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Human Medicines Division

Assessment report for paediatric studies submitted in accordance with article 46 of regulation (EC) No 1901/2006, as amended

Xarelto

rivaroxaban

procedure no: EMEA/H/C/000944/P46/050

Note

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

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List of abbreviations

AE	adverse event
AESI	adverse events of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
ASA	acetylsalicylic acid
AST	aspartate aminotransferase
BSA	body surface area
CAD	coronary artery disease
CHD	congenital heart disease
CIAC	central independent adjudication committee
CL	creatinine clearance
CRNM	clinically relevant non-major
CV	cardiovascular
DRC	data review committee
DVT	deep vein thrombosis
eCRF	electronic case report form
ESMD	early study medication discontinuation
ISTH	International Society on Thrombosis and Haemostasis
LMWH	low-molecular-weight heparin
MI	myocardial infarction
MRI	magnetic resonance imaging
NSAID	non-steroidal anti-inflammatory drug
PBPK	physiology-based pharmacokinetic
PD	pharmacodynamics
PE	pulmonary embolism
PK	pharmacokinetics
popPK	population pharmacokinetics
PT	prothrombin time
SAE	serious adverse event
SD	standard deviation
SOC	system organ class

SoC	standard of care
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
ULN	upper limit of normal
VKA	vitamin K antagonist
VTE	venous thromboembolism

1. Introduction

On 11 January 2021, the MAH submitted a completed paediatric study for rivaroxaban (study 18226, EudraCT number: 2015-002610-76), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

2.2. The MAH stated that study 18226, EudraCT number: 2015-002610-76, is submitted as a stand-alone study. Information on the pharmaceutical formulation used in the study

Rivaroxaban was to be administered twice daily in an open-label fashion as a 0.1% (1 mg/ml) oral suspension (age- and body weight-adjusted dosing [see Table 1]). Rivaroxaban had to be taken in the morning and in the evening (approximately 12 hours apart) at approximately the same times each day. Dose adjustment, due to increased body weight was to be performed at Month 6 (both Part A and Part B).

Table 1: Dosing Table for Rivaroxaban Administration

Body weight [kg]	BID Dose[a] [mg or mL]	Total Daily Dose[b] [mg]
7 to <8	1.1	2.2
8 to <10	1.6	3.2
10 to<12	1.7	3.4
12 to <20	2.0	4.0
20 to <30	2.5	5.0

BID=twice daily.
[a] Oral suspension 0.1% (1 mg/mL)
[b] Equivalent to exposure of 10 mg once daily in adults

The target exposure of rivaroxaban was to match that of rivaroxaban 10 mg total daily dose (oral) in adults.

Acetylsalicylic acid was to be provided as 81-mg or 100-mg tablets according to local practice. Subjects randomized to ASA were to receive approximately 5 mg/kg of ASA to a maximum of 1 whole tablet as a single daily dose. Tablets could be split in half, if necessary (eg. children weighing ≤10 kg), to meet the daily dose, and the dose was documented. It was recommended that tablets were not split more than in half.

Dose adjustments due to increased body weight were made at Month 6.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- Study 18226; EudraCT number: 2015-002610-76, "UNIVERSE"

2.3.2. Clinical study

Clinical study 18226 "UNIVERSE"

Description

A prospective, open-label, active-controlled study to evaluate the pharmacokinetics, pharmacodynamics, safety, and efficacy of rivaroxaban for thromboprophylaxis in paediatric subjects 2 to 8 years of age after the Fontan procedure.

Methods

Objectives

Primary Objectives

Part A

To characterize the single- and multiple-dose PK and PK/PD profiles after oral rivaroxaban therapy administered to paediatric subjects 2 to 8 years of age with single ventricle physiology who had completed the Fontan procedure within 4 months prior to enrolment.

Part B

To evaluate the safety and efficacy of rivaroxaban, administered twice daily (exposure matched to rivaroxaban 10 mg once daily in adults) compared to ASA, given once daily (approximately 5 mg/kg) for thromboprophylaxis in same population as Part A.

Secondary Objectives

Part A

To assess the safety and tolerability of rivaroxaban treatment.

Part B

To further characterize the PK and PK/PD profiles of rivaroxaban.

Study design

A prospective, open-label, active-controlled, multicenter study conducted at multiple sites in North America, Latin America, Western Europe, and in Asia-Pacific countries to evaluate the PK and PK/PD profiles, safety, and efficacy of rivaroxaban for thromboprophylaxis in paediatric subjects 2 to 8 years of age with single-ventricle physiology who had completed the Fontan procedure within 4 months prior to enrolment. Subjects were to be enrolled and randomized to receive the first dose of study drug on Visit 2/Day 1 after meeting all of the eligibility criteria.

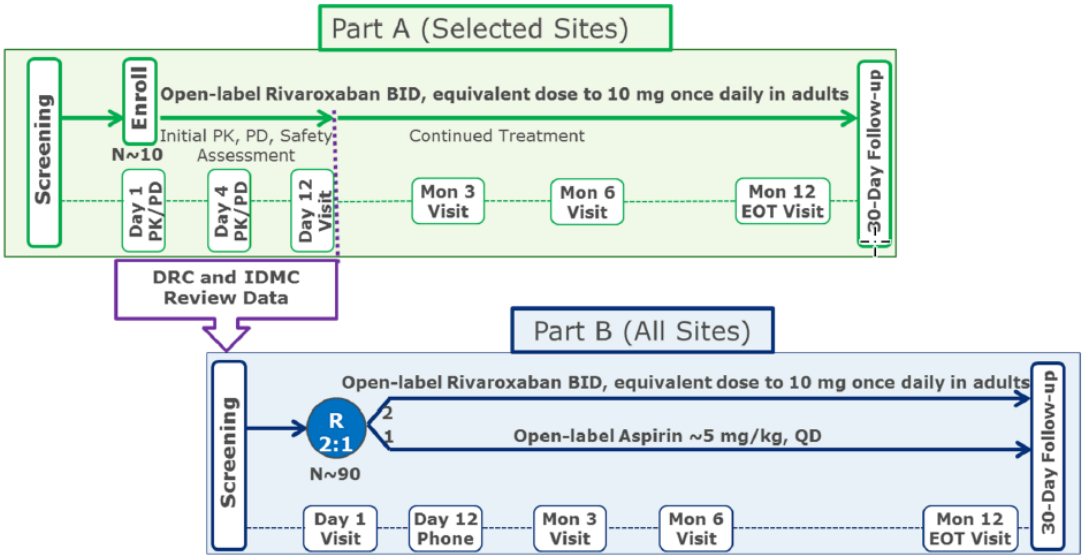
This study consisted of 2 parts:

Part A: This was the 12-month, single-arm part of the study, which included a 12-day initial PK, PD, and safety assessment period. Subjects received the first dose of rivaroxaban oral suspension on Day 1 (on site). Rivaroxaban was given twice daily for 12 days (+9 days). Pharmacokinetic and PD samples were collected on Day 1 and Day 4 (+2 days) of rivaroxaban administration. An internal DRC assessed before the subject returned for Day 12 the PK, PD, and the safety data available from each subject, prior to the subject continuing in the study to complete the planned 12 months of open-label rivaroxaban therapy. The subjects who could continue the 12-month treatment also had PK and PD

samples collected at Month 3 and Month 12. Safety and efficacy were evaluated throughout the study. Subjects in Part A did not participate in Part B.

Part B: Randomization in Part B of this study began once the cumulative data from the Initial PK, PD, and Safety Assessment Period in Part A were deemed acceptable by the Independent Data Monitoring Committee (IDMC). This was the 2-arm, randomized, open-label, active-controlled part of the study that evaluated the safety and efficacy of rivaroxaban compared to ASA for thromboprophylaxis for 12 months. Subjects randomized to rivaroxaban also had PK and PD assessments. There was an up to a 21-day Screening Period, a 12-month Open-Label Treatment Period and a 30-day Follow-Up Contact (phone contact).

Figure 1: Schematic Overview of Study 39039039CHD3001 (UNIVERSE)



BID=twice daily, DRC= Data Review Committee, EOT=end of treatment; IDMC=Independent Data Monitoring Committee, Mon=month; PD= pharmacodynamics, PK= pharmacokinetic(s); QD=once daily; R=randomization.
Note: An internal DRC assessed by Day 12 the PK, PD, and the safety data from each subject, prior to the continuing subject in the study to complete the planned 12 months of open-label rivaroxaban therapy.
Enrollment in Part A ended, and enrollment in Part B was started, once the cumulative data from all subjects in the Initial PK, PD, and Safety Assessment Period of Part A were deemed acceptable by the IDMC.

Study population /Sample size

Part A and B applied the same set of selection criteria. Paediatric subjects 2 to 8 years of age who have single-ventricle physiology and who have completed the Fontan procedure within 4 months prior to enrolment were potentially eligible. For Part A, the screening assessments took place after the Fontan procedure and up to 21 days before the first dose of rivaroxaban. During the screening period, baseline laboratory blood testing was done, and a transthoracic echocardiogram was performed to rule out thrombosis.

For both parts, subjects who did not meet all of the enrolment criteria for the study could be rescreened 1 additional time as long as enrolment was within 4 months of their Fontan procedure.

Inclusion criteria:

1. Boys or girls 2 to 8 years of age with single ventricle physiology and who had completed the initial Fontan procedure within 4 months prior to enrolment

2. Considered to be clinically stable by the investigator and were able to tolerate oral or enteral administration of a suspension formulation and oral/enteral feedings

3. Satisfactory initial post-Fontan transthoracic echocardiographic screening as defined in the Post-Fontan Echocardiographic Examination Research Protocol.

4. Parent/legally acceptable representative had signed an informed consent form (ICF) and child assent, if applicable, according to local requirements.

Exclusion criteria:

1. Evidence of thrombosis, including asymptomatic confirmed by post-Fontan procedure transthoracic echocardiogram, or other imaging techniques, during the screening period of the study

2. History of gastrointestinal disease or surgery associated with clinically relevant impaired absorption

3. History of or signs/symptoms suggestive of protein-losing enteropathy

4. Active bleeding or high risk for bleeding contraindicating antiplatelet or anticoagulant therapy, including a history of intracranial bleeding

5. Indication for anticoagulant or antiplatelet therapy other than current study, however:

- A subject who had received VKA after the Fontan procedure was eligible provided that the subject had discontinued VKA before the screening visit. Baseline laboratory samples were obtained at least 7 days after the last dose of VKA.

- A subject who was receiving ASA at the time of the screening visit was eligible and could continue ASA provided the last dose was taken at least 24 hours prior to the first dose of study drug.

- A subject who was receiving heparin or LMWH after the Fontan procedure was eligible and could continue receiving either of these anticoagulants during the screening period provided the study drug (rivaroxaban or ASA) was started 0 to 2 hours prior to the next scheduled administration of either of these anticoagulants and omit their administration thereafter.

6. Chronic use of non-steroidal anti-inflammatory drug (NSAIDs)

7. Platelet count <50 x 109/L at screening

8. Estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m2.

9. Known clinically significant liver disease (eg, cirrhosis, acute hepatitis, chronic active hepatitis, or alanine aminotransferase [ALT]) >3x upper limit of normal [ULN] with concurrent total bilirubin >1.5x ULN with direct bilirubin >20% of the total at screening)

10. Known contraindication to ASA, was suffering or recovering from chicken pox or flu-like symptoms (subjects participating in Part B only)

11. Known allergies, hypersensitivity, or intolerance to rivaroxaban, ASA or its excipients

12. Inability to cooperate with study procedures

13. Combined P-glycoprotein (P-gp) and strong cytochrome P450 3A4 (CYP3A4) inhibitors (such as but not limited to ketoconazole, telithromycin, or protease inhibitors) use within 4 days before enrolment, or planned use during the study. Itraconazole use within 7 days before enrolment or planned use during the study

14. Combined P-gp and strong CYP3A4 inducers (such as but not limited to rifampin/rifampicin, rifabutin, rifapentine, phenytoin, phenobarbital, carbamazepine, or St. John's Wort) use within 2 weeks before enrolment, or planned use during the study

15. Planned use of drugs that were moderate CYP3A4 inhibitors (such as erythromycin) during the Initial PK, PD, and Safety Assessment Period of Part A only

16. Participation in a clinical study with an investigational drug or medical device in the previous 30 days prior to enrolment

17. Any condition for which, in the opinion of the investigator, participation was not in the best interest of the subject (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments

18. Family member of an employee of the investigator or study site with direct involvement in the proposed study or other studies under the direction of that investigator or study site

Approximately 10 paediatric subjects were planned to be enrolled in Part A and approximately 90 paediatric subjects were planned to be randomly assigned in a 2:1 ratio to receive rivaroxaban oral suspension or ASA for 12 months in Part B.

Treatments

Rivaroxaban was supplied as 0.1% (1 mg/mL) oral suspension with target exposure matching to that of rivaroxaban 10 mg total daily dose (oral) in adults. For reference therapy, acetylsalicylic acid (ASA) was supplied as 81 mg or 100 mg tablets for oral administration.

Table 9-1 UNIVERSE Study: Rivaroxaban (oral suspension) used in the study

INN Substance code number	Rivaroxaban BAY 59-7939
Material name (bulk)	BAY 59-7939 granules 2% for oral suspension
Composition	Active ingredient: rivaroxaban / BAY 59-7939 micronized Excipients: citric acid anhydrous, flavor sweet and creamy, hypromellose, mannitol, microcrystalline cellulose and carmellose sodium, sodium benzoate, sucralose, and xanthan gum
Strength (amount of drug per unit) or concentration	0.02 g of BAY 59-7939 per g granules resulting in a suspension containing 1 mg BAY 59-7939 per mL
Type of packaging and content	Brown glass bottle 250 mL type 3 closed with screw cap PP white opaque child resistant Content: 5.25 g of BAY 59-7939 granules 2 % for oral suspension

For posologies, see section 2.2 above.

Outcomes/endpoints

For both study parts, the primary efficacy outcome was evaluated as any venous or arterial thrombotic event, which was defined as the appearance of a new thrombotic burden within the CV system on either routine surveillance or clinically indicated imaging, or the occurrence of a clinical event known to be strongly associated with thrombus (such as cardioembolic stroke, pulmonary embolism).

All thrombotic events and the primary cause of any death were adjudicated by the CIAC. Transthoracic echocardiograms were centrally read by an echocardiographic core laboratory. Per protocol, subjects were to be withdrawn from the study treatment if they reached an efficacy outcome. After cessation of study treatment, it was at the investigator's discretion to continue with other antithrombotic therapy.

The primary safety outcome was major bleeding events adjudicated by the CIAC using the International Society on Thrombosis and Haemostasis (ISTH) definition. Clinically relevant non-major (CRNM) and trivial (minimal) bleeding were secondary safety outcomes. All bleeding events were adjudicated by the CIAC.

Major bleeding was defined as overt bleeding and:

☐ Associated with a fall in hemoglobin of 2 g/dL or more; or

☐ Leading to a transfusion of the equivalent of 2 or more units of packed red blood cells (RBCs) or whole blood in adults; or

☐ Occurring in a critical site: intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal; or

☐ Contributing to death.

Clinically relevant non-major bleeding was defined as overt bleeding not meeting the criteria for major bleeding but associated with:

☐ Medical intervention, or

☐ Unscheduled contact (visit or telephone call) with a physician, or

☐ (Temporary) cessation of study treatment, or

☐ Discomfort for the subject such as pain, or

☐ Impairment of activities of daily life (such as loss of school days or hospitalization).

Trivial (minimal) bleeding was defined as any other overt bleeding event that does not meet criteria for clinically relevant non major bleeding.

The definitions of major bleeding, CRNM bleeding, and trivial bleeding events were based on the criteria defined by the ISTH. However, some criteria were adjusted to the paediatric population, eg, for the quantity of blood transfused to meet the criteria for major bleeding, instead of "leading to a transfusion of ≥2 units of packed RBCs or whole blood" in this study it was defined as "leading to a transfusion of the equivalent of ≥2 units of packed RBCs or whole blood in adults". In the CIAC charter, it was specified to be "10 mg/kg of body weight". In addition, in order to harmonize the approach to adjudicating all bleeding events across the rivaroxaban paediatric program (VTE treatment and CHD prophylaxis) with agreement from the IDMC, the UNIVERSE CIAC charter was amended to include the same guidance on CRNM bleeding events used in all the VTE treatment studies.

Safety was also evaluated based on adverse events, adverse events of special interest (AESIs), clinical laboratory tests (haematology, serum chemistry, prothrombin time [PT], and activated partial thromboplastin time [aPTT]), and other safety events. AESIs were to be reported as SAEs and included: Suspected toxic effect on the bone marrow including severe thrombocytopenia (platelet count less than 50 x 109/L), severe neutropenia (white blood cell countless than 500/mL), pancytopenia, aplastic anaemia; Suspected severe hypersensitivity reaction (eg, anaphylaxis, angioedema, severe urticaria, bronchospasm, etc.); Severe skin reactions such as Stevens-Johnson Syndrome; Suspected severe liver injury and concurrent elevations of ALT >5x ULN and total bilirubin >2x ULN.

Pharmacokinetic and PD samples were collected on Day 1, Day 4, Month 3, and Month 12 of rivaroxaban treatment in Part A. Pharmacokinetic and PD samples were also collected on Day 1, Month 3, and Month 12 in Part B.

Statistical Methods

For general statistical considerations see CSR Section 16.1.9 SAP (incl Amendment 1). Full Analysis Set: All subjects in Part A who received at least 1 dose of study drug and all subjects in Part B who were randomized and received at least 1 dose of study drug. Safety Analysis Set: The same as Full Analysis Set. Per-protocol Set: This analysis set excluded subjects with key protocol deviations from the full analysis set. These deviations included the following: ☐ Did not meet the following key inclusion or exclusion criteria: INT-1: inclusion criteria 1, exclusion criteria 1, 4, 6 (>90 consecutive days), 7, 8, 13, 14, 15, 18; INT-2: inclusion criteria 1, exclusion criteria 1, 4, 6 (>90 consecutive days), 7, 8.1, 13, 14, 15, 18; ☐ Took incorrect study drug; ☐ Did not discontinue study drug permanently according to the protocol; ☐ Had been taking prohibited concomitant therapies as specified in the protocol. PK Analysis Set: All subjects who received at least 1 dose of study drug and had quantifiable rivaroxaban plasma concentrations were included in the descriptive PK analysis. PD Analysis Set: All subjects who received at least 1 dose of study drug and had quantifiable and time-matched PT, aPTT, and/or anti-FXa activity values were included in the descriptive PD analysis.

On-Treatment Period: All data from the first dose of study drug to 2 days after the last dose of the study drug administration (inclusive). Up-to-End-of-Treatment Period: All data from first dose to end of treatment visit (ie, last efficacy-evaluation date - Month 12 or ESMD visit). Up-to-Last-Follow Up (last contact): All data from first dose to trial reference end date.

Descriptive Pharmacokinetic Analyses: Summary statistics were prepared for the plasma rivaroxaban concentration-time data from Parts A and B of the study. In addition. plasma rivaroxaban concentrations as function of time were graphically compared between paediatric subjects who were enrolled in this study and adults who were enrolled in Phase 2 studies that evaluated rivaroxaban for the prevention of VTE following in total hip- and knee replacement (THR, TKR) (THR: Study 10944 and Study 11527, and TKR: Study 10945). Summary statistics were also prepared for PT and aPTT values and anti-FXa activity from Parts A and B of the study. In addition, PT and aPTT as function of time were graphically compared between paediatric subjects who were enrolled in this study and adults who were enrolled in Phase 2 studies. Furthermore, the relationship between the PD of rivaroxaban (ie., PT and aPTT values and anti-FXa activity) and plasma rivaroxaban concentrations was assessed graphically.

Population PK analysis: A population pharmacokinetic (popPK) model of rivaroxaban was used to describe the PK profile of rivaroxaban in the paediatric subjects in this study. The analysis included plasma rivaroxaban concentration-time data from Part A and Part B, totaling 76 subjects, of whom 12 subjects were from Part A. The popPK model was used to fit data and referred to as the UNIVERSE popPK model.

For rivaroxaban-treated subjects, the systemic exposure metrics of rivaroxaban at steady state, ie, AUC24h,ss, Cmax,ss, and Ctrough,ss, were derived using the UNIVERSE popPK model. These exposure metrics were compared to those in adults who underwent THR and had received 10 mg rivaroxaban once daily while enrolled in a Phase 2 VTE prevention study.

The exposure metrics of the paediatric population in this study were also compared to those for the paediatric population from the Phase 3 EINSTEIN Jr study (Study 14372) that were simulated using an EINSTEIN Jr popPK model (Report R-12947 [18376]) with the dose regimen of this study. The comparison to the Phase 3 EINSTEIN Jr study utilized a simulated PK data, rather than actual subject exposures, mainly because the Phase 3 EINSTEIN Jr study used a dose regimen that was intended to produce rivaroxaban exposures that are similar to those in adults who received rivaroxaban 20 mg once daily and therefore the exposures could not be directly compared.

All bleeding events (including major, clinically relevant non-major, and trivial bleeding events) and all thrombotic events (including any thromboembolism [TE] and/or PE) reported in subjects in the rivaroxaban group were collected and datasets were created for all rivaroxaban-treated subjects with available estimated PK parameters. The exposure metrics AUC24h,ss, Cmax,ss, and Ctrough,ss in the rivaroxaban treatment arm were compared between subjects with or without thrombotic events or bleeding events. Pharmacokinetic/PD data analysis plan was provided separately before database lock.

For efficacy, no formal hypothesis testing was performed. The main efficacy analysis was based on Full Analysis Set, excluding subjects who started on study drug but were discontinued if central reading by the core laboratory reported thrombosis on the Screening transthoracic echocardiogram (these subjects were to be included however in the safety analysis) based on up-to-the-end-of-treatment period (outcomes confirmed by the CIAC). Events that were reported after Month 12 or ESMD visit were to be described in additional summaries or listings. Additionally, data were also summarized based on Full Analysis Set and up-to-last-FU (last contact) period or Per-protocol Analysis Set and On-treatment period. Incidences rates (number of subjects with efficacy event during the period divided by number of subjects at risk at the beginning of the period) and the respective 95% CIs were calculated for the primary efficacy outcome by treatment group. Cumulative incidences (time to first event; Kaplan-Meier) were also calculated for the efficacy outcomes. In addition, listings of all efficacy outcomes were provided. Baseline demographics and disease characteristics relationship to thrombotic risk could be explored.

For safety, no formal hypothesis testing was performed. If the date of an outcome event was missing or partially missing, the earliest logically possible date after enrolment was used as the event date. The date of an outcome event was defined as the maximum of date of enrolment and the first day of the month if only day was missing and was defined as maximum of date of enrolment and the first day of the year if both day and month are missing. Unless otherwise stated, all safety summaries and analyses were performed based on the Safety Analysis Set. The safety analysis was based on the Safety Analysis Set during the On-treatment period (bleeding events confirmed by the CIAC). Incidence rates (number of subjects with bleeding event during the period divided by the number of subjects at risk at the beginning of the period) and the respective 95% CIs were calculated for the major and clinically relevant non major bleeding events by treatment group. Cumulative incidence rates (time to first event; Kaplan-Meier) were calculated for major bleeding and CRNM bleeding. For all bleeding events, listings were provided, including those that were reported more than 2 days after stop of study medication. Baseline demographics and disease characteristics relationship to bleeding risk could be explored.

Results

Recruitment/ Number analysed

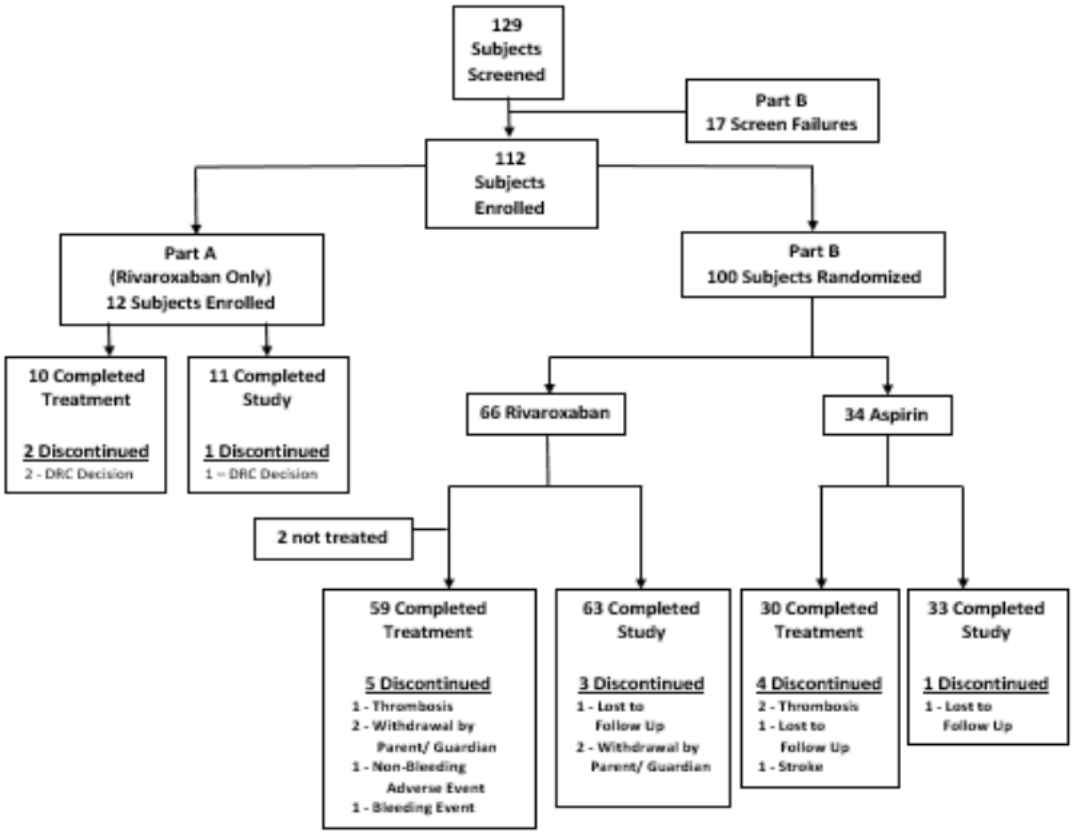
The study was conducted between 17 November 2016 (date first parent/caregiver signed informed consent) and 16 July 2020 (date of last observation for last subject recorded as part of the database).

A total of 129 subjects with single ventricle physiology were screened at 36 sites in 10 countries (Argentina, Belgium, Brazil, Canada, Japan, Malaysia, Mexico, the Netherlands, Spain, and the United States of America). Of these screened children, 17 (13.2%) were screen failures (with the primary reason being ineligible for entry) and 112 (86.8%) subjects were enrolled in this study; 100 in the Part B group (66 in the rivaroxaban group and 34 in the ASA group) and 12 in the rivaroxaban Part A group (Attachment TSIDEM03). There were 3 subjects who were rescreened.

Of the 112 subjects enrolled, 110 (98.2%) subjects (64 [97.0%] in the rivaroxaban Part B group, 34 [100.0%] in the ASA Part B group, and 12 [100.0%] in the rivaroxaban Part A group) received at least

1 dose of study drug, and were included in the full and the safety analysis set. A total of 108 (96.4%) subjects (62 [93.9%] in the rivaroxaban Part B group, 34 [100.0%] in the ASA Part B group, and 12 [100.0%] in the rivaroxaban Part A group) were included in the per-protocol analysis set. A total of 76 (67.9%) subjects (64 [97.0%] in the rivaroxaban Part B group and 12 [100.0%] in the rivaroxaban Part A group) were included in the PK analysis set while a total of 92 [82.1%] subjects (64 [97.0%] in the rivaroxaban Part B group and 12 [100.0%] in the rivaroxaban Part A group) were included in the PD analysis set.

Figure 2: Study 39039039CHD3001 (UNIVERSE) Study Flow



Of the 112 subjects enrolled, 107 (95.5%) subjects completed the study (63 [95.5%] in the rivaroxaban Part B group and 33 [97.1%] in the ASA Part B group; and 11 [91.7%] subjects in the rivaroxaban Part A group) and 5 (4.5%) subjects discontinued the study prematurely. In Part A, the reason for premature discontinuation of study participation was DRC decision (1 [8.3%]). In Part B, the reasons for premature discontinuation of study participation were lost to follow-up (1 [1.5%] subject in the rivaroxaban group and 1 [2.9%] subject in the ASA group) and withdrawal by parent or guardian (2 [3.0%] subjects in the rivaroxaban group).

In the Safety Analysis Set, the most frequent reason for premature discontinuation of study treatment was thrombosis for 3 (2.7%) subjects (1 [1.6%] in the rivaroxaban Part B group and 2 [5.9%] in the ASA Part B group) followed by withdrawal by parent or guardian (2 [1.8%] subjects in the rivaroxaban group). One (1.6%) subject had the study treatment discontinued with a major bleeding event (at non-critical site, epistaxis) in the rivaroxaban Part B group. In Part A, 2 [16.7%] subjects in the rivaroxaban Part A group prematurely discontinued study drug due to a per-protocol's DRC decision (for reaching an AUC at steady state above the pre-specified upper threshold of the target AUC range). These subjects did not have any bleeding or a reported AE while they were in the study.

Baseline data

Table 2-1 UNIVERSE Study: Demographics and baseline characteristics

Analysis set: Enrolled		Rivaroxaban Part A	Rivaroxaban Part B	Rivaroxaban Total	Aspirin Part B	Total
Age at screening (years)	N =	12	66	78	34	112
	Mean (SD)	2.5 (0.67)	4.1 (1.74)	3.8 (1.72)	4.2 (1.80)	3.9 (1.74)
	Median	2.0	4.0	3.5	4.0	4.0
	Range	(2; 4)	(2; 8)	(2; 8)	(2; 8)	(2; 8)
Sex	N =	12	66	78	34	112
	Female	5 (41.7%)	30 (45.5%)	35 (44.9%)	11 (32.4%)	46 (41.1%)
	Male	7 (58.3%)	36 (54.5%)	43 (55.1%)	23 (67.6%)	66 (58.9%)
Race	N =	12	66	78	34	112
Asian		0	14 (21.2%)	14 (17.9%)	7 (20.6%)	21 (18.8%)
Black or African American		3 (25.0%)	8 (12.1%)	11 (14.1%)	1 (2.9%)	12 (10.7%)
White		8 (66.7%)	40 (60.6%)	48 (61.5%)	20 (58.8%)	68 (60.7%)
Other		1 (8.3%)	2 (3.0%)	3 (3.8%)	3 (8.8%)	6 (5.4%)
Not reported		0	2 (3.0%)	2 (2.6%)	3 (8.8%)	5 (4.5%)
Weight, (kg)	N =	12	66	78	34	112
	Mean (SD)	13.8 (2.37)	15.8 (3.66)	15.5 (3.55)	15.7 (3.14)	15.6 (3.42)
	Median	13.3	15.5	14.9	15.4	15.2
	Range	(10; 18)	(10; 25)	(10; 25)	(10; 23)	(10; 25)
Height, (cm)	N =	12	66	78	34	112
	Mean (SD)	90.4 (7.12)	101.0 (12.53)	99.3 (12.43)	103.0 (11.98)	100.4 (12.36)
	Median	89.3	100.0	98.2	100.8	100.0
	Range	(82; 101)	(78; 133)	(78; 133)	(79; 127)	(78; 133)
Heart rate (beats/min)	N =	12	66	78	34	112
	Mean (SD)	110.7 (13.38)	109.0 (16.40)	109.2 (15.91)	106.6 (15.47)	108.4 (15.75)
	Median	108.0	108.5	108.5	108.5	108.5
	Range	(93; 132)	(60; 145)	(60; 145)	(68; 157)	(60; 157)
Blood pressure Systolic (mmHg)	N =	12	66	78	34	112
	Mean (SD)	108.7 (8.76)	99.3 (12.76)	100.8 (12.65)	102.3 (10.56)	101.2 (12.03)
	Median	107.0	97.5	100.0	102.0	100.5
	Range	(95; 121)	(68; 129)	(68; 129)	(80; 130)	(68; 130)
Diastolic	N =	12	65	77	34	111
	Mean (SD)	62.8 (11.16)	59.2 (11.11)	59.7 (11.12)	62.9 (9.01)	60.7 (10.58)
	Median	61.5	58.0	60.0	63.0	60.0
	Range	(44; 82)	(39; 113)	(39; 113)	(44; 82)	(39; 113)
Duration between Fontan procedure and first dose of study agent, (days)[a]	N =	12	64	76	34	110
	Mean (SD)	11.6 (16.77)	45.3 (41.21)	40.0 (40.26)	36.7 (34.52)	39.0 (38.45)
	Median	4.0	34.0	18.5	24.0	21.0
	Range	(2; 61)	(2; 124)	(2; 124)	(2; 117)	(2; 124)
	<= 30 days	11 (91.7%)	31 (48.4%)	42 (55.3%)	19 (55.9%)	61 (55.5%)
	> 30 days	1 (8.3%)	33 (51.6%)	34 (44.7%)	15 (44.1%)	49 (44.5%)

SD = standard deviation.
Notes: Age is defined as a patient's age at screening.
Enrolled: all subjects in Part A who receive at least 1 dose of study agent and all subjects in Part B who are randomized.
[a] Duration between Fontan procedure and first dose of study agent is calculated as date of first dose of study agent - date of Fontan procedure.

The demographic and baseline characteristics were generally balanced between the rivaroxaban and the ASA groups; however, the percentage of male paediatric subjects was lower in the rivaroxaban Part B group (36 [54.5%]) than in the ASA Part B group (23 [67.6%]) and there was a slightly longer duration between the Fontan procedure and first study drug dose in the rivaroxaban Part B group (a median of 34.0 days) than in the ASA Part B group (a median of 24.0 days). The number of males in the rivaroxaban Part A group was 7 (58.3%) while duration between the Fontan procedure and first study dose was a median of 4.0 days.

The rivaroxaban Part A group had a younger mean (SD) age (2.5 [0.67] years), a lower mean weight, and a shorter median duration between the Fontan procedure and first dose than both groups in Part B. The markedly shorter duration between the Fontan procedure and the first dose of study drug in Part A was probably due to the study design, which required frequent blood draws on Day 1 and Day 4 for PK/PD testing in Part A. The frequency of blood draws would therefore have been minimized by performing them while the subjects were still in the hospital, with an intravenous catheter still in place due to their Fontan procedure.

Relevant medical history reported for >5% subjects is summarized in Table 2-2. No clinically relevant differences between treatment groups were seen. The most frequently reported procedure in both groups was cardiac catheterization (88.4%), followed by cavopulmonary anastomosis (82.1%) and

Norwood procedure (61.6%). The most common congenital heart abnormality in both groups included congenital tricuspid valve atresia (in Part B, 42.4% in the rivaroxaban group and 38.2% in the ASA group) and hypoplastic left heart syndrome (in Part B, 30.3% in the rivaroxaban group, and 23.5% in the ASA group).

Table 2-2 UNIVERSE Study: Medical history

Analysis set: Enrolled	Rivaroxaban			Aspirin	Total
System Organ Class	Part A	Part B	Total	Part B	
Dictionary-Derived Term	12	66	78	34	112
Congenital, familial and genetic disorders	12 (100.0%)	66 (100.0%)	78 (100.0%)	34 (100.0%)	112 (100.0%)
Congenital tricuspid valve atresia	1 (8.3%)	28 (42.4%)	29 (37.2%)	13 (38.2%)	42 (37.5%)
Double outlet right ventricle	3 (25.0%)	13 (19.7%)	16 (20.5%)	4 (11.8%)	20 (17.9%)
Hypoplastic left heart syndrome	5 (41.7%)	20 (30.3%)	25 (32.1%)	8 (23.5%)	33 (29.5%)
Congenital pulmonary valve atresia	2 (16.7%)	12 (18.2%)	14 (17.9%)	8 (23.5%)	22 (19.6%)
Multiple cardiac defects	3 (25.0%)	9 (13.6%)	12 (15.4%)	2 (5.9%)	14 (12.5%)
Hypoplastic right heart syndrome	0	10 (15.2%)	10 (12.8%)	3 (8.8%)	13 (11.6%)
Mitral valve atresia	3 (25.0%)	7 (10.6%)	10 (12.8%)	3 (8.8%)	13 (11.6%)
Atrioventricular septal defect	3 (25.0%)	5 (7.6%)	8 (10.3%)	3 (8.8%)	11 (9.8%)
Double inlet left ventricle	0	5 (7.6%)	5 (6.4%)	4 (11.8%)	9 (8.0%)
Heterotaxia	3 (25.0%)	5 (7.6%)	8 (10.3%)	0	8 (7.1%)
Atrial septal defect	0	3 (4.5%)	3 (3.8%)	3 (8.8%)	6 (5.4%)
Surgical and medical procedures	12 (100.0%)	66 (100.0%)	78 (100.0%)	34 (100.0%)	112 (100.0%)
Cavopulmonary anastomosis	5 (41.7%)	57 (86.4%)	62 (79.5%)	30 (88.2%)	92 (82.1%)
Norwood procedure	5 (41.7%)	45 (68.2%)	50 (64.1%)	19 (55.9%)	69 (61.6%)
Systemic-pulmonary artery shunt	6 (50.0%)	16 (24.2%)	22 (28.2%)	9 (26.5%)	31 (27.7%)
Pulmonary artery banding	3 (25.0%)	7 (10.6%)	10 (12.8%)	5 (14.7%)	15 (13.4%)
Aorta coarctation repair	2 (16.7%)	7 (10.6%)	9 (11.5%)	5 (14.7%)	14 (12.5%)
Atrial septal defect repair	0	4 (6.1%)	4 (5.1%)	3 (8.8%)	7 (6.3%)
Investigations	11 (91.7%)	60 (90.9%)	71 (91.0%)	28 (82.4%)	99 (88.4%)
Catheterisation cardiac	11 (91.7%)	60 (90.9%)	71 (91.0%)	28 (82.4%)	99 (88.4%)
Respiratory, thoracic and mediastinal disorders	1 (8.3%)	22 (33.3%)	23 (29.5%)	8 (23.5%)	31 (27.7%)
Pleural effusion	0	4 (6.1%)	4 (5.1%)	4 (11.8%)	8 (7.1%)
Nervous system disorders	1 (8.3%)	16 (24.2%)	17 (21.8%)	3 (8.8%)	20 (17.9%)
Vocal cord paralysis	0	6 (9.1%)	6 (7.7%)	0	6 (5.4%)
Gastrointestinal disorders	1 (8.3%)	14 (21.2%)	15 (19.2%)	7 (20.6%)	22 (19.6%)
Constipation	0	4 (6.1%)	4 (5.1%)	4 (11.8%)	8 (7.1%)
Gastrooesophageal reflux disease	0	5 (7.6%)	5 (6.4%)	2 (5.9%)	7 (6.3%)
Vascular disorders	1 (8.3%)	14 (21.2%)	15 (19.2%)	5 (14.7%)	20 (17.9%)
Hypertension	0	5 (7.6%)	5 (6.4%)	2 (5.9%)	7 (6.3%)
Arterial thrombosis	0	3 (4.5%)	3 (3.8%)	3 (8.8%)	6 (5.4%)
Immune system disorders	0	5 (7.6%)	5 (6.4%)	5 (14.7%)	10 (8.9%)
Drug hypersensitivity	0	4 (6.1%)	4 (5.1%)	4 (11.8%)	8 (7.1%)
General disorders and administration site conditions	0	7 (10.6%)	7 (9.0%)	2 (5.9%)	9 (8.0%)
Developmental delay	0	6 (9.1%)	6 (7.7%)	2 (5.9%)	8 (7.1%)

Notes: Percentages calculated with the total number of subjects in each group as denominator.
Sorted in descending order of number of subjects with abnormalities based on Rivaroxaban
Enrolled: all subjects in Part A who receive at least 1 dose of study agent and all subjects in Part B who are randomized

Of the 112 subjects enrolled, a large proportion of subjects (90.2%; 92.4% in rivaroxaban Part B group and 85.3% in ASA Part B group; and 91.7% in rivaroxaban Part A group) underwent the Fontan procedure using an extracardiac conduit. GORE-TEX was the most common baffle or conduit used (77.7% subjects; 80.3% in rivaroxaban Part B group and 67.6% in ASA Part B group; and 91.7% in rivaroxaban Part A group) and fenestration was done in 48.2% subjects (45.5% in rivaroxaban Part B group and 61.8% in ASA Part B group; and 25.0% in rivaroxaban Part A group) (Table 2-3).

Table 2-3 UNIVERSE Study: Summary of index Fontan procedure

		Rivaroxaban			Aspirin	Total
		Part A	Part B	Total	Part B	
	Analysis set: Enrolled	12	66	78	34	112
Type of Fontan procedure	Atriopulmonary connection	0	0	0	0	0
	Extracardiac conduit	11 (91.7%)	61 (92.4%)	72 (92.3%)	29 (85.3%)	101 (90.2%)
	TCPC Lateral tunnel	0	0	0	0	0
	Other	1 (8.3%)	5 (7.6%)	6 (7.7%)	5 (14.7%)	11 (9.8%)
	Fenestrated lateral tunnel	0	1 (1.5%)	1 (1.3%)	0	1 (0.9%)
	Intra-extracardiac Fontan	0	0	0	1 (2.9%)	1 (0.9%)
	Intracardiac conduit	1 (8.3%)	0	1 (1.3%)	0	1 (0.9%)
	Intracardiac fenestrated Fontan	0	1 (1.5%)	1 (1.3%)	0	1 (0.9%)
	Intracardiac Fontan	0	0	0	1 (2.9%)	1 (0.9%)
	Intracardiac with fenestration	0	0	0	2 (5.9%)	2 (1.8%)
	Pulmonary trunk to IVC connection (Marceletti)	0	1 (1.5%)	1 (1.3%)	0	1 (0.9%)
	Redo sternotomy, 18 mm extracardiac fenestrated Fo	0	1 (1.5%)	1 (1.3%)	0	1 (0.9%)
	Supra hepatic vein inclusion with extracardiac con	0	1 (1.5%)	1 (1.3%)	0	1 (0.9%)
	TCPC extracardiac tunnel	0	0	0	1 (2.9%)	1 (0.9%)
	Hepatic vein to azygous vein connection	0	0	0	0	0
Fenestration	Yes	3 (25.0%)	30 (45.5%)	33 (42.3%)	21 (61.8%)	54 (48.2%)
	No	9 (75.0%)	36 (54.5%)	45 (57.7%)	13 (38.2%)	58 (51.8%)
Type of baffle or conduit used	GORE-TEX	11 (91.7%)	53 (80.3%)	64 (82.1%)	23 (67.6%)	87 (77.7%)
	Homograft	0	1 (1.5%)	1 (1.3%)	0	1 (0.9%)
	Other	1 (8.3%)	12 (18.2%)	13 (16.7%)	11 (32.4%)	24 (21.4%)
	60RE-FIX	1 (8.3%)	0	1 (1.3%)	0	1 (0.9%)
	Autologous	0	1 (1.5%)	1 (1.3%)	0	1 (0.9%)
	Dacron	0	4 (6.1%)	4 (5.1%)	3 (8.8%)	7 (6.3%)
	Polytetrafluoroethylene	0	0	0	2 (5.9%)	2 (1.8%)
	PTFE	0	5 (7.6%)	5 (6.4%)	6 (17.6%)	11 (9.8%)
	PTFE Conduit	0	1 (1.5%)	1 (1.3%)	0	1 (0.9%)
	PTFE Expand	0	1 (1.5%)	1 (1.3%)	0	1 (0.9%)

IVC=inferior vena cava; PTFE=polytetraflouroethylene; TCPC=total cavulopulmonary connection.
Notes: Percentages calculated with the number of subjects in each group as denominator.
Enrolled: all subjects in Part A who receive at least 1 dose of study agent and all subjects in Part B who are randomized.

Efficacy results

A lower percentage of thromboembolic events was observed in Part B of the study for subjects in the rivaroxaban group (1 [1.6%]) compared to the ASA group (3 [8.8%]). There was 1 (1.6%) thrombotic event in the rivaroxaban Part B group which was adjudicated as pulmonary embolism and 3 (8.8%) thrombotic events in the ASA Part B group; 2 (5.9%) venous thrombotic events (superior vena cava and extra cardiac Fontan conduit) and 1 (2.9%) ischemic stroke. There was 1 (8.3%) subject with a venous thrombotic event (left suprahepatic vein) reported in the rivaroxaban Part A group (Table 3-1).

Table 3-1 UNIVERSE Study: Primary efficacy outcome, up-to-end-of-treatment by CIAC

	Rivaroxaban			Aspirin	Total
Analysis set: Full	Part A	Part B	Total	Part B	
N =	12	64	76	34	110
Primary efficacy outcome	1 (8.3%)	1 (1.6%)	2 (2.6%)	3 (8.8%)	5 (4.5%)
Ischemic stroke	0	0	0	1 (2.9%)	1 (0.9%)
Pulmonary embolism	0	1 (1.6%)	1 (1.3%)	0	1 (0.9%)
Venous thrombosis	1 (8.3%)	0	1 (1.3%)	2 (5.9%)	3 (2.7%)
Arterial/intracardiac thrombosis	0	0	0	0	0
Other thrombosis	0	0	0	0	0

CIAC = Central Independent Adjudication Committee.
Notes: Full Analysis Set : all subjects in Part A who receive at least 1 dose of study agent and all subjects in Part B who are randomized and receive at least 1 dose of study agent.
Up-to-End-of-Treatment is defined as the period starting from first dose of study agent to end of treatment visit.
Percentages calculated with the number of subjects in each group as denominator.

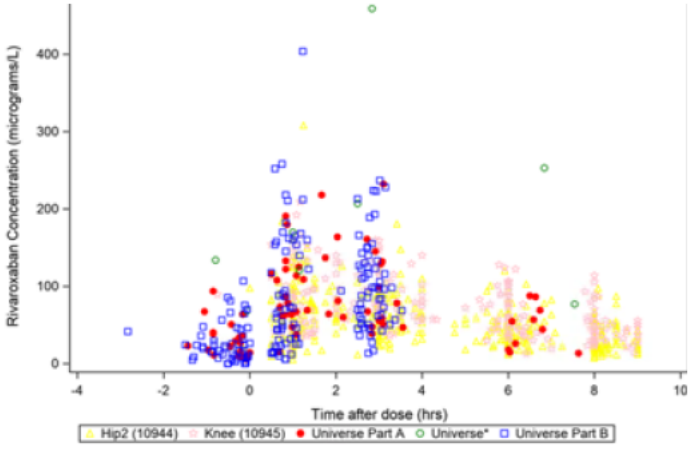
The primary efficacy outcome by subgroup analysis did not show any trends for age, sex, race, ethnicity, region, and Fontan fenestration. All 5 subjects with the occurrence of any thrombotic event in the study did not have any history of previous thrombotic event.

There were no primary efficacy outcomes reported after Month 12 or after early discontinuation of study drug.

PK/PD

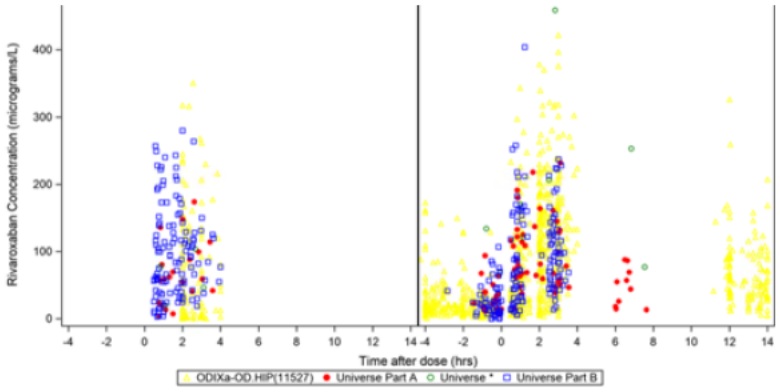
In general, the observed rivaroxaban concentrations in the paediatric subjects were within the range of corresponding values that were observed in adults after 5 mg twice daily (Studies ODIXa- HIP2 and ODIXa-KNEE) or 10 mg once daily (Study 11527) administration of rivaroxaban.

Figure 5-1 Rivaroxaban concentrations in plasma over time in children and adults - Rivaroxaban twice daily



Data from the rivaroxaban 5 mg twice daily dose from the adult ODIXa-HIP2 (10944) (Days 6 or 7) and ODIXa-KNEE (10945) (Days 5 to 9) studies and from Day 4 (Part A) and Month 3 (Parts A and B) of the UNIVERSE study.
Open circles represent the values from 2 subjects in Part A of the UNIVERSE study who prematurely discontinued the study drug.

Figure 5-2 Rivaroxaban concentrations in plasma over time in children and adults - Rivaroxaban once daily



Includes data from the rivaroxaban 10 mg once daily dose from Study ODIXa HIP-OD [Study 11527] in adults (left panel: Day 2; right panel: Days 3 or 4, 5 to 7, and 10) and from the UNIVERSE study (left panel: Day 1 (Parts A and B); right panel: Day 4 (Part A) and Month 3 (Parts A and B).
Open circles represent the values from 2 subjects in Part A of the UNIVERSE study who prematurely discontinued the study drug.

Population pharmacokinetic (PopPK) analyses

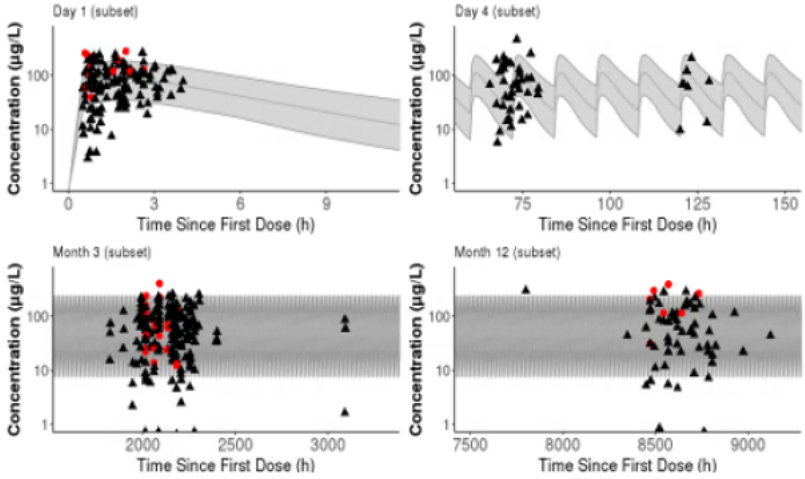
PopPK parameter estimates

The observed plasma concentration-time data of rivaroxaban were adequately described by a 2-compartment popPK linear model with diagnostic plots showing good model fit and minimal bias. The model was parameterized in terms of clearance (CL) estimated at 3.30 L/h, volume of distribution in the central compartment (Vc) estimated at 17.6 L, intercompartmental clearance (Q) estimated at 1.09 L/h and volume of distribution in the peripheral compartment (Vp) estimated at 33.4 L/h. CL and Vc were scaled exponentially with body weight normalized by the median body weight (15 kg) and the exponent was estimated to be 1.01 and 1.20, respectively. The first-order absorption rate constant was estimated to be 1.12 /h. The bioavailability (F1) parameter included weight-normalized dose as a covariate, similar to the EINSTEIN Jr popPK model, which established that the dose-dependent bioavailability, F1, was adequately characterized by weight normalized dose as a covariate.

Comparison of exposure metrics

The rivaroxaban concentrations observed in this study were superimposed on the range of simulated concentrations from the adult reference Study 11527 (Figure 5-3). The adult reference range was defined as the 2.5th to 97.5th percentile range as observed in Study 11527, which enrolled adults who underwent total hip replacement, to establish exposure matching to the adult 10 mg once daily dose.

Figure 5-3 Superimposition of rivaroxaban concentration observed in children (UNIVERSE) and the simulated range of concentrations in adults (Study 11527) in Log Scale



Black triangles: Non-Japanese subjects; Red circles: Japanese subjects.
Shaded areas refer to 95% prediction interval of rivaroxaban concentration in adult reference (Study ODIXa HIP OD [Study 11527])).

The exposure metrics (AUC24h,ss, Cmax,ss, and Ctrough,ss) of rivaroxaban in this study are descriptively summarized in Table 5-1. The geometric mean AUC24h,ss, the primary PK metric for exposure matching, was similar between subjects in this study and the adult reference. Furthermore the 90% confidence intervals (CIs) of the geometric means for these 2 groups largely overlapped. Since subjects in this study received a twice daily dosing regimen that was intended to match the 10 mg once daily dosing in adults, the rivaroxaban concentrations in the paediatric subjects had a narrower range with slightly lower Cmax,ss and slightly higher Ctrough,ss in comparison to the adult reference ranges.

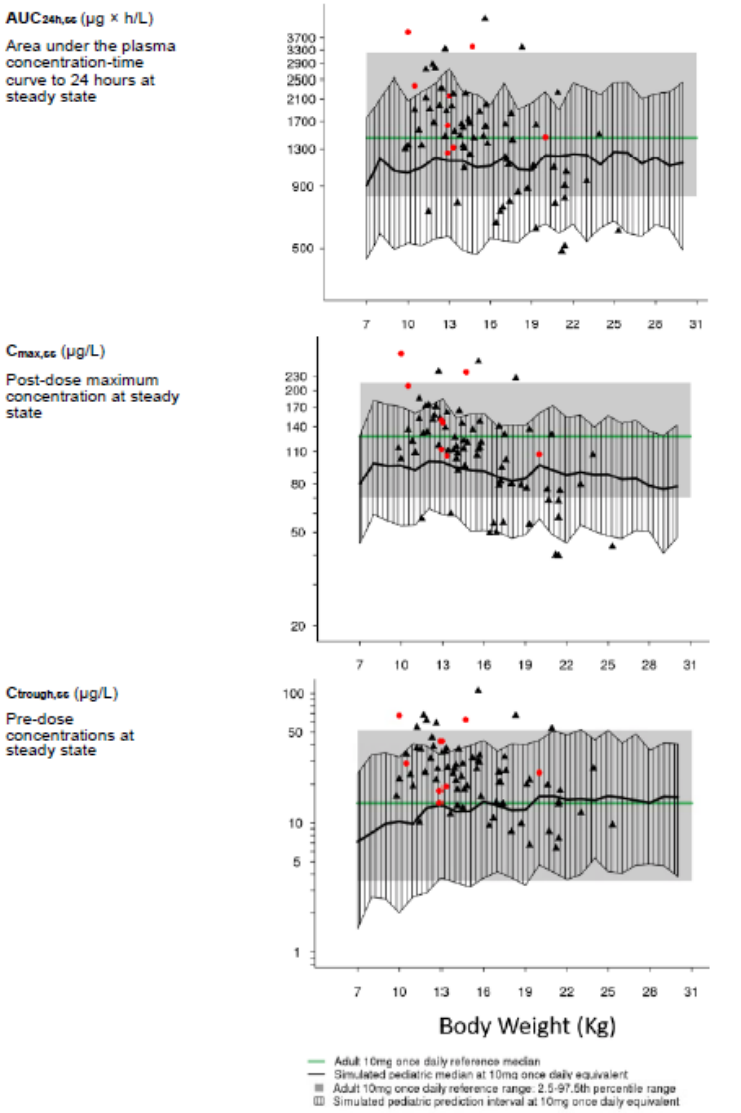
Table 5-1 Rivaroxaban exposure: Children (UNIVERSE) vs adults (Study 11527)

Variables	Exposure metrics	Children N = 76	Adult reference 10 mg once daily (Study 11527) N = 140
$AUC_{24h,ss}$ (µg*h/L)	Geometric Mean (90% CI)	1440 (1317, 1576)	1494 (1425, 1565)
	Median (Range)	1477 (484.2, 4444)	1452 (565.4, 4747)
$C_{max,ss}$ (µg/L)	Geometric Mean (90% CI)	109.0 (100.4, 118.5)	125.8 (120.6, 131.3)
	Median (Range)	113.3 (39.7, 287.1)	127.6 (54.0, 292.8)
$C_{trough,ss}$ (µg/L)	Geometric Mean (90% CI)	22.8 (20.4, 25.5)	13.9 (12.6, 15.4)
	Median (Range)	23.2 (6.4, 104.7)	14.3 (0.8, 99.3)

$AUC_{24h,ss}$ = area under the plasma concentration-time curve to 24 hours at steady state; CI = confidence interval; Cmax,ss = post-dose maximum concentration at steady state; $C_{trough,ss}$ = predose concentrations at steady state.

Individual results for main exposure metrics (AUC24h,ss, Cmax,ss, and Ctrough,ss) as a function of body weight from this study at a rivaroxaban 10 mg-equivalent regimen were compared with the adult reference at rivaroxaban 10 mg once daily (Figure 5-4). The AUC24h,ss values from this study were largely contained within the 2.5th to 97.5th percentile exposure range of the adult reference, indicating that the overall rivaroxaban exposures in subjects in this study were similar to those in adults. In addition, the overall PK characteristics were similar between this study and EINSTEIN Jr program, with exposure metrics (AUC24h,ss, Cmax,ss, and Ctrough,ss) largely overlapping with the paediatric prediction range based on the EINSTEIN Jr popPK model assuming 10 mg equivalent dose (Figure 5-4). Further analyses on a potential trend of exposure metrics as a function of age and/or body weight and in comparison to results from the EINSTEIN Jr program using popPK as well as PBPK modeling are still ongoing and will be reported under separate cover.

Figure 5-4 Rivaroxaban exposure in children (UNIVERSE) versus adults (Study 11527) at rivaroxaban 10 mg once daily, and with the simulated pediatric range using the EINSTEIN Jr PopPK Model and UNIVERSE dosing regimen



▲Black triangles: Non-Japanese subjects; ●Red circles: Japanese subjects.

Note: 2.5th to 97.5th percentile exposure ranges of the adult reference are $AUC_{24h,ss}$: 820 to 3216 µg*h/L; $C_{max,ss}$: 70.2 to 215.8 µg/L; $C_{trough,ss}$: 3.55 to 52.0 µg/L

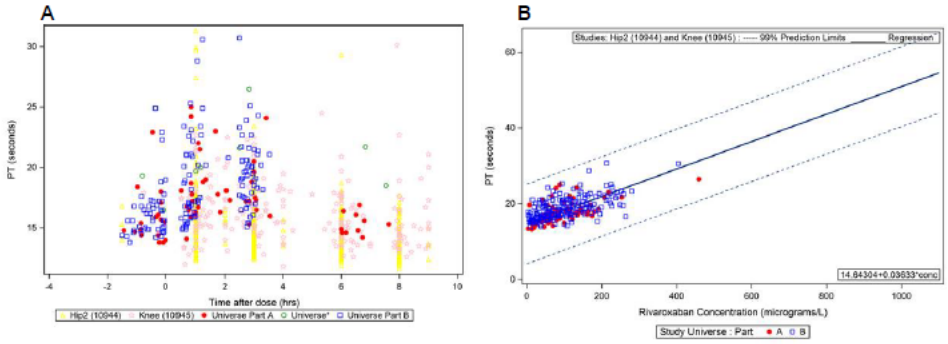
Pharmacodynamics

Prothrombin time (Figure 6-1) and aPTT (Figure 6-2) profiles were compared between children who were enrolled in the UNIVERSE study and adults enrolled in studies ODIXa-HIP2 and ODIXa-KNEE. In general, PT values in the paediatric subjects were within the range of corresponding values that were observed in adults. A much wider range of aPTT values was observed in adult compared to paediatric subjects. A linear relationship was observed for PT in paediatric and adult subjects. The observed values for the paediatric subjects were contained within the 99% prediction interval based on adult data. Similar results were obtained based on the analysis of aPTT; however, the changes in aPTT as a function of rivaroxaban concentrations were smaller relative to the observed changes in PT. The change from baseline in PT also increased with an increase in plasma rivaroxaban concentrations,

whereas the change from baseline in aPTT as a function of rivaroxaban concentration was much less evident.

Anti-FXa activity displays a close relationship between with the plasma rivaroxaban concentrations as described by a simple linear model. The model has an intercept value of -3.14 (µg/L) and a slope of 0.885.

Figure 6-1 Prothrombin time as a function of time (A) and plasma rivaroxaban concentrations (B) in children and adults who received a twice-daily regimen of rivaroxaban

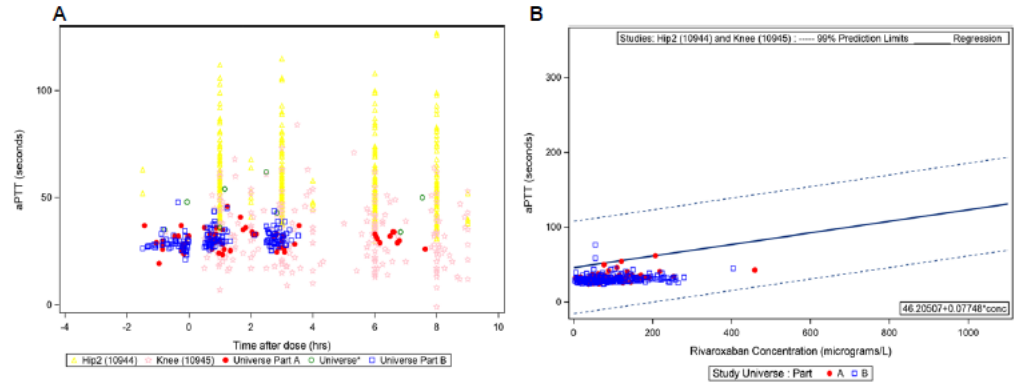


PT = prothrombin time

A: Data are from the 5 mg rivaroxaban twice daily dose from the adult ODIXa-HIP2 (10944) (Days 6 or 7) and ODIXa-KNEE (10945) (Days 4 to 9) studies and from Day 4 (Part A) and Month 3 (Parts A and B) of the UNIVERSE study. Open circles (left figure) represent the values from 2 subjects in Part A of the UNIVERSE study who prematurely discontinued the study drug.

B: Includes line of regression and 99% prediction intervals of data from the 2.5 to 30 mg rivaroxaban twice daily dose from the adult ODIXa-HIP2 (10944) (Days 3 and 6 or 7) and ODIXa-KNEE (10945) (Days 2 to 9) studies. Observed data are from Day 1 (Parts A and B), Day 4 (Part A), and Month 3 (Parts A and B) of the UNIVERSE study.

Figure 6-2 Activated partial thromboplastin time as a function of time (A) and plasma rivaroxaban concentrations (B) in children and adults who received a twice daily regimen of rivaroxaban



aPPT = activated partial thromboplastin time

A: Data are from the 5 mg rivaroxaban twice daily dose from the adult ODIXa-HIP2 (10944) (Days 6 or 7) and ODIXa-KNEE (10945) (Days 4 to 9) studies and from Day 4 (Part A) and Month 3 (Parts A and B) of the UNIVERSE study. Open circles (left figure) represent the values from 2 subjects in Part A of the UNIVERSE study who prematurely discontinued the study drug.

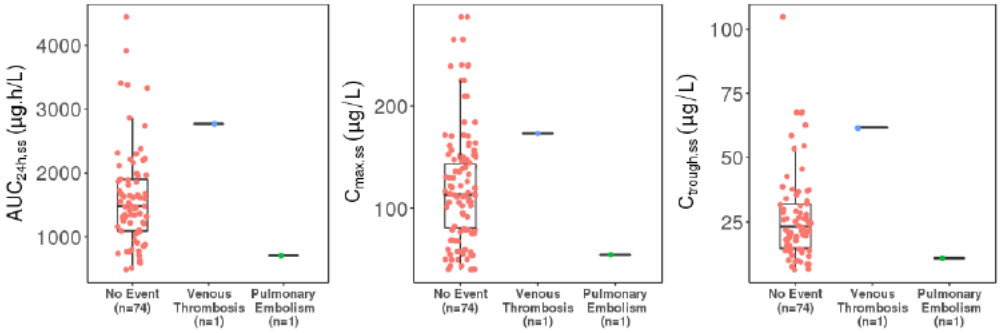
B: Includes line of regression and 99% prediction intervals of data from the 2.5 to 30 mg rivaroxaban twice daily dose from the adult ODIXa-HIP2 (10944) (Days 3 and 6 or 7) and ODIXa-KNEE (10945) (Days 2 to 9) studies. Observed data are from Day 1 (Parts A and B), Day 4 (Part A), and Month 3 (Parts A and B) of the UNIVERSE study.

Correlation of exposure to study outcomes

Within the rivaroxaban treatment arm, 2 thrombotic events were observed, including 1 venous thrombotic event in 1 subject and 1 pulmonary embolism in another subject. Bleeding events were observed in 27 subjects. Three subjects experienced multiple bleeding events and 24 subjects experienced 1 event. Among the bleeding events, there was 1 major bleeding, 5 clinically relevant non major bleeding, and 24 trivial bleeding events. Rivaroxaban exposure metrics (AUC24h,ss, Cmax,ss, and Ctrough,ss) were compared in subjects with or without thrombotic events (Figure 7-1) and in subjects with or without bleeding events (Figure 7-2). The ranges of AUC24h,ss, Cmax,ss, and

Ctrough,ss largely overlapped between subjects with or without thrombotic or bleeding events. These results suggest that within the exposure range studied, higher or lower rivaroxaban exposures are not likely to influence thrombosis or bleeding outcomes.

Figure 7-1 UNIVERSE Study: Relationship between rivaroxaban exposure and thrombosis event



$AUC_{24h,ss}$=area under the plasma concentration-time curve to 24 hours at steady state; $C_{max,ss}$=post-dose maximum concentration at steady state; $C_{trough,ss}$=predose concentrations at steady state; VTE=venous thromboembolism

Red circles: Patients who did not experience a thrombotic event;

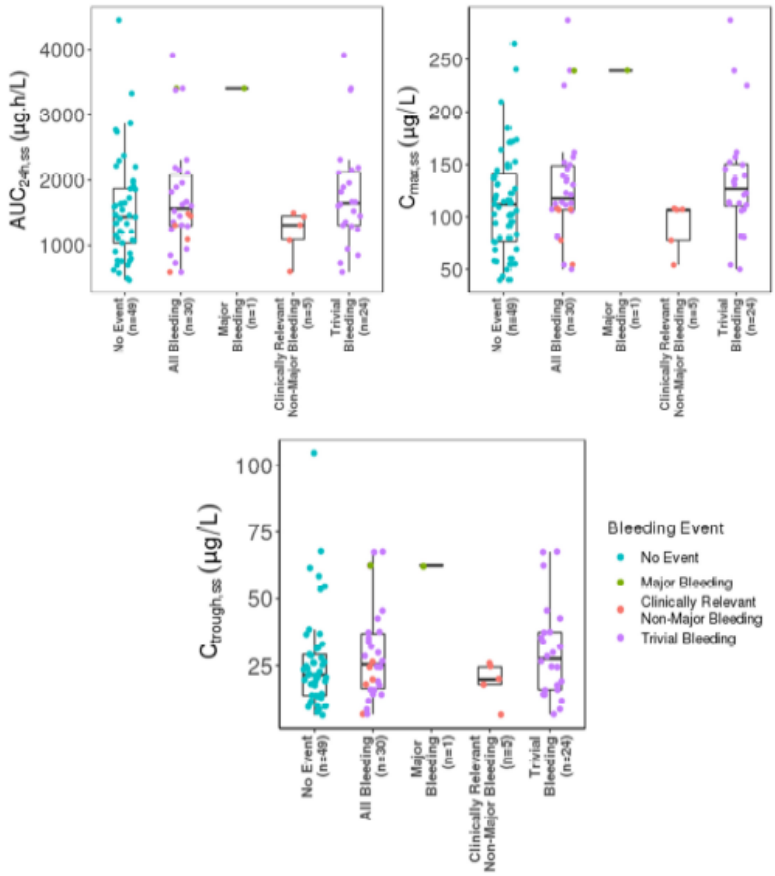
Blue circle: Patient who experienced a venous thrombotic event;

Green circle: Patient who experienced a pulmonary embolism.

Notes: The solid line in the box is the median. The boundaries of the box represent the 25th and 75th percentiles. The whiskers are the nearest values within 1.5-times the inter-quartile range below and above the 25th and 75th percentile respectively. Individual values are provided where n=1.

2.5th to 97.5th percentile exposure ranges of the adult reference are $AUC_{24h,ss}$: 820 to 3216 µg*h/L; $C_{max,ss}$: 70.2 to 215.8 µg/L; $C_{trough,ss}$: 3.55 to 52.0 µg/L

Figure 7-2 UNIVERSE Study: Relationship between rivaroxaban exposure and bleeding events



$AUC_{24h,ss}$ = area under the plasma concentration-time curve to 24 hours at steady state; $C_{max,ss}$ = post-dose maximum concentration at steady state; CRNM = clinically relevant non-major bleeding; $C_{trough,ss}$= predose concentrations at steady state.

Turquoise circles: Patients who did not experience a bleeding event
Green circles: Patients who experienced a major bleeding event
Red circles: Patients who experienced a clinically relevant non-major bleeding event
Violet circles: Patients who experienced a trivial bleeding event.

Notes: The solid line in the box is the median. The boundaries of the box represent the 25th and 75th percentiles. The whiskers are the nearest values within 1.5-times the inter-quartile range below and above the 25th and 75th percentile respectively.
All bleeding includes the 3 bleeding categories: major, trivial, and clinically relevant non-major.
Individual values are provided where n=1.
2.5th to 97.5th percentile exposure ranges of the adult reference are $AUC_{24h,ss}$: 820 to 3216 µg*h/L
$C_{max,ss}$: 70.2 to 215.8 µg/L
$C_{trough,ss}$: 3.55 to 52.0 µg/L

Safety results

Bleeding events

Table 4-1 UNIVERSE Study: Bleeding events - Frequencies

		Rivaroxaban			Aspirin	Total
		Part A	Part B	Total	Part B	
Analysis set: Safety	N =	12 (100%)	64 (100%)	76 (100%)	34 (100%)	110 (100%)
Any on-treatment bleeding event		4 (33.3%)	23 (35.9%)	27 (35.5%)	14 (41.2%)	41 (37.3%)
Major bleeding		0	1 (1.6%)	1 (1.3%)	0	1 (0.9%)
Clinically relevant non-major bleeding	Any	1 (8.3%)	4 (6.3%)	5 (6.6%)	3 (8.8%)	8 (7.3%)
	Gastrointestinal	0	2 (3.1%)	2 (2.6%)	1 (2.9%)	3 (2.7%)
	GI-Lower	0	2 (3.1%)	2 (2.6%)	1 (2.9%)	3 (2.7%)
	Gingival	0	1 (1.6%)	1 (1.3%)	0	1 (0.9%)
	Hematoma	0	0	0	1 (2.9%)	1 (0.9%)
	Skin	1 (8.3%)	1 (1.6%)	2 (2.6%)	1 (2.9%)	3 (2.7%)
	Subconjunctival	0	0	0	1 (2.9%)	1 (0.9%)
Major and CRNM bleeding		1 (8.3%)	5 (7.8%)	6 (7.9%)	3 (8.8%)	9 (8.2%)
Trivial bleeding	Any	3 (25.0%)	21 (32.8%)	24 (31.6%)	12 (35.3%)	36 (32.7%)
	Epistaxis	0	7 (10.9%)	7 (9.2%)	3 (8.8%)	10 (9.1%)
	Gastrointestinal	0	1 (1.6%)	1 (1.3%)	1 (2.9%)	2 (1.8%)
	GI-Lower	0	0	0	1 (2.9%)	1 (0.9%)
	GI-Upper	0	1 (1.6%)	1 (1.3%)	0	1 (0.9%)
	Gingival	1 (8.3%)	3 (4.7%)	4 (5.3%)	1 (2.9%)	5 (4.5%)
	Hematoma	2 (16.7%)	7 (10.9%)	9 (11.8%)	2 (5.9%)	11 (10.0%)
	Skin	0	14 (21.9%)	14 (18.4%)	8 (23.5%)	22 (20.0%)
	Vascular access site	0	2 (3.1%)	2 (2.6%)	0	2 (1.8%)

CRNM = clinically relevant non-major; GI = gastrointestinal; ISTH = International Society on Thrombosis and Haemostasis

Notes: Percentages calculated with the number of subjects in each group as denominator.
Incidence is based on the number of subjects not the number of events.
A subject may appear in different sites/categories.
On-treatment is defined as the period starting from the first dose of study agent to 2 days after the last dose of the study agent administration inclusively.
Safety Analysis Set: all subjects in Part A who receive at least 1 dose of study agent and all subjects in Part B who are randomized and receive at least 1 dose of study agent.
The primary safety outcome is major bleed that meets the ISTH definition.
The only major bleeding occurred in non-critical site - Epistaxis.
Major bleeding is defined as overt bleeding and: 1) Associated with a fall in hemoglobin of 2 g/dL or more; or 2) Leading to a transfusion of the equivalent of 2 or more units of packed red blood cells or whole blood in adults; or 3) Occurring in a critical site: intracranial, intraspinal, intraocular, pericardial, intraarticular, intramuscular with compartment syndrome, retroperitoneal; or 4) Contributing to death.

A major bleeding event, as adjudicated by CIAC, was seen in 1 (1.6%) subject in the rivaroxaban Part B group which occurred on Day 108 after first dose of study drug at a non-critical site (epistaxis). This bleeding was associated with a fall of haemoglobin of 2 g/dL or more and led to transfusion. As per protocol, the subject had to discontinue the study drug permanently. No major bleeding event was reported in either the ASA Part B or the rivaroxaban Part A groups.

In Part B, the results for CRNM bleeding were similar amongst the treatment groups, with 4 (6.3%) subjects in the rivaroxaban group and 3 (8.8%) subjects in the ASA group. In the rivaroxaban Part B group, these events occurred in the lower gastrointestinal tract (2 [3.1%]), gingival (1 [1.6%]), and the skin (1 [1.6%]), and in the ASA Part B group, they occurred in the lower gastrointestinal tract (1 [2.9%]), the skin (1 [2.9%]), hematoma (1 [2.9%]), and subconjunctival (1 [2.9%]). In the rivaroxaban Part A group, there was 1 (8.3%) subject reported with a CRNM bleeding event occurring in the skin.

In Part B, the proportion of trivial bleeding events was similar between the rivaroxaban group with 21 (32.8%) subjects and the ASA group with 12 (35.3%) subjects. The most frequent site of trivial bleeding was skin in both groups (14 [21.9%] in the rivaroxaban group and 8 [23.5%] in the ASA group). In the rivaroxaban Part A group, 3 (25.0%) subjects were reported with trivial bleeding events (the most frequently reported site was hematoma, 2 [16.7%]).

Summary of all adverse events

Treatment-emergent AEs were defined as those AEs that started on or after the first dose of study drug and up to 2 days after the last dose of study drug. The incidences of TEAEs and TESAEs were balanced between the rivaroxaban and ASA groups in Part B. There were 55 (85.9%) and 29 (85.3%) subjects who experienced at least 1 TEAE and 18 (28.1%) and 8 (23.5%) subjects who experienced at least 1 TESAE in the rivaroxaban Part B group and in the ASA Part B group, respectively. In the rivaroxaban Part A group, there were 11 (91.7%) subjects with at least 1 TEAE and 6 (50.0%) subjects with at least 1 TESAE reported.

There were 20 (31.3%) and 9 (26.5%) subjects in the rivaroxaban Part B group and in the ASA Part B group, respectively, who had AEs that were considered by the investigators to be related to study drug (most of them related to the reported bleeding events). Only 1 (1.6%) subject in the rivaroxaban Part B group had an SAE (major bleeding) that was considered by the investigator to be related to study drug. In the rivaroxaban Part A group, 3 (25.0%) subjects had AEs considered by the investigators to be related to study drug. Most AEs were in the SOC of Infections and Infestations and the Respiratory, Mediastinal Disorders; none were considered related to study drug by the investigators.

In Part B, there were 11 (17.2%) subjects in the rivaroxaban group and 3 (8.8%) subjects in the ASA group with AEs that occurred off-treatment (events that occurred between 3 days after the study drug was stopped and the date of last study contact, inclusively).

Table 4-3 UNIVERSE Study: Adverse events

		Rivaroxaban			Aspirin	Total
		Part A	Part B	Total	Part B	
Analysis set: Safety	N =	12	64	76	34	110
AEs	Any	11 (91.7%)	56 (87.5%)	67 (88.2%)	30 (88.2%)	97 (88.2%)
	Pre-treatment	0	8 (12.5%)	8 (10.5%)	2 (5.9%)	10 (9.1%)
	Treatment emergent	11 (91.7%)	55 (85.9%)	66 (86.8%)	29 (85.3%)	95 (86.4%)
	Off-treatment	1 (8.3%)	11 (17.2%)	12 (15.8%)	3 (8.8%)	15 (13.6%)
Non-bleeding AEs	Any	11 (91.7%)	54 (84.4%)	65 (85.5%)	29 (85.3%)	94 (85.5%)
	Pre-treatment	0	6 (9.4%)	6 (7.9%)	2 (5.9%)	8 (7.3%)
	Treatment emergent	11 (91.7%)	53 (82.8%)	64 (84.2%)	28 (82.4%)	92 (83.6%)
	Off-treatment	1 (8.3%)	11 (17.2%)	12 (15.8%)	3 (8.8%)	15 (13.6%)
SAEs	Any	6 (50.0%)	19 (29.7%)	25 (32.9%)	8 (23.5%)	33 (30.0%)
	Pre-treatment	0	0	0	0	0
	Treatment emergent	6 (50.0%)	18 (28.1%)	24 (31.6%)	8 (23.5%)	32 (29.1%)
	Off-treatment	0	1 (1.6%)	1 (1.3%)	0	1 (0.9%)
Non-bleeding SAEs	Any	6 (50.0%)	18 (28.1%)	24 (31.6%)	8 (23.5%)	32 (29.1%)
	Pre-treatment	0	0	0	0	0
	Treatment emergent	6 (50.0%)	17 (26.6%)	23 (30.3%)	8 (23.5%)	31 (28.2%)
	Off-treatment	0	1 (1.6%)	1 (1.3%)	0	1 (0.9%)
Resulting in permanent discontinuation of study agent	TEAEs	0	2 (3.1%)	2 (2.6%)	0	2 (1.8%)
	TESAEs	0	1 (1.6%)	1 (1.3%)	0	1 (0.9%)
	TENSAEs	0	1 (1.6%)	1 (1.3%)	0	1 (0.9%)
AE relationship to study agent	Any	3 (25.0%)	20 (31.3%)	23 (30.3%)	9 (26.5%)	32 (29.1%)
	Possibly	3 (25.0%)	17 (26.6%)	20 (26.3%)	9 (26.5%)	29 (26.4%)
	Probably	0	3 (4.7%)	3 (3.9%)	0	3 (2.7%)
	Very likely	1 (8.3%)	1 (1.6%)	2 (2.6%)	0	2 (1.8%)
SAE relationship to study agent	Any	0	1 (1.6%)	1 (1.3%)	0	1 (0.9%)
	Possibly	0	1 (1.6%)	1 (1.3%)	0	1 (0.9%)
	Probably	0	0	0	0	0
	Very likely	0	0	0	0	0

AE=adverse event; SAE=serious adverse event; SMQ=Standardised MedDRA Query; TEAE=treatment-emergent adverse event; TENSAE=treatment-emergent non-serious adverse event; TESAE=treatment-emergent serious adverse event.

Notes: Percentages calculated with the number of subjects in each group as denominator.

Incidence is based on the number of subjects not the number of events.

Treatment-emergent adverse event is defined as an adverse event that occurs after the first dose and up to 2 days after the last dose of study agent.

Off-treatment adverse event is defined as an adverse event that starts from 3 days after the last dose of study agent to last contact date inclusively.

Pre-treatment adverse event is defined as an adverse event that starts before the first dose of study agent.

Safety Analysis Set: all subjects in Part A who receive at least 1 dose of study agent and all subjects in Part B who are randomized and receive at least 1 dose of study agent.

Bleeding adverse events are selected by using the haemorrhages SMQ excluding lab Terms. Those unselected are non-bleeding adverse events.

The relationship to adverse events is per investigator assessment.

Treatment-emergent adverse events

Table 4-4 summarises TEAEs with >10% in either treatment group by system organ class and preferred term. The proportion of children with at least 1 TEAE was similar across all treatment groups. There were 55 (85.9%) and 29 (85.3%) subjects who experienced at least 1 TEAE in the rivaroxaban Part B group and in the ASA Part B group, respectively. There were 11 (91.7%) subjects who experienced at least 1 TEAE in the rivaroxaban Part A group. The most frequently reported TEAEs in Part B were pyrexia (23.4% in the rivaroxaban and 20.6% in the ASA Part B groups) and nasopharyngitis (21.9% in the rivaroxaban and 17.6% in the ASA Part B groups). Two (3.1%) subjects had TEAEs leading to permanent treatment discontinuation (1 with major bleeding and 1 with parental consent withdrawal due to mood disturbance) in the rivaroxaban Part B group.

Infections and infestations was the system organ class with more frequently reported TEAEs in all 3 groups (40 [62.5%] in rivaroxaban Part B group and 22 [64.7%] in ASA Part B group; and 8 [66.7%] in rivaroxaban Part A group). In Part B, TEAEs were, in general, balanced between the rivaroxaban and the ASA groups except for pleural effusion, which was more frequently reported in the rivaroxaban group than in the ASA group (12 [18.8%] versus 2 [5.9%]).

Table 4-4 UNIVERSE Study: Treatment-emergent adverse events – Preferred terms

System organ class	Rivaroxaban			Aspirin	Total
Preferred term	Part A	Part B	Total	Part B	
Analysis set: Safety N =	12	64	76	34	110
Subjects with 1 or more TEAEs	11 (91.7%)	55 (85.9%)	66 (86.8%)	29 (85.3%)	95 (86.4%)
Infections and infestations	8 (66.7%)	40 (62.5%)	48 (63.2%)	22 (64.7%)	70 (63.6%)
Nasopharyngitis	1 (8.3%)	14 (21.9%)	15 (19.7%)	6 (17.6%)	21 (19.1%)
Upper respiratory tract infection	2 (16.7%)	9 (14.1%)	11 (14.5%)	5 (14.7%)	16 (14.5%)
Respiratory, thoracic and mediastinal disorders	5 (41.7%)	29 (45.3%)	34 (44.7%)	9 (26.5%)	43 (39.1%)
Pleural effusion	3 (25.0%)	12 (18.8%)	15 (19.7%)	2 (5.9%)	17 (15.5%)
Cough	0	10 (15.6%)	10 (13.2%)	3 (8.8%)	13 (11.8%)
Gastrointestinal disorders	6 (50.0%)	19 (29.7%)	25 (32.9%)	9 (26.5%)	34 (30.9%)
Vomiting	3 (25.0%)	9 (14.1%)	12 (15.8%)	3 (8.8%)	15 (13.6%)
Injury, poisoning and procedural complications	4 (33.3%)	18 (28.1%)	22 (28.9%)	10 (29.4%)	32 (29.1%)
Fall	0	2 (3.1%)	2 (2.6%)	5 (14.7%)	7 (6.4%)
Skin and subcutaneous tissue disorders	3 (25.0%)	19 (29.7%)	22 (28.9%)	9 (26.5%)	31 (28.2%)
Ecchymosis	0	6 (9.4%)	6 (7.9%)	5 (14.7%)	11 (10.0%)
General disorders and administration site conditions	1 (8.3%)	17 (26.6%)	18 (23.7%)	8 (23.5%)	26 (23.6%)
Pyrexia	1 (8.3%)	15 (23.4%)	16 (21.1%)	7 (20.6%)	23 (20.9%)

MedDRA=Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event.

Notes: Treatment-emergent adverse event is defined as an adverse event that occurs after the first dose and up to 2 days after the last dose of study agent.

Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event.

Percentages calculated with the number of subjects in each group as denominator.

Adverse events are coded using MedDRA Version 23.0

The organ classes and preferred terms are sorted in descending order of incidence based on Rivaroxaban (total).

Safety Analysis Set: all subjects in Part A who receive at least 1 dose of study agent and all subjects in Part B who are randomized and receive at least 1 dose of study agent.

Deaths

No deaths were reported during the study.

Serious adverse events

Table 4-5 summarises TESAEs with >10% in either treatment group by system organ class and preferred term. There were 18 (28.1%) subjects, 8 (23.5%) subjects, and 6 (50.0%) subjects who experienced at least 1 TESAE in the rivaroxaban Part B group, ASA Part B group, and rivaroxaban Part A group, respectively. One (1.6%) subject in the rivaroxaban Part B group had an SAE (major bleeding) that was considered by the investigator to be related to the study drug. Across all groups,

respiratory, thoracic, and mediastinal disorders was the system organ class with the most frequently reported TESAEs (9 [14.1%] in rivaroxaban Part B group.

Table 4-5 UNIVERSE Study: Treatment-emergent serious adverse events

System organ class		Rivaroxaban			Aspirin	Total
Preferred term		Part A	Part B	Total	Part B	
Analysis set: Safety	N =	12	64	76	34	110
Any		6 (50.0%)	18 (28.1%)	24 (31.6%)	8 (23.5%)	32 (29.1%)
Respiratory, thoracic and mediastinal disorders		2 (16.7%)	9 (14.1%)	11 (14.5%)	3 (8.8%)	14 (12.7%)
Pleural effusion		2 (16.7%)	9 (14.1%)	11 (14.5%)	2 (5.9%)	13 (11.8%)
Infections and infestations		3 (25.0%)	5 (7.8%)	8 (10.5%)	4 (11.8%)	12 (10.9%)

MedDRA=Medical Dictionary for Regulatory Activities

Notes: Treatment-emergent adverse event is defined as an adverse event that occurs after the first dose and up to 2 days after the last dose of study agent.

Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event.

Percentages calculated with the number of subjects in each group as denominator.

Adverse events are coded using MedDRA Version 23.0

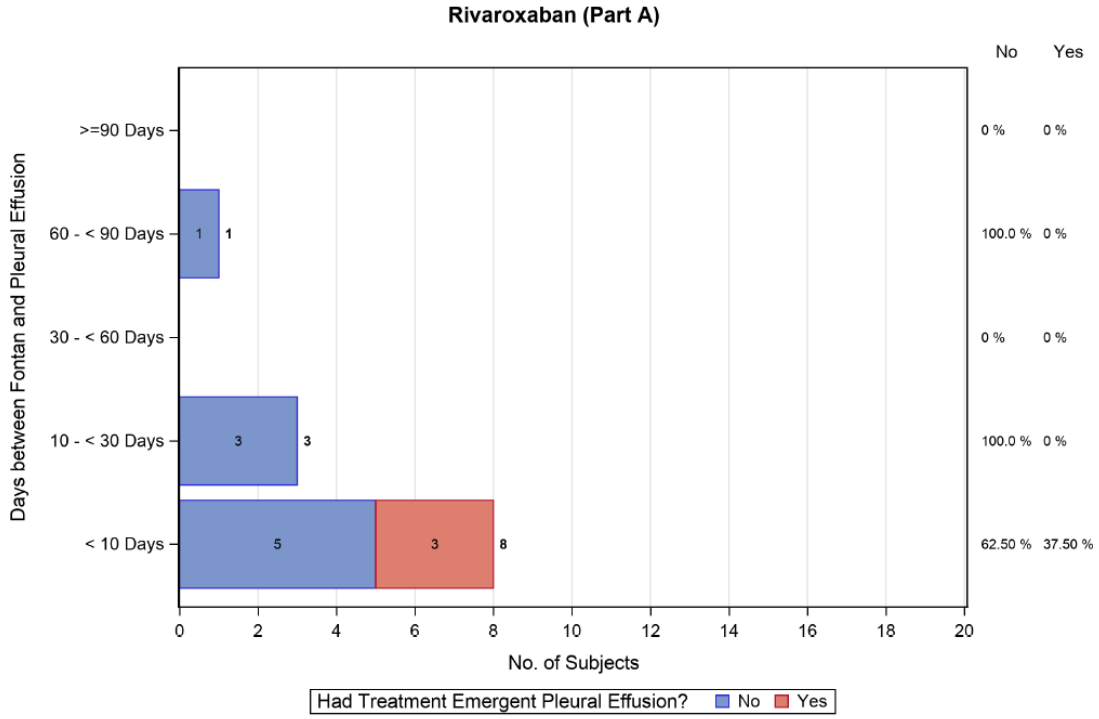
The organ classes and preferred terms are sorted in descending order of incidence based on Rivaroxaban (total).

Safety Analysis Set: all subjects in Part A who receive at least 1 dose of study agent and all subjects in Part B who are randomized and receive at least 1 dose of study agent.

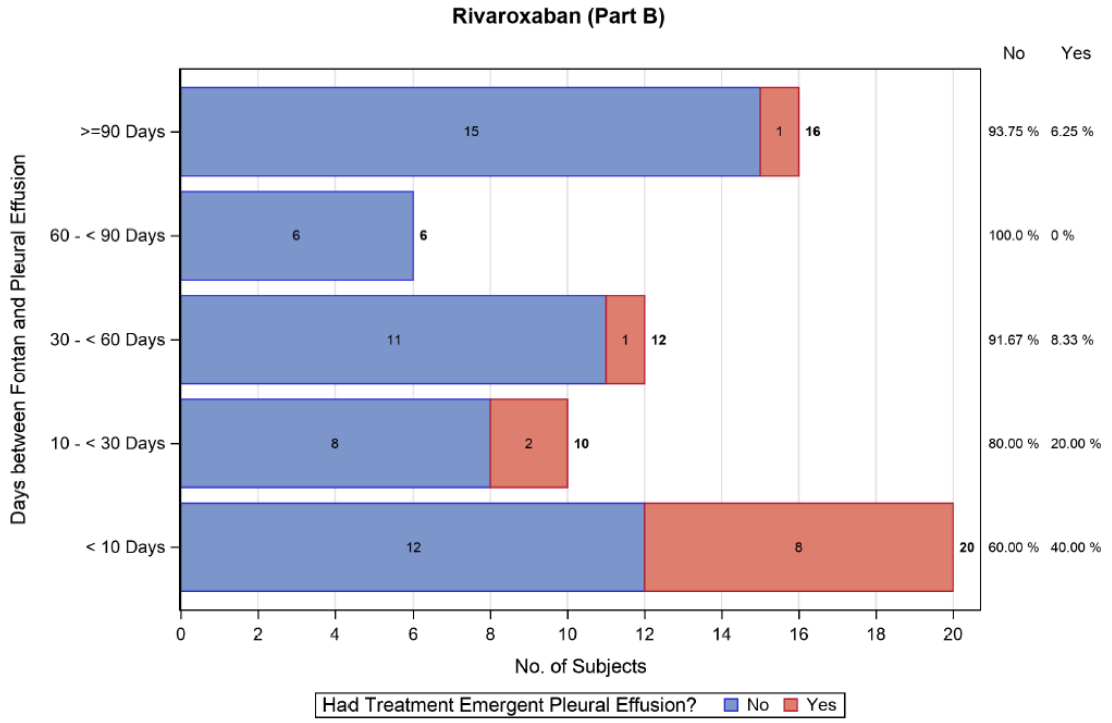
A total of 2 (3.1%) subjects in the rivaroxaban Part B group had at least 1 TEAE resulting in permanent discontinuation of study drug (Table 4-3). One (1.6%) subject was discontinued as per protocol due to reaching the primary safety outcome (major bleeding) and 1 (1.6%) subject was withdrawn by the parent due to the AE of mood disturbance.

<u>Additional analyses on pleural effusions (from CSR)</u>

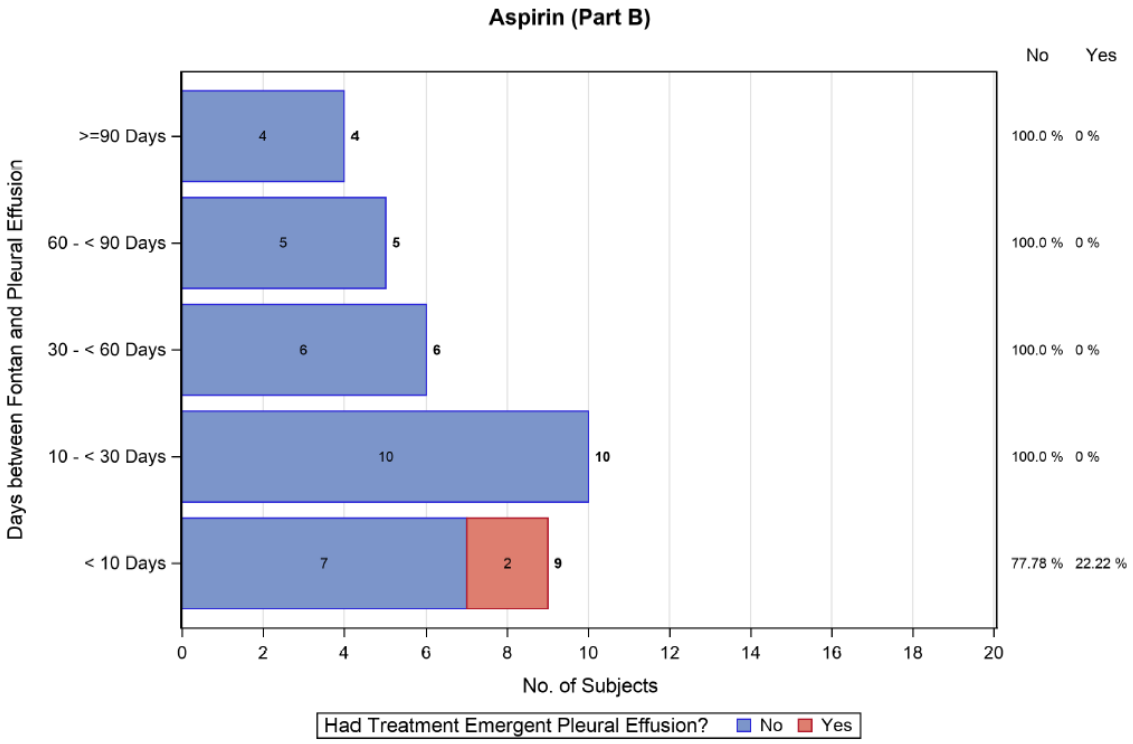
GSFAEPH01: Bar Plot of the Occurrence of Treatment-Emergent Pleural Effusion and Duration Between Fontan and Treatment; Safety Analysis Set (Study 39039039CHD3001)



GSFAEPH01: Bar Plot of the Occurrence of Treatment-Emergent Pleural Effusion and Duration Between Fontan and Treatment; Safety Analysis Set (Study 39039039CHD3001)



GSFAEPH01: Bar Plot of the Occurrence of Treatment-Emergent Pleural Effusion and Duration Between Fontan and Treatment; Safety Analysis Set (Study 39039039CHD3001)



Adverse events of special interest

No AESIs were reported in this study.

Laboratory evaluation

Haematology

Overall, the majority of haematological parameters showed a minimal change from baseline to Month 12. None of these changes were considered clinically significant by the investigators and were not reported as an AE for any subject in the study. No individual subjects had clinically significant abnormalities from baseline to Month 12 or ESMD for haematology.

Chemistry

The laboratory test results for chemistry parameters (ALP, ALT, AST, direct bilirubin, creatinine, and creatinine clearance adjusted for BSA) at baseline, at Month 12, and change from baseline to Month 12 have been provided. The mean values of all the chemistry parameters did not show a considerable change from baseline to Month 12 in all the 3 groups. None of these changes were reported as an AE. One subject in the rivaroxaban Part B group had ALT >3×ULN at baseline (1/63 [1.6%]) but was eligible to participate in the study because of no concurrent total bilirubin >1.5x ULN, with direct bilirubin >20% of the total at screening. At Month 12, 1 subject (1/57 [1.8%]) had bilirubin >3×ULN in the rivaroxaban Part B group. It was not considered clinically significant and was not reported as an AE or SAE. There were no subjects with pre-specified combined laboratory abnormalities for ALT and bilirubin.

2.3.3. Discussion on clinical aspects

This procedure concerns the final study results from study 18226 ("UNIVERSE"), a prospective, open-label, active-controlled study to evaluate the pharmacokinetics, pharmacodynamics, safety, and efficacy of rivaroxaban for thromboprophylaxis in paediatric subjects 2 to 8 years of age after the Fontan procedure, using acetyl salicylic acid (ASA) as active control.

The Fontan operation is a palliative surgical procedure performed in children with a functional or anatomic single ventricle. It is the most common operation performed for patients with any type of single ventricle and is the definitive surgical palliation for patients with congenital heart disease in which septation into a biventricular system is not possible. Following the Fontan procedure, systemic venous blood is returned to the lungs without a separate pump; instead, pulmonary blood flow is driven by central venous pressure. However, complications are frequent; apart from periprocedural complications, long-term morbidity include heart failure, arrhythmia, venous congestion with decreased perfusion causing protein-losing enteropathy and plastic bronchitis, liver failure and thromboembolism. Patients with Fontan circulation are at risk for both systemic and pulmonary thromboembolic events given the low flow in the Fontan circuit and associated alterations in levels of clotting and fibrinolysis factors, with a reported prevalence ranging from 2 to 33 percent. However, patients with Fontan circulation are also at risk for bleeding complications, and the optimal antithrombotic strategy in patients with Fontan circulation has not yet been determined. (Johnson J et al. *Management of complications in patients with Fontan circulation.* In UpToDate, Post, TW (Ed), UpToDate, Waltham, MA, 2021) Current guidelines suggest ASA for all patients with Fontan circulation, with anticoagulation reserved for those with presumed risk factors or previous thrombosis or older patients (Giglia TM et al. *Prevention and treatment of thrombosis in pediatric and congenital heart disease: a scientific statement from the American Heart Association.* Circulation. 2013;128:2622–2703).

Study 18226 consisted of 2 parts. Part A was 12-month, single-arm, with a 12-day initial PK, PD, and safety assessment period prior to continuing 12 months of open-label rivaroxaban therapy. Subjects in

Part A did not participate in Part B. Randomization in Part B began once the cumulative data from the initial PK, PD, and Safety Assessment Period in Part A were deemed acceptable; this was the 2-arm, randomised, open-label, active-controlled part of the study to evaluate the safety and efficacy of rivaroxaban compared to ASA for thromboprophylaxis for 12 months. Eligible patients were children 2 to 8 years of age with single ventricle physiology who had completed the Fontan procedure within 4 months prior to enrolment. Patients with evidence of thrombosis, protein-losing enteropathy, active bleeding or high risk for bleeding and patients with an indication for anticoagulant or antiplatelet therapy other than current study were excluded, however, subjects who had been treated with VKA, ASA, heparin or LMWH after the Fontan procedure were eligible provided that such treatment was discontinued before screening or starting study drug. Rivaroxaban was supplied as 0.1% (1 mg/mL) oral suspension with target exposure matching to that of rivaroxaban 10 mg total daily dose (oral) in adults. For reference therapy, acetylsalicylic acid (ASA) was supplied as 81 mg or 100 mg tablets for oral administration. The use of ASA as active control appears in line with current guidelines. In general, given the recruitment difficulties in paediatric studies on thromboses, such studies are not expected to be powered to demonstrate statistically significant results; however, this relies on the ability to extrapolate adult data to the paediatric population. There is no approved adult indication for rivaroxaban pertaining to similar surgery as the Fontan procedure; for primary prophylaxis of venous thromboses, rivaroxaban is approved for hip and knee replacement surgery only. Rivaroxaban is not approved as single-therapy for prevention of arterial events in adults; it is approved in addition to ASA for prevention of atherothrombotic events in adult patients with acute coronary syndrome and in coronary artery disease/peripheral artery disease at high risk of ischaemic events. Further assessment of the overall study design and the ability to extrapolate adult data to paediatric subjects for primary prevention of thrombosis will be required.

More than 95% of the 112 enrolled subjects completed the study. Eleven (10.0%) subjects discontinued study treatment prematurely (5 [7.8%] in the rivaroxaban Part B group and 4 [11.8%] in the ASA Part B group; and 2 [16.7%] subjects in the rivaroxaban Part A group). It is noted that the premature discontinuations in the rivaroxaban part A were due to reaching an AUC at steady state above the pre-specified upper threshold of the target AUC range.

The demographic and baseline characteristics were overall balanced between the rivaroxaban and the ASA groups. The rivaroxaban Part A group had a younger mean (SD) age (2.5 [0.67] years), a lower mean weight, and a shorter median duration between the Fontan procedure and first dose than both groups in Part B.

The primary efficacy outcome was evaluated as any venous or arterial thrombotic event, which was defined as the appearance of a new thrombotic burden within the CV system on either routine surveillance or clinically indicated imaging, or the occurrence of a clinical event known to be strongly associated with thrombus (such as cardioembolic stroke, pulmonary embolism). Overall, very few thrombotic events were reported during the study, which could limit the ability to assess efficacy; a clear justification for the appropriateness of extrapolating adult efficacy data to the paediatric population in primary prevention of post-surgical thrombotic events needs to be provided. In total 2 thrombotic events occurred in the rivaroxaban Part A + B groups (2/76 or 2.6%), one pulmonary embolism and one venous thrombosis. In the ASA group, there were 3 thrombotic events (3/34 or 8.8%), one ischaemic stroke and two venous thromboses. There was no apparent relation between anti-FXa activity and thrombotic events, which is in line with previous rivaroxaban data, also for paediatric subjects, however the low number of thrombotic events in this study precludes any firm conclusions. The primary efficacy outcome by subgroup analysis did not show any trends for age, sex, race, ethnicity, region, and Fontan fenestration; however, given the small study size and the low number of thrombotic events, subgroup analyses should be interpreted with caution. There were no

primary efficacy outcomes reported after Month 12 or after early discontinuation of study drug, thus, there was no apparent rebound phenomenon after study drug cessation.

For PK/PD, in general, the observed rivaroxaban concentrations in the paediatric subjects were within the range of corresponding values that were observed in adults after 5 mg twice daily or 10 mg once daily administration of rivaroxaban. The overall PK characteristics were similar between this study and the EINSTEIN Jr program (which was assessed in the recently approved paediatric extension and type II variation EMEA/H/C/000944/X/0074/G), with exposure metrics (AUC24h,ss, Cmax,ss, and Ctrough,ss) largely overlapping with the paediatric prediction range based on the EINSTEIN Jr popPK model assuming 10 mg equivalent dose. In general, prothrombin time values in the paediatric subjects were within the range of corresponding values that were observed in adults in the hip and knee replacement studies, with a linear relationship. A much wider range of aPTT values was observed in adult compared to paediatric subjects. The change from baseline in PT also increased with an increase in plasma rivaroxaban concentrations, whereas the change from baseline in aPTT as a function of rivaroxaban concentration was much less evident; this is also in line with previous rivaroxaban PD data. As expected, anti-FXa activity displayed a close relationship between with the plasma rivaroxaban concentrations as described by a simple linear model. Within the exposure range studied, higher or lower rivaroxaban exposures were not associated with thrombosis or bleeding outcomes.

For safety, a major bleeding event was seen in 1 (1.6%) subject in the rivaroxaban Part B group (Day 108 after study drug initiation; epistaxis associated with a fall of haemoglobin of 2 g/dL or more and led to transfusion). There was no difference in CRNM bleeding and trivial bleeding amongst the treatment groups. No deaths occurred during the study.

There were 55 (85.9%) and 29 (85.3%) subjects who experienced at least 1 TEAE and 18 (28.1%) and 8 (23.5%) subjects who experienced at least 1 TESAE in the rivaroxaban Part B group and in the ASA Part B group, respectively. There were 20 (31.3%) and 9 (26.5%) subjects in the rivaroxaban Part B group and in the ASA Part B group, respectively, who had AEs that were considered by the investigators to be related to study drug (most of them related to bleeding events).

In Part B, TEAEs of pleural effusion were more frequently reported in the rivaroxaban group than in the ASA group (12 [18.8%] versus 2 [5.9%]). In Part A (all rivaroxaban-treated), 2 (16.7%) serious TEAEs of pleural effusion occurred. Notably, there was a higher proportion of subjects with a history of pleural effusions in the ASA group (4/34 vs 4/66 in the rivaroxaban part B group). For Part A, all events of pleural effusions occurred within 10 days after the Fontan procedure. For Part B, treatment emergent pleural effusions in rivaroxaban treated subjects predominantly occurred within 10 days of the Fontan procedure, but additional events occurred 10-<30, 30-<60 and more than 90 days after the Fontan procedure. For Part B, both events of pleural effusions in the ASA group occurred within 10 days after the Fontan procedure. Based on the data from study 14372 (Einstein Jr; children with VTE), there was no apparent imbalance with regards to pleural effusion in that study; there were slightly more respiratory, thoracic and mediastinal disorders reported in the rivaroxaban group, 81/329 (24.6%) vs 34/162 (21.0%) in comparator group. Of these, however, pleural effusion was rare, reported in 2 children (0.6%) in the rivaroxaban group and 1 (0.6%) in the comparator group; 1 event of pleurisy was also reported in the rivaroxaban group (0.3%). During the entire study period (including extended treatment periods), one additional case of pleural effusion was reported in the rivaroxaban group. (source: CSR for Study 14372, tables 14.3.2.1/15 and 14.3.2.1/19) Taking these data into account, the findings of the study 18226 are considered primarily related to the specific population studied (children who have recently undergone a Fontan procedure) which are not covered by the currently approved indications for rivaroxaban. The imbalance between treatment groups should be further addressed ; of note, although pleural effusions could be relatively common after the Fontan surgical procedure, such events could contribute significantly to morbidity and prolonged

hospitalization. It is important to consider whether the pleural effusions were further characterised including any analyses of pleural fluid, whether haemothorax was adequately excluded, any relation between rivaroxaban-concentration and pleural effusion, the proportion of patients with pleural effusion and concomitant bleeding and/or anaemia, a thorough discussion on pre-existing or periprocedural risk factors that could have contributed to the development of pleural effusion and a pathophysiological discussion on whether FXa inhibition could predispose for non-haemothorax causes of pleural effusion.

No adverse events of special interest were reported during study 18226 (such events included suspected toxic effect on the bone marrow including severe thrombocytopenia, severe neutropenia, pancytopenia, aplastic anaemia; suspected severe hypersensitivity reaction, severe skin reactions, suspected severe liver injury and concurrent elevations of ALT >5x ULN and total bilirubin >2x ULN). On a group level, there were no substantial changes in laboratory haematology parameters from baseline to Month 12. It is noted that there was an increase in alkaline phosphatase levels in both treatment groups (median values in rivaroxaban and ASA at baseline: 166 and 149 respectively; after 12 months 259 and 266 respectively). Since there were no imbalances between the treatment groups, this is not further pursued within this procedure. There was no significant increase in AST, ALT or bilirubin in any of the treatment groups.

Overall, there were no emergent safety findings that are considered to warrant any regulatory action at this time point.

3. CHMP overall conclusion and recommendation

☒ Fulfilled:

No further regulatory action required.

With this procedure, the Xarelto MAH has provided the results from study 18226, a prospective, open-label, active-controlled study to evaluate the pharmacokinetics, pharmacodynamics, safety, and efficacy of rivaroxaban for thromboprophylaxis in paediatric subjects 2 to 8 years of age after the Fontan procedure, using acetyl salicylic acid (ASA) as active control.

Xarelto was recently approved for paediatric use (procedure EMEA/H/C/000944/X/0074/G) in children with venous thrombosis. The results from study 18226 are noted. The following points remain to be addressed : the ability to extrapolate adult data on primary prevention of thrombotic events to the paediatric population, and the imbalance between treatment groups (rivaroxaban vs ASA) with regards to pleural effusions; aspects to consider include whether the pleural effusions were further characterised including any analyses of pleural fluid, whether haemothorax was adequately excluded, the proportion of patients with pleural effusion and concomitant bleeding and/or anaemia, any relation between rivaroxaban-concentration and pleural effusion, a thorough discussion on pre-existing or periprocedural risk factors that could have contributed to the development of pleural effusion in this study and a pathophysiological discussion focusing on whether FXa inhibition could predispose for non-haemothorax causes of pleural effusion.

There were no emergent safety findings from this study that are considered to warrant any regulatory action at this time point.