Rivaroxaban, a direct Factor Xa inhibitor, versus acetylsalicylic acid as thromboprophylaxis in children post–Fontan procedure: Rationale and design of a prospective, randomized trial (the UNIVERSE study)

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Background The Fontan procedure is the final step of the 3-stage palliative procedure commonly performed in children with single ventricle physiology. Thrombosis remains an important complication in children after this procedure. To date, guideline recommendations for the type and duration of thromboprophylaxis after Fontan surgery are mainly based on extrapolation of knowledge gained from adults at risk for thrombosis in other clinical settings. Warfarin is being used off-label, and because of its multiple interactions with other drugs and food, a new alternative is highly desirable. Rivaroxaban, a direct Factor Xa inhibitor with a predictable pharmacokinetic profile, is a candidate to address this medical need.

Study design The UNIVERSE study is a prospective, open-label, active-controlled, multicenter study in children 2 to 8 years of age who have single ventricle physiology and had the Fontan procedure within the 4 months preceding enrollment. This study consists of 2 parts. In Part A, rivaroxaban pharmacokinetics, pharmacodynamics, safety, and tolerability are assessed to validate the pediatric dosing selected. In Part B, safety and efficacy of rivaroxaban versus acetylsalicylic acid are evaluated for thromboprophylaxis in children post–Fontan procedure. Children in each part will receive study drug for 12 months. Part A has been completed with 12 children enrolled. Enrollment into Part B is currently ongoing.

Conclusions The UNIVERSE study aims to provide dosing, pharmacokinetics/pharmacodynamics, safety, and efficacy information on the use of rivaroxaban, an oral anticoagulant, versus acetylsalicylic acid, an antiplatelet agent, in children with single ventricle physiology after the Fontan procedure. (Am Heart J 2019;213:97-104.)

Functionally, univentricular heart or single ventricle physiology is a condition in which only 1 ventricle sustains systemic circulation. Approximately 10% of children with congenital heart disease (CHD) have this condition.[1,2] The Fontan procedure is the final palliative surgery in a 3-stage procedure for children with single ventricle physiology.[2,3] It has become the most common procedure performed in children with CHD over the age of 2 years. Improvements in early outcomes have led to an increase in the number of children surviving into adulthood after this palliative procedure.[4] In response to the need for population-based data, Fontan patient registries have been established in North America (Society of Thoracic Surgeons Congenital Heart Surgery Database), Europe (European Congenital Heart Surgeons Association Congenital Database), and Australia and New Zealand (Fontan Registry). Collectively, these registries reported about 1,570 Fontan procedures per year between 2013 and 2015, capturing most of the Fontan procedures performed in those regions.[5-7] Thrombosis remains an important complication after the Fontan procedure for patients with single ventricle physiology; however, the true frequency of thrombotic events is not

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well established.[8,9] Several studies have estimated that the prevalence of thrombotic events occurring post–Fontan procedure ranges from 17% to 33%, with a reported mortality of 25% due to an associated post-Fontan thromboembolism.[10-12] The risk for thrombotic complications is highest within 6 months after the Fontan procedure, and the risk diminishes somewhat over the first 2.5 years thereafter.[2]

The National Heart, Lung, and Blood Institute convened a Working Group in 2012 to explore the issues related to thrombosis in children with CHD.[13] The report from the Working Group identified single ventricle patients as a priority population and further noted that studies to evaluate thromboprophylaxis in this patient population were a top research priority both before and after the Fontan procedure. Therefore, there is an important unmet medical need for additional therapies with well-controlled studies on which to base treatment decisions for thromboprophylaxis in children after the Fontan procedure.

The only published prospective study of anticoagulation prophylaxis in Fontan patients demonstrated a peak incidence of venous thromboembolism (VTE) in the first 6 months and no significant difference in event rates between the treatment groups, with thrombosis occurring in 21% of patients treated with acetylsalicylic acid (ASA) and 24% of those treated with warfarin.[14] A meta-analysis of 1,075 patients in 20 observational studies of antiplatelet (ASA or ticlopidine) therapy versus anticoagulant (warfarin) therapy by Marrone et al[15] showed no difference between warfarin (with or without ASA) and antiplatelet alone (thromboembolic complications incidences were 5% and 4.5%, respectively; $I^2 = 0$, $P = .80$). However, observational studies have shown that some form of antithrombotic prophylaxis rather than nothing is necessary.[16,17] Results from a more recent meta-analysis of 1,200 patients in 9 retrospective studies and 1 prospective, randomized study by Alsaied et al agree with the above findings.[18] This analysis showed that thromboembolic complication incidence in patients who received thromboprophylaxis (ASA or warfarin) was significantly lower than that in patients who received no thromboprophylaxis (odds ratio 0.425, 95% CI 0.194-0.929, $I^2 = 37\%$, $P < .01$), whereas there was no difference in thromboembolic complication incidence between patients who received warfarin versus ASA (odds ratio 0.936, 95% CI 0.609-1.438, $I^2 = 0$, $P = .54$). These findings, and the residual event rate for both regimens, support the need to study new alternatives, with a study design that includes an active comparator for which there is a perceived equipoise.

To date, no consensus has been reached in the literature or in routine clinical practice for the optimal type of therapy or the duration of antithrombotic therapy for thromboprophylaxis after Fontan surgery. Moreover, much of the data for pediatric recommendations are still extrapolated from adult data obtained in non-Fontan clinical settings.[1,2] Current guidelines recommend the use of ASA, or unfractionated heparin followed by a vitamin K antagonist (VKA) for thromboprophylaxis in pediatric subjects after the Fontan procedure.[1,2,19] However, these recommendations are based on limited available literature and expert opinion, and are variably followed by pediatric cardiologists, pediatric hematologists, and other health care providers because no anticoagulant is currently approved for use in children for treatment or prophylaxis of thromboembolism in the United States or the European Union. Instead, anticoagulants (namely, VKAs and heparins) are currently used off-label in children for any indication.

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. Rivaroxaban has been approved in multiple indications worldwide under the tradename Xarelto. As of September 2017, more than 90,000 subjects had been treated with rivaroxaban in clinical trials (Phase 1 through Phase 4), covering several indications, including the prophylaxis of VTE in adults undergoing elective hip or knee replacement surgery, the treatment of deep vein thrombosis and/or pulmonary embolism (PE), the reduction in the risk for recurrence of deep vein thrombosis and PE, and the reduction in the risk of stroke and systemic embolism in nonvalvular atrial fibrillation. Rivaroxaban is also approved in the European Union for the prevention of atherothrombotic events (cardiovascular death, myocardial infarction, or stroke) after an acute coronary syndrome in adults with elevated cardiac biomarkers.

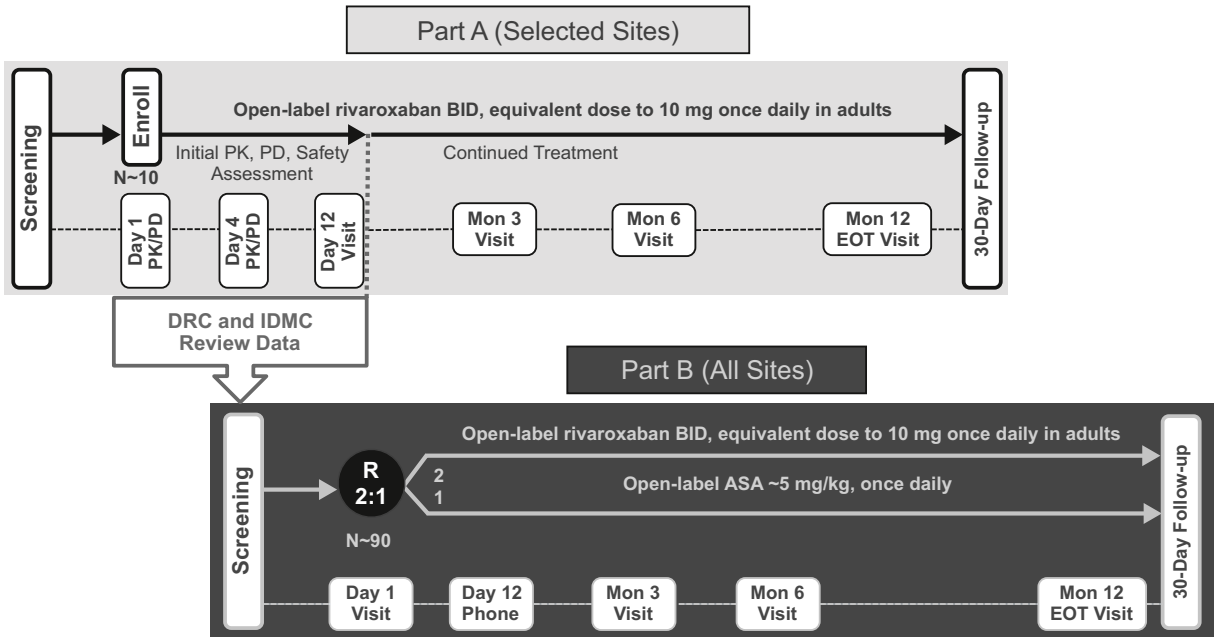
The objectives of this study are to provide dosing, safety, and efficacy information on the use of rivaroxaban, an oral anticoagulant, compared with ASA, an antiplatelet agent, for thromboprophylaxis in the studied pediatric population.

Methods

Rationale

The working hypothesis of this study is that children with CHD who have undergone a Fontan procedure will respond to Factor Xa inhibition by achieving rivaroxaban exposures similar to (and pharmacodynamics [PD] similar to) those seen in adults at risk for thrombosis. This hypothesis is supported by ex vivo spiking experiments, which covered the entire range, up to 500 ng/mL, of rivaroxaban concentrations used in clinical studies. In these ex vivo spiking experiments, similar exposure-response relationships existed in samples collected from healthy adults and children of different age groups (23 days to 23 months, 2 to 6 years, 7 to 11 years, 12 to 16 years).[20,21] Because of

Figure 1



UNIVERSE study flow diagram.*BID*, twice daily; *EOT*, end of treatment.

limited availability of the study population and the expected low event rates, there is no statistical hypothesis testing for this study.

Study design

The UNIVERSE study (www.clinicaltrials.gov RCT#: NCT02846532,) is a prospective, open-label, active-controlled, multicenter study designed to evaluate the pharmacokinetic (PK) and PD profiles, safety, and efficacy of rivaroxaban for thromboprophylaxis in children 2 to 8 years of age with single ventricle physiology who have completed the Fontan procedure within 4 months before enrollment. A study design flow diagram is shown in Figure 1. (See Table 1 for key inclusion/exclusion criteria.)

Because this is the first clinical study of rivaroxaban in children who have undergone the Fontan procedure, this study is designed to first evaluate the single- and multiple-dose PK properties of rivaroxaban in this population (Part A) to confirm the dose scheme chosen and, second, to evaluate the safety and efficacy profiles of rivaroxaban when used for thromboprophylaxis for 12 months compared with ASA (Part B).

Part A, the 12-month, nonrandomized, open-label part of the study, includes a 12-day initial PK, PD, and safety assessment period. An internal Data Review Committee (DRC) will assess the single- and multiple-dose rivaroxaban PK, PD, and the initial safety and tolerability data available for each subject before they return for their day 12 visit to determine whether they can continue the planned 12 months of open-label rivaroxaban therapy in this part of the study.

Randomization in Part B will begin once the cumulative data from the initial PK, PD, and safety assessment period in Part A are deemed acceptable by the Independent Data Monitoring Committee (IDMC).

Part B, the randomized, open-label, active-controlled part of the study, will evaluate the safety and efficacy of rivaroxaban compared with ASA for thromboprophylaxis for 12 months. Subjects randomized to rivaroxaban will also have PK and PD assessments.

Patient population

Children 2 to 8 years of age with single ventricle physiology who recently completed the Fontan procedure at multiple investigational sites around the world will be enrolled into the study to receive study treatment for 12 months. Because this is a prophylaxis study, patients with thrombosis requiring treatment will be excluded. Patients with active bleeding or with a high risk for bleeding contraindicating antiplatelet or anticoagulant therapy, including a history of intracranial bleeding, will also be excluded from the study. Table I provides the key inclusion/exclusion criteria of the study.

Dose selection and treatment duration

The rivaroxaban dose to be used in this study was determined via an adapted physiologically based PK

Table 1. Key inclusion/exclusion criteria (the UNIVERSE Study)

Inclusion criteria	Exclusion criteria
Boys or girls 2 to 8 y of age with single ventricle physiology and who have completed the initial Fontan procedure within 4 m prior to enrollment Considered to be clinically stable by the investigator and able to tolerate oral or enteral administration of a suspension formulation and oral/enteral feedings Satisfactory initial post-Fontan transthoracic echocardiographic screening as defined in the Post-Fontan Echocardiographic Examination Research Protocol	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 study History of gastrointestinal disease or surgery associated with clinically relevant impaired absorption Active bleeding or high risk for bleeding contraindicating antiplatelet or anticoagulant therapy, including a history of intracranial bleeding History of or signs/symptoms suggestive of protein-losing enteropathy Platelet count <50 × 10^9/L at screening Chronic use of nonsteroidal anti-inflammatory drugs Estimated glomerular filtration rate < 30 mL/min/1.73 m^2 Known clinically significant liver disease Known contraindication to ASA, or has or is recovering from chicken pox or flu-like symptoms (subjects participating in Part B only) Combined P-gp and strong CYP3A4 inhibitors (such as but not limited to ketoconazole, telithromycin, or protease inhibitors) use within 4 d before enrollment or planned use during the study. Itraconazole use within 7 d before enrollment or planned use during the study 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 wk before enrollment or planned use during the study

P-gp, P-glycoprotein; *CYP*, cytochrome P450.

(PBPK) modeling approach based on previously established rivaroxaban PBPK modeling used for the VTE pediatric studies and adapted to reflect the special physiology of the pediatric post-Fontan population.[22,23] Rivaroxaban will be administered to the pediatric post-Fontan population as body weight–adjusted dosing targeting exposure, as measured by area under the concentration-time curve from 0 to 24 hours ($AUC_{0\text{-}24}$) at steady state, matching that of the rivaroxaban 10-mg total daily dose in adults (adult reference range), a dose that has been shown to be safe and effective for thromboprophylaxis in adult subjects after major orthopedic surgery (Phase 3 RECORD studies).[24]

Results from the Phase 3 RECORD program, which investigated rivaroxaban for the prevention of VTE after total hip replacement and total knee replacement in adults, demonstrated that rivaroxaban (10 mg once daily) was significantly superior to enoxaparin (40 mg once daily) in the prevention of VTE after total hip replacement (35 days of prophylaxis)[25,26] and total knee replacement (10-14 days of prophylaxis),[27] with rates of major bleeding that were not statistically significantly different compared with enoxaparin in any study and with an otherwise similar safety profile.[25-28]

The pediatric PBPK model was also used to compare once- or twice-daily dosing options. Twice-daily dosing was chosen because it was expected to provide a maximum plasma concentration (C_{max}) that would stay within the adult reference range and a sufficiently high trough plasma concentration (C_{trough}) without falling below the adult reference range.

Subjects participating in this study will receive study therapy for 1 year because thrombus formation is most significant immediately after the Fontan procedure and has been noted to peak within the first postoperative year.[6,16]

Comparator selection

Subjects in Part B will be randomized 2:1 to either rivaroxaban or ASA. ASA was considered an appropriate comparator to evaluate the benefit-risk profile of rivaroxaban as a thromboprophylactic agent in the studied pediatric population. This decision was based on careful consideration of the literature, existing guidelines for the standard-of-care practice, and current clinical practice in many centers.

Using ASA (approximately 5 mg/kg body weight, to a maximum of 81 mg or 100 mg per local practice) as the comparator in this study, rather than another anticoagulant, will allow a descriptive comparison of results across 2 different drug classes—antiplatelet versus anticoagulant therapy—within the period of highest incidence of thrombosis (up to 12 months after the Fontan procedure).

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Evaluations

Pharmacokinetics and pharmacodynamics

Blood samples for rivaroxaban PK and PD, including rivaroxaban plasma concentration, absolute prothrombin time, activated partial thromboplastin time, and anti–Factor Xa activity measurements, will be taken at prespecified time points from subjects enrolled in Part A (on day 1, day 4, month 3, and month 12) and from those randomized to rivaroxaban in Part B (on day 1, month 3, and month 12). Rivaroxaban plasma concentration will be determined using the validated liquid chromatography–mass spectrometry/mass spectrometry method.

Safety and efficacy

The primary safety outcome is *major bleeding events*, defined as overt bleeding, associated with a fall in hemoglobin of ≥2 g/dL, leading to a transfusion of the equivalent of ≥2 U of packed red blood cells or whole blood in adults; occurring in a critical site including intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, and retroperitoneal; or contributing to death. Clinically relevant nonmajor bleeding events and trivial (minimal) bleeding are secondary safety outcomes, defined as overt bleeding not meeting the criteria for major bleeding but associated with medical intervention; unscheduled contact (visit or telephone call) with a physician; (temporary) cessation of study treatment; discomfort for the subject, such as pain; or impairment of activities of daily life (such as loss of school days or hospitalization). These definitions are based on International Society on Thrombosis and Haemostasis recommendations.[29-31] All bleeding events will be adjudicated by the Central Independent Adjudication Committee (CIAC).

The primary efficacy outcome is *any thrombotic event* (venous or arterial), defined as the appearance of a new thrombotic burden within the cardiovascular 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 or PE). Subjects who develop either a symptomatic or asymptomatic thrombotic event during the study will have to permanently discontinue the study drug. All thrombotic events and the primary cause of any death will be adjudicated by the CIAC. Transthoracic echocardiograms following a specific echocardiography protocol will be performed at screening, the month 6 visit, and the month 12 visit. These will be centrally read by an echocardiographic core laboratory to detect any asymptomatic thrombosis.

Analysis plan

Sample size determination

As there are feasibility challenges to conducting powered safety and efficacy studies of anticoagulation in children with CHD, and certain aspects of thromboembolic pathophysiology are similar between adults and children, this study was designed on the premise that evidence of clinical efficacy was going to be extrapolated from prophylaxis studies in adults. Many regulatory agencies (including the United States Food and Drug Administration and the European Medicines Agency/Paediatric Committee) support partial extrapolation of safety and efficacy data from adult patients to pediatric patients provided there are adequate PK and PD bridging data to determine the appropriate dose in children. In addition, the safety profile of rivaroxaban in children has also been evaluated in more than 500 children exposed to at least 1 dose of rivaroxaban in other pediatric studies of this program, and its safety profile will be compared to that of ASA in this study.

A total of at least 100 pediatric subjects overall are planned to be enrolled in this study. Because of the limited availability of the study population and the expected low event rates, this study is not powered to test a formal hypothesis for safety or efficacy. The total sample size is based on regulatory feedback to obtain sufficient PK/PD and safety data in this pediatric population.

The sample size of approximately 10 subjects for Part A is considered adequate for the initial assessment of the rivaroxaban PK in the studied pediatric population. Approximately 90 subjects will be enrolled into Part B of the study with 2:1 block randomization between rivaroxaban and ASA (block size = 6).

PK/PD analysis

Descriptive statistics will be used to summarize rivaroxaban PK data for each time interval. PD measurements, including prothrombin time, activated partial thromboplastin time, and anti–Factor Xa activity, will be plotted against rivaroxaban plasma concentrations and will also be summarized by time point.

Rivaroxaban PK parameters including $AUC_{0\text{-}24}$, C_{max}, and C_{trough} at steady state will be derived through model-based methods. The PK/PD relationship will be quantified. When appropriate, PK and PD data collected in this study may be used for ad hoc meta-analyses to further explore PK/PD relationships of rivaroxaban in pediatric subjects and bridge the data in adults.

Safety and efficacy analyses

Bleeding events that occur during the on-treatment period will be summarized by treatment group. Bleeding events observed more than 2 days after stopping the study drug will be summarized separately. Overall safety will also be assessed by summarizing adverse events by treatment group.

Thrombotic events that occur during the period up to the end of treatment will be summarized by treatment received. Events that occur after the end of the treatment

period (after month 12 or early study medication discontinuation visit) will be summarized separately.

Data will be analyzed for the following groups: (*a*) subjects participating in Part A only (all rivaroxaban subjects); (*b*) subjects randomized in Part B only (rivaroxaban group versus ASA group), and (*c*) subjects in Part A combined with subjects randomized to rivaroxaban Part B (all rivaroxaban subjects) versus subjects randomized to ASA in Part B.

Study oversight committees

An Executive Committee will provide overall academic leadership for the study and oversee the conduct of the study and the publication of the results.

An internal DRC will evaluate PK information relative to the adult ranges and pediatric model predictions, as well as PD and safety data for each individual subject in Part A before the day 12 visit, to determine if the subject can continue receiving rivaroxaban for 12 months.

An IDMC will evaluate PK, PD, safety, and efficacy data to ensure subject safety throughout the study. The IDMC is an independent expert advisory group external to the sponsor and study. For Part A only, the IDMC will review the cumulative data from the initial PK, PD, and safety assessment period and provide the recommendation to the Executive Committee and Sponsor Committee to cease enrollment in Part A and start enrollment directly into Part B.

A CIAC has been commissioned for this study to adjudicate and classify efficacy and safety outcome events in a consistent and unbiased manner while blinded to treatment assignment according to definitions in the CIAC charter.

Discussion

The Fontan procedure is a palliative surgical repair performed to bypass the right or left ventricle to pump blood into the pulmonary circulation. It offers the best alternative to improve the survival of patients with single ventricle physiology. However, thrombosis remains an important complication after the Fontan procedure, although its true frequency is not well established.[8,9] Therefore, conducting powered studies within a reasonable time period in the CHD population is not feasible because the target population is small. In addition, the incidence of thromboembolic events after the procedure cannot be clearly estimated to allow accurate calculation of the number of patients needed to prove efficacy in a confirmatory study. There is, therefore, room for an innovative approach when studying this population because anticoagulation data in the pediatric population are clearly needed.

The purpose of the UNIVERSE study is to evaluate rivaroxaban, an oral, direct Factor Xa inhibitor, in children post–Fontan procedure to confirm the absence of PK differences compared to the pediatric population in general, which might be due to the specific circulatory conditions that prevail in children with CHD, and to provide safety and efficacy information in this population. Background risk factors and timing of occurrence of the efficacy events will be carefully observed and documented. In terms of safety, occurrence and timing of all types of bleeding events and other adverse events will be described by study group. All bleeding and efficacy events will be adjudicated by an independent adjudication committee.

In summary, this study aims to give essential guidelines in the use of rivaroxaban in the pediatric post-Fontan population by providing (1) descriptive summaries of safety and efficacy outcomes and (2) dosing guidelines. Although not a primary goal of the study, if efficacy and safety differences are found between the rivaroxaban and ASA treatment groups, this information could be of substantial value to the thromboprophylaxis management of children post-Fontan operation. An oral, direct anti–Factor Xa inhibitor anticoagulant such as rivaroxaban, which in adult studies has been demonstrated to be noninferior regarding efficacy and with more predictable PK profile than warfarin, may be a potential alternative to ASA or VKA treatment in the post-Fontan population. Currently, Part A of the study has been completed with 12 children enrolled, and enrollment into Part B is ongoing.

Acknowledgements

The UNIVERSE study patient safety is monitored by an IDMC consisting of Dr Alain Leizorovicz, Service de Pharmacologie Clinique, France; Dr Lisa M. Bomgaars, Baylor College of Medicine, USA; and Dr Lawrence J. Lesko, University of Florida, USA. The IDMC is constituted with a charter to perform regular data review to ensure patient safety. The IDMC will provide recommendations regarding terminating, continuing, or modifying the study protocol in the event of unexpected PK and PD results or safety concerns.

The independent, blinded CIAC at Stanford Center for Clinical Research chaired by Dr Kenneth W Mahaffey reviews reports of all investigator-reported bleeding and efficacy outcome events and adjudicates and classifies these events.

The Echocardiogram Core Laboratory at Boston Children's Hospital led by Dr Steve Colan performs blinded reading of all screening echocardiograms to confirm subject eligibility and subsequent echocardiograms performed per protocol during the study to minimize intersite variability and bias.

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Declarations of interest

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