	
95% Confidence Interval [2]	(0.0, 7.8)	
p-value [2]	NE	
Symptomatic or Asymptomatic PE		
Number (%) of Subjects With Event	0	0
95% Confidence Interval [1]		
Relative Risk (Apixaban vs. Standard of Care)		
95% Confidence Interval [2]		
p-value [2]		
New Symptomatic or Asymptomatic PE		
Number (%) of Subjects With Event	0	0
95% Confidence Interval [1]		
Relative Risk (Apixaban vs. Standard of Care)		
95% Confidence Interval [2]		
p-value [2]		
Other Symptomatic or Asymptomatic VTE**		
Number (%) of Subjects With Event	3 (2.1)	1 (1.4)
95% Confidence Interval [1]	(0.4, 6.2)	(0.0, 8.2)
Relative Risk (Apixaban vs. Standard of Care)	1.49	
95% Confidence Interval [2]	(0.2, 14.1)	
p-value [2]	NE	
New Other Symptomatic or Asymptomatic VTE**		
Number (%) of Subjects With Event	0	0
95% Confidence Interval [1]		
Relative Risk (Apixaban vs. Standard of Care)		
95% Confidence Interval [2]		
p-value [2]		
VTE*-related Mortality		
Number (%) of Subjects With Event	0	0
95% Confidence Interval [1]		
Relative Risk (Apixaban vs. Standard of Care)		
95% Confidence Interval [2]		
p-value [2]		

All Cause Death		
Number (%) of Subjects With Event	2 (1.4)	1 (1.4)
95% Confidence Interval [1]	(0.1, 5.2)	(0.0, 8.2)
Relative Risk (Apixaban vs. Standard of Care)	0.99	
95% Confidence Interval [2]	(0.1, 10.8)	
p-value [2]	NE	
Stroke		
Number (%) of Subjects With Event	0	0
95% Confidence Interval [1]		
Relative Risk (Apixaban vs. Standard of Care)		
95% Confidence Interval [2]		
p-value [2]		

[1] 95% CI was from the Agresti-Coull method. [2] 95% CI and p-value were calculated using the Cochran-Mantel-Haenszel test stratified by age group.
*Recurrent VTE defined as either contiguous progression or non-contiguous new thrombus and including, but not limited to DVT, PE and paradoxical embolism. **Other VTE: 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.

Index VTE Status**.** Index VTE status was defined as the last image obtained in the Main Treatment Phase for each participant compared to baseline. Index VTE status results are reported in (Table *26*).

Table 19. Summary of Index VTE Status at End of Main Treatment Phase Compared to Baseline - FAS

	Apixaban (N=145)	Standard Of Care (N=72)
Index VTE Status		
Recurrence-contiguous		
Number (%) of Subjects With Event	2 (1.4)	0
95% Confidence Interval [1]	(0.1, 5.2)	
Recurrence-new		
Number (%) of Subjects With Event	0	0
95% Confidence Interval [1]		
Unchanged		
Number (%) of Subjects With Event	7 (4.8)	7 (9.7)
95% Confidence Interval [1]	(2.2, 9.8)	(4.5, 19.0)
Regression		
Number (%) of Subjects With Event	25 (17.2)	11 (15.3)
95% Confidence Interval [1]	(11.9, 24.3)	(8.6, 25.5)
Resolution		
Number (%) of Subjects With Event	76 (52.4)	37 (51.4)
95% Confidence Interval [1]	(44.3, 60.4)	(40.1, 62.6)
Indeterminate/Nondiagnostic		
Number (%) of Subjects With Event	21 (14.5)	7 (9.7)
95% Confidence Interval [1]	(9.6, 21.2)	(4.5, 19.0)

1] 95% CI was calculated using the Agresti-Coull method.
For a subject who entered Extension Phase, includes the last image data for this subject up to the latest date of last dose or last image in Main Phase.
For a subject who didn't enter Extension Phase, includes the last image data for this subject up to the last dose in Main Phase+7 days.

Extension phase of study CV185325

In 53 subjects who entered the extension phase and were treated with apixaban, no event of symptomatic and asymptomatic recurrent VTE or VTE related mortality was reported.

Ancillary analyses

Palatability assessment

In study CV185325, palatability assessment was administered to participant and/or legal guardian in the form of a questionnaire, assessed at the Day14 study visit. Of the taste assessment data collected, 1(50%) participant who took apixaban 0.1 mg sprinkle capsule, 19 (95.0%) participants who took apixaban oral solution and 22 (75.9%) participants who took the 0.5 mg tablet formulation (which was dissolved in a specific medium) provided taste responses. Taste assessment data were not collected for the 5 mg tablet formulation.

Of all the responses for three formulations, a higher proportion of participants (13 [44.8%]) who took the 0.5 mg tablet dissolved in a specific medium either liked a little or liked very much the taste of it compared to participants (4 [20.0%]) who took the oral solution formulation. Seven (35.0%) participants who took the oral solution disliked the taste of it very much.

- **Summary of main efficacy results**

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 20. Summary of efficacy for trial CV185325

<table>
<tr><td></td><td colspan="3">Title: Study CV185325: a randomized (2:1), multicenter, open-label, active-controlled, safety and descriptive efficacy study in paediatric subjects requiring anticoagulation treatment for VTE and prevention of recurrent VTE.</td></tr>
<tr><td>Study identifier</td><td></td><td colspan="2">Study CV185325, EudraCT Number: 2014-002606-20</td></tr>
<tr><td>Design</td><td></td><td colspan="2">randomized (2:1), multicenter, open-label, active-controlled</td></tr>
<tr><td></td><td></td><td>Duration of screening phase
Duration of main phase

Duration of follow-up period
Extension phase</td><td>2 weeks
6 weeks (subjects < 2 years of age)
12 weeks (subjects 2 to <18 years of age)
35 days
6 to 12 weeks</td></tr>
<tr><td>Hypothesis</td><td></td><td colspan="2">Safety and Descriptive efficacy study (predefined interim-analysis)</td></tr>
<tr><td>Treatments groups</td><td></td><td>Apixaban subgroup</td><td>Fixed dose, weight-tiered regimen
<table>
<tr><th>Body weight</th><th>Days 1-7</th><th>Days 8 and there-after</th></tr>
<tr><td>>= 35 kg</td><td>10 mg BID</td><td>5 mg BID</td></tr>
<tr><td>25 to < 35 kg</td><td>8 mg BID</td><td>4 mg BID</td></tr>
<tr><td>18 to < 25 kg</td><td>6 mg BID</td><td>3 mg BID</td></tr>
<tr><td>12 to < 18 kg</td><td>4 mg BID</td><td>2 mg BID</td></tr>
<tr><td>9 to < 12 kg</td><td>3 mg BID</td><td>1.5 mg BID</td></tr>
<tr><td>6 to < 9 kg</td><td>2 mg BID</td><td>1 mg BID</td></tr>
<tr><td>5 to < 6 kg</td><td>1 mg BID</td><td>0.5 mg BID</td></tr>
<tr><td>4 to < 5 kg</td><td>0.6 mg BID</td><td>0.3 mg BID</td></tr>
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		Standard-of-Care SOC (VKA, LMWH or UFH)	Based on usual care per local practices. For subjects < 2 years of age, SOC was limited to heparin (UFH or LMWH).		
Endpoints and definitions		Primary Safety endpoint	Composite of major and clinically relevant non-major bleeding		
		Primary Efficacy endpoint	Composite of (i) all image-confirmed and adjudicated symptomatic and asymptomatic recurrent VTE defined as either contiguous progression or non-contiguous new thrombus and including, but not limited to, DVT, PE and paradoxical embolism and (ii) VTE-related mortality.		
		Secondary endpoints	All cause death; VTE related mortality; Index VTE status; Stroke; new or recurrent symptomatic DVT or PE; VTEs other than DVT or PE; major bleeding, CRNM bleeding, minor bleeding, apixaban concentrations, Anti-FXa activity		
		Other endpoint	Palatability assessment		
Database lock		25th March 2022			
Results and Analysis					
Analysis description		**Primary Analysis (Interim analysis)**			
Analysis population and time point description		Efficacy endpoints: Full analysis Set (FAS, all randomized subjects) Safety endpoints: Safety analysis Set (SAS, all randomized subjects who received at least one dose of apixaban) Period: main phase			
Descriptive statistics[c]		Treatment group	Arm 1: apixaban	Arm 2: Standard of Care (SOC)	
		Number of subjects	145 FAS, 143 SAS	72 FAS 71 SAS	
Primary efficacy endpoint		Composite (a)symptomatic recurrent VTE and VTE-related mortality	N=4 (2.8%)[a]	N=2 (2.8%)	RR 0.99 (95%CI 0.2, 5.3) P=0.994
Secondary efficacy endpoints		All cause death	N=2 (1.4%)	N=1 (1.4%)	RR 0.99 (95%CI 0.1,10.8) P=NE
		VTE related mortality	0	0	
		Stroke	0	0	
		New/recurrent (a)symptomatic DVT	N=1 (0.7%)	N=1 (1.4%)	RR 0.50 (95%CI 0.0, 7.8) P= NE
		New/recurrent (a)symptomatic PE	0	0	
		VTE other than DVT/PE[b]	N=3 (2.1%)	N=1 (1.4%)	RR 1.49 (95%CI 0.2,14.1) P=NE
		Index VTE status[d]: resolution	76 (52.4%)	37 (51.4%)	

	regression Unchanged Contiguous recurrence	25 (17.2%) 7 (4.8%) 2 (1.4%)	11 (15.3%) 7 (9.7%) 0	
Primary safety endpoint	Composite major and CRNM bleeding	2 (1.4%)	1 (1.4%)	RR 0.99 (95%CI 0.1, 10.8) P=0.995
Secondary safety endpoints	Major bleeding	0	0	
	CRNM bleeding	2 (1.4%)	1 (1.4%)	RR 0.98 (95%CI 0.1,10.7) P=0.985
	Minor bleeding	51 (35.7%)	21 (29.6%	RR 1.19 (95%CI 0.8, 1.8) P=0.380

[a]: In one case the event occurred prior to dosing of apixaban
[b]: Per definition include cerebral sinovenous thrombosis, renal vein thrombosis, portal vein thrombosis, catheter-related VTE, and splanchnic thrombosis
[c]: Relative risk of apixaban vs SOC and 95%CI based on Cochran-Mantel-Haenszel (CMH) test stratified by age group. The nominal p-value from CMH test stratified by age group
[d]: defined as the last image obtained in the Main Treatment Phase compared to baseline

2.6.5.3. Clinical studies in special populations

Not applicable.

2.6.5.4. In vitro biomarker test for patient selection for efficacy

Not applicable.

2.6.5.5. Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable.

2.6.5.6. Supportive study(ies)

Supportive studies are PIP01 Studies CV185155 and CV185362 in VTE primary prophylaxis in 735 paediatric subjects, 385 of whom received apixaban. Results from study CV185118 are not included, since efficacy was not a defined endpoint in this single-dose pharmacokinetics (PK), safety and tolerability Study.

In study CV185155, the dosing regimen was targeted on achieving exposure similar to exposure in adult patients treated with apixaban 2.5 mg BID for the prevention of recurrent VTE in adult patients in the AMPLIFY-EXT.

In study CV185362, similar to study CV185325, the dosing regimen was targeted on achieving exposure similar to exposure in patients treated with apixaban 5 mg BID for VTE treatment (AMPLIFY, AMPLIFY-EXT) or prevention of VTE associated with NVAF (ARISTOTLE trial). In study CV185362 no loading dose was administered.

Study CV185155 was a Phase 3, randomized, multi-center, open-label study, to assess the safety and efficacy of apixaban for thromboembolism prevention during induction chemotherapy in paediatric subjects aged 1 to <18 years (weighing >= 6 kg) with newly diagnosed ALL or LL (T or B cell) and a new CVAD inserted, treated with asparaginase. Exclusion criteria were similar to main study CV185325. The study included 4 study periods including a treatment period of 29 +/- 5 days. A total of approximately 500 randomized subjects were planned to be allocated with 1:1 ratio to the systemic

thromboprophylaxis with apixaban (intervention) or standard-of-care which consisted of no systemic anticoagulant prophylaxis (control). Randomization was stratified by age groups as < 10 years or >= 10 to < 18 years and by risk stratification criteria for acute lymphoblastic leukemia (ALL) in children.

The *dosing regimen* was targeted on achieving exposure, 620 ng•hr/mL based on the median AUC(TAU) in adult patients treated with apixaban 2.5 mg BID for the prevention of recurrent VTE in adult patients in the AMPLIFY-EXT. The control group received SOC that consists of no systemic anticoagulant prophylaxis.

The primary efficacy endpoint was a composite of non-fatal, asymptomatic and symptomatic DVT, PE, cerebral venous sinus thrombosis (CVST), and VTE related death. Secondary efficacy endpoints were the individual components of the primary efficacy endpoint.

Results. A total of 537 subjects were enrolled in 74 centers, 512 (95.3%) were randomized (256 subjects in each arm). The treatment period was completed by 86.5% of subjects. The most common reason for not completing the treatment period was adverse events (AEs); 13.7% and 2.0% in the apixaban and SOC arms, respectively.

Study participants. In general, the baseline demographics were balanced. The baseline disease characteristics were balanced between the treatment arms and across age-groups. Per the inclusion criteria, all subjects had ALL (94.7%) or LL (5.3%) at baseline. Haematologic abnormalities were common including a large proportion of subjects (63.1%) with thrombocytopenia (platelet count $\leqslant$ 100,000 / mm3). The majority (83.8%) had normal estimated glomerular filtration rate (eGFR) at baseline and mild renal impairment was observed in 10.7% of subjects, as determined from the Schwartz formula.

Exposure to assigned treatment was ~47 years (2463 patient-weeks), with 22.5 years (1173.3 patient-weeks) for exposure to treatment with apixaban. The mean (SD) extent of exposure in the apixaban arm was 23.5 days (6.25), or, after excluding days of dose interruption, 21.5 days (5.93).

Analysis of the primary efficacy endpoint (a composite of non-fatal [asymptomatic or symptomatic] DVT, PE, and CVST; and VTE related death) showed a numerically lower incidence in the apixaban arm vs the SOC arm (relative risk = 0.69 [95% CI 0.45, 1.05]), but did not reach significance (two sided p = 0.08/ one sided p=0.04)). Sensitivity analyses were consistent. The numerical improvement for the primary composite efficacy endpoint was mostly attributable to a numerical improvement in asymptomatic DVT events (27 (10.5%) vs 38 (14.8%)).

Analysis of the secondary efficacy endpoints, which represented the individual components of the primary efficacy endpoint (non fatal asymptomatic DVT, non fatal symptomatic DVT, non fatal PE, CVST, and VTE related death), showed similar results to those for the primary efficacy endpoint.

Study CV185362 was a phase 2, randomized, multi-center, open label study to evaluate pharmacokinetics (PK) and pharmacodynamics (PD), safety and tolerability of apixaban versus VKA or LMWH, in paediatric subjects with congenital or acquired heart disease (CAHD) requiring chronic anticoagulation for thromboembolism prevention. Exclusion criteria were similar to main study CV185325. The study included 3 study periods including a treatment period of 12 months.

The study could not be powered to show statistically significant treatment differences for any of the endpoints. With a treatment period of up to 12 months, a sample size of approximately 200 subjects (approximately 133 in the apixaban arm and approximately 67 in the SOC arm) was considered both feasible, and sufficient for descriptive efficacy and safety analyses, as well as for PK and pharmacodynamics (PD) modeling. Randomization was stratified by age group (28 days to < 2 years, 2 to < 12 years, or 12 to < 18 years) as well as disease diagnosis (Single-Ventricle Physiology SVP vs non-SVP) to ensure a consistent distribution between the two treatment arms.

The dosing regimen was targeted on achieving exposure of 1,200 ng • h/mL based on the median AUC(TAU) in adult patients treated with apixaban 5 mg BID for VTE treatment (AMPLIFY, AMPLIFY-EXT) or prevention of VTE associated with NVAF (ARISTOTLE trial) (Table 28). The control group was treated with VKA or LMWH, following the local SOC guidelines that were aligned with the ACCP guidelines. The dose of VKA was recommended to be titrated to achieve a target INR of 2.0 to 3.0, and the dose of LMWH was recommended to target an anti-Xa level between 0.5 and 1.0 unit/mL.

Table 21. Apixaban Doses for Ages 28 Days to <18 Years- Study CV185362

Body weight range	Dose
3 to < 4 kg	0.2 mg BID
4 to < 5 kg	0.3 mg BID
5 to < 6 kg	0.5 mg BID
6 to < 9 kg	1 mg BID
9 to < 12 kg	1.5 mg BID
12 to < 18 kg	2 mg BID
18 to < 25 kg	3 mg BID
25 to < 35 kg	4 mg BID
≥ 35 kg	5 mg BID

There was no primary efficacy endpoint. Secondary efficacy endpoints were (1) Composite of adjudicated thromboembolic events and TE-related death, and (2) QOL (PedsQLTM scores, and KIDCLOT scores).

Results. A total of 198 subjects were enrolled in 33 centers, 192 (97.0%) of whom were randomized (129 to apixaban and 63 to VKA/LMWH). The treatment period was completed by 167 (87.0%) subjects. Adverse events as reason for not completing the treatment period was reported in 6 (4.7%) vs 1 (1.6%) of subjects on apixaban vs VKA/LMWH.

Study participants. The baseline demographics were balanced between the apixaban and VKA/LMWH arms except for sex (male subjects: 48.1% and 63.5% in the apixaban and VKA/LMWH arms, respectively). The baseline disease characteristics were comparable between the treatment arms and across age-groups.

The median extent of exposure in the apixaban group (n=126) was 358 days (mean(SD): 330.6 (83.04) days).

No primary efficacy endpoint was defined. The secondary efficacy endpoint of a composite of adjudicated thromboembolic events and thromboembolic event-related deaths was not reported in either treatment arm (n=0 vs n=0).

The data from the QOL questionnaires were of limited interpretability due to small sample sizes. There were no clinically meaningful post baseline differences in mean changes in scores from baseline between the treatment arms.

Extrapolation exercise based on criterium of clinical response to treatment: efficacy

a. Apixaban for the treatment of VTE

Efficacy**.** Apixaban for the treatment of VTE was investigated in adult studies CV185056 (2609 subjects) and extension study CV185057 (1653 subjects), and paediatric study CV185325 (145 subjects). The primary efficacy outcome, recurrence of VTE or VTE-related death, was comparable in the adult (2.3%) and paediatric studies (2.8%) (Table 29). A limited number of 22 patients aged 28 days to 2 years were treated with apixaban in study CV185325, with none of them experiencing a recurrent VTE or VTE-related death.

Table 22. Key Efficacy Outcomes - Studies CV185056, CV185057, and CV185325

Study	Key efficacy outcome	Apixaban, n/N (%)	SOC*, n/N (%)
CV185056	Recurrent symptomatic VTE or VTE-related death	59/2609 (2.3)	71/2635 (2.7)
CV185057	Same as above	2.5 mg BID: 32/840 (3.8) 5.0 mg BID: 34/813 (4.2)	96/829 (11.6)
CV185325 (Main Phase)	Symptomatic+asymptomatic recurrent VTE or VTE-related mortality	4/145 (2.8)	2/72 (2.8)
CV185325 (Extension Phase)		0/53 (0.0)	NA**
CV185325 (Main Phase; Group 3 [age 28 days to <2 years])		0/22 (0.0)	NA**
*SOC: Standard of care treatment arm; **NA: Not applicable (Extension Phase was for apixaban-treated participants only)			

b. Apixaban for the prevention of VTE

The Phase 3 CV185030, CV185048, and CV185036 adult clinical trials, and the Phase 3 and 2 paediatric studies, CV185155 and CV185362, respectively, were all conducted to evaluate the benefit-risk associated with the use of apixaban for the prevention of thromboembolic events in at-risk patients; however, they differed in terms of the more specific type of thromboembolic event evaluated.

In study CV185155, any type of VTE (including cerebral venous sinus thrombosis) was investigated in paediatric patients with newly diagnosed ALL and LL undergoing induction chemotherapy with an asparaginase-containing regimen administered via an indwelling CVAD. Accordingly, the efficacy outcomes from this paediatric study are best compared to the outcomes from two of the adult studies that included patients at increased risk of VTE due to cancer who were enrolled in Study CV185036, along with the CV185056 post-hoc sub-study analysis of apixaban versus enoxaparin plus warfarin for the treatment of VTE in patients with cancer. In study CV185362, any type of thromboembolic (TE) event was investigated in paediatric patients with heart disease, whether congenital (primarily single ventricle physiology requiring second- or third-stage palliative surgery) or acquired (primarily Kawasaki disease). Accordingly, the efficacy outcomes from this paediatric study will be compared to those (primary and/or secondary efficacy outcomes that most closely align with them) of adults with cardiac disease (AF) enrolled in the CV185030 and CV185048 adult studies.

Efficacy

Study CV185155. The duration of the treatment phases in paediatric Study CV185155 and the CV185036 medically ill adult study were similar, with mean (SD) and median apixaban exposures of 23.5 (6.3) and 25.0 days, and 25.2 (9.9) and 30.0 days, respectively. During these same time intervals, primary efficacy events of symptomatic and asymptomatic VTE were reported for 31/256 (12.1%) of the paediatric patients in CV185155. All but 4 (1.6%) of them were asymptomatic (clinically unsuspected) in nature. Primary efficacy events of any type of VTE were reported for 60/2,211 (2.7%) of the medically ill adult patients in CV185036. Despite the higher overall incidence of any (symptomatic or asymptomatic) VTE events in paediatric Study CV185155 (12.1%) when compared to that reported in the cancer sub-group post hoc analysis of adult Study CV185056 (3.7%), the key efficacy outcome measured in the latter study included only symptomatic VTE events (and VTE-related deaths). In this regard, only 4 (1.6%) of the 31 VTE events reported in paediatric Study CV185155 were symptomatic, a rate closer to the 3 events (3.7%) reported in the adult CV185056 cancer post-hoc analysis. The primary efficacy endpoint for the cancer sub-group analysis of CV185056 was the same as that for the overall study and was reported as having occurred in 3 (3.7%) of the 81 patients with cancer who had been randomized to apixaban therapy, and who were evaluable for efficacy in the sub-group analysis. Given that the primary efficacy endpoint for Study CV185056 included only symptomatic VTE events as well as VTE-related deaths, and that there were no VTE-

related deaths in paediatric Study CV185155, the efficacy outcomes presented in Table 30 for that study and the CV185036 and CV185056 cancer sub-study appear to be similar to one another.

Of the 256 paediatric patients randomized to the apixaban treatment arm of Study CV185155, only 1 was < 2 years of age; no efficacy events of any kind were reported for this patient.

Table 23. Key Efficacy Outcomes from the Post-hoc Adult Cancer Sub-study of CV185056, adults study CV185036, and paediatric study CV185155

Study	Key efficacy outcome(s)	Apixaban, n/N (%)	SOC¶, n/N (%)
CV185056 post-hoc sub-study (Agnelli G. et al[3])	Recurrent symptomatic VTE or VTE-related death	3/81 (3.7)	5/78 (6.4)
CV185036	Primary: 30-day composite of death related to VTE, PE, symptomatic DVT, or asymptomatic proximal DVT	60/2211 (2.7)	70/2284 (3.1)
	Secondary: Total VTE and death related to VTE	43/2485 (1.7)	40/2488 (1.6)
CV185155	Primary: Composite of non-fatal [symptomatic or asymptomatic] DVT*, PE**, and CVST***; and VTE-related death confirmed by adjudication	31/256 (12.1)	45/256 (17.6)
	Secondary:		
	Non-fatal, asymptomatic DVT	27 (10.5)	38 (14.8)
	Non-fatal, symptomatic DVT	4 (1.6)	6 (2.3)
	Non-fatal PE	0	0
	Non-fatal CVST	0	1 (0.4)
	VTE-related death	0	0
CV185155 (age <2 years)		Primary: 0/1 (0.0)	Primary: 1/7 (14.3)

¶ SOC: standard of care treatment arm
* DVT: deep vein thrombosis; ** PE: pulmonary embolism; *** CVST: cerebral venous sinus thrombosis

Study 185362. No TE events or TE event-related deaths were reported in Study CV185362 on the safety and exploratory efficacy of apixaban vs SOC in paediatric patients at increased risk due to congenital or acquired heart disease. This compares to crude rates of stroke/systemic embolism of 2.3% and 1.8% among the apixaban-treated participants in the CV185030 and CV185048 stroke prevention studies, respectively, all of whom were adults with cardiac disease in the form of paroxysmal or persistent, NVAF. The actual exposure-adjusted rates of the primary efficacy outcomes were 1.27% and 1.62% per year of exposure to apixaban in CV185030 and CV185048, respectively (Table 31). There were pronounced differences between the absolute numbers of apixaban-treated paediatric vs adult patients at risk for efficacy events in the CV185362 vs. CV185030 and CV185048 studies (N=129 vs 9,120 and 2,807, respectively), despite which the relative differences between the observed event rates were quite small: 0% in the paediatric study vs. 1.27%/year and 1.6%/year in the 2 adult studies, respectively. While the secondary efficacy outcome rates in both of the adult studies were clearly higher and further discrepant from the 0% exploratory efficacy outcome in Study CV185362, this additional increment in the difference in events rates between the (absence of) paediatric events in CV185362 and the secondary efficacy outcomes in CV185030 and CV185048 was entirely attributable to all-cause fatal events which, in turn, is almost certainly attributable to the marked differences between the age ranges of the adult and paediatric study populations.

Of 129 study participants randomized to apixaban treatment, 8 were <2 years of age. No efficacy events were reported in either treatment arm in this age group.

Table 24. Crude and Exposure Adjusted Duration of Exposure of Apixaban treated Participants in Adult Studies CV185030 and CV185048 and paediatric study CV185362

Study	Crude efficacy outcome rates, apixaban participants, %	Duration of apixaban exposure, days	Exposure-adjusted efficacy outcome events, %/year
CV185030	Primary: 2.3	Mean (SD): 624 (300) Median: 629	Primary: 1.27
CV185048	Primary: 1.8 Secondary: 4.7	Mean (SD): 417 (200) Median: 409	Primary: 1.62 Secondary: 4.21
CV185362	Exploratory efficacy: 0.0	Mean (SD); 331 (83) Median: 358	Not applicable
CV185362 (28 days to <2 years)	Exploratory efficacy: 0.0	Mean (SD): 260 (110) Median: Not available	Not applicable

2.6.6. Discussion on clinical efficacy

Apixaban is indicated for prevention of venous thromboembolism (VTE) following knee or hip replacement surgery in adults, prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation (NVAF) with one or more risk factors, and treatment of deep venous thrombosis (DVT) or pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults. The applicant now applies for an extension to add:
"*Treatment of VTE and prevention of recurrent VTE in paediatric patients from 28 days to less than 18 years of age.*"

Efficacy-data are mainly based on results from a pre-specified interim-analysis of study CV185325. PIP01 studies CV185155 and CV185362 are considered supportive since these concern studies on apixaban for primary thrombo-embolism prevention.

Pivotal study CV185325
Single, pivotal study CV185325 is a randomized, open-label, active-controlled, descriptive safety and efficacy study in paediatric subjects requiring anticoagulation treatment for VTE and prevention of recurrent VTE, performed in the target population of patients aged 28 days to < 18 years for treatment of VTE. Enrollment of neonates (birth to < 28 days) is ongoing, and this age-category is not included in the current application.

Methods
Study design. There were 4 study periods. The main treatment phase lasted 42 days for subjects aged <2 years, and 84 days in subjects aged >= 2 years. Subjects from age groups 1, 2, or 3 (age groups 12 - <18 years, 2- <12 years and 28 days-<2 years) who were randomized to receive apixaban had the option to continue apixaban treatment beyond the Day 84 visit for 6 to 12 additional weeks in the Extension Phase. The duration of treatment, 12 weeks in subjects >= 2 years, and 6 to 12 weeks in subjects < 2 years, is in line with guidelines (American College of Chest Physicians (ACCP) pediatric guidelines, 2018 American Society of Haematology (ASH)), that state that younger patients with VTE have causes of their disease which differ from older patients (e.g. indwelling intravascular catheters/devices) and that these younger patients can be treated for a shorter period than older patients. In the American Society of Haematology 2018 guideline it is suggested using anticoagulation for ⩽3 months rather than anticoagulation for >3 months in paediatric patients with provoked DVT or PE, and using anticoagulation for 6 to 12 months rather than anticoagulation for >6 to 12 months in

pediatric patients with unprovoked DVT or PE (both conditional recommendation based on very low certainty in the evidence of effects). The current clinical practice based on input from practicing clinicians is consistent. It was agreed by PDCO that according to scientific recommendations and current practice in clinical setting, a reduced treatment of 6 to 12 weeks was acceptable and would enhance recruitment (EMEA-000183-PIP02-12-MO3).

With regard to the indication of prevention of recurrent VTE in paediatric patients, in "the Paediatric Addendum on the guidelines on clinical investigation of medicinal products for the treatment and prophylaxis of venous thromboembolic disease" (January 2023), it is stated that for secondary prevention, an extension of the study for the initial treatment of VTE from month 3 until month 6 to 12, is preferred, in order to support long-term, sometimes indefinite treatment. The duration of anticoagulation treatment in studies CV185362 and CV185325 was only to continue until the clinical need was assessed as having resolved. Accordingly, the duration of exposure to apixaban in each of the above studies often did not exceed 3-6 months and was generally even shorter among infants and young children, with the exception of primary prophylactic treatment among participants in the CV185362 study, with congenital heart disease and single ventricle physiology. In study CV185325, median (min, max) duration of exposure was 84 (1, 114) days in 143 paediatric subjects during the main study phase, and 168 (91-176) days in 53 subjects that also participated in the extensions phase. In addition, in study CV185362, median (min, max) duration of exposure was 358 (5, 392) days in 129 paediatric subjects. This duration of exposure is comparable with data from the EINSTEIN JR study on rivaroxaban (91 (IQR 87-95) days in 304 subjects), and the DIVERSITY study on dabigatran (98 (0, 69) days in 363 patients). Data for age-group 28 days -< 2 years are limited to a median (range) of 80 (2, 93) days in 21 subjects on apixaban as compared with 31 (IQR 29-35) days in 25 subjects on rivaroxaban. In the SmPC it is appropriately advised to individualise duration of overall therapy after assessment of treatment benefit and risk for bleeding.

Population.
In study CV185325 paediatric subjects requiring anticoagulation treatment for VTE and prevention of recurrent VTE were included. The index VTE was required to be confirmed by imaging, and was adjudicated by a blinded, independent adjudication committee (EAC). Exclusion criteria included subjects with a high risk of bleeding, and subjects with a mechanical heart valve, abnormal liver function tests or impaired renal function (equivalent to < 30 ml/min/1.73m2 in adults), thrombocytopenia, uncontrolled hypertension, and subjects treated with thrombectomy or thrombolytic therapy. Antiplatelet therapy (including ASA > 165 mg/day) was not allowed. No further stratification e.g. related to type of VTE or underlying morbidities is performed.

Treatments.
Apixaban dose regimen. The rationale of the dose regimen in study CV185325 was based on an exposure-matching strategy to adult exposures in the AMPLIFY study where apixaban was investigated for treatment of VTE. The target AUC(TAU) was 1,200 ng•hr/mL. Population PK modeling and simulation approach was used for selection and subsequent recommendation of fixed-dose by body weight-tiered dosing regimen for pediatric subjects from 28 days to less than 18 years of age. In the AMPLIFY study in 5395 patients with acute venous thromboembolism apixaban, apixaban at a dose of 10 mg twice daily for 7 days, followed by 5 mg twice daily for 6 months, was noninferior to conventional therapy (subcutaneous enoxaparin, followed by warfarin; $p<0.001$) for recurrent symptomatic VTE or death related to VTE. The indication of acute venous thromboembolism is in line with the proposed paediatric indication, and therefore a dosing regimen aimed at matching the exposure in the AMPLIFY study is justified.
Similar to the dosing regimen in adults, a loading dose during 7 days is followed by a maintenance dose. The proposed dose-regimen for paediatric patients is similar to the dose-regimen in study

CV185325. In the SmPC it is stated that duration of treatment should be individualised after careful assessment of the treatment benefit and the risk for bleeding, which can be endorsed.

Table 25. Dose recommendations for treatment of VTE and prevention of recurrent VTE in paediatric patients, by weight in kilograms (kg) 4 mg

	Days 1-7		Day 8 and beyond	
Body weight (kg)	Dosing schedule	Maximum daily dose	Dosing schedule	Maximum daily dose
4 to <5	0.6 mg twice daily	1.2 mg	0.3 mg twice daily	0.6 mg
5 to <6	1 mg twice daily	2 mg	0.5 mg twice daily	1 mg
6 to <9	2 mg twice daily	4 mg	1 mg twice daily	2 mg
9 to <12	3 mg twice daily	6 mg	1.5 mg twice daily	3 mg
12 to <18	4 mg twice daily	8 mg	2 mg twice daily	4 mg
18 to <25	6 mg twice daily	12 mg	3 mg twice daily	6 mg
25 to <35	8 mg twice daily	16 mg	4 mg twice daily	8 mg
≥35	10 mg twice daily	20 mg	5 mg twice daily	10 mg

In order to enable dosing in paediatric subjects in the clinical studies, apixaban 0.5 mg tablets, as well as 0.1 mg sprinkle capsules were developed. Further, an oral solution 0.4 mg/ml was available, but only for children >= 5 years of age since daily intake of propylene glycol was too high for younger patients. The proposed commercial formulations for paediatric patients include 0.15 mg granules in capsules for opening, as well as 0.5, 1.5 and 2.0 mg coated granules in sachets, in addition to the currently available 2.5 and 5 mg film-coated tablets. Appropriate guidance on the formulations to be used are provided in the SmPC.

Active control treatment in arm 2 consisted of SOC, either VKA or LMWH. Though VKA and LMWH have no formal MA for treatment of paediatric patients, they are used in clinical practice and are in line with the current, internationally recognized ACCP and ASH guidelines. Therefore the choice of active control is acceptable. In the AMPLIFY trial in adults apixaban was compared with conventional anticoagulation that was specified as warfarin for six months co-administered with subcutaneous (SC) enoxaparin for at least the first five days and until an INR of 2 was achieved. In current guidelines and clinical practice, the recommended therapeutic INR ranges for VKA in children are directly extrapolated from recommendations for adult patients, for most indications a therapeutic target INR of 2.5 (range 2.0-3.0). The UFH dose is selected based on aPTT by protamine titration of 0.2 to 0.4 units/mL or an anti-FXa level of 0.35 to 0.7 units/mL, and therapeutic ranges for LMWH are extrapolated from adults and based on anti-FXa level of 0.50 to 1.0 units/mL (4 to 6 hours following sc injection BID [Monagle et al, 2012]. In study CV185325, a total of 73 patients randomized to SOC anticoagulant treatment received LMWH, UFH or VKA in 90.4%, 8.2% and 28.8%, respectively. LMWH dosing, UFH titration and INR target (VKA) was to be performed per ASH and ACCP guidelines and therefore, though no further data are provided, are considered to reflect standard-of-care.

According to protocol, initial anticoagulant treatment at the moment of diagnosing the index VTE was similar for both arms, and could consist of SOC for a maximum of 7 days in subjects from 2 to < 18 years and 14 days for subjects aged 28 days to < 2 years. Median duration of prior SOC anticoagulation was 4 days, and only 7.7% of patients started beyond day 7. At day 5, a total of 96/143 (67.2%) of subjects had been started on apixaban. Most frequently prescribed anticoagulant treatment consisted of LMWH (119/143; 83.2%), UFH (51/143; 35.7%), and warfarin in a limited

number (5/143; 3.5%). This is in support of the proposed posology, to initiate apixaban after 5 days of initial parenteral anticoagulant therapy.
The initial weight-based dosing regimen of apixaban (October 2014) was amended upon updating of the pediatric-PPK model (March 2017), and was further amended towards a fixed dose, body weight tiered regimen after apixaban oral solution was no longer available for patients < 5 years of age due to the propylene glycol content. This final dosing regimen is in line with the proposed posology in the current MAA. Participants who were randomized prior to the final dosing amendment in October 2017 were continued on their weight-based regimen. When comparing the final dosing regimen with the actual doses that were prescribed according to the initial weight-based dosing regimen only limited differences in dose are noticed, and comparable steady-state AUCs on both dosing regimen was seen in 48 subjects, for weight-range of 4 to > 35 kg.

Objectives and endpoints. The objectives are considered standard and acceptable. With regard to endpoints, VTE-diagnosis was confirmed by imaging, with planned follow-up imaging at mid-point and EOT in subjects >= 2 years of age and at EOT in subjects < 2 years of age and unplanned additional imaging when medically indicated. Recurrent VTE is defined as either contiguous progression or non-contiguous new thrombus and including, but not limited to, DVT, PE and paradoxical embolism, which is agreed upon. Endpoints and imaging are reviewed and adjudicated by a blinded, independent adjudication committee.

Statistical methodology. With regard to the statistical analysis, the current grouped application for extension of indication to paediatric patients is based on a prespecified interim analysis, introduced by amendment of study protocol in February 2020, that include interim efficacy and safety analysis. The interim-analysis was introduced due to recruitment problems for neonates and has been accepted by PDCO. Descriptive statistics on efficacy and safety outcome will be presented, including relative risk of apixaban versus SOC and two-sided 95% confidence interval based on Cochran-Mantel-Haenszel (CMH) test stratified by age group. No further formal testing is performed, and no imputation of missing data has been performed.

No power calculation was performed since there was no formal pre-defined hypothesis testing. Initially, approximately 150 subjects were planned to be randomized, with a target of 30 subjects in each age-group. Throughout the trial, it was expected that a sample size of 250 was needed to provide reasonable safety and pharmacokinetic data and the protocol was amended accordingly (Protocol amendment 6, 06 September 2019). No further stratification is performed, therefore, imbalances e.g. related to type of VTE or underlying morbidities may occur, but is considered acceptable in view of feasibility. Study CV185325 is an open-label study, as opposed to the AMPLIFY study, where the DB design required a triple dummy treatment. This is considered unfeasible in paediatric patients. Further, diagnosis of index VTE and endpoints are adjudicated by an independent adjudication committee, contributing to the internal validity.

Results

Participants

Study disposition. A total of 217 subjects were randomized, less than the number of subjects that was estimated to be required for safety- and PK- evaluation (250). Though the number of subjects included in the three age-groups all were in excess of 30, the number of 29 subjects in age group 2-12 years and 21 subjects in age group 28 days to < 2 years that were randomized to apixaban is limited. Recruitment for the youngest age-group of neonates is still ongoing.

The number of subjects discontinuing from the study is slightly higher for the SOC-group (n= 14; 9.7% vs n= 9; 12.5% for apixaban vs SOC), with no clear imbalances across age-groups. The most

common reason for not completing were AEs (n= 6 ; 4.1% vs n=0; 0% for apixaban vs SOC). A total of 55 subjects (25.3%) entered the Extension Phase of the study. The Full Analysis Set (all randomized subjects) was used for the efficacy results of the main treatment phase, and reflects the intention-to-treat population.

Protocol deviations leading to randomization of subjects that were not eligible in 6 (2.8%) participants. Two were discontinued prior to receiving treatment. In 4 (2.8%) subjects on apixaban, exclusion criteria were single cases of abnormal liver function, preceding anticoagulant treatment exceeding 7 days, prohibited concomitant medication and high risk of bleeding. In 2 (2.8%) subjects on SOC, this concerned single cases of abnormal liver function and index VTE not confirmed by imaging. A total of 4 (1.8%) of subjects was not discontinued despite meeting a discontinuation criterion. In all cases this concerned either a recurrent VTE or additional therapy (thrombolysis and thrombectomy). No safety issue with regard to bleeding event was seen. The total of 8 out of 217 (3.7%) subjects who either were started or continued on study treatment despite not meeting eligibility criteria is quite substantial, but distribution across treatment arms was comparable, mitigating potential impact on interpretability of study results.

Baseline demographics and characteristics. The most frequently reported index VTE were DVT (n=76; 52.4% on apixaban vs n=41; 56.9% on SOC) and PE (n=30; 20.7% vs n=13; 18.1%). Though data on presence of a CVAD are lacking, DVTs were located in the upper extremity in 33 (22.8%) vs 25 (34.7%) subjects on apixaban vs SOC, respectively, and according to literature a high frequency of CVAD-associated VTE can be expected at this location. Based on the frequency of DVTs located in the lower extremity of 43 (29.7%) vs 16 (22.2%) subjects, that are unlikely to be CVAD-associated, it is considered likely that relevant proportions of DVTs associated with as well as without CVAD were included in the study, though adequate balance of distribution across treatment arms cannot be affirmed. In VTE-prevention study CV185155, comparable effect of apixaban in patients with vs without CVAD was seen, and also in public literature no differential effects of anticoagulants related to presence of a CVAD are reported. Intracardiac thrombus was reported more frequently in the apixaban group (n= 9; 6.2% vs n=2; 2.8%).

In a total of 26 (12.0%) of subjects the index event cases were adjudicated as negative with an increased frequency in the apixaban group (n=20; 13.8% vs n=6; 8.3%). Further, in a total of 10 (4.6%) of subjects the index event was determined as indeterminate/non-diagnostic, again with an increased frequency in the apixaban group (n=9; 6.2% vs n=1; 1.4%). In 4 cases, two imaging index events were reported, out of which one was positive. Therefore, based on imaging, in a total of 22 cases an index VTE event was not confirmed by the external adjudication committee (EAC), 16 (11%) vs 6 (8.3%) for apixaban vs SOC. Per protocol, the diagnosis of VTE and subsequent decision on indication for anticoagulant treatment were at the discretion of the health care provider and local investigator. Confirmation of the index-VTE by the independent EAC was not required, and findings were not reported back to the local investigator or health care provider. It is stated that no effect on the primary efficacy endpoint (recurrent VTE defined as contiguous progression or non-contiguous new thrombus) is likely, since both recurrent as well as new signs of thrombus formation are included. However, a substantially higher frequency of non-confirmed VTE may suggest an increased number of patients at a reduced TE risk in the apixaban subgroup, or it may be related to an increased number of patients with diagnostic difficulties due to location of the VTE or other factors influencing diagnostic performance. This reduced TE risk may have biased the number of events in the apixaban arm downwards and is therefore not considered to be a conservative approach. The fact that in 5 out of 6 subjects who reached the primary endpoint, the index VTE was confirmed by the adjudication committee, would indeed suggest that in patients in whom the index VTE is not confirmed have a low likelihood of developing a (recurrent) VTE. In descriptive study CV185325, no formal predefined

hypothesis was tested and no power calculation for sample size estimation was performed. At least 1 adjudicated, symptomatic, or asymptomatic recurrent VTE event was seen in 4 (2.8%) subjects in the apixaban group and 2 (2.8%) subjects in the SOC group (RR 0.99 (95% CI 0.2,5.3 ; p=0.994). This included one patient in the apixaban group in whom the index VTE was not confirmed by the EAC. If patients would have been withdrawn from the study in case of a non-confirmed index VTE, frequencies of the primary endpoint would have been 3/(143-20) vs 2/(71-6), or 2.4% vs 3.1% for apixaban vs SOC. Therefore, it seems unlikely that not-withdrawing patients with a non-confirmed index VTE from the study would have altered the efficacy result and the issue is not further pursued. Though, it may be questioned as to whether this lack of communication between investigator/EAC and health care provider on a negative index VTE event can be considered ethically justified, and should be reconsidered for the final age-cohort that is currently investigated, aged from birth to 28 days.

Baseline demographic characteristics generally were balanced across apixaban and SOC groups for the entire group as well as within each age group. Similar weight estimates were seen, with median (range) of 56.50 (2.90-147.5) kg vs 57.60 (2.70-141.0) kg for apixaban vs SOC. The majority of subjects were of white origin, and 10 to 15% was of black origin. Age-distribution was similar for both treatment arms, with inclusion of 137 (63.1%), 44 (20.3%), 32 (14.7%), and 4 (1.8%) subjects in age-group 1, 2, 3 and 4, respectively.

Past and ongoing diseases were reported in 97 (66.9%) and 138 (95.2%) participants in the apixaban group vs 55 (76.4%) and 67 (93.1%) participants in the SOC group. Most frequently encountered concomitant conditions were infectious diseases (19.3% vs 29.2%), obesity (17.9% vs 16.7%), malignancy (15.2% vs 12.5%), congenital cardiovascular disease or cardiac condition (24.8% vs 22.2%), trauma/fracture (9.7% vs 6.9%), surgery (8.3% vs 1.4%), and sex hormone use (17.9% vs 18.1%). These conditions reflect known risk factors for developing VTE, and were balanced between treatment arms.

Endpoints

The primary efficacy endpoint of composite of all image-confirmed and adjudicated symptomatic and asymptomatic recurrent VTE and VTE-related mortality was reported in 4 (2.8%) subjects in the apixaban group and 2 (2.8%) subjects in the SOC group. No subjects experienced VTE related death. Though not formally tested, the primary composite efficacy endpoint numerically is similar. The prespecified sensitivity analysis was in line with the primary results.

When analyzed **across age-groups** as prespecified, for the primary efficacy endpoint numerically an increase was seen on apixaban in the age-group of 2 to <12 years (n=1; 1.1% vs n=2; 4.3% at age 12 to <18 years, n=3; 10% vs 0% at age 2 to <12 years and 0% vs 0% at age 28 days to < 2 years). However, the low number of events and the lack of formal testing limit further interpretation.

In the secondary efficacy endpoint analysis of the individual components of the primary efficacy endpoint, similar results were seen on apixaban vs SOC for recurrent symptomatic or asymptomatic VTE (n=4; 2.8% vs n=2; 2.8%), and all cause death (n=2; 1.4% vs n=1; 1.4%). No VTE-related death or stroke occurred.

The results on secondary endpoint of index VTE status were comparable for most categories (resolution in 76 (52.4%) vs 37 (51.4%) subjects, regression 25 (17.2%) vs 11 (15.3%) and unchanged 7 (4.8%) vs 7 (9.7%)), though contiguous recurrence was seen more often on apixaban (in 2 vs 0 subjects). In both cases brief interruptions of apixaban treatment had occurred, that may have contributed to the events. This highlights the relevance of adequate guidance on missed dose and on temporary interruption of apixaban in case of intercurrent disorders or interventions, as provided in section 4.2 and 4.4 of the SmPC.

The number of primary efficacy endpoints is low, raising questions on the power of the study to detect differences in outcome. No power calculation, nor formal testing for inferiority has been performed. In the AMPLIFY study in 5395 adults with acute venous thromboembolism, the primary efficacy endpoint of recurrent symptomatic VTE or VTE-related death was seen in 2.3% of subjects on apixaban vs 2.7% of subjects on SOC, with recurrent DVT in 0.8% vs 1.3%, non-fatal recurrent PE in 1.0% vs 0.9% and fatal recurrent PE in <0.1% vs 0.1%. These numbers are comparable with the findings in study CV185325, which is reassuring. Index VTE status was not a formal endpoint in this study.

The frequency of recurrent VTE was comparable with findings in the EINSTEIN study investigating rivaroxaban vs SOC in paediatric patients, where symptomatic recurrent venous thromboembolism was reported in 1% on rivaroxaban vs 3 % on SOC. In the DIVERSITY study comparing dabigatran with SOC in paediatric patients, freedom from recurrent VTE was demonstrated in 96% on dabigatran vs 92% on SOC.

In 53 subjects who entered the extension phase and were treated with apixaban, no event of symptomatic and asymptomatic recurrent VTE or VTE related mortality was reported.

Data in 42 subjects on palatability suggest that the taste of the 0.5 mg dissolved in a specific medium was more appreciated than the taste of the oral solution.

Supportive studies

Supportive studies are PIP01 Studies CV185155 and CV185362 in VTE primary prophylaxis in 735 paediatric subjects, 385 of whom received apixaban. These studies have been assessed by the CHMP in the context of Article 46 procedures (EMEA/H/C/002148/P46/038, EMEA/H/C/002148/P46/039), and of a type II variation to update sections 4.2 and 5.1 of the SmPC in order to update efficacy and safety information in the paediatric population, without seeking a paediatric indication for VTE prophylaxis has been completed (EMEA/H/C/002148/II/0088). No new data are submitted on studies CV185155 and CV185362.

The dosing regimen of apixaban investigated in study CV185155 was aimed at similar exposure as adults dosed 2.5 mg BID (dose for the prevention of venous thromboembolism (VTEp) in adults, based on results of AMPLFY-EXT, with exposure AUC(TAU of 620 ng•hr/mL). For the CV185362 study, the dosing regimen of apixaban was aimed at similar exposure as adults dosed 5 mg BID (maintenance dose for the treatment of VTE in adults, based on AMPLIFY and AMPLIFY-EXT (VTE-treatment) and on ARISTOTLE trial (prevention of VTE associated with NVAF, with exposure of 1,200 ng • h/mL). The dosing and target AUC in study CV185362 is similar to study CV185325.

Study CV185155 was a Phase 3, randomized, multi-center, open-label study, to assess the safety and efficacy of apixaban for thromboembolism prevention during induction chemotherapy in paediatric subjects aged 1 to <18 years, with newly diagnosed ALL or LL (T or B cell) and a new CVAD inserted, treated with asparaginase. The *indication* for anti-coagulant treatment was for prevention of VTE, which differs from the indication of treatment of VTE or prevention of recurrent VTE in the current application. The control group received SOC management, which did not include an active comparator in line with current literature that does not provide a clear recommendation for the use of (systemic) anticoagulation in this specific setting.

Results. The study included 512 patients. The mean (SD) extent of exposure in the apixaban arm was 23.5 days (6.25), and total exposure to apixaban treatment was 22.5 years (1173.3 patient-weeks).

Apixaban resulted in a numerical improvement of the primary composite endpoint of non-fatal deep vein thrombosis (asymptomatic or symptomatic), pulmonary embolism, and cerebral venous sinus

thrombosis (CVST); and VTE related death, as compared to SOC, with a RR of 0.69 (95% CI 0.45-1.05; p=0.08 (1-sided 0.04) with respectively 31 (12.1%) and 45 (17.6%) events, though not reaching statistical significance. This numerical improvement was mostly attributable to a numerical improvement in asymptomatic DVT events (10.5% vs 14.8%). Embolism occurred at a similar rate for apixaban vs SOC (5.1% vs 4.3%). Any of the other (exploratory) endpoints showed too limited events to conclude on, including all cause death (1 vs 2), and catheter related endpoints of infections and catheter patency.

Study CV185362 was a phase 2, randomized, multi-center, open label study to evaluate pharmacokinetics (PK) and pharmacodynamics (PD), safety and tolerability of apixaban versus VKA or LMWH, in paediatric subjects aged 28 days to < 18 years, with congenital or acquired heart disease (CAHD) requiring chronic anticoagulation for thromboembolism prevention. The main treatment period was 12 months which can be considered sufficient to assess the safety of apixaban especially when considering the proposed duration of treatment in the current application, ranging between 6 to 12 weeks. The indication for anticoagulant treatment concerns the (primary) prevention of arterial/ venous thrombo-embolism in patients with a cardiac condition predisposing them to thrombo-embolisms. This indication is therefore different from the proposed indication of treatment of VTE and prevention of recurrent VTE in the current application. The dosing-regimen in study CV185362 and CV185325 are similar, though in study CV185362 no loading dose was given. Active control treatment consisted of VKA (target INR of 2.0 to 3.0) or LMWH (target anti-Xa level between 0.5 and 1.0 unit/mL).

Results. The study included 192 patients. In general, the baseline demographics, and disease demographics were balanced between the arms. A large proportion of patients completed the study (n=167, 87%), although a larger proportion discontinued treatment in the apixaban group compared to the VKA/LMWH group (n=19; 14.7% vs n=6; 9.5%) and there was a disbalance seen in the adverse events as reason for not completing the treatment period (n=6; 4.7% vs n=1; 1.6%). Most randomized subjects received treatment for ⩾337 days in both treatment arms.

In this study, no primary efficacy endpoint was included. The secondary efficacy endpoint, the composite of adjudicated thromboembolic events and thromboembolic event-related deaths, was not reported in either treatment arm. Therefore no meaningful comparison of the efficacy of apixaban vs VKA/LMWH could be established, though these results can be considered reassuring.

The quality of life (QOL) of the patients was also evaluated as a secondary efficacy endpoint. This was measured using the PedsQL and KIDCLOT instruments. Although, PedsQL questionnaires are validated questionnaires applicable in clinical trials, and clinical practice, while KIDCLOT questionnaires are not. Changes in mean scores from baseline were small and not consistent over the different categories in both treatment arms. No clear clinically relevant post-baseline differences and trends or patterns could have been observed between the treatment arms.

Efficacy in the subgroup aged 28 days to < 2 years

A limited number of 22 patients aged 28 days to 2 years were treated with apixaban in study CV185325, with none of them experiencing a recurrent VTE or VTE-related death.

Of the 256 paediatric patients randomized to the apixaban treatment arm of Study CV185155, only 1 was < 2 years of age; no efficacy events of any kind were reported for this patient. Similarly, in study CV185362, of 129 study participants randomized to apixaban treatment, 8 were < 2 years of age. No efficacy events were reported in either treatment arm in this age group. Therefore, no signal of reduced or different efficacy as compared with the other age groups can be discerned, though the

number of subjects is low. However, comparable number of subjects in age-group < 2 years were investigated for other DOACS. In the EINSTEIN Junior study, 37 out of 335 paediatric subjects randomized to rivaroxaban were < 2 years of age, and in the DIVERSITY study, 22 out of 177 paediatric patients randomized to dabigatran were < 2 years of age.

2.6.7. Conclusions on the clinical efficacy

Based on the results of main clinical study CV185325, in paediatric patients aged from 28 days to < 18 years requiring anticoagulant treatment for VTE and prevention of recurrent VTE, the efficacy of apixaban as compared with SOC (VKA, LMWH, or UFH) on the primary endpoint of number of symptomatic and asymptomatic recurrent VTE and VTE-related mortality was found to be numerically similar, though not formally tested. The results were confirmed by sensitivity analysis, and results on secondary endpoints were congruent. Subgroup analysis across age did not show age-dependent differences, though not robustly due to low number of events. Further, in supportive study CV185362, using a similar dosing regimen, the composite outcome of adjudicated thromboembolic events and thromboembolic event-related deaths, did not occur in either treatment arm (apixaban vs VKA/LMWH), though in a different population of subjects with a cardiac condition predisposing to arterial or venous VTE.

These efficacy outcome results for the treatment of VTE in paediatric subjects are consistent with efficacy outcome (recurrence of VTE or VTE-related death) seen in adult studies CV185056/CV185057.

In study CV185325 SOC anticoagulation was administered prior to randomization, and apixaban was initiated after a median duration of 4 days, with only 7% of subjects starting after day 7. This is reflected in the proposed posology to initiate VTE treatment with SOC for at least 5 days, followed by treatment with apixaban.

For the proposed indication "prevention of recurrent VTE" treatment duration is not specified. The duration of anticoagulation by using apixaban should be in line with prevailing guidelines including current 2018 ASH guideline, and the extent and duration of exposure on apixaban in paediatric studies CV185325 and CV185362 is considered sufficient to justify not imposing limitations on the duration of treatment with apixaban.

In subjects aged 28 days to 2 years, experience is limited (22, 1 and 8 patients treated with apixaban in studies CV185325, CV185155 and CV185362), with none of them experiencing a recurrent VTE or VTE-related death. The duration of exposure in this age-group is limited to a median of 80 days in 21 subjects, but is comparable with data for other DOACs, and is considered sufficient to support the advice to decide on duration of treatment based on an individualised careful assessment of benefits and risks.

2.6.8. Clinical safety

The safety data presented are from the pivotal PIP02 Study CV185325 for treatment of VTE and prevention of recurrent VTE, supplemented with the PIP01 Studies CV185155 and CV185362 in VTE primary prophylaxis and single-dose study CV185118, in 970 paediatric subjects, 568 of whom received apixaban. The pre-specified interim data from age groups 1-3 (ages 28 days to < 18 years) of Study CV185325 are summarized. Enrollment for age group 4 (neonates from birth to 27 days of age) is ongoing; available data are included for information.

Due to differences in study design, dosing, treatment durations, and population characteristics, an integrated analysis or pooled comparison of the safety data from Studies CV185118, CV185155 CV185362, and CV185325 was not performed.

2.6.8.1. Patient exposure

Study CV185325

A total of 143 subjects were randomized to apixaban and received study treatment. These included 91, 29, 21, and 2 subjects in age-groups 1,2,3 and 4, respectively. At the time of the database cut-off for study CV185325, 4 subjects had been randomized into the neonatal group (group 4) and, as such, appear in summary tables.

The mean (SD) duration of treatment during the Main Phase of the study was similar (79.59 days [19.32]) on apixaban and 75.17 days [22.24] on SOC) . The majority of subjects (91.6%) were in the study ⩾ 43 days. The extent of exposure for the apixaban group was consistent with the assigned age-specific treatment duration (mean [SD] apixaban exposure for age group 12 to < 18 years: 81.95 days [17.12]; age group 2 to < 12 years: 81.34 days [16.95]; age group 28 days to < 2 years: 72.14 days [22.62]; age group birth to 27 days 25.5 days [27.58]).

Supportive studies

Study CV185155. The median extent of exposure in the apixaban group (n=250) was 25.0 days (mean(SD): 23.5 (6.25) days).

Study CV185362. The median extent of exposure in the apixaban group (n=126) was 358 days (mean(SD): 330.6 (83.04) days. Exposure was similar for both treatment arms, mean (SD) 328.8 (83.70) days on apixaban and 339.0 (57.62) days on VKA/LMWH. Total patient years exposure to apixaban was 114.1 years.

2.6.8.2. Bleeding events: primary and secondary endpoints

Study CV185325

Primary Safety Endpoint (composite of Major and CRNM bleeding): No subjects in either treatment group had an adjudicated Major bleeding event (Table 33). There were 2 (1.4%) subjects in the apixaban group and 1 (1.4%) subject in the SOC group who had at least 1 adjudicated CRNM bleeding event (for age-group 1 n=1; 1.1% vs n=1; 2.2% for apixaban vs SOC, for age-group 2 n=1; 4.8% vs 0; 0%, for age-group 3 n= 0 vs n=0):

- On apixaban one adjudicated treatment-emergent CRNM bleeding event of epistaxis was reported in a subject aged 12 to < 18 years, reported as mild (Grade 1) in intensity, not serious, and assessed as not treatment-related by the investigator. The outcome was reported as recovered/resolved.
- On apixaban one adjudicated treatment-emergent CRNM bleeding event of pericardial haemorrhage was reported in subject aged 28 days to < 2 years reported as moderate (Grade 2) in intensity, not serious, and assessed by the investigator as not related to study intervention and related to postcardiotomy syndrome. The outcome was reported as recovered/resolved.
- On SOC one adjudicated treatment-emergent CRNM bleeding event of haematoma was reported in a subject aged 12 to < 18 years, reported as moderate (Grade 2) in intensity, not serious, and assessed as treatment-related by the investigator. The outcome was reported as recovered/resolved.

Secondary Safety Endpoints. The secondary safety endpoints were the individual components of the primary safety endpoint (ie, Major bleeding and CRNM bleeding), and Minor bleeding. There were 51 (35.7%) subjects in the apixaban group and 21 (29.6%) subjects in the SOC group who had Minor

bleeding events. Similar trends for the proportion of subjects who had Minor bleeding events were observed in each age group compared with the overall population: n=39; 42.9% vs n=18; 40.0%), RR 1.07 (95%CI 0.07-1.6) in subjects aged 12-<18 years, n=11; 37.9% vs n=3; 21.4%, RR 1.77 (95%CI 0.6-5.3) in subjects aged 2-<12 years and n=1; 4.8% vs n=0 in subjects aged 28 days -<2 years.

No clinically significant observations were made with respect to the primary and secondary safety endpoints by age group.

Table 26. Bleeding Event Summary - Safety Analysis Set - CV185325

Objective Endpoint (unit)	Apixaban n = 143		SOC n = 71
Primary Safety Endpoint			
Composite of Adjudicated Major or CRNM Bleeding			
Subjects with an Event, n (%)	2 (1.4)		1 (1.4)
95% CI [1]	(0.1, 5.3)		(0.0, 8.3)
Relative Risk		0.99	
95% CI [2]		(0.1, 10.8)	
p-value [2]		0.9954	
Secondary Safety Endpoint			
Adjudicated Major Bleeding			
Subjects with an Event, n (%)	0		0
95% CI [1]			
Relative Risk (apixaban vs SOC)			
95% CI [2]			
p-value [2]			
Adjudicated CRNM Bleeding			
Subjects with an Event, n (%)	2 (1.4)		1 (1.4)
95% CI [1]	(0.1, 5.3)		(0.0, 8.3)
Relative Risk (apixaban vs SOC)		0.98	
95% CI [2]		(0.1, 10.7)	
p-value [2]		0.9846	
Adjudicated Minor Bleeding			
Subjects with an Event, n (%)	51 (35.7)		21 (29.6)
95% CI [1]	(28.3, 43.8)		(20.2, 41.1)
Relative Risk (apixaban vs SOC)		1.19	
95% CI [2]		(0.8, 1.8)	
p-value [2]		0.3795	
Adjudicated All Bleeding			
Subjects with an Event, n (%)	52 (36.4)		21 (29.6)
95% CI [1]	(28.9, 44.5)		(20.2, 41.1)
Relative Risk (apixaban vs SOC)		1.22	
95% CI [2]		(0.8, 1.8)	
p-value [2]		0.3309	

[1] 95% CI was calculated using the Agresti-Coull method.
[2] 95% CI and p-value were calculated using the Cochran-Mantel-Haenszel test stratified by age group.

Extension phase of study CV185325. Fifty-five subjects entered the Extension Phase of the study and 53 were treated with apixaban. No subjects in the Extension Phase experienced an adjudicated Major or a CRNM bleeding event. Eight (8/53; 15.1%) subjects in the Extension Phase experienced Minor bleeding events.

Supportive studies

Study CV185155. For the primary safety endpoint of adjudicated major bleeding during treatment with induction chemotherapy, the incidence in the apixaban and SOC arms was the same, with events reported in 2 subjects (0.8%) in each arm. The frequency of the secondary safety endpoint (composite of adjudicated major bleeding and adjudicated CRNM bleeding) numerically was higher in the apixaban

treatment arm (n=13 (5.1%) vs n=5 (2.0%)), RR 2.60 (95% CI: 0.94 to 7.17; 2-sided nominal p = 0.0546).

CRNM bleeding events were reported more frequently in the apixaban arm compared to the SOC arm (n=11; 4.3%; 95% CI: 2.33 to 7.62 vs n=3; 1.2%; 95% CI: 0.24 to 3.55, RR: 3.67; 95% CI: 1.04 to 12.97; nominal p = 0.0303).

Minor bleeding events were reported more frequently in the apixaban arm compared to the SOC arm (n=37; 14.5%; 95% CI: 10.64 to 19.32 vs n=20; 7.8%; 95% CI: 5.06 to 11.82, RR: 1.85; 95% CI: 1.10 to 3.10; nominal p = 0.0169). The imbalance was predominately due to an imbalance in the number of reported events of epistaxis. The majority of those events were of mild to moderate intensity.

Study CV185362. During the treatment period, 1 (0.79%) subject in the apixaban arm and 3 (4.84%) subjects in the VKA/LMWH arm met the primary safety endpoint of the composite of adjudicated major or CRNM bleeding events (RR not estimable). Among these 4 subjects across both treatment arms who met the primary safety endpoint, there were a total of 6 events reported: 2 events in a single subject in the apixaban arm and 4 in the VKA/LMWH arm. The subject in the apixaban arm had both a CRNM and a major bleeding event 283 and 286 days after start of dosing, respectively. Of the 3 subjects in the VKA/LMWH arm, 1 had 2 CRNM bleeding events (1 gingival bleeding and 1 contusion; both events occurred during the same VKA intoxication episode 139 days after start of dosing, 1 had a major bleeding event 13 days after start of dosing, and 1 had a CRNM bleeding event 33 days after start of dosing.

When incidence rates were exposure-adjusted, the incidence rates per 100 person-years of exposure for the composite of adjudicated major or CRNM bleeding events during the treatment period were 1.8 and 6.8 in the apixaban and VKA/LMWH arms, respectively.

Secondary safety endpoints. An adjudicated major bleeding event during the treatment period was reported in 1(0.79%) vs 1(1.61%) subject for apixaban vs VKA/LMWH, and an adjudicated CRNM bleeding event reported in 1(0.79%) vs 2 (3.23%) subjects.

An adjudicated bleeding event (CRNM, major, or minor) during the treatment period was reported in 47 (37.30%) subjects in the apixaban arm and 23 (37.10%) in the VKA/LMWH arm. An imbalance was mainly seen for minor bleeding events, specifically epistaxis (14.3% of subjects on apixaban vs 6.5% of subjects on VKA/LMWH).

2.6.8.3. Adverse events

Study CV185325

Common adverse events

In total, 678 AEs vs 383 AEs were reported in the apixaban and SOC group, respectively, during the Main Phase of the study (Table 34). The proportion of participants in the apixaban group who had at least 1 all-causality TEAE, SAE, or severe (Grade 3, Grade 4, and Grade 5) AE was comparable to the SOC group. Discontinuation from the study or study intervention due to AEs reported in $\leqslant$2.1% of participants, all in the apixaban group. The proportion of participants who had their dose of study intervention reduced or temporarily discontinued due to AEs was 17 (11.9%) participants in the apixaban group and 12 (16.9%) participants in the SOC group.

AEs were reported in 124 (86.7%) and 59 (83.1%) subjects in the apixaban and SOC groups respectively. The most frequently reported AEs (>= 15% in either treatment group) were headache (17.5% vs 15.5% for apixaban vs SOC), epistaxis (16.8% vs 19.7%) and injection site bruising (0 vs

16.9%). A similar pattern was seen across age groups 12 to < 18 years and 2 to < 12 years, with few or none of these events reported in the 28 days to < 2 years age group.

AEs reported in ⩾ 1% of subjects in either treatment group and with a higher incidence in the apixaban group compared with the SOC group (ie, a notable positive risk difference [% subjects in the apixaban group minus that in the SOC group] with a 95% CI excluding 0) were heavy menstrual bleeding (7.7% difference (95% CI: 0.6, 14.7); n=17 (11.9%) vs n=3 (4.2%) for apixaban vs SOC), cough (6.3% difference (95% CI: 1.1, 11.4); n=11 (7.7%) vs n=1 (1.4%) , and rash (3.5% difference (95% CI: 0.5, 6.5); n=5 (3.5%) vs none).

Table 27. Treatment-Emergent Adverse Events Summary (All Causalities) With a Cutoff of 5% - Safety Analysis Set - CV185325

Number of Subjects Evaluable for AEs Number (%) of Subjects by SYSTEM ORGAN CLASS and Preferred Term	Apixaban (N=143) n (%)	Standard Of Care (N=71) n (%)
With Any Adverse Event	124 (86.7)	59 (83.1)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	18 (12.6)	12 (16.9)
Anaemia	5 (3.5)	7 (9.9)
Febrile neutropenia	2 (1.4)	4 (5.6)
Leukopenia	3 (2.1)	4 (5.6)
Thrombocytopenia	5 (3.5)	4 (5.6)
GASTROINTESTINAL DISORDERS	53 (37.1)	25 (35.2)
Abdominal discomfort	0	4 (5.6)
Abdominal pain	9 (6.3)	5 (7.0)
Abdominal pain upper	7 (4.9)	4 (5.6)
Constipation	10 (7.0)	2 (2.8)
Diarrhoea	13 (9.1)	6 (8.5)
Nausea	10 (7.0)	5 (7.0)
Vomiting	18 (12.6)	4 (5.6)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	44 (30.8)	33 (46.5)
Fatigue	5 (3.5)	4 (5.6)
Injection site bruising	0	12 (16.9)
Injection site haemorrhage	0	4 (5.6)
Non-cardiac chest pain	10 (7.0)	6 (8.5)
Pyrexia	13 (9.1)	7 (9.9)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	28 (19.6)	15 (21.1)
Contusion	11 (7.7)	10 (14.1)
METABOLISM AND NUTRITION DISORDERS	8 (5.6)	8 (11.3)
Hypokalaemia	3 (2.1)	4 (5.6)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	34 (23.8)	15 (21.1)
Arthralgia	8 (5.6)	3 (4.2)
Pain in extremity	13 (9.1)	6 (8.5)
NERVOUS SYSTEM DISORDERS	37 (25.9)	18 (25.4)
Headache	25 (17.5)	11 (15.5)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	22 (15.4)	6 (8.5)
Heavy menstrual bleeding	17 (11.9)	3 (4.2)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	56 (39.2)	27 (38.0)
Cough	11 (7.7)	1 (1.4)
Dyspnoea	7 (4.9)	6 (8.5)
Epistaxis	24 (16.8)	14 (19.7)
Nasal congestion	8 (5.6)	1 (1.4)
Oropharyngeal pain	8 (5.6)	6 (8.5)

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.

Subjects were only counted once per treatment per event.

MedDRA v24.0 coding dictionary applied.

Severity. Mild (Grade 1) all-causality TEAEs were reported in 62 (43.4%) vs 21 (29.6%) on apixaban vs SOC. Moderate (Grade 2) all-causality TEAEs were reported in 31 (21.7%) vs 19 (26.8%), and severe (Grade 3) all-causality TEAEs were reported in 23 (16.1%) vs 12 (16.9%).Life-threatening (Grade 4) all-causality TEAEs were reported in 5 (3.5%) vs 6 (8.5%) participants in the SOC group.

The most frequently reported (⩾3 participants in either treatment group) severe (Grade 3) or life-threatening (Grade 4) all-causality TEAEs were anaemia (n=3 (2.1%) vs n=3 (4.2%) for apixaban vs SOC), neutropenia (n=3 (2.1%) vs n=1 (1.4%)), thrombocytopenia (n 3 (2.1%) vs n=4 (5.6%), Leukopenia (n=2 (1.4%) vs n=3 (4.2%), and Alanine aminotransferase increased (n=3 (2.1%) vs 1 (1.4%).

Treatment-related TEAEs

Treatment-related TEAEs were reported in 39 (27.3%) participants in the apixaban group and 22 (31.0%) participants in the SOC group. The most frequently reported treatment-related TEAEs (>5% in either treatment group) were: Injection site bruising (n=0 (0.0%) vs n=8 (11.3%) for apixaban vs SOC), Contusion (n=3 (2.1%) vs n=8 (11.3%)), Heavy menstrual bleeding (n=15 (10.5%) vs n=1 (1.4%)), and epistaxis (n=15(10.5%) vs n=7 (9.9%)).

Severity. Most of the treatment-related TEAEs in both treatment groups were mild (Grade 1) to moderate (Grade 2) in severity. One apixaban-treated participant in the 2 to <12 years age group had a treatment-related life-threatening (Grade 4) TEAE of cerebral venous sinus thrombosis that was serious and resulted in discontinuation from the study. The outcome was reported as not recovered/not resolved. One SOC-treated participant in the 12 to <18 years ago group had severe (Grade 3) treatment-related TEAEs of International normalized ratio increased and prothrombin time prolonged that were not serious and resulted in temporary interruption of the SOC treatment. The outcomes were reported as not recovered/not resolved.

Supportive studies

Study CV185155. AEs were reported for 232 (90.6%) and 215 (84.0%) subjects in the apixaban and SOC (no anticoagulant prophylaxis) arms, respectively. The most common AEs were anaemia (n=85; 33.2% vs n=90; 35.5%), constipation (n=59; 23.0% vs n=52; 20.3%) for the apixaban and SOC arm, respectively, and platelet count decreased (n=55; 21.5% in each arm).

Treatment related AEs were reported in 38 (14.8%) and 3 (1.2%) subjects in the apixaban and SOC arms, respectively. The most commonly reported treatment related AEs were epistaxis (n=8; 3.1% vs none), ALT increased (n=6; 2.3% vs n=1; 0.4%), AST increased (n=5; 2.0% vs none) and blood bilirubin increased (n=4; 1.6% vs none), for the apixaban arm vs the SOC arm, respectively.

Study CV185362. AEs were reported in 107 (84.9%) and 53 (85.5%) subjects in the apixaban and VKA/LMWH arms, respectively. The most frequently reported AEs (15% in either treatment arm) were vomiting (15.9% vs 14.5%), epistaxis (15.9% vs 9.7%), pyrexia (15.9% vs 12.9%) and headache (15.1% vs 4.8%) for apixaban and VKA/LMWH, respectively.

In the apixaban arm, all of the 38 epistaxis events (in 20 subjects) were mild (Grade 1) and adjudicated as minor bleeds. Epistaxis is consistent with the known safety profile of apixaban in adult patients and therefore is not a new or unexpected event.

There were 19 headache AEs in the apixaban arm compared to 3 in the VKA/LMWH arm. None of the headache AEs were reported as treatment-related by the Investigators. All but 3 of the headache AEs were reported as Grade 1. The remaining 3 headaches were Grade 2, and only 1 of those occurred in an apixaban-treated subject. Since headaches are commonly reported after a Fontan procedure, the apixaban-treated subjects with headaches who were not status post-Fontan were reviewed for other

identifiable causes of headache. Among these 8 subjects, 5 had potentially confounding explanations for the headache AE.

Grade 3 AEs were reported in 11 (8.7%) subjects in the apixaban arm and 12 (19.4%) subjects in the VKA/LMWH arm. All types of Grade 3 AEs were reported in single subjects in each arm. One Grade 4 AE of procedural complication was reported in a single subject in the apixaban arm (0.8%) while no Grade 4 AEs were reported in the VKA/LMWH arm.

Treatment-related AEs were reported in 41 (32.5%) and 16 (25.8%) subjects in the apixaban and VKA/LMWH arms, respectively. The most frequently reported treatment-related AEs (5% in either treatment arm) were epistaxis (7.1% vs 3.2%) and INR increased (0% vs 6.5%) for apixaban and VKA/LMWH, respectively.

2.6.8.4. Serious adverse event/deaths/other significant events

Study CV185325

Death

A total of 3 deaths were reported in the apixaban group (1 in each of age groups 12 to < 18 years, 2 to < 12 years, and 28 days to < 2 years) and 1 death in the SOC group (age group 12 to < 18 years). The causes of death in the apixaban treated group were meningitis with sepsis; progression of underlying embryonal rhabdomyosarcoma; and pseudomonas bacteremia. The cause of death in the SOC group was gunshot wound. All 4 deaths were assessed as not treatment-related by the investigator. None of these deaths were due to a VTE or bleeding event per the adjudication performed by the blinded independent event adjudication committee (EAC).

Other Serious Adverse events

A total of 48 (22.4%) participants had at least 1 all-causality SAE: 32 (22.4%) participants in the apixaban group and 16 (22.5%) participants in the SOC group. All events were reported in single subjects in each group except for the following: Sickle cell anaemia with crisis (n=2 (1.4%) vs 0 , for apixaban vs SOC), Febrile neutropenia (n=1 (0.7%) vs n=2 (2.8%), Pyrexia: 3 (2.1%) vs 1 (1.4%), Mucosal inflammation (n=2 (1.4%) vs n=0), Alanine aminotransferase increased (n=2 (1.4%) vs n= 0), and Cerebral venous sinus thrombosis (n=2 (1.4%) vs n=0).

Treatment-related SAEs that were reported in 2 (1.4%) participants in the apixaban group and no participants in the SOC group. The treatment-related SAEs were: moderate haematochezia, with an outcome of recovered/resolved in a subject in the 12 to < 18 years age group; and life-threatening cerebral venous sinus thrombosis with an outcome of not recovered/not resolved in a subject in the 2 to < 12 years age group. The investigator assessed that there was a reasonable probability that the event of cerebral venous sinus thrombosis was related to study intervention; however, the adjudication committee classified the SAE of cerebral venous sinus thrombosis as related to index event and 'other: right internal jugular vein thrombosis'. As compared to the index event, the status of the thrombus was recorded as 'recurrence-contiguous'.

Supportive studies

Study CV185155. Five (1.0%) deaths were reported during the study, 4 (0.8%) of which occurred while on study drug or within 30 days after the end of the Treatment Period: 1 subject (0.4%) and 3 subjects (1.2%) in the apixaban and SOC arms, respectively. The cause of death of the subject in the apixaban arm was cardiac arrest with disseminated intravascular coagulation, acute coronary syndrome, and retroperitoneal hemorrhage. The causes of death of the 3 subjects in the SOC arm

were "infection," "cardiac arrest", and "complications of sinus venous thrombosis / intracranial hemorrhage."

SAEs were reported for 92 (35.9%) and 82 (32.0%) subjects in the apixaban and SOC arms, respectively. The most common SAEs were Febrile neutropenia (n=15;5.9% vs n= 16; 6.3%); Pyrexia (n=7; 2.7% in each arm), Embolism (n=9; 3.5% vs n= 3; 1.2%) and Sepsis (n=7; 2.7 vs n=4; 1.6%) in the apixaban and SOC arms, respectively. Treatment related SAEs were reported in 7 subjects (2.7%) in the apixaban arm and, as expected (given the open-label design of the study and absence of an active comparator group), no subjects in the SOC arm.

Study CV185362. There were no deaths reported.

SAEs were reported in 26 (20.6%) and 13 (21.0%) subjects in the apixaban and VKA/LMWH arms, respectively. All events were reported in single subjects except for shunt thrombosis (reported as thrombus in Fontan conduit), which occurred in 2 subjects (1.6%) in the apixaban arm and 0 subjects in the VKA/LMWH arm. In both cases, the independent, blinded EAC determined that the thrombi were non-events as they were present on imaging studies performed prior to study participation. Treatment-related SAEs were reported in 6 (4.8%) subjects in the apixaban arm and 5 (8.1%) subjects in the VKA/LMWH arm. All treatment-related events were reported in single subjects (incorrect dose administered, post procedural haematoma, procedural hemorrhage, pulmonary artery increased, haematuria on apixaban, and contusion, rib/spinal fracture, subdural haematoma, gingival bleeding and pulmonary haemorrhage on VKA/LMWH.

2.6.8.5. Laboratory findings

Haematology

Study CV185325. No clinically meaningful differences in haematology parameters were observed between the apixaban and SOC treatment groups for the overall study population, or between the treatment groups for all age groups.

Study CV185155. Out of reference-range haematologic laboratory abnormalities were observed for all subjects at baseline and during the study, which is consistent with their underlying diagnosis of ALL or LL. Platelet count decreases to < 20,000/mm3 were reported for 62 subjects: 31/254 (12.2%) in each treatment group. All subjects in the apixaban group with a platelet count decrease to < 20,000/mm3, experienced the event during the treatment period.

Study CV185362. No clinically relevant differences between treatment groups were observed for haemoglobin, haematocrit, leukocyte count, or platelet count.

Clinical Chemistry

Study CV185325. No clinically meaningful differences in mean or median change from baseline to last observation for clinical chemistry parameters were observed between the apixaban and SOC treatment groups for the overall study population or between the treatment groups for age groups 1 to 3. The following SAEs related to clinical chemistry laboratory investigations were reported; none were assessed as treatment-related by the investigator: ALT increased: 2 (1.4%) vs 0 (0.0%) for apixaban vs SOC; Blood urea increased: 0 (0.0%) vs 1 (1.4%). No treatment-related SAEs corresponding to hepatobiliary disorders were reported.

AST, ALT, and gamma-glutamyl transferase (GGT) elevations > 3× the ULN were reported for 4/127 (3.1%), 8/131 (6.1%), and 6/131 (4.6%) subjects respectively in the apixaban treatment group, and for 0/60 (0%), 5/62 (8.1), and 0/59 (0%) subjects respectively in the SOC treatment group. AST or ALT elevations to > 3 x ULN and direct bilirubin elevations to > 2 x ULN on the same day were

reported in one subject in the apixaban treatment group; attributed by the investigator to concomitant antitumor chemotherapy. No subjects in either treatment group met Hy's law criteria for possible drug-induced liver injury (DILI).

Study CV185155. Shifts in laboratory parameters from a normal value at baseline to an out of range value at the Day 29 study visit were most frequently observed for: ALT; 82 (73.9%) vs 102 (79.1%) for apixaban vs SOC , AST; 37 (34.9%) vs 37 (34.6%), and bilirubin; 10 (18.9%) vs 9 (14.5%) subjects.

Serum AST or ALT elevations to > 3× the ULN, associated with subsequent elevations of serum total bilirubin concentrations to > 2× the ULN, findings consistent with the Hy's Law criteria for possible DILI, were reported for 13 subjects for whom the combined findings were available: 5/247 (2.0%) and 8/248 (3.2%) subjects in the apixaban and SOC treatment groups, respectively.

AST and ALT elevations > 3× the ULN were reported on the same date for 37 subjects for whom both results were available: 19/247 (7.7%) and 18/248 (7.3%) subjects in the apixaban and SOC treatment groups, respectively. Treatment discontinuation occurring within 2 weeks of liver function test elevations occurred in 7 subjects (2.7%) in the apixaban group; since recipients in the SOC group received no anticoagulation, discontinuation from study treatment was, in effect, not possible.

Study CV185362. Laboratory values that met the marked abnormality criteria were infrequent in the apixaban and SOC treatment groups. Shifts in laboratory parameters from a normal value at baseline to an out-of-range value at the Month 3 visit were most frequently (>5%) observed in subjects with available measurements for the following: ALT (9 (10.0%) vs 5 (11.6%) for apixaban vs VKA/LMWH), AST (9 (10.7%) vs 7 (15.2%)), Conjugated bilirubin (7 (8.0%) vs 3 (6.7%)).

Serum ALT or AST elevations > 3 × ULN associated with subsequent elevations of serum total bilirubin concentrations > 2 × ULN (findings consistent with the Hy's Law criteria for possible DILI) were reported in none of the subjects with available measurements in either treatment group.

AST and ALT elevations > 3 × ULN on the same date were reported in none of the subjects with available measurements in either treatment group. There were no treatment discontinuations related to liver function tests in either treatment group.

2.6.8.6. In vitro biomarker test for patient selection for safety

Not applicable

2.6.8.7. Safety in special populations

Not applicable

2.6.8.8. Immunological events

Not applicable

2.6.8.9. Safety related to drug-drug interactions and other interactions

Apixaban is metabolized by CYP3A4 and is a substrate for the efflux transporter P-gp. Co-administration of drugs that are *strong inhibitors of both CYP3A4 and P-gp* can increase apixaban blood concentrations. Patients with renal insufficiency or of low body weight may be at increased risk of increased drug exposure leading to excessive anticoagulation due to CYP34A and P-gp drug

interactions. Concomitant systemic treatment with strong inhibitors or inducers of both CYP3A4 and P-gp was prohibited in CV185155, CV185362 and CV185325.

Anticoagulant use or use of other agents that may increase the risk of bleeding was restricted in these studies. In CV185325, the following anticoagulant medications were prohibited: aspirin > 165 mg per day, other antiplatelet therapy such as thienopyridines (eg, clopidogrel, ticlopidine), other antithrombotic agents (eg, UFH, LMWH, direct thrombin inhibitors, factor Xa inhibitors, fondaparinux), and GP IIb/IIIa inhibitors (eg, abciximab, eptifibatide, tirofiban). In addition, care was to be taken if subjects were treated concomitantly with selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), or NSAIDs. In CV185362, low dose aspirin (≤ 5 mg) was allowed for some conditions such as Kawasaki disease and SVP.

2.6.8.10. Overdose

In CV185325, 2 incidences of overdose were reported. A 16-year-old female subject who received apixaban remained on apixaban 10 mg BID from day 8, due to misunderstanding. She experienced an AE of Heavy Menstrual Bleeding on Day 65, considered mild in intensity, as a result of the medication error. On Day 80, dose of study intervention was corrected to 5 mg BID. The event of Heavy Menstrual Bleeding had decreased greatly one month after stopping study intervention.

An 11-month-old male subject was administered a morning dose of 4.5 mg instead of the prescribed dose of 1.5 mg. The study intervention was temporarily held. No treatment was given, or AEs occurred due to the overdose.

2.6.8.11. Discontinuation due to adverse events

Study CV185325

Two participants in the apixaban group and no participants in the SOC group discontinued study intervention due to AEs and continued the study. One participant in the 28 days to <2 years age group discontinued study intervention due to TEAEs of cardiac arrest and cardiogenic shock. These TEAEs were life-threatening (Grade 4), serious, and assessed as not treatment-related by the investigator. The outcomes were reported as recovered/resolved with sequelae. This participant also experienced the TEAE of pseudomonal bacteraemia resulting in death. One participant in the 12 to <18 years age group discontinued study intervention due to TEAEs of mucosal inflammation. This TEAE was severe (Grade 3), and assessed as not treatment-related by the investigator. The outcome was reported as recovered/resolved.

Three participants in the apixaban group (one case of pseudomonal bacteraemia, one case of progressive embryonal rhabdomyosarcoma and one case of cerebral venous sinus thrombosis) and no participants in the SOC group discontinued the study due to AEs. All cases were assessed by the EAC as not-treatment related. The case of cerebral venous sinus thrombosis was classified as related to the index event (recorded as recurrence-contiguous) by the independent adjudication committee.

Supportive studies

Study CV185155. Off note, SOC consisted of no anticoagulant treatment. AEs leading to discontinuation from assigned therapy were reported in 35 (13.7%) and 2 (0.8%) subjects in the apixaban and SOC arms, respectively. The most common AEs leading to discontinuation were ALT increased (n=3; 1.2% vs 0), and blood bilirubin increased (n=3; 1.2% vs 0), for apixaban vs SOC. While AEs leading to discontinuation that corresponded to elevated ALT and bilirubin levels were more common in the apixaban arm, the overall frequency of aminotransferase and bilirubin elevations were

comparable between the apixaban and SOC arms. Treatment related AEs leading to discontinuation were reported in 13 subjects (5.1%) in the apixaban arm and none in the SOC arm. The most common treatment related AEs leading to discontinuation in the apixaban arm were haematuria (n=2; 0.8%) and Blood bilirubin increased (n= 2; 0.8%).

Study CV185362. Drug discontinuation due to AEs, intolerability, or bleeding was reported in 7 (5.56%) subjects in the apixaban arm and 1 (1.61%) subject in the VKA/LMWH arm with a relative risk of 3.11 (95% CI 0.44, 21.98). Most frequently reported were gastrointestinal haemorrhage (1.6% apixaban; 0% VKA/LMWH) and shunt thrombosis (1.6% apixaban; 0% VKA/LMWH). Both cases of shunt-thrombosis were assessed as non-events since they were present on imaging studies performed prior to study participation.

2.6.8.12. Post marketing experience

Not applicable

2.6.8.13. Extrapolation exercise based on criterium of clinical response to treatment: safety

a. Apixaban for the treatment of VTE

In the 2 adult studies (CV185056 and extension study CV185057), the overall incidence of major bleeding events in the apixaban treatment arms was <1%, comparable to that reported in paediatric Study CV185325, in which no major bleeding events were reported. The overall incidence of CRNM bleeding events in the apixaban treatment arms was slightly higher for the adult studies (ranging from 3.0% to 4.3%) as compared with paediatric study CV185325 (1.4%) (Table 35). In the subgroup of 22 subjects aged 28 days to < 2 years, 1 (4.8%) patient experienced a grade 2 CRNM bleeding event (pericardial haemorrhage) that recovered. Three minor bleeding events were reported in 2 patients.

Table 28. Key Primary and/or Secondary Safety Outcomes – Studies CV185056, CV185057, and CV185325

Study	Key safety outcome	Apixaban, n/N (%)	SOC*, n/N (%)
CV185056	Primary: Major bleeding alone Secondary: Major + CRNM bleeding	Primary safety: 15/2676 (0.6) Secondary safety: 115/2676 (4.3)	Primary safety: 49/2689 (1.8) Secondary safety: 261/2689 (9.7)
CV185057	Primary: Major bleeding alone Secondary: Major + CRNM bleeding	Primary safety: 2.5 mg: 2/840 (0.2) 5.0 mg: 1/811 (0.1) Secondary safety 2.5 mg: 27/840 (3.2) 5.0 mg: 35/811 (4.3)	Primary safety: 4/826 (0.5) Secondary safety: 22/826 (2.7)
CV185325 (Main Phase)	Major + CRNM bleeding	2/143 (1.4)	1/71 (1.4)
CV185325 (Extension Phase)	Major + CRNM bleeding	0/53 (0.0)	0/53 (0.0)
CV185325 (Main Phase; Group 3 [age 28 days to <2 years])	Major + CRNM bleeding	1/21 (4.8)**	0/10 (0.0)
*SOC: Standard of care treatment arm ** The isolated CRNM event was pericardial haemorrhage, of moderate (Grade 2) intensity, NOT serious, and investigator-assessed as recovered/resolved.			

b. Apixaban for the prevention of VTE

Study CV185155. The observed overall rates of major bleeding events were similar in the CV185036 and CV185155 studies (0.5% and 0.8% during mean apixaban exposure durations of 25 and 23.5 days, respectively) as compared to the proportionately higher rate of 2.3% in the cancer sub-study of CV185056, the latter over a mean duration of apixaban therapy of 154 days (Table 36).

The incidence of minor bleeding episodes was higher in paediatric Study CV185155 than in adult Study CV185036: 14.5% vs. 5.1%, respectively. This may have been due to differences in the definitions of CRNM bleeding events in these two studies, which would, in turn, have impacted the tabulation of minor events (see section IIIc).

In this study, only one subject < 2 years was treated with apixaban. No major or CRNM bleeding events were reported for either treatment group in this age group.

Table 29. Key Safety Outcomes from Adult Studies CV185036 and the Post hoc Cancer sub-study of CV185056, and Paediatric Study CV185155

Study	Key safety outcome(s)	Apixaban, n/N (%)	SOC¶, n/N (%)
CV185056 post-hoc cancer sub-study (Agnelli G. et al)[3]	Primary: Major bleeding alone Secondary: Major + CRNM bleeding Minor bleeding	Primary: 2/87 (2.3) Secondary: 11/87 (12.6) Minor: Not available	Primary: 4/80 (5.0) Secondary: 18/80 (22.5) Minor: Not available
CV185036	Primary: Major bleeding alone Secondary: Major +CRNM bleeding Minor bleeding	Primary: 15/3184 (0.5) Secondary: 85/3184 (2.7) Minor: 161/3184 (5.1)	Primary: 6/3217 (0.2) Secondary: 67/3217 (2.1) Minor: 152/3217 (4.7)
CV185155¶¶	Primary: Major bleeding alone Secondary: Major + CRNM bleeding Minor bleeding	Primary: 2/256 (0.8) Secondary: 13/256 (5.1) Minor: 37/256 (14.5)	Primary: 2/256 (0.8) Secondary: 5/256 (2.0) Minor:20/256 (7.8)
CV185155 (age <2 years)		Primary: 0/1 (0.0) Secondary: 0/1 (0.0) Minor: 1/1 (100.0)	Primary: 0/7 (0.0) Secondary: 0/7 (0.0) Minor: 2/7 (28.6)

¶ SOC: standard of care treatment arm;
¶¶ (Note: SOC in CV185155 was placebo [no anticoagulation]);
* DVT: deep vein thrombosis; ** PE: pulmonary embolism; *** CVST: cerebral venous sinus thrombosis

Study CV185362. As with the adult vs paediatric efficacy outcome comparisons presented earlier, the crude incidence rates of major plus CRNM bleeding events were higher in the adult studies than in the paediatric study (6.8% and 5.0% for CV185030 and CV185048 vs. 0.8% for CV185362, respectively), although the exposure adjusted rates were less discrepant, particularly for the CV185048 and CV185362 studies (4.5%/year vs. 1.8/100 P-Y of exposure, respectively). Minor bleeding events occurred more frequently among apixaban-treated patients in paediatric Study CV185362 than in the adult CV185030 and CV185048 studies, although the rates in the latter two studies differed considerably as well, at 19.2% and 7.2%, respectively (Table 37).

No major or CRNM bleeding events were reported among the 8 apixaban-treated participants < 2-years of age. Four of the 8 patients (50.0%) were reported to have experienced adjudicated minor bleeding events. All 4 of these events were investigator-assessed as being mild (Grade 1) in intensity and all resolved.

Table 30. Key Primary and/or Secondary Safety Outcomes – Studies CV185030, CV185048, and CV185362

Study	Key safety outcome	Apixaban, n/N (%)	SOC*, n/N (%)
CV185030	Primary: Major bleeding alone	327/9088 (3.6) overall 2.13%/year of exposure	462/9052 (5.1) overall 3.09%/year of exposure
	Secondary: Major + CRNM bleeding	613/9088 (6.8) overall 4.07%/year of exposure	877/9052 (9.7) overall 6.01%/year of exposure
	Minor bleeding	1,743/9,088 (19.2)	2,183/9052 (24.1)
CV185048	Primary: Major bleeding alone	45/2798 (1.6) overall 1.4%/year of exposure	29/2780 (1.0) overall 0.9%/year of exposure
	Secondary: Major + CRNM bleeding	140/2798 (5.0) overall 4.5%/year of exposure	101/2780 (3.6) overall 3.2%/year of exposure
	Minor bleeding	200/2798 (7.2)	153/2780 (5.5)

Study	Key safety outcome	Apixaban, n/N (%)	SOC*, n/N (%)
CV185362	Primary: Major + CRNM bleeding	1/126 (0.8) (1.8/100 P-Y of exposure)	3/62 (4.8) 6.8/100 P-Y of exposure)
	Secondary: Major bleeding alone	1/126 (0.8)	1/62 (1.6)
	Minor bleeding	46/126 (36.5)	20/62 (32.3)
CV185362 (age 28 days to <2 years)	Primary: Major + CRNM bleeding	0/8 (0.0)	0/3 (0.0)
	Secondary: Major bleeding alone	0/8 (0.0)	0/3 (0.0)
	Minor bleeding	4/8 (50.0)**	0/3 (0.0)
* SOC: Standard of care treatment arm ** All events were investigator-assessed as of mild (Grade 1) intensity.			

c. Definitions of bleeding events

In adult study CV185056

- **Major bleeding:** Acute clinically overt bleeding (i) Associated with a fall in haemoglobin of ≥2 g/dL (≥1.25 mmol/L); or (ii) Leading to a transfusion of ≥2 units of PRBCs or ≥1,000 mL whole blood or (iii) In a critical site: intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal, or another critical organ (to be specified); or (iiii) that is fatal.
- **CRNM bleeding**: bleeding that satisfies one of the following: (i) any bleeding compromising hemodynamics; (ii) any bleeding leading to hospitalization; (iii) Subcutaneous haematoma larger than 25 cm2, or 100 cm2 if there was a traumatic cause; (iv) Ultrasound-documented intramuscular haematoma, (v) Epistaxis: Lasted > 5 minutes, was repetitive (i.e. two or more episodes of bleeding more extensive than spots on a handkerchief within 24 hrs), or led to intervention (packing, electrocoagulation); (vi) Gingival bleeding occurring spontaneously (i.e. unrelated to eating or tooth brushing) or lasting for >5 minutes; (vii) Macroscopic haematuria (spontaneous or lasted >24 hours after G-U tract instrumentation); (viii) Macroscopic gastrointestinal hemorrhage with ≥1 episode of melena or hematemesis, if clinically apparent with positive results on a fecal occult-blood test; ☐ Rectal blood loss, if more than a few spots on toilet paper; (ix) Hemoptysis, if "more than a few speckles in the sputum and not occurring within the context of PE (x) Any other bleeding type considered to have clinical consequences for a subject, e.g.: medical intervention, need for unscheduled MD contact (visit or phone), temporary cessation of study drug, associated with pain or impairment of activities of daily life.

• M**inor bleeding:** All other acute, clinically overt bleeding episodes not meeting the criteria for either major or CRNM bleeding.
In paediatric studies CV185325 and Study CV185362 • **Major bleeding:** bleeding that satisfies one or more of the following criteria: a (i) fatal bleeding; (ii) clinically overt bleeding associated with a decrease in Hgb of at least 20 g/L (2 g/dL) in a 24-hour period; (iii) bleeding that is retroperitoneal, pulmonary, intracranial, or otherwise involves the central nervous system; and (iv) bleeding that requires surgical intervention in an operating suite (including interventional radiology). • **CRNM bleeding:** bleeding that satisfies one or both of the following: (i) overt bleeding for which a blood product is administered, and which is not directly attributable to the subject's underlying medical condition and (ii) bleeding that requires medical or surgical intervention to restore hemostasis, other than in an operating suite. • **Minor bleeding:** any overt or macroscopic evidence of bleeding that does not fulfill the above criteria for either major bleeding or CRNM bleeding. Additional in study CV185325: although menstrual bleeding may result in a medical consultation and/or intervention, this will be classified as a minor bleeding event rather than CRNM.

The Applicant noted no substantive differences between the respective definitions described in the 2016 EMA Guideline and the CV185056 study protocol. The definitions in Studies CV185325 and CV185362 are identical to one another; moreover, these definitions are more descriptive than quantitative in comparison to those for adults, as summarized below:

Major bleeding: The definitions in both Studies CV185362 and CV185325 are comparable to those provided in the 2016 EMA Guideline and adult Study CV185056, except that no criteria are provided in the paediatric studies for defining major bleeding events on the basis of the number of units of packed red blood cells (PRBCs) or the volume of whole blood transfused. However, volume-specific criteria for paediatric patients would require adjustment based on body weight or body surface area, criteria that are neither provided in the 2016 EMA Guideline nor available and generally accepted from published literature.

CRNM bleeding: In the 2016 EMA Guideline, as well as in the adult CV185056 and paediatric Study CV185362 protocols, descriptive criteria are provided regarding "overt bleeding" that does not meet criteria for major bleeding but requires "medical attention (hospitalization or medical treatment)", "medical intervention", or "surgical intervention other than in an operating room".

Whereas the Study CV185362 protocol also includes the requirement for administration of "blood product", without specifying any particular volumes of PRBCs or whole blood that must be administered, the 2016 EMA Guideline, and the CV185056 protocol, provide additional, more detailed examples and, in selected cases, quantitative, criteria regarding duration of bleeding (e.g., epistaxis or post-venipuncture bleeding "lasting >5 minutes", the occurrence of macroscopic hematuria-spontaneously or that lasting >24 hours post-urinary tract instrumentation, and development of spontaneously occurring haematomata >25 cm2 or post-traumatic haematomata >100 cm2 in surface area). These more specific, numerical criteria are absent from paediatric protocols CV185362 (approved as part of PIP01) and CV185325 (approved as part of PIP02), because they did not exist at the time the protocols were created, nor do they currently exist. Such numerical criteria might have

been used to qualify some of the minor bleeding events reported in one or both of the paediatric studies as being CRNM bleeding events.

Discussion by applicant of the Impact of the Differences in CRNM Bleeding Definitions Between the Adult and Paediatric Apixaban VTE Studies.

A summary of the independently adjudicated minor bleeding events in the paediatric studies CV185325 and CV185362 is presented in the Response to Day 120 Question 90. Therein, specific examples are provided in which strict application of the quantitative criteria from the 2016 EMA Guideline and the adult CV185056 study protocol could have technically resulted in reclassification of one or more of those as CRNM events. However, the following important considerations reclude any quantitative or aggregate reanalysis of the cumulative frequencies of CRNM vs. minor bleeding events in the apixaban and SOC arms of the paediatric studies:

- The 2016 EMA Guideline and the CV185056 study protocol criteria taken nearly verbatim from it, are applicable to most adults, but certainly not to most paediatric patients, in particular, those with body size and body surface area (BSA) substantially smaller than those of the "average" or idealized adult weighing ~70 kg and having a BSA of ~1.73 m2.

This is the case: (i) for criteria specifying the volume of PRBCs or whole blood required to re-establish hemodynamic stability. Further, infusions of PRBCs or whole blood are typically ordered for paediatric patients in increments of volume/kg body weight intended to increase the blood haemoglobin by a specified amount. (ii) for the criteria intended to differentiate a minor bleeding event (<25 cm2 skin surface area if atraumatic or <100 cm2 if secondary to trauma) from a CRNM event (≥25 or 100 cm2, respectively). For example, such criteria would not represent the same percentage of total BSA in a 1 year-old (~0.4 m2 BSA or a 10 year-old (~1.0 m2 BSA).

- In the final (14-Dec-2023) Day 120 Question 90, the 26-Jan-2023 Paediatric Addendum to the 2016 EMA Guideline is referenced, which provides the following guidance regarding assessment of safety events in paediatric patients with a VTE and receiving anticoagulation, in terms of classification of their bleeding events: "Safety evaluation in paediatric VTE is expected to be generally similar to adults (i.e., focused on major and clinically relevant non-major bleeding, as well as in related parameters, like blood tests that may indicate blood loss) [1-3]."

Thus, paediatric patient-specific numerical criteria, whether for the volume of blood product per kg of body weight that was required to restore haemodynamic stability, or the number of cm2 of skin surface area affected by a haematoma after adjustment for patient size, that should be used to differentially classify a bleeding event as CRNM instead of major, are not provided, either in the Paediatric Addendum, or in either the EMA Guideline for prevention of VTE in patients undergoing high VTE-risk surgery (EMA/CHMP/325170/2012) or that for prevention of VTE in non-surgical patients (EMA/CPMP/EWP/6235/04 Rev. 1, November 2016). Accordingly, it would not have been possible to incorporate, into either of the EMA-reviewed and approved protocols (CV1815325 for PIP02 or CV185362 for PIP01), numerical criteria for the single event of haematoma reported for the one apixaban-treated patient in CV185325 or the 15 apixaban-treated patients in CV185362.

The above issues notwithstanding, numerical criteria for duration of epistaxis (>5 minutes) and/or macroscopic haematuria post-urinary tract instrumentation (>24 hours), might have been incorporated into PIP01 Study CV185362 and PIP02 Study CV185325, but these were not specified in the Key Binding Elements of the respective, agreed PIPs. Had they been included, then one or more of the independently adjudicated bleeding events of epistaxis reported in either the apixaban or the standard of care arms of one or both of the above paediatric studies might have been classified as CRNM rather than minor bleeding episodes. Because those criteria were not, in fact, included in the respective protocols, the corresponding data were not collected and it is not now possible to re-estimate, with any

reasonable expectation of accuracy, the frequencies of any events of epistaxis, macroscopic haematuria, or haematoma based upon any post-hoc reclassification of individual events.

Finally, with regard to the responsibilities and function of the independent External Adjudication Committee (EAC), the exercise of clinical judgment is an expected and critical part of the responsibilities of the physician members of any EAC in reaching consensus decisions on bleeding event classifications. To rely solely on the objective, quantitative bleeding criteria detailed in a clinical research protocol would undermine the rationale for empaneling independent physicians as subject matter experts on an EAC. In summary, major and CRNM bleeding events were reported less frequently, and minor bleeding events more frequently in paediatric Study CV185362 than in adult Studies CV185030 and CV185048.

2.6.9. Discussion on clinical safety

The **safety data** are based on the prespecified interim-analysis of pivotal PIP02 Study CV185325 for treatment of VTE and prevention of recurrent VTE, supplemented with the PIP01 Studies CV185155 and CV185362 in VTE primary prophylaxis. No pooled analysis was performed, due to differences in study design, dosing, treatment durations, and population characteristics. No additional safety signals were retrieved from single-dose PIP01-PK/PD-study CV185118, that was assessed before (procedure EMEA/H/C/002148/II/0088) and therefore is not further discussed.

Methods

Main study CV185325. Data were collected for bleeding events, AEs, clinical laboratory test results, and vital signs. The primary safety endpoint was the composite of Major and Clinically Relevant non-major (CRNM) bleeding, and the secondary safety endpoints were the individual components of the primary safety endpoint. All bleeding events were adjudicated by a blinded, independent adjudication committee. This improves the internal validity of this open-label study. Bleeding definitions for major, clinically relevant non-major (CRNM) and minor bleeding are based on the Perinatal and Paediatric Haemostasis Subcommittee of the International Society on Thrombosis and Haemostasis (ISTH) criteria. The objectives and endpoints generally are in agreement with the PIP (EMEA-000183-PIP02-12-MO3) and are therefore acceptable.

No formal inferences were performed in this descriptive study. For the Safety analysis set, that included all subjects that received at least one dose of study medication, descriptive statistics were provided, including the event rate adjusted for time, 95% CI for the event rate, relative risk, with 95% CI.

Supportive studies. For study *CV185155*, descriptive results were based on events reported in the Safety Population during the treatment period. Similar to main study CV185325, the primary safety endpoint was adjudicated major bleeding. The secondary safety endpoint was the composite of major and CRNM bleeding. For study *CV185362*, the primary safety endpoint was the composite of adjudicated major or CRNM bleeding, similar to studies CV185325 and CV185155. Secondary safety endpoints included adjudicated major bleeding, adjudicated CRNM bleeding, all adjudicated bleeding, drug discontinuation due to adverse effects, intolerability, and all cause death.

For study CV185362, the assumptions on the sample size determination, estimating a bleeding event rate of 24% in the control group and 8% in the apixaban group, was not confirmed, with the primary safety endpoint (i.e. bleeding event rate during the treatment period) occurring in one (0.79%) subject in the apixaban arm and 3 (4.84%) subjects in VKA/LMWH arm. These low event rates however, were comparable with findings in the UNIVERSE study, which studied rivaroxaban dosing, safety, and efficacy in 112 paediatric patients who were status post Fontan palliation, a population quite similar to

study CV185362. In that study major bleeding was seen in 2% and CRNM bleeding was seen in 6% of patients in the rivaroxaban arm.

The safety population included all randomized subjects who received at least one dose of study drug (all treated subjects). Descriptive statistics were provided, including the event rate adjusted for time, 95% CI for the event rate, and relative risk with 95% CI.

Patient exposure

Main study CV185325. The median extent of exposure in 143 treated subjects in the apixaban arm was 84.0 days (mean; SD: 79.6; 19.3 days). Exposure exceeded 84 days in 67 (46.9%) of subjects.

In treatment arm 1 (on apixaban), 91 (62.8%), 30 (20.7%), 22 (15.2) and 2 (1.4%) subjects were included in age-groups 1, 2, 3, and 4, respectively. Therefore, data on subjects aged less than 12 years may be considered quite limited. The extent of exposure for the apixaban group was consistent with the assigned age-specific treatment duration, with mean (SD) treatment duration of 82.0 (17.1) days (age-group 1); 81.3 (17.0) days (age-group 2); 72.1(22.6) days (age-group 3); and 25.5 (27.6) days (age-group 4).

Supportive studies. In *study CV158155*, 512 patients with a mean age of 7 years (1 to 18 years) were included. The median extent of exposure in 250 subjects in the apixaban arm who received at least one dose of apixaban targeted at an exposure (AUC(TAU)) of 620 ng•hr/mL, was 25.0 days (mean [SD]: 23.5 [6.25]).

In *study CV185362*, in 192 paediatric subjects with congenital or acquired heart disease requiring chronic anticoagulation for thromboembolism prevention, out of whom 126 subjects received apixaban with a dosing regimen aimed at a target exposure of 1,200 ng • h/mL (similar to study CV185325), the median exposure of 358 days and total patient-years of 114.1 years is substantial, and is likely to provide relevant information on the safety profile in this population.

Bleeding events (primary and secondary safety endpoints)

Main Study CV185325. The *primary safety endpoint* of composite of Major and CRNM bleeding was seen in 2 (1.4%) subjects on apixaban vs 1 (1.4%) subject on SOC, with a RR of 0.99 (95% CI 0.1;10.8). In all cases this concerned a CRNM bleeding. The CRNM bleeding events on apixaban were epistaxis (n=1, graded mild, not serious, and with outcome resolved) and pericardial haemorrhage (n=1, graded moderate, not serious, assessed as related to postcardiotomy syndrome, and outcome resolved). On SOC the CRNM bleeding concerned a haematoma (n=1, graded moderate, not serious, and outcome resolved).

The *secondary safety endpoints* were the individual components of the primary safety endpoint and minor bleeding. Minor bleeding was reported in 51 (35.7%) subjects in the apixaban group and 21 (29.6%) subjects in the SOC group, with a RR of 1.19 (95% CI 0.8; 1.8).

Similar trends for bleeding events were seen across age-groups.

- In subjects aged 12 to < 18 years, major bleeding events occurred in 0/91 vs 0/45 subjects on apixaban vs SOC, CRNM bleeding events in 1/91 (1.1%) vs 1/45 (2.2%) subjects (RR 0.49 (95% CI 0.0; 7.7, p= 0.61) and minor bleeding events occurred in 39/91 (42.9%) vs 18/45 (40.0%) subjects, RR 1.07 (95% CI 0.7; 1.6, p=0.75).
- In subjects aged 2 to < 12 years, major bleeding events occurred in 0/29 vs 0/14 subjects on apixaban vs SOC, CRNM bleeding events in 0/29 vs 0/14 subjects and minor bleeding events occurred in 11/29 (37.9%) vs 3/14 (21.4%) subjects, RR 1.77 (95% CI 0.6; 5.3, p=0.28).

- In subjects aged 28 days to < 2 years, major bleeding events occurred in 0/21 vs 0/10 subjects on apixaban vs SOC, CRNM bleeding events in 1/21 (4.8%) vs 0/10 (0%) subjects (RR not estimable), and minor bleeding events occurred in 1/21 (4.8%) vs 0/10 (0%) subjects (RR not estimable).
- In the 4 subjects aged from neonates to < 28 days, no bleeding events occurred.

In study CV185325, no signal for increased safety risk was seen for paediatric patients, including those aged 28 days-2 years, with a lower incidence of major bleeding evens and CRNM bleeding events in paediatric patients as compared with adults (0% vs <1%; 1.4% vs 3.0%-4.3%, respectively for major and CRNM bleeds). In the EINSTEIN study comparing rivaroxaban and standard anticoagulation in paediatric patients treated for acute VTE, major and CRNM bleeding events were seen at comparable frequency, in 1% (on rivaroxaban) vs 3% on SOC. Further, in the DIVERSITY study comparing dabigatran with standard anticoagulation, major and any bleeding were reported in 2% vs 2%, and 22% vs 24% of subjects.

In general, minor bleeding events occurred more frequently in paediatric patients as compared with adults. A high frequency of minor bleeding events was also reported for paediatric subjects on dabigatran (19%, DIVERSITY study) and on rivaroxaban (32%, UNIVERSE study) and may therefore reflect age-related factors like physical activity. In study CV185325, minor bleeding events were reported at slightly increased frequency on apixaban, in 51/143 (35.7%) vs 21/71 (29.6%) of patients. In adult VTE-treatment studies CV185056 and CV185057, minor bleeding events were reported in 313/2676 (11.7%) of apixaban treated adult patients vs 505/2689 (18.8%) patients on SOC. Similar results were seen in TE-prevention studies. Also, minor bleeding events occurred more frequently among apixaban-treated patients in paediatric Study CV185362 (36.5% on apixaban vs 32.3% in SOC treated paediatric patients) than in adult CV185030 and CV185048 studies, although the rates in the latter two studies differed considerably as well, in 19.2% and 7.2% apixaban treated adults, respectively.

In view of the high frequency of minor bleeding events in paediatric patients as compared with adults, there may be discussion on some criteria that could have resulted in classification as CRNM instead of minor bleeding. The applicant provided a discussion on the definitions for classification of severity of bleeding events. Though minor differences with definitions used in adults were noted, mainly on criterium of number of PRBCs in case of blood transfusion, on duration of epistaxis and haematuria, and on size of subcutaneous echymoses, in general the definitions that were used in the paediatric studies were in line with the 2016 EMA guideline EMA/CHMP/41230/2015, and reflect types of bleeding events that are expected to have a minor impact on the patients. In the 2023 paediatric addendum EMA/CHMP/20507/2023 no specific guidance on number of blood transfusion, or other criteria in relation to patient size is provided. Therefore it is acknowledged that definitions of bleeding events as applied in the paediatric studies for the most part were in line with prevailing guidelines.

Looking in detail at the AEs that were reported and adjudicated as minor bleeding events, events in general were mild and self-limiting. Minor bleeding events reported in more than 5 apixaban-treated subjects in study CV185325 were contusion (n=10), epistaxis (n=23), gingival bleeding (n=6), and menstrual bleeding (n=17). The frequency of epistaxis was not increased on apixaban as compared with SOC (16.8% vs 19.7%). Minor events of epistaxis were graded as mild in 22/23 events on apixaban and moderate in 1/23, and all resolved without interruption of study medication. All minor gingival bleeding events were graded as mild and resolved without further action.

Heavy menstrual bleeding was reported more frequently on apixaban as compared with SOC (11.6% vs 4.2%). These events in general were graded as mild to moderate and no interruption or permanent

discontinuation was deemed necessary. Events may have occurred in the context of comorbidity and prior heavy menstrual bleeding. Mechanistically, this AE can be expected, and may have an impact on the patient due to the potential recurrence of events. There is no clear explanation for the difference between apixaban and SOC though the difference in frequency is quite substantial. In the SmPC, the increased frequency on apixaban as compared with SoC is mentioned appropriately.

From these data no signal is seen that these minor bleeding events potentially should have been classified as CRNM bleeding events. Further, the criteria for bleeding events were included in the study protocol that was approved in the PIP. Importantly, severity of bleeding events in this randomized controlled study has been adjudicated by an independent blinded external adjudication committee consisting of experienced clinicians, and therefore the classification of severity of bleeding events in the paediatric studies is considered acceptable and is reported appropriately in the SmPC.

Supportive studies. Interpretation of safety data from study CV185155 is limited due to the lower dose of apixaban used, the lack of an active control treatment, and the study population with severe comorbidity of ALL or LL. Apixaban treatment was not associated with an increased incidence of the primary safety endpoint of (adjudicated) major bleeding events (2 in each group), which appears to be reassuring. However, CRNM bleedings were observed with increased incidence (4.3% vs 1.2%; RR 3.67 (1.04-13.0). Most of these CRNM bleedings were epistaxis (3.1% vs 1.2%). Further, minor bleedings were also increased (14.5% vs 7.8%; RR 1.85 (1.10-3.10)).

In *study CV185362*, a limited number of the primary safety endpoint of the composite adjudicated major or CRNM bleeding events during the treatment period were found without any significant difference due to these low numbers: 1/126 (0.8%) subject in the apixaban arm and 3/62 (4.8%) subjects in VKA/LMWH arm. This was far below the estimated bleeding event rates of 24% in the control group and 8% in the apixaban group, thereby impacting the power of the study to detect a statistically significant treatment difference. Though, the low absolute rate of adjudicated major or CRNM bleeding events is in general reassuring, and similar bleeding rates were seen in the UNIVERSE study, thereby supporting external validity.

Regarding the secondary safety endpoints, an adjudicated major, CRNM, or minor bleeding events was reported in 1/126 (0.8%), 1/126 (0.8%), and 45/126 ((35.7%) of subjects in the apixaban arm and 1/62 (1.6%), 2/62(3.2%) and 20/62 (32.3%) in the VKA/LMWH arm. An imbalance was mainly seen for minor bleeding events, specifically epistaxis (14.3% of subjects on apixaban vs 6.5% of subjects on VKA/LMWH).

In subjects aged 28 days to 2 years, experience is limited, with 22, 1 and 8 patients treated with apixaban in studies CV185325, CV185155 and CV185362, respectively. No signal of increased bleeding risk is seen. Though the number of patients aged 28 days to < 2 years that was investigated for apixaban is limited, no structural dissimilarities of exposure for this age-group was seen. Also, a comparable number of subjects in age-group < 2 years were investigated for other DOACS. In the EINSTEIN Junior study, 37 out of 335 paediatric subjects randomized to rivaroxaban were < 2 years of age, and in the DIVERSITY study, 22 out of 177 paediatric patients randomized to dabigatran were < 2 years of age.

Adverse events

Main study CV185325. A generally similar incidence was observed for ***all-cause TEAEs*** in the apixaban arm (n=124 (86.7%) vs SOC (n=59 (83.1%). Most frequently reported were headache (17.5% vs 15.5% for apixaban vs SOC), epistaxis (16.8% vs 19.7%) and injections site bruising (0 vs 16.9%), similar across age-groups. Imbalances in frequencies across treatment-arms were seen for heavy menstrual bleeding (11.9% vs 4.2%), cough (7.7% vs 1.4%) and rash (3.5% vs none). Most

TEAEs were mild to moderate. Severe all-cause TEAEs were reported in 23 (16.1%) vs 12 (16.9%) subjects on apixaban vs SOC, most frequently reported severe or life-threatening all-causality TEAEs were anaemia (2.1% vs 4.2%), neutropenia (2.1% vs 1.4%), thrombocytopenia (2.1% vs 5.6%), Leukopenia (1.4% vs 4.2%), ALT increased (2.1% vs 1.4%). A total of 3 (2.1%) participants in the apixaban group and no participants in the SOC group discontinued the study due to AEs, single cases of pseudomonal bacteraemia, progressive embryonal rhabdomyosarcoma and one case of cerebral venous sinus thrombosis. All cases were assessed by the EAC as not-treatment related.

Treatment-related TEAEs were reported at a comparable frequency in both treatment groups (n=39 (27.3%) vs n=22 (31.0%) for apixaban vs SOC. Most frequently reported treatment-related TEAEs were: Injection site bruising (0.0% vs 11.3%), Contusion (2.1% vs 11.3%), Heavy menstrual bleeding (10.5% vs 1.4%) , and epistaxis (10.5% vs 9.9%). Most of the treatment-related TEAEs in both treatment groups were mild (Grade 1) to moderate (Grade 2) in severity. One apixaban-treated participant in the 2 to <12 years age group had a treatment-related life-threatening (Grade 4) TEAE of cerebral venous sinus thrombosis.

Rash was reported at increased frequency in paediatric patients (in 3.5% of subjects on apixaban vs 0% on SOC), and at increased frequency as compared with adults. These events in general were non-serious and mild, resolving without interruption or discontinuation. They were deemed non-treatment related, not related to a hypersensitivity reaction to apixaban, and are appropriately reported in the SmPC.

A generally similar incidence was observed for ***serious adverse events*** (SAEs) in the apixaban arm (n=32; 22.4%) vs SOC (n=16; 22.5%). Most frequently reported were Sickle cell anaemia with crisis (1.4% vs 0), Febrile neutropenia (0.7% vs 2.8%), Pyrexia (2.1% vs 1.4%, Mucosal inflammation (1.4% vs), ALT increased (1.4% vs 0), and Cerebral venous sinus thrombosis (1.4% vs 0). Treatment-related SAEs were reported in 2 (1.4%) participants in the apixaban group (a case of moderately severe haematochezia and a case of life-threatening cerebral venous sinus thrombosis that the EAC classified as related to the index VTE) and no participants in the SOC group.

Four ***deaths*** were reported, 3 in the apixaban group (meningitis with sepsis; progression of underlying embryonal rhabdomyosarcoma; and pseudomonas bacteraemia) and 1 on SOC (gunshot wound). It is agreed with the assessment that all deaths were not treatment-related.

Supportive studies. In study CV185155, the frequency of treatment-related AEs was lower as compared with study CV185325 (14.8% vs 27.3%), which might be related to the lower dose of apixaban in this study. However, interpretation of the AEs is complex due to the underlying disease and oncology treatment, the lack of an active comparator, and the open-label nature of the study. In this study 1 death occurred on apixaban, due to cardiac arrest with disseminated intravascular coagulation, acute coronary syndrome, and retroperitoneal haemorrhage, and 3 subjects on SOC.

In study CV185362, adverse events were reported at similar frequency for both treatment arms, 84.9% and 85.5% subjects in the apixaban and VKA/LMWH arms, respectively. The most frequently reported AEs were vomiting (15.9% and 14.5%), epistaxis (15.9% and 9.7%), pyrexia (15.9% and 12.9%) and headache (15.1% and 4.8%). Treatment-related AEs were reported in 32.5% and 25.8% of subjects in the apixaban and VKA/LMWH arms, respectively. Imbalances in adverse events were seen for epistaxis and headache. In this study, no deaths were reported. Treatment-related SAEs were reported in 4.8% subjects in the apixaban arm and 8.1% subjects in the VKA/LMWH arm. All treatment-related SAEs were reported in single subjects (post procedural haematoma, procedural haemorrhage, pulmonary artery pressure increased, haematuria on apixaban, and contusion, rib/spinal fracture, subdural haematoma, gingival bleeding and pulmonary haemorrhage on VKA/LMWH. Drug discontinuation due to AE, intolerability, or bleeding was reported with a higher incidence on apixaban (5.56% vs 1.61%; relative risk of 3.11 (95% CI 0.44, 21.98)). The case narratives did not reveal a

specific pattern in the occurrence of adverse events or reduced tolerability. No signal of a new safety issue could be detected.

An increased frequency of epistaxis on apixaban has been seen in study CV185362. In that study, in the apixaban arm, all of the 38 epistaxis events were mild (Grade 1) and adjudicated as minor bleeding events. None of the epistaxis events required treatment and all but one of the events resolved while the subjects continued receiving apixaban treatment. Although the reports of epistaxis were considered generally mild and were resolved without intervention, the incidence of epistaxis on treatment with apixaban seems to be higher in paediatric patients (in study CV185362 15.9%) compared to adults (ranging from 1/10-1/1000).

There were 19 headache adverse events in the apixaban arm compared to 3 in the VKA/LMWH arm. None of the headache AEs were reported as treatment related. Case narratives did not reveal a clear causality for apixaban and potential confounding factors related to Fontan procedure and reporting bias in this open-label study may play a role. Headache has not been previously identified as a common adverse event in apixaban-treated subjects.

Liver test abnormalities. In study CV185155, serum AST or ALT elevations to > 3 x ULN, associated with elevations of serum total bilirubin concentrations to > 2 x ULN, consistent with Hy's Law criteria, were reported in 13 subjects (5/247 (2%) subjects on apixaban and 8/248 (3.2%) subjects on SOC. In addition, elevated liver enzymes were reported in both treatment groups at similar frequency, likely reflecting the underlying disease and concomitant (oncology) treatment. In study CV185362, elevated liver enzyme was reported at similar frequencies for the apixaban and SOC group, and no cases of elevations >3 x ULN were reported. In study CV185325, no subjects in either treatment group was stated to have met Hy's law criteria for possible DILI. AST or ALT elevations to > 3 x ULN and direct bilirubin elevations to > 2 x ULN on the same day were reported in one subject in the apixaban treatment group, however these abnormalities were attributed to chemotherapy.

Two cases of ***accidental overdose*** were reported in study CV185325, in one case causing a mild bleeding complication. Apart from correcting the dosing error, no interventions were required. In adults, correction of anticoagulation by apixaban can be achieved by administering a reversal agent for factor Xa inhibitors (andexanet-alfa). This reversal agent however has not been approved for paediatric patients. The applicant provided data from the paediatric apixaban studies, as well as from public literature and mechanistic considerations, to support advice in the SmPC on potential actions for reversal or correction of anticoagulant effects of apixaban in paediatric patients in case of a bleeding event.

Additional safety parameters (or endpoints) that are important in long-term anticoagulation trials in children include growth retardation, delays in neuro-motor and neurocognitive development and reduced bone density (EMA guideline *Paediatric Addendum on the guidelines on clinical investigation of medicinal products for the treatment and prophylaxis of venous thromboembolic disease* (EMA/CHMP/20507/2023). Bone density was investigated in study CV185362, and no notable differences in mean bone mineral density between the treatment arms was detected. No further long-term safety parameters were investigated, which is acceptable in view of the limited treatment duration.

2.6.10. Conclusions on the clinical safety

Median exposure to apixaban at target dose was 84 days in 143 subjects (Study CV185325) and 358 days in 126 subjects (study CV185362). Though exposure is limited and results are mainly descriptive, major and CRNM bleeding events occurred at numerically similar (Study CV185325) or lower (Study CV185362) frequency on apixaban as compared to SOC, that included VKA or LMWH. No differences

were seen across age-groups. Duration and extent of exposure is considered sufficient to support the proposed indication for the patients aged 28 days to < 18 years.

Minor bleedings tended to occur slightly more frequently on apixaban vs SOC, with imbalances seen for epistaxis and heavy menstrual bleeding, that were generally mild and self-limiting.

Minor differences with definitions used in adults were noted, but in general the definitions that were used in the paediatric studies were in line with the 2016 EMA guideline EMA/CHMP/41230/2015. Further, severity of bleeding events in this randomized controlled study has been adjudicated by an independent blinded external adjudication committee.

Adverse events generally were similar for apixaban vs SOC, though imbalances were seen for heavy menstrual bleeding and rash in study CV185325, and for epistaxis and headache in study CV185362.

Discussion on extrapolation exercise of data for adults to the paediatric population

In addition to the data from pivotal study CV185325, extension of the indication to paediatric patients is based on an extensive extrapolation of results in adults based on the three criteria on pharmacology (including all available PK-PD data of study CV185325), on disease manifestation and progression, and on clinical response to treatment.

Pharmacology

Regarding **pathophysiologic considerations**, the role of the coagulation cascade, including factor X, in thrombus formation that results in VTE is comparable for adults and paediatric patients. Though different patterns of maturation of factors involved in the coagulation cascade were demonstrated, with lower concentrations for fII, V, VII, IX, X and Xii, antiplasmin, prekallikerein, protein C and S, and higher concentrations for TPA and PAI-I during childhood, general assessment of the coagulation system by standard tests, e.g. PT, aPTT and bleeding time (from neonatal period), is suggestive of a comparable function of the coagulation cascade across age-groups exceeding the neonatal or first-three months period.

Regarding **PK considerations**, no additional clinical PK studies are judged needed to support this application. The POPPK model predictions are overall acceptable.

Regarding **PD considerations**, the direct FXa inhibitory effects of apixaban result in inhibition of FXa activity, reduced thrombin generation and D-dimer formation. Type and extent of effects of apixaban on parameters of thrombin generation and D-dimer formation were comparable for adults (study CV185030, study CV185013) and paediatric patients (study CV185362). Also, the relationship between apixaban PK and AXA in paediatrics is generally similar to that observed in adults regardless of the AXA assay used.

Disease manifestation and progression

Regarding **underlying disorders** when diagnosing VTEs, the frequency is higher in paediatric patients (72-99%) as compared with adults (19 to 40%). However, the nature of the underlying disorders in general is comparable for adults and paediatric patients (e.g. malignancy, trauma, surgery, immobilisation), with the main difference between age categories seen for the high frequency of CVAD-associated VTEs in paediatric patients. The management of CVAD-associated VTE differs from other underlying disorders since it also includes decisions on maintenance or removal of the CVAD. The results of VTE-prevention study CV185155 suggested comparable effect of apixaban in patients with vs without CVAD. This can only provide limited support for the therapeutic use of apixaban in patients

with or without CVAD once VTE has occurred. However, further differentiation of effects in patients with or without CVAD in study CV185325 is not possible due to lack of data, and is unlikely to change the overall conclusion due to the low frequency of events.

In paediatric patients, VTE is more often located in the upper extremities (above the diaphragm; 40-60%), mostly associated with a CVAD, and most were asymptomatic (approximately 80%). The clinical presentation of VTEs located in the lower extremities and of PEs is comparable for paediatric patients and adults. In general, the clinical course with regard to recurrence, post-thrombotic syndrome and mortality is comparable for adults and paediatric patients.

Clinical response to treatment

For apixaban for the treatment of VTE, similar **efficacy outcome** (recurrence of VTE or VTE-related death) was seen in adult studies CV185056/CV185057, and paediatric study CV185325. Additionally, comparable results were also seen for the subgroups of 22 apixaban-treated subjects aged 28 days to < 2 years, though data on subjects weighing < 6 kg were limited.

In study CV185325, no signal for increased **safety risk** was seen for paediatric patients, including those aged 28 days-2 years, with a lower incidence of major bleeding evens and CRNM bleeding events in paediatric patients as compared with adults (0% vs <1% and 1.4% vs 3.0%-4.3%, respectively for major and CRNM bleeds). In the subgroup of 22 subjects aged 28 days to < 2 years, 1 (4.8%) patient experienced a grade 2 CRNM bleeding event (pericardial haemorrhage) that recovered. Three minor bleeding events were reported in 2 patients. In study CV185362, with exposure (AUC) comparable with CV185325, no increase was seen for major and CRNM bleeding events (0.8% vs 5.0-6.8% in adults).

In paediatric studies CV185325 and CV185362, an increase was seen on minor bleeding events, as compared with frequencies in adults studies (35.7% vs 11.7% for the treatment of VTE in CV185325, and 36.5% vs 7.2-19.2% for the prevention of VTE in cardiac disorders requiring VTE prophylaxis), that generally were mild and self-limiting. In view of the high frequency of minor bleeding events in paediatric patients as compared with adults, there may be discussion on some criteria (e.g. duration of epistaxis or haematuria) that could have resulted in classification as CRNM instead of minor bleeding. However, the criteria for bleeding events were included in the study protocol that was approved in the PIP, and no further data for additional analyses are available. Importantly, severity of bleeding events in this randomized controlled study has been adjudicated by an independent blinded external adjudication committee consisting of experienced clinicians, and therefore the classification of severity of bleeding events in the paediatric studies is considered acceptable.

Conclusion

In the extrapolation exercise, similarity between adults and paediatric subjects aged 28 days to < 2 years on main issues related to pharmacology, disease manifestation and progression and on clinical response to treatment was demonstrated.

2.7. Risk Management Plan

2.7.1. Safety concerns

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	Bleeding
Important potential risks	Liver Injury

	Potential risk of bleeding or thrombosis due to overdose or underdose
Missing information	Use in patients with severe renal impairment

'Medication errors with the formulations for paediatric use' will be included as important potential risk in the PSUR.

2.7.2. Pharmacovigilance plan

No ongoing and planned additional pharmacovigilance activities are imposed by the Competent Authority.

2.7.3. Risk minimisation measures

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Bleeding	**Routine risk minimisation measures:** SmPC Sections 4.2, 4.3, 4.4, 4.5, 4.8, and 4.9	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Post-marketing targeted bleeding questionnaire
	Additional risk minimisation measures: • Prescriber Guide • Patient Alert Card	**Additional pharmacovigilance activities:** None
Liver Injury	**Routine risk minimisation measures:** SmPC Sections 4.2, 4.3, 4.4, and 4.8	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Post-marketing questionnaire for spontaneous reports of liver events
	Additional risk minimisation measures: None	**Additional pharmacovigilance activities:** None
Potential risk of bleeding or thrombosis due to overdose or underdose	**Routine risk minimisation measures:** SmPC Sections 4.2 and 4.9,	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None
	Additional risk minimisation measures: Prescriber Guide	**Additional pharmacovigilance activities:** None
Use in patients with severe renal impairment	**Routine risk minimisation measures:** SmPC provides the dosing recommendation for patients with severe renal impairment for each indication	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	Additional risk minimisation measures: None	**Additional pharmacovigilance activities:** None

2.7.4. Conclusion

At the December 2023 meeting, the PRAC fully endorsed the PRAC Rapporteur's assessment of the Eliquis RMP version 21.0 (apixaban) submitted as part of this Eliquis grouped line extension. In particular, the Committee supported the following:

· *Safety specification:* The PRAC agreed that the current RMP safety concerns remain unchanged. In relation to the concern of medication errors linked to the paediatric formulation, the PRAC agreed that this should be included as an important potential risk in the summary of safety concerns in the PSUR and monitored in the upcoming PSURs accordingly.

· *Pharmacovigilance plan*: The PRAC agreed that no change to the existing Pharmacovigilance Plan is required.

· *Risk minimisation measures (RMMs):* The PRAC agreed with the PRAC Rapporteur's assessment of the RMMs in relation to the key elements of the additional RMM (prescriber's guide) to mitigate the risk of bleeding.

- Textual changes to Annex 6 (inclusion of reference to the patient caregiver) are acceptable.
- However, the inclusion of the key elements 'Paediatric formulations' and 'That all patients administered Eliquis and/or caregivers of paediatric patients administering Eliquis paediatric formulations should be counselled about the preparation and dosing of the Eliquis paediatric formulations' is not endorsed.

The MAH submitted an updated version of the RMP (version 21.3) in line with the PRAC outcome.

The CHMP considered that the risk management plan version 21.3 (dated 27-May-2024) is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the MAH fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the MAH for Eliquis 2.5 mg film coated tablets, Eliquis 0.5 mg coated granule in sachet, Eliquis 1.5 mg coated granules in sachet and Eliquis 2 mg coated granules in sachet show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

No full user consultation with target patient groups on the package leaflet has been performed for Eliquis 0.15 mg granules in single dose container and Eliquis 5 mg film coated tablets on the basis of bridging reports. The bridging reports submitted by the MAH has been found acceptable.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The current application concerns extension of indication to include the treatment of venous thromboembolism (VTE) and prevention of recurrent VTE in paediatric patients from 28 days to less than 18 years of age for Eliquis (apixaban).

VTE is rare in the paediatric population in comparison to the adult population. Increased survival of children with serious illnesses and improved diagnostic techniques have led to an increasing awareness of the occurrence and sequelae of VTE in the paediatric population. Once a VTE occurs, the progression of the disease and the aim of antithrombotic therapy are the same for both adults and children, that is (1) reduce the risk of death due to thrombus extension or embolization; (2) reduce the incidence of recurrent thrombosis; (3) reduce the incidence of post thrombotic syndrome by limiting vascular damage; and (4) maintain vessel patency and vascular access.

3.1.2. Available therapies and unmet medical need

In the ASH guidelines (2018) and ACCP guidelines (2012) recommended options for treatment of VTE in children include use of UFH, LMWH, and/or a VKA. These three classes of anticoagulants used for the treatment of VTE, which are well established and approved in adults, are adapted but yet not approved for use in children: VKA (e.g., warfarin), UFH, and LMWH, with the exception of one LMWH, FRAGMIN® (dalteparin sodium) injection.

At the time of establishing the ASH 2018 guideline, no results of clinical studies on DOACs in paediatric patients were available. Since then, several direct FXa inhibitors (dabigatran and rivaroxaban) have been approved for treatment of VTE and prevention of recurrence of VTE in paediatric patients. For both DOACs treatment has to be preceded by at least 5 days of parenteral treatment, e.g. with LMWH.

In the adult population apixaban was demonstrated to be safe and efficacious without the need for parenteral administration or monitoring. These features may address an unmet clinical need in paediatric patients.

3.1.3. Main clinical studies

The main evidence of efficacy and safety submitted is based on a prespecified interim-analysis of pivotal Study CV185325, a randomized (2:1), multicenter, open-label, active-controlled, descriptive safety and efficacy study, comparing apixaban (n=145) and Standard-of-Care (VKA, LMWH or UFH; n=72) in paediatric subjects requiring anticoagulation treatment for VTE and prevention of recurrent VTE. The pre-specified interim data from age groups 1-3 (ages 28 days to < 18 years) of Study CV185325 are summarized. Enrollment for age group 4 (neonates from birth to 27 days of age) is ongoing.

3.2. Favourable effects

Findings on pharmacodynamic biomarkers (chromogenic FX level, D-dimer, thrombin generation, FVIII, fibrinogen, protein C, protein S) in paediatric subjects were consistent with the previously characterized mechanism of action of apixaban as a direct FXa inhibitor. The pattern of effects on pharmacodynamic biomarkers of apixaban in paediatric patients has been demonstrated to be consistent with results in adults, also including demonstration of a linear PK-PD relationship for apixaban concentration and AXA.

The doses used for the pivotal study and proposed in the SmPC for treatment of VTE and prevention of recurrent VTE in paediatric subjects from 28 days to less than 18 years of age, resulted in comparable median AUCss in paediatric subjects and the adult VTEt population.

The initial weight-based dosing regimen of apixaban (October 2014) was amended towards a fixed dose, body weight tiered regimen after apixaban oral solution was no longer available for patients < 5 years of age due to the propylene glycol content. A comparable exposure is reached for the initial weight based dosing regimen and the final fixed-dose weight-tiered regimen, enabling interpretation of data on efficacy and safety for the entire study population.

In 53 subjects who entered the extension phase of study CV185325 and were treated with apixaban, no event of symptomatic and asymptomatic recurrent VTE or VTE related mortality was reported.

In the extrapolation exercise, similarity between adults and paediatric subjects aged 28 days to < 18 years on main issues related to pharmacology, disease manifestation and progression and on clinical response to treatment was demonstrated. The proposed posology, to initiate treatment of VTE with SoC anticoagulation for at least 5 days preceding initiation of apixaban is in accordance with treatments provided in pivotal study CV185325, using SOC anticoagulation for a median of 4 days prior to initiation of apixaban.

3.3. Uncertainties and limitations about favourable effects

Study CV185325 was an open-label descriptive safety and efficacy study, therefore no formal pre-defined hypothesis (e.g. non-inferiority) was tested. No power calculation for sample size determination was performed.

In the pivotal study CV185325, numerically similar results were seen for apixaban vs SOC on the primary efficacy endpoint composite of symptomatic and asymptomatic recurrent VTE and VTE-related mortality (2.8% (n=4) vs 2.8% (n=2), RR 0.99 (95%CI 0.2, 5.3)). However, the **number of events were very limited**. Further, 1 vs 2 were reported in the 12-18 years group, and 3 vs 0 were reported in the 2-12 years group and none in the age group of 28 days-2 years.

Congruent results were seen on the secondary efficacy endpoints of all cause death (1.4% vs 1.4%, RR 0.99 (95% CI 0.1, 10.8)), VTE-related mortality (0% vs 0%), stroke (0% vs 0%), new/recurrent (a)symptomatic DVT (0.7% vs 1.4%, RR 0.50 (95% CI 0.0, 7.8), new/recurrent (a)symptomatic PE (0% vs 0%), although endpoint data were also very limited.

In a supportive study CV185362 from the prevention of VTE in a different population of patients with congenital or acquired heart disease, a secondary efficacy endpoint of composite of adjudicated thromboembolic events and thromboembolic-related death no events in both treatment arms (apixaban vs VKA/LMWH) occurred: 0% vs 0%. Therefore, no meaningful comparison of efficacy of apixaban vs SOC could be established.

The number of patients treated with apixaban in the age-group 28 days to < 2 years is limited (22, 1 and 8 patients in studies CV185325, CV185155 and CV185362, respectively). No signal of reduced efficacy is seen. Comparable number of subjects in age-group < 2 years were investigated for other DOACS. In the EINSTEIN Junior study, 37 out of 335 paediatric subjects randomized to rivaroxaban were < 2 years of age, and in the DIVERSITY study, 22 out of 177 paediatric patients randomized to dabigatran were < 2 years of age.

In a total of 22 cases an index VTE event was not confirmed by the EAC, in 16 (11%) vs 6 (8.3%) cases for apixaban vs SOC. These findings of the EAC did not alter the treatment regimen, since they were not reported back during the study.

For the proposed indication "prevention of recurrent VTE" treatment duration is not specified. Extent and duration of exposure on apixaban in paediatric studies CV185325 (median of 84 days in 143 subjects during main phase and median of 168 days in 53 subjects during single-arm extension phase) and CV185362 (median of 358 days in 129 subjects) is limited though considered sufficient to justify not imposing limitations on the duration of treatment with apixaban.

3.4. Unfavourable effects

In main descriptive study CV185325, with a median exposure in 143 apixaban-treated subjects of 84 days, numerically similar results (though not formally tested) were seen on the **primary safety endpoint** of **composite of Major and CRNM bleeding** for apixaban vs SOC, 1.4% vs 1.4%, RR of 0.99 (95% CI 0.1;10.8), with no major bleeding events in both treatment arms.

In 53 subjects who entered the Extension Phase of study CV185325 and were treated with apixaban, no subjects in the Extension Phase experienced an adjudicated Major or a CRNM bleeding event. Eight (8/53; 15.1%) subjects in the Extension Phase experienced Minor bleeding events.

In supportive study CV185362, the primary safety endpoint of composite of adjudicated major or CRNM bleeding numerically was lower on apixaban as compared with SOC (VKA/LMWH), 1/126 (0.8%) vs 3/62 (4.8%), with a median exposure in 126 apixaban-treated patients of 358 days.

Though similar or reduced frequency in major and CRNM bleeding events was seen on apixaban vs SOC in studies CV185325 and CV185362, there was a tendency of **increased frequency of minor bleeding events** (35.7% vs 29.6% in study CV185325, and 35.7% vs 32.3% in study CV185362).

In main study CV185325, all-cause AEs (86.7% vs 83.1%) and Treatment-related AEs (27.3% vs 31.0%) were reported at a comparable frequency for both treatment arms. Also, no differences were seen for all-cause SAEs (22.4% vs 22.5%) and treatment-related SAEs (1.4% vs 0%). In supportive study CV185362, congruent results were seen for all-cause AEs (84.9% vs 85.5%) and all-cause SAEs (20.6% vs 21.0%), though results on treatment-related AEs (32.5% vs 25.8%) and SAEs (4.8% vs

8.1%) showed imbalance, that however was inconsistent, and the case narratives did not reveal a specific pattern in the occurrence of adverse events.

In main study CV185325, an increase in AEs for apixaban versus SOC of VKA/LMWH were seen for heavy menstrual bleeding (11.6% vs 4.2%), and rash (3.5% vs 0%).

In study CV185362, an increase was seen of epistaxis on apixaban vs SOC (14.3% vs 6.5%). In study CV185325, a similar frequency of epistaxis on apixaban was seen, though without an increase as compared with SOC (16.8% vs 19.7%).

In study CV185325, drug **discontinuation due to AEs** were limited and occurred in 1.4% vs 0%, all adjudicated as non-treatment related.

3.5. Uncertainties and limitations about unfavourable effects

Study CV185325 was a descriptive safety and efficacy study, therefore no formal pre-defined hypothesis (e.g. non-inferiority) was tested for the primary safety endpoint of bleeding events and no power calculation for sample size determination was performed.

All studies including study CV185325 were open-label studies which may cause bias for event reporting, although the bleeding events were independently adjudicated.

Exposure of apixaban in paediatric patients is still limited, with 143 subjects treated for a median of 84 days in the main phase of study CV185325, 168 days in 53 subjects that also participated in the extensions phase and 126 patients treated for a median of 358 days in study CV185362. In study CV185325, the number of patients in the age-groups < 12 years is limited. A total of 30 patients in age-group 2, and 22 in age-group 3 were treated with apixaban. Additional data on safety for paediatric subjects at similar maintenance exposure are retrieved from study CV185362, where mean exposure of apixaban was 332 (87) days in 87 subjects aged 2-12 years and 260 (110) days in 8 subjects aged 28 days to < 2 years. Rare or long-term adverse events and adverse events especially in young children aged 28 days to < 2 years and (to lesser extent) 2-12 years may still be uncertain.

In study CV185325, no signal for increased safety risk was seen for paediatric patients, including those aged 28 days-2 years, with a lower incidence of major bleeding evens and CRNM bleeding events in paediatric patients as compared with adults (0% vs <1%; 1.4% vs 3.0%-4.3%, respectively for major and CRNM bleeds).

Minor bleeding events occurred more frequently in paediatric patients as compared with adults. In study CV185325, minor bleeding events were reported at slightly increased frequency on apixaban, in 35.7% vs 29.6% of patients. In adult VTE-treatment studies CV185056 and CV185057, minor bleeding events were reported in 11.7% of apixaban treated adult patients vs 18.8% patients on SOC. Similar results were seen in TE-prevention studies. Minor differences with definitions of bleeding events used in adults were noted, though in general the definitions that were used in the paediatric studies were in line with the 2016 EMA guideline EMA/CHMP/41230/2015. Moreover, severity of bleeding events was adjudicated by an independent blinded external adjudication committee. Detailed analysis of minor bleeding events did not show signals of classification of minor instead of CRNM bleeding events.

3.6. Effects Table

Table 31. Effects Table for apixaban for the treatment of venous thromboembolism (VTE) and prevention of recurrent VTE in paediatric patients from 28 days to less than 18 years of age (Based on Study CV185325, data cut-off: 25th March 2022)

Effect	Unit	Apixaban (n=145)	SOC[c] (n=72)	Uncertainties (Unc)/ Strength of evidence (SoE)
Favourable Effects				
Composite of (a)symptomatic recurrent VTE and VTE-related death (primary endpoint)	Number (%) RR (95% CI)[b]	4 (2.8%) 0.99 (0.2, 5.3)	2 (2.8%)	**SoE:** • Endpoints independently adjudicated • Consistent in sensitivity analysis **Unc:** • descriptive data, not formally tested • (pre-defined) interim-analysis
All-cause death	Number (%) RR (95%CI)	2 (1.4%) 0.99 (0.1, 10.8)	1 (1.4%)	
New/recurrent (a)symptomatic DVT/PE	Number (%) RR (95%CI)	1 (0.7%) 0.50 (0.0, 7.8)	1 (1.4%)	
VTE other than DVT/PE[d]	Number (%) RR (95%CI)	3 (2.1%) 1.49 (0.2, 14.1)	1 (1.4%)	
VTE resolution[a]	Number (%)	76 (52.4%)	37 (51.4%)	
VTE regression[a]	Number (%)	25 (17.2%)	11 (15%)	
VTE unchanged[a]	Number (%)	7 (4.8%)	7 (9.7%)	
VTE contiguous recurrence[a]	Number (%)	2 (1.4%)	0 (0%)	
Unfavourable Effects				
Major bleeding events	Number (%)	0 (0%)	0 (0%)	**SoE:** • Endpoints independently adjudicated • No increase in major-CRNM bleeds on apixaban in study CV185362 (0.8%) vs 4.8%) • Similar numbers of Minor bleeds in study CV185362 (35.7% vs 32.3%) **Unc:** • descriptive data, not formally tested (pre-defined) interim-analysis
CRNM bleeding events	Number (%) RR (95%CI)	2 (1.4%) 0.98 (0.1, 10.7)	1 (1.4%)	
Minor bleeding events	Number (%) RR (95%CI)	51 (35.7%) 1.19 (0.8, 1.8)	21 (29.6%)	

[a]: The last image obtained in the Main Treatment Phase compared to baseline, of the index lesion
[b]: Relative risk of apixaban vs SOC and 95%CI based on Cochran-Mantel-Haenszel (CMH) test stratified by age group. The nominal p-value from CMH test stratified by age group
[c]: unfractionated heparin, low molecular weight heparin, or vitamin-K antagonist
[d]: Per definition include cerebral sinovenous thrombosis, renal vein thrombosis, portal vein thrombosis, catheter-related VTE, and splanchnic thrombosis

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Apixaban is a reversible, direct, selective inhibitor of FXa. It is indicated in adults for prevention of VTE after elective hip or knee replacement surgery and of stroke and systemic embolism in non-valvular atrial fibrillation, and for treatment of DVT and PE and prevention of recurrent DVT and PE. Extension of the indication of treatment of VTE and prevention of recurrent VTE to paediatric patients from 28 days to < 18 years of age is applied for.

The current application is mainly based on predefined interim-results of a descriptive safety and efficacy study CV185325 comparing apixaban to VKA/LMWH in paediatric patients requiring anticoagulation treatment for VTE and prevention of recurrent VTE. Patients aged 28 days to < 18 years (age-groups 1, 2 and 3) have been included, reflecting a broad paediatric age range. Recruitment in age-group 4 (aged from birth to < 28 days) is still ongoing, and not part of the proposed indication. Descriptive efficacy and safety data are summarized, and no formal statistical testing is performed. Although, this is considered acceptable as acknowledged by PDCO due to recruitment limitations, this limits the interpretability of the study.

In the pivotal study CV185325, numerically similar results were seen for apixaban vs SOC on the primary efficacy endpoint composite of symptomatic and asymptomatic recurrent VTE and VTE-related mortality (2.8% vs 2.8%). The number of efficacy endpoints for the composite of symptomatic and asymptomatic recurrent VTE and VTE-related mortality were very limited and do limit the robustness of conclusions. Any further efficacy cannot be extrapolated from supportive studies, e.g. in a study of prevention of VTE in a different population of congenital or acquired heart disease (CV185362) also comparing apixaban to VKA/LMWH SOC, as no such events occurred (defined as secondary endpoint).

As expected, the clinical safety database is limited, with 143 subjects treated with apixaban for a median of 84 days in current pivotal study in the randomised phase, and 53 patients entered the extension phase with median treatment of 168 days. Additionally, 126 patients were treated for a median of 358 days in a supportive study in patients in congenital heart disease. Nevertheless, understanding of rare or long-term adverse effects may still be limited. Exposure to apixaban in studies CV185325 and CV185362 is comparable with data from the EINSTEIN JR study on rivaroxaban (median exposure 91 days in 304 subjects, > 12 months in 9 subjects), and the DIVERSITY study on dabigatran (median exposure 98 days in 363 patients), < 42 weeks in 97 subjects).

The number of the primary safety endpoint of composite of major and CRNM bleeding were very limited and balanced between treatment arms (2 vs 1 event (1.4% in both groups)). Such low frequency of these events could be interpreted as reassuring, especially as also no such events were reported during the extension phase. In addition, a slight tendency of increased frequency of minor bleeding events (35.7% vs 29.6%) is seen, for which the clinical (and emotional) impact may be greater than for the adult population, although the frequency was reassuringly much lower during the extension phase (15%).

In study CV185325, the incidence of major bleeding events and CRNM bleeding events was lower in paediatric patients as compared with adults (0% vs <1%; and 1.4% vs 3.0%-4.3%, respectively for major and CRNM bleeds). Minor bleeding events occurred more frequently in paediatric patients as compared with adults: in 35.7% vs 29.6% of paediatric patients on apixaban vs SoC in paediatric VTE-treatment study CV185325, as compared with 11.7% vs 18.8% of adults on apixaban vs SOC in adult VTE-treatment studies CV185056 and CV185057. Similar results were seen in TE-prevention studies. Though minor differences in definitions of bleeding events used in adults were noted, in general the definitions that were used in the paediatric studies were in line with the 2016 EMA guideline EMA/CHMP/41230/2015, and classification of severity of bleeding events was adjudicated by an independent EAC blinded for treatment group. Further, detailed analysis of minor bleeding events did not show signals of classification of minor instead of CRNM bleeding events.

In main study CV185325, an increase on apixaban versus SOC was seen for adverse events of heavy menstrual bleeding (11.6% vs 4.2%), that were generally graded as mild to moderate and no interruption or permanent discontinuation of apixaban was deemed necessary, and rash (3.5% vs 0%; non-treatment related, and not related to a hypersensitivity reaction). Adverse event of epistaxis was reported at comparable frequency for subjects on apixaban in main study CV185325 (14.3%) and supportive study CV185362 (16.8%), with an imbalance as compared with SOC in study CV185362

(6.5%) that was not seen in study CV185325 (19.7%). Events of epistaxis in general were mild to moderate and required no treatment. For other adverse events, excluding bleedings, results appear reassuring, and apixaban appears well tolerated.

Extrapolation Exercise. A similar linear relation between apixaban plasma concentration and observed AXA level was seen in adults and paediatric patients, and in the extrapolation exercise similarity between adults and paediatric subjects on main issues related to pharmacology, to disease manifestation and progression, and to clinical response to treatment was demonstrated, thereby enabling bridging with data retrieved in adults.

Subgroup of patients aged 28 days to < 2 years. In subjects aged 28 days to 2 years, experience is limited, with 22, 1 and 8 patients treated with apixaban in studies CV185325, CV185155 and CV185362, respectively. No signal of reduced efficacy of apixaban in this age-group is seen, with none of them in study CV185325 experiencing a recurrent VTE or VTE-related death. No sign of increased bleeding risk is seen, with 1(4.8%) CRNM bleeding event and 3(13.6%) minor bleeding events in 2 subjects. In the extrapolation exercise, though some differences were noted for maturation of components of the coagulation cascade, in general a comparable function of the coagulation cascade was seen across age-groups. Further, on main issues related to pharmacology, disease manifestation and progression and on clinical response to treatment, consistency across age-groups including adults was demonstrated.

Though a limited number of patients aged 28 days to < 2 years was investigated for apixaban, comparable number of subjects in age-group < 2 years were investigated for other DOACs. In the EINSTEIN Junior study, 37 out of 335 paediatric subjects randomized to rivaroxaban were < 2 years of age, and in the DIVERSITY study 22 out of 177 paediatric patients randomized to dabigatran were < 2 years of age.

Posology. As opposed to the VTE-treatment studies in adults, in paediatric study CV185325 patients were treated with SOC anticoagulation in the initial screening/randomization phase after diagnosing VTE, for a median of 4 days, with only 7% of subjects starting after day 7. This is reflected in the proposed posology, to initiate treatment of VTE with SoC anticoagulation for at least 5 days preceding initiation of apixaban.
For the proposed indication "prevention of recurrent VTE" treatment duration is not specified. Extent and duration of exposure on apixaban in paediatric studies CV185325 and CV185362 is limited though considered sufficient to justify not imposing limitations on the duration of treatment with apixaban.

3.7.2. Balance of benefits and risks

In paediatric patients aged 28 days to < 18 years requiring anticoagulation treatment for VTE and prevention of recurrent VTE, efficacy data in support of comparable efficacy as compared with SoC anticoagulation (LMWH, UFH or VKA) is seen. The safety profile is generally considered to be reassuring on endpoints in terms of tolerability and bleeding risk. A small numerical increase of minor bleeding events is seen as compared with SoC anticoagulants, with mainly an increase for heavy menstrual bleedings, that were generally graded as mild to moderate with no need for interruption of apixaban.

These data are supported by an extensive dedicated extrapolation exercise, that demonstrated consistency between adults and paediatric subjects (including patients aged 28 days to < 2 years) on main issues related to pharmacology, disease manifestation and progression and on clinical response to treatment was demonstrated, enabling bridging with date from adults.

The proposed posology including initiation of VTE treatment with SoC anticoagulants for at least 5 days prior to initiation of apixaban is in line with treatments provided in the pivotal paediatric VTE-treatment study. Extent and duration of exposure on apixaban is considered sufficient to justify not imposing limitations on the duration of treatment with apixaban.

Overall, the benefit /risk for paediatric patients aged 28 days to < 18 years is positive.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable

3.8. Conclusions

The benefit /risk of Eliquis in paediatric patients aged 28 days to < 18 years is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Eliquis, Granules in capsules for opening, 0.15 mg and Coated granule(s) in sachet, 0.5, 1.5 and 2 mg, is favourable in the following indication(s):

- Treatment of venous thromboembolism (VTE) and prevention of recurrent VTE in paediatric patients from 28 days to less than 18 years of age.

The CHMP therefore recommends the extension(s) of the marketing authorisation for Eliquis subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The Marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being

reached.

- **Additional risk minimisation measures**

The MAH shall ensure that in each Member State where Eliquis is marketed, all healthcare professionals who are expected to prescribe Eliquis have access to/are provided with the following educational materials:

- Summary of Product Characteristics
- Prescriber Guide
- Patient Alert Cards

All patients and/or caregivers of paediatric patients who receive Eliquis shall be provided with a Patient Alert Card (provided within each medicine pack).

Key Elements of the Prescriber Guide:

- Details of populations potentially at higher risk of bleeding
- Recommended doses and guidance on the posology for different indications
- Recommendations for dose adjustment in at risk populations, including renal or hepatic impairment patients
- Guidance regarding switching from or to Eliquis treatment
- Guidance regarding surgery or invasive procedure, and temporary discontinuation
- Management of overdose situations and haemorrhage
- The use of coagulation tests and their interpretation
- That all patients and/or caregivers of paediatric patients should be provided with a Patient alert card and be counselled about:
    - Signs or symptoms of bleeding and when to seek attention from a health care provider
    - Importance of treatment compliance
    - Necessity to carry the Patient alert card with them at all times
    - The need to inform Health Care Professionals that they are taking Eliquis if they need to have any surgery or invasive procedure

Key Elements of the Patient Alert Card:

- Signs or symptoms of bleeding and when to seek attention from a health care provider
- Importance of treatment compliance
- Necessity to carry the Patient alert card with them at all times
- The need to inform Health Care Professionals that they are taking Eliquis if they need to have any surgery or invasive procedure

- ***Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.***

Not applicable.

In addition, CHMP recommends the variation(s) to the terms of the marketing authorisation, concerning the following change(s):

Variation(s) requested		**Type**	**Annex(es) affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II	I, II and IIIB

Extension of indication to include the treatment of venous thromboembolism (VTE) and prevention of recurrent VTE in paediatric patients from 28 days to less than 18 years of age for Eliquis (all strengths), based on a pre-specified interim analysis from Study CV185325; this is an open-label, multi-centre, randomized, active controlled trial to provide PK data and data on anti-Xa activity to support the extrapolation of efficacy to children, to evaluate safety and efficacy of apixaban in children who require anticoagulation for a venous thromboembolism; As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 4.9, 5.1 and 5.2 of the SmPCs are updated. The Package Leaflet and Annex II are updated in accordance. Version 21.3 of the RMP has also been submitted.