25 May 2023
EMA/CHMP/226986/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Eliquis

International non-proprietary name: apixaban

Procedure No. EMEA/H/C/002148/II/0088

Note

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

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List of abbreviations

AE	Adverse event
ALL	Acute lymphoblastic leukemia
ATE	Arterial thromboembolism
AUC(INF)	Area under the concentration-time curve from time zero extrapolated to infinite time
AUCss	Area under the concentration-time curve at steady state
AUC(TAU)	Area under the concentration-time curve in one dosing interval
AXA	Anti-factor Xa
BIC	Bayesian information criterion
BID	Twice daily
BMS	Bristol-Myers Squibb
CAHD	Congenital and/or acquired heart disease
CI	Confidence interval
CL/F	Apparent clearance
CO	Clinical Overview
CRNM	Clinically relevant non-major
CSR	Clinical Study Report
CV	Coefficient of variability
CVAD	Central venous access device
CVST	Cerebral venous sinus thrombosis
CYP	Cytochrome P450
DVT	Deep venous thrombosis
EMEA	European Medicines Agency
EU	European Union
F1	First-order absorption and dose dependent relative bioavailability
Frel	Relative bioavailability
FXa	Factor Xa
GT	Gastric tube
Ka	First-order absorption rate constant
KIDCLOT	Kids Informed Decrease Complications Learning on Thrombosis
LL	Lypmphoblastic lymphoma
LMWH	Low molecular weight heparin
MF	Maturation function
NA	Not applicable
NGT	Nasogastric tube
NVAF	Nonvalvular atrial fibrillation
PD	Pharmacodynamics
PE	Pulmonary embolism
PedsQL	Paediatric Quality of Life Inventory
P-gp	P-glycoprotein

PIP	Paediatric Investigation Plan
PK	Pharmacokinetics
PO	By mouth
PPK	Population pharmacokinetics
Q/F	Apparent intercompartmental clearance
QOL	Quality of life
SD	Standard deviation
SOC	Standard of care
SmPC	Summmary of Product Characteristics
Vc/F	Apparent volume of distribution in the central compartment
VKA	Vitamin K antagonist
VTE	Venous thromboembolism

1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Bristol-Myers Squibb / Pfizer EEIG submitted to the European Medicines Agency on 11 November 2022 an application for a variation.

The following changes were proposed:

Variation requested		Type	Annexes affected
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I

Update of sections 4.2 and 5.1 of the SmPC in order to update efficacy and safety information in the paediatric population based on results of the paediatric studies performed in compliance with the paediatric investigation plan (PIP), including studies CV185155 and CV185362. In addition, the MAH took the opportunity to introduce minor editorial changes to the PI.

The requested variation proposed amendments to the Summary of Product Characteristics.

Information on paediatric requirements

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

At the time of submission of the application, the PIP P/0198/2020 was completed.

The PDCO issued an opinion on compliance for the PIP P/0198/2020.

2. Overall conclusion and impact on the benefit/risk balance

The purpose of this Type II variation is to include paediatric information on venous thromboembolism (VTE) prophylaxis including a summary of the available paediatric clinical data in section 5.1 of the SmPC, but without seeking a paediatric indication for VTE prophylaxis, nor registering a paediatric formulation.

For this purpose, the MAH has submitted the results of the PIP01 clinical studies CV185118, CV185155 and CV185362.

The purpose of Study CV185155 was to investigate the use of apixaban (median 25 days) for the prevention of VTE in 512 subjects aged 1 up to 18 (mean 7 years) with acute lymphoblastic leukaemia (ALL) or lymphoblastic lymphoma (LL) undergoing induction chemotherapy with asparaginase via a central venous access device (CVAD). The study could not demonstrate a clear significant treatment benefit with only a numerical improvement in the primary endpoint of non-fatal deep vein thrombosis (asymptomatic or symptomatic), pulmonary embolism, and cerebral venous sinus thrombosis (CVST); and VTE related death for apixaban versus no treatment (relative risk (RR) 0.69 (95% confidence interval (CI) 0.45-1.05; p=0.08 (1 sided 0.04); 31 (12.1%) and 45 (17.6%) events). The effect was mainly driven by asymptomatic deep venous thrombosis (DVT), including a slight reduction in the number of CVAD related thrombi (n=17; 6.6% vs n=20; 7.8%), and a more substantial reduction of the number of thromboembolism (TE) events not (locally) related to the CVAD (n=9; 3.5% vs n=16; 6.3%). Considering that preventive anticoagulating treatment is currently not standard of care, it is difficult to justify any indication in these patients based on the presented efficacy data. Therefore, it is agreed with the MAH not to propose a preventive indication for these patients. Any indication for this setting has not been

(explicitly) approved for adults either. In terms of safety, apixaban appeared to be poorly tolerated in these patients with 13.7% vs 0.8% discontinuing treatment due to adverse events (AEs) (mainly gastrointestinal (GI) AEs, n=7; 2.7% vs n=1; 0.4%, no bleeding disorders). Further, although major bleedings were limited and balanced (2 in each arm), clinically relevant non-major bleedings were observed with increased incidence (11 (4.3%) vs 3 (1.2%); RR 3.67 (1.04-13.0)) with increased need for platelet transfusion (37.1% vs 32.8%), which may be regarded as a significant safety issue in such young patients.

The purpose of Study CV185362 was to investigate the safety of apixaban (median 358 days) for the prevention of arterial and venous thromboembolism in 192 subjects (28 days to 18 years) with congenital and/or acquired heart disease (CAHD) that require anticoagulation (apixaban vs vitamin K antagonist (VKA)/ low molecular weight heparin (LMWH)). Additional data on population PK and laboratory monitoring are provided from study CV185362, and from the formal PK/PD Study CV185118. Despite that based on the mechanism of action, some effect may be expected, there were no adjudicated thromboembolic events or thromboembolic event-related deaths in either treatment arm, which seriously limits interpretation of efficacy. Therefore, based on the (secondary) efficacy data provided, it is difficult to consider an indication statement. Further, a limited number of the (descriptive) primary safety endpoint of the composite adjudicated major or clinical relevant non-major (CRNM) bleeding events were found (1/126 (0.8% vs 3/62 (4.8%) RR 0.16 (CI: 0.02-1.54)), which also limits interpretation, but could be considered reassuring. Further, discontinuations due to bleedings was higher (7 (5.6%) vs 1 (1.6%), which may indicate somewhat lower tolerability, although caution is warranted due to the open-label design of the study.

Overall, it is agreed with the MAH that the data of both studies are too limited to justify a paediatric indication for the prevention of VTE and arterial thromboembolism (ATE) in both populations.

In section 4.2 of the SmPC, based on the currently presented data, safety as well as efficacy in paediatric subjects is not considered to be established. This has currently appropriately been addressed in section 4.2.

In section 5.1 of the SmPC, a summary of studies CV185155 and CV185362 is provided. The currently proposed wording in this section is agreed upon.

The benefit-risk balance of Eliquis remains positive.

3. Recommendations

Based on the review of the submitted data, this application regarding the following change:

Variation requested		**Type**	**Annexes affected**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I

Update of sections 4.2 and 5.1 of the SmPC in order to update efficacy and safety information in the paediatric population based on results of the paediatric studies performed in compliance with the paediatric investigation plan (PIP), including studies CV185155 and CV185362. In addition, the MAH took the opportunity to introduce minor editorial changes to the PI.

☒is recommended for approval.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I are recommended.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0198/2020 and the results of these studies are reflected in the SmPC and, as appropriate, the Package Leaflet.

Annex: Rapporteur’s assessment comments on the type II variation

4. Introduction

4.1. Background and rationale

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 was first approved in the EU[i] 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).

Apixaban is commercially available as 2.5-mg and 5-mg film-coated tablets.

Prophylactic anticoagulation in paediatric patients is currently indicated in only a small number of conditions. In virtually every instance, there are no data from clinical trials in paediatric patients; but rather, the dosing and regimens are taken from the adult literature. Further, no approved anticoagulants are currently approved for children, highlighting the need for clinical studies in this population.

In paediatric patients in almost all cases VTE occurs as a complication of an underlying medical condition. The main risk factor in paediatric patients to develop a VTE is the presence of a central venous catheter. The highest risk to develop a VTE is seen in children with acute lymphoblastic leukemia (ALL), treated with asparaginase, and having a Central Venous Access Device (CVAD.) Patients with ALL are at risk not only of CVAD-related thrombosis, but also cerebral venous sinus thrombosis (CVST) possibly leading to Pulmonary Embolism (PE), with the risk of stroke and death.

Thrombosis-related complications are increasingly recognized as important factors contributing to the morbidity and mortality in children with heart disease. Information is limited about the safety and efficacy of direct oral anticoagulants (DOACs) such as apixaban for the treatment and prevention of VTE in children at high risk for these complications.

4.2. Information on the Paediatric program for apixaban

Development of apixaban for paediatric use was initiated in 2014 pursuant to the following 2 Paediatric Investigation Plans (PIPs):

- PIP01 (EMEA-000183-PIP01-08-M08) was last modified and approved on 20-May-2020 and covers the VTE and arterial thromboembolism (ATE) prevention conditions in children from 28 days to < 18 years of age (Studies CV185155 and CV185362).
- PIP02 (EMEA-000183-PIP02-12-M03) was last modified and approved on 20-May-2020 and covers the VTE treatment condition in children from birth to < 18 years of age (Study CV185325).

The purpose of the PIP01 clinical studies was to investigate the use of apixaban for the prevention of VTE in subjects with ALL or LL undergoing induction chemotherapy with asparaginase via a CVAD (Study CV185155) and for the prevention of arterial and venous thromboembolism in subjects with Congenital and/or acquired heart disease (CAHD) that require anticoagulation (Study CV185362). The strategy, as

agreed under PIP01, was to demonstrate efficacy as thromboprophylaxis in the ALL/LL population (Study CV185155). The other PIP01 measures would provide additional data from the safety study in the CAHD population (Study CV185362), population PK and laboratory monitoring, and the formal PK/PD study (Study CV185118).

All studies under PIP01 are now complete and are the subject of this application. The study under PIP02 (CV185325) is ongoing and will be submitted in a future application. A line listing of the studies included in PIP01 (EMEA-000183-PIP01-08-M08) are mentioned below:

Study 1	Range-finding Juvenile toxicity study in rats, post-natal day 4-21
Study 2	Definitive Juvenile toxicity study in rats, post-natal day 4-90
Study 3	Bioavailability of Apixaban Solution Formulation Relative to Apixaban Tablets in Healthy Subjects
Study 4	CV185118: Single-Dose, Study to Evaluate the Pharmacokinetics, Pharmacodynamics, Safety and Tolerability of Apixaban in Paediatric Subjects;
Study 5	CV185155: Multicentre, randomized, open-label, parallel-group phase 3 trial in paediatric subjects to evaluate safety and efficacy of apixaban in children from 1 year to less than 18 years of age with a newly diagnosed acute lymphoblastic leukaemia (ALL) or lymphoma, (T or B cell), a functioning central venous access device (CVAD) and receiving asparaginase;
Study 6	CV185362: Prospective, randomized, open label, non-comparative safety trial to evaluate prevention of thromboembolism in children (from 28 days to <18 years) with cardiac disease, with a reference comparison of VKA and low molecular weight heparin (LMWH).
Study 7	Extrapolation study Model-based analysis of pharmacokinetic data accrued from Study 4) Paediatric Pharmacokinetics Study (CV185118), and Study 5) Safety and Efficacy Study (CV185155)
Study 8	Development of an age appropriate formulation of Apixaban
Study 9	Development of an age appropriate formulation of Apixaban for children < 5 years old

Table 1. Summary of PIP01 and Supporting Clinical Studies

Study PIP Study Identifier	Study Design Age Range	Primary Objective(s)	Endpoints	Study Drug and Dosage Regimens	Subject Type Randomized Apixaban Treated
CV185029[2] Study 3	Open label, randomized, 2 period, 2 treatment, crossover Phase 1 study in healthy subjects. Subjects were admitted to the clinical facility on Day -1. On Day 1, Period 1, subjects were randomized, in a 1:1 ratio, to receive a single oral dose of apixaban 10 mg as either 2 x 5 mg tablets or apixaban as 25 mL x 0.4 mg/mL solution. After a 4-day washout period (from the first dose), subjects began Period 2 on Day 5 and received the alternate treatment. ≥18 to ≤ 45 years	To assess the oral bioavailability of apixaban oral solution formulation relative to apixaban Phase 3 tablets in healthy subjects.	PK and safety	Apixaban solution (10 mg as 25 mL x 0.4 mg/mL) Apixaban tablets (10 mg as 2 x 5 mg)	Adult 14 14
CV185687[3] NA[a]	Open-label, Phase 1, randomized study to evaluate the bioavailability of apixaban sprinkle capsules relative to apixaban mini-tablets ≥18 to ≤ 45 years	To assess the bioavailability of apixaban 0.1-mg sprinkle capsules relative to apixaban 0.5 mg mini-tablets, both administered orally in healthy subjects	PK, safety, and tolerability	Apixaban mini-tablet (2.5 mg as 5 × 0.5 mg) Apixaban sprinkle capsule (2.5 mg as 25 × 0.1 mg)	Adult 30 30
CV185118[4] Study 4	Open-label, Phase 1, multi-site, single-dose study of apixaban in paediatric subjects at risk for venous or arterial thrombotic disorder Neonates to <18 years	To assess the PK of a single dose of apixaban in paediatric subjects.	PK, PD, safety, and tolerability	Apixaban oral solution (0.4 mg/mL) Apixaban sprinkle capsule (0.1 mg capsule) Administered by mouth or via an NGT or GT single dose Group 1: 0.1 mg Group 2a: 1.08 - 2.43 mg/m^2 Group 2b: 1.08 mg/m^2 Group 3: 1.17 mg/m^2 Group 4: 1.80 mg/m^2 Group 5: 2.19 mg/m^2	Paediatric NA 49

Study PIP Study Identifier	Study Design Age Range	Primary Objective(s)	Endpoints	Study Drug and Dosage Regimens	Subject Type Randomized Apixaban Treated
CV185155[5] Study 5	Randomized, open-label, multi-center, Phase 3 clinical trial in which paediatric subjects were randomized 1:1 to prophylactic apixaban for thromboembolism prevention versus no systemic anticoagulant during induction chemotherapy ≥ 1 to <18 years	To compare the effect of prophylactic oral or enteric apixaban versus no systemic anticoagulant during ~28 days of induction chemotherapy, including asparaginase, on the composite endpoint of adjudicated non-fatal DVT (including symptomatic and asymptomatic), PE, and CVST; and VTE-related-death To assess the effect of prophylactic oral or enteric apixaban versus no systemic anticoagulant during ~28 days of induction chemotherapy including asparaginase on adjudicated major bleeding events	PK, PD, efficacy, safety	Apixaban oral solution (0.4 mg/mL) Apixaban tablet (2.5 mg) Apixaban mini-tablet (0.5 mg) or no systemic anticoagulant Apixaban tablet or apixaban oral solution administered by mouth or via an NGT or GT as fixed-dose by weight-tier: ≥ 35 kg: 2.5 mg BID 25 to < 35 kg: 2 mg BID 18 to < 25 kg: 1.5 mg BID 10.5 to < 18 kg: 1 mg BID 6 to < 10.5 kg: 0.5 mg BID	Paediatric 512 250

CV185362[6] Study 6	Prospective, randomized, open-label, Phase 2, multi-center clinical trial of apixaban versus VKA or LMWH in paediatric subjects with CAHD requiring chronic anticoagulation for thromboembolism prevention ≥ 28 days to < 18 years	To assess the safety of apixaban compared to VKA or subcutaneous LMWH (SOC) in paediatric subjects with CAHD requiring chronic anticoagulation for thromboprophylaxis. To evaluate apixaban PK in paediatric subjects with CAHD requiring chronic anticoagulation for thromboprophylaxis.	PK, PD, safety, QOL, and exploratory efficacy and biomarker data	Apixaban oral solution (0.4 mg/mL), Apixaban tablet (5 mg) Apixaban mini-tablet (0.5 mg) Apixaban sprinkle capsule (0.1 mg) or SOC Apixaban oral solution, tablet or sprinkle capsule administered by mouth or via an NGT or GT as fixed-dose by weight-tier ≥ 35 kg: 5 mg BID 25 to < 25 kg: 4 mg BID 18 to < 25 kg: 3 mg BID 12 to < 18 kg: 2 mg BID 9 to < 12 kg: 1.5 mg BID 6 to < 9 kg: 1 mg BID 5 to < 6 kg: 0.5 mg BID 4 to < 5 kg: 0.3 mg BID 3 to < 4 kg: 0.2 mg BID	Paediatric 192 126

[a] Study CV185687 was not included as a separate PIP measure, but was part of the formulation development for the capsules

Abbreviations: BID, twice daily; CADH, congenital or acquired heart disease; CVST, cerebral venous sinus thrombosis; DVT, deep vein thrombosis; GT, gastric tube; LMWH, low molecular weight heparin; NGT, nasogastric tube; PD, pharmacodynamic; PE, pulmonary embolism; PK, pharmacokinetic; QOL, quality of life; SOC, standard of care; VKA, vitamin K antagonists; VTE, venous thromboembolism

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). This Type II variation application covers the totality of the PIP01 clinical and extrapolation measures. The purpose of this Type II variation is to include a summary of the available paediatric clinical data in the SmPC for the prescriber's information, without seeking a paediatric indication for VTE prophylaxis, nor registering a paediatric formulation.

The following updates are being proposed to the apixaban SmPC:

- Section 5.1 to reflect clinical outcomes from PIP01 Studies CV185155 and CV185362
- Section 4.2 to reflect the content of this variation application

5. Description and objectives of the studies

All studies included in this Type II variation were conducted in accordance with the principles of Good Clinical Practice as defined by the International Council on Harmonisation and were conducted to meet the ethical requirement of European Directive 2001/20/EC. For each study, the protocol, amendments, administrative letters, and subject informed consent form received Institutional Review Board/Independent Ethics Committee approval prior to implementation. Compliance audits were performed as part of implementing quality assurance, and audit certificates are provided as applicable in the individual study reports. The quality of data collected and analysed was monitored according to Bristol-Myers Squibb (BMS) standard operating procedures.

The clinical outcome of studies CV185155 and CV185362 is proposed to be added to section 5.1 of the SmPC (Table 2).

Table 2. Apixaban Paediatric Studies Conducted under PIP01 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 and (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 arm: fixed-dose by weight-tier regimen PO or via a NGT or GT BID for 29±5 days; SOC arm: No systemic anticoagulant
CV185362	A Phase 2, prospective, randomized, open-label, multi-center study of the safety 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 and (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 arm: fixed-dose by weight-tier regimen PO or via a NGT or GT BID for up to 12 months; VKA/LMWH arm: per local SOC

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; VKA = vitamin K antagonist; VTE = venous thromboembolism.

6. Clinical Pharmacology aspects

6.1. Background

The pharmacokinetics (PK) and pharmacodynamics (PD) of apixaban have been characterized in healthy adults and adult patients. Apixaban oral bioavailability is approximately 50% and exposure increases are dose-proportional throughout the therapeutic dose range (2.5 mg to 10 mg). Apixaban has a total clearance of approximately 3.3 L/h and an apparent half-life of approximately 12 hours following oral administration.[ii] Apixaban PK in adult subjects was characterized by a 2-compartment population PK (PPK) model with first-order absorption and elimination. Covariates predictive of apparent clearance (CL/F) included age, sex, Asian race, renal function, and concomitant strong/moderate cytochrome P450 (CYP)3A4 and P-glycoprotein (P-gp) inhibitors. The magnitude of individual covariate effects was generally < 25% compared to a reference NVAF subject (non-Asian, male, aged 65 years, weighing 70 kg without concomitant CYP3A4 and P-gp inhibitors), except in severe renal impairment, which resulted in 55% higher exposure compared to the reference subject.[iii]

The PK/PD model of anti-FXa activity (AXA) has been developed using data from healthy adults and adult subjects treated for VTE.[iv] 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 negligible between-subject variability.

In summary, the adult PK and PD data described above was used as a starting point to guide the development of the paediatric program. Information from apixaban clinical pharmacology studies conducted by BMS and Pfizer, characterizing the human PK, PPK, and PK/PD relationship of paediatric patients treated with apixaban, is outlined below.

6.2. PPK model and data from Study CV185118

Apixaban 2.5 mg BID was shown to be safe and effective in adults for the prevention of VTE following elective knee and hip surgery (ADVANCE-2 and -3 studies), and the prevention of recurrent DVT and PE in a Phase 3 study (AMPLIFY-EXT study). In addition, apixaban, 5 mg BID was shown to be safe and effective for the prevention of stroke and systemic embolism in patients with NVAF and one or more risk factors (ARISTOTLE). PPK modeling was used to establish the steady-state median area under the concentration-time curve in one dosing interval (AUC[TAU]) in each of these adult populations; these values were then used to guide target AUCs in the apixaban paediatric studies.

The median AUC(TAU), 800 ng•hr/mL, in adult patients treated with apixaban 2.5 mg for the prevention of VTE in the ADVANCE-2 and -3 trials served as the target exposure for the CV185118 study. An iterative model-based approach was used to identify the initial paediatric doses for this study and served to guide dose adjustments over the course of the study to help ensure the predicted median AUC from time zero extrapolated to infinity (AUC[INF]) was similar to the 800 ng•hr/mL target. Apixaban was administered using a body surface area-based dosing approach for all groups except for neonates in this study, who were administered a flat 0.1 mg dose of apixaban.

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) in paediatric patients 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 instituted a fixed-dose, body weight-tiered dosing approach during the study.

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.

This model-based approach, in conjunction with the staggered cohort design of the CV185118 study and subsequent phased enrollment into the CV185155 and CV185362 studies, allowed for adaptations to the apixaban formulation and dose selection that significantly contributed to the successful completion of this paediatric plan.

6.2.1. Apixaban formulations used in paediatric clinical studies

Apixaban is approved for use in adults as a 2.5 mg and a 5 mg film-coated tablet that can be administered orally with or without food. For adult patients who are unable to swallow whole tablets, apixaban tablets can be crushed and suspended in water, 5% glucose in water, or apple juice or mixed with apple puree and immediately administered orally. Alternatively, apixaban may be crushed and suspended in 60 mL of water or 5% glucose water and delivered through a nasogastric tube.

Apixaban has been studied in the paediatric development program using 4 age-appropriate formulations 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 mg tablet 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, 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, as cited in a European Medicines Agency (EMA) draft report that was to be incorporated in an EMA guideline shortly thereafter. To resume enrollment of paediatric subjects < 5 years of age, a new 0.5 mg mini-tablet was developed for use in subjects >= 3 months of age. This tablet is relatively small, being ~3 mm in diameter, and the composition (drug to excipient ratio) and manufacturing process (up to compression) is identical to that for the approved adult 2.5 mg and 5 mg tablets. Therefore, the new 0.5 mg mini-tablets have the pharmaceutical characteristics of the tablets already approved for the adult population, but proportionally scaled to a lower strength for paediatric use. The 0.5 mg mini-tablet was used in both the CV185155 and CV185362 studies.

The 0.1 mg sprinkle capsule was developed as 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.

Development of the 0.5 mg mini-tablet and 0.1 mg sprinkle capsule together with application of the apixaban paediatric model allowed for an informed transition from a body surface area-based dosing approached used in Study CV185118 to the fixed-dose by weight-tier dose regimens that were ultimately employed in Study CV185362 using appropriate formulations appropriate for neonate through adolescent subjects.

6.2.2. Dose selection rationale

The dose selection rationale for apixaban in these studies was based on the results of the CV185118 study, which had the primary objective of assessing the PK of a single oral dose of apixaban in paediatric subjects (using an iterative PPK modeling approach consistent with steady state observations after an adult regimen of 2.5 mg twice daily).

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, as cited in a European Medicines Agency (EMA) draft report that was to be incorporated in an EMA guideline shortly thereafter. A new 0.5 mg mini-tablet was developed for use in subjects >= 3 months of age. This tablet is relatively small, being ~3 mm in diameter, and the composition and manufacturing process is identical to that for the approved adult 2.5 mg and 5 mg tablets. Therefore, the new 0.5 mg mini-tablets have the pharmaceutical characteristics of the tablets already approved for the adult population, but proportionally scaled to a lower strength for paediatric use.

With the introduction of 0.5 mg mini-tablets, the dosing regimen for apixaban changed from being weight based (mg/kg) to a fixed-dose by weight-tier regimen that was supported by modeling and simulation results. The fixed-dose by weight-tier regimen consisted of weight ranges that corresponded to an apixaban dose, regardless of apixaban formulation (ie, oral solution or tablets). With the introduction of the 0.1 mg capsule formulation, a body weight-tiered dosing regimen was expanded to subjects ⩾3 kg and as young as 28 days of age.

In CV185155, the 9 to < 12 kg weight tier corresponded to a 0.75 mg dose. However, there was no practical formulation to achieve a 0.75 mg dose, so enrollment into this weight-tier remained closed. In Revised Protocol 05 (CV185155 Appendix 1.1) this weight tier was redistributed into the 2 adjacent weight tiers and dosed as follows: 6 to < 10.5 kg subjects received 0.5 mg and 10.5 to < 18 kg subjects received 1 mg. The redistributed regimen provided similar exposures to that of the 0.75 mg dose

originally listed in the protocol.

6.2.3. Study CV185118

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.

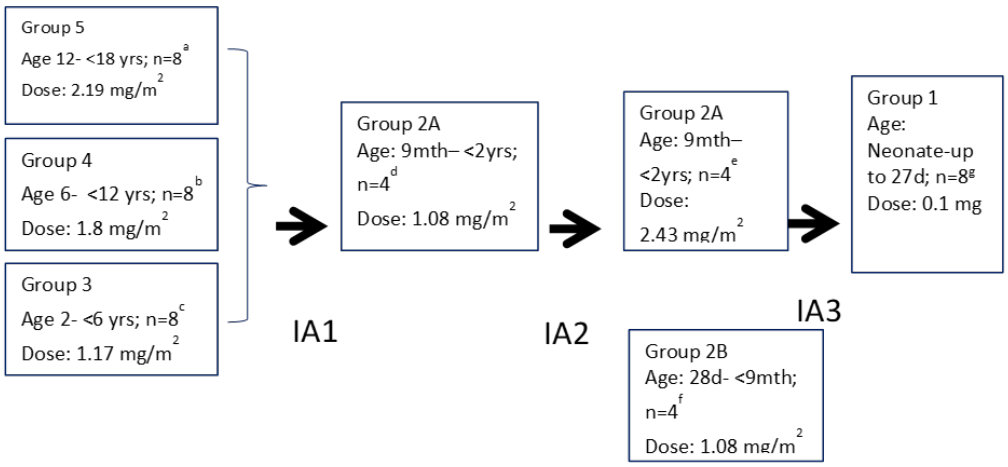
Exclusion criteria included a history or evidence of abnormal bleeding, active bleeding or a high risk of bleeding (e.g known gastrointestinal ulcer), central nervous system lesions or other risk factors for intracranial bleed, presently receiving an anticoagulant, except warfarin or antiplatelet therapy which required a 5 days washout. In subjects with Kawasaki's disease low dose aspirin was acceptable. Other exclusion criteria were 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/mm^3.

General study design

The study was performed in paediatric subjects at risk for venous or arterial thrombotic disorder in the following age groups:

- Group 1: Neonates up to 28 days of age (≥ 34 weeks gestational age or ≥ 37 weeks post conceptual age)
- Group 2B: Infants 28 days to < 9 months
- Group 2A: Young children 9 months to < 2 years
- Group 3: Young children 2 years to < 6 years
- Group 4: Children 6 years to <12 years
- Group 5: Adolescents 12 years to <18 years

Figure 1. Study Design - Study CV185118



Interim Analysis (IA) 1: Completed based on 16 subjects from Grps 3,4,5; ≥2 per Grp. Purpose: Confirm Grp 2 dose or adjust as needed.

Interim Analysis 2: Completed based on 4 subjects from Grp 2A and subjects from All Group 3-5. Purpose: Confirm Grp 2B dose or adjust as needed.

Interim Analysis 3: Completed based on all subjects from Grp 2 (A&B)-5. Purpose: Confirm Grp 1 dose or adjust as needed.

Final Analysis : Completed based on all subjects from all groups. Purpose: Final Analysis.

[a] n=8 planned; n=10 treated
[b] n=8 planned; n=10 treated,
[c] n=8 planned; n= 8 treated
[d] n=4 planned; n=5 treated
[e] n=4 planned; n=4 treated
[f] n=4 planned; n=11 treated
[g] n=8 planned; n=1 treated, before study termination

Study treatment

The CV185118 study utilised the apixaban oral solution (OS) formulation (0.4 mg/mL) for subjects from 28 days to <18 years of age. The dosing syringes were qualified in dosing accuracy studies to ensure accurate delivery of doses as low as 0.04 mg (0.1 mL).

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). The 2.5 mg BID dose was the selected dosing regimen to target for this study as it provides exposures at the lower end of the range investigated in adult Phase 3 clinical trials, and would allow for both accurate characterization of apixaban PK in the paediatric population while preserving a wide safety margin to account for ontogeny-related differences in drug disposition as well as hemostasis.

Table 3. Apixaban dose in each age group

Pediatric Subject Groups	Dose
Group 1 Neonates up to 27 days[a]	0.1 mg fixed dose
Group 2B Infants 28 days to <9 months	1.08 mg/m^2
Group 2A Young Children 9 months to <2 years	1.08 mg/ m^2
Group 2A[b] Young Children 9 months to <2 years	2.43 mg/ m^2
Group 3 Young Children 2 years to <6 years	1.17 mg/ m^2
Group 4 Children 6 years to <12 years	1.80 mg/ m^2
Group 5 Adolescents 12 years to <18 years	2.19 mg/ m^2

Source: Appendix 1.1 of CV185118 Clinical Study Report[2]

a Neonates up to 28 days of age (≥ 34 weeks gestational age or ≥ 37 weeks post conceptual age)

b (n=4 additional subjects)

Outcomes/Endpoints

Efficacy endpoints

There were no planned efficacy endpoints.

Safety endpoints

Safety endpoints included incidence of AEs, serious AEs, AEs leading to discontinuation, and death as well as results of clinical laboratory tests (including eGFR and marked laboratory abnormalities), vital sign measurements, and physical examinations. BMS standard Marked Laboratory Abnormality criteria and protocol specified criteria were be used.

Pharmacokinetic endpoints

Pharmacokinetic parameters of apixaban were derived from a population PK model developed using plasma concentration versus time data, with the following primary PK parameters:

Parameter	Definition
CL/F	Apparent plasma clearance
Vc/F	Apparent volume of distribution of the central compartment
Ka	Rate of absorption

These model-derived population and individual PK parameters were used to estimate Cmax, AUC(INF) and Tmax in each subject.

Apixaban in human plasma was assayed using 2 validated and cross-validated LC-MS/MS methods (Intertek for samples analysed through March 2015 and PPD for samples analysed after November 2016) during the period of known analyte stability.

Biomarker endpoints

The pharmacodynamics (PD) of apixaban were characterised using a population PK-PD (PopPKPD) model developed using both the plasma concentration and the measured anti-Xa activity vs. time data. The PD endpoint was:

- SLP Linear slope of the relationship between plasma concentration and anti-Xa activity

The individual estimated PK and PD parameters were used to derive the individual subjects' maximum anti-Xa activity (AXA_{max}); this variable was summarised by age group.

Exploratory endpoints

- Palatability

Palatability assessments using a hedonic scale were conducted in conjunction with the morning dose of apixaban on Day 1. The scale used for the palatability assessments is 1='Super Bad', 2='Bad', 3='Maybe Good or Maybe Bad", 4='Good' and 5='Super Good'. The assessment was to be completed by a caregiver for subjects in Group 1-3. Subjects in Groups 4 and 5 were to complete the assessment independently. Subjects that received apixaban via NG tube and subjects in groups 4 and 5 that could not complete the assessment independently were exempted from palatability assessment.

Statistical methodology

Sample size

The number of subjects was not based on statistical power considerations. A sample size of approximately 44 total subjects (at the end of the study), with 8 subjects in each age group (except for n=12 in Group 2), was expected to result in estimation of the population mean AUC(INF) for each age group with a 95% probability of being within 60 - 140% of the true mean.

Safety analyses

The evaluation of safety was based on clinical AEs, vital signs, and clinical laboratory results reported during the study. All recorded adverse events were listed and tabulated by system organ class and preferred term, age group and overall. If any, AEs associated with palatability would be listed by age group.

Physical examination abnormal findings were listed. Vital signs and clinical laboratory test results and corresponding change from baseline values were listed and summarised by age group. Marked abnormalities for clinical laboratory test results were also listed and summarised, using the standard BMS criteria as well as protocol specified criteria. In the summaries of marked laboratory abnormalities, both scheduled and unscheduled visits were included.

6.3. Results

6.3.1. Pharmacokinetic evaluation

Bioavailability of age-appropriate apixaban formulations used in paediatric studies was assessed in Studies CV185029 and CV185687 in healthy adults. Study CV185029 was submitted and discussed in a prior filing. Comparable bioavailability between the 0.1 mg apixaban sprinkle capsule and the 0.5 mg mini-tablet was established in Study CV185687. Study CV185687 is included in this submission. Study CV185029 assessed the bioavailability of apixaban oral solution formulation relative to apixaban tablets. Study CV185687 assessed the bioavailability of apixaban sprinkle capsules relative to apixaban tablets. The relative bioavailability of the apixaban oral solution (Frel = 105%) and sprinkle capsules (Frel = 110%) were both highly similar to the bioavailability of the tablet formulation, therefore no new bioavailability studies were required.

In Study CV185118 paediatric subjects received the apixaban oral solution or sprinkle capsule formulation. In PIP01 Studies CV185155 and CV185362 paediatric subjects received the apixaban oral solution or apixaban tablets. Apixaban sprinkle capsules were available for use in Study CV185362, but no subjects received the capsule formulation.

Apixaban oral bioavailability is approximately 50% and exposure increases are dose proportional throughout the therapeutic dose range (2.5 mg to 10 mg). Apixaban has a total clearance of approximately 3.3 L/h and an apparent half-life of approximately 12 hours following oral administration. Apixaban PK in adult subjects was characterized by a 2-compartment PPK model with first-order absorption and elimination. Covariates predictive of apparent clearance (CL/F) included age, sex, Asian race, renal function, and concomitant strong/moderate cytochrome P450 3A4 (CYP3A4) and P-glycoprotein (P-gp) inhibitors. The magnitude of individual covariate effects was generally < 25% compared to a reference NVAF subject (non-Asian, male, aged 65 years, weighing 70 kg without concomitant CYP3A4 and P-gp inhibitors), except in severe renal impairment, which resulted in 55% higher exposure compared to the reference subject.

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) in paediatric patients 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 instituted a fixed-dose, body weight-tiered dosing approach during the study. 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.

Similar to Study CV185118, the paediatric PPK model developed based on data from Study CV185155 was a 2-compartment model with first-order absorption and dose-dependent F1.17 The effect of the maturation of CYP enzymes on apixaban CL/F was included using an MF derived from the literature.14,15 Body weight was a significant predictor of apixaban CL/F and Vc/F. Apixaban CL/F and Vc/F increased with increasing body weight, whereas apixaban Q/F increased with increasing age. The effect of sprinkle capsule formulation (0.1 mg capsule) remained fixed to have 10% higher F1 compared to the conventional oral tablet formulation in order to characterize PK in subjects from previous studies who

received the capsule formulation. In addition, the apixaban Ka was approximately 253% higher in paediatric subjects aged 9 months to < 18 years compared to adults, overall. In paediatric subjects with ALL or LL at risk of VTE treated with asparaginase (Study CV185155), the Ka of apixaban was 81.1% lower as compared to paediatric subjects aged 9 months to < 18 years at risk of VTE (Studies CV185079 and CV185118). Apixaban Vc/F was approximately 43.1% lower in paediatric subjects with ALL or LL at risk of VTE treated with asparaginase as compared to adults of similar body weight or paediatric subjects at risk of VTE of similar body weight.

The previously developed PPK model for the paediatric population in Study CV185155 was used as a starting point for the development of the PPK model for Study CV185362. A full model approach was developed by incorporating the subject type effects on CL/F, Vc/F, and Ka in the final base model. Subject type was defined as:

- paediatric subjects at risk for VTE or ATE from Studies CV185079 and CV185118

- paediatric subjects with ALL or LL at risk of VTE treated with asparaginase (Study CV185155)

- paediatric subjects with congenital or acquired heart disease (Study CV185362)

The healthy adult subjects served as the reference population. Because of the confounding effect of subject type with the preexisting age effect of subjects 9 months to < 18 years on the Ka parameter, the subject type for subjects at risk of venous or arterial thromboembolism was not evaluated on the Ka parameter. The final model was developed from the full model by backward elimination based on Bayesian information criterion (BIC) reduction of the covariate effects of subject type on CL/F, Ka, and Vc/F.

The PPK analysis of the pooled dataset combined all paediatric Phase 1 data from study CV185079 and CV185118 and adult Phase 1 data. The data from young adults (aged ≤ 50 years) included 7 Phase 1 studies (CV185002, CV185013, CV185022, CV185046, CV185058, CV185059, and CV185074) in healthy male and female adult subjects, and 1 Phase 1 study (CV185018) in healthy and renally impaired male and female adult subjects. Leveraging the adult data in the modeling approach achieved 2 key objectives. The first was to allow precision in estimation of exposures despite sparse sampling, and the second, to anchor the adult clearance values so the paediatric clearances could be estimated in the context of adult values, and covariate evaluation could allow for predictors of differences across the paediatric continuum. The final apixaban PPK model included a comprehensive and iterative covariate evaluation to quantify the intrinsic/extrinsic factors that influence the exposure of apixaban across the paediatric age range from young infants to young adults. The final PPK analysis dataset used for model development included 5,220 apixaban concentrations from 254 subjects. Of the 5,220 concentrations, 236 concentrations were from 48 subjects in Study CV185118.

Table 4. Summary Statistics of Covariates for Paediatric Subjects by Study in the Final Population Pharmacokinetic Model

Variable		CV185079 (n = 8)	CV185118 (n = 48)	CV185155 (n = 224)	CV185362 (n = 124)	Overall (n = 404)
Age (years)	Mean (SD)	13.9 (3.87)	5.44 (5.39)	7.86 (4.41)	8.48 (4.62)	7.88 (4.74)
	Median	15	4.04	6.47	7.5	6.73
	Min, Max	6, 17	0.044, 16.9	1.94, 18	0.378, 18	0.044, 18
Baseline Body Weight (kg)	Mean (SD)	57.9 (21.4)	21.4 (19.5)	33 (22.6)	29.3 (18.1)	31 (21.5)
	Median	52	13.3	22.8	23.6	22.6
	Min, Max	26.6, 92.9	3, 80.9	11.5, 121	6.1, 133	3, 133
Estimated GFR ($mL/min/1.73\ m^2$)[a]	Mean (SD)	169 (29.3)	157 (70.6)	191 (61.9)	159 (38.5)	176 (58.4)
	Median	159	152	184	154	167
	Min, Max	136, 229	44, 416	64.5, 529	70.5, 332	44, 529
	Missing	0	0	4	1	5
Age Groups, n (%)	< 28 days	0 (0)	1 (2.08)	0 (0)	0 (0)	1 (0.248)
	28 days to < 9 months	0 (0)	11 (22.9)	0 (0)	2 (1.61)	13 (3.22)
	9 months to < 2 years	0 (0)	9 (18.8)	1 (0.446)	6 (4.84)	16 (3.96)
	2 years to 6 years	0 (0)	8 (16.7)	105 (46.9)	37 (29.8)	150 (37.1)
	6 years to < 12 years	2 (25)	9 (18.8)	72 (32.1)	48 (38.7)	131 (32.4)
	12 years to < 18 years	6 (75)	10 (20.8)	46 (20.5)	31 (25)	93 (23)
Subject Type, n (%)	Paediatrics at risk of VTE or ATE	8 (100)	48 (100)	0 (0)	0 (0)	56 (13.9)
	Paediatrics with cancer	0 (0)	0 (0)	224 (100)	0 (0)	224 (55.4)
	Paediatrics with heart disease	0 (0)	0 (0)	0 (0)	124 (100)	124 (30.7)
Race, n (%)	White	3 (37.5)	41 (85.4)	168 (75)	105 (84.7)	317 (78.5)
	Black	3 (37.5)	5 (10.4)	11 (4.91)	7 (5.65)	26 (6.44)
	AI/AN	0 (0)	0 (0)	0 (0)	1 (0.806)	1 (0.248)
	Asian	0 (0)	0 (0)	24 (10.7)	6 (4.84)	30 (7.43)
	Native Hawaiian or Other Pacific Islander	0 (0)	0 (0)	1 (0.446)	0 (0)	1 (0.248)
	Other	2 (25)	2 (4.17)	20 (8.93)	5 (4.03)	29 (7.18)
Sex, n (%)	Male	6 (75)	21 (43.8)	126 (56.2)	60 (48.4)	213 (52.7)
	Female	2 (25)	27 (56.2)	98 (43.8)	64 (51.6)	191 (47.3)

Table 5. Summary Statistics of Covariates for Paediatric Subjects by Study in the Final Population Pharmacokinetic Model

Variable		CV185079 (n = 8)	CV185118 (n = 48)	CV185155 (n = 224)	CV185362 (n = 124)	Overall (n = 404)
Weight Groups, n (%)	< 4 to 3 kg	0 (0)	5 (10.4)	0 (0)	0 (0)	5 (1.24)
	< 5 to 4 kg	0 (0)	2 (4.17)	0 (0)	0 (0)	2 (0.495)
	< 6 to 5 kg	0 (0)	4 (8.33)	0 (0)	0 (0)	4 (0.99)
	< 9 to 6 kg	0 (0)	6 (12.5)	0 (0)	6 (4.84)	12 (2.97)
	< 12 to 9 kg	0 (0)	5 (10.4)	2 (0.893)	2 (1.61)	9 (2.23)
	< 18 to 12 kg	0 (0)	4 (8.33)	71 (31.7)	28 (22.6)	103 (25.5)
	< 25 to 18 kg	0 (0)	7 (14.6)	50 (22.3)	29 (23.4)	86 (21.3)
	< 35 to 25 kg	1 (12.5)	5 (10.4)	30 (13.4)	24 (19.4)	60 (14.9)
	≥ 35 kg	7 (87.5)	10 (20.8)	71 (31.7)	35 (28.2)	123 (30.4)

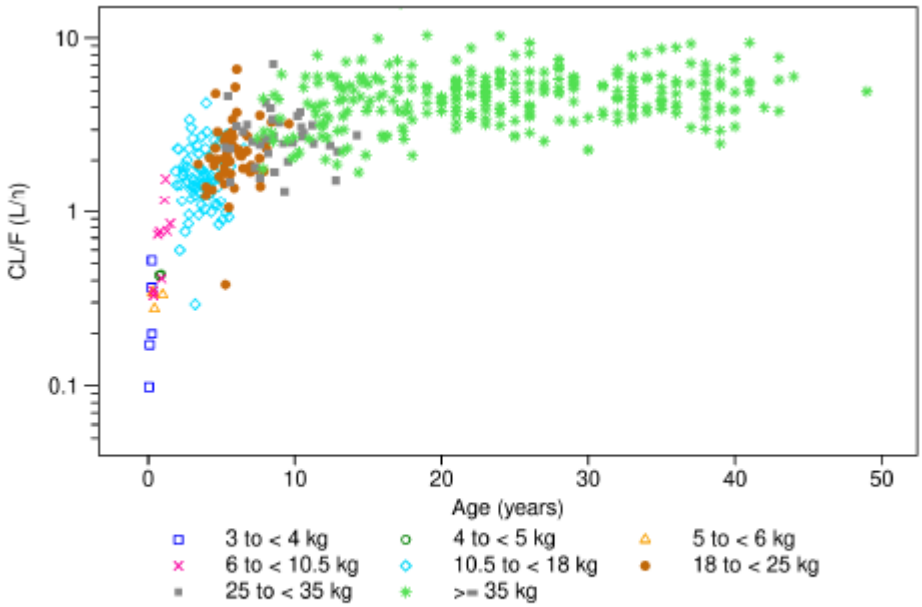
[a] Calculated using Schwartz method.

Abbreviations: AI/AN = American Indian/Alaskan native; ATE = arterial thromboembolism; GFR = glomerular filtration rate; Max = maximum; Min = minimum; n = number of subjects; SD = standard deviation; VTE = venous thromboembolism.

Analysis-Directory:

Source: Table 3.3.1.6-2 of the CV185362 Pharmacometric Analysis Report[23]

Figure 2. Scatterplot of Estimated Individual Apparent Clearance Versus Age, Colored by Weight Tiers for Adult and Paediatric Subjects in Analysis Dataset Using the Final Population Pharmacokinetic Model, Semi-log Scale

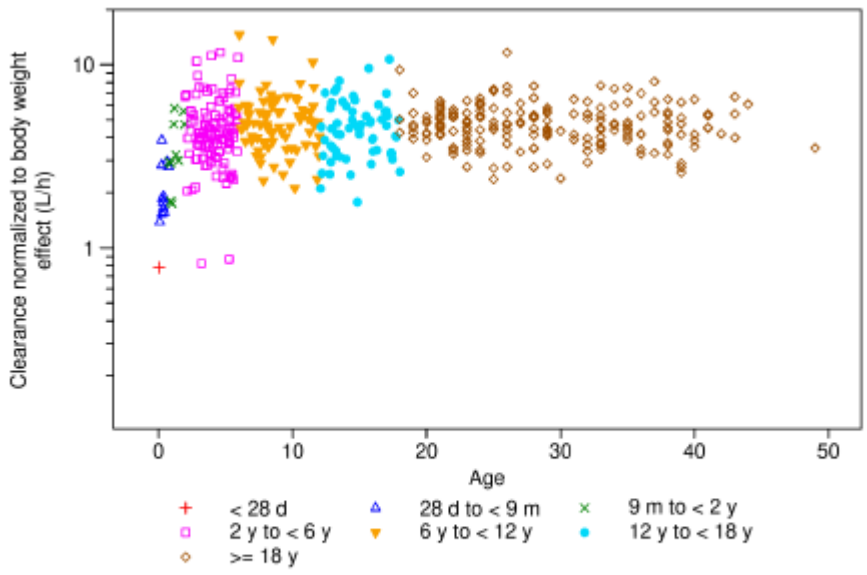


KIWI Version 4.202111 - File ID: 2332176 - Scatterplot Profile: 4423

Abbreviations: CL/F = apparent clearance.

Source: Figure 5.1.3.1-1 of the CV185155 Pharmacometric Analysis Report[17]

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



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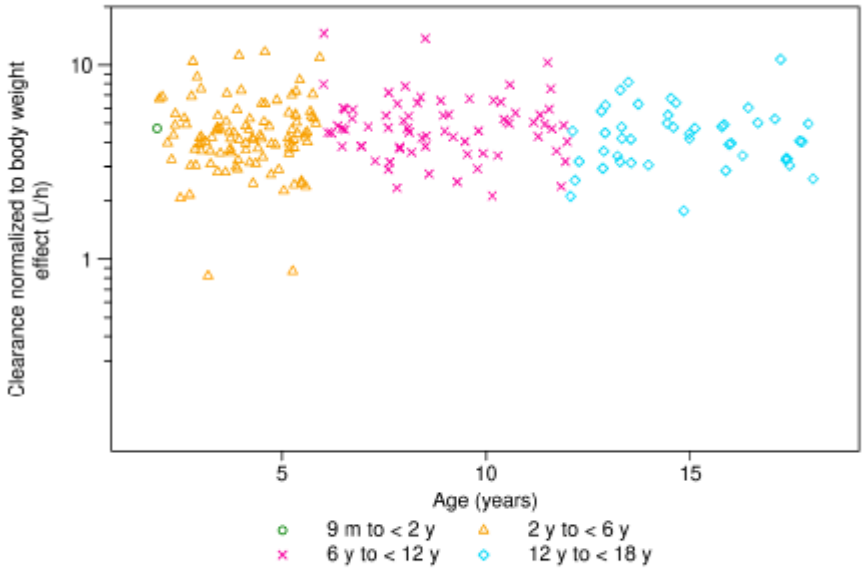
Abbreviations: d = days; m = months; y = years.

Source: Figure 5.1.3.1-2 of the CV185155 Pharmacometric Analysis Report[17]

Figure 4. Scatterplot of Estimated Individual Apparent Clearance Normalized to Body Weight Effect Versus Age, Colored by Age Group for Adult and Paediatric Subjects in Study CV185155 Using the Final

Population Pharmacokinetic Model, Semi-log Scale



KIWI Version 4.202111 - File ID: 2332178 - Scatterplot Profile: 4838

Abbreviations: m = months; y = years.

Source: Figure 5.1.3.1-3 of the CV185155 Pharmacometric Analysis Report[17]

Stochastic simulations were performed using virtual paediatric subjects with ALL or LL to confirm a fixed-dose by weight-tier dose regimen approach in patients aged 1 to < 18 years. Although Study CV185155 was designed to include a 9 to < 12 kg weight tier that would receive a 0.75 mg dose, this regimen was not initially feasible with the available formulations. The 9 to < 12 kg weight tier was redistributed into 2 adjacent weight tiers and dosed as 6 to < 10.5 kg and 10.5 to < 18 kg to provide similar exposures to the 0.75 mg dose originally listed in the protocol. The apixaban dose regimens were 0.5 mg and 1 mg BID respectively for the 6 to < 10.5 kg and 10.5 to < 18 kg weight tiers. Stochastic simulation was performed using the final model and weight-tiered dosing regimen (2.5, 2, 1.5, 1, and 0.5 mg BID regimens for ≥ 35 kg, 25 to < 35 kg, 18 to < 25 kg, 10.5 to < 18 kg, and 6 to < 10.5 kg weight tiers, respectively) to generate steady state AUC(TAU). The simulated steady-state AUC(TAU) values from the virtual paediatric subjects by weight tiers were compared with exposures observed in the adult VTEp population from the AMPLIFY-EXT study receiving 2.5 mg BID apixaban. In addition, predicted steady-state AUC(TAU) exposures for paediatric subjects with ALL or LL in Study CV185155 were overlaid on the boxplots to show that apixaban exposures are consistent with expectations. The median simulated exposures by weight tiers were similar to the median observed exposures in the adult population, with relatively higher variability in paediatric subjects compared to adults. These results confirm that the fixed-dose weight-tiered approach used to provide target exposures for paediatric subjects in Study CV185155 achieved the anticipated outcome.

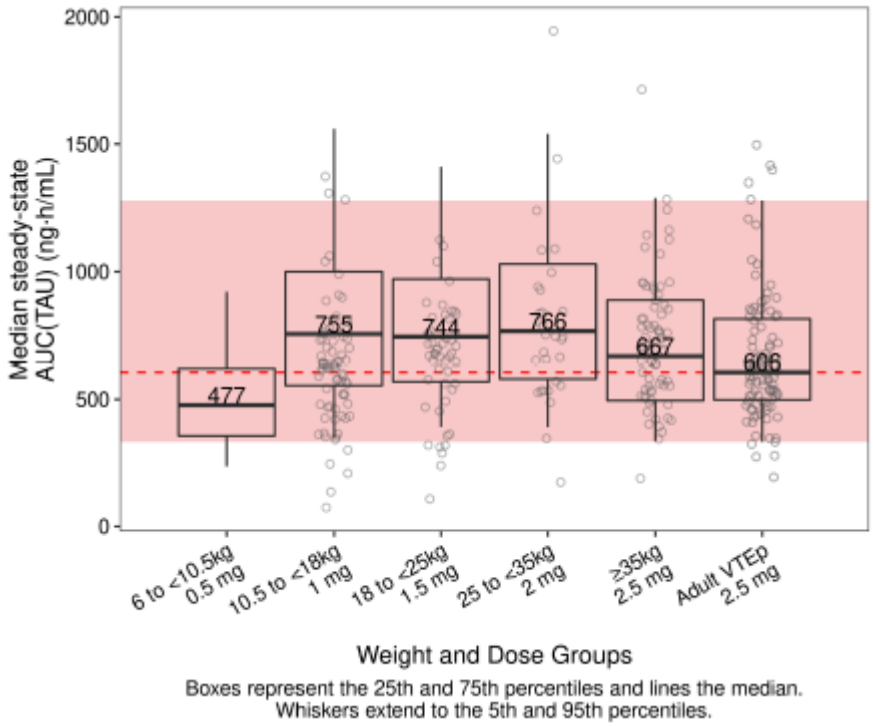
Table 6.Summary of Covariates for Virtual Paediatric Population Aged 1 to < 18 Years Used for Stochastic Simulations

Overall							
Variable		6 to < 10.5 kg (n = 1000)	10.5 to < 18 kg (n = 1000)	18 to < 25 kg (n = 1000)	25 to < 35 kg (n = 1000)	≥ 35 kg (n = 1000)	Overall (n = 5000)
Age (months)	Mean (SD)	14.6 (2.28)	31 (14.5)	74.4 (12.1)	111 (13.1)	173 (26.1)	80.8 (59.1)
	SE	0.0722	0.458	0.383	0.414	0.826	0.836
	Median	14	25.8	72.8	111	174	72.8
	Min, Max	12, 23.3	12, 78.5	45, 116	79.7, 155	111, 215	12, 215
	N	1000	1000	1000	1000	1000	5000
Age (years)	Mean (SD)	1.22 (0.191)	2.58 (1.21)	6.2 (1.01)	9.27 (1.09)	14.4 (2.18)	6.73 (4.93)
	SE	0.00602	0.0382	0.0319	0.0345	0.0689	0.0697
	Median	1.17	2.15	6.07	9.26	14.5	6.07
	Min, Max	0.997, 1.94	0.997, 6.54	3.75, 9.7	6.64, 12.9	9.29, 17.9	0.997, 17.9
	N	1000	1000	1000	1000	1000	5000
Body Weight (kg)	Mean (SD)	9.91 (0.441)	13.4 (2.13)	21 (1.96)	29.7 (2.9)	51 (9.04)	25 (15.3)
	SE	0.0139	0.0675	0.062	0.0916	0.286	0.217
	Median	10	12.8	20.7	29.6	51	20.7
	Min, Max	7.88, 10.4	10.5, 17.9	18, 24.9	25, 34.9	35, 75.8	7.88, 75.8
	N	1000	1000	1000	1000	1000	5000
Age Group, N (%)	1 y to < 2 y	1000 (100)	467 (46.7)	0 (0)	0 (0)	0 (0)	1467 (29.3)
	2 y to 6 y	0 (0)	532 (53.2)	477 (47.7)	0 (0)	0 (0)	1009 (20.2)
	6 y to < 12 y	0 (0)	1 (0.1)	523 (52.3)	991 (99.1)	172 (17.2)	1687 (33.7)
	12 y to < 18 y	0 (0)	0 (0)	0 (0)	9 (0.9)	828 (82.8)	837 (16.7)
Gender, N (%)	Male	258 (25.8)	553 (55.3)	532 (53.2)	503 (50.3)	477 (47.7)	2323 (46.5)
	Female	742 (74.2)	447 (44.7)	468 (46.8)	497 (49.7)	523 (52.3)	2677 (53.5)

Abbreviations: Max = maximum; Min = minimum; N = number of records; n = number of individuals; SD = standard deviation; SE = standard error of the mean; y = years.

Source: Table 5.1.3.2-1 of the CV185155 Pharmacometric Analysis Report[17]

Figure 5. Comparison of Median Steady-State AUC(TAU) Exposure Between Paediatric Subjects Aged 1 to < 18 Years by Weight Tiers and Adult VTEp Population From AMPLIFY-EXT Study



6.3.2. Pharmacokinetic/Pharmacodynamic evaluations

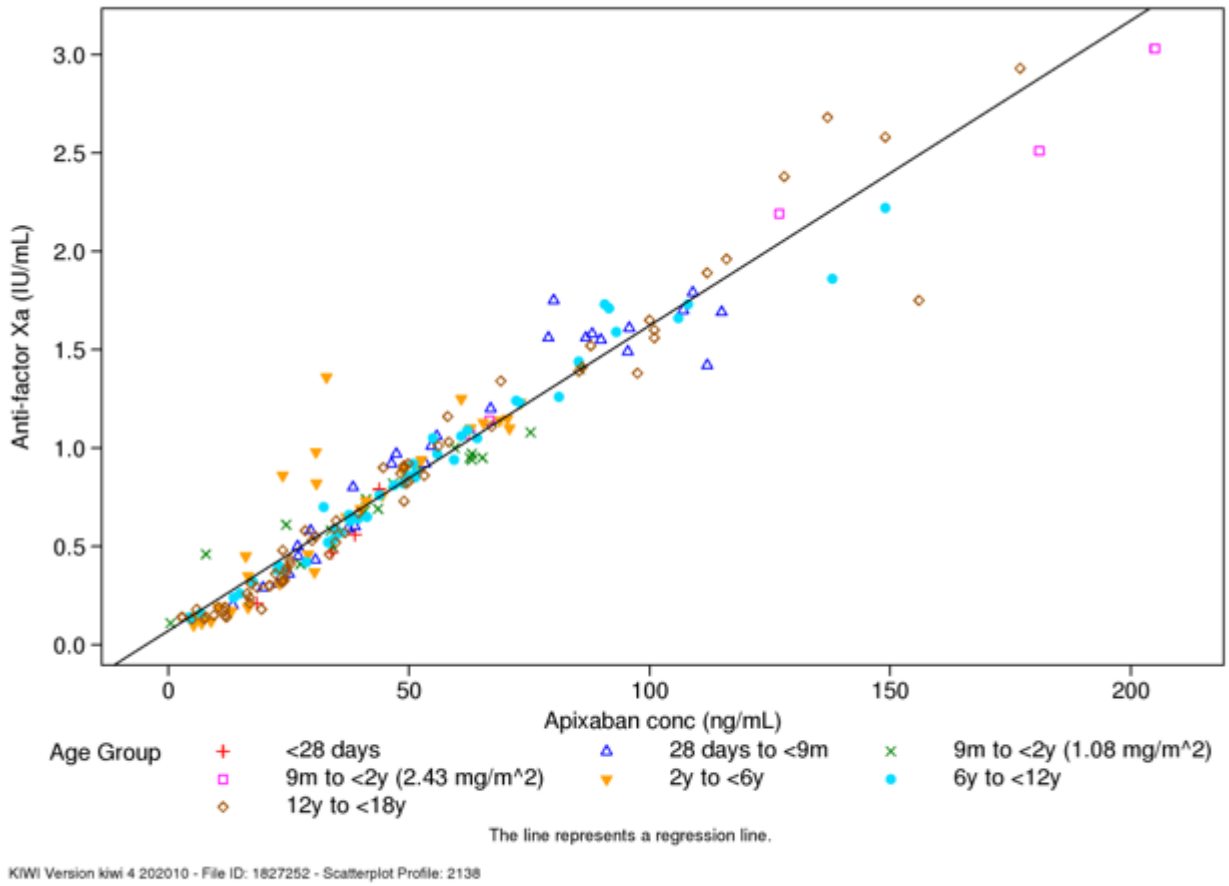
6.3.2.1. Study CV185118

The PK/PD model of anti FXa activity (AXA) has been developed using data from healthy adult subjects

and adult subjects treated for VTE. 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 negligible between-subject variability.

The PK/PD model of AXA in paediatric subjects was developed using data from Phase 1 Studies CV185079 and CV185118. Similar to adult subjects, the PK/PD relationship between apixaban concentration and AXA in paediatric subjects was linear. The slope estimate for the linear relationship in paediatric subjects based on the 2 Phase 1 studies was 0.0155 IU/ng with no apparent age-dependent differences in slope. Based on the general similarity of the slopes, the relationship does not seem to differ across age groups, and thus, the overall slope value was used in the calculation of maximum AXA (AXAmax) (Figure 6). Individual simulated AXAmax values for paediatric subjects in Study CV185118 by age group are summarized in Table 7. Note that AXAmax is highly dependent on PK sampling time (which differs by age group). A comparison of the slope would be a more accurate representation of the utility of the assay in the paediatric population.

Figure 6. Observed Plasma AXA Level vs Apixaban Concentration Stratified by Age Group in paediatric Subjects (CV185118)



Note: The regression line was prepared using linear equation: $Y = 0.0155 \cdot X + 0.0710$

Conc: concentration; m: months; y: years

Source: Figure 10.1-1 of the CV185118 Final CSR[19]

Table 7. Summary of Estimated Maximum AXA for Paediatric Subjects in Study CV185118 by Age Group

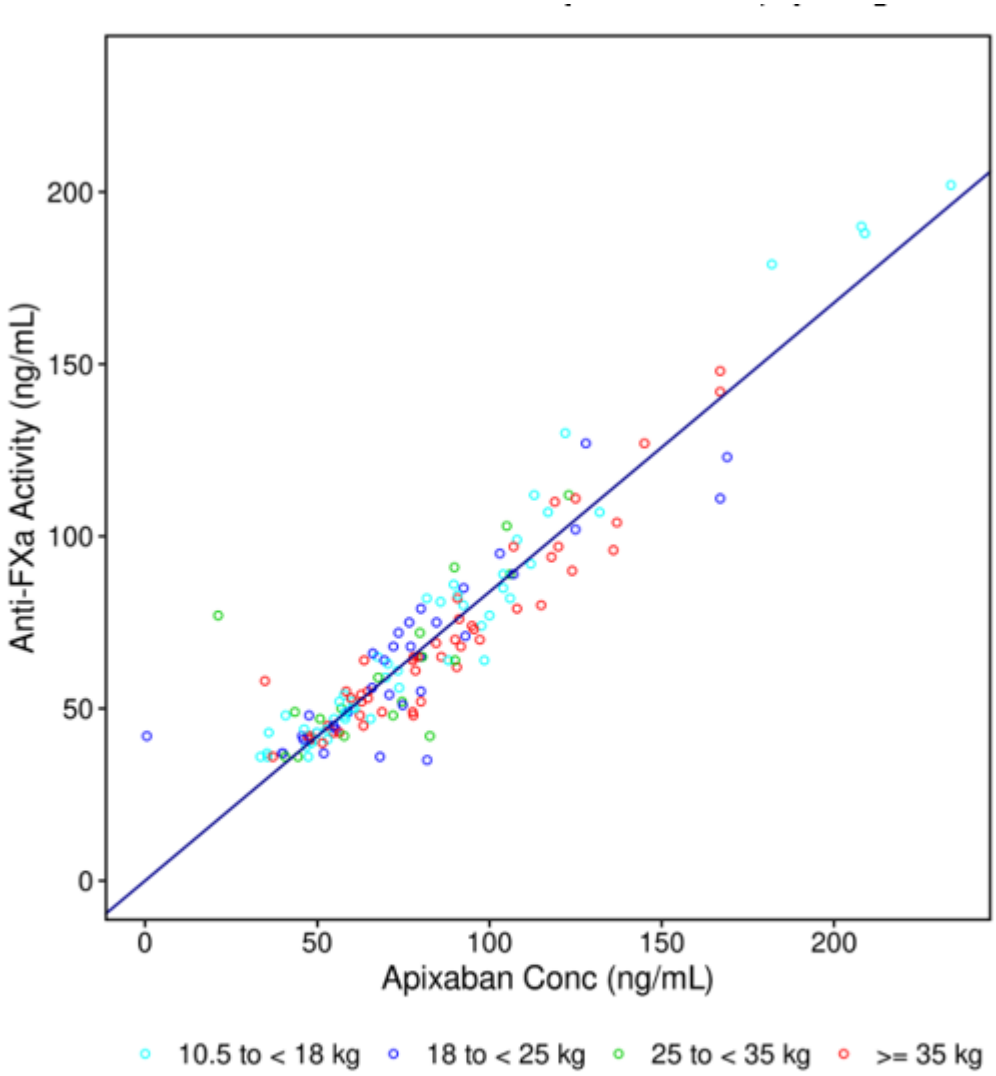
	Statistics	AXAmax (IU/mL)
Group 1 (< 28 Days) 0.44 mg/m^2 (0.1 mg)	Geometric Mean	0.0837
	%CV	NA
	N	1
Group 2B (28 Days to < 9 Months) 1.08 mg/m^2	Geometric Mean	0.456
	%CV	226
	N	11
Group 2A (9 Months to < 2 Years) 2.43 mg/m^2	Geometric Mean	0.309
	%CV	427
	N	3
Group 2A (9 Months to < 2 Years) 1.08 mg/m^2	Geometric Mean	0.204
	%CV	216
	N	6
Group 3 (2 to < 6 Years) 1.17 mg/m^2	Geometric Mean	0.464
	%CV	157
	N	8
Group 4 (6 to < 12 Years) 1.80 mg/m^2	Geometric Mean	0.303
	%CV	243
	N	9
Group 5 (12 to < 18 Years) 2.19 mg/m^2	Geometric Mean	0.307
	%CV	293
	N	10
Overall	Geometric Mean	0.332
	%CV	219
	N	48

N: number of records
KIWI Version kiwi framework - File ID: 1818910 - Summary statistics table Profile: 2050
Source: Table 10.1-2 of the CV185118 Final CSR[19]

6.3.2.2. Study CV185155

In study **CV185155**, PK/PD analysis was performed using time-matched apixaban concentrations and AXA data. These data were not pooled with AXA data from Studies CV185079 and CV185118 because a different assay was used for Study CV185155. Generally, AXA showed a linear relationship with apixaban concentrations across different age and weight groups (Figure *7*).

Figure 7 . Goodness-of-Fit Plot for the Final Apixaban Pharmacokinetic/Pharmacodynamic Model, by Weight Tier



Note: Circles represent observed data and the solid line represent model prediction.
Abbreviations: Conc = concentration; FXa = coagulation factor Xa.
Source: Figure 5.2.1-1 of the CV185155 Pharmacometric Analysis Report[17]

6.3.2.3. Study CV185362

The final PK/PD model was a linear mixed effect regression model with intercept fixed to zero, a slope parameter, and IIV in the slope parameter described the relationship between apixaban concentration and AXA in paediatric subjects from Studies CV185155 and CV185362 well. The parameter estimates and

standard errors for the final PK/PD model are summarized in Table 8 and the goodness-of-fit plot showing the model fitting to the observed PK/PD data is presented in Figure 8.

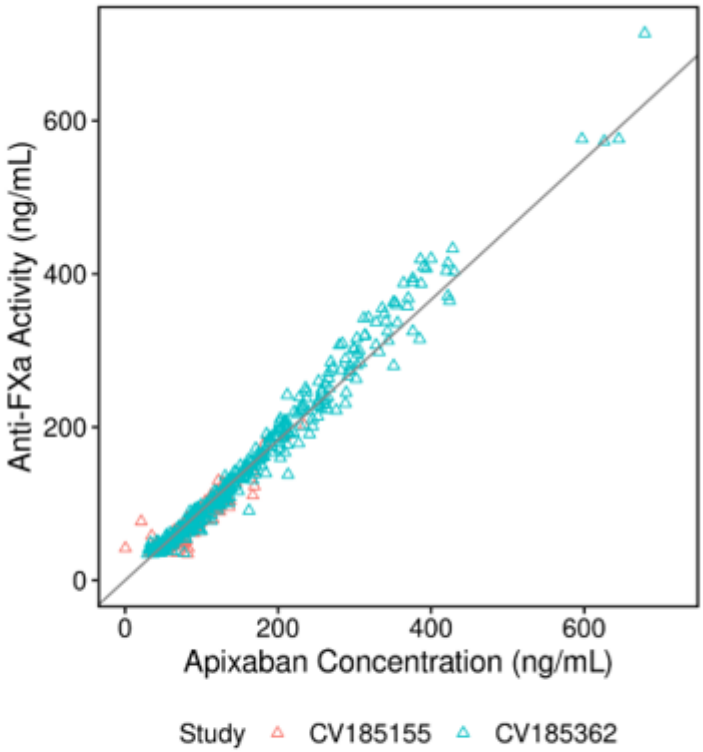
Table 8. Parameter Estimates and Standard Errors for the Final Pharmacokinetic/Pharmacodynamic Model for AXA

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

Abbreviations: CI = confidence interval.

Source: Table 5.2.1-1 of the CV185362 Pharmacometric Analysis Report[23]

Figure 8. Goodness-of-Fit Plot for the Final Apixaban harmacokinetic/Pharmacodynamic Model, by Weight Tier



Note: Triangles represent observed data and the solid line represents model prediction.
Abbreviations: FXa = factor Xa.

Source: Figure 5.2.1-1 of the CV185362 Pharmacometric Analysis Report[23]

In the overall PD population, 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. There were increased AXA levels post-dose at Day 1, Week 2, and Month 3. Two hours post-dose, mean values for AXA at Week 2 and Month 3 were similar at 242.34 and 228.88 ng/mL, respectively (Table 9 and Figure 9). Results for AXA across age groups (Figure 10) were consistent with those in the overall PD population (Figure 9).

Table 9. Summary Statistics for AXA (ng/mL) in Subjects Treated with Apixaban - PD Population

Visit	Time (h)	N	Mean (SE)	Median (Min - Max)	Geometric Mean (%CV)
DAY 1	4 HRS POSTDOSE	116	147.69 (7.24)	133.00 (17.5 - 419.0)	127.52 (52.82)
WEEK 2	PREDOSE	113	86.24 (7.65)	62.00 (17.5 - 573.0)	61.53 (94.32)
	2 HRS POSTDOSE	44	242.34 (18.97)	207.00 (49.0 - 576.0)	210.34 (51.91)
MONTH 3	2 HRS POSTDOSE	68	228.88 (14.26)	209.00 (17.5 - 714.0)	197.49 (51.39)
MONTH 6	PREDOSE	100	66.93 (6.53)	50.00 (17.5 - 409.0)	48.44 (97.60)

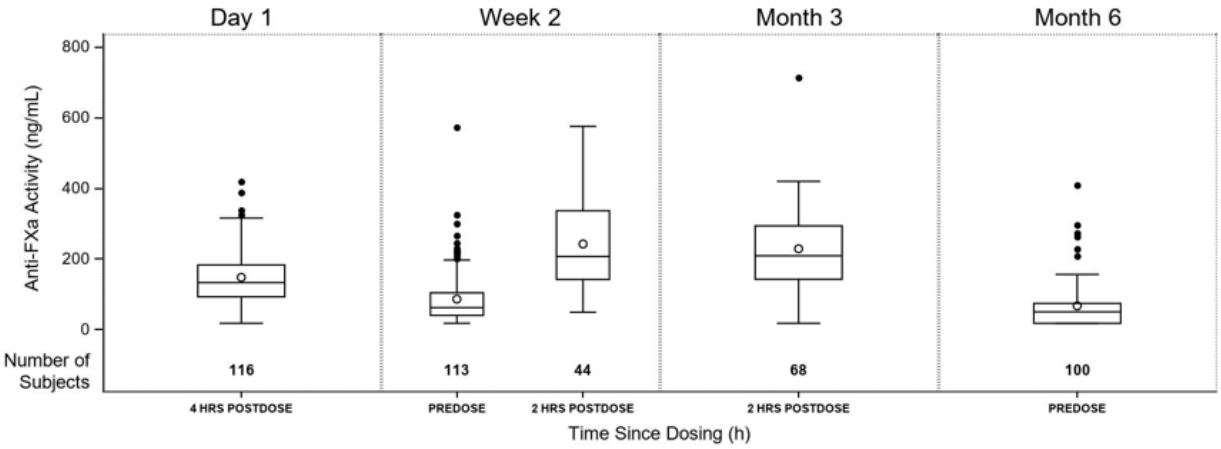
PD (pharmacodynamic) population included subjects who received at least one dose of apixaban and had chromogenic FX assay and/or anti-FXa samples collected.

AXA <LLOQ (35 ng/mL) post-dose was analyzed as 1/2 LLOQ (17.5 ng/mL)

Abbreviations: %CV = coefficient of variation expressed as a percent; LLOQ = lower limit of quantification; Max = maximum; Min = minimum; SE = standard error.

Source: Table 14.7.1 of the CV185362 Final CSR[24]

Figure 9. Box and Whisker Plot of AXA (ng/mL) in Subjects Treated with Apixaban - PD Population



PD (pharmacodynamic) population included subjects who received at least one dose of apixaban and had chromogenic FX assay and/or anti-FXa samples collected.

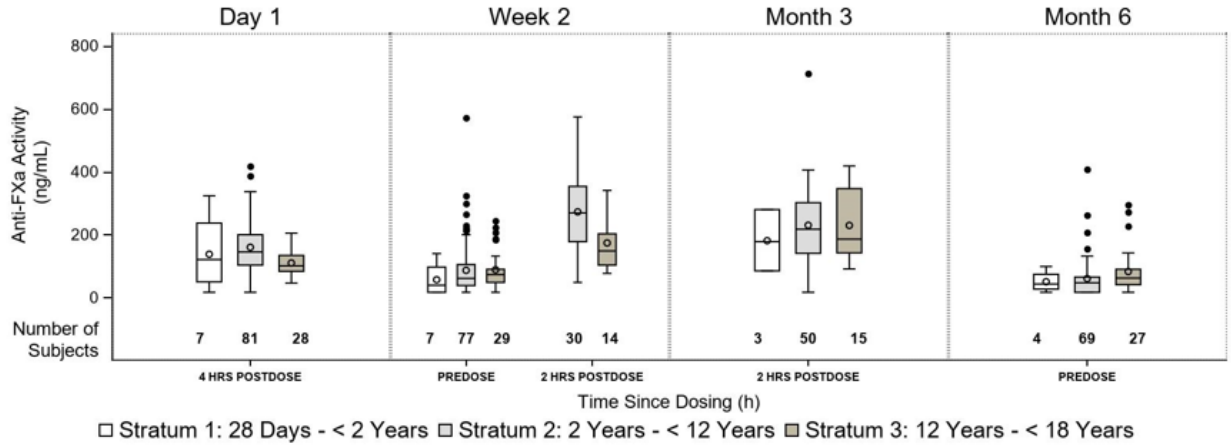
AXA <LLOQ (35 ng/mL) post-dose was analyzed as 1/2 LLOQ (17.5 ng/mL).

Symbols: open circle = mean; solid circle = outlier; horizontal bar = median; vertical bar = range

Abbreviation: LLOQ = lower limit of quantification

Source: Figure 14.7.1 of the CV185362 Final CSR[24]

Figure 10. Box and Whisker Plot of AXA (ng/mL) in Subjects Treated with Apixaban by Age - PD Population



PD (pharmacodynamic) population included subjects who received at least one dose of apixaban and had chromogenic FX assay and/or anti-FXa samples collected.
AXA <LLOQ (35 ng/mL) post-dose was analyzed as 1/2 LLOQ (17.5 ng/mL).
Symbols: open circle = mean; solid circle = outlier; horizontal bar = median; vertical bar = range
Abbreviation: LLOQ = lower limit of quantification
Source: Figure 14.7.2 of the CV185362 Final CSR[24]

6.3.2.4. Summary of Biomarkers

In Study CV185362, in the overall PD population, 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 2-4 hours post-dose (near apixaban peak plasma concentrations) compared with that at pre-dose (near apixaban trough plasma concentrations) (Table 10 and Figure 11

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)

PD (pharmacodynamic) 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 1/2 LLOQ (5.5%).
Abbreviations: LLOQ = lower limit of quantification; Max = maximum; Min = minimum; SE = standard error
Source: Table 14.7.3 of the CV185362 Final CSR[24]

).

Results for percent change from baseline of chromogenic FX assay across age groups (Figure 12) are consistent with those in the overall PD population (Figure 11).

Table 10. Summary Statistics for Chromogenic FX Assay (%) in Subjects Treated with Apixaban - PD Population

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)

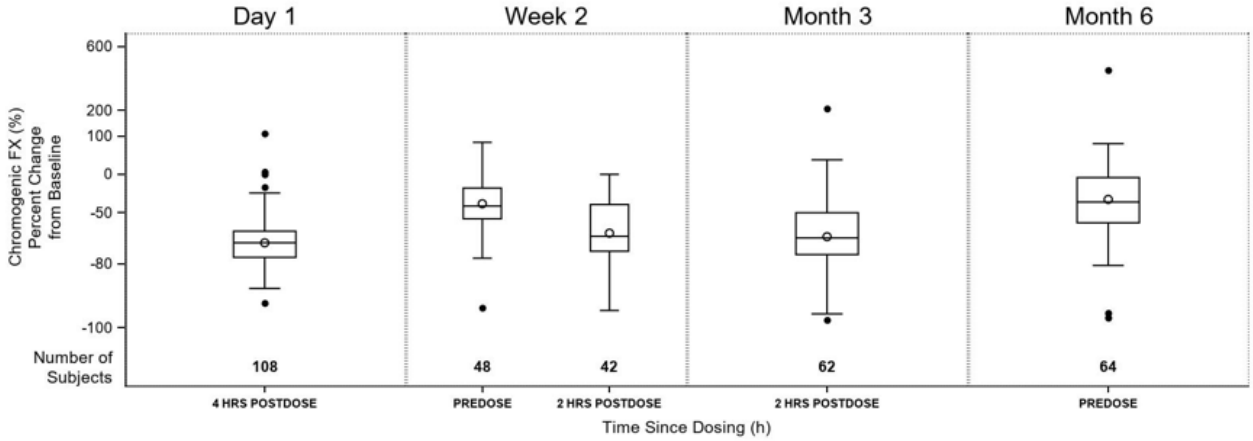
PD (pharmacodynamic) population included subjects who received at least one dose of apixaban and had chromogenic FX assay and/or anti-FXa samples collected.

Chromogenic FX <LLOQ (11%) pre-dose and post-dose was analyzed as 1/2 LLOQ (5.5%).

Abbreviations: LLOQ = lower limit of quantification; Max = maximum; Min = minimum; SE = standard error

Source: Table 14.7.3 of the CV185362 Final CSR[24]

Figure 11. Box and Whisker Plot of Chromogenic FX Assay (%) Percent Change from Baseline in Subjects Treated with Apixaban - PD Population



PD (pharmacodynamic) population included subjects who received at least one dose of apixaban and had chromogenic FX assay and/or anti-FXa samples collected.

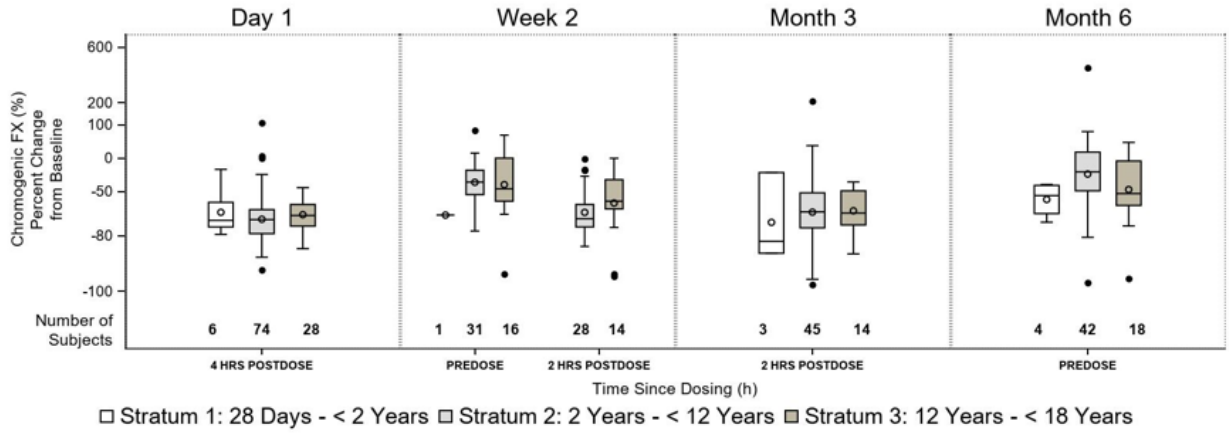
Chromogenic FX <LLOQ (11%) pre-dose and post-dose was analyzed as 1/2 LLOQ (5.5%).

Symbols: open circle = mean; solid circle = outlier; horizontal bar = median; vertical bar = range

Abbreviation: LLOQ = lower limit of quantification

Source: Figure 14.7.7 of the CV185362 Final CSR[24]

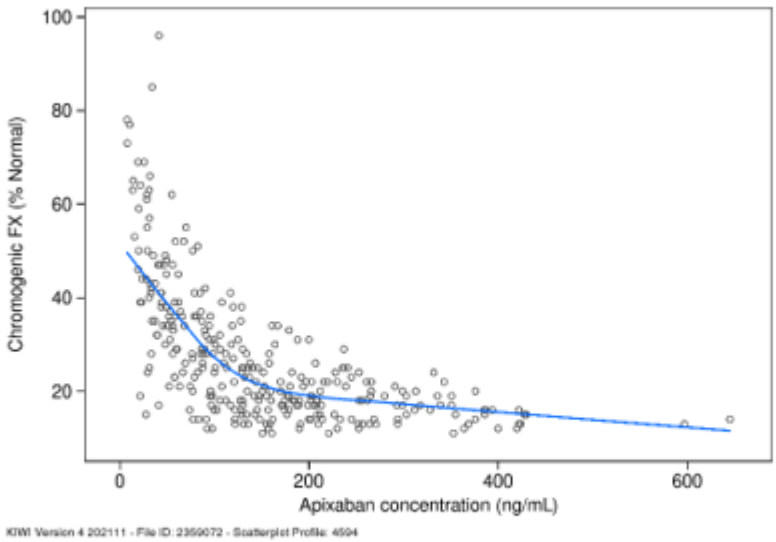
Figure 12. Box and Whisker Plot of Chromogenic FX Assay (%) Percent Change from Baseline in Subjects Treated with Apixaban by Age - PD Population



PD (pharmacodynamic) 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 1/2 LLOQ (5.5%).
Symbols: open circle = mean; solid circle = outlier; horizontal bar = median; vertical bar = range
Abbreviation: LLOQ = lower limit of quantification.
Source: Figure 14.7.8 of the CV185362 Final CSR[24]

A graphical assessment of the relationship between apixaban concentration and FX is shown in Figure 13. 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 13. Scatterplot of the Relationship Between Apixaban Concentration and Chromogenic FX (%) Overall, Linear Scale

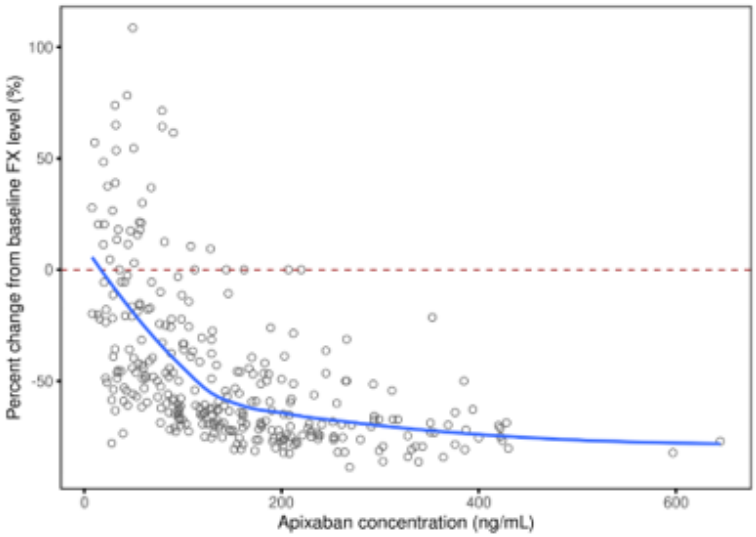


Abbreviation: FX = factor X.
Source: Figure 5.2.4-1 of the CV185362 Pharmacometric Analysis Report[23]

In Figure 14 the relationship between apixaban concentration and percent change from baseline in FX level is shown. The y-axis is truncated at a percent change of 100% for visualization purposes (2 data

points > 200% change). With increasing apixaban concentration, the percent reduction in FX level increases, suggesting inhibition of FXa.

Figure 14. Scatterplot of the Relationship Between Apixaban Concentration and Percent Change from Baseline in Chromogenic FX (%), Linear Scale



Abbreviation: FX = factor X.

Source: Figure 5.2.4-2 of the CV185362 Pharmacometric Analysis Report[23]

In Study **CV185362**, the exploratory biomarker evaluation is based on data from 182 subjects who had baseline and/or post-baseline biomarker data available (apixaban, n = 123; SOC n = 59). The biomarkers included D-dimer, factor VIII (FVIII), fibrinogen, protein C, protein S, and thrombin generation assay (TGA). Plasma samples were collected at 3 timepoints: Baseline (prior to the start of study medication), as well as 2 weeks and 6 months post start of study medication. Eighty-six (70%) patients randomized to apixaban were treated with VKA prior to study entry. Due to the extensiveness of the data and the consistency with the mechanism of action, these are not presented in detail in this report.

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.

For the purpose of clarity, a summary of the data on the exploratory biomarkers is presented, since providing a detailed report would not add relevant extra information.

D-dimer levels decreased in both apixaban and SOC groups at Month 6, although the changes from baseline in the apixaban subgroup with prior VKA treatment did not reach statistical significance.

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.

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.

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 reversible factor Xa (FXa) inhibitor.

6.4. Discussion

General

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 the prevention of stroke and systemic embolism in patients with NVAF and 1 or more risk factors (ARISTOTLE). PPK modeling was used to establish the steady-state median area under the concentration-time curve in one dosing interval (AUC[TAU]) in each of these adult populations; these values were then used to guide target AUCs in the apixaban paediatric studies.

Pharmacokinetic evaluation

For the paediatric population, a fixed-dose, body weight-based dosing was developed. 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. For the CV185362 study, the target AUC(TAU) of 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).

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 comparable to that observed in adults. A 2-compartment model with first-order absorption and dose-dependent bioavailability adequately described the plasma PK of apixaban in paediatric subjects across the different populations studied. Body weight was a predictor of apixaban CL/F and Vc/F in paediatric subjects. Apixaban CL/F and Vc/F increased with increasing body weight. Age was a statistically significant predictor of apixaban Q/F. Increase in age was associated with an increase in Apixaban Q/F. Apixaban Ka was higher in paediatric subjects aged 9 months to < 18 years across the different populations studied compared to adults. Upon inclusion of paediatric subjects with ALL or LL into the PPK analysis, these subjects were estimated to have a lower Ka of apixaban as compared to adults or paediatric subjects at risk of VTE. In addition, the inclusion of paediatric subjects with congenital or acquired heart disease into the PPK analysis indicated a lower apixaban CL/F in this patient population.

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 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 comparable to that observed in adults.

PK/PD evaluation

The relationship between anti-FXa and apixaban concentration was linear with an overall slope estimate of 0.0155 IU/ng with no apparent age-dependent differences in slope. In study CV185362 in paediatric subjects with congenital or acquired heart disease, chromogenic FX level decreased with increasing apixaban concentrations.

Coagulation biomarkers, including D-dimer, thrombin generation, FVIII, fibrinogen, protein C, and protein S were assessed. 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. The increases in ETP observed in the apixaban subgroup with prior VKA exposure can be explained by the lower ETP observed at baseline that likely resulted from the effects of prior VKA therapy, and the recovery of ETP values upon discontinuation of VKA, thereby offsetting the expected inhibitory effects of apixaban.

Overall, apixaban treatment was associated with a reduction in D-dimer levels in the subgroup without prior VKA exposure; apixaban treatment was also associated with reduction in *ex vivo* thrombin generation, prolongation of thrombin generation lag time and time to peak. These findings are consistent with the previously characterized mechanism of action of apixaban as a direct FXa inhibitor.

7. Clinical Efficacy aspects

Due to the differences in study design and population characteristics, an integrated analysis or comparison of the data from Studies CV185155 and CV185362 was not performed. Separate description and discussion of both studies CV185155 and CV185362 are provided below.

Study CV185155

7.1. Methods

Introduction

Study CV185155 is 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 with newly diagnosed ALL or LL (T or B cell) and a new CVAD inserted, treated with asparaginase.

Study participants

Inclusion criteria

Subjects aged 1 to < 18 years (weighing equal to or > 6 kg) with newly diagnosed ALL or lymphoblastic lymphoma (T or B cell) and a new CVAD inserted (including external tunneled CVAD, implantable ports,

and peripherally inserted central catheters (PICC), who were to undergo treatment with a SOC of 3- or 4-drug systemic induction chemotherapy regimen consisting of a corticosteroid, vincristine, and single or multiple dose asparaginase (with or without daunorubicin), were eligible to participate in the study.

Exclusion criteria

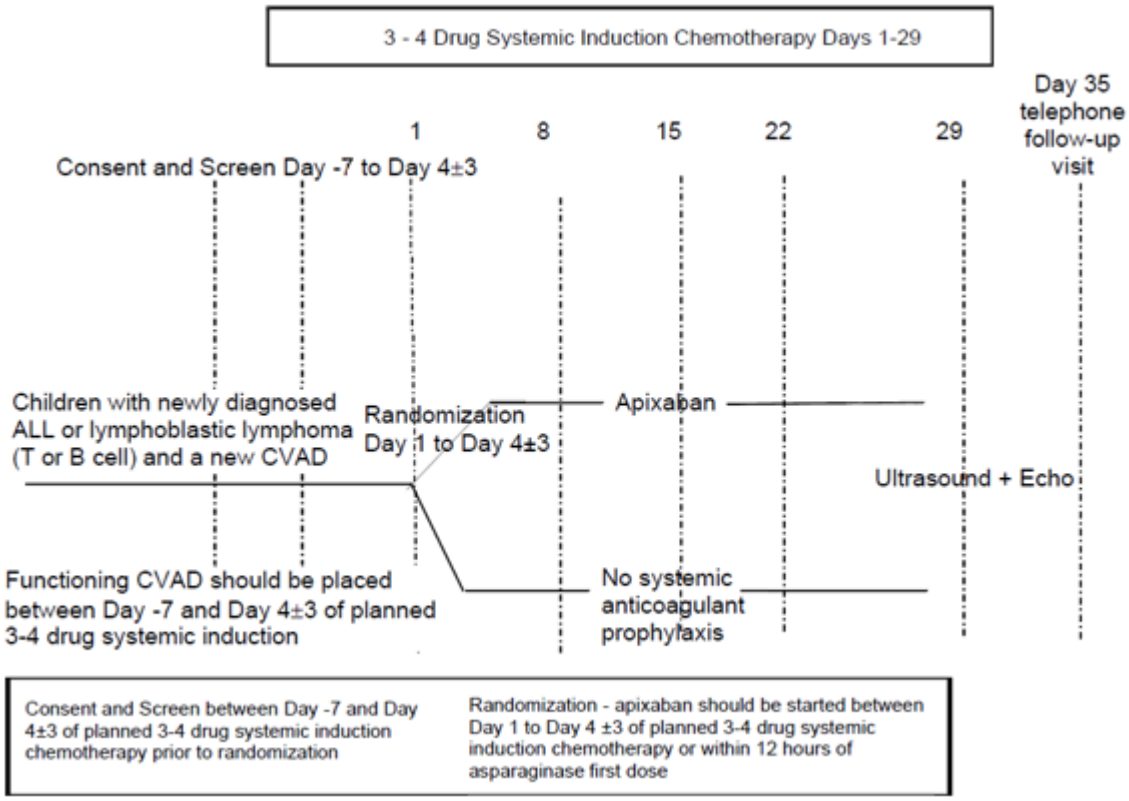
Exclusion criteria included central nervous system (CNS) stage 3, history of DVT or PE in the past three months, known inherited bleeding disorder or coagulopathy, major surgery within the last 30 days, uncontrolled severe hypertension, and laboratory test abnormalities (White blood cell count > 200 x 10^9/l, liver disfunction (ALT or AST > 5xULN or direct bilirubin >2xULN), renal function < 30% of normal, abnormal coagulation test for PT,PTT or INR, or platelet counts < 20.000/mm^3.

General study design

There are four study periods extending up to a maximum total of approximately five weeks in duration (Figure 15).

1. A Screening Period between day -7 to day 4 ±3 days of planned 3-4 drug systemic induction chemotherapy prior to randomization
2. A Randomization Period occurring between days 1 to 4±3 of planned 3-4 drug systemic induction chemotherapy
3. A Treatment Period, starting with the day of randomization, and extending through day 29 +/- 5 days of planned 3-4 drug systemic induction chemotherapy.
4. A Follow-Up period starting the day after the day 29 +/- 5 days visit.

Figure 15. Study design study CV185155



Dose Selection and Study treatment

The dose selection rationale for apixaban in this study was based on the results of the CV185118 study, which had the primary objective of assessing the PK of a single oral dose of apixaban in paediatric subjects (using an iterative PPK-modeling approach consistent with the steady state levels of exposure previously observed with an adult regimen of 2.5 mg BID).

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 (PG), a key solubilizing excipient in the formulation, was found to exceed the recommended maximum daily intake, as cited in a European Medicines Agency (EMA) draft report that was to be incorporated in an EMA guideline shortly thereafter.[v] To resume enrollment of paediatric subjects < 5 years of age, a new 0.5 mg mini-tablet was developed for use in subjects ³ 3 months of age. This tablet is relatively small, being ~3 mm in diameter, and the composition (drug-to-excipient ratio) and manufacturing process (up to compression) is identical to that for the approved adult 2.5 mg and 5 mg tablets. Therefore, the new 0.5 mg mini-tablets have the pharmaceutical characteristics of the tablets already approved for the adult population, but proportionally scaled to a lower strength for paediatric use.

Subjects randomized to apixaban were administered apixaban twice daily (BID) by mouth or via a nasogastric or gastric tube (NGT/GT) according to weight, during approximately 28 days of induction chemotherapy including asparaginase. The apixaban formulations used were the apixaban solution (0.4 mg/ml), 2.5 mg tablet or 0.5 mg mini-tablet administered by mouth of via an NGT or GT. The administered dosage of apixaban ranges from 0.5 to 2.5 mg twice daily, based on weight. Subjects in the control group did not receive systemic anticoagulant prophylaxis (standard-of-care).

Table 11. Apixaban Doses for Ages 1- <18 Years of Age

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

The previously communicated dosing for the body weight tier of 9 to < 12 kg has been redistributed into a 6 to < 10.5 kg weight tier and a 10.5 to < 18 kg weight tier.

Efficacy objectives and endpoints

The primary efficacy endpoint was a composite of non-fatal, asymptomatic and symptomatic DVT, PE, cerebral venous sinus thrombosis (CVST), and VTE related death designed to assess the study hypothesis that apixaban would reduce the incidence of VTE (Table 12). These endpoints are consistent with those recommended by the International Society on Thrombosis and Haemostasis (ISTH) for paediatric clinical trials.

All events reported as, or suspected to be, components of the primary efficacy endpoint were adjudicated by a blinded, independent adjudication committee (BIAC) to minimize investigator bias. Subjects with no symptomatic event and no ultrasound or echocardiogram assessment were counted as not having had an event.

On the last day of the treatment period (Day 29 ± 5 days), imaging studies were to be performed for all randomized subjects. These included a bilateral Doppler ultrasound for both the ipsilateral and the

contralateral sides relative to the site in the neck, thorax, or extremity at which the central venous access device (CVAD) was placed, and an echocardiogram to assess for right atrial thrombi. Doppler ultrasound from the ipsilateral side alone was acceptable if there were difficulties with the contralateral imaging. Doppler ultrasound and echocardiogram were to be performed in the apixaban arm within 3 days (not exceeding 5 days) after termination of the study medication (including early discontinuation) or in the SOC arm on Day 29±5.

Table 12. Summary of Efficacy Objectives and Associated Endpoints - CV185155

Objective	Endpoints
PRIMARY	
To compare the effect of prophylactic oral or enteric apixaban vs no systemic anticoagulant during ~28 days of induction chemotherapy including asparaginase on the composite endpoint of adjudicated non-fatal DVT (including symptomatic and asymptomatic), PE, and CVST; and VTE-related-death	Composite of BIAC adjudicated: • Non-fatal symptomatic DVT • Non-fatal asymptomatic DVT • PE • CVST • VTE-related death
SECONDARY	
To assess the effect of prophylactic apixaban vs no systemic anticoagulant during ~28 days of induction chemotherapy including asparaginase on single adjudicated endpoints of non-fatal DVT (including symptomatic and asymptomatic), PE, and CVST, and VTE-related-death	Single BIAC adjudicated: • Non-fatal symptomatic DVT • Non-fatal asymptomatic DVT • PE • CVST • VTE-related death
OTHER	
To assess the effect of prophylactic apixaban vs no systemic anticoagulant during ~28 days of induction chemotherapy including asparaginase on single adjudicated endpoints of all cause death; arterial thromboembolic events including paradoxical embolism and stroke and CVAD-related infection events	Single BIAC adjudicated: • All cause death • Arterial thromboembolic events (including paradoxical embolism and stroke) • CVAD-related infection events
To assess the effect of prophylactic oral or enteric apixaban vs no systemic anticoagulant during ~28 days of induction chemotherapy including asparaginase on single endpoints of number of catheter replacements needed during the study; superficial vein thrombosis, events of CVAD dysfunction with improvement after thrombolytic therapy; and number of platelet transfusions	• Number of catheter replacements needed • Superficial vein thrombosis • Events of CVAD dysfunction with improvement after thrombolytic therapy • Number of platelet transfusions

Abbreviations: BIAC = blinded, independent adjudication committee; CVAD = central venous access device; DVT = deep vein thrombosis; CVST = cerebral venous sinus thrombosis; PE = pulmonary embolism; VTE = venous thromboembolism.

Statistical Methodology

Sample size and power

A total of approximately 500 randomized subjects allocated with 1:1 ratio to the systemic thromboprophylaxis with apixaban (intervention) or no systemic anticoagulant prophylaxis (control) groups, would provide more than 80% power to demonstrate superiority at a one-sided 0.025 level, assuming the true event rates of primary endpoint (composite of non-fatal asymptomatic and symptomatic DVT, pulmonary embolism (PE), and CVST; and VTE-related-death) are 17% and 8.5% in the control and the apixaban groups, respectively.

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.

Efficacy Analysis

Efficacy endpoints were analyzed for randomized subjects based on events occurring during the Intended Treatment Period, defined as the time from the day of randomization through to the end of treatment period.

For all efficacy endpoints, event rate, 95% confidence interval (CI) for event rate, relative risk, and 95% CI for relative risk were calculated. The 95% CI for the relative risk was computed using the Cochran-Mantel-Haenszel method stratified by age group and the 95% CIs for single event rates were based on the Agresti-Coull method.

To conclude superiority of apixaban vs SOC on the primary efficacy endpoint during the Intended Treatment Period, the upper bound of the two-sided 95% CI for the relative risk (p_a/ p_e) must have been less than 1. This condition corresponds to a test of hypothesis H_0: $p_a = p_e$ against the alternative H_a: $p_a < p_e$ using the Cochran-Mantel-Haenszel test stratified by age group performed at the one-sided $\alpha = 0.025$ level. Here, p_a and p_e represent the proportions of subjects who met the primary efficacy endpoint in the apixaban and SOC arms, respectively.

Two-sided 95% CI for the relative risk (p_a/p_e) was reported for the primary efficacy endpoint. The p-value associated with the superiority test was calculated.

Two-sided 95% CIs for the relative risk (p_a/p_e) were reported for key secondary efficacy endpoints. The nominal p-values associated with the tests were also reported.

For efficacy subgroup analyses, Wald's chi-square test was used to determine whether treatment had a statistically significantly different ($p < 0.1$) effect on the event rate of an endpoint across subgroups based on a logistic model with terms for treatment, stratification variable age, subpopulation, and treatment by subpopulation interaction.

7.2. Efficacy Results

Disposition

Seventy four study centers in 10 countries enrolled 537 subjects, 512 (95.3%) of whom were randomized (256 subjects in each arm) (Table 13). One subject was randomized prior to providing informed consent. This subject was excluded from all analyses.

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. No subjects in either treatment arm discontinued treatment due to lack of efficacy. The study (including follow-up) was completed by 95.9% of subjects. The 1 subject in the SOC arm with a documented study discontinuation reason of "Administrative Reason by Sponsor" was found to be ineligible for the study following randomization, because the subject had an inherited coagulopathy (prothrombotic gene mutation).

Table 13. Subject Disposition - All Randomized Subjects - CV185155

Status (%)	Apixaban N = 256	SOC N = 256	Total N = 512
COMPLETED TREATMENT PERIOD	198 (77.3)	245 (95.7)	443 (86.5)
NOT COMPLETED TREATMENT PERIOD	58 (22.7)	11 (4.3)	69 (13.5)
REASON FOR NOT COMPLETING TREATMENT PERIOD			
LACK OF EFFICACY	0	0	0
ADVERSE EVENT	35 (13.7)	5 (2.0)	40 (7.8)
SUBJECT REQUEST TO DISCONTINUE STUDY TREATMENT	8 (3.1)	2 (0.8)	10 (2.0)
SUBJECT WITHDREW CONSENT	12 (4.7)	3 (1.2)	15 (2.9)
DEATH	0	0	0
LOST TO FOLLOW-UP	0	0	0
POOR/NON-COMPLIANCE	0	0	0
PREGNANCY	0	0	0
SUBJECT NO LONGER MEETS STUDY CRITERIA	2 (0.8)	1 (0.4)	3 (0.6)
ADMINISTRATIVE REASON BY SPONSOR	0	0	0
COVID-19 RELATED	0	0	0
OTHER	1 (0.4)	0	1 (0.2)
COMPLETED STUDY	242 (94.5)	249 (97.3)	491 (95.9)
NOT COMPLETED STUDY	14 (5.5)	7 (2.7)	21 (4.1)
REASON FOR NOT COMPLETING STUDY			
SUBJECT WITHDREW CONSENT	13 (5.1)	3 (1.2)	16 (3.1)
DEATH	1 (0.4)	2 (0.8)	3 (0.6)
LOST TO FOLLOW-UP	0	1 (0.4)	1 (0.2)
ADMINISTRATIVE REASON BY SPONSOR	0	1 (0.4)	1 (0.2)

Source: Table 14.1.3.2 of the CV185155 CSR[2]

Baseline characteristics

General

A total of 512 paediatric subjects were randomized to either the apixaban arm or the SOC arm in a 1:1 ratio. The baseline demographics were balanced between the apixaban and SOC arm in most categories, though a treatment allocation imbalance was observed between the apixaban and SOC arm (0.4% vs 2.7%) for the age categorization subgroup of 1 to < 2 years.

The baseline disease characteristics were balanced between the treatment arm. Per the inclusion criteria, all subjects had ALL (94.7%) or LL (5.3%) at baseline. Hematologic abnormalities were common including a large proportion of subjects (63.1%) with thrombocytopenia (platelet count ≤ 100,000 / mm^3). 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.

When comparing subjects across the prospectively defined, age-specific strata (subgroups of < 10 years of age [n = 358] and ≥ 10 to ≤ 18 years of age [n = 154]), baseline characteristics (other than age, height, and weight) were similar (see Section 5.3.1 of the CV185155 CSR).

Table 14. Demographic and baseline characteristics-CV185155

	Apixaban N = 256	Standard of Care N = 256	Total N = 512
AGE (YEARS)			
N	256	256	512
MEAN	7.2	7.1	7.2
MEDIAN	6.0	6.0	6.0
MIN , MAX	1, 18	1, 17	1, 18
SD	4.34	4.39	4.36
AGE CATEGORIZATION (%)			
1 - < 2 YEARS	1 (0.4)	7 (2.7)	8 (1.6)
2 - < 6 YEARS	119 (46.5)	109 (42.6)	228 (44.5)
6 - < 12 YEARS	87 (34.0)	83 (32.4)	170 (33.2)
12 - <= 18 YEARS	49 (19.1)	57 (22.3)	106 (20.7)
ALL RISK CATEGORIZATION			
STANDARD RISK (A)	168 (65.6)	171 (66.8)	339 (66.2)
HIGH RISK (B)	81 (31.6)	79 (30.9)	160 (31.3)
SEX (%)			
MALE	141 (55.1)	149 (58.2)	290 (56.6)
FEMALE	115 (44.9)	107 (41.8)	222 (43.4)
RACE (%)			
WHITE	194 (75.8)	194 (75.8)	388 (75.8)
BLACK OR AFRICAN AMERICAN	12 (4.7)	12 (4.7)	24 (4.7)
ASIAN	25 (9.8)	27 (10.5)	52 (10.2)
AMERICAN INDIAN OR ALASKA NATIVE	1 (0.4)	1 (0.4)	2 (0.4)
NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER	1 (0.4)	0	1 (0.2)
OTHER	23 (9.0)	22 (8.6)	45 (8.8)
ETHNICITY (%)			
HISPANIC OR LATINO	59 (23.0)	63 (24.6)	122 (23.8)
NOT HISPANIC OR LATINO	196 (76.6)	192 (75.0)	388 (75.8)
NOT REPORTED	1 (0.4)	1 (0.4)	2 (0.4)
COUNTRY BY GEOGRAPHIC REGION (%)			
NORTH AMERICA	199 (77.7)	203 (79.3)	402 (78.5)
CANADA	8 (3.1)	8 (3.1)	16 (3.1)
UNITED STATES	191 (74.6)	195 (76.2)	386 (75.4)
LATIN AMERICA	3 (1.2)	3 (1.2)	6 (1.2)
MEXICO	3 (1.2)	3 (1.2)	6 (1.2)
ASIA/PACIFIC	17 (6.6)	17 (6.6)	34 (6.6)
KOREA, REPUBLIC OF	17 (6.6)	17 (6.6)	34 (6.6)
EUROPE	31 (12.1)	27 (10.5)	58 (11.3)
BELGIUM	10 (3.9)	8 (3.1)	18 (3.5)
CZECH REPUBLIC	1 (0.4)	0	1 (0.2)
HUNGARY	7 (2.7)	5 (2.0)	12 (2.3)
POLAND	0	1 (0.4)	1 (0.2)
RUSSIA	13 (5.1)	13 (5.1)	26 (5.1)
ROW	6 (2.3)	6 (2.3)	12 (2.3)
AUSTRALIA	6 (2.3)	6 (2.3)	12 (2.3)
HEIGHT (CM)			
N	254	253	507
MEAN	125.94	124.90	125.42
MEDIAN	120.35	119.80	120.00
MIN , MAX	85.0, 190.0	79.5, 192.2	79.5, 192.2
SD	27.074	26.785	26.909
WEIGHT (KG)			
N	255	254	509
MEAN	32.26	31.46	31.86
MEDIAN	22.90	23.60	23.00
MIN , MAX	11.5, 120.6	10.5, 112.0	10.5, 120.6
SD	21.958	20.971	21.454
WEIGHT GROUP			
< 35 KG	176 (68.8)	175 (68.4)	351 (68.6)
>= 35 KG	79 (30.9)	79 (30.9)	158 (30.9)
NOT REPORTED	1 (0.4)	2 (0.8)	3 (0.6)

Abbreviations: MAX, maximum; MIN, minimum; ROW, rest of world; SD, standard deviation.
The denominator to calculate each percentage is the total number of randomized subjects in the treatment group(s).
(A) WBC count less than 50,000/Microliters and age 1 to younger than 10 years
(B) WBC count 50,000/Microliters or greater and/or age 10 years or older
Source: Table 14.2.1, Table 14.2.3, Table 14.5.4.1 (ALL risk categorization)

Table 15. Baseline disease characteristics-CV185155

	Apixaban N = 256	Standard of Care N = 256	Total N = 512
PLATELET COUNT			
0 - <20,000/MM3	16 (6.3)	13 (5.1)	29 (5.7)
20,000 - <= 100,000 /MM3	158 (61.7)	136 (53.1)	294 (57.4)
VITAL SIGNS SBP (MMHG)			
N	253	255	508
MEAN	108.2	109.7	109.0
MEDIAN	108.0	109.0	108.0
MIN , MAX	80, 142	78, 158	78, 158
SD	11.02	11.89	11.48
VITAL SIGNS DBP (MMHG)			
N	253	255	508
MEAN	65.7	65.6	65.7
MEDIAN	65.0	66.0	65.0
MIN , MAX	41, 95	41, 96	41, 96
SD	10.15	10.19	10.16
VITAL SIGNS HR (BEATS/MINS)			
N	252	255	507
MEAN	87.9	88.1	88.0
MEDIAN	86.5	85.0	86.0
MIN , MAX	52, 145	50, 158	50, 158
SD	18.47	21.64	20.11
LEVEL OF RENAL IMPAIRMENT:			
SEVERE	0	0	0
MODERATE	1 (0.4)	2 (0.8)	3 (0.6)
MILD	31 (12.1)	24 (9.4)	55 (10.7)
NORMAL	216 (84.4)	213 (83.2)	429 (83.8)
NOT REPORTED	8 (3.1)	17 (6.6)	25 (4.9)

The denominator to calculate each percentage is the total number of randomized subjects in the treatment group(s).
Calculated eGFR is used to define renal function as Normal: >=90 mL/min/1.73m2; Mild: 60-90 mL/min/1.73m2; Moderate: 30-59 mL/min/1.73m2; and Severe: =<29 mL/min/1.73m2. eGFR is calculated according to the Schwartz formula.

Source: Table 14.2.3

Table 16. Baseline Disease characteristics (Post-hoc analysis)-CV185155

	Apixaban N = 256	Standard of Care N = 256	Total N = 512
DIAGNOSIS (%)			
ALL	243 (94.9)	242 (94.5)	485 (94.7)
T-CELL	20 (7.8)	18 (7.0)	38 (7.4)
B-PRECURSOR	220 (85.9)	221 (86.3)	441 (86.1)
OTHER	3 (1.2)	3 (1.2)	6 (1.2)
LYMPHOBLASTIC LYMPHOMA	13 (5.1)	14 (5.5)	27 (5.3)
T-CELL	9 (3.5)	9 (3.5)	18 (3.5)
B-PRECURSOR	4 (1.6)	5 (2.0)	9 (1.8)
OTHER	0	0	0
SUBTYPE (%)			
T-CELL	29 (11.3)	27 (10.5)	56 (10.9)
B-PRECURSOR	224 (87.5)	226 (88.3)	450 (87.9)
OTHER	3 (1.2)	3 (1.2)	6 (1.2)
CNS RISK (%)			
CNS1	240 (93.8)	245 (95.7)	485 (94.7)
CNS2	15 (5.9)	11 (4.3)	26 (5.1)
NOT REPORTED	1 (0.4)	0	1 (0.2)
PRESENCE OF MEDIASTINAL MASS AT DIAGNOSIS (%)			
YES	19 (7.4)	16 (6.3)	35 (6.8)
NO	236 (92.2)	237 (92.6)	473 (92.4)
NOT REPORTED	1 (0.4)	3 (1.2)	4 (0.8)
WBC COUNT (%)			
<50X10*3/uL	242 (94.5)	240 (93.8)	482 (94.1)
>=50X10*3/uL	6 (2.3)	3 (1.2)	9 (1.8)
NOT REPORTED	8 (3.1)	13 (5.1)	21 (4.1)

The denominator to calculate each percentage is the total number of randomized subjects in the treatment group(s).

Source: Table 14.2.5

Exposure and concomitant therapy

In the 512 subjects that were randomized, exposure to assigned treatment was ~47 years (2463 patient-weeks), with 22.5 years (1173.3 patient-weeks) having been for exposure to treatment with apixaban. Subjects were in the study for a mean (SD) of 32.1 days (7.57) and 35.3 days (23.26) in the apixaban and SOC arms, respectively.

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). The mean (SD) extent of exposure was similar between the prospectively defined, age-specific strata in the apixaban arm (< 10 years of age [n = 179] and ≥ 10 to ≤ 18 years of age [n = 77]): 23.6 days (6.25) and 23.4 days (6.31), respectively.

Subjects were treated with induction chemotherapy for a mean (SD) of 26.8 days (7.20) and 29.1 days (3.78) in the apixaban and SOC arms, respectively.

Treatment Compliance

In the study, 190/256 (76.0%) subjects in the apixaban arm received between 80% and 120% of scheduled doses of apixaban. 60 subjects (24.0%) in the apixaban arm took < 80% of scheduled doses and none took > 120%, reflecting treatment interruptions including those that subsequently became permanent after an initial delay. Compliance rates were similar between the age strata in the apixaban arm.

Concomitant Therapy

Chemotherapy

Five hundred ten subjects were treated with asparaginase (L asparaginase or PEG L asparaginase) as part of induction chemotherapy. Vincristine was also received as part of induction chemotherapy by all subjects in the apixaban arm, and by all but one subject (99.6%) in the SOC arm. Daunorubicin (optional

per protocol) was also part of induction chemotherapy in 133 subjects (52.0%) and 125 subjects (48.8%) in the apixaban and SOC arms, respectively.

Additional chemotherapy, administered per local SOC, included Cyclophosphamide (n= 42 ; 8.2%), Cytarabine (n= 325 ; 63.5%), Mercaptopurine (n=60 ; 11.7%), and Methotrexate (n=430 ; 84.0%)/

Non chemotherapy

Five hundred eight subjects (99.2%) received at least one concomitant medication other than apixaban.

Systemic corticosteroids were administered to 138 subjects (53.9%) and 145 subjects (56.6%) in the apixaban and SOC arms, respectively.

Anti-thrombotic agents other than apixaban were administered to 84 subjects (32.8%) and 90 subjects (35.2%) in the apixaban and SOC arms, respectively. The agent most frequently administered was heparin (often used after completion of any infusion or blood sampling, at least once every 24 hours, via peripherally inserted central catheter (PICC) lines or small-bore central line catheters), to 68 subjects (26.6%) and 64 subjects (25.0%) in the apixaban and SOC arms, respectively. Alteplase (usually used to clear obstructed catheters) was administered to 8 subjects (3.1%) and 20 subjects (7.8%) in the apixaban and SOC arms, respectively. Enoxaparin was administered to 9 subjects (3.5%) and 14 subjects (5.5%) in the apixaban and SOC arms, respectively. With the exception of 1 subject (0.4%) in the SOC arm who received rivaroxaban, no FXa inhibitors other than apixaban were administered. All other individual anti-thrombotic agents were administered to < 1% of subjects.

Primary Efficacy Endpoint

Analysis of the primary efficacy endpoint (a composite of non-fatal [asymptomatic or symptomatic] DVT, PE, and CVST; and VTE related death, all objectively confirmed by BIAC) showed a 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 at the one-sided 0.025/2-sided 0.05 level (one-sided p = 0.04/two-sided p = 0.08) (Table 17).

Secondary Efficacy Endpoints

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 (Table 17).

There were no adjudicated events of non-fatal PE or VTE-related death in either arm. There were no subjects with adjudicated CVST events in the apixaban arm and 1 such subject (0.39%) with an event in the SOC arm.

The relative risk of adjudicated non-fatal asymptomatic DVT was 0.71 (95% CI: 0.45 to 1.13; two-sided p = 0.1427), with events in 27 subjects (10.55% [95% CI: 7.31% to 14.95%]) and 38 subjects (14.84% [95% CI: 10.98% to 19.75%]) in the apixaban and SOC arms, respectively.

The relative risk of adjudicated non-fatal symptomatic DVT was 0.67 (95% CI: 0.19 to 2.33; two-sided p = 0.5237), with events in 4 subjects (1.56% [95% CI: 0.46% to 4.09%]) and 6 subjects (2.34% [95% CI: 0.96% to 5.14%]) in the apixaban and SOC arms, respectively.

Other Efficacy Endpoints

Adjudicated all-cause death occurred in 1 subject (0.4%) and 3 subjects (1.2%) within 30 days of the Treatment Period in the apixaban and SOC arms, respectively.

There were no adjudicated arterial thromboembolic events in either arm.

Adjudicated CVAD-related infection occurred in 1 subject (0.39%) and 6 subjects (2.34%) in the apixaban and SOC arms, respectively.

Adjudicated CVAD-related infection occurred in 1 subject (0.39%) and 6 subjects (2.34%) in the apixaban and SOC arms, respectively

Catheter replacements were needed in 3 subjects (1.17%) and 2 subjects (0.78%) in the apixaban and SOC arms, respectively

No events of CVAD patency restoration after thrombolytic therapy were reported in either treatment arm. 11 (4.3%) subjects in the apixaban arm and 22 (8.6%) subjects in the SOC arm received thromboembolic agents .

Superficial vein thrombosis occurred in 4 subjects (1.56%) and 2 subjects (0.78%) in the apixaban and SOC arms, respectively

Table 17. Efficacy Summary – All Randomized Subjects – CV185155

Endpoint	Apixaban arm N = 256	SOC arm N = 256
Primary Composite Efficacy Endpoint		
Composite of Non-fatal DVT (including asymptomatic and symptomatic), PE, and CVST; and VTE-related Death Objectively Confirmed by Independent Adjudication		
Event Rate, n (%)	31 (12.11)	45 (17.58)
(95% CI)	(8.63, 16.71)	(13.38, 22.73)
Relative Risk (apixaban/SOC)	0.69	
(95% CI)	(0.45, 1.05)	
One-sided p-value for superiority test	0.0403	
Secondary Efficacy Endpoints		
Non-fatal asymptomatic DVT		
Event Rate, n (%)	27 (10.55)	38 (14.84)
(95% CI)	(7.31, 14.95)	(10.98, 19.75)
Non-fatal symptomatic DVT		
Event Rate, n (%)	4 (1.56)	6 (2.34)
(95% CI)	(0.46, 4.09)	(0.96, 5.14)
Relative Risk (apixaban/SOC)	0.67	
(95% CI)	(0.19, 2.33)	
Two-sided nominal p-value	0.5237	
Non-fatal PE		
Event Rate, n (%)	0	0
(95% CI)	(0, 1.78)	(0, 1.78)
Relative Risk (apixaban/SOC)	NE	
(95% CI)	NE	
Two-sided nominal p-value	NE	
Non-fatal CVST		
Event Rate, n (%)	0	1 (0.39)
(95% CI)	(0, 1.78)	(0, 2.41)
Relative Risk (apixaban/SOC)	0	
(95% CI)	(NE, NE)	
Two-sided nominal p-value	0.3173	
VTE-related Death		
Event Rate, n (%)	0	0
(95% CI)	(0, 1.78)	(0, 1.78)
Relative Risk (apixaban/SOC)	NE	
(95% CI)	NE	
Two-sided nominal p-value	NE	
Other Efficacy Endpoints		
Adjudicated All Cause Death		
Event Rate, n (%)	1 (0.39)	2 (0.78)
(95% CI)	(0, 2.41)	(0.03, 2.99)
Relative Risk (apixaban/SOC)	0.50	
(95% CI)	(0.05, 5.51)	
Two-sided nominal p-value	1.0000	
Arterial Thromboembolic Events		
Event Rate, n (%)	0	0
(95% CI)	(0, 1.78)	(0, 1.78)
Relative Risk (apixaban/SOC)	NE	
(95% CI)	NE	
Two-sided nominal p-value	NE	
CVAD-related Infection		
Event Rate, n (%)	1 (0.39)	6 (2.34)
(95%)	(0, 2.41)	(0.96, 5.14)
Relative Risk (apixaban/SOC)	0.17	
(95% CI)	(0.02, 1.38)	
Two-sided nominal p-value	0.1224	

Number of Catheter Replacements Needed		
Event Rate, n (%)	3 (1.17)	2 (0.78)
(95% CI)	(0.24, 3.55)	(0.03, 2.99)
Events of CVAD Patency Restoration after Thrombolytic Therapy		
Event Rate, n (%)	0	0
(95% CI)	(0, 1.78)	(0, 1.78)
Superficial Vein Thrombosis		
Event Rate, n (%)	4 (1.56)	2 (0.78)
(95% CI)	(0.46, 4.09)	(0.03, 2.99)

Adjudicated symptomatic events are included during the Intended Treatment Period.

Asymptomatic events are included from scans up to Day 40.

Abbreviations: CI = confidence interval; CVAD = central venous access device; CVST = cerebral venous sinus thrombosis; DVT = deep vein thrombosis; NE = not evaluable; PE = pulmonary embolism; SOC = standard of care; VTE = venous thromboembolism.

Source: Table 7.1-1 of the CV185155 CSR[2]

Sensitivity Analysis

The primary endpoint included a composite of symptomatic events and asymptomatic events detected using diagnostic imaging modalities. Subjects with no symptomatic event but no ultrasound or echocardiogram assessment results were treated as having missing data.

In the primary efficacy endpoint analysis, randomized subjects with missing data were prospectively defined as those not having had an event. Results of the sensitivity analyses based on alternate assumptions (in randomized subjects who either had an adjudicated event or had evaluable end of study imaging evaluations, including results from scans up to Day 40 (mITT population) or including the randomized population except those subjects with a protocol deviation that was deemed relevant for affecting the primary efficacy endpoint (the Evaluable population)), were consistent with those of the primary analysis (Table 18).

The primary efficacy endpoint analysis was performed in randomized subjects based on events occurring during the Intended Treatment Period, defined as the day of randomization through the Day 29 visit. Because VTE develops gradually, two hypothesis-generating post-hoc analyses were performed that included events from the composite primary efficacy endpoint reported up to 5 days after the Intended Treatment Period and 34 days after randomization. Up to 5 days after the Intended Treatment Period, the adjudicated composite primary efficacy endpoint event increased by 2 in the apixaban arm and 3 in the SOC arm: 33 subjects (12.89%, 95% CI: 9.29, 17.59) vs 48 subjects (18.75%, 95% CI: 14.42, 24.00), respectively (relative risk = 0.69 [95% CI 0.46, 1.03]; one-sided p = 0.0341. Up to 34 days after randomization, the adjudicated composite primary efficacy endpoint event increased by 3 in each arm: 34 subjects (13.28%, 95% CI: 9.63, 18.02) vs 48 subjects (18.75%, 95% CI: 14.42, 24.00) in the apixaban and SOC arms, respectively (relative risk = 0.71 [95% CI 0.47, 1.06]; one-sided p = 0.0452).

Table 18. Sensitivity analysis of adjudicated primary efficacy endpoint during the intended treatment period – all randomized subjects.

	Apixaban	Standard of Care
mITT Population	N = 219	N = 219
NON-FATAL ASYMPTOMATIC DVT/ NON-FATAL SYMPTOMATIC DVT/PE/CVST/VTE-RELATED DEATH , N	31	45
EVENT RATE (%)	14.16	20.55
95% CI FOR EVENT RATE	(10.11, 19.43)	(15.70, 26.41)
RELATIVE RISK	0.69	
95% CI FOR RELATIVE RISK	(0.45, 1.04)	
ONE-SIDED P-VALUE FOR - SUPERIORITY TEST ON RR*	0.0373	
Evaluable Population	N = 224	N = 246
NON-FATAL ASYMPTOMATIC DVT/ NON-FATAL SYMPTOMATIC DVT/PE/CVST/VTE-RELATED DEATH , N	28	42
EVENT RATE (%)	12.50	17.07
95% CI FOR EVENT RATE	(8.75, 17.52)	(12.86, 22.30)
RELATIVE RISK	0.73	
95% CI FOR RELATIVE RISK	(0.47, 1.14)	
ONE-SIDED P-VALUE FOR - SUPERIORITY TEST ON RR*	0.0801	

The mITT population included randomized subjects who have either an adjudicated event making-up the primary efficacy endpoint or evaluable end of study imaging evaluations, including ultrasound and echocardiogram. Symptomatic events are included during the Intended Treatment Period. Asymptomatic events were included from scans up to Day 40.

Evaluable population included the randomized population, except those subjects with relevant protocol deviations expected to affect the primary efficacy endpoint.

*denotes the result was statistically significant at the one-sided 0.025 level.

Subgroup Analyses for the Primary Endpoint

Pre-specified subgroup analyses showed that the numerically lower incidence of events in the apixaban arm vs the SOC arm appeared to be attributable to results in the subset of obese subjects (Table 14.5.4.1 and Section 7.2 of the CV185155 CSR). In the obese subgroup (n = 82), defined as subjects in the ≥ 95th percentile of their age- and sex-specific body mass index (BMI), 1/42 subjects (2.4%) and 10/40 subjects (25.0%) in the apixaban and SOC arms, respectively, experienced a primary efficacy event (nominal two-sided p = 0.0037). In the non-obese subgroup (N = 416), 30/210 subjects (14.3%) and 34/206 subjects (16.5%) in the apixaban and SOC arms, respectively, experienced a primary efficacy event (nominal two-sided p = 0.5136). The treatment-subgroup interaction p-value was 0.0307.

Other pre-specified subgroup analyses had trends similar to that of the primary efficacy analysis: geographic region (continent), alternative age category (ages 1 to < 2, 2 to < 6, 6 to < 12, 12 to < 18), ethnicity, gender, race, weight (< 35 kg or ≥ 35 kg), ALL risk category (high risk subjects: either those aged ≥ 10 years or white blood cell count ≥ 50,000/mm^3, or standard risk for all other subjects), and type of central line used (peripherally inserted central catheter, any tunneled vascular access that included an implanted port or other implanted device, or other line) (Table 14.5.4.1 and Section 7.2 of the CV185155 CSR).

Imaging

Ultrasound assessments were available for 456 subjects (89.1%) and missing for 56 (10.9%) (Table 19). The most common reasons an ultrasound assessment was missing was either a prior withdrawal of consent for further study participation or parent/patient refusal, which occurred in 21/56 subjects. Echocardiogram results were available for 466 subjects (91.0%) and missing (required assessments were not available) for 46 subjects (9.0%). Again, the most common reasons why an echocardiogram assessment was missing was refusal by the subject or subject's guardian, which occurred in 18/46 subjects (39.1%): 10 subjects and 8 subjects in the apixaban and SOC arms, respectively.

Subjects with no symptomatic event and no ultrasound or echocardiogram assessment are considered as having missing data and were removed from the modified ITT (mITT) analysis. Overall, 219 (85.5%) in each arm were included in the mITT analysis.

Table 19. Imaging Status Summary – All randomized Subjects

	ULTRASOUND			ECHOCARDIOGRAM		
Status (%)	Apixaban N = 256	Standard of Care N = 256	Total N = 512	Apixaban N = 256	Standard of Care N = 256	Total N = 512
PERFORMED	230 (89.8)	226 (88.3)	456 (89.1)	230 (89.8)	236 (92.2)	466 (91.0)
NOT PERFORMED	26 (10.2)	30 (11.7)	56 (10.9)	26 (10.2)	20 (7.8)	46 (9.0)
REASONS NOT PERFORMED						
ADMINISTRATIVE REASON BY SPONSOR	0	1 (0.4)	1 (0.2)	0	1 (0.4)	1 (0.2)
CHILD UNABLE TO LIE STILL	3 (1.2)	3 (1.2)	6 (1.2)	2 (0.8)	0	2 (0.4)
DEATH	0	1 (0.4)	1 (0.2)	0	1 (0.4)	1 (0.2)
INVESTIGATOR DECISION	2 (0.8)	1 (0.4)	3 (0.6)	3 (1.2)	1 (0.4)	4 (0.8)
PARENT REFUSED	4 (1.6)	5 (2.0)	9 (1.8)	4 (1.6)	3 (1.2)	7 (1.4)
PROCEDURE PERFORMED OUT OF ASSESSMENT WINDOW	4 (1.6)	7 (2.7)	11 (2.1)	3 (1.2)	6 (2.3)	9 (1.8)
SUBJECT MISSED APPOINTMENT	0	6 (2.3)	6 (1.2)	1 (0.4)	1 (0.4)	2 (0.4)
SUBJECT REFUSED	6 (2.3)	2 (0.8)	8 (1.6)	5 (2.0)	2 (0.8)	7 (1.4)
SUBJECT WITHDREW CONSENT	4 (1.6)	0	4 (0.8)	4 (1.6)	0	4 (0.8)
TECHNICAL REASONS	0	0	0	0	1 (0.4)	1 (0.2)
OTHER	2 (0.8)	4 (1.6)	6 (1.2)	3 (1.2)	4 (1.6)	7 (1.4)
UNKNOWN	1 (0.4)	0	1 (0.2)	1 (0.4)	0	1 (0.2)

Source: Table 7.2-2 of the CV185155 CSR**Error! Bookmark not defined.**

Investigator-assessed Primary Endpoint

Analysis of the composite primary efficacy endpoint of non-fatal (symptomatic and asymptomatic) DVT, PE, CVST, and VTE-related death events, as assessed by the investigator, showed a lower incidence in the apixaban arm compared with the SOC arm, with events in 23 subjects (8.98%) and 38 subjects (14.84%), respectively (nominal one-sided p = 0.021/nominal two-sided p = 0.041) (Table 14.5.1.1a of the CV185155 CSR).

7.3. Discussion

Study CV158155 was a phase 3 randomized, open-label, multi-center trial, to evaluate the efficacy and safety of apixaban compared to no prophylactic anticoagulation (the current standard of care) in pediatric patients with acute lymphoblastic lymphoma (ALL) or lymphoblastic lymphomas (T or B cell) (LL) aged 1 up to 18 with a CVAD (central vein access device) who were undergoing induction chemotherapy with regimens that included asparaginase, to evaluate whether prophylaxis with apixaban during induction chemotherapy could reduce the risk of VTE.

The study included 512 patients with a mean age of 7 years (range 1-18 years), although the number of patients in the 1 to 2 years age range were underrepresented and imbalanced (8 patients; 1 in the apixaban group). Other baseline characteristics were generally reasonably well balanced. A large proportion of patients completed the study (95%), although a larger proportion discontinued treatment

(22.7% vs 4.3%) despite the short-term treatment period, which may indicate a general poor tolerability and/or treatment burden distinct from the underlying treatment burden.

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 (27 vs 38). From the data provided, it is not clear as to whether the numerical reduction of asymptomatic DVT only concerns CVAD-related thrombi. No data are provided on the location of the thrombi, especially in relation to the position of the CVAD, as well as on the severity, treatment required and clinical outcome of DVT events. The applicant is asked to provide these data (**OC)**.

Any of the other single components of the primary endpoint were very limited and could also not show any significant improvement for apixaban. Further, additional sensitivity analyses to evaluate the impact of missing data (15% missing imaging data in each arm), were generally consistent with the primary endpoint analysis. The results of pre-specified subgroup analyses were consistent with the primary efficacy findings for the overall population. Although, some increased efficacy could be observed in the obese subpopulation (n=82), but such data should be taken with caution due to multiplicity considerations, the relatively small subgroup and lack of any obvious explanation for such increased efficacy. 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.

Despite that such patients have a risk of thrombo-embolic events, current literature does not provide a clear recommendation for the short-term use of (systemic) anticoagulation in this specific setting. This may be associated with the lack of high quality data demonstrating a clear beneficial effect for this specific setting, as such, there is no anticoagulation therapy formally approved for this population. Therefore, in a clinical setting where preventive anticoagulating treatment is not common practice, it is agreed that any indication can only be poorly justified. In particular, in the context of absence of a clear efficacy benefit, despite that it may be anticipated based on the mechanism of action. Moreover, such data are also not clearly supported by adult data. Apixaban has also been studied in adult patients with cancer at intermediate to high risk for VTE and showed a reduction in VTE, however, at the cost of an increase in major bleeding. Any indication for this setting has not been (explicitly) approved for adults either. Also, any comparison or extrapolation of adult findings to current study findings appears difficult due to e.g. differences in the risk profile of VTE, treatment period, oncology treatment differences, possible localization of VTE events specific for the paediatric and treatment setting that included the insertion of a CVAD, amongst others, which further limits any possibility for considering any indication.

Study CV185362

7.4. Methods

Introduction

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.

Study participants

Inclusion criteria

Subjects eligible for the study included male and female children, 28 days to <18 years of age and weighing ≥3kg, with congenital or acquired heart disease who were at risk for clot formation that could result in vascular, intracardiac or coronary artery thrombosis, or embolization to other organs or tissues, and who required chronic anticoagulation for thromboprophylaxis as determined by the treating physician based on the major current guidelines (e.g. American College of Chest Physicians [ACCP] 2012 guideline). To be eligible for the study, subjects <2 years of age at the time of randomization were expected to require anticoagulation for a minimum of 1 month; whereas subjects ≥2 years of age were expected to require anticoagulation for a minimum of 6 months, although the full treatment duration of 12 months was most desirable. Eligible subjects included those who newly started anticoagulants and those who were currently on VKA or LMWH for thromboprophylaxis.

Exclusion criteria

Subjects were excluded if they had any thromboembolic event <6 months prior to enrolment, a known inherited bleeding disorder or coagulopathy, liver, renal, or platelet laboratory abnormalities. Subjects with a previous history of thromboembolic events >6 months prior to enrolment were eligible, provided there was evidence (by previously obtained clinical imaging data) for thrombus stability or resolution.

General study design

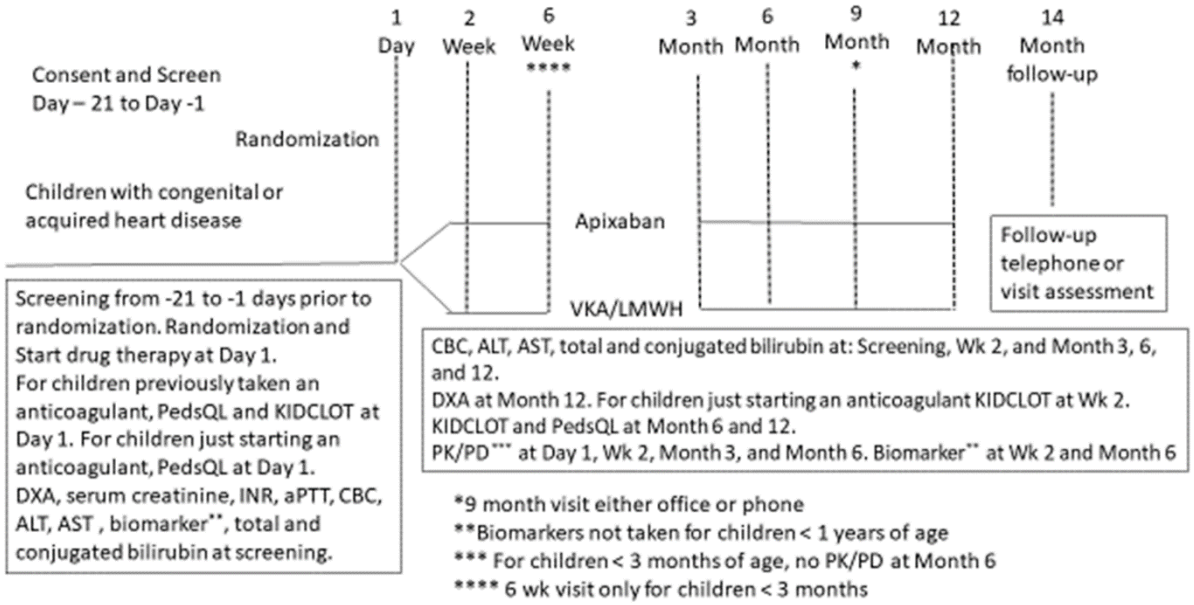
There were 3 study periods extending up to 14 months total (Figure 16):

Screening / Randomization Period (day -21 to day 1)

Treatment Period (day 1 to month 12 or until anticoagulation was no longer needed): The fixed-dose by weight-tier apixaban regimen was administered BID. VKA and LMWH were administered as per local SOC.

Follow-up Period (month 12 to month 14 ± 2 weeks or 2 months ± 2 weeks following cessation of study drug if duration of therapy was less than 12 months)

Figure 16. schematic study design of study CV185362



Abbreviations: ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; CBC = complete blood count; DXA = dual energy X-ray absorptiometry; INR = international normalized ratio; KIDCLOT = Kids Informed Decrease Complications Learning on Thrombosis; LMWH = low molecular weight heparin; PD = pharmacodynamics; PedsQL = Pediatric Quality of Life Inventory; PK = pharmacokinetics; VKA = vitamin K antagonist; Wk = week

Dose selection and study treatment

The dose selection rationale for apixaban in this study was the same as that used for Study CV185155.

Subjects randomized to apixaban received apixaban twice daily, orally, by a fixed-dose weight-tiered regimen. The SOC (VKA or LMWH was dosed per local SOC aligned with the current ACCP guidelines.

The apixaban formulations used were the apixaban solution (0.4 mg/ml), 5 mg tablet, 0.5 mg mini-tablet, or 0.1 mg sprinkle canule, administered by mouth or via a NGT or GT.

Subjects were treated for up to 12 months or until anticoagulation was no longer needed, whichever was shorter. Subjects who received LMWH were allowed to switch to VKA at any time during the study and vice versa. Intermittent treatment with other anticoagulants (e.g. UFH, LMWH) was allowed in the apixaban arm when patients could not tolerate oral intake or for bridging around surgeries or procedures.

Table 20. Apixaban Doses for Ages 28 Days to <18 Years

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

Source: Table 3.4.5-1 of the CV185362 CSR[3]

Use of VKA or LMWH followed the local SOC guidelines that was 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.

Objectives and endpoints

Primary objectives of the study were

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

2. to evaluate apixaban PK in pediatric subjects with congenital or acquired heart disease requiring chronic anticoagulation for thromboprophylaxis.

Secondary objectives were

1. to assess apixaban PD by measuring FX using chromogenic assay and anti-FXa activity in pediatric subjects with CAHD requiring chronic anticoagulation for thromboprophylaxis,

2. to compare the effects of apixaban on QOL measures versus VKAs or subcutaneous LMWH in pediatric subjects with CAHD requiring chronic anticoagulation for thromboprophylaxis,

3. to gather exploratory data on the efficacy of apixaban in pediatric subjects with CAHD requiring chronic anticoagulation for thromboprophylaxis.

Other objectives were

1. to evaluate biomarkers that may inform anticoagulant efficacy or risk of thrombosis in pediatric subjects with CAHD requiring chronic anticoagulation for thromboprophylaxis; and

2. To assess effects of apixaban on bone density in pediatric subjects with congenital or acquired heart disease requiring chronic anticoagulation for thromboprophylaxis.

No primary efficacy endpoint was defined for this study. The secondary efficacy endpoints selected (Table 21) were standard and validated measures consistent with those recommended by the ISTH for paediatric clinical trials. Thromboembolic events were adjudicated by the BIAC to minimize investigator bias.

Table 21. Summary of Efficacy Objectives and Associated Endpoints - CV185362

Objectives	Endpoints	Endpoint Description
SECONDARY		
To gather exploratory data on the efficacy of apixaban in paediatric subjects with congenital or acquired heart disease requiring chronic anticoagulation for thromboprophylaxis	Secondary efficacy endpoint: • Composite of adjudicated thromboembolic events and thromboembolic event-related deaths Other efficacy endpoints: • Adjudicated thromboembolic events requiring treatment change, medical intervention, hospitalization or prolongation of hospitalization • Adjudicated thromboembolic event-related deaths	Thromboembolic events for the secondary efficacy endpoint included any thromboembolic events (intra-cardiac, shunt, inside Fontan pathway, PE, stroke, other arterial or venous thromboembolic events, etc.) detected by imaging or clinical diagnosis. Thromboembolic events and thromboembolic event-related deaths were adjudicated by BIAC. Routine mandatory images for thromboembolic events were not required for the study. However, any clinical, radiologic and catheter evaluations prompted by clinical suspicion of any thromboembolic events, bleeding or death were performed at the discretion of the site principal investigator and/or treating clinician.
To compare the effects of apixaban on QOL measures versus VKAs antagonists or subcutaneous LMWH in paediatric subjects with congenital or acquired heart disease requiring chronic anticoagulation for thromboprophylaxis	Secondary endpoints: • PedsQL™ scores • KIDCLOT© scores	QOL instruments were given only to English-speaking subjects. These included patient/proxy reported outcome using PedsQL generic core and cardiac modules, and KIDCLOT.[13,14] Subjects who had previous exposure to anticoagulants were given PedsQL and KIDCLOT on Day 1. Subjects starting an anticoagulant at study entry were given PedsQL at the Day 1 visit and KIDCLOT at the Week 2 visit, because some exposure to anticoagulation therapy was necessary to complete KIDCLOT. The QOL instruments were to be completed at the time of the visit, with post-baseline assessments collected at Month 6 and Month 12.

Abbreviations: BIAC = blinded, independent adjudication committee; KIDCLOT = Kids Informed Decrease Complications Learning on Thrombosis; LMWH = low molecular weight heparin; PE = pulmonary embolism; PedsQL = Paediatric Quality of Life Inventory; QOL = quality of life; VKA = vitamin K antagonist.

Source: Table 3.5.1-1 of the CV185362 CSR[3]

Statistical methodology

Sample size and power

Based upon the available literature and the resulting expectation that only a limited number of children with congenital or acquired heart disease requiring thromboprophylaxis would be available for recruitment to this 2:1 randomized clinical trial, the study could not be powered to show statistically significant treatment differences for any of the endpoints specified in the protocol. With a treatment period of up to 12 months, the sample size of approximately 200 subjects (approximately 133 in the apixaban arm and approximately 67 in the SOC arm) was considered both feasible to recruit and randomize, and sufficient for descriptive efficacy and safety analyses, as well as for PK and pharmacodynamics (PD) modeling. This approach is consistent with the recommendations of the Subcommittee on Pediatric and Neonatal Hemostasis and Thrombosis of the ISTH.

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 (SVP vs non-SVP) to ensure a consistent distribution between the two treatment arms.

Exploratory Efficacy

Efficacy endpoints were analysed for the randomized subjects based on events occurring during the intended treatment period. There was no primary efficacy endpoint for this study. For the secondary efficacy endpoint (composite of adjudicated thromboembolic events and thromboembolic event-related deaths), and other efficacy endpoints (adjudicated thromboembolic events requiring treatment change, medical intervention, hospitalization, or prolongation of hospitalization; and adjudicated thromboembolic event-related deaths), descriptive statistics including event rates were provided. Difference of event rates and 95% confidence intervals (CIs) were also provided, and relative risk and 95% CI for relative risk were to be calculated based on the stratified Mantel-Haenszel's method if the total number of events were above 5.

Quality of Life

The analysis populations included randomized subjects who participated in the QOL evaluation during the Intended Treatment Period. Descriptive statistics (mean and SD) were provided for score by visit and for the change in score from baseline by post baseline visit for each treatment arm. Post-baseline differences in mean change in score from baseline between the treatment arms, along with associated 95% CIs, were also provided.

Safety Analyses

The safety population included all randomized subjects who received at least one dose of study drug (all treated subjects). Safety endpoints were analysed for the safety population based on events occurring during the treatment period.

For the primary safety endpoint of the composite of adjudicated major or CRNM bleeding events during the treatment period, descriptive were calculated based on the stratified Mantel-Haenszel's method if the total number of events was above 5. Additional summaries included components of the primary safety endpoint (adjudicated major bleeding and CRNM bleeding) as well as all adjudicated bleeding events.

Event rates adjusted for time were calculated for both the composite of adjudicated major or CRNM bleeding events as well as all adjudicated bleeding events. The frequencies and percentages of bleeding occurring within 24 hours after cardiac catheterization or bleeding occurring within 48 hours after surgery were summarized by treatment group. All bleeding events were listed.

Rates for the primary safety endpoint as well as for all bleeding events, were summarized by treatment group for age stratification and clinical diagnosis stratification subgroups.

Bone Density Measurements

For the other safety endpoint of bone density, descriptive statistics including mean change from baseline by treatment group and by measurement location were summarized.

Adverse Events

All AEs were coded and grouped into Preferred Terms (PTs) by System Organ Class (SOC). The incidence of bleeding-related AEs occurring through the end of the treatment period were summarized by treatment group. The incidence of AEs, SAEs, and AEs leading to discontinuation of study drug was summarized by treatment group.

Laboratory Data

Laboratory measurements and their changes from baseline for liver function as well as for haematocrit, haemoglobin, leukocyte count, and platelets were summarized at each visit by treatment group, including the frequency of subjects with laboratory marked abnormalities based on pre-specified criteria and shift analyses to evaluate qualitative changes that occurred during the treatment period for liver function and platelets.

Pharmacodynamic Analyses

Summary statistics were tabulated for the chromogenic FX assay and anti-FXa activity. Plots of corresponding changes from baseline and percentage change from baseline for chromogenic FX assay, and plots of mean ± SE values for anti-FXa activity vs time point were generated.

Biomarker data were analyzed to evaluate whether there were treatment and time dependent changes. Linear mixed-effects models were used to model biomarker values (log2-transformed), with a random intercept for subject and fixed effects including treatment, visit, treatment-by-visit interaction, age and primary diagnosis as additional covariates. Unadjusted p-values from contrasts of interest are presented. Eighty-six (70%) patients randomized to apixaban were treated with VKA prior to study entry. As VKA affects coagulation biomarkers, the treatment groups were stratified and analyzed as four subgroups, apixaban or SOC, with and without prior VKA.

7.5. Efficacy Results

Subject Disposition

Thirty three study centers in 12 countries enrolled 198 subjects, 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 (Table 22). Of the 25 (13.0%) subjects (19 in the apixaban and 6 in the VKA/LMWH group) who did not complete the treatment period, 4 (3 in the apixaban and 1 in the VKA/LMWH group) did not receive treatment. In the apixaban arm, 1 subject no longer met study criteria because of a pre-existing coagulopathy discovered only after randomization. The remaining 3 subjects withdrew consent before being treated. This resulted in a total of 188 treated subjects (126 in the apixaban group and 62 in the VKA/LMWH group).

Table 22. Subject Disposition Summary - All Randomized Subjects - CV185362

Status (%)	Apixaban N = 129	VKA/LMWH N = 63	Total N = 192
COMPLETED TREATMENT PERIOD	110 (85.3)	57 (90.5)	167 (87.0)
NOT COMPLETING TREATMENT PERIOD	19 (14.7)	6 (9.5)	25 (13.0)
REASON FOR NOT COMPLETING TREATMENT PERIOD			
ADVERSE EVENT	6 (4.7)	1 (1.6)	7 (3.6)
SUBJECT WITHDREW CONSENT (A)	3 (2.3)	1 (1.6)	4 (2.1)
LOST TO FOLLOW-UP	0	1 (1.6)	1 (0.5)
SUBJECT NO LONGER MEETS STUDY CRITERIA (B)	10 (7.8)	3 (4.8)	13 (6.8)
COMPLETED STUDY	123 (95.3)	61 (96.8)	184 (95.8)
NOT COMPLETING STUDY	6 (4.7)	2 (3.2)	8 (4.2)
REASON FOR NOT COMPLETING STUDY			
SUBJECT WITHDREW CONSENT	4 (3.1)	1 (1.6)	5 (2.6)
LOST TO FOLLOW-UP	1 (0.8)	1 (1.6)	2 (1.0)
SUBJECT NO LONGER MEETS STUDY CRITERIA	1 (0.8)	0	1 (0.5)

(A) 2 of the 3 subjects in the apixaban arm and the subject in the VKA/LMWH arm did not receive study treatment.

(B) 9 subjects in the apixaban arm and all 3 subjects in the VKA/LMWH arm discontinued treatment prior to 12 months because they no longer required anticoagulation, but were still considered to have completed the protocol-specified treatment.

The denominator to calculate each percentage was the total number of randomized subjects within each treatment arm.

Baseline characteristics

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)
(Table 23). The percentage of subjects allocated to the SOC arm was higher than that in the apixaban arm in North America (49.2% vs 38.8%) and lower in Europe (25.4% vs 40.3%).

Table 23. Demographic Characteristics Summary - All Randomized Subjects - CV185362

	Apixaban N = 129	VKA/LMWH N = 63	Total N = 192
AGE (YEARS)			
N	129	63	192
MEAN	7.96	7.56	7.83
MEDIAN	7.00	6.00	7.00
MIN , MAX	0.4, 17.0	0.6, 16.0	0.4, 17.0
SD	4.553	4.408	4.499
RANDOMIZATION AGE STRATUM (%)			
28 DAYS - < 2 YEARS	8 (6.2)	3 (4.8)	11 (5.7)
2 YEARS - < 12 YEARS	89 (69.0)	45 (71.4)	134 (69.8)
12 YEARS - < 18 YEARS	32 (24.8)	15 (23.8)	47 (24.5)
AGE CATEGORIZATION (%)			
28 DAYS - < 2 YEARS	8 (6.2)	3 (4.8)	11 (5.7)
2 YEARS - < 6 YEARS	40 (31.0)	22 (34.9)	62 (32.3)
6 YEARS - < 12 YEARS	49 (38.0)	23 (36.5)	72 (37.5)
12 YEARS - < 18 YEARS	32 (24.8)	15 (23.8)	47 (24.5)
SEX (%)			
MALE	62 (48.1)	40 (63.5)	102 (53.1)
FEMALE	67 (51.9)	23 (36.5)	90 (46.9)
RACE (%)			
WHITE	109 (84.5)	51 (81.0)	160 (83.3)
BLACK OR AFRICAN AMERICAN	7 (5.4)	2 (3.2)	9 (4.7)
ASIAN	6 (4.7)	4 (6.3)	10 (5.2)
AMERICAN INDIAN OR ALASKA NATIVE	1 (0.8)	0	1 (0.5)
NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER	0	0	0
OTHER	6 (4.7)	6 (9.5)	12 (6.3)
ETHNICITY (%)			
HISPANIC OR LATINO	20 (15.5)	14 (22.2)	34 (17.7)
NOT HISPANIC OR LATINO	105 (81.4)	47 (74.6)	152 (79.2)
NOT REPORTED	4 (3.1)	2 (3.2)	6 (3.1)
GEOGRAPHIC REGION (%)			
NORTH AMERICA	50 (38.8)	31 (49.2)	81 (42.2)
LATIN AMERICA	14 (10.9)	7 (11.1)	21 (10.9)
ASIA/PACIFIC	1 (0.8)	0	1 (0.5)
EUROPE	52 (40.3)	16 (25.4)	68 (35.4)
REST OF WORLD	12 (9.3)	9 (14.3)	21 (10.9)

Source: Table 5.3.1-1 of the CV185362 CSR[3]

The baseline disease characteristics, including primary disease diagnosis, prior single ventricle palliative cardiac surgery history, prior indications for thromboprophylaxis, and prior bleeding or thromboembolic events were comparable between the treatment arms (Table 24). The primary diagnosis was congenital or acquired heart disease for all randomized subjects; the most common diagnosis was hypoplastic left heart syndrome (31.8%). The majority (66.7%) of subjects had undergone prior stage 3 (Fontan) single ventricle palliative surgery. The most common primary indication for thromboprophylaxis was routine anticoagulation after a Fontan procedure (51.0%).

Numbers of randomized subjects across treatment arms with single ventricle physiology (SVP) and non-SVP were 3 and 8, respectively, in the 28 days to < 2 years age group; 107 and 27 in the 2 to < 12 years age group; and 29 and 18 in the 12 to < 18 years age group. Baseline characteristics by age and clinical diagnosis (SVP and non-SVP) were balanced between the apixaban and VKA/LMWH arms.

Table 24. Baseline Characteristics Summary - All Randomized Subjects - CV185362

	Apixaban N = 129	VKA/LMWH N = 63	Total N = 192
PRIMARY DISEASE DIAGNOSIS (%)			
PULMONARY HYPERTENSION	2 (1.6)	0	2 (1.0)
SV HYPOPLASTIC LEFT HEART SYNDROME	38 (29.5)	23 (36.5)	61 (31.8)
SV TRICUSPID ATRESIA	11 (8.5)	8 (12.7)	19 (9.9)
SV PULM ATRESIA WITH INTACT VENTR SEPTUM	7 (5.4)	4 (6.3)	11 (5.7)
SV DOUBLE INLET LEFT VENTRICLE	6 (4.7)	4 (6.3)	10 (5.2)
SV DOUBLE OUTLET RIGHT VENTRICLE	11 (8.5)	3 (4.8)	14 (7.3)
SV HETEROTAXY SYNDROME	2 (1.6)	1 (1.6)	3 (1.6)
OTHER SINGLE VENTRICLE DEFECT	19 (14.7)	5 (7.9)	24 (12.5)
TWO VENTRICLE CONGENITAL HEART DISEASE	7 (5.4)	1 (1.6)	8 (4.2)
DILATED CARDIOMYOPATHY	1 (0.8)	1 (1.6)	2 (1.0)
KAWASAKI DISEASE WITH CORONARY ANEURYSMS	16 (12.4)	11 (17.5)	27 (14.1)
ATRIAL PRIMARY ARRHYTHMIA	3 (2.3)	0	3 (1.6)
OTHER: ANOMALOUS PULMONARY VENOUS RETURN	1 (0.8)	0	1 (0.5)
OTHER: COARCTATION OF THE AORTA	0	1 (1.6)	1 (0.5)
OTHER: DEXTROCARDIA, VA DISCORDANCE, AVSD, PULMONARY STENOSIS	1 (0.8)	0	1 (0.5)
RIGHT: AORTIC ARCH, RIGHT ATRIAL ISOMERISM			
OTHER: EBSTEIN'S ANOMALY, PDA	1 (0.8)	0	1 (0.5)
OTHER: EBSTEINS ANOMALY WITH PULMONARY ATRESIA	0	1 (1.6)	1 (0.5)
OTHER: POLYARTERITIS NODOSA SYSTEM WITH CORONARY ANEURYSMS	1 (0.8)	0	1 (0.5)
OTHER: PULMONAR ATRESIA AND ARTERIAL VENTRICLE DISCORDANCE	1 (0.8)	0	1 (0.5)
OTHER: TAKAYASU ARTHERITIS	1 (0.8)	0	1 (0.5)
PRIOR SINGLE VENTRICLE HEART SURGERIES (%)			
STAGE 3	83 (64.3)	45 (71.4)	128 (66.7)
PRIMARY INDICATIONS FOR THROMBOPROPHYLAXIS (%) - MOST COMMON			
FONTAN: ROUTINE ANTICOAGULATION	62 (48.1)	36 (57.1)	98 (51.0)
GIANT CORONARY ARTERY ANEURYSMS	17 (13.2)	9 (14.3)	26 (13.5)
INTRAVASCULAR/INTRACARDIAC DEVICE/STENT	13 (10.1)	4 (6.3)	17 (8.9)
FONTAN: PREDISPOSING CONDITION FOR TE	7 (5.4)	1 (1.6)	8 (4.2)
POOR MYOCARDIAL SYSTOLIC FUNCTION	4 (3.1)	4 (6.3)	8 (4.2)
HISTORY OF ATRIAL TACHYARRHYTHMIAS	6 (4.7)	1 (1.6)	7 (3.6)
SECONDARY INDICATIONS FOR THROMBOPROPHYLAXIS (%) - MOST COMMON			
INTRACARDIAC THROMBUS	5 (3.9)	5 (7.9)	10 (5.2)
STROKE	7 (5.4)	1 (1.6)	8 (4.2)
CORONARY ARTERY THROMBOSIS	4 (3.1)	3 (4.8)	7 (3.6)
DVT OTHER	4 (3.1)	2 (3.2)	6 (3.1)
PRIOR BLEEDING OR THROMBOEMBOLIC EVENTS (%)			
MAJOR BLEEDING	1 (0.8)	1 (1.6)	2 (1.0)
CRNM BLEEDING	6 (4.7)	2 (3.2)	8 (4.2)
STROKE	11 (8.5)	2 (3.2)	13 (6.8)
MYOCARDIAL INFARCTION	5 (3.9)	2 (3.2)	7 (3.6)
PULMONARY EMBOLUS	1 (0.8)	1 (1.6)	2 (1.0)
CORONARY THROMBUS WITHOUT INFARCTION IN KD	2 (1.6)	2 (3.2)	4 (2.1)
INTRACARDIAC THROMBUS	7 (5.4)	4 (6.3)	11 (5.7)
SHUNT THROMBOSIS	6 (4.7)	1 (1.6)	7 (3.6)
OTHER THROMBOEMBOLIC EVENT	12 (9.3)	11 (17.5)	23 (12.0)
COAGULOPATHY	0	2 (3.2)	2 (1.0)
WEIGHT (KG)			
MEAN	29.18	26.38	28.26
MEDIAN	23.00	20.70	22.25
MIN , MAX	6.1 , 132.8	7.9 , 68.9	6.1 , 132.8
SD	18.017	13.937	16.802

The denominator to calculate each percentage was the total number of randomized subjects within each treatment group.
Abbreviations: AVSD = atrioventricular septal defect; CRNM = clinically relevant non-major; DVT = deep vein thrombosis; KD = Kawasaki disease; PDA = patent ductus arteriosus; SV = single ventricle; TE = thromboembolism; VA = ventriculoarterial.

Treatment Compliance

125/126 (99.2%) treated subjects in the apixaban arm and 61/62 (98.4%) treated subjects in the VKA/LMWH arm received between 80% and 120% of the expected number of doses of the study treatment.

Concomitant Medication

Concomitant medications were used by 99.2% and 98.4% of subjects in the apixaban and VKA/LMWH arms, respectively. The use of concomitant medications by medication class appeared generally similar between the treatment arms.

Primary Efficacy Endpoint

No primary efficacy endpoint was defined for this study.

Secondary Efficacy Endpoint

The secondary efficacy endpoint of a composite of adjudicated thromboembolic events and thromboembolic event-related deaths was not reported in either treatment arm (Table 25). Of note, an adjudicated thromboembolic event of stroke was reported in 1 subject in the apixaban arm during the follow-up period, 316 days after start of dosing and 33 days after the last dose of study treatment and was, therefore, not included in the secondary analysis. There were no subjects with adjudicated thromboembolic events in the VKA/LMWH arm.

Investigator-identified thromboembolic events of shunt thrombosis (thrombus in the Fontan conduit) were reported in 2 subjects (11 and 58 days after start of dosing) in the apixaban arm and no subjects in the VKA/LMWH arm during the Intended Treatment Period. For the 2 subjects (1.6%) in the apixaban arm, the per-protocol review conducted by the BIAC determined that these thrombi were non-events, because they had been present on imaging studies performed prior to study participation and, therefore, were not treatment-emergent. There were no investigator-identified thromboembolic event-related deaths reported during the Intended Treatment Period in either treatment arm.

There were no adjudicated thromboembolic events requiring treatment change, medical intervention, hospitalization, or prolongation of hospitalization in either treatment arm, nor were there any thromboembolic event-related deaths (Table 25).

There were no adjudicated thromboembolic events or thromboembolic event-related deaths reported with onset during the Intended Treatment Period in either treatment arm (Table 25).

Table 25. Summary of Adjudicated Efficacy Endpoints During Intended Treatment Period - All Randomized Subjects - CV185362

	Apixaban N = 129	VKA/LMWH N = 63
Secondary Efficacy Endpoint		
Composite of Adjudicated Thromboembolic Events and Thromboembolic Event-related Death		
SUBJECTS WITH EVENT, n	0	0
EVENT RATE (%)	0.00	0.00
95% CI FOR EVENT RATE	(0.00, 2.82)	(0.00, 5.69)
Other Efficacy Endpoints		
Adjudicated Thromboembolic Events Requiring Treatment Change, Medical Intervention, Hospitalization, or Prolongation of Hospitalization		
SUBJECTS WITH EVENT, n	0	0
EVENT RATE (%)	0.00	0.00
95% CI FOR EVENT RATE	(0.00, 2.82)	(0.00, 5.69)
Adjudicated Thromboembolic Event-related Death		
SUBJECTS WITH EVENT, n	0	0
EVENT RATE (%)	0.00	0.00
95% CI FOR EVENT RATE	(0.00, 2.82)	(0.00, 5.69)

Abbreviation: CI = confidence interval.

Source: Table 7.1-1 of the CV185362 CSR[3]

Quality of Life

PedsQOL questionnaires were administered only to English-speaking subjects and their parents/proxies. PedsQL questionnaires were to be completed by English-speaking subjects who were >= 5 years of age, or by the parents/proxies of English speaking subjects >= 2 years of age.

Parent and child-reported PedsQL mean scores were calculated at baseline and post-baseline visits (Month 6 and Month 12), as were the changes in mean scores from baseline for both post-baseline visits. Post baseline differences in mean changes in scores from baseline between the treatment arms, along with 95% CIs, were also calculated. Among these surveys, those with missing data for > 50% of items were excluded from the analyses. Only subjects who completed questionnaires at both baseline and post-baseline visits were included in the analyses.

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

KIDCLOT questionnaires were to be completed by English-speaking subjects ≥ 8 years of age, or by parents/proxies of English-speaking subjects ≥ 34 weeks of age. Only subjects who were administered apixaban or warfarin were eligible to complete the questionnaire. Parent- and child-reported mean KIDCLOT scores were calculated at baseline and post-baseline visits (Month 6 and Month 12), as were the changes in mean scores from baseline for post-baseline visits. Post-baseline differences in mean changes in scores from baseline between apixaban and warfarin treatments were also calculated.

Changes from baseline were small in both the apixaban- and warfarin-treated subjects. There were no clinically meaningful post-baseline differences in mean changes in scores from baseline between the treatments.

7.6. Discussion

The prospective, randomized, open label study CV185362, was primarily initiated as a safety study in children (from 28 days to <18 years) with congenital or acquired heart disease requiring chronic anticoagulation for thromboprophylaxis, compared to VKA and low molecular weight heparin (LMWH).

Therefore, the study included no primary efficacy endpoints, only secondary efficacy endpoints and was not powered to establish any efficacy outcome, which likely limits interpretation of efficacy in this paediatric population.

The study included 192 patients. The apixaban and VKA/LMWH arms were well-balanced with respect to baseline demographics and disease characteristics. The majority of subjects had congenital heart disease, most commonly with SVP. Overall, 66.7% of subjects were status post a Fontan procedure, the third of three standard palliative surgeries for single ventricle disease. Routine anticoagulation after the Fontan procedure was the most common reason for thromboprophylaxis.

In this study, there were no adjudicated thromboembolic events or thromboembolic event-related deaths in either treatment arm. This is understandable, given the low incidence of such events in this population and that, as a result, the study was not powered to evaluate them. A recent study examining the use of rivaroxaban in subjects after a Fontan procedure also reported a low event rate.[vi]

Subject QOL was measured in the CV185362 study using the PedsQL and KIDCLOT instruments. Neither survey found improved QOL for subjects in the apixaban arm compared to the SOC arm. The relatively small number of subjects and parents who completed questionnaires limits the interpretability of the data collected.

Overall, despite that, based on the mechanism of action some effect may be expected. However, with such limited data limiting interpretation of the efficacy in this clinical setting, it is agreed that any indication may not be warranted.

8. Clinical Safety aspects

All safety evaluations were conducted and reported according to Good Clinical Practice (GCP) guidelines. Data were collected for bleeding events, AEs, clinical laboratory test results, and vital signs.

8.1. Methods – analysis of data submitted

8.1.1. Study CV185118

The evaluation of safety was based on clinical AEs, vital signs, and clinical laboratory results reported during the study. All recorded adverse events were listed and tabulated by system organ class and preferred term, age group and overall. If any, AEs associated with palatability would be listed by age group.

Physical examination abnormal findings were listed. Vital signs and clinical laboratory test results and corresponding change from baseline values were listed and summarised by age group. Marked abnormalities for clinical laboratory test results were also listed and summarised, using the standard BMS criteria as well as protocol specified criteria. In the summaries of marked laboratory abnormalities, both scheduled and unscheduled visits were included.

8.1.2. Study CV185155

The primary safety endpoint was adjudicated major bleeding, defined as per International Society on Thrombosis and Haemostasis (ISTH) criteria as bleeding that satisfies 1 or more of the following criteria: (i) fatal bleeding; (ii) clinically overt bleeding associated with a decrease in hemoglobin of at least 20 g/L (ie, 2 g/dL) in a 24-hour period; (iii) bleeding that is retroperitoneal, pulmonary, intracranial, or otherwise involves the CNS; and/or (iv) bleeding that requires surgical intervention in an operating suite, including interventional radiology.

The secondary safety endpoint was the composite of major and CRNM bleeding. CRNM bleeding is defined as bleeding that satisfies one or both of the following: (i) overt bleeding for which blood product is administered and 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 room

Descriptive results were based on events reported in the Safety Population during the treatment period. To construct nominal p-values and 95% CIs for relative risk, the Cochran- Mantel-Haenszel test, stratified by age groups of < 10 years and $\geq$ 10 years old was used at the 2-sided α =0.05 level. Construction of CIs for single event rates were based on the Agresti-Coull method.

8.1.3. Study CV185362

The primary safety endpoint was the composite of adjudicated major or CRNM bleeding per ISTH criteria.

Secondary safety endpoints included adjudicated major bleeding, adjudicated CRNM bleeding, all adjudicated bleeding, drug discontinuation due to adverse effects, intolerability, or bleeding, and all cause death.

For the primary safety endpoint of a composite of adjudicated major or CRNM bleeding events during the treatment period, descriptive statistics including event rates, difference of event rates, and 95% CI were provided, and relative risk and 95% CI for relative risk was calculated based on the stratified Mantel-

Haenszel's method if the total number of events was above 5. Additional summaries included components of the primary safety endpoint, as well as all bleeding events.

Adjudicated major bleeding and adjudicated CRNM bleeding, as well as all adjudicated bleeding events were also assessed using the event rate adjusted for time, 95% CI for the event rate, relative risk, and 95% CI for relative risk were displayed.

The frequencies and percentages of bleeding occurring within 24 hours after cardiac catheterization and bleeding occurring within 48 hours after surgery were summarized by treatment group.

8.2. Results on Safety

8.2.1. Exposure

Study therapy

- Subjects in CV185118 received a single dose of apixaban.
- The median extent of exposure in the apixaban arm in CV185155 was 25.0 days (mean: 23.5, standard deviation [SD]: 6.25).
- The median extent of exposure in the apixaban arm in CV185362 was 358 days (mean 330.6, SD 83.04).

8.2.1.1. Study CV185118

All 49 treated subjects received a single oral dose based on the treatments listed in (Table 26).

Table 26. Apixaban dose in each age group – CV185118

Paediatric Subject Groups	Dose	Number Treated
Group 1 Neonates up to 27 days[a]	0.1 mg	1
Group 2B Infants 28 days to < 9 months	1.08 mg/m^2	11
Group 2A Young Children 9 months to < 2 years	1.08 mg/ m^2	5
Group 2A[b] Young Children 9 months to < 2 years	2.43 mg/ m^2	4
Group 3 Young Children 2 years to < 6 years	1.17 mg/ m^2	8
Group 4 Children 6 years to <12 years	1.80 mg/ m^2	10
Group 5 Adolescents 12 years to <18 years	2.19 mg/ m^2	10

[a]Neonates up to 27 days of age (≥ 34 weeks gestational age or ≥ 37 weeks post conceptual age)

[b](n=4 additional subjects)

Source: CV185118 Final CSR Figure 3.4.1-1, CV198118 CSR Appendix 4.1.

In this study, there were 49 patients aged 9 days to 16 years enrolled at risk for a venous or arterial thrombotic disorder who had a mean age of 5.1 years, mean BMI of 16.3 (range 10.1-27.2) kg/m^2 and of whom 43% were males and 57% females. No children were included aged 16 to 18 years. Group 4 and Group 5 included subjects with a BMI up to 26.7, 27.2 kg/m^2, respectively. There were no other notable demographic differences.

All subjects had medical conditions and were at risk for a venous or arterial thrombotic disorder, with or without a central venous catheter or arterial line. The body system related to the primary medical conditions for the subjects reported included neoplasia or other cancers (n=10), musculoskeletal (n=5), cardiovascular (n=19), respiratory (n=4), gastrointestinal (n=4), hematologic-lymphatic (n= 5), dermatologic (n=1) and peripheral vascular (n=1).

Table 27. Subject demographic summaries and screening physical collection

Parameter	Group 5 (N=10)	Group 4 (N=10)	Group 3 (n=8)	Group 2A (N=9)	Group 2B (N=11)	Group 1 (N=1)	All Subjects (N=49)
Age, years, months or days	(years)	(years)	(years)	(months)	(days)	(days)	(years)
Mean (SD)	13.7 (1.4)	7.4 (1.2)	3.6 (1.2)	13.3 (4.2)	126.9 (67.2)	9.0 (-)	5.1 (5.2)
Range	12.0-16.0	7.0-8.0	2.3-4.5	10.0-15.0	85.0-151.0	-	0 -16.0
Gender, N (%)							
Male	4 (40)	4 (40)	4 (50)	4 (44)	5 (45)	0	21 (43)
Female	6 (60)	6 (60)	4 (50)	5 (56)	6 (55)	1 (100)	28 (57)
Race, %							
White	7 (70)	8 (80)	8 (100)	9 (100)	9 (82)	1 (100)	42 (86)
Black or African American	3 (30)	2 (20)	0	0	0	0	5 (10)
Other	0	0	0	0	2 (18)	0	2 (4)
Ethnicity, %							
Hispanic/Latino	0	3 (30)	1 (12)	0	5 (46)	1 (100)	10 (20)
Not Hispanic/Latino	6 (60)	5 (50)	2 (25)	4 (44)	3 (27)	0	20 (41)
Not Reported	4 (40)	2 (20)	5 (63)	5 (56)	3 (27)	0	19 (39)
Weight, kg							
Mean (SD)	49.9 (17.1)	29.8 (11.1)	15.9 (4.7)	8.3 (2.4)	4.9 (1.7)	3.1 (-)	21.5 (19.3)
Range	32.1-80.9	19.4-47.6	10.8-25.2	4.0-11.8	3.0-8.5	-	3.0-80.9
Body Surface Area, m^2							
Mean (SD)	1.5 (0.3)	1.0 (0.2)	0.7 (0.1)	0.4 (0.1)	0.3 (0.1)	0.2 (-)	0.8 (0.5)
Range	1.2 -2.0	0.8-1.4	0.5-0.9	0.3-0.5	0.2-0.4	-	0.30-1.2
Body Mass Index, kg/m^2							
Mean (SD)	19.4 (4.5)	17.7 (4.3)	14.9 (1.8)	15.6 (2.55)	14.4 (2.35)	11.9 (-)	16.3 (3.8)
Range	14.3-27.2	13.5-26.7	11.4-17.2	10.1-17.9	10.9-17.5	-	10.1-27.2

Source: Appendix 3.1 (Demography), Appendix 3.2 (Physical Measurements) Table S.3.1 (Summary Demography) and Table S.3.2 (Summary Physical Measurements)

Group 5: Adolescents 12 years to <18 years; Group 4: Children 6 years to <12 years Group 3: Young Children 2 years to < 6 years; Group 2B: Infants 28 days to < 9 months; Group 2A: Young Children 9 months to < 2 years; Group 1: Neonates up to 27 days old

BMI: Body Mass Index = weight(kg) / height$(m)^2$

$$BSA(m^2) = \sqrt{\frac{weight\ (kg) \times height\ (cm)}{3600}}$$

[a] Enrollment/screening procedures began when subject was 9 days old; at the time study drug administration, subject was 15 days old.

8.2.1.2. Study CV185155

Exposure

The median extent of exposure in the apixaban arm in CV185155 was 25.0 days (mean: 23.5, standard deviation [SD]: 6.25). The median extent of exposure was the same between the prospectively defined, age-specific strata in the apixaban arm (< 10 years of age [n = 179] and ≥ 10 to ≤ 18 years of age [n = 77]): 25.0 days (mean of 23.6, SD: 6.25) and 25.0 days (mean of 23.4, SD: 6.31), respectively.

Subjects were treated with induction chemotherapy for a median of 29.0 days (mean of 26.8; SD: 7.20) in the apixaban arm and 29.0 days (mean of 29.1; SD: 3.78) in the SOC arm (Table 28). This represented ~18.75 years (981.1 patient-weeks) of exposure to treatment in the apixaban arm and 20.25 years (1062.6 patient-weeks) in the SOC arm.

Table 28. Summary of exposure – CV185155

Exposure (Days)	Apixaban N = 256	SOC N = 256	Total N = 512
Induction Chemotherapy			
Number of Subjects	256	256	512
Mean (SD)	26.8 (7.20)	29.1 (3.78)	27.9 (5.85)
Median	29.0	29.0	29.0
Min, Max	1 ,53	1 ,52	1 ,53
Total Patient Weeks	981.1	1062.6	2043.7
Apixaban			
Number of Subjects			250
Mean (SD)			23.5 (6.25)
Median			25.0
Min, Max			1, 41
Total Patient Weeks			840.9

Source: CV185155 CSR Table 14.4.1.1, CV185155 Table 14.4.1.2a.

8.2.1.3. Study CV185362

Exposure

The majority of randomized subjects received treatment for 337 days in both treatment arms; the mean (SD) exposure was 330.6 (83.04) days and 344.4 (56.41) days in the apixaban and VKA/LMWH arms, respectively (Table 29). The mean (SD) exposure after excluding days of dose interruption was 328.8 (83.70) days and 339.0 (57.62) days in the apixaban and VKA/LMWH arms, respectively.

The mean (SD) exposures in the 28 days to < 2 years, 2 to < 12 years, and 12 to < 18 years age groups were 260.4 (109.9), 332.0 (86.9), and 344.8 (52.5) days, respectively, in the apixaban arm; and 204.0 (119.6), 348.4 (47.3), and 360.7 (19.7) days, respectively, in the VKA/LMWH arm.

Table 29. Extent of Exposure from First Through Last Day of Dosing - All Randomized Subjects - CV185362

Days of Exposure	Apixaban N = 129	VKA/LMWH N = 63
NUMBER OF SUBJECTS	126	62
<= 30	4 (3.2)	0
31 - 180	4 (3.2)	3 (4.8)
181 - 336	17 (13.5)	12 (19.4)
337 - 360	43 (34.1)	15 (24.2)
> 360	58 (46.0)	32 (51.6)
MEAN (SD)	330.6 (83.04)	344.4 (56.41)
MEDIAN	358.0	362.5
MIN , MAX	5 , 392	108 , 448
TOTAL PATIENT-DAYS	41653	21353

The denominator to calculate each percentage was the total number of treated subjects within each treatment group.
Exposure was defined as: last dose date - first dose date + 1.
Total patient-days was defined as the sum of the individual exposures (in days).
Source: CV185362 CSR Table 14.4.1.1

8.2.2. Bleeding events: primary, secondary and exploratory safety endpoints

- In CV185118, AEs of clinical interest were defined as those relating to major bleeding or CRNM bleeding events. One subject had an AE of mild contusion considered by the investigator to be a procedural complication and not related to apixaban treatment and 1 subject had a clinical laboratory AE of prolonged aPTT that was not associated with any bleeding events.
- In CV185155, the incidence of major bleeding during treatment with induction chemotherapy (primary safety endpoint), was the same in the apixaban and SOC (no prophylaxis) arms. The incidence of the composite of adjudicated major bleeding and adjudicated CRNM bleeding events during treatment with induction chemotherapy (secondary safety endpoint) was numerically higher in the apixaban treatment arm as compared to that in the SOC arm.
- In CV185362, 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. The frequency of all adjudicated bleeding events (major, CRNM, or minor) was 37% in each treatment arm.

8.2.2.1. Study CV185155

Primary safety objective

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 having occurred in 2 subjects (0.8%) in each arm (Table 30). Of note, 1 of the major bleeding events in the apixaban arm occurred after randomization but prior to administration of the first dose of apixaban and was therefore not considered treatment-emergent.

Secondary safety objective

The *secondary safety objective* was the incidence of a composite of adjudicated major bleeding and adjudicated CRNM bleeding events during treatment with induction chemotherapy. The percentage of subjects who met this endpoint was numerically 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).

Other bleeding events

The relative risk of CRNM bleeding events occurring during the Intended Treatment Period (the period from the date of randomization through 2 days (or through 30 days for SAE tabulations) after discontinuation of study drug), was higher in the apixaban arm compared to the SOC arm (relative risk: 3.67; 95% CI: 1.04 to 12.97; nominal p = 0.0303). One or more events were observed in 11 subjects (4.3%; 95% CI: 2.33 to 7.62) and 3 subjects (1.2%; 95% CI: 0.24 to 3.55), in the 2 treatment arms, respectively (Table 30).

The relative risk of minor bleeding events occurring during the Intended Treatment Period was increased in the apixaban arm compared to the SOC arm (relative risk: 1.85; 95% CI: 1.10 to 3.10; nominal p = 0.0169); one or more events were observed in 37 subjects (14.5%; 95% CI: 10.64 to 19.32) and 20 subjects (7.8%; 95% CI: 5.06 to 11.82) in the 2 treatment arms, respectively).

The relative risk of any bleeding events occurring during the Intended Treatment Period was increased in the apixaban arm compared to the SOC arm (relative risk: 1.96; 95% CI: 1.24 to 3.10; nominal p = 0.0032); events were observed in 47 subjects (18.4%; 95% CI: 14.07 to 23.58) and 24 subjects (9.4%; 95% CI: 6.33 to 13.62) in the 2 treatment arms, respectively (CV185155 CSR

Table 14.6.1.8), predominately due to an imbalance in the number of reported events of epistaxis. The majority of those events were of mild to moderate intensity. Two adjudicated bleeding events occurred in subjects in the apixaban arm who were not treated with apixaban, resulting in an incidence of 18% (95% CI: 13.71 to 23.26) in subjects treated with apixaban (CV185155 CSR Table 14.6.1.8a).

Platelet transfusions were administered to 179 subjects: 95 (37.1%) and 84 (32.8%) in the apixaban and SOC arms, respectively (CV185155 CSR Table 14.6.1.7). Platelet transfusions were administered a total of 514 times: 266 and 248 times in the apixaban and SOC arms, respectively.

Table 30. Bleeding Event Summary - Safety Population - CV185155

Objective Endpoint (unit)	Apixaban n = 256	SOC n = 256
Primary Safety Endpoint		
Adjudicated Major Bleeding Events		
Event Rate, n (%)	2 (0.8%)	2 (0.8%)
(95% CI lower bound, upper bound)	(0.03%, 2.99%)	(0.03%, 2.99%)
Relative Risk (apixaban / SOC)	1.00	
(95% CI lower bound, upper bound)	(0.14, 7.01)	
Nominal p-value	1.00	
Secondary Safety Endpoint		
Composite of Adjudicated Major Bleeding and CRNM Bleeding Events		
Event Rate, n (%)	13 (5.1%)	5 (2.0%)
(95% CI lower bound, upper bound)	(2.91%, 8.57%)	(0.71%, 4.62%)
Relative Risk (apixaban / SOC)	2.60	
(95% CI lower bound, upper bound)	(0.94, 7.17)	
Nominal p-value	0.0546	
Other Endpoints		
Adjudicated CRNM Bleeding Events		
Event Rate, n (%)	11 (4.3%)	3 (1.2%)
(95% CI lower bound, upper bound)	(2.33%, 7.62%)	(0.24%, 3.55%)
Relative Risk (apixaban / SOC)	3.67	
(95% CI lower bound, upper bound)	(1.04, 12.97)	
Nominal p-value	0.0303	
Adjudicated Minor Bleeding Events		
Event Rate, n (%)	37 (14.5%)	20 (7.8%)
(95% CI lower bound, upper bound)	(10.64%, 19.32%)	(5.06%, 11.82%)
Relative Risk (apixaban / SOC)	1.85	
(95% CI lower bound, upper bound)	(1.10, 3.10)	
Nominal p-value	0.0169	
Platelet Transfusions During the Treatment Period[a]		
Subjects given a transfusion, n (%)	95 (37.1%)	84 (32.8%)
Number of transfusions given	266	248

95% confidence interval for single event rates is constructed based on Agresti-Coull's method.

Two-sided p-value and 95% CI for relative risk are calculated using Cochran-Mantel-Haenszel test stratified by age at baseline. Adjusted relative risk of event rates takes into consideration age at baseline as a stratification factor.

Treatment period refers to the period from the day of randomization through either 2 days after early discontinuation or end of treatment Day 29 ±5 visit.

Percentage is calculated based on number of randomized subjects

Abbreviations: AE, adverse event; CI, confidence interval; CRNM, clinically relevant non-major; NE, not estimable; SAE, serious adverse event.

8.2.2.2. Study CV185362

Primary safety endpoint

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 (Table 31).

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.

Table 31. Bleeding Event Summary - Safety Population - CV185362

Objective Endpoint (unit)	Apixaban n = 126	VKA/LMWH n = 62
Primary Safety Endpoint		
Composite of Adjudicated Major or CRNM Bleeding		
Subjects with an Event, n (%)	1 (0.79)	3 (4.84)
(95% CI lower bound, upper bound)	(0.02, 4.34)	(1.01, 13.50)
Difference from VKA/LMWH	-4.05	
(95% CI lower bound, upper bound)	(-12.77, 0.79)	
Relative Risk	NE	
Secondary Safety Endpoint		
Adjudicated Major Bleeding		
Subjects with an Event, n (%)	1 (0.79)	1 (1.61)
(95% CI lower bound, upper bound)	(0.02, 4.34)	(0.04, 8.66)
Difference from VKA/LMWH	-0.82	
(95% CI lower bound, upper bound)	(-8.14, 3.29)	
Relative Risk	NE	
Adjudicated CRNM Bleeding		
Subjects with an Event, n (%)	1 (0.79)	2 (3.23)
(95% CI lower bound, upper bound)	(0.02, 4.34)	(0.39, 11.17)
Difference from VKA/LMWH	-2.43	
(95% CI lower bound, upper bound)	(-10.54, 1.94)	
Relative Risk	NE	
Adjudicated All Bleeding		
Subjects with an Event, n (%)	47 (37.30)	23 (37.10)
(95% CI lower bound, upper bound)	(28.86, 45.75)	(25.07, 49.12)
Difference from VKA/LMWH	0.20	
(95% CI lower bound, upper bound)	(-14.49, 14.90)	
Relative Risk	1.01	
(95% CI lower bound, upper bound)	0.68, 1.51	

Abbreviations: CI, confidence interval; CRNM, clinically relevant non-major; LMWH, low molecular weight heparin; VKA, vitamin K antagonist.

Relative risk and 95% CI calculated based on Mantel-Haenszel's method stratified by age and clinical diagnosis were to be evaluated if the total number of events is above 5. This was applicable to primary and secondary endpoints only.

Included events with onset between first dose and within 2 days of last dose of study medication.

95% CI of event rate was calculated based on normal approximation, if the number of events in that treatment group is ≥ 5, otherwise exact approximation was used. This was applicable to primary and secondary endpoints only.

Sources (all from CV185362 CSR): Table 14.6.1.1 (Primary endpoint), Table 14.6.1.2 (adjudicated major bleeding), Table 14.6.1.3 (Secondary endpoint), Table 14.6.1.4 (all bleeding), Table 14.6.1.5 (CRNM bleeding).

Secondary Safety Endpoints

One (0.79%) subject in the apixaban arm and 1 (1.61%) in the VKA/LMWH arm had an *adjudicated major bleeding* event during the treatment period.

One (0.79%) subject in the apixaban arm and 2 (3.23%) in the VKA/LMWH arm had an *adjudicated CRNM bleeding* event during the treatment period.

A total of 47 (37.30%) subjects in the apixaban arm and 23 (37.10%) in the VKA/LMWH arm had an *adjudicated bleeding event (CRNM, major, or minor)* during the treatment period. Adjudicated bleeding

events during the treatment period were reported in 1/4 (25.0%) subjects treated with enoxaparin and 18/47 (38.30%) subjects treated with warfarin.

Drug Discontinuation due to AEs, Intolerability, or Bleeding: 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) (CV185362 CSR Table 14.6.1.6). Two subjects in the apixaban arm discontinued treatment due to shunt thrombosis. These thrombi were adjudicated by the independent, blinded EAC as non-events and were not treatment-emergent.

Subgroup Analyses for Age

Subgroup analysis across age-ranges was performed. None of the subjects in the 28 days to < 2 years or 12 to < 18 years age group experienced an *adjudicated major or CRNM bleeding event*. All 4 subjects with the composite of adjudicated major or CRNM bleeding events were reported in the 2 to < 12 years age group (1/87 [1.15%] apixaban; 3/44 [6.82%] VKA/LMWH).

Results for all adjudicated bleeding events in the apixaban and VKA/LMWH arms by age-based subgroup were as follows:

Age 28 days to < 2 years: 4/8 (50.0%) vs 0/3 subjects for apixaban vs VKA/LMWH. Of note, all events in this age group were mild in intensity (Grade 1).

Age 2 to < 12 years: 34/87 (39.08%) vs 18/44 (40.91%) for apixaban vs VKA/LMWH.

Age 12 to < 18 years: 9/31 (29.03%) vs 5/15 (33.33%) for apixaban vs VKA/LMWH.

Incidence rates per 100 person-years

When incidence rates were adjusted by time of exposure and included all events, the incidence rates per 100 person-years of exposure for all adjudicated bleeding events during the treatment period were 100.0 and 58.2 in the apixaban and VKA/LMWH arms, respectively.

Bleeding-related AEs

The most frequently reported (≥ 5% in either treatment arm) bleeding-related AEs were as follows:
Epistaxis: apixaban 14.3%; VKA/LMWH 6.5%
Contusion: apixaban 6.3%; VKA/LMWH 6.5%
Hematoma: apixaban 6.3%; VKA/LMWH 1.6%

Bone density

The body locations assessed by DXA scan were hips, lumber spine, and total body less head. Summary statistics for bone mineral density changes from baseline to 12 months in subjects with both baseline and Month 12 measurements are provided in Table 32. There were minimal changes in mean bone mineral density at Month 12 relative to baseline at all 3 locations in both treatment arms and no notable differences in mean bone mineral density between the treatment arms.

Table 32. : Summary Statistics for Bone Mineral Density Change from Baseline (g/cm2) - All Treated Subjects.

Visit	Location	Statistics	Apixaban N = 126	VKA/LMWH N = 62
BASELINE	HIPS	n	31	15
		MEAN	0.7010	0.6099
		SD	0.16191	0.21424
	LUMBAR SPINE L1-L4	n	50	23
		MEAN	0.6669	0.5813
		SD	0.23763	0.15146
	TOTAL BODY LESS HEAD	n	47	22
		MEAN	0.6390	0.6244
		SD	0.13011	0.13013
MONTH 12	HIPS	n	14	10
		MEAN	0.6814	0.6287
		SD	0.13073	0.15425
		MEAN CHANGE FROM BASELINE (SD)	0.0384 (0.04015)	-0.0109 (0.08910)
	LUMBAR SPINE L1-L4	n	19	12
		MEAN	0.6922	0.5968
		SD	0.15782	0.11649
		MEAN CHANGE FROM BASELINE (SD)	0.0516 (0.07868)	0.0344 (0.03035)
	TOTAL BODY LESS HEAD	n	18	12
		MEAN	0.6794	0.6362
		SD	0.13251	0.12803
		MEAN CHANGE FROM BASELINE (SD)	0.0421 (0.02424)	0.0210 (0.01884)

8.2.3. Adverse Events

8.2.3.1. Analysis of Adverse Events

- Single oral doses of apixaban were generally safe and well-tolerated by the 49 paediatric subjects in CV185118. SAEs were rare. All of the SAEs and most AEs in CV185118 were considered not related to study drug by the investigator (*Table 33*).
- Across the 3 studies, there was 1 death in an apixaban-treated subject (CV185155), which was due to cardiac arrest with disseminated intravascular coagulation, acute coronary syndrome, and retroperitoneal hemorrhage.
- Rates of all-causality AEs and SAEs were similar between apixaban and SOC groups in CV185155 and between apixaban and VKA/LMWH groups in CV185362 (*Table 33*). Epistaxis was observed more frequently in apixaban-treated subjects than in SOC or VKA/LMWH groups. Epistaxis events were mild, responded to treatment, and did not lead to hospitalizations or discontinuation of apixaban. Epistaxis is consistent with the known safety profile of apixaban in adult patients and therefore not a new or unexpected event.
- Treatment-related SAEs occurred at low rates in the apixaban arm in CV185155 and, in CV185362, in both the apixaban and VKA/LMWH arms. Treatment-related AEs were more frequent in in the apixaban arms in CV185155 and CV185362 (*Table 33*).
- Treatment-related AEs leading to discontinuation in apixaban-treated subjects were reported in 13 subjects (5.1%) in CV185155 and in 5 (4.0%) subjects in CV185362. In CV185362, 2 AEs leading to discontinuation were due to shunt thrombosis (these events were also reported as treatment-related SAEs). In both cases, the per-protocol review conducted by the independent, blinded EAC

determined that the thrombi were non-events as they were present on imaging studies performed prior to study participation, and, therefore, were not treatment-emergent.

Table 33. Overall Safety Summary Safety Population

	CV185118	CV185155		CV185362	
	Apixaban n =49	Apixaban n = 256	SOC n = 256	Apixaban n = 126	VKA/LMWH n = 62
Deaths, n (%)	0	1 (0.4)	3 (1.2)	0	0
All-causality SAEs, n (%)	2 (4.1)	92 (35.9)	82 (32.0)	26 (20.6)	13 (21.0)
Treatment-related SAEs, n (%)	0	7 (2.7)	0	6 (4.8)	5 (8.1)
AEs Leading to Discontinuation, n (%)	0	35 (13.7)	2 (0.8)	6 (4.8)	1 (1.6)
Treatment-related AEs Leading to Discontinuation, n (%)	0	13 (5.1)	0	5 (4.0)	1 (1.6)
All-causality AEs, n (%)	15 (30.6)	232 (90.6)	215 (84.0)	107 (84.9)	53 (85.5)
Treatment-related AEs, n (%)	4 (8.2)	38 (14.8)	3 (1.2)	41 (32.5)	16 (25.8)

Abbreviations: AE, adverse event; LMWH, low molecular weight heparin; SAE, serious adverse event; SOC, standard of care; VKA, vitamin K antagonist.
Source: CV185118 CSR Table S.6.4 (AEs), CV185118 CSR Table S.6.7 (SAEs), CV185118 CSR Table S.6.5.1 (related AEs), CV185118 CSR Table S.6.6 (discontinuations), CV185118 CSR Appendix 6.2 (related SAEs), CV185155 CSR Table 8.1-1, CV185362 CSR Table 8.1-1.

8.2.3.2. Common Adverse Events

8.2.3.2.1. Study CV185118

Fifteen (15) of the 49 (30.6%) treated subjects had treatment-emergent AEs. The most frequently occurring AE was pyrexia, which occurred in 4/49 (8.2%) subjects overall (n=2 in Group 4, n=1 in Group 3 and n=1 in Group 2B) and 2/49 (4.1%) subjects overall had AEs of vomiting (n=2 in Group 4). The remaining AEs each occurred in 1/49 (2.0%) subject (Table 34).

Four (4) subjects had AEs considered by the Investigator to be related to study drug (n=1 in Group 3 elevation in aPTT, n=1 in Group 4 headache and vomiting, n=1 Group 2B diaphoresis and n=1 in Group 2B bleeding gums). The most frequently occurring AE was pyrexia, which occurred in 4/49 (8.2%) subjects overall (n=2 in Group 4, n=1 in Group 3 and n=1 in Group 2B).

Table 34. Adverse Event Summary - CV185118

System Organ Class Preferred Term n (%)	Group 5 (N=10)	Group 4 (N=10)	Group 3 (N=8)	Group 2A (N=9)	Group 2B (N=11)	Group 1 (N=1)	All Subjects (N=49)
Total Subjects with an Event n (%)	3 (30.0)	3 (30.0)	2 (25.0)	3 (33.3)	4 (36.4)	0	15 (30.6)
General Disorders and Administration Site Conditions							
Pyrexia	0	2 (20.0)	1 (12.5)	0	1 (9.1)	0	4 (8.2)
Non-cardiac chest pain	1 (10.0)	0	0	0	0	0	1 (2.0)
Pain	0	1 (10.0)	0	0	0	0	1 (2.0)
Gastrointestinal Disorders							
Vomiting	0	2 (20.0)	0	0	0	0	2 (4.1)
Gastroesophageal reflux disease	1 (10.0)	0	0	0	0	0	1 (2.0)
Gingival bleeding	0	0	0	0	1 (9.1)	0	1 (2.0)
Nausea	1 (10.0)	0	0	0	0	0	1 (2.0)
Infections and Infestations							
Device Related Infection	0	0	0	1 (11.1)	0	0	1 (2.0)
Injury, Poisoning and Procedural Complications							
Contusion	1 (10.0)	0	0	0	0	0	1 (2.0)
Post procedural hemorrhage	0	0	0	0	1 (9.1)	0	1 (2.0)
Investigations							
Activated partial thromboplastin time prolonged	0	0	1 (12.5)	0	0	0	1 (2.0)
Nervous System Disorders							
Headache	0	1 (10.0)	0	0	0	0	1 (2.0)
Seizure	0	1 (10.0)	0	0	0	0	1 (2.0)
Product Issues							
Device malfunction	0	0	0	1 (11.1)	0	0	1 (2.0)
Psychiatric Disorders							
Restlessness	0	0	0	1 (11.1)	0	0	1 (2.0)
Respiratory, Thoracic and Mediastinal Disorders							
Hypoxia	0	0	0	1 (11.1)	0	0	1 (2.0)
Skin and Subcutaneous Tissue Disorders							
Hyperhidrosis	0	0	0	0	1 (9.1)	0	1 (2.0)
Rash	0	0	0	1 (11.1)	0	0	1 (2.0)
Vascular Disorders							
Venous thrombosis limb	0	1 (10.0)	0	0	0	0	1 (2.0)

Source: CV185118 CSR Table S.6.4. Group 5: Adolescents 12 years to <18 years; Group 4: Children 6 years to <12 years; Group 3: Young Children 2 years to < 6 years; Group 2B: Infants 28 days to < 9 months; Group 2A: Young Children 9 months to < 2 years; Group 1: Neonates up to 27 days old

8.2.3.2.2. 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 anemia (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) (Table 35):

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 (Table 36).

Table 35. Adverse Events Summary with a Cutoff of 5% - Safety Population - CV185155

System Organ Class (%) Preferred Term (%)	Apixaban N = 256	Standard of Care N = 256
TOTAL SUBJECTS WITH AN EVENT	232 (90.6)	215 (84.0)
Investigations	127 (49.6)	122 (47.7)
Platelet count decreased	55 (21.5)	55 (21.5)
Alanine aminotransferase increased	47 (18.4)	39 (15.2)
Aspartate aminotransferase increased	29 (11.3)	18 (7.0)
Neutrophil count decreased	22 (8.6)	26 (10.2)
White blood cell count decreased	21 (8.2)	28 (10.9)
Blood bilirubin increased	17 (6.6)	16 (6.3)
Blood fibrinogen decreased	12 (4.7)	13 (5.1)
Gastrointestinal disorders	123 (48.0)	130 (50.8)
Constipation	59 (23.0)	52 (20.3)
Abdominal pain	34 (13.3)	49 (19.1)
Diarrhoea	26 (10.2)	16 (6.3)
Vomiting	19 (7.4)	17 (6.6)
Nausea	18 (7.0)	20 (7.8)
Abdominal distension	17 (6.6)	12 (4.7)
Stomatitis	12 (4.7)	15 (5.9)
Blood and lymphatic system disorders	114 (44.5)	108 (42.2)
Anaemia	85 (33.2)	90 (35.2)
Thrombocytopenia	29 (11.3)	24 (9.4)
Febrile neutropenia	27 (10.5)	22 (8.6)
Neutropenia	17 (6.6)	18 (7.0)
Metabolism and nutrition disorders	92 (35.9)	92 (35.9)
Hyponatraemia	37 (14.5)	30 (11.7)
Hypoalbuminaemia	29 (11.3)	34 (13.3)
Hyperglycaemia	22 (8.6)	30 (11.7)
Hypocalcaemia	12 (4.7)	21 (8.2)
Musculoskeletal and connective tissue disorders	77 (30.1)	70 (27.3)
Back pain	29 (11.3)	19 (7.4)
Pain in extremity	28 (10.9)	25 (9.8)
Pain in jaw	14 (5.5)	15 (5.9)
Arthralgia	12 (4.7)	14 (5.5)
Muscular weakness	9 (3.5)	14 (5.5)
Vascular disorders	64 (25.0)	63 (24.6)
Hypertension	25 (9.8)	26 (10.2)
Embolism	13 (5.1)	11 (4.3)
Deep vein thrombosis	4 (1.6)	15 (5.9)
Respiratory, thoracic and mediastinal disorders	60 (23.4)	48 (18.8)
Epistaxis	24 (9.4)	14 (5.5)
Cough	16 (6.3)	12 (4.7)
General disorders and administration site conditions	59 (23.0)	63 (24.6)
Pyrexia	19 (7.4)	18 (7.0)
Fatigue	14 (5.5)	20 (7.8)
Nervous system disorders	52 (20.3)	56 (21.9)
Headache	17 (6.6)	20 (7.8)
Psychiatric disorders	34 (13.3)	36 (14.1)
Irritability	9 (3.5)	13 (5.1)
Cardiac disorders	33 (12.9)	29 (11.3)
Tachycardia	15 (5.9)	13 (5.1)

MedDRA Version 24.0
AEs are included up to end of treatment period + 2 days.
SAEs are included up to end of treatment period + 30 days.
Source: CV185155 CSR Table 14.6.2.6, CV185155 CSR Table 14.6.2.7 (with a 5% cutoff), CV185155 CSR Table 14.6.2.8 (by intensity)

Table 36. Treatment-related Adverse Events Summary Occurring in > 1 Subject - Safety Population - CV185155

System Organ Class (%) Preferred Term (%)	Apixaban N = 256	Standard of Care N = 256
TOTAL SUBJECTS WITH AN EVENT	38 (14.8)	3 (1.2)
Investigations	11 (4.3)	1 (0.4)
Alanine aminotransferase increased	6 (2.3)	1 (0.4)
Aspartate aminotransferase increased	5 (2.0)	0
Blood bilirubin increased	4 (1.6)	0
Bilirubin conjugated increased	2 (0.8)	0
Respiratory, thoracic and mediastinal disorders	9 (3.5)	0
Epistaxis	8 (3.1)	0
Gastrointestinal disorders	6 (2.3)	1 (0.4)
Haematochezia	2 (0.8)	0
Rectal haemorrhage	2 (0.8)	0
Injury, poisoning and procedural complications	5 (2.0)	0
Contusion	2 (0.8)	0
Vascular access site haemorrhage	2 (0.8)	0
Blood and lymphatic system disorders	3 (1.2)	0
Anaemia	2 (0.8)	0
Renal and urinary disorders	3 (1.2)	0
Haematuria	3 (1.2)	0

MedDRA Version 24.0
AEs are included up to end of treatment period + 2 days.
SAEs are included up to end of treatment period + 30 days.
Source: CV185155 CSR Table 14.6.2.9

8.2.3.2.3. Study CV185362

AEs were reported in 107 (84.9%) and 53 (85.5%) subjects in the apixaban and VKA/LMWH arms, respectively (Table 37). 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 (Table 37). 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 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.

Table 37. Adverse Events Summary with a Cutoff of 5% - All Treated Subjects - CV185362

	Apixaban N = 126	VKA/LMWH N = 62
TOTAL SUBJECTS WITH AN EVENT	107 (84.9)	53 (85.5)
Infections and infestations	61 (48.4)	26 (41.9)
Upper respiratory tract infection	14 (11.1)	4 (6.5)
Nasopharyngitis	13 (10.3)	8 (12.9)
Gastroenteritis	8 (6.3)	4 (6.5)
Gastrointestinal disorders	43 (34.1)	22 (35.5)
Vomiting	20 (15.9)	9 (14.5)
Diarrhoea	12 (9.5)	4 (6.5)
Respiratory, thoracic and mediastinal disorders	35 (27.8)	15 (24.2)
Epistaxis	20 (15.9)	6 (9.7)
Cough	8 (6.3)	4 (6.5)
General disorders and administration site conditions	34 (27.0)	19 (30.6)
Pyrexia	20 (15.9)	8 (12.9)
Injury, poisoning and procedural complications	34 (27.0)	19 (30.6)
Contusion	10 (7.9)	6 (9.7)
Nervous system disorders	26 (20.6)	10 (16.1)
Headache	19 (15.1)	3 (4.8)
Dizziness	4 (3.2)	4 (6.5)
Vascular disorders	14 (11.1)	3 (4.8)
Haematoma	8 (6.3)	1 (1.6)
Investigations	8 (6.3)	8 (12.9)
International normalised ratio increased	0	5 (8.1)

MedDRA Version: 24.1

Included AEs with onset between first dose and within 2 days of last dose of study medication or within 30 days of last dose of study medication for SAEs.

Source: CV185362 CSR Table 14.6.3.4.2

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 (Table 38).

Table 38. Treatment-related Adverse Events Summary Occurring in > 1 Subject - All Treated Subjects - CV185362

	Apixaban N = 126	VKA/LMWH N = 62
TOTAL SUBJECTS WITH AN EVENT	41 (32.5)	16 (25.8)
Gastrointestinal disorders	14 (11.1)	2 (3.2)
Tooth loss	3 (2.4)	0
Diarrhoea	2 (1.6)	0
Gastrointestinal haemorrhage	2 (1.6)	0
Vomiting	2 (1.6)	0
Injury, poisoning and procedural complications	10 (7.9)	8 (12.9)
Shunt thrombosis	2 (1.6)	0
Skin laceration	2 (1.6)	1 (1.6)
Respiratory, thoracic and mediastinal disorders	9 (7.1)	3 (4.8)
Epistaxis	9 (7.1)	2 (3.2)
Investigations	5 (4.0)	5 (8.1)
International normalised ratio increased	0	4 (6.5)
Skin and subcutaneous tissue disorders	5 (4.0)	1 (1.6)
Ecchymosis	3 (2.4)	1 (1.6)
Vascular disorders	4 (3.2)	1 (1.6)
Haematoma	4 (3.2)	0
Blood and lymphatic system disorders	3 (2.4)	0
Increased tendency to bruise	2 (1.6)	0
Ear and labyrinth disorders	2 (1.6)	0
Ear haemorrhage	2 (1.6)	0

MedDRA Version: 24.1

Included AEs with onset between first dose and within 2 days of last dose of study medication or within 30 days of last dose of study medication for SAEs.

Source: CV185362 CSR Table 14.6.3.5.2

When incidence rates were exposure-adjusted, *all-causality AE incidence rates per 100 person-years* within the treatment period were 523.5 in the apixaban arm and 434.5 in the VKA/LMWH arm. The most frequently reported preferred terms (PTs; incidence rate per 100 person-years of ≥ 25) were vomiting (34.2 vs 23.9), epistaxis (33.3 vs 17.1) and headache (29.8 vs 5.1), for apixaban and VKA/LMWH, respectively.

8.2.3.3. Deaths

8.2.3.3.1. Study 185118

There were no deaths reported in CV185118.

8.2.3.3.2. Study 185155

In CV185155, there were 5 deaths (1.0%) 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 reported as "other" and specified as "*cardiac arrest with disseminated intravascular coagulation, acute coronary syndrome, and retroperitoneal hemorrhage*" in the death case report form.

The causes of death of the 3 subjects in the SOC arm who died during or within 30 days after the Treatment Period were "infection," "other" specified as "*cardiac arrest*", or "other" specified as "*complications of sinus venous thrombosis / intracranial hemorrhage.*"

One subject randomized to the SOC arm died 33 days after the end of the Treatment Period. This death was attributed to infection.

8.2.3.3.3. Study 185362

There were no deaths reported in CV185362.

8.2.3.4. Other Serious Adverse Events

8.2.3.4.1. Study CV185118

Two subjects in Group 4 had 1 SAE each, both of which were considered not related to apixaban, as confirmed by the Sponsor and DMC (CV185118 CSR Table S.6.7 and CV185118 CSR Appendix 6.2). One subject with a prior history of seizures had a seizure on Day 2 and 1 subject had a venous thrombosis of the right brachial vein on Day 8. A pretreatment SAE of cardiac arrest was recorded for 1 subject; therefore, the subject was not treated in the study.

8.2.3.4.2. Study CV185155

SAEs were reported for 92 (35.9%) and 82 (32.0%) subjects in the apixaban and SOC arms, respectively (Table 39). 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.

Table 39. Serious Adverse Events Reported in > 1 Subject - Safety Population - CV185155

System Organ Class (%) Preferred Term (%)	Apixaban N = 256	Standard of Care N = 256
TOTAL SUBJECTS WITH AN EVENT	92 (35.9)	82 (32.0)
Infections and infestations	23 (9.0)	17 (6.6)
Sepsis	7 (2.7)	4 (1.6)
Device related infection	3 (1.2)	2 (0.8)
Meningitis	2 (0.8)	0
Appendicitis	1 (0.4)	2 (0.8)
Pneumonia	1 (0.4)	3 (1.2)
Sinusitis	1 (0.4)	1 (0.4)
Vascular disorders	19 (7.4)	13 (5.1)
Embolism	9 (3.5)	3 (1.2)
Hypertension	3 (1.2)	0
Deep vein thrombosis	2 (0.8)	6 (2.3)
Thrombosis	2 (0.8)	1 (0.4)
Jugular vein thrombosis	1 (0.4)	2 (0.8)
Blood and lymphatic system disorders	17 (6.6)	23 (9.0)
Febrile neutropenia	15 (5.9)	16 (6.3)
Coagulopathy	1 (0.4)	1 (0.4)
Anaemia	0	3 (1.2)
Neutropenia	0	3 (1.2)
Gastrointestinal disorders	13 (5.1)	22 (8.6)
Colitis	2 (0.8)	5 (2.0)
Pancreatitis	2 (0.8)	3 (1.2)
Abdominal pain	1 (0.4)	3 (1.2)
Constipation	1 (0.4)	5 (2.0)
Ileus	1 (0.4)	1 (0.4)
Nausea	1 (0.4)	3 (1.2)
Pancreatitis acute	1 (0.4)	1 (0.4)
Vomiting	1 (0.4)	1 (0.4)
Metabolism and nutrition disorders	12 (4.7)	7 (2.7)
Hyperglycaemia	4 (1.6)	2 (0.8)
Decreased appetite	3 (1.2)	0
Dehydration	1 (0.4)	4 (1.6)
Hyponatraemia	1 (0.4)	1 (0.4)
General disorders and administration site conditions	11 (4.3)	8 (3.1)
Pyrexia	7 (2.7)	7 (2.7)
Mucosal inflammation	2 (0.8)	0
Nervous system disorders	5 (2.0)	10 (3.9)
Leukoencephalopathy	2 (0.8)	0
Seizure	2 (0.8)	2 (0.8)
Cerebral venous sinus thrombosis	0	3 (1.2)
Encephalopathy	0	2 (0.8)
Posterior reversible encephalopathy syndrome	0	2 (0.8)
Injury, poisoning and procedural complications	4 (1.6)	3 (1.2)
Vascular access complication	1 (0.4)	2 (0.8)
Renal and urinary disorders	4 (1.6)	1 (0.4)
Nephrolithiasis	2 (0.8)	0
Respiratory, thoracic and mediastinal disorders	4 (1.6)	2 (0.8)
Pneumonitis	2 (0.8)	0
Pneumothorax	2 (0.8)	1 (0.4)
Cardiac disorders	2 (0.8)	3 (1.2)
Cardiac arrest	1 (0.4)	1 (0.4)
Immune system disorders	1 (0.4)	2 (0.8)
Anaphylactic reaction	0	2 (0.8)

MedDRA Version 24.0
SAEs are included up to end of treatment period + 30 days.
Source: CV185155 CSR Table 14.6.2.2

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 (Table 40).

Table 40. Treatment-related Serious Adverse Event Summary - Safety Population - CV185155

System Organ Class (%) Preferred Term (%)	Apixaban N = 256	Standard of Care N = 256
TOTAL SUBJECTS WITH AN EVENT	7 (2.7)	0
Investigations	2 (0.8)	0
Alanine aminotransferase increased	1 (0.4)	0
Aspartate aminotransferase increased	1 (0.4)	0
Hepatic enzyme increased	1 (0.4)	0
Vascular disorders	2 (0.8)	0
Deep vein thrombosis	1 (0.4)	0
Jugular vein thrombosis	1 (0.4)	0
Blood and lymphatic system disorders	1 (0.4)	0
Coagulopathy	1 (0.4)	0
Cardiac disorders	1 (0.4)	0
Cardiac arrest	1 (0.4)	0
Injury, poisoning and procedural complications	1 (0.4)	0
Epidural haemorrhage	1 (0.4)	0
Renal and urinary disorders	1 (0.4)	0
Haematuria	1 (0.4)	0

MedDRA Version 24.0
SAEs are included up to end of treatment period + 30 days.
Source: CV185155 CSR Table 14.6.2.3

8.2.3.4.3. Study CV185362

SAEs were reported in 26 (20.6%) and 13 (21.0%) subjects in the apixaban and VKA/LMWH arms, respectively (Table 41). All events were reported in single subjects in each arm 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 per-protocol review conducted by the independent, blinded EAC determined that the thrombi were non-events as they were present on imaging studies performed prior to study participation, and, therefore, were not treatment-emergent.

Table 41. Serious Adverse Events - All Treated Subjects - CV185362

	Apixaban N = 126	VKA/LMWH N = 62
TOTAL SUBJECTS WITH AN EVENT	26 (20.6)	13 (21.0)
Injury, poisoning and procedural complications	9 (7.1)	3 (4.8)
Shunt thrombosis	2 (1.6)	0
Contusion	1 (0.8)	1 (1.6)
Incorrect dose administered	1 (0.8)	0
Overdose	1 (0.8)	0
Post procedural haematoma	1 (0.8)	0
Procedural complication	1 (0.8)	0
Procedural haemorrhage	1 (0.8)	0
Vascular pseudoaneurysm	1 (0.8)	0
Rib fracture	0	1 (1.6)
Spinal fracture	0	1 (1.6)
Subdural haematoma	0	1 (1.6)
Toxicity to various agents	0	1 (1.6)
Infections and infestations	8 (6.3)	3 (4.8)
COVID-19	1 (0.8)	1 (1.6)
Dengue fever	1 (0.8)	0
Gastroenteritis	1 (0.8)	0
Influenza	1 (0.8)	1 (1.6)
Nasopharyngitis	1 (0.8)	0
Respiratory syncytial virus bronchiolitis	1 (0.8)	0
Sepsis	1 (0.8)	0
Viral upper respiratory tract infection	1 (0.8)	0
Pneumonia viral	0	1 (1.6)
Cardiac disorders	5 (4.0)	2 (3.2)
Arrhythmia	1 (0.8)	1 (1.6)
Cardiac dysfunction	1 (0.8)	0
Cardiac failure	1 (0.8)	0
Cardiac failure congestive	1 (0.8)	0
Ventricular fibrillation	1 (0.8)	0
Atrial septal defect acquired	0	1 (1.6)
Supraventricular tachycardia	0	1 (1.6)
Gastrointestinal disorders	3 (2.4)	3 (4.8)
Gastrointestinal haemorrhage	1 (0.8)	0
Inguinal hernia	1 (0.8)	0
Protein-losing gastroenteropathy	1 (0.8)	1 (1.6)
Gingival bleeding	0	1 (1.6)
Haematochezia	0	1 (1.6)
General disorders and administration site conditions	2 (1.6)	0
Generalised oedema	1 (0.8)	0
Impaired healing	1 (0.8)	0
Nervous system disorders	2 (1.6)	0
Seizure	1 (0.8)	0
Syncope	1 (0.8)	0
Renal and urinary disorders	2 (1.6)	0
Acute kidney injury	1 (0.8)	0
Haematuria	1 (0.8)	0
Investigations	1 (0.8)	2 (3.2)
Pulmonary arterial pressure increased	1 (0.8)	0
International normalised ratio increased	0	1 (1.6)
Intracardiac pressure increased	0	1 (1.6)
Psychiatric disorders	1 (0.8)	0
Suicidal ideation	1 (0.8)	0
Suicide attempt	1 (0.8)	0

Reproductive system and breast disorders	1 (0.8)	0
Penile haematoma	1 (0.8)	0
Respiratory, thoracic and mediastinal disorders	1 (0.8)	4 (6.5)
Acute respiratory failure	1 (0.8)	0
Pleural effusion	1 (0.8)	1 (1.6)
Hypoxia	0	1 (1.6)
Pneumothorax spontaneous	0	1 (1.6)
Pulmonary haemorrhage	0	1 (1.6)
Congenital, familial and genetic disorders	0	2 (3.2)
Congenital cystic kidney disease	0	1 (1.6)
Hypoplastic left heart syndrome	0	1 (1.6)
Metabolism and nutrition disorders	0	1 (1.6)
Dehydration	0	1 (1.6)
Musculoskeletal and connective tissue disorders	0	1 (1.6)
Pain in extremity	0	1 (1.6)

MedDRA Version: 24.1

Included SAEs with onset between first dose and within 30 days of last dose of study medication.

Source: CV185362 CSR Table 14.6.3.2.1

Treatment-related SAEs were reported in 6 (4.8%) subjects in the apixaban arm and 5 (8.1%) subjects in the VKA/LMWH arm (Table 42). All treatment-related events were reported in single subjects in each arm except for the 2 aforementioned shunt thrombosis events. These thrombosis events were adjudicated by the independent, blinded EAC as non-events and were not treatment-emergent.

Table 42. Treatment-related Serious Adverse Events - All Treated Subjects - CV185362

	Apixaban N = 126	VKA/LMWH N = 62
TOTAL SUBJECTS WITH AN EVENT	6 (4.8)	5 (8.1)
Injury, poisoning and procedural complications	5 (4.0)	3 (4.8)
Shunt thrombosis	2 (1.6)	0
Incorrect dose administered	1 (0.8)	0
Post procedural haematoma	1 (0.8)	0
Procedural haemorrhage	1 (0.8)	0
Contusion	0	1 (1.6)
Rib fracture	0	1 (1.6)
Spinal fracture	0	1 (1.6)
Subdural haematoma	0	1 (1.6)
Toxicity to various agents	0	1 (1.6)
Investigations	1 (0.8)	1 (1.6)
Pulmonary arterial pressure increased	1 (0.8)	0
International normalised ratio increased	0	1 (1.6)
Renal and urinary disorders	1 (0.8)	0
Haematuria	1 (0.8)	0
Gastrointestinal disorders	0	1 (1.6)
Gingival bleeding	0	1 (1.6)
Respiratory, thoracic and mediastinal disorders	0	1 (1.6)
Pulmonary haemorrhage	0	1 (1.6)

MedDRA Version: 24.1

Included SAEs with onset between first dose and within 30 days of last dose of study medication.

Source: CV185362 CSR Table 14.6.3.2.2

8.2.3.5. Adverse Events leading to discontinuation

8.2.3.5.1. Study CV185118

There were no AEs leading to discontinuation.

8.2.3.5.2. Study CV185155

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 (Table 43). The most common AEs leading to discontinuation were Alanine aminotransferase increased (n=3; 1.2% vs 0), and blood bilirubin increased (n=3; 1.2% vs 0), for the apixaban arm and the SOC arm, respectively.

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 (Table 47). The increased frequency of AEs leading to discontinuation resulting from liver abnormalities seen in the apixaban arm may have been due to increased reporting in this open-label study and the fact that there was no intervention to discontinue in the SOC arm.

Table 43. Adverse Events Leading to Discontinuation Summary - Safety Population - CV185155

System Organ Class (%) Preferred Term (%)	Apixaban N = 256	Standard of Care N = 256
TOTAL SUBJECTS WITH AN EVENT	35 (13.7)	2 (0.8)
Gastrointestinal disorders	7 (2.7)	1 (0.4)
Pancreatitis	2 (0.8)	0
Anal ulcer	1 (0.4)	0
Colitis	1 (0.4)	0
Pancreatitis acute	1 (0.4)	1 (0.4)
Pneumatosis intestinalis	1 (0.4)	0
Vomiting	1 (0.4)	0
Investigations	7 (2.7)	0
Alanine aminotransferase increased	3 (1.2)	0
Blood bilirubin increased	3 (1.2)	0
Activated partial thromboplastin time prolonged	1 (0.4)	0
Aspartate aminotransferase increased	1 (0.4)	0
Bilirubin conjugated increased	1 (0.4)	0
Hepatic enzyme increased	1 (0.4)	0
Liver function test abnormal	1 (0.4)	0
Injury, poisoning and procedural complications	5 (2.0)	1 (0.4)
Vascular access complication	2 (0.8)	0
Epidural haemorrhage	1 (0.4)	0
Vascular access site haemorrhage	1 (0.4)	0
Wound dehiscence	1 (0.4)	0
Vascular access site thrombosis	0	1 (0.4)
Vascular disorders	3 (1.2)	0
Embolism	2 (0.8)	0
Deep vein thrombosis	1 (0.4)	0
Blood and lymphatic system disorders	2 (0.8)	0
Coagulopathy	1 (0.4)	0
Thrombocytopenia	1 (0.4)	0
Cardiac disorders	2 (0.8)	0
Cardiac arrest	1 (0.4)	0
Intracardiac thrombus	1 (0.4)	0
Hepatobiliary disorders	2 (0.8)	0
Drug-induced liver injury	1 (0.4)	0
Hyperbilirubinaemia	1 (0.4)	0
Infections and infestations	2 (0.8)	0
Device related infection	1 (0.4)	0
Meningitis	1 (0.4)	0
Renal and urinary disorders	2 (0.8)	0
Haematuria	2 (0.8)	0
Eye disorders	1 (0.4)	0
Retinal haemorrhage	1 (0.4)	0
Metabolism and nutrition disorders	1 (0.4)	0
Diabetic ketoacidosis	1 (0.4)	0
Nervous system disorders	1 (0.4)	0
Leukoencephalopathy	1 (0.4)	0
Seizure	1 (0.4)	0
Reproductive system and breast disorders	1 (0.4)	0
Heavy menstrual bleeding	1 (0.4)	0
Respiratory, thoracic and mediastinal disorders	1 (0.4)	0
Pneumothorax	1 (0.4)	0

MedDRA Version 24.0
AEs are included up to end of treatment period + 2 days.
SAEs are included up to end of treatment period + 30 days.
Source: CV185155 CSR Table 14.6.2.4

Treatment-related AEs leading to discontinuation were reported in 13 subjects (5.1%) in the apixaban arm and none in the SOC arm (Table 44). The most common treatment-related AEs leading to

discontinuation in the apixaban arm were hematuria (n=2; 0.8%) and Blood bilirubin increased (n= 2; 0.8%)

Table 44. Treatment-related Adverse Events Leading to Discontinuation Summary Safety Population - CV185155

System Organ Class (%) Preferred Term (%)	Apixaban N = 256	Standard of Care N = 256
TOTAL SUBJECTS WITH AN EVENT	13 (5.1)	0
Investigations	5 (2.0)	0
Blood bilirubin increased	2 (0.8)	0
Activated partial thromboplastin time prolonged	1 (0.4)	0
Alanine aminotransferase increased	1 (0.4)	0
Aspartate aminotransferase increased	1 (0.4)	0
Bilirubin conjugated increased	1 (0.4)	0
Hepatic enzyme increased	1 (0.4)	0
Injury, poisoning and procedural complications	2 (0.8)	0
Epidural haemorrhage	1 (0.4)	0
Vascular access site haemorrhage	1 (0.4)	0
Renal and urinary disorders	2 (0.8)	0
Haematuria	2 (0.8)	0
Blood and lymphatic system disorders	1 (0.4)	0
Coagulopathy	1 (0.4)	0
Cardiac disorders	1 (0.4)	0
Cardiac arrest	1 (0.4)	0
Gastrointestinal disorders	1 (0.4)	0
Vomiting	1 (0.4)	0
Reproductive system and breast disorders	1 (0.4)	0
Heavy menstrual bleeding	1 (0.4)	0
Vascular disorders	1 (0.4)	0
Deep vein thrombosis	1 (0.4)	0

MedDRA Version 24.0
AEs are included up to end of treatment period + 2 days.
SAEs are included up to end of treatment period + 30 days.
Source: CV185155 CSR Table 14.6.2.5

8.2.3.5.3. 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).

AEs leading to premature discontinuation from assigned therapy were reported in 6 (4.8%) subjects in the apixaban arm and 1 (1.6%) subject in the VKA/LMWH arm (Table 45). AEs leading to premature discontinuation occurring in 2 subjects in either treatment arm were gastrointestinal hemorrhage (1.6% apixaban; 0% VKA/LMWH) and shunt thrombosis (1.6% apixaban; 0% VKA/LMWH). In both cases, the per-protocol review conducted by the independent, blinded EAC determined that the thrombi were non-events as they were present on imaging studies performed prior to study participation, and, therefore, were not treatment-emergent. All other events were reported in single subjects in each arm.

Treatment-related AEs leading to discontinuation were reported in 5 (4.0%) subjects in the apixaban arm and 1 (1.6%) subject in the VKA/LMWH arm (Table 46). All treatment-related AEs leading to

discontinuation were reported in single subjects in each arm except for the 2 aforementioned events of shunt thrombosis.

Table 45. : Adverse Events Leading to Discontinuation Summary - All Treated Subjects - CV185362

	Apixaban N = 126	VKA/LMWH N = 62
TOTAL SUBJECTS WITH AN EVENT	6 (4.8)	1 (1.6)
Gastrointestinal disorders	2 (1.6)	0
Gastrointestinal haemorrhage	2 (1.6)	0
Injury, poisoning and procedural complications	2 (1.6)	1 (1.6)
Shunt thrombosis	2 (1.6)	0
Rib fracture	0	1 (1.6)
Spinal fracture	0	1 (1.6)
General disorders and administration site conditions	1 (0.8)	0
Gait deviation	1 (0.8)	0
Investigations	1 (0.8)	0
Pulmonary arterial pressure increased	1 (0.8)	0
Renal and urinary disorders	1 (0.8)	0
Dysuria	1 (0.8)	0
Haematuria	1 (0.8)	0
Musculoskeletal and connective tissue disorders	0	1 (1.6)
Fracture pain	0	1 (1.6)

MedDRA Version: 24.1

Included AEs with onset between first dose and within 2 days of last dose of study medication or within 30 days of last dose of study medication for SAEs.

Source: CV185362 CSR Table 14.6.3.3.1

Table 46. Treatment-related Adverse Events Leading to Discontinuation Summary - All Treated Subjects - CV185362

	Apixaban N = 126	VKA/LMWH N = 62
TOTAL SUBJECTS WITH AN EVENT	5 (4.0)	1 (1.6)
Injury, poisoning and procedural complications	2 (1.6)	1 (1.6)
Shunt thrombosis	2 (1.6)	0
Rib fracture	0	1 (1.6)
Spinal fracture	0	1 (1.6)
Gastrointestinal disorders	1 (0.8)	0
Gastrointestinal haemorrhage	1 (0.8)	0
General disorders and administration site conditions	1 (0.8)	0
Gait deviation	1 (0.8)	0
Investigations	1 (0.8)	0
Pulmonary arterial pressure increased	1 (0.8)	0
Renal and urinary disorders	1 (0.8)	0
Dysuria	1 (0.8)	0
Haematuria	1 (0.8)	0
Musculoskeletal and connective tissue disorders	0	1 (1.6)
Fracture pain	0	1 (1.6)

MedDRA Version: 24.1

Included AEs with onset between first dose and within 2 days of last dose of study medication or within 30 days of last dose of study medication for SAEs.

Source: CV185362 CSR Table 14.6.3.3.2

8.2.3.6. Clinical Laboratory Evaluations

8.2.3.6.1. Study CV185118

The most frequently occurring laboratory marked abnormality was prolonged aPTT, in 14/49 (28.6%) subjects > 1.0xULN, and in 5/49 (10.2%) subjects > 1.5xULN. Of these, elevations in 4 subjects were considered sample collection or laboratory analysis errors. There was 1 AE related to out-of-range results for laboratory investigations of prolonged aPTT, which was not associated with a bleeding events.

8.2.3.6.2. Study CV185155

Hematology

Out-of-reference-range hematologic laboratory abnormalities were observed for all subjects at baseline, which is consistent with their underlying diagnosis of ALL or LL. Leukocyte elevations to > 200,000/mm^3 were not reported for any subject. Platelet count decreases to < 20,000/mm^3 were reported for 62 subjects: 31/254 (12.2%) in each treatment arm. All subjects in the apixaban arm with a platelet count decrease to < 20,000/mm^3, experienced the event during the treatment period.
The most common laboratory-related AE reported was anemia, in 175 subjects: 85 (33.2%) and 90 (35.2%) in the apixaban and SOC arms, respectively (Table 35).

Clinical Chemistry

AEs related to out-of-range results for laboratory investigations were reported in 249 subjects: 127 (49.6%) and 122 (47.7%) in the apixaban and SOC arms, respectively (Table 35).
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 (n=82; 73.9% and n=102; 79.1%), AST (n=37; 34.9% and n=37; 34.6%) and bilirubin (n=10; 18.9 and n=9; 14.5%), for subjects in the apixaban and SOC arms, respectively (CV185155 CSR Table 14.6.3.4).

Liver Abnormalities

While SAEs corresponding to hepatobiliary disorders were not reported in either treatment arm, 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 drug-induced liver injury, 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 arms, 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 arms, respectively. Treatment discontinuation occurring within 2 weeks of liver function test elevations occurred in 7 subjects (2.7%), all in the apixaban arm (Table 47).

Table 47. Summary of Liver Related Elevations During the Treatment Period SI Units Randomized Subjects with Available Measurements - CV185155

	Apixaban N = 256	Standard of Care N = 256
AST ELEVATION		
> 3xULN, n/N (%)	21/247 (8.5)	23/247 (9.3)
> 5xULN, n/N (%)	13/247 (5.3)	9/247 (3.6)
> 10xULN, n/N (%)	5/247 (2.0)	4/247 (1.6)
> 20xULN, n/N (%)	0/247	2/247 (0.8)
ALT ELEVATION		
> 3xULN, n/N (%)	76/247 (30.8)	79/248 (31.9)
> 5xULN, n/N (%)	42/247 (17.0)	35/248 (14.1)
> 10xULN, n/N (%)	15/247 (6.1)	17/248 (6.9)
> 20xULN, n/N (%)	4/247 (1.6)	5/248 (2.0)
ALT OR AST ELEVATION (NOT NECESSARILY ON SAME DATE)		
> 3xULN, n/N (%)	78/247 (31.6)	83/248 (33.5)
> 5xULN, n/N (%)	43/247 (17.4)	38/248 (15.3)
> 10xULN, n/N (%)	15/247 (6.1)	17/248 (6.9)
> 20xULN, n/N (%)	4/247 (1.6)	5/248 (2.0)
BOTH ALT AND AST ELEVATION ON SAME DATE		
> 3xULN, n/N (%)	19/247 (7.7)	18/248 (7.3)
> 5xULN, n/N (%)	12/247 (4.9)	6/248 (2.4)
> 10xULN, n/N (%)	4/247 (1.6)	4/248 (1.6)
> 20xULN, n/N (%)	0/247	2/248 (0.8)
CONJUGATED BILIRUBIN ELEVATION		
> 1.5xULN, n/N (%)	24/179 (13.4)	21/164 (12.8)
> 2xULN, n/N (%)	17/179 (9.5)	12/164 (7.3)
DIRECT BILIRUBIN (BILDIR) > 2XULN	17/179 (9.5)	12/164 (7.3)
TOTAL BILIRUBIN (BILI) > 2XULN	8/101 (7.9)	10/102 (9.8)
AT AND TOTAL BILIRUBIN (BILI) ELEVATION		
(ALT>3XULN OR AST>3XULN) AND BILI>2XULN ON SAME DATE, n/N (%)	5/247 (2.0)	8/248 (3.2)
(ALT>3XULN OR AST>3XULN) AND BILI>1.5XULN ON SAME DATE, n/N (%)	6/247 (2.4)	10/248 (4.0)
TREATMENT DISCONTINUATIONS RELATED TO ELEVATION IN LIVER FUNCTION TESTS (%) WITHIN 14 DAYS PRIOR TO THE ONSET OF THE AE THAT LED TO DISCONTINUATION:	7 (2.7)	0
(ALT>3xULN or AST>3xULN) AND TBILI >2xULN ON SAME DATE	3 (1.2)	1 (0.4)
ALT>5xULN ON TWO CONSECUTIVE LAB DRAWS	1 (0.4)	0

The denominator to calculate percentages for each event is the total number of treated subjects with available laboratory results associated with that event during Treatment Period.
Marked Abnormality Criteria are based on the result in SI units.
Source: CV185155 CSR Table 14.6.3.5, CV185155 CSR Table 14.6.3.1 (direct and total bilirubin), CV185155 CSR Table 14.6.3.7 (discontinuations)

8.2.3.6.3. Study CV185362

Hematology

No clinically relevant differences between treatment arms were observed for hemoglobin, hematocrit, leukocyte count, or platelet count. No subjects with available measurements had platelet counts decreased from baseline to <50,000/mm^3 in either treatment arm.

Clinical Chemistry

Laboratory values that met the marked abnormality criteria were infrequent in the apixaban and SOC arms (Table 48).

Table 48. Summary of Laboratory Marked Abnormalities During Treatment Period - SI Units - CV185362

	Apixaban N = 126	VKA/LMWH N = 62
Aspartate Aminotransferase (AST) > 3XULN	0/125	2/62 (3.2)
Aspartate Aminotransferase (AST) > 5XULN	0/125	0/62
Aspartate Aminotransferase (AST) > 10XULN	0/125	0/62
Aspartate Aminotransferase (AST) > 20XULN	0/125	0/62
Alanine Aminotransferase (ALT) > 3XULN	2/125 (1.6)	0/62
Alanine Aminotransferase (ALT) > 5XULN	0/125	0/62
Alanine Aminotransferase (ALT) > 10XULN	0/125	0/62
Alanine Aminotransferase (ALT) > 20XULN	0/125	0/62
Total Bilirubin (TBILI) > 2XULN	7/125 (5.6)	4/62 (6.5)
Conjugated Bilirubin (DBILI) > 2XULN	5/114 (4.4)	2/57 (3.5)
Platelets (PLAT) < 50X10*9/L	0/124	0/62

The denominator to calculate percentages for each analyte was the total number of treated subjects with available laboratory results for that analyte and treatment group.

Marked Abnormality Criteria were based on the results in SI units during treatment period (first dose up to 2 days after last dose of study medication).

Source: CV185362 CSR Table 14.6.4.1

Liver Abnormalities

SAEs corresponding to hepatobiliary disorders were not reported in either treatment arm. 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 arm. AST and ALT elevations > 3 × ULN on the same date were reported in none of the subjects with available measurements in either treatment arm. There were no treatment discontinuations related to liver function tests in either treatment arm.

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: apixaban (n=9; 10.0% vs n=5; 11.6%), AST (n=9; 10.7% vs n=7; 15.2%), and Conjugated bilirubin (n=7; 8.0% vs n=3; 6.7%) , for apixaban vs VKA/LMWH.

8.2.3.7. Vital signs, physical findings, and other observations related to safety

There were no changes from baseline in mean vital signs or trends over time in Study CV185118, CV185155, or CV185362.

8.2.3.8. Safety in special groups and situations

Intrinsic Factors

Prospective subgroup analyses for bleeding events were performed in CV185155 for intrinsic factor groupings of age, ethnicity, gender, weight, race, BMI, and ALL risk. In the subgroup of obese subjects (n = 82), he incidences of the secondary safety endpoint of a major bleeding and/or CRNM bleeding event were similar in the apixaban and SOC arms (3/42 subjects (7.1%) and 2/40 subjects (5.0%) in the

apixaban and SOC arms, respectively; 2-sided nominal p = 0.6145; CV185155 CSR Table 14.6.1.4). In the alternative non-obese subgroup (n = 416), a major bleeding and/or CRNM bleeding event was reported in 10/210 subjects (5.8%) and 3/206 subjects (1.5%) in the apixaban and SOC arms, respectively (2-sided nominal p = 0.0544).

Extrinsic Factors

Study CV185155 enrolled subjects with ALL or LL who received systemic induction chemotherapy regimen consisting of a corticosteroid, vincristine, and single or multiple dose asparaginase (with or without daunorubicin) concomitantly with apixaban. Leukocyte elevations to > 200,000/mm^3 were not reported either in apixaban or SOC arms, and platelet count decreases to < 20,000/mm^3 were observed at similar frequencies in each arm). AEs related to out-of-range laboratory results and the frequency of findings consistent with the Hy's Law criteria for possible drug-induced liver injury were similar in the apixaban and SOC arms, suggesting that the concomitant use of apixaban with this chemotherapy regimen raises no additional safety concerns.

8.2.3.9. Drug 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, and avoidance of certain drug combinations should be considered.
In CV185118, subjects were excluded if they received treatment with a strong inhibitor or inducer of CYP3A4 or P-gp within 2 weeks of enrollment. In the event that a strong inhibitor of CYP3A4 and/or P-gp was needed, a minimum of a 48-hour washout from apixaban prior to the administration of the strong inhibitor of CYP3A4 and/or P-gp was to have been allowed for, if clinically possible. Concomitant systemic treatment with strong inhibitors or inducers of both CYP3A4 and P-gp was prohibited in CV185155 and CV185362.

Anticoagulant use or use of other agents that may increase the risk of bleeding was restricted in these studies. In CV185155, any anti-platelet therapy with aspirin or thienopyridines such as clopidogrel or ticagrelor was prohibited, as was concurrent prophylactic or therapeutic treatment with LMWH, unfractionated heparin, other oral anticoagulants, or systemic tissue plasminogen activator. In CV185362, low dose aspirin (≤ 5 mg) was allowed for some conditions such as Kawasaki disease and SVP. Otherwise, chronic daily use of nonsteroidal anti-inflammatory drugs (NSAIDs), mono anti-platelet therapy with thienopyridines such as clopidogrel, ticagrelor, or prasugrel, and dual anti-platelet therapy was prohibited.

8.2.3.10. Use in Pregnancy and Lactation

N/A

8.2.3.11. Overdose

There were no instances of intentional overdose in CV185118, CV185155, or CV185362. One case of unintentional overdose was reported in CV185362, consisting of an evening dose administered twice, without adverse effects.

8.2.3.12. Drug Abuse

N/A

8.2.3.13. Withdrawal and Rebound

In these studies, bleeding and thromboembolic events were important endpoints of the study. Post study follow-up was of critical importance and was essential to preserving subject safety and the integrity of the study. Subjects who discontinued study drug prior to completing treatment were to be followed for collection of efficacy and safety outcomes and/or survival follow-up data as per protocol.

8.2.3.14. Effects on ability to drive or operate machinery or impairment of mental ability

N/A

8.3. Postmarketing data

Apixaban is not approved for use in paediatric patients and the paediatric use of apixaban in the post-marketing setting constitutes off-label use. Upon review of off-label use data with apixaban, no new safety signals were identified.

8.4. Discussion

Apixaban for thromboembolism prevention during induction chemotherapy in paediatric subjects with newly diagnosed ALL or LL (T or B cell) and a new CVAD inserted

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, was 25.0 days (mean [SD]: 23.5 [6.25]), which may be considered limited.

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, clinical relevant non-major bleedings were observed with increased incidence (11 (4.3%) vs 3 (1.2%); RR 3.67 (1.04-13.0)) with increased need for platelet transfusion (37.1% vs 32.8%), which may be a regarded as a significant safety issue in such young. Most of these CRNM bleedings were epistaxis (8 vs 3). Further, minor bleedings were also increased (n=37 (14.5%) vs n=20 (7.8%; RR 1.85 (1.10-3.10).

Further, the frequency of AEs and treatment-related AEs were numerically increased for apixaban vs SOC (232/256 (90%) vs 215/256 (84.0%), and 38/256 (14.8%) vs 3/256 (1.2%)). Furthermore, a small increased incidence was observed for serious adverse events (35.9% vs 32%). However, interpretation of the AEs is complex due to the underlying disease and oncology treatment, and the open-label nature of the study. There was an increased frequency of discontinuation due to adverse events (13.7% vs 0.8%) on apixaban, mostly due to GI disorders (n=7; 2.7% vs n=1; 0.4%, no bleeding disorders) and liver enzyme elevations (n=7; 2.7% vs n=0), which are known AEs of apixaban, but may also be attributed to the underlying setting.

SAEs corresponding to hepatobiliary disorders were not reported, however 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.

Serious AE of embolism was reported more frequently on apixaban (n=9; 3.5% vs n= 3; 1.2%). No data are provided on the location of the embolism and on the clinical outcome. The applicant is requested to provide case narratives on all adverse events of embolisms that are reported, providing data on location, severity, treatment required and clinical outcome (**OC**).

Paediatric subjects with congenital or acquired heart disease (CAHD) requiring chronic anticoagulation for thromboembolism prevention

In **study CV185362**, a prospective, randomized, open label, multi-center study, safety and pharmacokinetics of apixaban versus vitamin K antagonist or LMWH were investigated in 192 paediatric subjects with congenital or acquired heart disease requiring chronic anticoagulation for thromboembolism prevention. The median exposure was substantial with 358 days (mean 330.6, SD 83.04) and could provide relevant information on the safety profile in this population.

A limited number of the primary safety endpoint of the composite adjudicated major or CRNM (clinical relevant non-major) 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 ((RR) of 0.16 (CI: 0.02-1.54)). 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 and limits drawing any conclusions on the risk of significant bleedings. Although, the low absolute rate of adjudicated major or CRNM bleeding events is in general reassuring, the substantially lower event rate than expected questions the external validity of the study. This implication in relation to the results should be further discussed (**OC**).

Regarding the secondary safety endpoints, one (0.79%) subject in the apixaban arm and 1 (1.61%) in the VKA/LMWH arm had an adjudicated major bleeding event during the treatment period. Further, one (0.79%) subject in the apixaban arm and 2 (3.23%) in the VKA/LMWH arm had an adjudicated CRNM bleeding event during the treatment period. In total, 47 (37.30%) subjects in the apixaban arm and 23 (37.10%) in the VKA/LMWH arm had an adjudicated bleeding event (major, minor, or CRNM) during the treatment period. 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).

Adverse events were reported at similar frequency with 107 (84.9%) and 53 (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 41 (32.5%) and 16 (25.8%) subjects in the apixaban and VKA/LMWH arms, respectively. Imbalances in adverse events were seen for epistaxis and headache.

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.

In this study, elevated liver enzyme were reported at similar frequencies for the apixaban and SOC group, and no cases of elevations >3 x ULN were reported.

A generally similar incidence was observed for serious adverse events (SAEs) in the apixaban arm (n=26 (20.6%)) vs the VKA/LMWH arm (n=13 (21.0%)). The investigator considered SAEs treatment-related in 6 (4.8%) subjects in the apixaban arm and 5 (8.1%) subjects in the VKA/LMWH arm. Any clear specific factor contributing to these findings appears difficult to identify and interpretation of such data are limited by the open-label nature of the study. The SAEs all relate to bleeding complications and are consistent with adult data. The case narratives did not reveal new relevant concerns, though no information was provided on exposure to apixaban when developing a bleeding complication, e.g. anti-FXa-activity.

Drug discontinuation due to AE, intolerability, or bleeding was reported with a higher incidence of 7 (5.56%) subjects in the apixaban arm compared to the 1 (1.61%) subject in the VKA/LMWH arm (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 from the current data.

9. PRAC advice

n/a

10. Changes to the Product Information

As a result of this variation, section(s) 4.2 and 5.1 of the SmPC are being updated to provide relevant information available on efficacy and safety information of apixaban in the paediatric population.

In this application, the MAH is not claiming a new indication for VTE prophylaxis in the paediatric population, nor registering a paediatric formulation.

The following addition is proposed in section 4.2:

Paediatric population
The ~~safety and~~ efficacy of Eliquis in children and adolescents below age 18 has~~ve~~ not been established for the indication of thromboembolism prevention. Currently available data are described in section 5.1 but no recommendation on a posology can be made. ~~No data are available.~~

Assessor's comment:

In study 185362, apixaban dosed at a target exposure of 1200 ng*hr/ml was not associated with an increased risk of bleeding, as compared with VKA or LMWH. However, the external validity of study CV185362 to evaluate the bleeding risk may be questioned. Further, in study CV185155, for apixaban dosed at a target exposure of 620 ng*hr/ml, an increase of the frequency of CRNM bleeding as well as minor bleeding on apixaban as compared to Standard-Of-Care (no thromboprophylaxis) was observed. Therefore, it cannot be concluded that the safety of Eliquis in paediatric patients has been established.

Further, data on the treatment of thrombo-embolism have not been evaluated yet.

Therefore, it is requested to rephrase (**MO**):

Paediatric population
The **safety and** efficacy of Eliquis in children and adolescents below age 18 has~~ve~~ not been established ~~for the indication of thromboembolism prevention~~. Currently available data **on thromboembolism prevention** are described in section 5.1 but no recommendation on a posology can be made.

The following addition is proposed in section 5.1:

Paediatric population

Assessor's Comment:

In accordance with "A guideline on Summary of Product Characteristics (SmPC), sept 2009", a cross-reference should be made with section 4.2. Therefore it is required to add the following (**OC**):

"**There is no authorised paediatric indication (see section 4.2).**"

Prevention of VTE in paediatric patients with acute lymphoblastic leukaemia or lymphoblastic lymphoma (ALL, LL)

In the PREVAPIX-ALL study, a total of 512 patients age ≥1 to <18 with newly diagnosed ALL or LL, undergoing induction chemotherapy including asparaginase via an indwelling central venous access device, were randomised 1:1 to open-label thromboprophylaxis with apixaban or standard of care (with no systemic anticoagulation). 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 (see Table 14). Apixaban was provided as a 2.5 mg tablet, 0.5 mg tablet, or 0.4 mg/mL oral solution. The median duration of exposure in the apixaban arm was 25 days.

Table 14: Apixaban dosing in the PREVAPIX-ALL study

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

The primary efficacy endpoint was a composite of adjudicated symptomatic and asymptomatic non-fatal deep vein thrombosis, pulmonary embolism, cerebral venous sinus thrombosis, and venous thromboembolism-related death. The incidence of the primary efficacy endpoint was 31 (12.1%) in the apixaban arm versus 45 (17.6%) in the standard of care arm. The relative risk reduction did not achieve significance.

Safety endpoints included adjudicated major bleeding and a composite of adjudicated major and CRNM bleeding, using ISTH defined criteria. Major bleeding occurred in 0.8% of patients in each treatment arm. The difference between study arms for the composite of major and CRNM bleeding was not statistically significant.

Assessor's comment:

In study 185155 (Prevapix-ALL), 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, the incidence of adjudicated CRNM bleeding was increased in the apixaban treatment arm as compared to standard-of-care (n=11; 4.3% vs n=3; 1.2%, RR 3.67 (95% CI 1.04-13.0). Also, minor bleedings were observed with increased frequency on apixaban (n=37; 14.5% vs n=20; 7.8%; RR 1.85 (1.10-3.10).

The applicant is asked to describe these data in this section of the SmPC (**OC**).

Comment Concerned Member State:

We generally agree on the proposed text in 5.1, however, we find it sufficient to express that the participants received a dose designed to produce exposures comparable to those seen in adults and hence we suggest that the tables can be removed.

Assessment of the CMS comment:

The dose scheme in table 14 has been developed using complex dose-modelling, and without the information in table 14, the appropriate dosages for each weight range cannot be evidently retrieved from the dose used in adults. Therefore, it is considered relevant to include the table containing the dose schedule, as this cannot be retrieved easily in any other way. Therefore, it is not agreed with the CMS to delete the table.

Prevention of TE in paediatric patients with congenital or acquired heart disease
SAXOPHONE was a randomised 2:1 open-label, multi-center comparative study of patients 28 days to <18 years of age with congenital or acquired heart disease who require anticoagulation. Patients received either apixaban or standard of care thromboprophylaxis with a vitamin K antagonist or low molecular weight heparin. 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 (see Table 15). Apixaban was provided as a 5 mg tablet, 0.5 mg tablet, or 0.4 mg/mL oral solution. The mean duration of exposure in the apixaban arm was 331 days.

Table 15: Apixaban dosing in the SAXOPHONE study

Weight Range	Dose schedule
6 to <9 kg	1 mg twice daily
9 to <12 kg	1.5 mg twice daily
12 to <18 kg	2 mg twice daily

Weight Range	Dose schedule
18 to <25 kg	3 mg twice daily
25 to <35 kg	4 mg twice daily
≥35 kg	5 mg twice daily

The primary safety endpoint, a composite of adjudicated ISTH defined major and CRNM bleeding, occurred in 1 (0.8%) of 126 patients in the apixaban arm and 3 (4.8%) of 62 patients in the standard of care arm. The secondary safety endpoints of adjudicated major, CRNM, and all bleeding events were similar in incidence across the two treatment arms. The secondary safety endpoint of drug discontinuation due to adverse event, intolerability, or bleeding was reported in 7 (5.6%) subjects in the apixaban arm and 1 (1.6%) subject in the standard of care arm. No patients in either treatment arm experienced a thromboembolic event. There were no deaths in either treatment arm.

Assessor's comment:

For study **CV185362** (SAXOPHONE), no superiority for the composite primary safety endpoint of adjudicated major and CRNM bleeding was demonstrated. The proposed text for this study can be agreed upon. In addition, in line with the guideline on Summary of Product Characteristics, it is advised to add that the findings of this study are considered inconclusive (**OC**).

Comment Concerned Member State:

We generally agree on the proposed text in 5.1, however, we find it sufficient to express that the participants received a dose designed to produce exposures comparable to those seen in adults and hence we suggest that the tables can be removed.

Assessment of the CMS comment:

The dose scheme in table 15 has been developed using complex dose-modelling, and without the information in table 15, the appropriate dosages for each weight range cannot be evidently retrieved from the dose used in adults. Therefore, it is considered relevant to include the table containing the dose schedule, as this cannot be retrieved easily in any other way. Therefore, it is not agreed with the CMS to delete the table.

The European Medicines Agency has deferred the obligation to submit the results of studies for the treatment of venous thromboembolism with Eliquis in one or more subsets of the paediatric population ~~in venous and arterial embolism and thrombosis~~ (see section 4.2 for information on paediatric use).

Assessor's comment:

This remark is agreed upon.

Please refer to Attachment 1 which includes all the changes to the Product Information as proposed by the Applicant (including an additional editorial change in section 5.1), including the Rapporteur's assessment.

11. Request for supplementary information

11.1. Major objections

Clinical aspects

1. In study CV185362, apixaban dosed at a target exposure of 1200 ng*hr/ml was not associated with an increased risk of bleeding, as compared with VKA or LMWH. However, the external validity of study CV185362 to evaluate the bleeding risk may be questioned. Further, in study CV185155, for apixaban dosed at a target exposure of 620 ng*hr/ml, an increase of the frequency of clinical relevant non-major (CRNM) bleeding as well as minor bleeding on apixaban as compared to Standard-Of-Care (no thromboprophylaxis) was observed. Therefore, it cannot be concluded that the safety of Eliquis in paediatric patients has been established. Further, data on the treatment of thrombo-embolism have not been evaluated yet. Therefore, it is requested to rephrase the statement in section 4.2 as follows:

   Paediatric population
   The **safety and** efficacy of Eliquis in children and adolescents below age 18 has~~ve~~ not been

established ~~for the indication of thromboembolism prevention~~. Currently available data **on thromboembolism prevention** are described in section 5.1 but no recommendation on a posology can be made.

11.2. Other concerns

Clinical aspects

2. In study CV185155, 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), with 31 (12.1%) and 45 (17.6%) events for apixaban vs SOC, though not reaching statistical significance. This numerical improvement was mostly attributable to a numerical improvement in asymptomatic deep venous thrombosis (DVT) events (27 vs 38). From the data provided, it is not clear as to whether the numerical reduction of asymptomatic DVT only concerns central venous access device (CVAD)-related thrombi. No data are provided on the location of the thrombi, especially in relation to the position of the CVAD, as well as on the severity, treatment required and clinical outcome. The applicant is asked to provide these data.

3. In study CV185155, serious adverse event (AE) of embolism was reported more frequently on apixaban (n=9; 3.5% vs n=3;1.2%). No data are provided on the location of the embolism and on the clinical outcome. The applicant is requested to provide case narratives on all adverse events of embolisms that are reported, providing data on location, severity, treatment required and clinical outcome.

4. In study CV185362, a very limited number of 1 vs 3 events of the primary safety endpoint has been observed, which is far below the estimated bleeding event rate of 8% vs 24% to power the study. Although such numbers appear to be reassuring, these numbers limits drawing any conclusions on the risk of significant bleedings and questions the external validity of the study. The MAH is requested to discuss the value/external validity of this study also in relation to the observed findings.

5. In accordance with ”A guideline on Summary of Product Characteristics (SmPC), sept 2009”, in section 5.1 of the SmPC, subsection Paediatric Population, a cross-reference should be made with section 4.2. Therefore, it is required to add the following: ” There is no authorised paediatric indication (see section 4.2).”

6. In study CV185155 (Prevapix-ALL), 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, the incidence of adjudicated clinical relevant non-major (CRNM) bleeding was increased in the apixaban treatment arm as compared to standard -of-care (n=11; 4.3% vs n=3; 1.2%, RR 3.67 (95% CI 1.04-13.0). Also, minor bleedings were observed with increased frequency on apixaban (n=37; 14.5% vs n=20; 7.8%; RR 1.85 (1.10-3.10). The applicant is asked to describe these data in section 5.1 of the SmPC (please refer to the annotated SmPC).

7. For study CV185362 (SAXOPHONE), no superiority for the composite primary safety endpoint of adjudicated major and CRNM bleeding was demonstrated. The proposed text for this study in section 5.1 of the SmPC can be agreed upon. However, in line with the guideline on Summary of Product Characteristics, it is advised to add that the findings of this study are considered inconclusive (please refer to the annotated SmPC).

12. Assessment of the responses to the request for supplementary information

12.1. Major objections

Clinical aspects

1. In study CV185362, apixaban dosed at a target exposure of 1200 ng*hr/ml was not associated with an increased risk of bleeding, as compared with VKA or LMWH. However, the external validity of study CV185362 to evaluate the bleeding risk may be questioned. Further, in study CV185155, for apixaban dosed at a target exposure of 620 ng*hr/ml, an increase of the frequency of CRNM bleeding as well as minor bleeding on apixaban as compared to Standard-Of-Care (no thromboprophylaxis) was observed. Therefore, it cannot be concluded that the safety of Eliquis in paediatric patients has been established. Further, data on the treatment of thrombo-embolism have not been evaluated yet. Therefore, it is requested to rephrase the statement in section 4.2 as follows:

Paediatric population

The **safety and** efficacy of Eliquis in children and adolescents below age 18 has**ve** not been established ~~for the indication of thromboembolism prevention~~. Currently available data **on thromboembolism prevention** are described in section 5.1 but no recommendation on a posology can be made.

Summary of the MAH's Response

A response is provided below regarding the validity of safety results observed in studies CV185155 and CV185362. However, considering that a positive benefit/risk balance was not established in thromboembolism prevention, the Marketing Authorization Holder (MAH) agrees with the request of the CHMP to modify the Summary of Product Characteristics (SmPC) statement in Section 4.2 as requested (a revised version of the Product Information is provided in Module 1).

Regarding the exposure data from studies CV185155 and CV185362, the MAH would like to call attention to the following observations:

- Despite the lower apixaban exposures observed in Study CV185155 relative to those in Study CV185362, the safety of apixaban in the former was being compared to that of no systemic anticoagulation, which was the Standard of Care (SOC) at the time for this patient population with newly diagnosed Acute Lymphoblastic Leukemia / Lymphoblastic Lymphoma (ALL/LL). Accordingly, it is reasonable to expect a higher incidence of bleeding events among patients receiving anticoagulation compared to those receiving none.
- Attention is further directed to the observed rates of Major, Clinically Relevant Non-major (CRNM), as well as Minor bleeding events in the apixaban and comparator groups of studies CV185155 (no systemic anticoagulation) and CV185362 (vitamin K antagonist [VKA] / Low Molecular Weight Heparin [LMWH]), summarized in Table 1.1-1:
- For Study CV185155 the sum totals of any bleeding events reported were 50 (19.5%) in the apixaban group and 25 (9.8%) in the SOC group. These rates are compared to those for any bleeding events in Study CV185362, of 47 (37.3%) and 23 (37.1%) in the apixaban

and VKA/LMWH groups, respectively.

- The incidence of any bleeding events was higher in the apixaban group of Study CV185362 than in the apixaban group of Study CV185155, consistent with the higher exposures targeted for the apixaban group in study CV185362.
- The incidence of any bleeding events was substantially higher in the SOC active comparator group (treated with VKA/LMWH) in Study CV185362 than in the SOC placebo comparator group of Study CV185155, also consistent with outcomes for patients exposed to anticoagulation (VKA/LMWH) compared to those who were not exposed to any, respectively.

The reported rate of bleeding events in Study CV185155 was comparable to that seen in other paediatric direct oral anticoagulants studies (Table 1.1-2).

Overall, in the paediatric apixaban clinical development program encompassing studies CV185118, -155, and -362, 970 paediatric patients at increased risk of thromboembolism were randomized, including 579 to apixaban; of whom 568 were treated. Collectively, this represents the single largest group of paediatric patients exposed to a single oral anticoagulant in the randomized clinical studies that have been conducted in this age group to-date. As such, this is a robust and reasonably sufficient overall population from which to characterize the safety of apixaban treatment in paediatric patients.

Further discussion on the external validity of Study CV185362 is provided in the response to Question 4 (See Section 4.1).

Table 1.1-1: Adjudicated Bleeding Events in Apixaban Clinical Studies

	Study CV185155		Study CV185362	
Type of bleeding events	**Apixaban (n=256)**	**Standard of Care (No anticoagulant) (n=256)**	**Apixaban (n=126)**	**Standard of Care (VKA/LMWH) (n=62)**
Major	2 (0.8)	2 (0.8)	1 (0.8)	1 (1.6)
Major + CRNM, n (%)	13 (5.1)	5 (2.0)	1 (0.8)	3 (4.8)
CRNM*, n (%)	11 (4.3)	3 (1.2)	1 (0.8)	2 (3.2)
Minor, n (%)	37 (14.5)	20 (7.8)	46 (36.5)	21 (33.9)
Any adjudicated bleeding events, n (%)	50 (19.5)	25 (9.8)	47 (37.3)	23 (37.1)

*The most common adjudicated CRNM bleeding event contributing to the treatment difference in Study CV185155 was epistaxis, identified in 8 and 3 subjects in the apixaban and Standard of Care groups, respectively.

Source: CV185155 final CSR, Table 8.1-1[1] and CV185362 final CSR, Table 8.1-1[2]; Table S.1 for CV185362 Minor bleeding events

Table 1.1-2: Bleeding Events Reported for Other Direct Oral Anticoagulants

	UNIVERSE[3]		EINSTEIN-JR[4]		ENNOBLE-ATE[5]		DIVERSITY[6]	
	Rivaroxaban	ASA	Rivaroxaban	VKA/ Heparin	Edoxaban	VKA/ LMWH	Dabigatran	SOC
	n=66	n=34	n=329	n=162	n=109	n=58	n=176	n=90
Major	1 (2%)	0	0	2 (1%)	0	0	4 (2%)	2 (2%)
CRNM	4 (6%)	3 (9%)	10 (3%)	1 (1%)	1 (0.9%)	1 (1.7%)	2 (1%)	1 (1%)
Trivial/ Minor	21 (33%)	12 (35%)	-	-	-	-	33 (19%)	21 (23%)
All Bleeding	-	-	-	-	4 (3.7%)	2 (3.4%)	38 (22%)	22 (24%)

Abbreviations: Apix: apixaban; ASA: aspirin; Dabi: dabigatran; Edox: edoxaban; LMWH: Low Molecular Weight Heparin; Riva: rivaroxaban; SOC: standard of care; VKA: vitamin K antagonist
Study duration: CV185155 = ~29 days; CV185362 = Up to 12 months; UNIVERSE = 12 months; EINSTEIN-JR = 3 months; ENNOBLE-ATE = 12 months; DIVERSITY = 3 months

Assessment of the MAH's Response

It is agreed with the applicant that the frequency of bleeding events in study CV185155 is limited, and reduced as compared with study CV185362 (with sum totals of any bleeding events in subjects on apixaban of 50 (19.5%) in study CV185155 vs 47 (37.3%) in study CV185362), logically due to the lower exposure. However, as compared with Standard-of-Care, that consists of not administering anticoagulation, the frequency of bleeding events is increased, e.g. for CRNM bleeds (n=13; 5.1% vs n=5; 2.0%). This of course can be understood from a mechanistic perspective, but it does imply that the administration of apixaban results in an increase of bleeding events, while a beneficial effect on thrombo-embolic events has not been demonstrated. Therefore, though the frequency of bleeding events is considered low, safety is not considered demonstrated as compared to standard-of-care. For that reason the statement that safety of apixaban is established cannot be agreed upon. Nevertheless, the MAH agrees with the statement as requested in section 4.2, therefore, the issue is considered resolved.

Conclusion

Issue is resolved.

☒Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☐No need to update overall conclusion and impact on benefit-risk balance

12.2. Other concerns

Clinical aspects

2. In study CV185155, 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), with 31 (12.1%) and 45 (17.6%) events for apixaban vs SOC, though not reaching statistical significance. This numerical improvement was mostly attributable to a numerical improvement in asymptomatic DVT events (27 vs 38). From the data provided, it is not clear as to whether the numerical reduction of asymptomatic DVT only concerns CVAD-related thrombi. No data are provided on the location of the thrombi, especially in relation to the position of the CVAD, as well as on the severity, treatment required and clinical outcome. The applicant is asked to provide these data.

Summary of the MAH's Response

Tabulated descriptive statistics for asymptomatic adjudicated Deep Vein Thrombosis (DVT) events are provided, including location and Central Venous Access Device (CVAD) relationship as well as severity, treatment requirement, and outcome from adverse events (AEs) associated with these clinical events. Additionally, information for location and CVAD involvement in individual subjects with both symptomatic and asymptomatic events is included in Appendix 1, and severity, treatment requirement, and outcome from the AEs associated with these clinical events is included in Appendix 2. Information on location and CVAD involvement was obtained from either individual adjudication reviewers, core lab review of images, or site assessment, in that order of preference. Regarding AEs, adjudicated clinical events were associated events first using verbatim term; for remaining non-matching events, a secondary association was made based on closest matching thrombus event, based on event date. Adverse Event Preferred Terms considered for this match included: thrombosis, vascular access site thrombosis, deep vein thrombosis, and peripheral embolism.

Among subjects with asymptomatic DVT events in Study CV185155, 17 of 27 (63%) in the apixaban group and 20 of 38 (53%) in the SOC group were adjudicated as CVAD-related (Table S.2). Accordingly, 37% of the asymptomatic thrombi in the apixaban group and 47% of those in the SOC group - were not CVAD-related. Therefore, the numerically lower incidence of adjudicated events of asymptomatic thrombi seen in the apixaban group relative to the SOC group was not limited to CVAD-related thrombi.

Among those asymptomatic thrombi that were, in fact, CVAD-related, the majority in both groups were located in the upper extremities, right more often than left, with the next most common location having been in the right atrium. The majority of the asymptomatic thrombi in both groups were of grade I or II (mild to moderate) intensity. More than half of the asymptomatic thrombi in both study groups required treatment. In the apixaban group, half of the asymptomatic thrombi were reported as recovered/recovering or resolved/resolving. This was similar to the finding in the SOC group.

In summary, the characteristics of the asymptomatic DVTs were similar in both groups in terms of anatomic location and CVAD-relatedness. CVAD-related DVTs comprised more than half of the total number of DVTs in both study groups. However, the numerically lower incidence of asymptomatic DVTs in apixaban-treated participants was observed among those whose events were CVAD-related, as well as those whose events were not CVAD-related.

Assessment of the MAH's Response

In study CV185155, asymptomatic DVT was detected in 27 (10.5%) of subjects on apixaban vs 38 (14.8%) of subjects on Standard-of-Care (no systemic anticoagulation). This numerical reduction of DVT on apixaban was driven by a slight reduction in the number of CVAD related thrombi(n=17; 6.6% vs

n=20; 7.8%), and more substantially by the number of TE events not (locally) related to the CVAD (n=9; 3.5% vs n=16; 6.3%). Embolism occurred at a similar rate for apixaban vs SoC (n=13; 5.1% vs n=11; 4.3%), and treatment was required less often on apixaban (n=15; 5.9% vs n=26; 10.2). In conclusion, the numerical reduction in asymptomatic DVT on apixaban was not only driven by a reduction in CVAD-associated thrombosis but also related to a reduction in systemic (non-catheter-related) DVT.

Conclusion:

Issue is resolved.

3. In study CV185155, serious AE of embolism was reported more frequently on apixaban (n=9; 3.5% vs n=3;1.2%). No data are provided on the location of the embolism and on the clinical outcome. The applicant is requested to provide case narratives on all adverse events of embolisms that are reported, providing data on location, severity, treatment required and clinical outcome.

Summary of the MAH's Response

In Study CV185155, 13 AEs in the apixaban group and 11 in the SOC group coded to the MedDRA preferred term of "embolism". These events are summarized in Table S.3; and Appendix 3 provides a line listing for these subjects. The line listing provides location, severity, treatment required, and outcome. Severity, treatment, and outcome are from the AE dataset, with outcome for non-serious events listed as resolved or not resolved, depending on the presence of an event end date. Information for AEs is available in Appendix 16.2.6.2 to the CV185155 final CSR. Narratives for serious adverse events (SAEs) in apixaban-treated subjects are also available in Table S.600 to the CV185155 final CSR.

Among these AEs, 9 SAEs were reported in the apixaban group, and 3 other SAEs were reported in the SOC group. A total of 6 of 9 SAEs in the apixaban group were reported by the investigator as asymptomatic DVT on the end-of-study scans. According to the study protocol, all AEs of thromboembolism were sent for adjudication except for those determined at the site to be superficial venous thromboses. In the apixaban group, 10 of the 13 embolism-associated AEs were adjudicated as an event while, similarly in the SOC group, 8 of the 11 embolism-associated AEs were adjudicated as an event. The remaining events were either adjudicated as non-events or were superficial venous thromboses. In both groups, all the adjudicated events were DVTs; none were emboli. The explanation for this finding is that the investigator-reported AE terms as listed in Appendix 3 are mapped to the MedDRA term "embolism" even though there was no embolic event.

The AEs were grade 1 or 2 in 11 of 13 AEs in the apixaban group and 10 of 11 in the SOC group. Of the remaining 2 AEs in the apixaban group, one grade 3 and one was grade 4. Treatment was required for 10 of 13 AEs in the apixaban group and 7 of 11 in the SOC group. In the apixaban group, 11 of 13 AE were recovered/recovering or resolved/resolving, compared to 6 of 11 in the SOC group.

In summary, while AEs and SAEs that were mapped to the MedDRA preferred term of "embolism" were reported in both treatment groups, in fact none of these events were adjudicated as having been an embolic event. There was, therefore, no imbalance in adjudicated embolism events between the 2 study groups during the intended treatment period.

Assessment of the MAH's Response

In study CV185155 13 vs 11 AEs were coded as MedDRA preferred term "embolism" for apixaban vs SoC, with 9 vs 3 graded serious. Upon adjudication, 10/13 and 8/11 were DVTs and 3/13 vs 3/11 were superficial venous thrombosis. No AE was adjudicated as embolism. From the data provided, no difference for AEs reported as embolism between both treatment groups was seen.

Conclusion:

Issue is resolved.

4. In study CV185362, a very limited number of 1 vs 3 events of the primary safety endpoint has been observed, which is far below the estimated bleeding event rate of 8% vs 24% to power the study. Although such numbers appear to be reassuring, these numbers limits drawing any conclusions on the risk of significant bleedings and questions the external validity of the study. The MAH is requested to discuss the value/external validity of this study also in relation to the observed findings.

Summary of the MAH's Response

In Study CV185362, the primary safety endpoint was a composite of adjudicated Major or CRNM bleeding. One (0.79%) subject in the apixaban group and 3 (4.84%) subjects in the SOC group met the primary safety endpoint.

Study CV185362 was not powered to identify statistically significant treatment differences that might exist, given the limited number of thromboembolic events expected to occur in this study population; instead, it was designed as a safety and pharmacokinetic/pharmacodynamic (PK/PD) study in which the efficacy variables were summarized using descriptive statistics only, and not analyzed for statistical significance. The apixaban and SOC event rates (8% and 24%, respectively) that are cited in Question 4 of the Assessment Report, are taken from Table 8.1-4 in the CV185362 protocol; Table 8.1-4 is entitled "Possible Power to Detect a Significant Difference between Comparator Group and Apixaban Group for the Primary Safety Endpoint". The MAH would like to point out that these were not put forward as the actual event rates expected in this study. Table 8.1-4 presents a range of hypothetical treatment group event rates and corresponding treatment differences that might be seen in the study at different hypothetical levels of statistical power.

The rates of key safety events (Major and CRNM bleeding) that were observed in Study CV185362 are comparable to those reported in other studies involving thromboprophylaxis with rivaroxaban[4] and edoxaban[5] in paediatric patients with heart disease at increased risk of thromboembolic events (Table 1.1-2). Therefore, the low rates observed do not invalidate study CV185362 in light of other, contemporaneous studies with similar rates:

- In the UNIVERSE study (Part B, n=66 subjects), 1 participant (2%) experienced a single adjudicated Major bleeding event. No participants were reported to have experienced any Major bleeding events in the aspirin comparator group. The proportion of participants with CRNM

bleeding events was lower in the rivaroxaban treatment group (6%) than in the aspirin group (9%). These rates were higher than those in the apixaban and VKA/LMWH groups (0.8% and 4.8%, respectively).

- In the ENNOBLE-ATE study, adjudicated CRNM bleeding events occurred in 1 patient (0.9%) in the edoxaban treatment group at 15 days and 1 (1.7%) in the SOC anticoagulant group at 54 days, corresponding to annualized rates of 0.04 and 0.07, respectively. During the extension period (treatment through a maximum of year post-enrollment), there was 1 adjudicated clinically relevant bleeding event (0.7%).

Further, the observed rates are comparable to those reported in studies of other direct oral anticoagulants used for treatment of paediatric patients:

- DIVERSITY: 6/176 (3.4%) vs. 3/90 (3.3%) of dabigatran and heparin/VKA treated patients, respectively
- EINSTEIN-Jr: 10/329 (3.0%) vs. 3 (1.9%) of rivaroxaban and heparin and/or VKA-treated patients, respectively

In summary, the MAH considers that the low rates of Major or CRNM bleeding in Study CV185362 are consistent with those reported in other studies of direct oral anticoagulants in paediatric patients. Furthermore, when the safety results of Study CV185362 are viewed together with those from Study CV185155, the MAH believes they do, in fact, support the external validity of the study in paediatric patients with congenital or acquired cardiac disease or other conditions that place them at increased risk of thromboembolic events.

Assessment of the MAH's Response

In study CV185362 the use of apixaban was investigated in paediatric subjects with congenital or acquired heart disease. As explained by the applicant, it was not feasible to design a study that was adequately powered to show statistically significant treatment differences for any of the endpoints due to the low frequency of events related to the endpoints and due to anticipated limitations in recruitment of patients. The number of patients included was based upon feasibility and was expected to provide sufficient data for descriptive statistics on efficacy and safety. This reasoning is considered acceptable.

The power-calculation for the primary safety endpoint of the composite of adjudicated major or CRNM bleeding events, that was presented in the study protocol, was hypothetical and performed as assessments of precision. The event rate estimates of 8 vs 24% were not based on data from literature.

In fact, In the UNIVERSE study investigating rivaroxaban in children post-Fontan procedure, major bleeding occurred in 1 (2%) and CRNM bleeding in 6% of participants, vs 9% of subjects on ASA. In the ENNOBLE-ATE study, the use of edoxaban was investigated for primary or secondary thromboprophylaxis in paediatric patients with heart disease. Here, CRNM bleeding events occurred in 1 (0.9%) vs 1 (1.7%) of subjects on edoxaban vs SOC anticoagulants, and TE events occurred on no subject on edoxaban and 1 subject on SOC.

The low number of event rates for the primary safety endpoint (the composite of adjudicated major or CRNM bleeding events) that were reported in study CV185362, 1 (0.79% vs 3 (4.84%) for apixaban vs VKA/LMWH indeed is in line with the event rates that have been encountered in similar patient categories. Therefore, the external validity of the study is considered confirmed.

Conclusion:

Issue is resolved.

5. In accordance with ”A guideline on Summary of Product Characteristics (SmPC), sept 2009”, in section 5.1 of the SmPC, subsection Paediatric Population, a cross-reference should be made with section 4.2. Therefore it is required to add the following: ” There is no authorised paediatric indication (see section 4.2).”

Summary of the MAH’s Response

The MAH agrees with the request and has added the cross-reference with section 4.2 in the SmPC section 5.1, subsection Paediatric Population (a revised version of the Product Information is provided in Module 1.

Assessment of the MAH’s Response

The applicant has adapted the wording in the SmPC appropriately.

Conclusion

Issue is resolved.

6. In study CV185155 (Prevapix-ALL), 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, the incidence of adjudicated CRNM bleeding was increased in the apixaban treatment arm as compared to standard -of-care (n=11; 4.3% vs n=3; 1.2%, RR 3.67 (95% CI 1.04-13.0). Also, minor bleedings were observed with increased frequency on apixaban (n=37; 14.5% vs n=20; 7.8%; RR 1.85 (1.10-3.10). The applicant is asked to describe these data in section 5.1 of the SmPC (please refer to the annotated SmPC).

Summary of the MAH’s Response

The MAH agrees with the request and has added a description of the data on adjudicated CRNM bleeding and Minor bleeding in the description of Study CV185155 in the SmPC section 5.1 (a revised version of the Product Information is provided in Module 1).

Safety endpoints were adjudicated according to ISTH criteria. The primary safety endpoint, major bleeding, occurred in 0.8% of patients in each treatment arm. CRNM bleeding occurred in 11 patients (4.3%) in the apixaban arm and 3 patients (1.2%) in the standard of care arm. The most common CRNM bleeding event contributing to the treatment difference was mild to moderate intensity epistaxis. Minor bleeding events occurred in 37 patients in the apixaban arm (14.5%) and 20 patients (7.8%) in the standard of care arm.

Assessment of the MAH's Response

The addition of information on bleeding events for study CV185155 in section 5.1 of the SmPC adequately reflects the study findings.

Conclusion

Issue is resolved.

7. For study CV185362 (SAXOPHONE), no superiority for the composite primary safety endpoint of adjudicated major and CRNM bleeding was demonstrated. The proposed text for this study in section 5.1 of the SmPC can be agreed upon. However, in line with the guideline on Summary of Product Characteristics, it is advised to add that the findings of this study are considered inconclusive (please refer to the annotated SmPC).

Summary of the MAH's Response

The MAH understands that the results of CV185362 do not allow for a definitive assessment of efficacy. In this regard, it is important to note that this was never the intent of the study. Nevertheless, the MAH considers that the alternative language proposed below for section 5.1 of the SmPC accurately reflects the study results: "This study was prospectively designed for descriptive efficacy and safety because of the expected low incidence of TE and bleeding events in this population. Due to the observed low incidence of TE in this study, a definitive risk benefit assessment could not be established."

In agreement with the PIP, CV185362 was a randomized, controlled study of apixaban versus SOC in paediatric patients with congenital or acquired heart disease. Its main objectives, as detailed in the PIP, were to assess the safety and PK/PD characteristics of apixaban in this population. As stated in the protocol, "The reported low incidence of thromboembolic and bleeding events in children limits the feasibility for a phase III trial. However, there remains a need to understand the safety and PK/PD profile of apixaban in children with heart disease… Therefore, the current study is designed to characterize apixaban safety and PK/PD profile, and is a descriptive study for which the safety, PK/PD, and efficacy variables will be summarized." The protocol also states that CV185362 was, "not expected to be fully powered for either efficacy or safety due to the low incidence of thromboembolic and bleeding events in children".

The study results achieved the objectives of CV185362. The safety of apixaban was demonstrated to be comparable to SOC. Furthermore, the bleeding rates seen in the study were also similar to those in other pediatric direct oral anticoagulants studies. The PK/PD of apixaban were also elucidated and was consistent with its known mechanism of action. The study findings were therefore clinically meaningful, as attested to by the study Steering Committee. While it is true that there were no efficacy events in either group of the study, precluding the establishment of a benefit-risk assessment, that does not mean that the study as a whole was inconclusive or not interpretable.

" **This study was prospectively designed for descriptive efficacy and safety because of the expected low incidence of TE and bleeding events in this population. Due to the observed low incidence of TE in this study a definitive risk benefit assessment could not be established.**"

Assessment of the MAH's Response

The data on efficacy and safety from study CV185362 are reported in a balanced way. The reasoning on the interpretability of data is acknowledged and the added text in the SmPC is agreed upon.

Conclusion

Issue is resolved.

☒Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☐No need to update overall conclusion and impact on benefit-risk balance

[i] ELIQUIS (apixaban) Summary of Product Characteristics (SmPC), January 2021.
[ii] Eliquis, US Prescribing Information, Bristol-Myers Squibb and Pfizer Inc., 2012.
[iii] Cirincione B, Kowalski K, Nielsen J, et al. Population pharmacokinetics of apixaban in subjects with nonvalvular atrial fibrillation. CPT *Pharmacometrics Syst Pharmacol.* 2018;7(11):728-38.
[iv] Byon W, Sweeney K, Frost C, Boyd RA. Population pharmacokinetics, pharmacodynamics, and exploratory exposure-response analyses of apixaban in subjects treated for venous thromboembolism. *CPT Pharmacometrics Syst Pharmacol*. 2017 May;6(5):340-349.
[v] EMA. Background review for the excipient propylene glycol. Doc. Ref. EMA/CHMP/334655/2013, Committee for Human Medicinal Products (CHMP), European Medicines Agency 2014-Nov-20 (Adopted: 09-Oct-2017). Accessed at: ema.europa.eu/en/documents/report/background-review-excipient-propylene-glycol-context-revision-guideline-excipients-label-package_en.pdf