

ORIGINAL RESEARCH

Thromboprophylaxis for Children Post-Fontan Procedure: Insights From the UNIVERSE Study

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BACKGROUND: Patients with single-ventricle physiology who undergo the Fontan procedure are at risk for thrombotic events associated with significant morbidity and mortality. The UNIVERSE Study evaluated the efficacy and safety of a novel liquid rivaroxaban formulation, using a body weight–adjusted dosing regimen, versus acetylsalicylic acid (ASA) in children post-Fontan.

METHODS AND RESULTS: The UNIVERSE Study was a randomized, multicenter, 2-part, open-label study of rivaroxaban, in children who had undergone a Fontan procedure, to evaluate its dosing regimen, safety, and efficacy. Part A was the single-arm part of the study that determined the pharmacokinetics/pharmacodynamics and safety of rivaroxaban in 12 participants before proceeding to part B, whereby 100 participants were randomized 2:1 to open-label rivaroxaban versus ASA. The study period was 12 months. A total of 112 participants were enrolled across 35 sites in 10 countries. In part B, for safety outcomes, major bleeding occurred in one participant on rivaroxaban (epistaxis that required transfusion). Clinically relevant nonmajor bleeding occurred in 6% of participants on rivaroxaban versus 9% on ASA. Trivial bleeding occurred in 33% of participants on rivaroxaban versus 35% on ASA. For efficacy outcomes, 1 participant on rivaroxaban in part B had a pulmonary embolism (2% overall event rate); and for ASA, 1 participant had ischemic stroke and 2 had venous thrombosis (9% overall event rate).

CONCLUSIONS: In this study, participants who received rivaroxaban for thromboprophylaxis had a similar safety profile and fewer thrombotic events, albeit not statistically significant, compared with those in the ASA group.

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Key Words: children ■ Fontan ■ major bleeding ■ rivaroxaban ■ thrombotic events

Single ventricle is a complex cardiac disorder representing 7.7% of congenital heart disease diagnosed in childhood.¹ The Fontan procedure separates pulmonary and systemic circulations by directing all systemic venous return to the pulmonary vascular bed while the functional single ventricle is committed to supporting the systemic circulation. This

results in venous hypertension and passive pulmonary blood flow, predisposing to stasis and endothelial dysfunction, which, together with developmental and acquired coagulation system abnormalities, may predispose to both bleeding and thrombotic events.² Thromboembolism is associated with an increased risk of morbidity and mortality. In 2 retrospective series

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CLINICAL PERSPECTIVE

What Is New?

- Patient care providers are aware that the standard of care for thromboprophylaxis in children post-Fontan procedure lacks evidence-based recommendations.
- This study shows data on an anticoagulant that has adequate safety and efficacy profiles and a new oral formulation that is age appropriate, with evidence-based and body weight–adjusted dosing regimens for children after they undergo the Fontan procedure.

What Are the Clinical Implications?

- The study highlights a potential new use in pediatrics of an oral anticoagulant that does not require regular laboratory monitoring or parenteral administration.

Nonstandard Abbreviations and Acronyms

ASA acetylsalicylic acid

published, the prevalence of thromboembolism in patients following the Fontan procedure was estimated to be between 17% and 33%.^{3,4} Thromboembolic risk appears to be highest within the first 3 to 12 months after the operation, yet it may persist over the following years.⁵ There has been considerable debate about the optimal thromboprophylaxis duration and strategy. There are limited evidence-based guidelines,^{6,7} given the rarity of both single-ventricle patients and thrombotic events that have precluded large-scale definitive clinical trials. Observational data have suggested that some thromboprophylaxis is better than none,^{8,9} but studies have suggested equipoise on antiplatelet versus anticoagulant therapies.^{10,11} However, with the use of either anticoagulant or antiplatelet agents, an important residual risk of thrombotic events remains. Anticoagulant use is problematic given the difficulties, especially in children, associated with vitamin K antagonists (most commonly warfarin), which require dietary modifications, and low-molecular-weight heparins, which require subcutaneous injections; both forms of anticoagulation also require relatively frequent phlebotomy for monitoring of anticoagulation effect. For aspirin (acetylsalicylic acid, hereafter referred to as ASA), there are no data on ASA resistance or the optimal dose for thromboprophylaxis in children.

ASA inhibits platelet aggregation. The mechanism of action of ASA is suppression of thromboxane A₂

production by irreversible inactivation of the prostaglandin cyclo-oxygenase enzyme required for thromboxane synthesis. Because it inhibits platelet aggregation at lower doses, ASA is indicated as part of the standard treatment of acute angina pectoris, acute myocardial infarction, stroke, and other thrombosis.¹² Antiplatelet therapy for long-term antithrombotic therapy is recommended after the Fontan procedure. However, long-term therapy with warfarin may be indicated after the Fontan procedure for higher-risk patients (eg, patients with anatomic or hemodynamic risk factors).⁶ Adverse reactions associated with the use of ASA include allergic reactions and increased risk of gastrointestinal bleeding.¹²

Rivaroxaban is an oral, highly selective, direct factor Xa inhibitor. Inhibition of factor Xa interrupts the intrinsic and extrinsic pathways of the blood coagulation cascade, inhibiting both thrombin formation and the development of thrombi. It has been widely used in adults for thromboprophylaxis and for the treatment and the reduction in the risk of recurrence of deep vein thrombosis and pulmonary embolism.^{13–15} Rivaroxaban has the advantage over conventional anticoagulants, like warfarin, of being an oral medication with no food-drug interactions, limited drug-drug interactions, and no requirement for venipunctures for monitoring, as well as possibly a more favorable safety profile.¹⁶ Use of rivaroxaban may lead to greater acceptability, compliance, and a more stable anticoagulation profile in the young population of patients who have had the Fontan procedure, thereby making rivaroxaban a good candidate for long-term use in this population.

In the UNIVERSE Study, we sought to determine the optimal dosing, and comparative efficacy and safety of rivaroxaban versus ASA for the prevention of thrombotic events in pediatric patients with single-ventricle physiology who had recently undergone the Fontan procedure, using a novel, age-appropriate, liquid formulation.

METHODS

Because of the sensitive nature of the data collected for this study, requests to access the data set from qualified researchers trained in human subject confidentiality protocols may be sent to the Yale University Open Data Access Project. Information on how to request data can be found at <https://yoda.yale.edu/how-request-data>.

Trial Design

The UNIVERSE Study was a prospective, multicenter, open-label, active controlled, 2-part study of rivaroxaban in children with single-ventricle physiology who had the Fontan procedure within 4 months before

enrollment. The pediatric dose regimen in the trial was designed to match the exposure range in adults treated with rivaroxaban, 10 mg once daily, which is an effective dose for the prevention of thrombotic events in adults. The study rationale and trial design have been published previously.¹⁷ The protocol was approved by the Institutional Review Board or Ethics Committee for each participating center. Part A evaluated the single- and multiple-dose pharmacokinetic and pharmacodynamic properties of rivaroxaban to confirm the dose and dosing regimen selected. Part B evaluated the comparative safety and efficacy of rivaroxaban versus ASA when used for thromboprophylaxis for 12 months. Participants in part B were randomized 2:1 to receive body weight–adjusted rivaroxaban administered twice daily or ASA, given once daily (~5 mg/kg) (Figure 1).

Oversight

An independent data and safety monitoring board evaluated all pharmacokinetic, pharmacodynamic, safety, and efficacy data to ensure participant safety throughout the study. In part A only, the independent data and safety monitoring board reviewed cumulative data from the initial pharmacokinetic, pharmacodynamic, and safety assessment period, providing a recommendation to the executive committee to stop enrollment in part A and start enrollment into part B.

The central independent adjudication committee was composed of specialist physicians. Its members

did not enroll patients, were not involved in study monitoring, and did not have operational responsibilities for the conduct of the study. Members reviewed and adjudicated all safety (bleeding) and efficacy (thrombotic) outcomes that occurred post enrollment (Table S2).

Patients

Pediatric patients were eligible for participation in the trial if they were between 2 and 8 years of age with single-ventricle congenital heart disease and had completed an initial Fontan procedure within 4 months before enrollment. Eligible patients were required to be clinically stable and able to tolerate oral or nasogastric feedings. Because the objective of the study was to evaluate rivaroxaban for primary thromboprophylaxis, all patients were required to have an initial post-Fontan transthoracic echocardiographic screening without any evidence of thrombosis.

Patients were excluded from participation if they had thrombosis, a history of gastrointestinal disease or surgery associated with impaired absorption, active bleeding or high risk of bleeding contraindicating antiplatelet or anticoagulant therapy, including history of intracranial hemorrhage, or contraindications to ASA or rivaroxaban. A full listing of the inclusion and exclusion criteria is in Table S1. Written informed consent for trial participation was obtained from the parent or guardian of each participant; a child’s assent was also obtained if required per local guidelines.

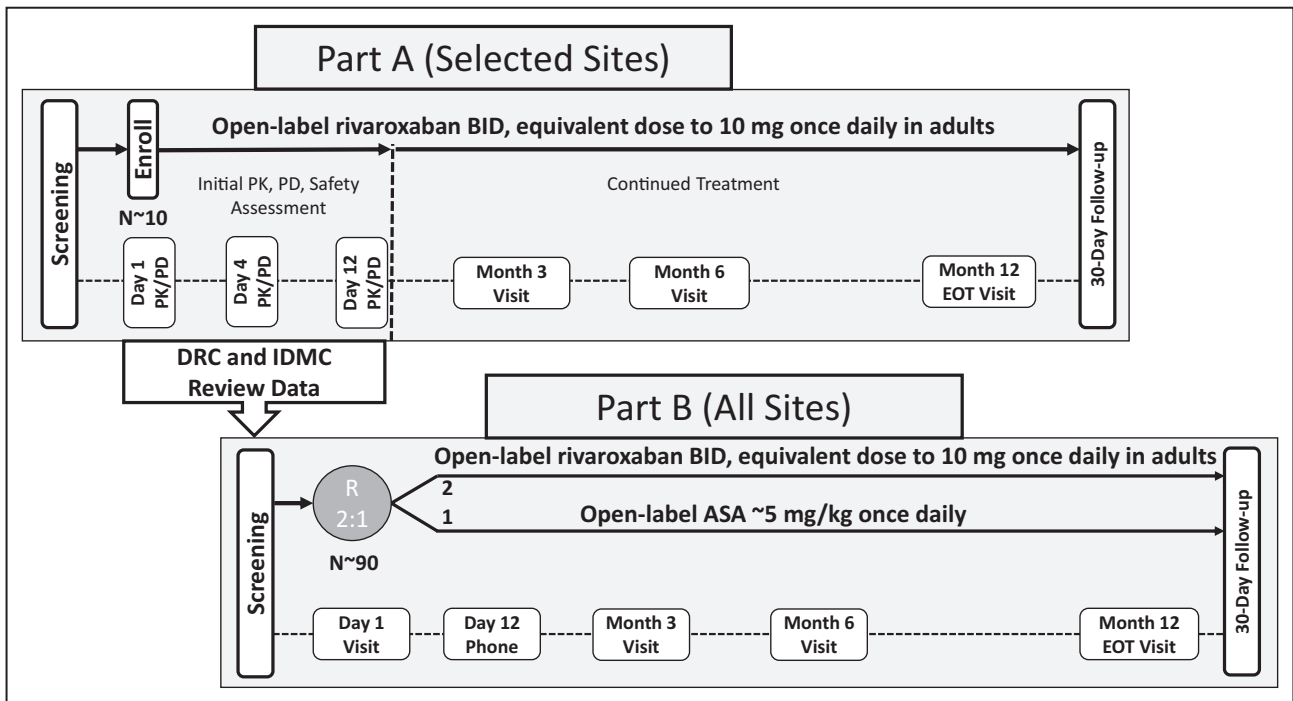


Figure 1. Trial design.

ASA indicates acetylsalicylic acid; BID, twice daily; DRC, Data Review Committee; EOT, end of treatment; IDMC, independent data monitoring committee; PD, pharmacodynamics; PK, pharmacokinetics; and R, randomization.

Trial Regimen and Follow-Up

Participants in part A had a 12-day initial pharmacokinetic, pharmacodynamic, and safety assessment period, a 12-month open-label treatment period, and a 30-day follow-up telephone contact. Pharmacokinetic and pharmacodynamic blood samples were collected on day 1 and day 4 of rivaroxaban administration, and the results were assessed by day 12 by the independent data monitoring committee before the participant continued in the study to complete the planned 12-month treatment period. Safety and efficacy were evaluated throughout the study. Participants had additional pharmacokinetic and pharmacodynamic samples collected at month 3 and month 12. Pharmacokinetic/pharmacodynamic results will be published separately.

Participants in part B were randomized on day 1 to receive either rivaroxaban oral suspension or ASA for 12 months. Pharmacokinetic and pharmacodynamic samples for those participants randomized to rivaroxaban in part B were obtained at day 1, month 3, and month 12. Safety and efficacy were evaluated throughout the study for all participants.

The rivaroxaban dose used in UNIVERSE Study was determined via an adapted physiologically based pharmacokinetics modeling approach previously established in healthy children.^{18,19} This model was reparameterized to reflect the special physiology of the pediatric Fontan population (lower body weight, smaller body height, and reduced cardiac output). The dose-exposure relation of rivaroxaban in these post-Fontan patients was comparable to that in healthy children if liver function is not impaired.²⁰

Rivaroxaban was administered twice daily in an open-label manner using a novel, 0.1% (1 mg/mL) oral suspension (body weight–adjusted dosing [Table 1]) that targeted exposure (Area under the plasma concentration time curve from 0 to 24 hours at steady state) matching the exposure range of rivaroxaban, 10 mg total daily dose, effectively used in adults for thromboprophylaxis. ASA was provided as 81- or 100-mg tablets, according to local practice. Participants who were randomized to ASA received approximately 5 mg/kg of ASA as a single daily dose. Dose adjustments were

made at month 6 on the basis of body weight changes for all subjects in both part A and part B as needed.

Outcome Measures

The primary safety outcome was major bleeding events, as defined by the International Society on Thrombosis and Haemostasis.²¹ The secondary safety outcomes were clinically relevant nonmajor bleeding and trivial (minimal) bleeding events.

The primary efficacy outcome was any thrombotic event (venous or arterial), defined as the appearance of a new thrombotic burden within the cardiovascular system noted on either routine surveillance or clinically indicated imaging, or the occurrence of a clinical event known to be strongly associated with thrombus (eg, stroke or pulmonary embolism).

All safety and thrombotic events were adjudicated by the central independent adjudication committee.

Statistical Analysis

Safety and efficacy results were summarized using appropriate descriptive statistics. The central independent adjudication committee–adjudicated results were used in the final analysis for all subjects. Because of the limited availability of the study population and the expected low event rates, the study was not powered to test formal hypotheses for efficacy. A total of at least 100 pediatric participants were planned to be enrolled in this study based on regulatory feedback to obtain sufficient pharmacokinetics/pharmacodynamic and safety data in this unique pediatric population.

RESULTS

Baseline Participant Characteristics

A total of 129 children with single-ventricle congenital heart disease were screened at 36 sites in 10 countries (Argentina, Belgium, Brazil, Canada, Japan, Malaysia, Mexico, the Netherlands, Spain, and the United States). Of these, 112 participants met the eligibility criteria and were enrolled in the UNIVERSE Study (12 in the rivaroxaban part A group, 66 in the rivaroxaban part B group, and 34 in the ASA part B group) (Figure 2).

The demographic and baseline characteristics were generally balanced between the rivaroxaban and the ASA groups in part B (Table 2); however, there were slightly more male patients in the ASA group (68%) versus the rivaroxaban group (55%). There was a slightly shorter duration between the Fontan procedure and first study drug dose in the ASA group (mean, 37 days) than in the rivaroxaban group (mean, 45 days). The rivaroxaban part A group had

Table 1. Dosing Table for Rivaroxaban Administration

Body weight, kg	BID dose, mg or mL*	Total daily dose, mg†
7–<8	1.1	2.2
8–<10	1.6	3.2
10–<12	1.7	3.4
12–<20	2.0	4.0
20–<30	2.5	5.0

BID indicates twice daily.

*Oral suspension 0.1% (1 mg/mL).

†Equivalent to exposure of 10 mg once daily in adults.

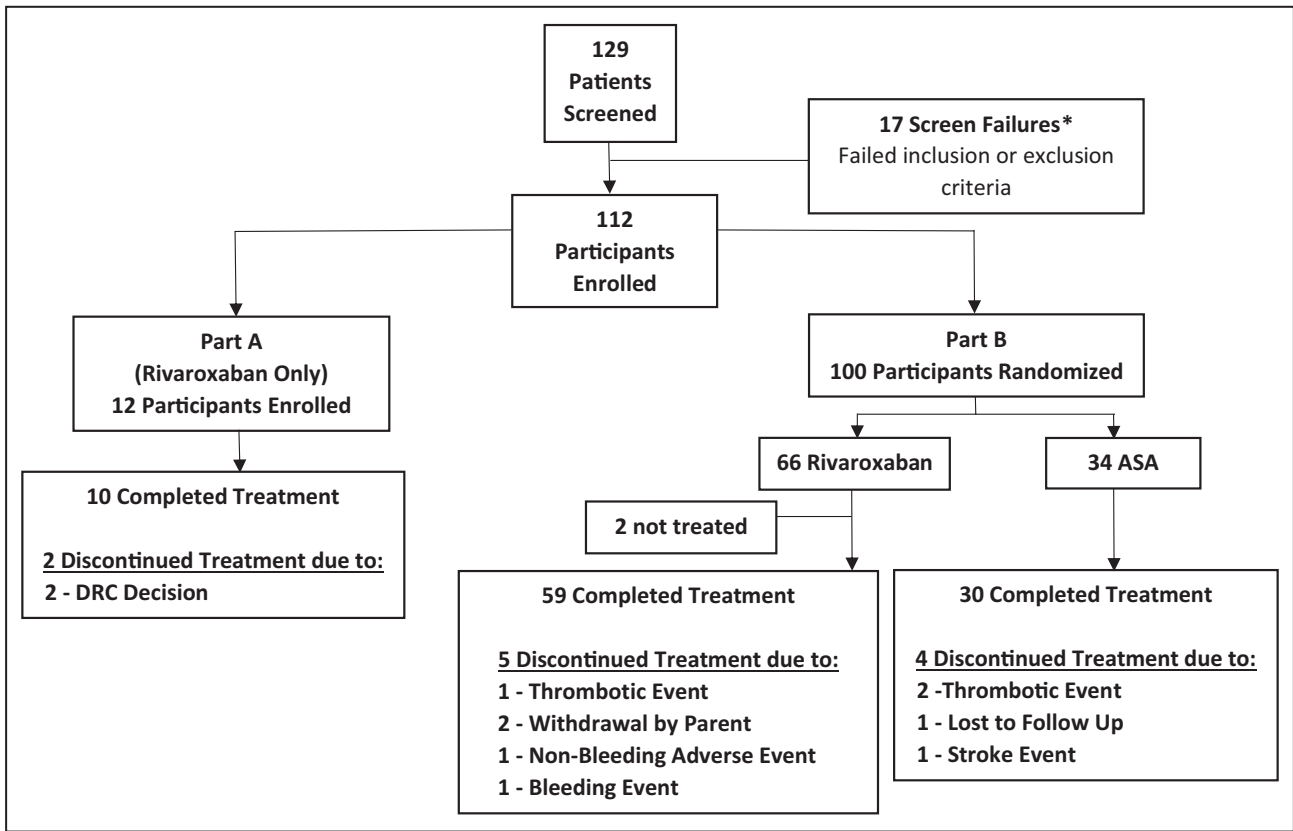


Figure 2. UNIVERSE Study flow.

*Reasons for screen failures: of the 17 subjects, 8 did not meet inclusion criteria (2 did not have the Fontan procedure within 4 months of enrollment, 4 did not tolerate oral feedings, and 2 had nonsatisfactory screening echocardiogram) and 11 met at least 1 exclusion criterion (3 had evidence of thrombosis on screening echocardiogram, 4 were on prohibited medications, 1 had a known contraindication to acetylsalicylic acid (ASA), and 3 were not considered appropriate candidates for the study by their physicians). DRC indicates Data Review Committee.

a younger mean age (2.5±0.7 years), a lower mean weight, and a shorter mean duration (mean, 12 days) between the Fontan procedure and first dose than both groups in part B. The shorter duration in days between the Fontan procedure and the first dose of study drug in part A was probably attributable to the study design, which required frequent blood draws on day 1 and day 4 for pharmacokinetic/pharmacodynamic testing in part A. Most investigators planned to have day 1 and day 4 blood work conveniently performed while the children were still hospitalized postoperatively from the Fontan procedure and with an intravenous catheter still in place, to avoid multiple venipunctures.

The pharmacokinetic/pharmacodynamic results of part A of the UNIVERSE Study showed that exposure of rivaroxaban in children after the Fontan procedure receiving a body weight–adjusted dosing regimen was similar to the exposure in adults who received 10-mg total daily dose for thromboprophylaxis. The UNIVERSE Study pharmacokinetic/pharmacodynamic work will be reported separately. The same body

weight–adjusted dosing regimen was used in part B of the study.

Safety Outcomes

Major Bleeds

There was 1 participant with a major bleeding event adjudicated in the rivaroxaban part B group (2%). This single event of major bleeding, epistaxis, reported in the rivaroxaban group was in a noncritical site, which had stopped by the time the child arrived at the hospital. The child was not evaluated by an ear, nose, and throat specialist. However, it was considered a major bleeding event because the participant required a blood transfusion. There were no participants with major bleeding events reported in the ASA part B or in the rivaroxaban part A group (Table 3).

Clinically Relevant Nonmajor Bleeds

In part B, the proportion of participants with clinically relevant nonmajor bleeding events was less in the

Table 2. Baseline Characteristics

Characteristics	Rivaroxaban		ASA
	Part A (N=12)	Part B (N=66)	Part B (N=34)
Age at screening, mean (SD), y	2.5 (0.7)	4.1 (1.7)	4.2 (1.8)
Male sex, n (%)	7 (58)	36 (55)	23 (68)
Weight, mean (SD), kg	13.8 (2.4)	15.8 (3.7)	15.7 (3.1)
Height, mean (SD), cm	90 (7)	101 (13)	103 (12)
Heart rate, mean (SD), beats/min	111 (13)	109 (16)	107 (15)
Systolic blood pressure, mean (SD), mm Hg	109 (9)	99 (13)	102 (11)
Diastolic blood pressure, mean (SD), mm Hg	63 (11)	59 (11)	63 (9)
Race, n (%)			
Asian	0	14 (21)	7 (21)
Black	3 (25)	8 (12)	1 (3)
White	8 (67)	40 (61)	20 (59)
Other	1 (8)	2 (3)	3 (9)
Not reported	0	2 (3)	3 (9)
Ethnicity, n (%)			
Hispanic or Latino	1 (8)	22 (33)	11 (32)
Not Hispanic or Latino	11 (92)	42 (64)	19 (56)
Not reported	0	2 (3)	4 (12)
Duration between Fontan procedure and first dose of study drug, d*			
Mean (SD)	12 (17)	45 (41)	37 (35)
Median	4	34	24
Range	2–61	2–124	2–117

Age is defined as a participant’s age at screening. Enrolled: all participants in part A who received at least 1 dose of study drug and all participants in part B who were randomized. ASA indicates acetylsalicylic acid.

*Duration between Fontan procedure and first dose of study drug is calculated as date of first dose of study drug–date of Fontan procedure.

rivaroxaban (4 [6%]) than in the ASA group (3 [9%]). In the rivaroxaban group, the bleeding events occurred in the lower gastrointestinal tract (2 [3%]), gingival tissue (1 [2%]), and the skin (1 [2%]). In the ASA group, these events occurred in the lower gastrointestinal tract (1 [3%]), the skin (1 [3%]), hematoma (1 [3%]), and subconjunctival (1 [3%]). In the rivaroxaban part A group, there was 1 (8%) participant reported with a clinically relevant nonmajor bleeding event in the skin (Table 3).

Trivial Bleeds

In part B, the proportion of participants with trivial bleeding was similar in the rivaroxaban and the ASA groups (21 [33%] versus 12 [35%], respectively). The most frequent site of trivial bleeding was the skin in both groups (14 [22%] in the rivaroxaban group and 8 [24%] in the ASA group). In the rivaroxaban part A group, there were 3 (25%) participants reported with trivial bleeds (2 skin hematomas and 1 gingival) (Table 3).

Table 3. Summary of Bleeding Events

Bleeding events	Rivaroxaban		ASA
	Part A (N=12)	Part B (N=64)	Part B (N=34)
Participant with ≥1 on-treatment bleeding events	4 (33)	23 (36)	14 (41)
Major bleeding	0	1 (2)	0
Clinically relevant nonmajor bleeding	1 (8)	4 (6)	3 (9)
Gastrointestinal	0	2 (3)	1 (3)
Lower gastrointestinal	0	2 (3)	1 (3)
Gingival	0	1 (2)	0
Hematoma	0	0	1 (3)
Skin	1 (8)	1 (2)	1 (3)
Subconjunctival	0	0	1 (3)
Trivial bleeding	3 (25)	21 (33)	12 (35)
Epistaxis	0	7 (11)	3 (9)
Gastrointestinal	0	1 (2)	1 (3)
Lower gastrointestinal	0	0	1 (3)
Upper gastrointestinal	0	1 (2)	1 (3)
Gingival	1 (8)	3 (5)	1 (3)
Hematoma	2 (17)	7 (11)	2 (6)
Skin	0	14 (22)	8 (24)
Vascular access site	0	2 (3)	0

Data are given as number (percentage). Percentages were calculated with the number of participants in each group as denominator. Incidence is based on the number of subjects, not the number of events. A participant may appear in different sites/categories. Safety analysis set: all participants in part A who received at least 1 dose of study drug and all participants in part B who were randomized and received at least 1 dose of study drug. The primary safety outcome is major bleed that meets the International Society on Thrombosis and Haemostasis definition: overt bleeding and: (1) associated with a decrease in hemoglobin of ≥2 g/dL; (2) leading to a transfusion of the equivalent of ≥2 units of packed red blood cells or whole blood in adults; (3) occurring in a critical site: intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, or retroperitoneal; or (4) contributing to death. ASA indicates acetylsalicylic acid.

Any Bleeding

In part B, the proportion of participants with any bleeding events was similar in the rivaroxaban group than in the ASA group (36% versus 41%) (Table 3).

Adverse Events, Including Bleeds

In part B, the proportion of participants who reported at least one adverse event or serious adverse event was similar in both groups, with adverse events of 86% versus 85% and serious adverse events of 28% versus 24% in the rivaroxaban group versus the ASA group, respectively (Table 4). Adverse events and serious adverse events were generally balanced between the rivaroxaban and the ASA groups. In the respiratory organ class, however, pleural effusions (nonhemorrhagic) were more frequently reported as adverse events or serious adverse events in the rivaroxaban

Table 4. Summary of Adverse Events

Adverse events	Rivaroxaban		ASA
	Part A (N=12)	Part B (N=64)	Part B (N=34)
Participants with ≥1 adverse events	11 (92)	55 (86)	29 (85)
Infections	8 (67)	40 (63)	22 (65)
Respiratory, thoracic, and mediastinal disorders	5 (42)	29 (45)	9 (26)
Pleural effusion	3 (25)	12 (19)	2 (6)
Gastrointestinal disorders	6 (50)	19 (30)	9 (26)
Injury, poisoning, and procedural complications	4 (33)	18 (28)	10 (29)
Skin and subcutaneous tissue disorders	3 (25)	19 (30)	9 (26)
General disorders and administration site conditions	1 (8)	17 (27)	8 (24)
Vascular disorders	2 (17)	3 (5)	1 (3)
Participants with ≥1 serious adverse events	6 (50)	18 (28)	8 (24)
Infections	3 (25)	5 (8)	4 (12)
Respiratory, thoracic, and mediastinal disorders	2 (17)	9 (14)	3 (9)
Pleural effusion	2 (17)	9 (14)	2 (6)

Data are given as number (percentage). Percentages were calculated with the number of participants in each group as denominator. All adverse events were treatment emergent. Treatment emergent is defined as an adverse event or serious adverse event that occurs after the first dose and up to 2 days after the last dose of study drug. Participants are counted only once for any given event, regardless of the number of times they experienced the event. The organ classes are sorted in descending order of incidence >10% based on rivaroxaban. ASA indicates acetylsalicylic acid.

group than in the ASA group (Table 4). Pleural effusions are expected events after the Fontan procedure and were considered unrelated to the study drug by the investigators. In part B, the adverse events more frequently reported were infections in both groups (40 [63%] in the rivaroxaban group and 22 [65%] in the ASA group). In part A, there were 11 (92%) participants who reported adverse events and 6 (50%) who reported serious adverse events (Table 4). The most frequently reported adverse events in all treatment groups were infections (eg, nasopharyngitis, upper respiratory tract infections, and bronchitis).

Efficacy Outcomes

In the rivaroxaban part B group, 1 participant (2%) was reported with pulmonary embolism on day 84 of study treatment (121 days post-Fontan procedure). In the ASA group, 3 participants (9%) were reported with thrombotic events (2 participants [6%] with venous thrombotic events reported on day 177 and day 179 of treatment [191 and 183 days post-Fontan procedure, respectively]; and 1 participant (3%) who had an ischemic stroke on day 122 of treatment [133 days post-Fontan procedure]). In the rivaroxaban part A group,

Table 5. Efficacy Outcomes

Efficacy outcomes	Rivaroxaban			ASA
	Part A (N=12)	Part B (N=64)	Total (N=76)	Part B (N=34)
Primary efficacy outcome: Any thrombotic event	1 (8)	1 (2)	2 (3)	3 (9)
Ischemic stroke	0	0	0	1 (3)
Pulmonary embolism	0	1 (2)	1 (1)	0
Venous thrombosis	1 (8)	0	1 (1)	2 (6)
Arterial/intracardiac thrombosis	0	0	0	0

Data are given as number (percentage). Percentages were calculated with the number of participants in each group as denominator. Full analysis set: all participants in part A who received at least 1 dose of study drug and all participants in part B who were randomized and received at least 1 dose of study drug. ASA indicates acetylsalicylic acid.

1 participant (8%) had a venous thrombotic event on day 362 of treatment (364 days post-Fontan procedure) (Table 5). This study was not powered for efficacy hypothesis testing (post hoc log-rank test $P=0.095$). Overall, the rivaroxaban group had a proportion of thrombotic events of 3% versus 9% in the ASA group (Table 5).

DISCUSSION

The UNIVERSE Study specifically targeted a pediatric cardiac population at high risk for thrombosis at a vulnerable age. The study showed a low prevalence of both thrombotic and bleeding events in the rivaroxaban and the ASA groups during a high-risk period early after Fontan procedure. In the rivaroxaban group, there was only one major bleeding episode (epistaxis) and a slightly lower prevalence of clinically relevant and trivial bleeding compared with ASA. The prevalence and pattern of adverse events were comparable. Although the study was not powered for efficacy outcomes, there was a lower proportion of thrombotic events in the rivaroxaban group relative to the ASA group, although this did not reach statistical significance. Together, this suggests a trend toward a favorable risk/benefit profile for rivaroxaban in this clinical scenario.

The Fontan physiology for a patient with a single functional ventricle is characterized by the lack of an underlying subpulmonic ventricle and, hence, passive pulmonary blood flow. This sets the stage for systemic venous hypertension and sluggish flow, which, together with both developmental and acquired imbalances of prothrombotic, antithrombotic, and fibrinolytic circulating factors, predisposes to thrombosis.² Although there is an increased prevalence of thrombosis in the stages of single-ventricle management preceding the Fontan procedure,⁸ the 3-to 12-month

period immediately after Fontan has been identified as a particularly high-risk period.⁵ The UNIVERSE Study targeted this specific high-risk period.

The reported prevalence of thrombosis post-Fontan procedure in the literature varies widely depending on the study design. There is a high degree of variability about the presence and type of surveillance strategies, the time since Fontan, the duration of time period covered, and the inclusion of asymptomatic events.³ A systematic review and meta-analysis by Marrone et al that included 1075 patients (20% on ASA and 80% on warfarin) showed an overall thromboembolism rate of 5%, with no significant difference between warfarin and ASA.¹⁰ This is similar to the overall event rate reported herein. A further meta-analysis by Alsaied et al of 1200 patients showed that although some thromboprophylaxis was better than none, warfarin was no more effective than ASA (odds ratio, 0.94).⁹ A randomized trial by Monagle et al of ASA versus warfarin during the 2 year period immediately after Fontan procedure showed no significant difference, with an overall prevalence of thrombosis events of 19%, a higher prevalence than in other studies because of greater surveillance with transesophageal echocardiography.¹¹ Iyengar et al studied the time-related freedom from a thrombotic event for patients >1 year after Fontan. Of 475 patients included, the 10-year freedom from thrombosis event was 91%, with no significant difference between those treated with ASA versus warfarin after both propensity score adjustment and propensity score matching.²² Despite the lack of difference between an antiplatelet agent, ASA, and an anticoagulant, warfarin, an important residual risk of thrombosis event remains.

Given the probable equivalency on thromboprophylaxis efficacy between ASA and warfarin, other considerations, particularly safety, may drive preference for a given therapy. Warfarin is a challenging medication to manage, particularly in young patients. It has significant food-drug and drug-drug interactions, and dose titration can be difficult in a child experiencing rapid somatic growth. Management with warfarin requires close monitoring with inconvenient blood draws to maintain anticoagulation within a narrow target range. This was evident in the randomized trial of ASA versus warfarin described above,¹¹ whereby a secondary analysis of the data showed that an important proportion of those on warfarin frequently failed to maintain an international normalized ratio within the target range.⁵ Compared with those on ASA or on well-maintained warfarin, those on poorly controlled warfarin (<30% of international normalized ratios within target range) had a significantly increased risk of thrombotic events, with a hazard ratio of 3.53. A retrospective review by Faircloth et al showed that for those on warfarin, a greater time spent in the therapeutic range was associated with

reduced thrombosis and bleeding events.²³ Because of these challenges with warfarin, the appeal of a direct oral anticoagulant, such as rivaroxaban, is evident, given the limited food and drug interactions and the lack of need for monitoring.

Recommendations for thromboprophylaxis after the Fontan procedure are limited by the suboptimal quality of the evidence. Guidelines from the American College of Chest Physicians in 2012 recommended ASA or unfractionated heparin followed by a vitamin K antagonist for thromboprophylaxis in children after the Fontan procedure.⁷ A Scientific Statement from the American Heart Association in 2013 indicated that a range of strategies might be considered, including using warfarin or low-molecular-weight heparin for the first 3 to 12 months after Fontan, using antiplatelet therapy for long-term thromboprophylaxis, and using warfarin for long-term thromboprophylaxis for those patients with risk factors for thrombotic events.⁶ As patients undergoing the Fontan procedure age, their thromboembolic risk increases because of a higher incidence of atrial arrhythmias and ventricular dysfunction during adulthood. A longitudinal real-world data study from Germany showed an increasing use of novel oral anticoagulants, including rivaroxaban, in adults with congenital heart disease over time.²⁴ A recent systematic review demonstrated an annual thromboembolic and major bleeding event rate of 3.13% (95% CI, 1.18%–8.03%) and 3.17% (95% CI, 0.15%–41.39%), respectively, in adult patients undergoing the Fontan procedure and concluded that non-vitamin K oral anticoagulants appear safe and effective in adults with congenital heart disease without mechanical prostheses.²⁵ Further prospective studies are needed to define the benefit/risk profile for rivaroxaban in the population undergoing the Fontan procedure, but the current study suggests a favorable comparison to ASA. Given the advantages of rivaroxaban over warfarin, if efficacy and safety prove to be similar to well-managed warfarin, rivaroxaban may be preferred in scenarios where long-term anticoagulation is recommended.

The current randomized study shows a comparable prevalence and pattern of bleeding events between rivaroxaban and ASA. Comparisons of the risk of bleeding events with different thromboprophylactic strategies in nonrandomized studies are fraught by differing periods of observation, differing classifications of bleeding events, and different clinical scenarios. Randomized clinical trials, such as the present UNIVERSE Study, are rare, and pediatric experience with direct oral anticoagulants is limited. A clinical trial of rivaroxaban versus standard anticoagulants for short-term treatment of venous thromboembolism in children (EINSTEIN-Jr Phase 3 Trial) showed a similar prevalence of major or clinically relevant nonmajor bleeding (3% with rivaroxaban and 2% with standard

anticoagulation).²⁶ In the randomized trial of ASA versus warfarin after the Fontan procedure described above, major bleeding occurred in 2% on ASA and 2% on warfarin, but minor bleeding was significantly more frequent with warfarin at all bleeding sites (33% with warfarin and 14% with ASA, overall).¹¹

This study must be considered in light of some potential limitations. Although the study was open label and not powered to test a formal hypothesis for efficacy because of recognized unique challenges in this pediatric population,²⁷ the study does suggest a benefit/risk ratio with rivaroxaban that is likely similar, and possibly favorable when compared with ASA. The observation period was limited to up to 12 months after the Fontan procedure, and although this does cover the high-risk period for thrombotic events, it would be expected that thromboprophylaxis might need to be extended. The limited systematic surveillance for thrombosis (ie, transthoracic echocardiogram) likely restricted the detection of asymptomatic thromboses, which do have clinical relevance, particularly in increasing the risk of postthrombotic syndrome and of subsequent thrombotic events.²⁸ Given that the single-ventricle population is limited and that thrombotic events are relatively infrequent, time related, and somewhat unpredictable, there are considerable challenges to performing a definitive study.²⁷

CONCLUSIONS

Although this randomized study of thromboprophylaxis in children with single-ventricle physiology after the Fontan procedure was not powered for efficacy, the participants who received rivaroxaban had a lower prevalence of thrombotic events, albeit not achieving statistical significance, and similar safety profile compared with those in the ASA group.

Further studies are necessary to support definitive recommendations, although these studies are expected to be exceedingly challenging.

ARTICLE INFORMATION

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Disclosures

Dr McCrindle has served on the scientific advisory board for Janssen R&D, LLC, Chiesi, and Esperion; was the Data and Safety Monitoring Board Chair for Amryt Pharma; and was an investigator for Janssen R&D, LLC. Dr Michelon has served on the scientific advisory board for Janssen R&D, LLC, AstraZeneca, Chiesi, and Stasys. Dr Justino has served on the scientific advisory board for Janssen R&D, LLC, and PediaStent; has been a consultant for Abiomed, Edwards Lifesciences, and Medtronic; has intellectual property for PolyVascular; and has a grant from W.L. Gore. Dr Harris received consultant/honoraria fees from Janssen R&D, LLC. Dr Pina is an employee with equity ownership of Janssen R&D, LLC. C. Peluso is an employee with equity ownership of Janssen R&D, LLC. W. Lu is an employee with equity ownership of Janssen R&D, LLC. Dr Li has served on the scientific advisory board for Janssen R&D, LLC. The remaining authors have no disclosures to report.

Supplementary Material

Tables S1–S2

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APPENDIX

UNIVERSE STUDY INVESTIGATORS

Guillermo Chantada, Alejandro Peirone (Argentina), Marc Gewillig, Daniel De Wolf, Thierry Sluysmans (Belgium), Andrea Wirich Lenzi, Maria Angelica Binotto, Estela Suzana Horowitz (Brazil), Brian McC Crindle, Kevin Harris, Nagib Dahdah (Canada), Keisuke Sato, Hiroshi Ono, Koichi Sagawa, Jun Muneuchi (Japan), Hasri Samion (Malaysia), Sergio Ruiz, Juan Sandoval, Alexis Palacios (Mexico), J.M.P.J Breur (the Netherlands), Federico Gutierrez-Iarraya, Teresa Alvarez, Dimpna Albert, Fernando Rueda (Spain), Joseph Rossano, Kevin Hill, Haleh Heydarian, Robert Niebler, Howard Weber, Biagio Pietra, Andrew Van Bergen, Juan Alejos, Shaji Menon, Marie Steiner, Jonathan Cramer, Ben Reinking (United States).

SUPPLEMENTAL MATERIAL

Table S1. UNIVERSE Inclusion/Exclusion criteria.

<p>Inclusion Criteria:</p> <ol style="list-style-type: none">1. Boys or girls 2 to 8 years of age with single ventricle physiology and who have completed the initial Fontan procedure within 4 months prior to enrollment2. Considered to be clinically stable by the investigator and able to tolerate oral or enteral administration of a suspension formulation and oral/enteral feedings3. Satisfactory initial post-Fontan transthoracic echocardiographic screening as defined in the Post-Fontan Echocardiographic Examination Research Protocol4. Parent/legally acceptable representative must sign an informed consent form (ICF) and child assent will also be provided, if applicable, according to local requirements
<p>Exclusion Criteria:</p> <ol style="list-style-type: none">1. Evidence of thrombosis, including those that are asymptomatic confirmed by post-Fontan procedure transthoracic echocardiogram, or other imaging techniques, during the screening period of the study2. History of gastrointestinal disease or surgery associated with clinically relevant impaired absorption3. History of or signs/symptoms suggestive of protein-losing enteropathy4. Active bleeding or high risk for bleeding contraindicating antiplatelet or anticoagulant therapy, including a history of intracranial bleeding5. Criterion modified per Amendment INT-2<ol style="list-style-type: none">5.1 Indication for anticoagulant or antiplatelet therapy other than current study, however:<ul style="list-style-type: none">– A subject who has received vitamin K antagonist (VKA) after the Fontan procedure may be eligible provided that the subject has discontinued VKA before the screening visit. Baseline laboratory samples must be obtained at least 7 days after the last dose of VKA.– A subject who is receiving ASA at the time of the screening visit may be eligible and may continue receiving ASA provided the last dose is taken at least 24 hours prior to the first dose of study drug.– A subject who is receiving heparin or LMWH after the Fontan procedure may be eligible and may continue receiving either of these anticoagulants during the screening period provided the study drug (rivaroxaban or ASA) is 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 nonsteroidal anti-inflammatory drugs (NSAIDs)7. Platelet count $<50 \times 10^9/L$ at screening8. Criterion modified per Amendment INT-2<ol style="list-style-type: none">8.1 Estimated glomerular filtration rate (eGFR) $<30 \text{ mL/min/1.73m}^2$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. Criterion modified per Amendment INT-2<ol style="list-style-type: none">10.1 Known contraindication to ASA, or has or is recovering from chicken pox or flu-like symptoms (subjects participating in Part B only)11. Criterion modified per Amendment INT-2<ol style="list-style-type: none">11.1 Known allergies, hypersensitivity, or intolerance to rivaroxaban, ASA or its excipients12. Inability to cooperate with study procedures13. 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 enrollment, or planned use during the study. Itraconazole use within 7 days before enrollment 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 enrollment, or planned use during the study.15. Planned use of drugs that are moderate CYP3A4 inhibitors (such as erythromycin) during the Initial PK, PD, and Safety Assessment Period of Part A only16. Participation in a clinical study with an investigational drug or medical device in the previous 30 days prior to enrollment17. Any condition for which, in the opinion of the investigator, participation would not be in the best interest of the subject (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments18. 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

Table S2. Study Committees: List of Collaborators.

Executive committee	
Brian McCrindle	Hospital for Sick Children, Toronto, ON
Jennifer Li	Duke University Medical Center, Durham, NC
Alan Michelson	Boston Children's Hospital, Harvard Medical School, Boston, MA
Henri Justino	Texas Children's Hospital, Houston, TX
Central independent adjudication committee	
Ken Mahaffey	Stanford University School of Medicine, Stanford, CA
Christopher Almond	Stanford University School of Medicine, Stanford, CA
Doff McElhinney	Stanford University School of Medicine, Stanford, CA
Sarah Lee	Stanford University School of Medicine, Stanford, CA
Independent data monitoring committee	
Alain Leizorovicz	University of Lyon, Lyon, France
Lisa Bomgaars	Baylor College of Medicine, Houston, TX
Lawrence Lesko	University of Florida, Department of Pharmaceutics, Gainesville, FL