21 July 2022
EMA/899943/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Eliquis

apixaban

Procedure no.: EMEA/H/C/002148/P46/039

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Status of this report and steps taken for the assessment			
Current step	**Description**	**Planned date**	**Actual Date**
☒	Start of procedure	21 Mar 2022	21 Mar 2022
☒	CHMP Rapporteur Assessment Report	25 Apr 2022	26 Apr 2022
☒	CHMP members comments	10 May 2022	10 May 2022
☒	Updated CHMP Rapporteur Assessment Report	12 May 2022	12 May 2022
☒	CHMP adoption of conclusions:	19 May 2022	19 May 2022
☒	Submission	21 Jun 2022	20 Jun 2022
☒	Re-start	22 Jun 2022	22 Jun 2022
☒	CHMP Rapporteur Assessment Report	06 Jul 2022	06 Jul 2022
☒	CHMP members comments	11 Jul 2022	11 Jul 2022
☒	Updated CHMP Rapporteur Assessment Report	14 Jul 2022	14 Jul 2022
☒	CHMP adoption of conclusions:	21 Jul 2022	21 Jul 2022

Table of contents

1. Introduction

On 17 March 2022, the MAH submitted a completed paediatric study for apixaban (Eliquis), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

These data are submitted as part of the paediatric investigation plan for Apixaban (Eliquis) (EMEA-000183-PIP01-08-M08, study 6, last modified and approved on 20-May-2020), covering the safety and PK of apixaban vs vitamin K antagonist or LMWH in paediatric patients with congenital or acquired heart disease requiring chronic anticoagulation for thromboembolism prevention.

This clinical study report (CSR) provides results from the pre-specified final analyses of the primary safety endpoint which was a composite of major or clinically relevant non-major (CRNM) bleeding events, all secondary endpoints, and selected exploratory endpoints based on the database lock (DBL) on 15-Nov-2021. Apixaban PK and PK-PD results will be presented in a separate report. An additional report will summarize the exploratory biomarker data.

A short critical expert overview has also been provided.

Apixaban (Eliquis, Bristol-Myers Squibb and Pfizer), a factor Xa (FXa) inhibitor, was approved on 18-May-2011 in the European Union (EU) for the indication of prevention of venous thromboembolism (VTE) following knee and hip replacement surgeries in adults. Marketing authorization approval for the indication of prevention of stroke and systemic embolism in adults with nonvalvular atrial fibrillation (NVAF) with one or more risk factors was obtained on 19-Nov-2012 in the EU. Marketing Authorisation for the indication of treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults was obtained on 28-Jul-2014 in the EU.

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.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that Study CV185362 (Prospective, open-label, noncomparative 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)) is part of a clinical development program PIP01 (EMEA-000183-PIP01-08-M08). The variation application consisting of the full relevant data package (i.e containing several studies) is expected to be submitted later in 2022, after completion of all studies included in the program.

Development of apixaban for paediatric use is underway pursuant to the details provided in 2 Paediatric Investigational Plans (PIP):

- 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 less than 18 years of age.
- 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 less than 18 years of age.

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 (DN08064).

Study 2 Definitive Juvenile toxicity study in rats, post-natal day 4-90 (DN09014).

Study 3 Bioavailability of Apixaban Solution Formulation Relative to Apixaban Tablets in Healthy Subjects (CV185029).

Study 4 Single-Dose, Study to Evaluate the Pharmacokinetics, Pharmacodynamics, Safety and Tolerability of Apixaban in Paediatric Subjects (CV185118).

Study 5 Multicentre, randomized, open-label, parallel-group 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 (CV185155).

Study 6 Prospective, 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) (CV185362).

A line listing of the studies included in PIP02 (EMEA-000183-PIP02-12-M03) is mentioned below:

Study 1 Open-label, multi-centre, randomized, active controlled trial to provide PK data and data on anti-Xa activity to support the extrapolation of efficacy to children, to evaluate safety and efficacy of apixaban in children (full term neonates of a least 2.6 kg to less than 18 years of age) who required anticoagulation for a venous thromboembolism (CV185325).

The purpose of study CV185362 was to assess the safety of apixaban compared to standard-of-care (SOC; vitamin K antagonist [VKA] or subcutaneous low molecular weight heparin [LMWH]) and to evaluate apixaban pharmacokinetics (PK) in paediatric subjects with congenital or acquired heart disease requiring chronic anticoagulation for thromboprophylaxis.

2.2. Information on the pharmaceutical formulation used in the study

In study CV185362, Apixaban film-coated tablets in 2.5-mg and in 0.5-mg were used. For children unable to swallow the 0.5-mg tablet, the tablet could be mixed with semi-solid food or dispersed in baby formula, apple juice, or water for administration using an oral dosing syringe. The drug dispersion in baby formula, apple juice, or water could be administered by nasogastric or gastrostomy tube, followed by a flush with 5% dextrose injection.

The study CV185362 also utilized the apixaban oral solution (OS) formulation (0.4 mg/mL) for subjects from 5 to <18 years of age. The solution was packaged in vials (110 mL/vial) and was administered orally via oral-graduated dosing syringes (1.0 and 5.0 mL) provided for the administration of the apixaban OS. The dosing syringes were qualified in dosing accuracy studies to ensure accurate delivery of doses as low as 0.04 mg (0.1 mL).

However, in April 2017, use of the apixaban oral solution in children <5 years of age in this study was discontinued, because the amount of propylene glycol, a key solubilizing excipient in the formulation, would exceed the recommended maximum daily intake described in the European Medicines Agency (EMA) guidance.

To resume enrolment of paediatric subjects <5 years of age, a new 0.5 mg tablet was developed for use in subjects ≥3 months of age. This tablet was relatively small, being ~3 mm in diameter, and had a total weight of 20 mg. The composition (drug-to-excipient ratio) and manufacturing process (up to compression) was identical to that for the approved adult 2.5 mg and 5 mg tablets. Therefore, the new 0.5 mg tablets had the pharmaceutical characteristics of the tablets already approved for the adult population but was proportionally scaled to a lower strength for paediatric use. Since tablets were not suitable for administration in children <3 months of age, an apixaban formulation (BMS-562247-01 capsule, 0.1 mg) with suitable properties was developed for use in neonate and young infant population.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

Study CV185362, which is a Prospective, Randomized, Open Label, Multi-centre Study of the Safety and Pharmacokinetics of Apixaban versus Vitamin K Antagonist or LMWH in Paediatric Subjects with Congenital or Acquired Heart Disease Requiring Chronic Anticoagulation for Thromboembolism Prevention.

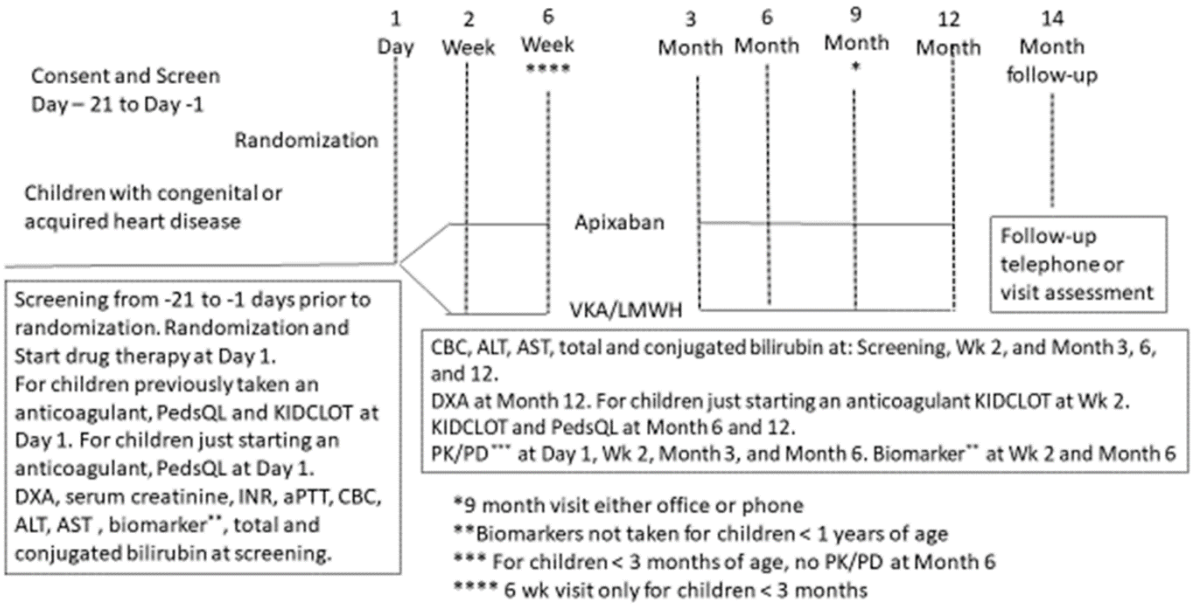
The purpose of CV185362 was to assess the safety of apixaban compared to standard-of-care (SOC; vitamin K antagonist [VKA] or subcutaneous low molecular weight heparin [LMWH]) and to evaluate apixaban pharmacokinetics (PK) in paediatric subjects with congenital or acquired heart disease requiring chronic anticoagulation for thromboprophylaxis.

2.3.2. Clinical study CV185362 (PIP01 study 6)

Description

The study design schematic for Study CV185362 is presented in Figure 1.

Figure 1. 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

There were 3 study periods extending up to 14 months total. These included:

- Screening/randomization period from Day -21 to Day 1
- Treatment period from Day 1 to Month 12 (or until anticoagulation was no longer needed)
- Follow-up period from Month 12 to Month 14 (or 2 months following cessation of study drug if the duration of therapy was less than 12 months).

The screening/randomization period occurred after written informed consent was obtained. Subjects who met all the eligibility criteria were randomized to receive open-label thromboprophylaxis with either apixaban or a SOC (VKA or LMWH per treating physician) for up to 12 months or until anticoagulation was no longer needed, whichever was shorter. At the randomization visit, the subjects and/or their parents/guardians were trained on drug preparation and administration.

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

The total duration of the trial was estimated to be approximately 4 years and included an estimated recruitment period of 3 years and a study period up to 14 months.

CHMP comment

Generally, the study design is in line with the outline presented in the PIP (EMEA-000183-PIP01-08-M08) and is therefore generally acceptable.

A main treatment period of 12 months to assess the safety of apixaban can be considered sufficient

and is in agreement with the PIP (EMEA-000183-PIP01-08-M08).

Methods

Study participants

Approximately 200 subjects were planned to be randomized.

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. Subjects who were expected to be chronically anticoagulated (>1 year), should have had a study treatment duration of 12 months. Eligible subjects included those who newly started anticoagulants and those who were currently on VKA or LMWH for thromboprophylaxis. The investigator was responsible for working with the treatment team to determine if a subject met the criteria for thromboprophylaxis per the current ACCP guideline. The reasons the subject was receiving prophylaxis were documented on the electronic case report form (eCRF).

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.

CHMP comment

The inclusion criteria are sufficient to identify the target paediatric population with congenital or acquired heart disease who were at risk for clot formation. The population was diagnosed based on major current guidelines, which is acceptable and in line with the PIP (EMEA-000183-PIP01-08-M08).

Exclusion criteria can also be accepted.

Treatments

Subjects were randomized in a 2:1 ratio to either of the 2 following treatment arms:

- Apixaban: Oral, fixed-dose, body weight-tiered regimens twice daily
- SOC (VKA or LMWH): Dosing per local SOC aligned with the current ACCP guidelines

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 (eg, UFH, LMWH) was allowed in the

apixaban arm when patients could not tolerate oral intake or when bridging around surgeries or procedures.

Selection of Doses Used in the Study

The dose selection rationale for apixaban in this study was based on the results of Study CV185118, which had the primary objective of assessing the PK of a single oral dose of apixaban in paediatric subjects aged 28 days to < 18 years. In this study, the clearance (CL) of orally administered apixaban increased with increasing age and reached values in paediatric subjects older than 12 years similar to those reported in adults. In addition, oral CL, when normalized to body weight, was constant across the paediatric age range of 3 months to 18 years, with a trend towards age dependence on CL in infants < 3 months of age. A linear relationship between apixaban concentration and anti-FXa activity was observed, consistent with that observed in adult subjects. The dose of apixaban was determined by a population PK (PPK) modeling method that was developed using paediatric data pooled with adult data. Apixaban exposure was adequately characterized by a 2-compartment model with first-order absorption and first-order elimination with the primary influential covariate of body weight for scaling of CL and volume (V) in this patient population. Based on PK simulations performed with this model, a weight-based dosing scheme was selected. Simulations showed that this dosing scheme achieved a similar median steady-state area under the concentration-time curve in one dosing interval, AUC (TAU), in this population to that observed in adults who received apixaban.

Selection and Timing of Dose for Each Subject

A phased recruitment for this study has been used, based on the informed dose selection from the single dose PK/PD study CV185118. Recruitment started first in January 2017 for children aged 2 to <18 years and was extended to children aged 3 months to <2 years in December 2017. Recruitment opened to children 28 days to <3 months in February 2020.

In April 2017, use of the apixaban oral solution in children <5 years of age in this study was discontinued, because the amount of propylene glycol, a key solubilizing excipient in the formulation, would exceed the recommended maximum daily intake described in the European Medicines Agency (EMA) guidance. To resume enrolment of paediatric subjects <5 years of age, a new 0.5 mg tablet was developed for use in subjects ≥3 months of age. This tablet was relatively small, being ~3 mm in diameter, and had a total weight of 20 mg. The composition (drug-to-excipient ratio) and manufacturing process (up to compression) was identical to that for the approved adult 2.5 mg and 5 mg tablets. Therefore, the new 0.5 mg tablets had the pharmaceutical characteristics of the tablets already approved for the adult population but was proportionally scaled to a lower strength for pediatric use. Since tablets were not suitable for administration in children <3 months of age, an apixaban formulation (BMS-562247-01 capsule, 0.1 mg) with suitable properties was developed for use in neonate and young infant population.

With the introduction of 0.5 mg tablets, the dosing paradigm of apixaban changed from mg/kg dosing to fixed-dose, body weight-tiered regimen, as outlined in Table 1. The fixed-dose, body weight-tiered regimen for infants and children ≥6 kg and ≥3 months of age used apixaban doses in increments of 0.5 to 1 mg according to the appropriate weight range for both oral solution and 0.5 mg tablets. With the introduction of the 0.1 mg capsule formulation, a body weight-tiered dosing regimen was expanded to subjects ≥3 kg and as young as 28 days of age. Apixaban doses were administered orally or via a nasogastric tube (NGT) or gastric tube (GT) approximately 12 hours apart. Subjects 28 days to <3 months were required to tolerate oral/NGT/GT feeds for at least 5 days prior to randomization.

Table 1. Apixaban Doses for Ages 28 Days to <18 Years.

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

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. Patient diaries were used to record study drug administration.

CHMP comment

The dose selection rationale for apixaban in this study was based on the results of Study CV185118. Study CV185118 was assessed under procedure number EMEA/H/C/002148/P46/037. This was a Phase 1 study to evaluate the PK, PD, safety, and tolerability of apixaban in paediatric subjects aged 0-<18 years at risk for a venous or arterial thrombotic disorder. The agreed study was considered fulfilled as the study provided information on apixaban dosing for children from 28 days to <18 years of age, but the initial predicted and used doses in study CV185118 should be further refined with the final updated PopPK model and potentially further paediatric data to be collected, in upcoming requests for extension of indication to paediatrics. Data regarding the development of the pharmacokinetic model are currently not presented, therefore further evaluation of the validity of this model is currently not possible. The Applicant should provide this, or in the absence of these data a discussion is needed.

Further, an age specific formulation of a 0.5 mg tablet (in additional to the existing approved 2.5 mg tablet) has been used for patients <5 years of age (replacing an oral solution due to too high levels of propylene glycol), which is also part of the PIP process. Unfortunately, any further insight on the formulations being used during the study has not been given and should be presented during any further type II variation procedure.

Objective(s), Outcomes/endpoints

The study objectives and endpoints are presented below.

Objectives	Endpoints	Included in this Report?
PRIMARY		

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.	• Primary safety endpoint: • Composite of adjudicated major or CRNM bleeding per ISTH criteria. • Secondary safety endpoints: • Adjudicated major bleeding • Adjudicated CRNM bleeding • All bleeding • Drug discontinuation due to adverse effects, intolerability, or bleeding • All cause death	Yes
To evaluate apixaban PK in pediatric subjects with congenital or acquired heart disease requiring chronic anticoagulation for thromboprophylaxis.	Individual PK parameters (eg, Cmax, Cmin, AUC (TAU), CL/F, Vc/F)	No. Results will be presented in a separate report.
SECONDARY		
To assess apixaban PD by measuring FX using chromogenic assay and anti-FXa activity in pediatric subjects with congenital or acquired heart disease requiring chronic anticoagulation for thromboprophylaxis.	• Percent change in the chromogenic FX assay • Anti-FXa activity	Yes
To compare the effects of apixaban on QOL measures versus VKAs or subcutaneous LMWH in pediatric subjects with congenital or acquired heart disease requiring chronic anticoagulation for thromboprophylaxis.	• PedsQL scores • KIDCLOT scores	Yes
To gather exploratory data on the efficacy of apixaban in pediatric subjects with congenital or acquired heart disease requiring chronic anticoagulation for thromboprophylaxis.	• Secondary efficacy endpoint: • Any adjudicated thromboembolic events detected by imaging or clinical diagnosis and thromboembolic event-related deaths (composite of adjudicated thromboembolic events and thromboembolic event-related deaths) • Other efficacy endpoints: • Adjudicated thromboembolic events requiring treatment change, medical intervention, hospitalization, or prolongation of hospitalization	Yes
	• Adjudicated thromboembolic event-related deaths	
OTHER		
• To evaluate biomarkers that may inform anticoagulant efficacy or risk of thrombosis in pediatric subjects with congenital or acquired heart disease requiring chronic anticoagulation for thromboprophylaxis.	Thrombin generation, factor VIII, d-dimer, proteins C and S, and fibrinogen	No. Results will be presented in a separate report.

To assess effects of apixaban on bone density in pediatric subjects with congenital or acquired heart disease requiring chronic anticoagulation for thromboprophylaxis.	Bone density change from baseline	Yes

CHMP comment

Primary (composite of adjudicated major or CRNM bleeding per ISTH criteria) and secondary objectives and endpoints included evaluation of the safety of apixaban by bleeding event rates and parameters of the blood profile. These appear valuable for assessment of safety in children with congenital or acquired heart disease who were at risk for clot formation and the objectives and endpoints are generally in agreement with the PIP (EMEA-000183-PIP01-08-M08) and are therefore acceptable.

Although the study was open-label, endpoints were adjudicated independently and blinded, which improves the internal validity of the study.

Of note, evaluation of PK and other biomarkers and exploratory data on efficacy has not been further discussed in the Applicants report, but is expected to be reported and discussed in the variation for extension of indication or the Applicant is requested to provide timelines on when these data will be provided.

Sample size

Due to anticipated low rates of thromboembolic and bleeding events in the study population and other numerous barriers, a Phase 3 trial requiring an excessively large sample size would not have been possible. However, there remains a need to understand the safety and PK/PD profile of apixaban in children with heart disease and to gather preliminary data on efficacy in this population that could be used to develop future studies. Accordingly, the study was designed to collect data for descriptive efficacy and safety, as well as for PK/PD analyses. Further, the protocol-specified random assignment of patients, in 2:1 fashion, to receive clinically indicated thromboprophylaxis with either apixaban or VKA/LMWH per local SOC also enabled descriptive comparisons to be made between the cumulative rates of AEs associated with bleeding and thromboembolism in paediatric patients treated with apixaban or VKA/LMWH. This approach is consistent with the recommendations of the Subcommittee on Pediatric and Neonatal Hemostasis and Thrombosis of the ISTH.

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 randomize and sufficient for descriptive efficacy and safety analyses, as well as for PK and PD modelling in paediatric subjects with acquired or congenital heart disease requiring thromboprophylaxis. It was expected that data collected in the current study would be combined with available data from other paediatric PK studies for population PK/PD analyses, providing the ability to capture the PK disposition in this special patient population. In addition, these analyses would provide adequate data to inform apixaban dosing in the paediatric cardiac population across age groups of 28 days to < 2 years, 2 to < 12 years, and 12 to < 18 years. The observed AEs, bleeding events, QOL, and efficacy data from this study would provide insight into the expected event rates for the paediatric population treated with apixaban or SOC to inform the benefit-risk profile.

Based upon the expectation that 2:1 randomization of approximately 200 paediatric patients with congenital or acquired heart disease requiring thromboprophylaxis with apixaban or VKA/LMWH could be recruited for study participation, and an anticipated primary safety event rate between 2% and

24%, at a 2-sided, Type I error (alpha) of 0.05, the estimated power of the study to detect a statistically significant treatment difference is summarized in Table 2.

Table 2. Power to Detect a Significant Difference between Comparator Group and Apixaban Group for the Primary Safety Endpoint (Assuming Apixaban is Better)

Comparator			Apixaban			Power to Detect a Significant Difference
Sample Size	Event Rate	Expected Number of Events	Sample Size	Event Rate	Expected Number of Events	
67	11.9%	8	133	2.3%	3	75%
	13.4%	9		2.3%	3	83%
	11.9%	8		3.8%	5	65%
	16.4%	11		3.8%	5	82%
	11.9%	8		6%	8	27%
	23.9%	16		8.3%	11	81%

CHMP comment

The sample size of 200 patients was estimated on an bleeding event rate of 24% in the control group and 8% in the apixaban group, to achieve more than 80% power to demonstrate superiority at a two-sided 0.05 level.

In the current study, the primary safety endpoint (i.e. bleeding event rate during the treatment period) was found to be in one (0.79%) subject in the apixaban arm and 3 (4.84%) subjects in VKA/LMWH arm, which is much lower than expected, indicating that the sample size estimations in Table 2 for a power to detect a statistically significant treatment difference cannot be confirmed.

With the current available figures of the primary safety endpoint, the Applicant should provide the estimated power of the study to detect a statistically significant treatment difference. Further, a discussion is needed on the impact of the newly estimated power on the findings in Study CV185362.

Randomisation and blinding (masking)

Randomisation

Subjects were randomized in a 2:1 ratio to either of the 2 following treatment arms:

- Apixaban: Oral, fixed-dose, body weight-tiered regimens twice daily
- SOC (VKA or LMWH): Dosing per local SOC aligned with the current ACCP guidelines

At enrolment, each subject was assigned a unique sequential number by the IWRS. Subjects were randomized to apixaban or SOC in a 2:1 ratio by the IWRS. 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.

Blinding

Blinding was not applicable. The study was open-label.

CHMP comment

Randomization is acceptable.

Although the study was open-label, endpoints were adjudicated independently and blinded, which improves the internal validity of the study.

Statistical Methods

Treatment Compliance

Treatment compliance was monitored by drug accountability as well as by the subject's medical record and eCRF. Doses administered had to have been between ≥80% and ≤120% of that prescribed, excluding any necessary dose interruptions.

For inpatients, apixaban was administered and recorded under the supervision of site study staff. For outpatients, the subject/guardian was instructed to bring the study medication for investigator review. Outpatient compliance was assessed based upon a count of the tablets or volume of solution returned and a subject/guardian interview. Any regurgitation of a portion of or the entire drug product during or after administration was to be recorded in the eCRF.

Efficacy Analyses

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

QOL instruments were administered only to English-speaking patients and/or their proxies (parents or guardians). Two PedsQL modules, the generic core and cardiac modules, were used. The analysis populations included randomized subjects who participated in the QOL during the intended treatment period. For both modules, descriptive statistics (mean, SD, mean difference between treatment groups, and two-sided 95% CI) were provided by visit and for the change from baseline for each post-baseline visit. The PedsQL generic core module included statistics for each dimension, psychosocial health, and total while the PedsQL cardiac module included statistics for each dimension only.

KIDCLOT was used only for subjects taking apixaban or warfarin. Descriptive statistics (mean, SD, mean difference between treatment groups, two-sided 95% CI) were provided for the total (IMPACT) score by treatment group for each visit, and for the change from baseline in the IMPACT score by treatment group for each post-baseline visit.

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.

Bleeding Events

For the primary safety endpoint of the composite of adjudicated major or CRNM bleeding events during the treatment period, descriptive statistics including event rates, difference of event rates, and 95% CIs were 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 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. Event rates of all bleeding were also presented descriptively for apixaban, enoxaparin, and warfarin.

Subgroup Analysis

Rates for the primary safety endpoint were summarized by treatment group for age stratification and clinical diagnosis stratification subgroups. Additionally, the total number and rate (exposure adjusted) of occurrences for all bleeding events were summarized by treatment group for the age 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), using the Medical Dictionary for Regulatory Activities (MedDRA) version 24.1. Listings and summaries were based on the resulting SOCs and PTs. 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. The frequency of subjects with laboratory marked abnormalities during the treatment period based on pre-specified criteria were tabulated by treatment group for each analyte. Shift analyses were performed 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. For the chromogenic FX assay, summary statistics included corresponding changes from baseline and percentage change from baseline by study day and time point. For the anti-FXa activity, summary

statistics included mean, standard error (SE), mean-time profile by age group and nominal time, geometric mean, and percent coefficient of variation (% CV), by study day and time point. 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.

CHMP comment

The definition of the analysis population is considered standard and acceptable. The primary and secondary analyses can be considered adequate for the evaluation of the safety of apixaban.

Results

Participant flow

Disposition of Subjects

A total of 198 subjects were enrolled. Of the subjects enrolled, 192 (97.0%) were randomized: 129 to receive apixaban and 63 to receive VKA/LMWH. The reasons why 6 subjects were not randomized were: subject no longer met study criteria (4 subjects); poor/noncompliance and other/investigator decision (1 subject each).

Of the 192 randomized subjects, 167 (87.0%) completed the treatment period (85.3% and 90.5% in the apixaban and VKA/LMWH arms, respectively). Of the 25 (13.0%) randomized subjects (19 and 6 in the apixaban and VKA/LMWH arms, respectively) who did not complete the treatment period:

- 4 did not receive treatment. In the apixaban arm, 1 subject no longer met study criteria because of a pre-existing coagulopathy (an exclusion criterion) discovered only after randomization, and 2 withdrew consent before being treated. In the VKA/LMWH arm, 1 subject withdrew consent before being treated. This resulted in a total of 188 treated subjects (126 in the apixaban arm and 62 in the VKA/LMWH arm).
- 21 subjects started treatment but did not complete the 12-month treatment period:
    - 12 subjects (9 apixaban-treated and 3 VKA/LMWH-treated) discontinued treatment prior to 12 months, in each case after anticoagulation was no longer clinically required. These 12 subjects were documented in the CRF as 'subject no longer meets study criteria', which included an additional field specifying that, for these subjects, anticoagulation was no longer required. Although these subjects are recorded as discontinuing the treatment period early, they have completed treatment as specified by the protocol (were treated for up to 12 months or until anticoagulation was no longer needed, whichever was shorter).
    - The 9 remaining subjects did not complete the treatment period, due to AEs (6 apixaban and 1 VKA/LMWH), consent withdrawal (1 apixaban), or loss to follow-up(1 VKA/LMWH).

Of all randomized subjects, 95.3% and 96.8% in the apixaban and VKA/LMWH arms, respectively, completed the study.

Table 3. Subject Disposition Summary - All Randomized Subjects.

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)

CHMP comment

Of the 198 patients who were screened, only 6 failed and could not be randomized. Randomization was generally balanced between groups.

A large proportion of patients completed the study (87%), although a larger proportion discontinued treatment in the apixaban group compared to the VKA/LMWH group (14.7% vs 9.5%) and there was a disbalance seen in the adverse events as reason for not completing the treatment period. The Applicant should provide a discussion on this, since this may indicate a generally poor tolerability to apixaban.

Recruitment

A total of 33 study centres in 12 countries (Australia, Austria, Brazil, Canada, Finland, Germany, Israel, Italy, Mexico, Russia, United Kingdom, and United States; see Table 3) enrolled 198 subjects, 192 of whom were randomized.

The first patient's first visit (FPFV) date was 19-Jan-2017, the first patient's first treatment (FPFT) date was 23-Jan-2017, the last patient's first treatment (LPFT) date was 30-Nov-2020, the last patient's last treatment (LPLT) was 01-Sep-2021, and the last patient's last visit (LPLV) date was 18-Oct-2021. The DBL took place on 15-Nov-2021.

CHMP comment

A large proportion (149/192; 78%) of the patients were recruited from Europe (40% apixaban and 25% VKA/LMWH) and North America (39% apixaban and 49% VKA/LMWH, mainly USA).

Similar to the discussions usually held around the assessment of the risk of VTE with the use of oestrogen containing hormonal contraception in studies performed in the US vs EU, meaningful differences in weight and weight-related baseline characteristics might exist and could impact VTE outcomes. These recruitment rates from the US might be considered more unfavourable, as compared to EU data, regarding the baseline risk of bleeding, as obesity is a known risk factor of bleeding rates.

Important Protocol Deviations

Relevant Protocol Deviations Relevant protocol deviations (RPDs) occurred in 6 subjects: 3 (2.3%) in the apixaban arm and 3 (4.8%) in the VKA/LMWH arm. In the apixaban arm, 2 RPDs were due to subjects receiving prohibited and/or restricted treatments during the study period and 1 RPD was due to a subject who was randomized and then discovered to have a coagulopathy. The latter subject was discontinued from the study before being treated, because pre-existing coagulopathy was an exclusion criterion. All 3 RPDs in the VKA/LMWH arm were due to subjects receiving prohibited and/or restricted treatments during the study period.

CHMP comment

Major protocol deviations were only 4% and mainly included prohibited and/or restricted treatments. This is therefore not considered to impact data interpretation.

Baseline data

Demographics

The majority of subjects were male (53.1%) and white (83.3%), and the median age was 7.0 (range: 0.4 - 17.0) years. The baseline demographics were generally balanced between the apixaban and VKA/LMWH arms except for sex (male subjects: 48.1% in the apixaban arm vs 63.5% in the VKA/LMWH arm; Table 4).

Table 4. Demographic Characteristics Summary - All Randomized Subjects.

	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)
COUNTRY BY GEOGRAPHIC REGION (%)			
NORTH AMERICA	50 (38.8)	31 (49.2)	81 (42.2)
CANADA	8 (6.2)	3 (4.8)	11 (5.7)
UNITED STATES OF AMERICA	42 (32.6)	28 (44.4)	70 (36.5)
LATIN AMERICA	14 (10.9)	7 (11.1)	21 (10.9)
BRAZIL	4 (3.1)	1 (1.6)	5 (2.6)
MEXICO	10 (7.8)	6 (9.5)	16 (8.3)
ASIA/PACIFIC	1 (0.8)	0	1 (0.5)
ISRAEL	1 (0.8)	0	1 (0.5)
EUROPE	52 (40.3)	16 (25.4)	68 (35.4)
AUSTRIA	7 (5.4)	0	7 (3.6)
FINLAND	6 (4.7)	0	6 (3.1)
GERMANY	9 (7.0)	9 (14.3)	18 (9.4)
ITALY	17 (13.2)	5 (7.9)	22 (11.5)
RUSSIA	2 (1.6)	0	2 (1.0)
UNITED KINGDOM	11 (8.5)	2 (3.2)	13 (6.8)
REST OF WORLD	12 (9.3)	9 (14.3)	21 (10.9)
AUSTRALIA	12 (9.3)	9 (14.3)	21 (10.9)

Baseline disease characteristics

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 5). Primary disease diagnosis was heart disease for all randomized subjects with the most common diagnosis being hypoplastic left heart syndrome (31.8%). The majority (66.7%) of subjects had prior stage 3 (Fontan) single ventricle palliative surgeries. The most common primary indication for thromboprophylaxis was routine anticoagulation after a Fontan procedure (51.0%).

Numbers of randomized subjects across treatment arms with 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 (Table 4). Baseline characteristics by age and clinical diagnosis (SVP and non-SVP) were generally balanced between the apixaban and VKA/LMWH arms.

Per the inclusion criteria, all subjects had congenital or acquired heart disease at baseline (Table 5). 92.7% of the randomized subjects reported abnormal medical history. An abnormal medical history was reported most frequently (20% in either treatment arm) in the cardiovascular system (apixaban 80.6%; VKA/LMWH 85.7%) and gastrointestinal system (apixaban 13.2%; VKA/LMWH 22.2%).

Table 5. Baseline Characteristics Summary - All Randomized Subjects.

	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 RIGHT: AORTIC ARCH, RIGHT ATRIAL ISOMERISM	1 (0.8)	0	1 (0.5)
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

Extent of 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. 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 (109.92), 332.0 (86.86), and 344.8 (52.52) days, respectively, in the apixaban arm; and 204.0 (119.62), 348.4 (47.31), and 360.7 (19.65) days, respectively, in the VKA/LMWH arm.

Table 6. Extent of Exposure from First Through Last Day of Dosing – All Randomized Subjects.

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

CHMP comment

The study included 192 patients. Most subjects were male (53.1%) and white (83.3%), and the median age was 7.0 (range: 0.4 - 17.0) years, although male patients (male subjects: 48.1% in the apixaban arm vs 63.5% in the VKA/LMWH arm) and patients in the youngest age range (8 patients in the apixaban group vs 3 in the VKA/LMWH arm) were underrepresented and imbalanced. Further, most randomized subjects received treatment for ≥337 days in both treatment arms. In general, the baseline demographics, disease demographics and exposure data were generally balanced between the arms, which is reassuring for the interpretation of the data.

The study population can be considered representative for the target paediatric population with congenital or acquired heart disease who were at risk for clot formation.

Number analysed

Table 7. Populations Analysed.

Population	Apixaban	VKA/LMWH	Total
All Enrolled Subjects, n: All subjects who signed an informed consent.	-	-	198
All Randomized Subjects, n: All randomized subjects. This population was used for the efficacy and quality of life (QOL) analyses.	129	63	192
All Treated Subjects, n: All randomized subjects who received at least one dose of study drug during the treatment period. This population was used for the safety analyses.	126	62	188
Pharmacodynamic (PD) Population, n: Subjects who received at least one dose of apixaban and had chromogenic FX assay and/or anti-FXa samples collected. This population was used for the PD analyses.	125	Not Applicable	125

Efficacy results

Table 8. Summary of Adjudicated Efficacy Endpoints During Intended Treatment Period - All Randomized Subjects.

	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

Primary efficacy endpoint

There was no primary efficacy endpoint in this study.

CHMP comment

The study included no primary efficacy endpoints, but only secondary efficacy endpoints.

Secondary Efficacy Endpoint

Adjudicated Thromboembolic Events and Thromboembolic Event- Related Deaths

The composite of adjudicated thromboembolic events and thromboembolic event-related deaths was the secondary efficacy endpoint. There were no adjudicated thromboembolic events or thromboembolic event-related deaths reported with onset during the intended treatment period in either treatment arm.

Of note, an adjudicated thromboembolic event of stroke was reported in 1 subject in the apixaban arm in 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 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 independent, blinded EAC determined that these thrombi were non-events, as they were 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.

CHMP comment

The composite of adjudicated thromboembolic events and thromboembolic event-related deaths was the secondary efficacy endpoint. There were no adjudicated thromboembolic events or thromboembolic event-related deaths reported with onset during the intended treatment period in either treatment arm. Therefore no meaningful comparison of the efficacy of apixaban vs VKA/LMWH could be established.

Quality of Life

QOL instruments were given only to English-speaking subjects and their parents/proxies. 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.

PedsQL

PedsQL questionnaires were to be completed by English-speaking subjects who were ≥5 years of age. PedsQL questionnaires were also to be completed by the parents/proxies of English-speaking subjects ≥2 years of age.

Parent- and child-reported PedsQL mean scores at baseline and post-baseline visits (Month 6 and Month 12) and the changes in mean scores from baseline for both post-baseline visits as well as the post-baseline differences in mean scores between the treatment arms were calculated. Mean scores at baseline and Month 12 and the changes in mean scores from baseline for the Month 12 visit are presented in Table 9. The changes in mean scores from baseline were small in both treatment arms. There were no clinically meaningful post-baseline differences between the treatment arms. These data were of limited interpretability due to small sample sizes.

Table 9. Summary of Child and Parent Reports of PedsQL During the Intended Treatment Period – All Randomized Subjects.

	Apixaban N = 129		VKA/LMWH N = 63	
	Baseline	Month 12	Baseline	Month 12
GENERAL-SPECIFIC MODULE ASSESSED BY CHILD				
TOTAL				
n	32	32	18	18
MEAN (SD)	69.64 (15.512)	73.37 (19.998)	60.71 (17.374)	64.81 (22.327)
MEAN CHANGE FROM BASELINE (SD)		3.73 (13.217)		4.10 (17.530)
GENERAL-SPECIFIC MODULE ASSESSED BY PARENT				
TOTAL				
n	43	43	25	25
MEAN (SD)	65.61 (16.625)	70.00 (19.560)	65.42 (18.000)	70.32 (21.949)
MEAN CHANGE FROM BASELINE (SD)		4.40 (17.915)		4.90 (15.391)
CARDIAC-SPECIFIC MODULE ASSESSED BY CHILD				
HEART PROBLEMS AND TREATMENT				
n	34	34	17	17
MEAN (SD)	65.34 (22.130)	69.46 (21.119)	64.70 (18.465)	63.44 (19.836)
MEAN CHANGE FROM BASELINE (SD)		4.11 (18.644)		-1.26 (22.881)
TREATMENT II				
n	32	32	17	17
MEAN (SD)	87.39 (22.994)	91.77 (10.896)	85.68 (15.857)	86.27 (16.400)
MEAN CHANGE FROM BASELINE (SD)		4.38 (20.432)		0.59 (11.731)
PERCEIVED PHYSICAL APPEARANCE				
n	33	33	17	17
MEAN (SD)	75.51 (27.477)	80.56 (22.408)	78.44 (23.390)	81.37 (30.689)
MEAN CHANGE FROM BASELINE (SD)		5.05 (28.710)		2.93 (23.912)
TREATMENT ANXIETY				
n	34	34	17	17
MEAN (SD)	80.52 (23.420)	80.71 (25.480)	60.31 (34.162)	60.31 (38.333)
MEAN CHANGE FROM BASELINE (SD)		0.18 (15.418)		0.00 (34.855)
COGNITIVE PROBLEMS				
n	34	34	17	17
MEAN (SD)	69.85 (20.871)	68.24 (24.367)	53.24 (20.382)	53.53 (26.796)
MEAN CHANGE FROM BASELINE (SD)		-1.62 (21.663)		0.29 (25.768)
COMMUNICATION				
n	32	32	16	16
MEAN (SD)	66.15 (30.000)	70.31 (26.681)	63.55 (28.998)	57.28 (38.948)
MEAN CHANGE FROM BASELINE (SD)		4.16 (24.685)		-6.27 (27.800)

	Baseline	Month 12	Baseline	Month 12
CARDIAC-SPECIFIC MODULE ASSESSED BY PARENT				
HEART PROBLEMS AND TREATMENT				
n	41	41	25	25
MEAN (SD)	63.68 (20.727)	66.37 (20.811)	67.71 (22.668)	69.00 (23.688)
MEAN CHANGE FROM BASELINE (SD)		2.69 (22.915)		1.28 (15.910)
TREATMENT II				
n	39	39	25	25
MEAN (SD)	91.41 (11.557)	90.30 (12.381)	85.27 (17.325)	83.80 (18.915)
MEAN CHANGE FROM BASELINE (SD)		-1.11 (15.264)		-1.46 (21.537)
PERCEIVED PHYSICAL APPEARANCE				
n	40	40	25	25
MEAN (SD)	79.16 (22.571)	79.38 (21.012)	79.66 (22.958)	74.33 (26.998)
MEAN CHANGE FROM BASELINE (SD)		0.22 (21.721)		-5.33 (18.925)
TREATMENT ANXIETY				
n	41	41	25	25
MEAN (SD)	61.44 (30.804)	64.03 (29.567)	56.27 (33.997)	57.77 (34.199)
MEAN CHANGE FROM BASELINE (SD)		2.59 (22.781)		1.50 (21.753)
COGNITIVE PROBLEMS				
n	41	41	25	25
MEAN (SD)	60.29 (29.558)	58.69 (29.560)	61.60 (25.807)	58.53 (33.432)
MEAN CHANGE FROM BASELINE (SD)		-1.60 (24.858)		-3.07 (18.584)
COMMUNICATION				
n	38	38	25	25
MEAN (SD)	65.57 (27.342)	68.20 (24.037)	67.33 (28.257)	66.17 (28.067)
MEAN CHANGE FROM BASELINE (SD)		2.63 (25.124)		-1.16 (22.622)

KIDCLOT

KIDCLOT questionnaires were to be completed by English-speaking subjects ≥8 years of age. KIDCLOT questionnaires were also to be completed 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 at baseline and post-baseline visits (Month 6 and Month 12) and the changes in mean scores from baseline for post-baseline visits as well as the post-baseline differences in mean scores between apixaban and warfarin treatments were calculated. Mean scores at baseline and post-baseline visits and the changes in mean scores from baseline for post-baseline visits are presented in Table 10. Changes from baseline were small in both the apixaban- and warfarin-treated subjects. There were no clinically meaningful differences between the treatments. These data were of limited interpretability due to small sample sizes.

Table 10. Summary of Parent- and Child-Reported KIDCLOT IMPACT Score and Change from Baseline During the Intended Treatment Period - All Randomized Subjects.

Visit/Dimension		Apixaban N = 129	VKA/LMWH N = 63
PARENT-REPORTED			
MONTH 6/TOTAL SCORE			
	n	46	30
	BASELINE MEAN (SD)	37.97 (20.493)	39.02 (17.932)
	POST-BASELINE MEAN (SD)	32.32 (17.060)	37.94 (20.626)
	MEAN CHANGE FROM BASELINE (SD)	-5.65 (16.935)	-1.08 (13.315)
MONTH 12/TOTAL SCORE			
	n	43	25
	BASELINE MEAN (SD)	38.37 (18.874)	39.36 (16.057)
	POST-BASELINE MEAN (SD)	31.10 (16.021)	33.61 (17.943)
	MEAN CHANGE FROM BASELINE (SD)	-7.26 (15.477)	-5.75 (10.631)
CHILD-REPORTED			
MONTH 6/TOTAL SCORE			
	n	24	15
	BASELINE MEAN (SD)	24.35 (12.887)	26.45 (12.114)
	POST-BASELINE MEAN (SD)	22.81 (13.380)	22.57 (16.049)
	MEAN CHANGE FROM BASELINE (SD)	-1.54 (12.356)	-3.88 (14.637)
MONTH 12/TOTAL SCORE			
	n	25	14
	BASELINE MEAN (SD)	22.50 (11.787)	25.32 (11.719)
	POST-BASELINE MEAN (SD)	21.52 (13.251)	18.01 (10.408)
	MEAN CHANGE FROM BASELINE (SD)	-0.98 (9.415)	-7.31 (11.477)

CHMP comment

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

It should, however, be noted that only English-speaking patients and their parents/proxies have completed the questionnaires. The QOL instruments used in this study were not validated in other languages. Selection bias may have played a role. Further, selection of English-speaking patients and their parents/proxies resulted in a small sample size. The bias and small sample size limited therefore the generalizability of the QOL results and can therefore not be interpreted adequately.

Other Efficacy Endpoints

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.

Safety results

Primary Safety Endpoint - Composite Adjudicated Major or CRNM Bleeding Events

One (0.79%) subject in the apixaban arm and 3 (4.84%) subjects in VKA/LMWH arm met the primary safety endpoint of the composite of adjudicated major or CRNM bleeding events during the treatment period (Table 11).

Table 11. Summary of Safety by Treatment - All Treated Subjects.

	Apixaban N = 126	VKA/LMWH N = 62
Primary Safety Endpoint		
Composite of Adjudicated Major or CRNM Bleeding		
SUBJECTS WITH EVENT (%) (95% CI)	1 (0.79) (0.02, 4.34)	3 (4.84) (1.01, 13.50)
DIFFERENCE FROM VKA/LMWH (95% CI)	-4.05 (-12.77, 0.79)	
RELATIVE RISK	NE	
Secondary Safety Endpoints		
Adjudicated Major Bleeding		
SUBJECTS WITH EVENT (%) (95% CI)	1 (0.79) (0.02, 4.34)	1 (1.61) (0.04, 8.66)
DIFFERENCE FROM VKA/LMWH (95% CI)	-0.82 (-8.14, 3.29)	
RELATIVE RISK	NE	
Adjudicated CRNM Bleeding		
SUBJECTS WITH EVENT (%) (95% CI)	1 (0.79) (0.02, 4.34)	2 (3.23) (0.39, 11.17)
DIFFERENCE FROM VKA/LMWH (95% CI)	-2.43 (-10.54, 1.94)	
RELATIVE RISK	NE	
Adjudicated All Bleeding		
SUBJECTS WITH EVENT (%) (95% CI)	47 (37.30) (28.86, 45.75)	23 (37.10) (25.07, 49.12)
DIFFERENCE FROM VKA/LMWH (95% CI)	0.20 (-14.49, 14.90)	
RELATIVE RISK (95% CI)	1.01 (0.68, 1.51)	
Safety per Investigator		
DEATH (%)	0	0
SAE (%)	26 (20.6)	13 (21.0)
RELATED SAE (%)	6 (4.8)	5 (8.1)
DISCONTINUATION DUE TO AE (%)	6 (4.8)	1 (1.6)
DISCONTINUATION DUE TO RELATED AE (%)	5 (4.0)	1 (1.6)
DISCONTINUATION DUE TO SAE (%)	4 (3.2)	1 (1.6)
AE (%)	107 (84.9)	53 (85.5)
RELATED AE (%)	41 (32.5)	16 (25.8)
COMPOSITE OF MAJOR BLEEDING AND CRNM BLEEDING (%)	3 (2.4)	2 (3.2)

The denominator to calculate each percentage was the total number of treated subjects within each treatment group.

Among these 4 subjects across both treatment arms, there were a total of 6 events: 2 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.

Of note, 1 subject in the VKA/LMWH arm experienced a major bleeding event in the follow-up period 374 days after start of dosing and 8 days after last dose and was, therefore, not included in the analysis.

When incidence rates were exposure-adjusted, the incidence rates per 100 person-years of exposure for 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.

CHMP comment

The primary safety endpoint of the study concerned the composite adjudicated major or CRNM bleeding events during the treatment period. 1/126 (0.8%) subject in the apixaban arm and 3/62 (4.8%) subjects in VKA/LMWH arm had major or CRNM bleeding events, but the study could not demonstrate a significant effect for apixaban versus VKA/LMWH with a relative risk (RR) of 0.16 (CI: 0.02-1.54) on these major or CRNM bleeding events.

In general, the number of bleeding events was low in both groups and has impacted the estimated power of the study to detect a statistically significant treatment difference (see sample size discussion). Adequate conclusions on a treatment difference between the groups can therefore not be drawn.

Secondary Safety Endpoints

Adjudicated Major Bleeding

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.

Adjudicated CRNM Bleeding

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 (Table 11).

All Adjudicated Bleeding

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 (Table 11).

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.

When incidence rates were exposure-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 .

Drug Discontinuation due to AE, Intolerability, or Bleeding

Drug discontinuation due to AE, 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). Two subjects in the apixaban arm discontinued treatment to due shunt thrombosis. These thrombi were adjudicated by the independent, blinded EAC as non-events and were not treatment-emergent.

All Cause Death

There were no deaths reported in this study.

Subgroup Analyses Composite Adjudicated Major or CRNM Bleeding Events and All Adjudicated Bleeding Events

Subgroups analyses for the composite of adjudicated major or CRNM bleeding and all adjudicated bleeding occurring during the treatment period were performed for subgroups based on the age stratum (28 days to <2 years, 2 to <12 years, and 12 to <18 years) and clinical diagnosis (SVP and non-SVP).

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).

Of the 4 subjects with the composite of adjudicated major or CRNM bleeding events across both treatment arms, 3 (1/91 [1.10%] apixaban; 2/45 [4.44%] VKA/LMWH) were subjects with SVP and 1 (1/17 [5.88%] VKA/LMWH) was a subject with a non-SVP. 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%) subjects in the apixaban arm and 0/3 subjects in the VKA/LMWH arm. Of note, all events in this age group were mild in intensity (Grade 1).
- Age 2 to < 12 years: 34/87 (39.08%) subjects in the apixaban arm and 18/44 (40.91%) subjects in the VKA/LMWH arm.
- Age 12 to < 18 years: 9/31 (29.03%) subjects in the apixaban arm and 5/15 (33.33%) subjects in the VKA/LMWH arm.

CHMP comment

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. 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. Although, the Applicant submitted the listings of the major, CRNM and minor bleeding events, no further details of these events have been provided, and are expected to be presented in response to this report.

Further, 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)), which is not supportive for use of apixaban in the target population, although adequate conclusions could not be made due to the limited numbers and the lack of power of the study.

Others Results

There were no bleeding events reported within 24 hours after cardiac catheterization or within 48 hours after surgery.

Bleeding-related Adverse Events (Non-adjudicated)

Non-adjudicated bleeding-related AEs with onset during the treatment period were reported in 33.3% and 33.9% of subjects in the apixaban and VKA/LMWH arms, respectively. 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 12. 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. No clinically relevant conclusions can be drawn from these data.

Table 12. 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)

CHMP comment

In terms of bone density, there was a slight trend to an increase observed in mean bone mineral density at Month 12 relative to baseline at all 3 locations in both treatment arms. However, these changes were also seen in the comparator arm for lumbar spine and total body. Numbers were too low and therefore no relevant conclusions can be drawn from these data.

Deaths

No deaths were reported in either treatment arm of the study.

Other Serious Adverse Events

SAEs were reported in 26 (20.6%) and 13 (21.0%) subjects in the apixaban and VKA/LMWH arms, respectively. All events were reported in single subjects 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 subject in the VKA/LMWH arm.

Treatment-related SAEs were reported in 6 (4.8%) subjects in the apixaban arm and 5 (8.1%) subjects in the VKA/LMWH arm. All treatment-related events were reported in single subjects 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 13. Serious Adverse Events - All Treated Subjects.

	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

Table 14. Treatment-related Serious Adverse Events - All Treated Subjects.

	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)

CHMP comment

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 case narratives of these cases have been provided. The Applicant is therefore asked to provide a cumulative review with causality assessment on all these available bleeding cases. The Applicant should provide for this review a structured/ step-wise approach, including an overview of cases with insufficient information that precludes further assessment, cases with confounding factors and a clear causal assessment of the individual remaining cases. The Applicant should provide a discussion on this and the imbalance of the figures within the response of this assessment report.

No subjects died during the study.

Adverse Events Leading to Discontinuation of Study Therapy

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 15). AEs leading to premature discontinuation occurring in 2 subjects in either treatment arm were gastrointestinal haemorrhage (1.6% apixaban; 0% VKA/LMWH) and shunt thrombosis (1.6% apixaban; 0% VKA/LMWH). 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 15). All treatment-related AEs leading to discontinuation were reported in single subjects in each arm except for the 2 aforementioned events of shunt thrombosis. These thrombosis events were adjudicated by the independent, blinded EAC as non-events and were not treatment-emergent.

Table 15. Adverse Events Leading to Discontinuation Summary - All Treated Subjects.

	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)

CHMP comment

There was an increased discontinuation rate reported due to adverse events (n=5 (4.0%) vs n=1 (1.6%)) in the apixaban arm when compared to the VKA/LMWH arm. This was mostly due to GI disorders (haemorrhage), which are known AEs of apixaban, but may also be attributed to the underlying setting.

Overall Adverse Events

AEs were reported in 107 (84.9%) and 53 (85.5%) subjects in the apixaban and VKA/LMWH arms, respectively (Table 16). All thromboembolic and bleeding events that were identified were reviewed by the EAC as prospectively specified per protocol. The most frequently reported AEs (≥15% in either treatment arm) were as follows:

- Vomiting: apixaban 15.9%; VKA/LMWH 14.5%
- Epistaxis: apixaban 15.9%; VKA/LMWH 9.7%

- Pyrexia: apixaban 15.9%; VKA/LMWH 12.9%
- Headache: apixaban 15.1%; VKA/LMWH 4.8%

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.

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 as follows (Table 16):

- Epistaxis: apixaban 7.1%; VKA/LMWH 3.2%.
- INR increased: apixaban 0%; VKA/LMWH 6.5%

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 PTs (incidence rate per 100 person-years of ≥25) were as follows:

- Vomiting: apixaban 34.2; VKA/LMWH 23.9
- Epistaxis: apixaban 33.3; VKA/LMWH 17.1
- Headache: apixaban 29.8; VKA/LMWH 5.1

Table 16. Adverse Events Summary with a Cut-off of 5% - All Treated Subjects.

	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)

Table 17. Treatment-related Adverse Events Summary Occurring in >1 Subject - All Treated Subjects.

	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

CHMP comment

AEs were reported in 107 (84.9%) and 53 (85.5%) subjects in the apixaban and VKA/LMWH arms, respectively. The most frequently reported AEs 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. With similar findings within the SOCs. Some imbalances have been observed between the groups, but no discussion on this has been provided by the Applicant.

Clinical Laboratory Evaluations

Marked Laboratory Test Abnormalities

Laboratory values that met the marked abnormality criteria were infrequent in both treatment arms (Table 18).

Table 18. Summary of Laboratory Marked Abnormalities During the Treatment Period - SI Units - All Treated Subjects with Available Measurements.

	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

Liver Abnormalities

SAEs corresponding to hepatobiliary disorders were not reported in either treatment arm. Serum ALT or AST elevations > 3x the upper limit of normal (ULN) associated with subsequent elevations of serum total bilirubin concentrations > 2xULN (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 (Table 18).

AST and ALT elevations > 3xULN 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 9 (10.0%) subjects; VKA/LMWH 5 (11.6%) subjects
- AST: apixaban 9 (10.7%) subjects; VKA/LMWH 7 (15.2%) subjects
- Conjugated bilirubin: apixaban 7 (8.0%) subjects; VKA/LMWH 3 (6.7%) subjects.

Hematologic Abnormalities

No clinically relevant changes between treatment arms were observed for haemoglobin, haematocrit, leukocyte count, or platelet count. No subjects with available measurements had platelet counts decreased from baseline to <50,000/mm3 in either treatment arm

CHMP comment

Regarding the clinical laboratory evaluations, no clinically relevant differences between treatment arms were observed, also not in the liver enzymes.

Pharmacodynamic results

The PD of apixaban was assessed by measuring apparent FX using the FX chromogenic assay and anti-FXa activity using the STA-Liquid Anti-FXa apixaban assay. The PD analysis population included subjects who had received at least one dose of apixaban and had chromogenic FX assay and/or anti-FXa samples collected.

Anti-FXa Activity - Secondary Endpoint

Apixaban levels as measured by anti-FXa activity were consistent with the mechanism of action of apixaban as a direct FXa inhibitor.

In the overall PD population, the pre-dose anti-FXa activity levels were similar at Week 2 and Month 6, with mean values of 86.24 and 66.93 ng/mL, respectively. There were increased anti- FXa activity levels post-dose at Day 1, Week 2, and Month 3. Two hours post-dose, mean values for anti-FXa activity at Week 2 and Month 3 were similar at 242.34 and 228.88 ng/mL, respectively (Table 19 and Figure 2).

Results for anti-FXa activity across age groups were consistent with those in the overall PD population.

Table 19. Summary Statistics for Anti-FXa Activity (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)

Figure 2. Box and Whisker Plot of Anti-FXa Activity (ng/mL) in Subjects Treated with Apixaban - PD Population.

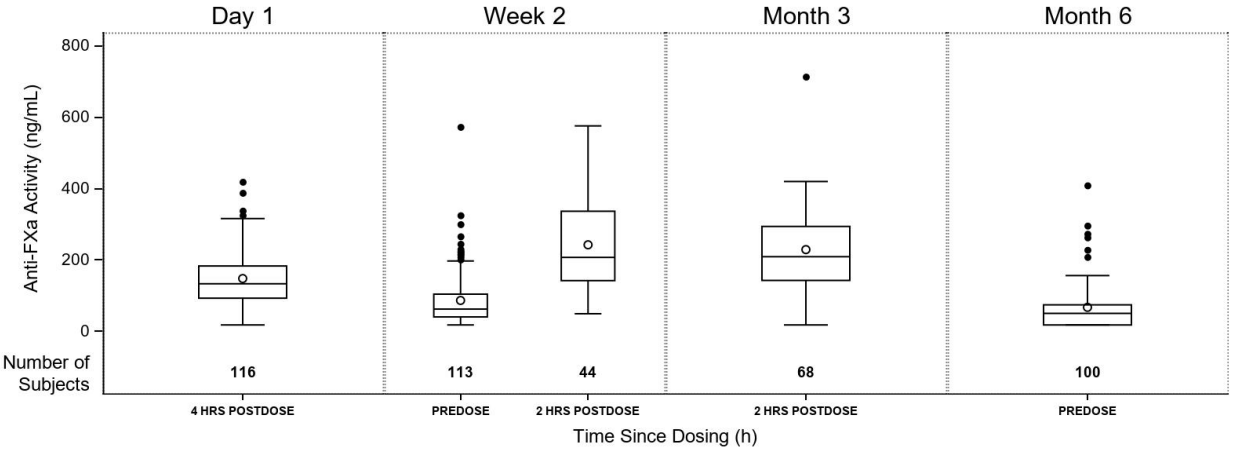
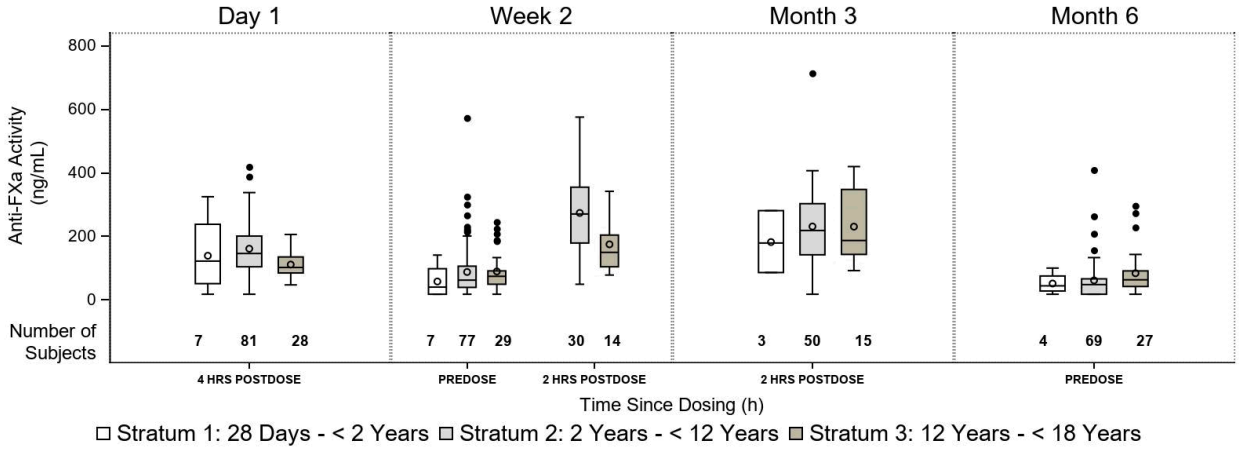


Figure 3. Box and Whisker Plot of Anti-FXa Activity (ng/mL) in Subjects Treated with Apixaban by Age – PD Population.



Chromogenic FX Assay - Secondary Endpoint

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 20 and Figure 4).

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

Table 20. 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)

Figure 4. Box and Whisker Plot of Chromogenic FX Assay (%) Percent Change from Baseline in Subjects Treated with Apixaban - PD Population

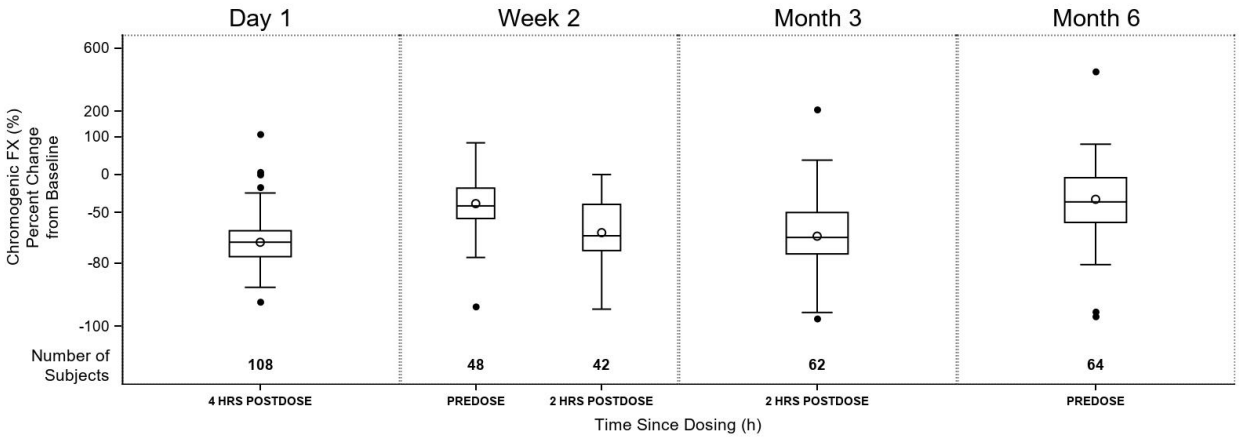
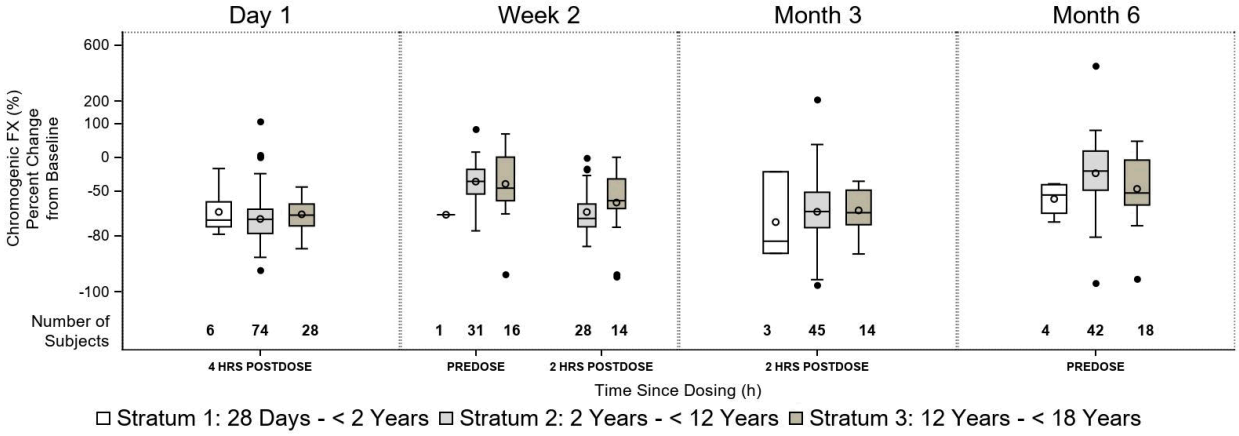


Figure 5. Box and Whisker Plot of Chromogenic FX Assay (%) Percent Change from Baseline in Subjects Treated with Apixaban by Age - PD Population.



CHMP comment

The PD results reflected the mechanism of action of apixaban as a direct FXa inhibitor.

The Applicant is asked to provide a discussion on whether there is an association of apixaban levels and efficacy/safety.

2.3.3. Discussion on clinical aspects

In accordance with the PIP (EMEA-000183-PIP01-08-M08), the MAH submitted the results of study CV185362, a prospective, open label, non-comparative safety trial, to evaluate the safety of apixaban in children (from 28 days to <18 years) in paediatric subjects with congenital or acquired heart disease requiring chronic anticoagulation for thromboprophylaxis, with a reference comparison of VKA and low molecular weight heparin (LMWH).

Of note, evaluation of PK and other biomarkers and exploratory data on efficacy has not been further discussed in the Applicants report. The Applicant is requested to provide timelines on when these data will be provided.

Conduct of the study

There were 3 study periods extending up to 14 months total. These included a screening/ randomization period from Day -21 to Day 1, a treatment period from Day 1 to Month 12 (or until anticoagulation was no longer needed) and a follow-up period from Month 12 to Month 14 (or 2 months following cessation of study drug if the duration of therapy was less than 12 months). Generally, the study design is in line with the outline presented in the PIP and is therefore generally acceptable.

The inclusion and exclusion criteria are sufficient to identify the target paediatric population with congenital or acquired heart disease who were at risk for clot formation. The population was diagnosed based on major current guidelines, and are therefore acceptable.

Subjects were randomized in a 2:1 ratio to either, apixaban (oral, fixed-dose, body weight-tiered regimens twice daily) or VKA or LMWH (dosing per local SOC aligned with the current ACCP guidelines). The dose selection rationale for apixaban in this study was based on the results of Study CV185118. Study CV185118 was assessed under procedure number EMEA/H/C/002148/P46/037. This was a Phase 1 study to evaluate the PK, PD, safety, and tolerability of apixaban in paediatric subjects aged 0-<18 years at risk for a venous or arterial thrombotic disorder. The agreed study was considered fulfilled as the study provided information on apixaban dosing for children from 28 days to <18 years of age, but the initial predicted and used doses in study CV185118 should be further refined with the final updated PopPK model and potentially further paediatric data to be collected, in upcoming requests for extension of indication to paediatrics. Data regarding the development of the pharmacokinetic model are currently not presented, therefore further evaluation of the validity of this model is currently not possible. Further, an age specific formulation of a 0.5 mg tablet (in additional to the existing approved 2.5 mg tablet) has been used for patients <5 years of age (replacing an oral solution due to too high levels of propylene glycol), which is also part of the PIP process. Unfortunately, any further insight on the formulations being used during the study has not been given and should be presented during any further type II variation procedure.

Primary (composite of adjudicated major or CRNM bleeding per ISTH criteria) and secondary objectives and endpoints included evaluation of the safety of apixaban by bleeding event rates and parameters of the blood profile. These appear valuable for assessment of safety in children with congenital or acquired heart disease who were at risk for clot formation and the objectives and endpoints are generally in agreement with the PIP and are therefore acceptable. Although the study was open-label, endpoints were adjudicated independently and blinded, which improves the internal validity of the study.

The sample size of 200 patients was estimated on an bleeding event rate of 24% in the control group and 8% in the apixaban group, to achieve more than 80% power to demonstrate superiority at a two-sided 0.05 level. In the current study, the primary safety endpoint (i.e. bleeding event rate during the treatment period) was found to be in one (0.79%) subject in the apixaban arm and 3 (4.84%) subjects in VKA/LMWH arm, which is much lower than expected, indicating that the sample size estimations for sufficient power to detect a statistically significant treatment difference cannot be confirmed. With the current available figures of the primary safety endpoint, the Applicant should provide the estimated power of the study to detect a statistically significant treatment difference. Further, a discussion is needed on the impact on the findings in Study CV185362.

The definition of the analysis population is considered standard and acceptable. The primary and secondary analyses can be considered adequate for the evaluation of the safety of apixaban.

Results

Patient disposition

Of the 198 patients who were screened, only 6 failed and could not be randomized. Randomization was generally balanced between groups. A large proportion of patients completed the study (87%), although a larger proportion discontinued treatment in the apixaban group compared to the VKA/LMWH group (14.7% vs 9.5%) and there was a disbalance seen in the adverse events as reason for not completing the treatment period. The Applicant should provide a discussion on this, since this may indicate a generally poor tolerability to apixaban.

A large proportion (149/192; 78%) of the patients were recruited from Europe (40% apixaban and 25% VKA/LMWH) and North America (39% apixaban and 49% VKA/LMWH, mainly USA). Similar to the discussions usually held around the assessment of the risk of VTE with the use of oestrogen containing hormonal contraception in studies performed in the US vs EU, meaningful differences in weight and weight-related baseline characteristics might exist and could impact VTE outcomes. These recruitment rates from the US might be considered more unfavourable, as compared to EU data, regarding the baseline risk of bleeding, as obesity is a known risk factor of bleeding rates.

Major protocol deviations were only 4% and mainly included prohibited and/or restricted treatments. This is therefore not considered to impact data interpretation.

Baseline data

The study included 192 patients. Most subjects were male (53.1%) and white (83.3%), and the median age was 7.0 (range: 0.4 - 17.0) years, although male patients (male subjects: 48.1% in the apixaban arm vs 63.5% in the VKA/LMWH arm) and patients in the youngest age range (8 patients in the apixaban group vs 3 in the VKA/LMWH arm) were underrepresented and imbalanced. Further, most randomized subjects received treatment for ≥337 days in both treatment arms. In general, the baseline demographics, disease demographics and exposure data were generally balanced between the arms, which is reassuring for the interpretation of the data. The study population can be considered representative for the target paediatric population with congenital or acquired heart disease who were at risk for clot formation.

Efficacy data

The study included no primary efficacy endpoints, but only secondary efficacy endpoints. The composite of adjudicated thromboembolic events and thromboembolic event-related deaths was the secondary efficacy endpoint. There were no adjudicated thromboembolic events or thromboembolic event-related deaths reported with onset during the intended treatment period in either treatment arm. Therefore no meaningful comparison of the efficacy of apixaban vs VKA/LMWH could be established.

The quality of life (QOL) of the patients was also evaluated as a secondary efficacy endpoint. This was measured using the PedsQL and KIDCLOT instruments. Although, PedsQL questionnaires are validated questionnaires applicable in clinical trials, research, clinical practice, while KIDCLOT questionnaires are not. From these data the changes in mean scores from baseline were small and not consistent over the different categories in both treatment arms. No clear clinically relevant post-baseline differences and trends or patterns could have been observed between the treatment arms. It should, however, be noted that only English-speaking patients and their parents/proxies have completed the questionnaires. The QOL instruments used in this study were not validated in other languages. Selection bias may have played a role. Further, selection of English-speaking patients and their parents/proxies resulted in a small sample size. The bias and small sample size limited therefore the generalizability of the QOL results and can therefore not be interpreted adequately.

Safety data

The primary safety endpoint of the study concerned the composite adjudicated major or CRNM bleeding events during the treatment period. 1/126 (0.8%) subject in the apixaban arm and 3/62 (4.8%) subjects in VKA/LMWH arm had major or CRNM bleeding events, but the study could not demonstrate a significant effect for apixaban versus VKA/LMWH with a relative risk (RR) of 0.16 (CI: 0.02-1.54) on these major or CRNM bleeding events. In general, the number of bleeding events was low in both groups and has impacted the estimated power of the study to detect a statistically significant treatment difference (see sample size discussion). Adequate conclusions on a treatment difference between the groups can therefore not be drawn.

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. 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. Although, the Applicant submitted the listings of the major, CRNM and minor bleeding events, no further details of these events have been provided, and are expected to be presented in response to this report. Further, 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)), which is not supportive for use of apixaban in the target population, although adequate conclusions could not be made due to the limited numbers and the lack of power of the study.

In terms of bone density, there was a slight trend to an increase observed in mean bone mineral density at Month 12 relative to baseline at all 3 locations in both treatment arms. However, these changes were also seen in the comparator arm for lumbar spine and total body. Numbers were too low and therefore no relevant conclusions can be drawn from these data.

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 case narratives of these cases have been provided, although a discussion is lacking. The Applicant is therefore asked to provide a cumulative review with causality assessment on all these available bleeding cases. The Applicant should provide for this review a structured/ step-wise approach, including an overview of cases with insufficient information that precludes further assessment, cases with confounding factors and a clear causal assessment of the individual remaining cases. The Applicant should provide a discussion on this and the imbalance of the figures within the response of this assessment report.

No subjects died during the study.

AEs were reported in 107 (84.9%) and 53 (85.5%) subjects in the apixaban and VKA/LMWH arms, respectively. The most frequently reported AEs 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. With similar findings within the SOCs. Some imbalances have been observed between the groups, but no discussion on this has been provided by the Applicant.

Regarding the clinical laboratory evaluations, no clinically relevant differences between treatment arms were observed, also not in the liver enzymes.

Pharmacodynamic results

The PD results reflected the mechanism of action of apixaban as a direct FXa inhibitor. The Applicant is asked to provide a discussion on whether there is an association of apixaban levels and efficacy/safety.

3. CHMP overall conclusion and recommendation

Overall, the results of study CV185362 are currently not considered sufficient to conclude on a positive benefit-risk of apixaban use in paediatric patients from 28 days to <18 years of age with congenital or acquired heart disease requiring chronic anticoagulation for thromboprophylaxis, as the study has limitations and concerns. Therefore, inclusion for a formal indication for these patients and any related formal posology can currently not be recommended.

However, in accordance with the principles to inform prescribers on all available paediatric data for this medicinal product, inclusion of a concise description of this study (performed in accordance with the paediatric investigational plan) in section 5.1 of the SmPC might be recommended. The Applicant proposes to submit these study results in a type II variation later this year to include the information in the SmPC, when all data of the PIP have become available. According to the PIP, this approach is considered reasonable.

☒ Fulfilled:

No further action required, however further data are expected in the context of an extension prior any conclusion on product information amendments is made. The MAH should commit to submit this extension application by September 2022.

4. Request for supplementary information

Based on the data submitted, the MAH should address the following questions as part of this procedure:

Study conduct

1. Evaluation of PK and other biomarkers and exploratory data on efficacy has not been further discussed in the Applicants report. The Applicant is requested to provide timelines on when these data will be provided.
2. In the current study, the primary safety endpoint (i.e. bleeding event rate during the treatment period) was found to be in one (0.79%) subject in the apixaban arm and 3 (4.84%) subjects in VKA/LMWH arm, which is much lower than expected, indicating that the sample size estimations for sufficient power to detect a statistically significant treatment difference cannot be confirmed. With the current available figures of the primary safety endpoint, the Applicant should provide the estimated power of the study to detect a statistically significant treatment difference. Further, a discussion is needed on the impact on the findings in Study CV185362.

Results

3. A larger proportion discontinued treatment in the apixaban group compared to the VKA/LMWH group (14.7% vs 9.5%) and there was a disbalance seen in the adverse events as reason for not

completing the treatment period. The Applicant should provide a discussion on this, since this may indicate a generally poor tolerability to apixaban.

4. Although, the Applicant submitted the listings of the major, CRNM and minor bleeding events, no further details of these events have been provided, and are expected to be presented in response to this report.

5. AEs were reported in 107 (84.9%) and 53 (85.5%) subjects in the apixaban and VKA/LMWH arms, respectively. The most frequently reported AEs 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. With similar findings within the SOCs. Some imbalances have been observed between the groups, but no discussion on this has been provided by the Applicant.

6. The case narratives of the SAEs have been provided, although a discussion is lacking. The Applicant is therefore asked to provide a cumulative review with causality assessment on all these available bleeding cases. The Applicant should provide for this review a structured/ step-wise approach, including an overview of cases with insufficient information that precludes further assessment, cases with confounding factors and a clear causal assessment of the individual remaining cases. The Applicant should provide a discussion on this and the imbalance of the figures within the response of this assessment report.

7. The PD results reflected the mechanism of action of apixaban as a direct FXa inhibitor. The Applicant is asked to provide a discussion on whether there is an association of apixaban levels and efficacy/safety.

The timetable is a 30 day response timetable with clock stop.

5. MAH responses to Request for supplementary information

Question 1:

Evaluation of PK and other biomarkers and exploratory data on efficacy has not been further discussed in the Applicants report. The Applicant is requested to provide timelines on when these data will be provided.

Response of MAH:

There are two objectives of Study CV185362 and associated endpoints that were planned to be reported separately from the main CSR submitted as part of the initial submission:

- To evaluate apixaban PK in pediatric subjects with congenital or acquired heart disease requiring chronic anticoagulation for thromboprophylaxis.
    - Associated endpoints: Individual PK parameters (eg, Cmax, Cmin, AUC (TAU), CL/F, Vc/F)
- To evaluate biomarkers that may inform anticoagulant efficacy or risk of thrombosis in pediatric subjects with congenital or acquired heart disease requiring chronic anticoagulation for thromboprophylaxis.
    - Associated endpoints: Thrombin generation, factor VIII, d-dimer, proteins C and S, and fibrinogen

The reports covering these objectives will be provided and data discussed in the regulatory submission covering the entire programme from EMEA-000183-PIP01-08-M08, anticipated in September 2022. Of note, the Modeling and Simulation report became available after submission of this Art. 46 procedure and has been submitted to PDCO in March 2022 in the context of the request for final compliance check for EMEA-000183-PIP01-08-M08.

The study objective 'To gather exploratory data on the efficacy of apixaban in pediatric subjects with congenital or acquired heart disease requiring chronic anticoagulation for thromboprophylaxis' was associated with the endpoints listed below, as noted in Table 2-1 of the CV185362 CSR:

- Any adjudicated thromboembolic events detected by imaging or clinical diagnosis and thromboembolic event-related deaths (composite of adjudicated thromboembolic events and thromboembolic event-related deaths)
- Adjudicated thromboembolic events requiring treatment change, medical intervention, hospitalization, or prolongation of hospitalization
- Adjudicated thromboembolic event-related deaths

These endpoints are reported in the CSR (Sections 7.1: Efficacy Summary and 7.3.1: Adjudicated Thromboembolic Events and Thromboembolic Event-Related Deaths) and were discussed in the Clinical Overview (Section 4.3.2: Overview of Efficacy) provided in the initial submission.

Assessment of the Response of the MAH:

The evaluation of PK of apixaban in paediatric patients and on the evaluation of biomarkers that are potentially related to efficacy or safety outcome within Study CV185362, are planned to be submitted as part of the regulatory submission for the extension of indication, anticipated in September 2022.

Conclusion

Issue solved.

QUESTION 2

In the current study, the primary safety endpoint (i.e. bleeding event rate during the treatment period) was found to be in one (0.79%) subject in the apixaban arm and 3 (4.84%) subjects in VKA/LMWH arm, which is much lower than expected, indicating that the sample size estimations for sufficient power to detect a statistically significant treatment difference cannot be confirmed. With the current available figures of the primary safety endpoint, the Applicant should provide the estimated power of the study to detect a statistically significant treatment difference. Further, a discussion is needed on the impact on the findings in Study CV185362.

Response of MAH:

CV185362 was a Phase 2 study designed to assess the safety of apixaban, compared to VKA or subcutaneous LMWH and to evaluate apixaban pharmacokinetic (PK) data in pediatric subjects with congenital or acquired heart disease requiring chronic anticoagulation for thromboprophylaxis. As indicated in Protocol Section 8.1, the study was intended to provide safety and PK data for at least 133 patients exposed to apixaban, and was not powered for either efficacy or safety due to the low incidence of thromboembolic and bleeding events in children. In the current study, the event rates for the primary safety composite endpoint of major or clinically relevant non-major (CRNM) bleeding were

0.79% in the apixaban arm and 4.84% in the SOC arm. Despite these low event rates, they are not unique to the CV185362 study. In the UNIVERSE study1, which studied rivaroxaban dosing, safety, and efficacy in 112 pediatric patients who were status post Fontan palliation, major bleeding was seen in 2% and CRNM bleeding was seen in 6% of patients in the rivaroxaban arm. The population of the current study is quite similar to the UNIVERSE population, with 64% of patients in the apixaban arm being status post Fontan.

Protocol Section 8.1 provided assessments of precision both for the event rates within each group (Protocol Table 8.1-1 and 8.1-2) and between group (Protocol Table 8.1-3) based on a range of potential event rates. Protocol Tables 8.1-4 and 8.1-5 showed potential power to detect possible differences between apixaban and comparator in the primary safety endpoint, but these tables were provided for completeness, and are not intended as a statement of actual power for these comparisons. In particular, these tables show potential power for differences in either direction, i.e., Protocol Table 8.1-4 assumes a higher event rate in the control group, while Protocol Table 8.1-5 assumes a higher event rate in the apixaban group. The Sponsors believe that the tables expressing precision are more consistent with the aims of this study.

Also, calculating power once a study is completed may not be appropriate as the results are already known, and confidence limits express reasonable ranges for outcomes that are consistent with the data.

As requested, the Sponsors have performed additional calculations of potential power to approximate the results observed. For an event rate of 4.5% versus 0.75%, potential power would be 38%. However, this information should be interpreted with caution, given that the study was not designed as a powered study, the sample size calculations focused on precision, and the limited meaningfulness of an a posteriori power calculation.

Finally, the original sample size for this study was 150 subjects randomized (2:1 apixaban:VKA/LMWH). Protocol Amendment 2 increased the sample size to 200 randomized, in order to ensure a sufficient number of subjects would have adequate long-term follow-up.

With 192 patients randomized to the study and given that the aim of the study was descriptive safety and PK, not superiority, the Sponsor believes that Study CV185362 provides valuable safety information generated robust data to describe the PK behavior of apixaban in this pediatric population.

Assessment of the Response of the MAH:

The absence of a statistically significant effect of apixaban on the primary safety endpoint (bleeding event rate during the treatment period) might be related to limited power (i.e. estimated power of 38%, as mentioned by the applicant) to detect a difference in this study population. However, the absolute rate of bleeding events is considered to be low in this study population, for both treatment groups, although data should be interpreted with caution.

Conclusion

Issue solved.

QUESTION 3

A larger proportion discontinued treatment in the apixaban group compared to the VKA/LMWH group (14.7% vs 9.5%) and there was a disbalance seen in the adverse events as reason for not completing the treatment period. The Applicant should provide a discussion on this, since this may indicate a generally poor tolerability to apixaban.

Response of the MAH:

Overall, 19/129 patients in the apixaban arm (14.7%) and 6/63 in the VKA/LMWH arm (9.5%) were reported as discontinuing prematurely. In the apixaban arm, 6 participants (4.7 %) did not complete the treatment period due to an adverse event vs. 1 (1.6%) in the VKA/LMWH arm. Table 1 summarizes treatment discontinuations in CV185362.

Table 1: Treatment Discontinuations

Reason for Discontinuing Treatment Prematurely	Apixaban (n=129)	VKA/LMWH (n=163)
Randomized but never treated	3	1
Anticoagulation no longer needed[a]	9	3
Withdrew consent after beginning treatment	1	0
Lost to follow-up	0	1
Adverse event	6	1
Total	**19**	**6**

[a] permitted per protocol
Source: CV185362 CSR Table 8.4.3-1

The 1 subject who discontinued treatment in the VKS/LMWH group after 105 days of treatment had a rib/spinal fracture and associated fracture pain (all Grade 3/severe).

Of the 6 subjects in the apixaban arm who did not complete treatment due to an AE:

- 2 subjects discontinued due to Investigator-identified shunt thromboses which were subsequently found to be pre-existing events, present prior to randomization on pre-study imaging, and were adjudicated as non-events. See Appendix 2 for detailed narratives of these events
- 1 subject had mild (Grade 1), related gait deviation that resolved 6 days after discontinuation of apixaban treatment.
- 1 subject had apixaban treatment discontinued on Day 308 due to related adverse events of Grade 1 dysuria, Grade 2 hematuria and Grade 3 pulmonary hypertension.
- 1 subject had a Grade 1, related gastrointestinal bleeding on Day 21. The subject had epistaxis at the same time. No treatment was required. The gastrointestinal bleeding resulted in apixaban treatment discontinuation and resolved 2 days later. The event was adjudicated as a minor bleed.
- 1 participant with a history of a Fontan procedure and chylous effusions developed gastrointestinal bleeding that was attributed to hypoperfusion. The Investigator discontinued apixaban treatment due to the GI bleed and other AEs, all of which were considered unrelated to apixaban.

In conclusion, based upon the above data, only 3 (2.3%) of the 19 premature discontinuations of apixaban were possibly attributable to intolerance of study drug.

Assessment of the Response of the MAH:

In table 1, treatment discontinuations in patients who were randomized are summarized. The number of patients randomized to VKA/LMWH is assumed to be 63 instead of 163.

The main reason for treatment discontinuation in both groups was "anticoagulation no longer needed", 9/129 (7.0%) and 3/63 (4.8%) for apixaban and VKA/LMWH, respectively.

Adverse events as reason for discontinuation was seen in 6/129 (4.7%) and 1/63 (1.6%) subjects on apixaban and VKA/LMWH, respectively. The case narratives reveal 2 cases that were adjudicated as non-events, 2 cases with Grade 1 treatment related adverse events, and 2 cases with up to grade 3 treatment related adverse events. The type of adverse events varied and only gastro-intestinal bleed was reported in two cases, once adjudicated as minor bleed, once attributed to hypoperfusion leading to gastro-intestinal ischemia. No PD data, such as anti-FXa-activity or chromogenic FX-assay or additional biomarkers are provided, to explore whether increased exposure to apixaban was involved. Increased incidence of gastro-intestinal bleeds is seen in adult patients and is referred to in the SmPC of apixaban.

Conclusion

In conclusion, though study discontinuation points to an increase in the patients on apixaban, the case narratives do 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.

Issue is solved.

QUESTION 4

Although, the Applicant submitted the listings of the major, CRNM and minor bleeding events, no further details of these events have been provided, and are expected to be presented in response to this report.

Response of the MAH:

An updated, more detailed integrated listing of all adjudicated bleeding event data and associated adverse event data is provided in Appendix 1. All adverse events reported as bleeding events by the Investigator that were adjudicated as major, CRNM, and minor bleeding events are listed. The adjudication conclusion and diagnosis criteria selected by the adjudicators is provided. The adverse event relationship, intensity, action taken, treatment requirement, and outcome is also presented.

Furthermore, additional details concerning adjudicated major or CRNM bleeding events, related SAEs, and AEs leading to discontinuation are available in the safety narratives included in the CSR, and are also included with this response as Appendix 2 for convenience.

In this study, there was one major bleeding event in each arm. One CRNM bleeding event occurred in the apixaban arm while two CRNM bleeding events occurred in the VKA/LMWH arm.

Therefore, there was no imbalance between the treatment groups for major or CRNM bleeding. In addition, the overall percentage of patients with at least one bleeding event was the same in both arms (37%). the response to Question 3 provides more details on the treatment discontinuations.

Assessment of the Response of the MAH

The applicant has provided a detailed individualized listing on bleeding events.

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.

One (0.79%) subject in the apixaban arm and 3 (4.84%) subjects in VKA/LMWH arm met the primary safety endpoint of the composite of adjudicated major or CRNM bleeding events during the treatment period. The patient in the apixaban arm developed bleeding as a result of a procedure leading to coagulopathy, classified as very severe CRNM bleeding, for which the drug was interrupted. After three days, this patient developed a gastro-intestinal haemorrhage, classified as moderate, leading to withdrawal of apixaban. In the VKA/LMWH group, 1 patient developed a subdural hematoma, for which the drug was temporarily interrupted, resulting in resolution of the hematoma. Two patients developed a CRNM bleed, in one case a gastro-intestinal haemorrhage, for which the drug remained unchanged, and in the other case bruising and severe gingival bleeding, for which the study drug was temporarily interrupted, resulting in resolution of symptoms.

Conclusion

In conclusion, no new significant effect for apixaban versus VKA/LMWH on adverse events related to bleeding is demonstrated. No signal of unexpected safety issues related to bleeding could be detected for apixaban from the current available data. The results related to bleeding are generally consistent with findings in adults.

Issue is solved.

QUESTION 5

AEs were reported in 107 (84.9%) and 53 (85.5%) subjects in the apixaban and VKA/LMWH arms, respectively. The most frequently reported AEs 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. With similar findings within the SOCs. Some imbalances have been observed between the groups, but no discussion on this has been provided by the Applicant.

Response of the MAH:

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. One event resulted in treatment interruption and resolved the same day. The subject restarted treatment with apixaban and had no further bleeding events.

A listing of all adjudicated bleeding events and their associated adverse event details including relationship to treatment, intensity, duration, and adjudication conclusion can be found in Appendix 1. The apixaban SmPC lists epistaxis as uncommon (VTEp) and common (NVAF and VTEt) in the listing of adverse reactions. 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 adverse events in the apixaban arm compared to 3 in the VKA/LMWH arm. None of the headache AEs were reported as treatment related by the Investigators. All but three of the headache AEs were reported as Grade 1. The remaining 3 headaches were Grade 2; one occurring in

an apixaban-treated patient and 2 occurring in VKA/LMWH-treated subjects. Since headaches are commonly reported after a Fontan procedure, the apixaban-treated patients 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:

- Subject CV185362-7-99 was a 21-month-old with hypoplastic left heart syndrome (HLHS) who underwent a Glenn procedure and a had a history of a superior vena cava balloon dilatation 6 months prior. The subject was mildly cynanotic and had a Grade , unrelated headache while receiving apixaban treatment
- Subject CV185362-8-41 was a 6-year-old with history of transposition of the great arteries status post-arterial switch operation and severe pulmonary hypertension while receiving treatment with apixaban. The subject had Grade 1, unrelated headache on study Days 15, 18, and 120. The subject also had syncope on study Day 115 and had an atrial septostomy in the cardiac catheterization lab on study Day 143.
- Subject CV185362-11-68 was a 16-year-old male with a history of heterotaxy syndrome, pulmonary atresia, a Kawashima procedure, and depression while receiving apixaban treatment. On study Day 333, the subject had a Grade 1, unrelated headache. The same day, the subject had stomach ache and hematemesis. Three days later, the subject was evaluated for suicidal ideation. No action was taken regarding apixaban treatment.
- Subject CV185362-14-9 was an 8-year-old with a history of Kawasaki disease and coronary artery aneurysms. The subject had strep throat, fever, and a Grade 1 headache on study Day 131 that were all considered unrelated to study drug.
- Subject CV185362-44-79 was an 11-year-old with a history of single ventricle heart disease and pulmonary hypertension who had Grade 1 influenza and Grade 1 headache on study Day 169 which were both considered unrelated to study drug.

Headache has not been previously identified as a common adverse event in apixaban-treated subjects. Considering the Investigator's assessment of non-relatedness, confounding factors related to the Fontan procedure, and the possibility of reporting bias in an open-label study, there is no evidence of a correlation between apixaban treatment and headache at this time.

REFERENCES

1. McCrindle BW, Michelson AD, Van Bergen AH, Suzana Horowitz E, Pablo Sandoval J, et. al; UNIVERSE Study Investigators. Thromboprophylaxis for Children Post-Fontan Procedure: Insights From the UNIVERSE Study. J Am Heart Assoc. 2021. Nov 16;10(22):e021765. Epub 2021 Sep 24. Erratum in: J Am Heart Assoc. 2021 Dec 21;10(24):e020766.

Assessment of the Response of the MAH

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 pediatric patients (in study CV185362 15.9%) compared to adults (ranging from 1/10-1/1000). The applicant should provide a discussion on this concern and should consider an update the SmPC on this finding within the future regulatory submission of the extension of indication in September 2022.

Further, there is a numerical imbalance in the incidence of headache between apixaban and VKA/LMWH, occurring in 19 patients on apixaban, and 3 patients on VKA/LMWH. Also here, the applicant should provide a discussion on this concern and should consider an update the SmPC on this finding within the future regulatory submission of the extension of indication in September 2022.

The applicant states that headache is associated with the underlying condition in patients following a Fontan-procedure. Eleven out of the 19 patients on apixaban had undergone a Fontan-procedure. However, since patients are randomized and likely the proportion of patients on VKA/LMWH that have undergone a Fontan-procedure is comparable to the proportion of patients on apixaban (data not provided), this is unlikely to account for the difference in incidence rate of headache between both groups. In the remaining 8 patients on apixaban that complained of headache, in 5 patients confounding factors suggestive of comorbid conditions were detected. The case narratives and the reduced likelihood of causality for apixaban in these cases is acknowledged.

Conclusion

Issue is solved.

QUESTION 6

The case narratives of the SAEs have been provided, although a discussion is lacking. The Applicant is therefore asked to provide a cumulative review with causality assessment on all these available bleeding cases. The Applicant should provide for this review a structured/ stepwise approach, including an overview of cases with insufficient information that precludes further assessment, cases with confounding factors and a clear causal assessment of the individual remaining cases. The Applicant should provide a discussion on this and the imbalance of the figures within the response of this assessment report.

Response of the MAH:

In this study, there was one major bleeding event in each arm. One CRNM bleeding event occurred in the apixaban arm while two CRNM bleeding events occurred in the VKA/LMWH arm.

Therefore, there was no imbalance between the treatment groups for major or CRNM bleeding. In addition, the overall percentage of patients with at least one bleeding event was the same in both arms (37%). Therefore, the imbalance being referred to was limited to minor bleeding events, specifically epistaxis. All of the events of epistaxis were Investigator-assessed as mild in intensity and only 1 of 38 events resulted in premature discontinuation of apixaban treatment.

In this study, there were a total of 8 bleeding SAEs reported for 7 participants (5.4% of 129 randomized participants) in the apixaban arm. There were 5 SAEs involving bleeding for 4 participants (6.3% of 63 randomized participants) in the VKA/LMWH arm. Therefore, there was no imbalance of bleeding-related SAEs between the treatment arms.

In the apixaban arm, the 8 SAEs included:

- 1 adjudicated major bleeding event
- 1 CRNM event
- 5 minor bleeding events
- 1 SAE adjudicated as a bleeding non-event.

All cases were well documented with the required information needed for the assessment of causality. The independent adjudication committee received blinded medical records from the clinical sites and associated imaging, if applicable. The adjudication committee provided confirmation of event or non-event and assigned an ISTH bleeding classification to all bleeding events. Case narratives for subjects

who experienced SAEs determined by the Investigator to be related to apixaban were included in the submitted CSR as Table S.600 (also attached to this response for convenience). Additionally, a narrative was written for the one participant with the adjudicated major and CRNM bleeding events.

For the 7 subjects in the apixaban arm who had bleeding SAEs, the age range was from 1 to 12 years of age; 5 were male and 2 were female. All subjects had a history of cardiac disease, including 5 with single ventricle physiology. Several had extracardiac disease as well. Six of the 8 reported bleeding events (Table 2) were associated with the subject receiving concomitant aspirin that may have contributed to their bleeding risk. Three of the 8 events were reported by the Investigator as related to apixaban: a Grade 2 hematuria, Grade 2 procedural hemorrhage, and Grade 2 post-procedural hematoma. The assessment of relatedness by the MAH agreed with the Investigator in each of these cases. For 2 events, the subjects were discontinued from study treatment. Clinical, demographic, and safety information relative to the bleeding SAEs for the above 7 subjects are summarized below in Table 2.

- Subject CV185362-7-54 experienced mild (Grade 1) SAE of haematochezia not related to study treatment, which adjudicated as CRNM bleeding event.
- Subject CV185362-7-130 experienced severe (Grade 3) SAE of subdural haematoma related to study treatment, which adjudicated as a major bleeding event.
- Subject CV185362-15-202 experienced severe (Grade 3) SAE of pulmonary haemorrhage related to study treatment, which adjudicated as a major bleeding event. This event was not included in the study endpoint analysis as it occurred greater than 2 days after the end of study treatment during the follow-up period.
- Subject CV185362-20-143 experienced severe (Grade 3) SAE of gingival bleeding related to study treatment, which adjudicated as a CRNM bleeding event.
- Subject CV185362-20-143 experienced severe (Grade 3) SAE of contusion related to study treatment, which adjudicated as a CRNM bleeding event.

Table 2: Details for Bleeding SAEs in Study CV185362

Subject ID	Age (years)/ sex	Event Onset	Event Description	Adjudicated Bleeding Event Description	Investigator Intensity Assessment	Investigator Causality Assessment /Outcome	Key Potential Confounding Factors
1-116	5/F	Study Day 30	Right femoral artery pseudoaneurysm	Non-Event	Moderate (Grade 2)	Not related / Resolved	Clinical site characterized this event as a bleeding event but the event was adjudicated a non event
7-95	4/M	Study Day 61	Ecchymosis (head contusion)	Minor	Mild (Grade 1)	Not related / Resolved	Receiving aspirin 40.5 mg daily
7-99	1/M	Study Day 360	Penile hematoma	Minor	Moderate (Grade 2)	Not related / Resolved	Occured after circumcision. Was no longer receiving apixaban treatment. Had transitioned to enoxaparin and aspirin 40.5 mg daily after treatment period ended.
8-90	4/F	Study Day 283	Iatrogenic procedural complication	CRNM	Very severe (Grade 4)	Not related / Resolved	Possible inferior vena cava perforation during the lymphangiogram. Had been receiving aspirin 81 mg daily, stop date unknown.
		Study Day 286	GI hemorrhage	Major	Moderate (Grade 2)	Not related / Resolved	Bleeding in the duodenum consistent with hypoperfusion. Had been receiving aspirin 81 mg daily, stop date unknown.
15-71	10/M	Study Day 71	Post procedural hematoma	Minor	Moderate (Grade 2)	Related / Resolved	N/A
28-160	8/M	Study Day 3	Procedural hemorrhage	Minor	Moderate (Grade 2)	Related / Resolved	Occurred during treatment for infection of surgical incision site. Receiving 100 mg aspirin daily
30-63	12/M	Study Day 302	Hematuria	Minor	Moderate (Grade 2)	Related / Resolved	Had been receiving aspirin 100 mg daily, stop date unknown.

Assessment of the Response of the MAH

The applicant has provided information on severity, reversibility and causality of SAEs on treatment with apixaban. The SAEs all relate to bleeding complications, which are known for this medicinal product and consistent with adult data. Bleedings are currently sufficiently covered in the SmPC. No new relevant concerns could be identified from these data. However, data on exposure to apixaban when developing a bleeding complication, e.g. anti-FXa-activity, are lacking. Providing these data should be considered at regulatory submission of the extension of indication in September 2022 submission.

Conclusion

Issue solved.

QUESTION 7

The PD results reflected the mechanism of action of apixaban as a direct FXa inhibitor. The Applicant is asked to provide a discussion on whether there is an association of apixaban levels and efficacy/safety.

Response of the MAH:

As the Agency has noted, the pediatric PD results have reflected the known pharmacology and mechanism-of-action of apixaban as a direct, reversible FXa inhibitor.

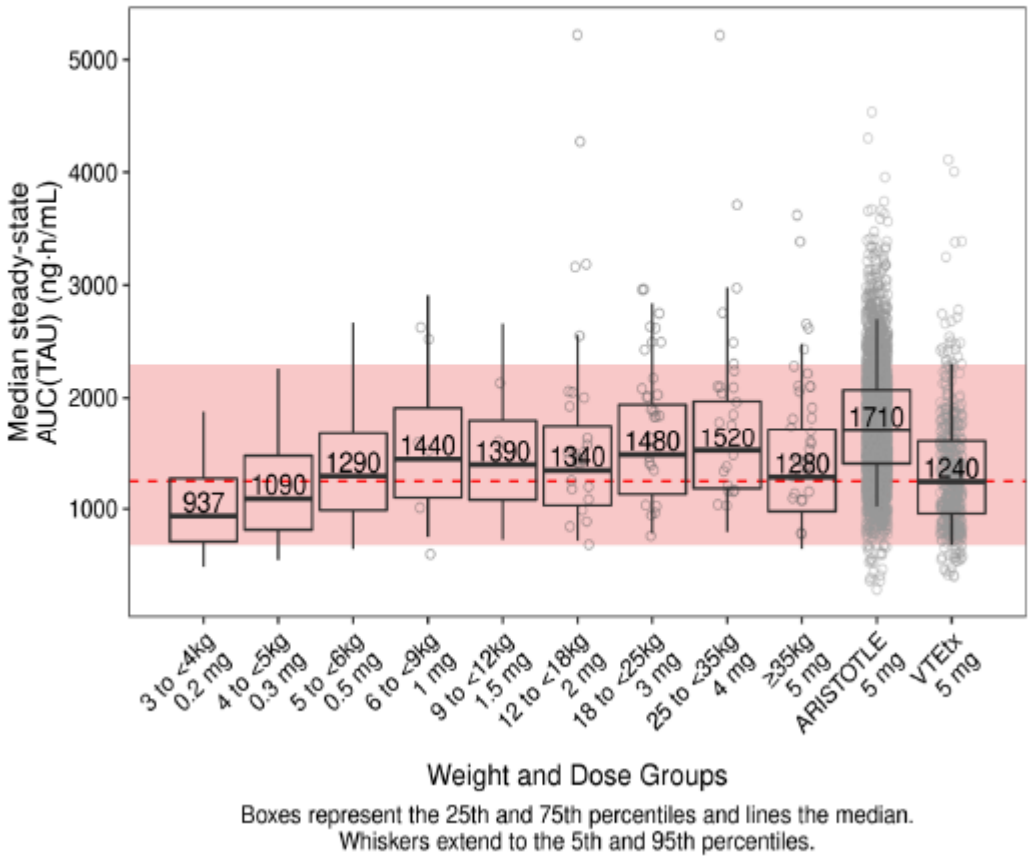
With respect to efficacy and safety, it is known that apixaban treatment in adults is associated with a wide range of plasma concentrations that have proven to be safe and efficacious. In addition, apixaban pediatric studies were based on exposure matching to adult exposures that are associated with clinical efficacy and safety. Therefore, the study was not powered to relate apixaban plasma concentration to efficacy or safety endpoints.

Additionally, due to the expectation of a low number of clinical events in the study, the per protocol sampling scheme was not planned to collect samples at the time of endpoint events to assess the relationship between the event and apixaban exposure.

Pharmacokinetic Similarity

In Study CV185362, the simulated steady-state AUC(TAU) values from the virtual pediatric subjects (by weight tier) were compared with exposures observed in the adult VTEtx population in Studies CV185017, CV185056, and CV185057 and the adult stroke prevention population in the ARISTOTLE study (CV185030) who received apixaban 5 mg BID (Figure 1). The results show that the median exposures across the weight tiers were similar to the median exposure (1,240 ng•h/mL) in the adult VTEtx population, with relatively lower (24.4%) compared to the adult reference steady-state AUC(TAU) for the 3 to <4 kg group compared to the other weight tiers. The median exposure in the ARISTOLE study population was higher (1,710 ng•h/mL) compared to the VTEtx population, but the overall range was generally similar between the ARISTOTLE population and the exposure ranges predicted for the pediatric age groups.

Figure 1: Comparison of Simulated Exposures Between Virtual Pediatric Subjects Aged 28 Days to <18 Years by Weight Tiers and the Adult VTEtx Population and ARISTOTLE Study



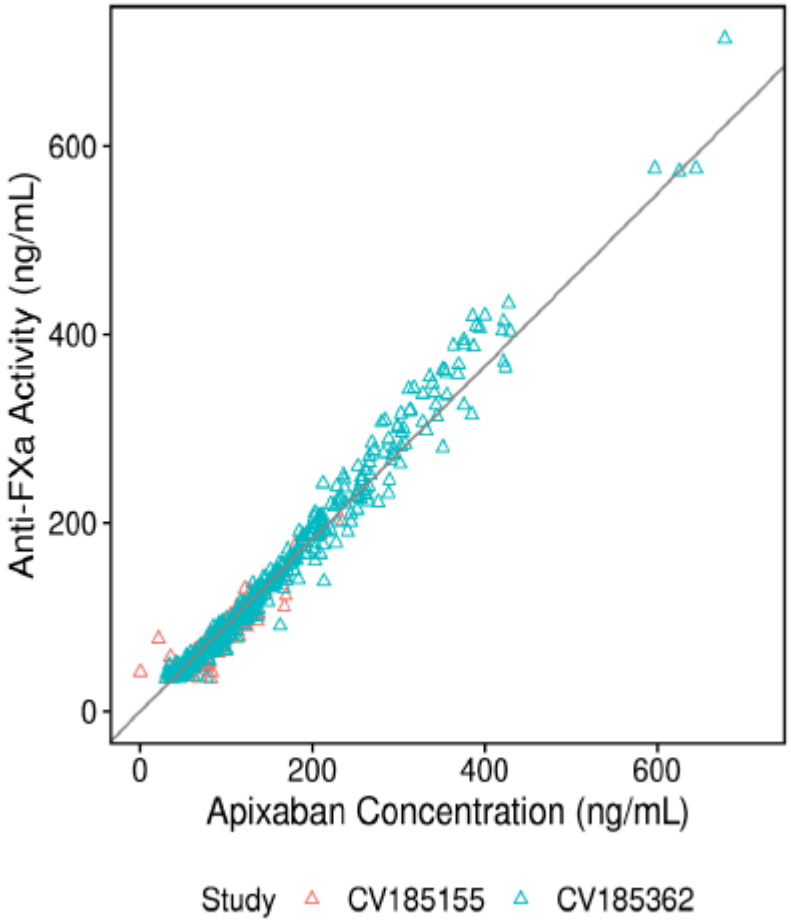
Boxes represent the 25th and 75th percentiles and lines the median.
Whiskers extend to the 5th and 95th percentiles.

Pharmacodynamic Similarity

Two previously developed PK/PD models for anti-FXa activity (AXA) in Studies CV185118 and CV185155 suggested a linear relationship between anti-FXa activity and apixaban concentration.

A summary of AXA in pediatric subjects for Study CV185362, by age groups and nominal time, and by weight groups and nominal time is shown in Figure 2. Confirming previous reports, a linear relationship between anti-FXa and apixaban concentration was noted.

Figure 2: **Goodness-of-Fit Plot for the Final Apixaban Pharmacokinetic/Pharmacodynamic Model for Anti-FXa Activity**



The exposures for subjects in Study CV185362 aligned well with adult exposures and the PD effect (AXA) was closely correlated with apixaban plasma concentrations, suggesting that the associated efficacy and safety in pediatric subjects should also be preserved.

Considering the totality of data that has been collected in the apixaban pediatric development program, the relationship between apixaban treatment and efficacy or safety outcomes in pediatric subjects is expected to be similar to adults.

Assessment of the Response of the MAH

Though the data presented on PK and PK-PD are limited, the likelihood that similar exposure to apixaban is reached in paediatric patients, as compared to adults, is acknowledged. However, a thorough evaluation of PK should be performed at the future submission of the extension of the indication.

Conclusion

Issue is solved.