Janssen Research & Development *

Clinical Protocol

A Prospective, Open-Label, Active-Controlled Study to Evaluate the Pharmacokinetics, Pharmacodynamics, Safety, and Efficacy of Rivaroxaban for Thromboprophylaxis in Pediatric Subjects 2 to 8 Years of Age after the Fontan Procedure

UNIVERSE Study

Protocol 39039039CHD3001; Phase 3
BAY59-7939/18226

Amendment INT-2

JNJ-39039039; BAY 59-7939 (rivaroxaban)

*Janssen Research & Development is a global organization that operates through different legal entities in various countries. Therefore, the legal entity acting as the sponsor for Janssen Research & Development studies may vary, such as, but not limited to Janssen Biotech, Inc.; Janssen Products, LP; Janssen Biologics, BV; Janssen-Cilag International NV; Janssen, Inc; Janssen Infectious Diseases BVBA; Janssen Sciences Ireland UC; or Janssen Research & Development, LLC. The term "sponsor" is used throughout the protocol to represent these various legal entities; the sponsor is identified on the Contact Information page that accompanies the protocol.

This compound is approved in adults for marketing in 6 indications in the United States and 7 indications in the European Union.

This study will be conducted under US Food & Drug Administration IND regulations (21 CFR Part 312).

EudraCT NUMBER: 2015-002610-76

Status: Approved
Date: 27 July 2017
Prepared by: Janssen Research & Development, LLC
EDMS number: EDMS-ERI-99005906, 5.0

GCP Compliance: This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

TABLE OF CONTENTS

LIST OF ATTACHMENTS

LIST OF IN-TEXT TABLES AND FIGURES

TABLES

FIGURES

PROTOCOL AMENDMENTS

Protocol Version	Issue Date
Original Protocol	30 June 2015
INT-1	7 April 2016
INT-2	27 July 2017

Amendments below are listed beginning with the most recent amendment.

Amendment 2 (27 July 2017)

This amendment is considered to be nonsubstantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union, in that it does not significantly impact the safety or physical/mental integrity of subjects, nor the scientific value of the study.

The overall reason for the amendment: The overall reason for the amendment is to address the feedback received from Investigators, regulatory authorities and ethics committees.

Applicable Section(s)	Description of Change(s)
Rationale: A working hypothesis for the study was added based on an expected similar FXa inhibition response between children and adults.	
Synopsis; Section 2.2 Hypothesis	The working hypothesis was added.
Rationale: Additional clarification provided for subjects participating in Part B.	
Synopsis; Section 9.1.2, Screening Period and Section 9.1.3.2, Open-label Treatment Period, Part B	Clarification relating to when subjects may be enrolled and randomized in Part B.
Rationale: List of committees commissioned for the study was revised and the role of Sponsor Committee was added.	
Synopsis; 3.1 Overview of Study Design, Committees and Advisors	The Sponsor Committee was added to the list of committees commissioned for the study.
Section 9.7.2, Independent Data Monitoring Committee; 9.7.6 Sponsor Committee	Clarified and defined the role of the Sponsor Committee.
Rationale: Exclusion Criteria revised to include detail and further clarification	
Synopsis, Section 4.2. Exclusion Criteria	Exclusion Criterion #5, additional clarification was provided to allow for continual treatment of heparin or LMWH during the screening period. Exclusion Criteria #8, replaced creatinine clearance with estimated glomerular filtration rate (eGFR). Exclusion Criteria #10, added text “or has or is recovering from chicken pox or flu-like symptoms” for subjects participating in Part B. Exclusion Criteria #11, known allergies, hypersensitivity or intolerance to ASA was added.
Rationale: Addition of study booklet as source documentation for dosage and administration of study drug	
Synopsis Dosage and Administration; Section 6. Dosage and Administration	Text “as described in the study booklet” added to the information regarding dosage to be given to subjects randomized to acetylsalicylic acid.

Applicable Section(s)	Description of Change(s)
Rationale: Selected time points were revised and study procedures were clarified.	
Time and Events Schedule, Part A	Removed the requirement for subject information to be entered into IWRS for phone contacts. Protocol activities were further clarified by modifying or adding more detailed footnotes (footnotes j, l, q, r and s), eg, deletion of text and addition of language, "at month 3 only serum chemistry laboratory tests are done".
Time and Events Schedule Part A and Part B	Removal of review of the core laboratory decision for final eligibility since enrollment can be done with local reader.
Time and Events Schedule Part B	Protocol activities were further clarified by modifying or adding more detailed footnotes (footnotes b, j, m, r, s, t, u, v and w), eg, some text deleted or added.
Time and Events Schedule, Part B, Section 9.2. Pharmacokinetics/Pharmacodynamics	Instructions for PT, aPTT and/or PK and anti-FXa samples to be obtained at specific time points pre-dose and post dose.
Rationale: Additional information regarding current anticoagulant use in children was added.	
Section 1.3, Overall Rationale for the Study	Further details related to current treatment guideline recommendations were included.
Rationale: Instructions on vomiting after dosing were given.	
Section 6, Dosage and Administration	Instructions were added to explain the procedure to be followed if the subject vomits and/or spits up the dose within a specified time frame.
Rationale: Clarification of concomitant medication and prohibited medications	
Section 8, Prestudy, Concomitant Therapy and Post study Therapy	Clarification of the definition of concomitant medications, "concomitant medications include all medications received between the first dose and the last dose of study drug". Also, text was revised to include "any anticoagulant/antiplatelet medication initiated at the end of the study treatment period will also be documented (see Section 9.1.5)". Details were added to clarify prohibited medication use for all subjects in the study. Clarification of time point for allowed therapy of ASA during the screening period and up to 24 hours prior to the first dose of study drug at Day 1 Visit was added. Additional clarification was provided to allow for continual treatment of heparin or LMWH during the screening period Occasional use of NSAID was explained under Allowed Therapy.
Rationale: Additional details related to study design and post-treatment procedure clarified.	
Section 9.1.2, Screening Period	More details related to screening evaluations for subjects participating in Part B was added.

Applicable Section(s)	Description of Change(s)
Section 9.1.2, Screening Period; Section 9.1.3.2, Open-label Treatment Period, Part B	Clarification regarding the time point for when the first dose of study drug should be given was added.
Section 9.1.5, Posttreatment Period (Follow-Up Contact); Transition at End of Treatment	Additional clarification was included to specify time periods for post treatment follow up contact in both Part A and Part B. Also, instructions for the use of any anticoagulant/antiplatelet medication initiated at the end of the study treatment period was added.
Rationale: Additional instructions provided in case of a bleeding event.	
Section 9.3.2, Approach to the Subject with a Bleeding Event	Instructions were added to explain the procedure to be followed if bleeding cannot be controlled.
Rationale: Clinical laboratory tests were specified	
Section 9.3.3, Other Safety Assessments	A full list of clinical laboratory tests for safety assessment was provided.
Rationale: Revised time point to better align with study design.	
Section 9.7.4, Central Independent Adjudication Committee	Replaced post randomization with post enrollment, since randomization is utilized only in Part B.
Rationale: Method of electronic serious adverse event reporting revised	
Section 12.3.1, All Adverse Events	Updated the process to report serious adverse events, including those spontaneously reported to the investigator within 30 days after the last dose of study drug.
Rationale: Consistent with the latest prescribing information additional storage instructions were added.	
Section 14.4, Preparation, Handling, and Storage	Specific temperature parameters for rivaroxaban and ASA were added.
Rationale: Study-Specific Materials updated	
Section 15, Study-Specific Materials	As the Diagnostic Testing Manual is no longer applicable, it was removed from the list of study-specific materials. Ancillary supplies were added. Use of an iPad® as a study management tool provided to the investigator applies to Part A of the study only.
Rationale: Additional details in the attachment sections were provided.	
Attachment 1, Volume of Blood to be Collected	The number of samples per subject and volume of blood to be collected for Part B was modified.
Attachment 2, Post-Fontan Echocardiographic Examination protocol	A note was provided to refer to the Technical Reference Manual for further details.
Attachment 3, Estimated glomerular filtration rate (eGFR)	Added the headings to describe original and updated Schwartz formula for clarity.
Rationale: Minor edits made for clarity.	
Throughout the protocol	Minor, consistency and logical clarifications were made throughout the document, which do not affect the overall study concept.

Please note that description of changes for INT-1 can be found in Attachment 4.

SYNOPSIS

STUDY TITLE

A Prospective, Open-Label, Active-Controlled Study to Evaluate the Pharmacokinetics, Pharmacodynamics, Safety, and Efficacy of Rivaroxaban for Thromboprophylaxis in Pediatric Subjects 2 to 8 Years of Age after the Fontan Procedure

DESCRIPTION OF THE COMPOUND

Rivaroxaban is an oral, highly selective direct Factor Xa (FXa) inhibitor. Inhibition of FXa interrupts the intrinsic and extrinsic pathway of the blood coagulation cascade, inhibiting both thrombin formation and development of thrombi. The clinical development program for rivaroxaban is extensive, covering the prevention and treatment of multiple thrombosis-mediated conditions. Rivaroxaban is marketed under the trade name XARELTO® and has been approved for multiple adult indications worldwide. As of September 2015, more than 60, 000 subjects have been treated with rivaroxaban in clinical trials (Phase 1 through Phase 4), covering several indications, including the prophylaxis of venous thromboembolism (VTE) in adults undergoing elective hip or knee replacement surgery, the treatment of deep vein thrombosis (DVT) and/or pulmonary embolism (PE) and the reduction in the risk of recurrence of DVT and PE, and to reduce the risk of stroke and systemic embolism in non-valvular atrial fibrillation (NVAF). XARELTO is also approved in the European Union (EU) for the prevention of atherothrombotic events (cardiovascular death, myocardial infarction, or stroke) after an acute coronary syndrome in adults with elevated cardiac biomarkers.

OBJECTIVES AND HYPOTHESIS

Primary Objectives

Part A

To characterize the single- and multiple-dose pharmacokinetics (PK) and PK/pharmacodynamics (PD) profiles after oral rivaroxaban therapy administered to pediatric subjects 2 to 8 years of age with single ventricle physiology who have completed the Fontan procedure within 4 months prior to enrollment.

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 acetylsalicylic acid (ASA), given once daily (approximately 5 mg/kg) for thromboprophylaxis in pediatric subjects 2 to 8 years of age with single ventricle physiology who have completed the Fontan procedure within 4 months prior to enrollment.

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.

Hypothesis

Children with congenital heart disease (CHD) who underwent the Fontan procedure will respond to FXa inhibition by rivaroxaban in a similar manner as seen in adults. This hypothesis is supported by ex vivo spiking experiments, which covered the entire rivaroxaban concentration in clinical studies ranging up to 500 ng/mL, and in which similar exposure-response relationships existed in healthy children and adults of different age groups (23 days to 23 months, 2 to 6 years, 7 to 11 years, 12 to 16 years, and adults).[1,2]

No statistical hypothesis testing is planned for this study.

OVERVIEW OF STUDY DESIGN

This is a prospective, open-label, active-controlled, multicenter study designed to evaluate the PK and PK/PD profiles, safety, and efficacy of rivaroxaban for thromboprophylaxis in pediatric subjects 2 to 8 years of age with single ventricle physiology who have completed the Fontan procedure within 4 months prior to enrollment.

This study consists of 2 parts:

- Part A: This is the 12-month, non-randomized, open-label part of the study, which includes a 12-day Initial PK, PD, and Safety Assessment Period. An internal Data Review Committee (DRC) will assess by Day 12 the single- and multiple-dose rivaroxaban PK, PD, and the initial safety and tolerability data available from each subject, prior to the subject continuing in the study to complete the planned 12 months of open-label rivaroxaban therapy of Part A. Subjects in Part A will not participate in Part B.

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

Subjects Participating in Part A

Part A of the study will consist of an up to 21-day Screening Period, a 12-day Initial PK, PD, and Safety Assessment Period, a 12-month Open-Label Treatment Period, and a 30-day Follow-Up Contact (phone contact). Approximately 10 pediatric subjects are planned to be enrolled in Part A.

Parental informed consent/child assent (as appropriate, typically at age ≥7 years or as defined by local regulations) must be obtained prior to performing any study-specific procedures. The screening assessments will take place after the Fontan procedure and up to 21 days before the first dose of rivaroxaban. During the screening period, baseline laboratory blood testing will be done and a transthoracic echocardiogram will be performed to rule out thrombosis. Laboratory parameters obtained as part of the post-surgery standard-of-care may be used for screening if they have been done within 21 days prior to receiving the first dose of rivaroxaban. The most recent post-Fontan clinical laboratory results will be used for screening if there are multiple laboratory results. Subjects who do not meet all of the enrollment criteria for the study may be rescreened 1 additional time as long as enrollment is within 4 months of their Fontan procedure. Subjects who are rescreened will be assigned a new subject number, undergo the informed consent process, and then restart a new screening phase.

Subjects who meet all of the inclusion and none of the exclusion criteria will be enrolled and will receive the first dose of rivaroxaban oral suspension on Day 1 (on site). Rivaroxaban will be given twice daily for 12 days (+9 days). Pharmacokinetic and PD samples will be collected on Day 1 and Day 4 (+2 days) of rivaroxaban administration. An internal DRC will assess before the subject returns 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 are allowed to continue the 12-month treatment will also have PK and PD samples collected at Month 3 and Month 12. Safety and efficacy will be evaluated throughout the study. The assessment criteria will be described in the DRC charter.

Randomization in Part B of this study will begin once the cumulative data from the Initial PK, PD, and Safety Assessment Period in Part A are deemed acceptable by the IDMC. The decision tree of rivaroxaban exposure acceptability criteria will be described in the IDMC charter.

Subjects Participating in Part B

For subjects randomized into Part B, there will be an up to 21-day Screening Period, a 12-month Open-Label Treatment Period, and a 30-day Follow-Up Contact (phone contact). Approximately 90 subjects who meet all the inclusion and none of the exclusion criteria will be randomly assigned in a 2:1 ratio to receive rivaroxaban oral suspension and ASA for 12 months.

Parental informed consent/child assent (as appropriate, typically at age ≥7 years or as defined by local regulations) must be obtained prior to performing any study-specific procedures. Subjects will undergo the same screening evaluations as in Part A. Eligible subjects will be enrolled and randomized on Day 1 and will receive their first dose of study drug on site at this visit. Subjects may be enrolled and randomized on the business day prior to Day 1 to facilitate logistics, provided the investigator ensures that the subject meets all eligibility criteria prior to randomization. Pharmacokinetic and PD samples will be obtained on Day 1, Month 3, and Month 12 for subjects randomized to rivaroxaban only. Safety and efficacy will be evaluated throughout the study for all subjects.

Early Study Medication Discontinuation

For subjects in Part A and Part B who prematurely discontinue study drug for any reason, the Early Study Medication Discontinuation (ESMD) visit will be performed as soon as possible after discontinuation. A Follow-Up Contact (phone contact) will be performed 30 days following the last dose of study drug and at Month 12, the end of the planned treatment period.

Note: An exception are subjects who are enrolled after local reading of the Screening transthoracic echocardiogram rules out thrombosis, and subsequently reported to have thrombosis after central reading by the core laboratory of the same transthoracic echocardiogram. These subjects will be withdrawn from the study when the result of the echocardiogram by the core laboratory becomes available. Subjects will be asked to return for the ESMD visit as soon as possible. They will not be required to have a repeat transthoracic echocardiogram as part of the ESMD. Subjects will go on to receive proper care according to the healthcare provider's judgment. They will be contacted by phone approximately 30 days (+/- 7 days) after last dose of study drug (Follow-Up Contact). An ESMD Month 12 follow up visit will not be required.

Committees

An Executive Committee (EC), an internal DRC, IDMC, Central Independent Adjudication Committee (CIAC), Steering Committee (SC), and a Sponsor Committee will be commissioned for this study.

SUBJECT POPULATION

Pediatric subjects 2 to 8 years of age who have single-ventricle physiology and who have completed the Fontan procedure within 4 months prior to enrollment are potentially eligible for Part A or Part B of this study.

Subjects must satisfy all of the following criteria to be enrolled in the study:

Inclusion Criteria

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 enrollment
2. Considered to be clinically stable by the investigator and 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 must sign an informed consent form (ICF) and child assent will also be provided, if applicable, according to local requirements

Subjects who meet any of the following criteria will be excluded from participating in the study:

Exclusion Criteria

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 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. Criterion modified per Amendment INT-2

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

   – 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 screening
8. Criterion modified per Amendment INT-2

   8.1 Estimated glomerular filtration rate (eGFR) <30 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

    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

    11.1 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 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 only
16. Participation in a clinical study with an investigational drug or medical device in the previous 30 days prior to enrollment
17. 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 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

DOSAGE AND ADMINISTRATION

Rivaroxaban: The rivaroxaban dose to be used in this study was determined via an adapted Physiologically-based Pharmacokinetics (PBPK) modeling approach. Rivaroxaban will be administered twice daily in an open-label fashion as a 0.1% (1 mg/ml) oral suspension with target exposure (area under the plasma concentration time curve from 0 to 24 hours [AUC_{0-24}]) at steady state matching to that of rivaroxaban 10 mg total daily dose in adults (age- and body weight-adjusted dosing). Because children with an estimated glomerular filtration rate below 30 mL/min/1.73 m^2 are excluded from the study, dose reduction for impaired renal function is not required. Rivaroxaban will be taken in the morning and in the evening (approximately 12 hours apart) and at approximately the same times each day as described in the study booklet. Dose adjustment, due to increased body weight, will be made at Month 6 (both Part A and Part B).

ASA: Acetylsalicylic acid will be provided as 81-mg or 100-mg tablets according to local practice. Subjects randomized to ASA will receive approximately 5 mg/kg of ASA to a maximum of 1 whole tablet as a single daily dose as described in the study booklet. Tablets can be split in half, if necessary (eg, children weighing ≤10 kg), to meet the daily dose, and the dose must be documented. It is recommended that tablets are not split more than in half. Dose adjustments due to increased body weight will be made at Month 6 as appropriate.

Temporary discontinuation of study drug is allowed for events, such as intercurrent illnesses. In this case, standard clinical practice should be followed.

PHARMACOKINETIC/PHARMACODYNAMIC EVALUATIONS

Blood samples for rivaroxaban PK and PD, including rivaroxaban plasma concentration, absolute prothrombin time (PT), activated partial thromboplastin time (aPTT), and anti-FXa activity measurements will be taken from pediatric subjects enrolled in Part A on Day 1 and Day 4 and for subjects continuing in Part A, at Month 3 and Month 12, and for subjects randomized to rivaroxaban in Part B on Day 1, Month 3, and Month 12. The dosing, exact time of rivaroxaban administration and PK and PD blood sampling will be documented in the electronic case report form (eCRF).

Sampling Schedule of the Initial PK, PD, and Safety Assessment Period (Day 1 and Day 4-6) (Part A)[a]

	Visit 2-D1/ Day 1		Visit 2-D4/ Day 4[b]			
	Postdose[c] 0.5-1.5 hours	**Postdose[c] 1.5-4 hours[e]**	**Predose[c,d]**	**Postdose[c] 0.5-1.5 hours**	**Postdose[c] 1.5-4 hours[e]**	**Postdose[c] 6.0-8 hours**
PK[f]	0.6 ml	0.6 ml	0.6 ml	0.6 ml	0.6 ml	0.6 ml
PD-1[g]	1.4 ml	1.4 ml	1.4 ml	1.4 ml	1.4 ml	1.4 ml
PD-2[h]	1.4 ml	1.4 ml	-	-	-	1.4 ml

D1=Day 1; D4=Day 4; PD=pharmacodynamics; PK=pharmacokinetics.

a) Subjects continuing in Part A will also have additional PK and PD assessments at Months 3 and 12.
b) Visit 2-D4 can be performed on Days 4, 5, or 6.
c) Sampling times are relative to morning dose.
d) Up to 3 hours predose.
e) Allow at least 30 minutes from the previous sample.
f) Blood volume per PK sample for rivaroxaban plasma concentration is approximately 0.6 mL; total blood volume for all PK samples is 3.6 mL (Day 1: 1.2 mL; Day 4: 2.4 mL); sites will send samples to the central laboratory on the day of collection for liquid chromatography/mass spectrometry/mass spectrometry (LC-MS/MS) determination.
g) PD-1 assessments will include prothrombin time (PT) and activated partial thromboplastin time (aPTT). Blood volume per PD-1 sample is approximately 1.4 mL; total blood volume for all PD-1 samples is 8.4 mL (Day 1: 2.8 mL; Day 4: 5.6 mL). Sites will send samples to the central laboratory after Day 4 of collection.
h) PD-2 assessment will be anti-FXa activity. Blood volume per PD-2 sample is approximately 1.4 mL; total blood volume for all PD-2 samples is 4.2 mL (Day 1: 2.8 mL; Day 4: 1.4 mL). Sites will send samples to the central laboratory.

SAFETY EVALUATIONS/OUTCOMES

The primary safety outcome will be major bleeding events, as defined below. Clinically relevant non-major bleeding events and trivial (minimal) bleeding will be secondary safety outcomes.

The safety and tolerability of rivaroxaban will also be evaluated by assessing adverse events and clinical laboratory values.

Bleeding events will be adjudicated by the CIAC using the International Society on Thrombosis and Hemostasis (ISTH) recommendations.

Major bleeding is 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 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 is 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 is defined as any other overt bleeding event that does not meet criteria for clinically relevant non major bleeding.

EFFICACY EVALUATIONS/OUTCOMES

The primary efficacy outcome will be 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, pulmonary embolism).

Subjects who develop either a symptomatic or asymptomatic thrombotic event during the study must permanently discontinue the study drug. All available imaging results (eg, transthoracic or transesophageal echocardiograms, or MRIs), should be sent to the CIAC. After cessation of the study drug, it is at the investigator's discretion to continue with other antithrombotic therapy. The investigator should document this therapy in the eCRF. Thrombotic events will not be reported as adverse events or serious adverse events, as they will be reported as efficacy outcomes.

Transthoracic echocardiograms will be centrally read by an echocardiographic core laboratory. All thrombotic events and the primary cause of any death will be adjudicated by the CIAC.

STATISTICAL METHODS

Sample Size Determination

A total of at least 100 pediatric subjects overall are planned to be enrolled in this study. The total sample size does not originate from a formal sample size calculation but is based on regulatory feedback to obtain sufficient safety data in this pediatric population. No statistical hypothesis will be tested in either part of this study.

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 subjects and determine the dosing regimen to be studied in Part B. Approximately 90 subjects will be enrolled into Part B of the study.

Pharmacokinetics, Pharmacodynamics, Safety, and Efficacy Analyses

No statistical hypothesis will be tested in Part A or Part B.

Descriptive statistics will be used to summarize rivaroxaban PK data for each time interval. Pharmacodynamics measurements, including PT, aPTT, and anti-FXa activity will be plotted against rivaroxaban plasma concentrations and will also be summarized by timepoint.

Rivaroxaban PK parameters, including AUC_{0-24}, maximum plasma concentration (C_{max}) after single dose, and AUC_{0-24}, C_{max}, and minimum plasma concentration (C_{min}) at steady sate, will be derived by model-based methods. Pharmacokinetics/PD relationship will be quantified. Results from PK and PK/PD analyses will be reported separately from the Clinical Study Report.

For both parts of the study, safety and efficacy (adverse events, bleedings, and thrombotic events) will be summarized.

EudraCT NUMBER: 2015-002610-76

TIME AND EVENTS SCHEDULE

TIME & EVENTS SCHEDULE – SUBJECTS PARTICIPATING IN PART A

	Screening Period[a]	Initial PK, PD, and SafetyAssessment Period Rivaroxaban Oral Suspension			12-month Open-Label Treatment Period[b] Rivaroxaban Oral Suspension				Follow-Up Contact[c]	ESMD Month 12 Follow-Up[d]
Visit	**Visit 1**	**Visit 2-D1**	**Visit 2-D4**	**Visit 2-D12**	**Visit 3**	**Visit 4**	**Visit 5**		**Phone Contact**	**Phone Contact**
Time	**Up to 21 Days**	**Day 1[e]**	**Day 4**	**Day 12**	**Month 3**	**Month 6**	**Month 12**	**ESMD[f]**	**30-days after last dose**	
Visit Type/ Window	**Visit**	**Visit**	**Visit +2 days**	**Visit +9 days**	**Visit ±7 days**	**Visit ±7 days**	**Visit ±7 days**		**Phone contact ±7 days**	**Visit ±14 days**
Screening/Administrative										
Informed consent (ICF)/assent[g]	X									
Enter subject information into IWRS	X	X		X	X	X	X	X		
Inclusion/exclusion criteria[h]	X									
Review medical history, demographics	X									
Obtain blood pressure, heart rate	X									
Obtain body weight, height	X	X				X	X	X		
Record prestudy medications	X									
Obtain baseline transthoracic echocardiogram[a]	X									
Enrollment		X								
Rivaroxaban Administration										
Dispense rivaroxaban		X		X[t]	X	X				
Rivaroxaban administration at the site[j]		X	X		X					
Rivaroxaban drug accountability			X	X	X	X	X	X		
Rivaroxaban dose adjustment due to growth						X				
Provide Study booklet		X								
Safety and Efficacy Assessments										
Assess study outcome events[k]		X	X	X	X	X	X	X	X	X[l]
Adverse events assessment[m]	X	X	X	X	X	X	X	X	X	
Review concomitant medications		X	X	X	X	X	X	X	X	X
Physical examination	X	X[n]		X	X[n]	X[n]	X	X		
Transthoracic echocardiogram[o]	X[a]					X	X	X		
Hematology, serum chemistry [p,q], PT, aPTT	X				X		X	X		
PK/PD										
Obtain PK and PD samples at the following timepoints[r] :										
Up to 3 hours pre-dose			X		X[s]					
0.5-1.5 hour postdose		X[s]	X		X					
1.5-4 hours postdose		X[u,s]	X[u]				X[t]			
2.5-4 hours postdose					X					
6-8 hours postdose			X[s]							

Key: AM=Ante Meridian (morning); aPTT= activated partial thromboplastin time; CBC= complete blood count; D1=Day 1; D4=Day 4; DRC=Data Review Committee; ESMD=Early Study Medication Discontinuation; IDMC = Independent Data Monitoring Committee; IWRS= interactive web response system; PD= pharmacodynamics, PK=pharmacokinetics; PT= prothrombin time

a) Screening procedures can be performed up to 21 days prior to Day 1/enrollment. For screening, the subjects transthoracic echocardiogram may be read locally to rule out thrombosis and proceed to enrollment of the subject if no thrombosis is reported and inclusion/exclusion criteria are satisfied. The transthoracic echocardiogram should also be sent to the core laboratory if subject is enrolled. See Section 9.1.6 for further instructions. Note: Hospital laboratory, local laboratory results or central laboratory results are acceptable at screening, and the most recent clinical laboratory results will be used for screening if there are multiple laboratory results. Subjects who do not meet all of the enrollment criteria for the study may be rescreened 1 additional time as long as enrollment is within 4 months of their Fontan procedure. Subjects who are rescreened will be assigned a new subject number, undergo the informed consent process, and then restart a new screening phase.
b) This period will include subjects who complete the Initial PK, PD, and Safety Assessment Period and are allowed to continue on open-label rivaroxaban oral suspension twice-daily therapy to complete 12 months.
c) Regardless of treatment duration, all subjects will have a Follow-Up Contact, 30 days after the last dose (+/- 7 days).
d) Only for subjects with ESMD. These subjects will also be contacted to determine vital status and efficacy outcomes at the end of the planned treatment period (Month 12).
e) Fontan procedure completed within 4 months prior to enrollment (Visit 2).
f) For subjects who prematurely discontinue study drug for any reason, the ESMD visit procedures will be performed as soon as possible after discontinuation. See Section 3.1 for detailed instructions for subjects returning for the ESDM because of core laboratory reading of the baseline transthoracic echocardiogram.
g) Must be signed before first study-related activity.
h) Minimum criteria for the availability of documentation supporting the eligibility criteria are described in Section 17.4, Source Documentation. Check clinical status again before first dose of study medication.
i) Rivaroxaban will be dispensed to those subjects who complete the Day 1 and Day 4 visits and after review and approval of their individual Day 1 and Day 4 PK, PD and safety data by the DRC.
j) Rivaroxaban (AM dose) to be administered at the site.
k) If a suspected outcome event (thrombotic or bleeding event) occurs, the adjudication package is to be completed.
l) Only vital status and thrombotic events (no bleeding events) will be assessed and an adjudication package will be completed.
m) Adverse event assessment includes a review of all ongoing and new adverse events since the last visit for all visits through Month 12.
n) A physical examination will be symptom-driven.
o) Transthoracic echocardiograms will be obtained at screening, Month 6, and Month 12, or ESMD and whenever medically necessary, and results sent to the core laboratory. For screening see footnote ‘a’.
p) Hematology (complete blood count [CBC] with differential, platelet count); blood chemistry (liver function tests [alanine aminotransferase, ALT; aspartate aminotransferase, AST; total and direct bilirubin; alkaline phosphatase] and creatinine).
q) Hematology and serum chemistry testing are done at screening (testing should be done after the Fontan procedure and results should be available within 21 days prior to Day 1, at Month 12 and ESMD visit). At Month 3 only serum chemistry laboratory tests are done. Prothrombin time and aPTT tests (should be done at screening visit only). Note: Hospital laboratory, local laboratory results, or central laboratory results are acceptable at screening, and the most recent clinical laboratory results will be used for screening if there are multiple laboratory results.
r) Pharmacokinetics and (PT and aPTT) samples will be collected at all timepoints for central testing. If a subject experiences a major bleeding event while being treated with rivaroxaban, obtain PK and PD samples (see also Section 9.3.2 for approach to the subject with a bleeding event and Section 9.5 for sample instructions).
s) Anti- factor Xa [FXa] assay samples will be collected only at these specific time points.
t) To be collected at any timepoint during the visit (PK, PT, aPTT, hematology and chemistry testing). Parent/legally acceptable representative should document timing of the administered AM study drug dose.
u) Allow at least 30 minutes from the previous sample.

TIME & EVENTS SCHEDULE – SUBJECTS PARTICIPATING IN PART B

	Screening Period[a]	Open-Label Treatment Period[c]						Follow-Up Contact[d]	ESMD Month 12 Follow-Up[e]
Visit	**Visit 1**	**Visit 2**	**Phone Contact**	**Visit 3**	**Visit 4**	**Visit 5**		**Phone Contact**	**Phone Contact**
Time	**Up to 21 days**	**Day 1[f]**	**Day 12**	**Month 3**	**Month 6**	**Month 12**	**ESMD[g]**	**30-days after last dose**	
Visit Type/Window	**Visit**	**Visit**	**Phone contact +9 days**	**Visit ±7 days**	**Visit ±7 days**	**Visit ±7 days**		**Phone contact ±7 days**	**Visit ±14 days**
Screening/Administrative									
Informed consent (ICF)/assent[h]	X								
Enter subject information into IWRS	X	X[j]		X	X	X	X		
Inclusion/exclusion criteria[i]	X								
Review medical history, demographics	X								
Obtain blood pressure, heart rate	X								
Obtain body weight, height	X	X			X	X	X		
Record prestudy medications	X								
Obtain baseline transthoracic echocardiogram[a]	X								
Enrollment		X[b]							
Study Drug Administration									
Randomization		X[j]							
Dispense study drug		X		X	X				
Study drug administration at the site[k]		X		X					
Study drug accountability				X	X	X	X		
Study drug dose adjustment due to growth					X				
Provide Study booklet		X							
Safety and Efficacy Assessments									
Assess study outcome events[l]		X	X	X	X	X	X	X	X[m]
Adverse events assessment[n]	X	X	X	X	X	X	X	X	
Review concomitant medications		X	X	X	X	X	X	X	X
Physical examination	X	X[o]		X[o]	X[o]	X	X		
Transthoracic echocardiogram[p]	X[a]				X	X	X		
Hematology, serum chemistry[q,r]	X[r]					X	X		
PK/PD – Rivaroxaban Subjects Only									
Obtain PK and PD samples at the following timepoints[s]									
Up to 3 hours pre-dose		X[v]		X[w]		X[t]			
0.5-1.5 hour postdose		X[w]		X[w]					
1.5-4 hours postdose		X[w, u]							
2.5-4 hours postdose				X[w]					

Key: AM=Ante Meridian (morning); aPTT= activated partial thromboplastin time; D1=Day 1; D4=Day 4; DRC=Data Review Committee; ESMD=Early Study Medication Discontinuation; IWRS=interactive web response system; PD= pharmacodynamics (PT and aPTT testing); PK= pharmacokinetics; PT= prothrombin time

a) Screening procedures can be performed up to 21 days prior to Day 1/enrollment. For screening, the subjects transthoracic echocardiogram may be read locally to rule out thrombosis and proceed to enrollment of the subject if no thrombosis is reported and inclusion/exclusion criteria are satisfied. The transthoracic echocardiogram should also be sent to the core laboratory if subject is enrolled. See Section 9 for further instruction. Note: Hospital laboratory, local laboratory results or central laboratory results are acceptable at screening, and the most recent clinical laboratory results will be used for screening if there are multiple laboratory results. Subjects who do not meet all of the enrollment criteria for the study may be rescreened 1 additional time as long as enrollment is within 4 months of their Fontan procedure. Subjects who are rescreened will be assigned a new subject number, undergo the informed consent process, and then restart a new screening phase.
b) Subjects will undergo the same screening evaluations as in Part A except for PT and aPTT testing which will be performed on Day 1 prior to first dose of study drug.
c) Subjects will receive either rivaroxaban oral suspension twice-daily or acetylsalicylic acid (ASA) approximately 5 mg/kg/day.
d) Regardless of treatment duration, all subjects will have a Follow-Up Contact, 30 days after the last dose (+/- 7 days).
e) Only for subjects with ESMD. These subjects will also be contacted to determine vital status and efficacy outcomes at the end of the planned treatment period (Month 12).
f) Fontan procedure completed within 4 months prior to enrollment (Visit 2).
g) For subjects who prematurely discontinue study drug for any reason, the ESMD visit procedures will be performed as soon as possible after discontinuation. See Section 3.1 for detailed instructions for subjects returning for the ESDM because of core laboratory reading of the baseline transthoracic echocardiogram.
h) Must be signed before first study-related activity.
i) Minimum criteria for the availability of documentation supporting the eligibility criteria are described in Section 17.4, Source Documentation. Check clinical status again before first dose of study medication.
j) Subjects will be enrolled and randomized on Visit 2/Day 1 after meeting inclusion and exclusion criteria. Subjects may be enrolled and randomized on the business day prior to Day 1 to facilitate logistics provided the investigator ensures that the subject meets all eligibility criteria prior to randomization. The first dose of study drug will be administered on site on Day 1 if the subject is still eligible.
k) For subjects randomized to rivaroxaban, the AM dose will be administered at the site.
l) If a suspected outcome event (thrombotic or bleeding event) occurs, the adjudication package is to be completed.
m) Only vital status and thrombotic events (no bleeding events) will be assessed and an adjudication package will be completed.
n) Adverse event assessment includes a review of all ongoing and new adverse events since the last visit for all visits through Month 12.
o) Physical examination of the subject will be symptom-driven.
p) Transthoracic echocardiograms will be obtained at screening, Month 6 and Month 12, or ESMD and whenever medically necessary, and results sent to core laboratory. For screening see footnote ‘a’.
q) Hematology (complete blood count [CBC] with differential, platelet count); blood chemistry (liver function tests [alanine aminotransferase, ALT; aspartate aminotransferase, AST; total and direct bilirubin, alkaline phosphatase] and creatinine).
r) Hematology and serum chemistry testing at screening (testing should be done after the Fontan procedure and results should be available within 21 days prior to randomization, at Month 12 and ESMD visit). Note: Hospital laboratory, local laboratory results or central laboratory results are acceptable at screening, and the most recent clinical laboratory results will be used for screening if there are multiple laboratory results.
s) If a subject experiences a major bleeding event while being treated with rivaroxaban, obtain PK and PD samples (see also Section 9.3.2 for approach to the subject with a bleeding event and Section 9.5 for sample instructions).
t) To be collected at any timepoint during the visit (PK, PT,and aPTT). Parent/legally acceptable representative should document timing of the administered AM study drug dose.
u) Allow at least 30 minutes from previous sample.
v) Only PT and aPTT samples will be collected.
w) PK, PT, aPTT, and anti- FXa assay samples will be collected.

ABBREVIATIONS

ACS	acute coronary syndrome
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
ASA	acetylsalicylic acid
AST	aspartate aminotransferase
AUC	area under the plasma concentration time curve
AUC_{0-24}	area under the plasma concentration time curve from 0 to 24 hours
CBC	complete blood count
CHD	congenital heart disease
CIAC	Central Independent Adjudication Committee
C_{max}	maximum plasma concentration
C_{min}	minimum plasma concentration
CrCl	creatinine clearance
CRF	case report form
CYP3A4	cytochrome P450 3A4
D	Day
DRC	Data Review Committee
EC	Executive Committee
eCRF	electronic case report form
eDC	electronic data capture
eGFR	estimated glomerular filtration rate
ESMD	early study medication discontinuation
EU	European Union
FXa	factor Xa
GCP	Good Clinical Practice
ICF	informed consent form
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
INR	international normalized ratio
IRB	Institutional Review Board
ISTH	International Society on Thrombosis and Hemostasis
IWRS	interactive web response system
LC-MS/MS	liquid chromatography/mass spectrometry/mass spectrometry
LMWH	low molecular-weight heparin
MedDRA	Medical Dictionary for Regulatory Activities
NSAID	non-steroidal anti-inflammatory drug
NVAF	non-valvular atrial fibriallation
PBPK	physiologically-based pharmacokinetics
PD	pharmacodynamic(s)
P-gp	P-glycoprotein
PK	pharmacokinetic(s)
PQC	product quality complaint
PT	prothrombin time
SAP	Statistical Analysis Plan
SC	Steering Committee
SCr	serum creatinine
SUSAR	suspected unexpected serious adverse reaction
ULN	upper limit of normal
VKA	vitamin K antagonist
VTE	venous thromboembolism

1. INTRODUCTION

Rivaroxaban is an oral, highly selective direct Factor Xa (FXa) inhibitor. Inhibition of FXa interrupts the intrinsic and extrinsic pathway of the blood coagulation cascade, inhibiting both thrombin formation and development of thrombi. The clinical development program for rivaroxaban is extensive, covering the prevention and treatment of multiple thrombosis-mediated conditions through a joint collaboration agreement between Bayer HealthCare AG and Ortho McNeil Pharmaceuticals, Inc (now Janssen Research and Development, LLC). Rivaroxaban has been approved in multiple indications worldwide under the trade name XARELTO®. As of September 2015, more than 60,000 subjects have been treated with rivaroxaban in clinical trials (Phase 1 through Phase 4), covering several indications, including the prophylaxis of venous thromboembolism (VTE) in adults undergoing elective hip or knee replacement surgery, the treatment of deep vein thrombosis (DVT) and/or pulmonary embolism (PE) and the reduction in the risk of recurrence of DVT and PE, and to reduce the risk of stroke and systemic embolism in non-valvular atrial fibrillation XARELTO is also approved in the EU for the prevention of atherothrombotic events (cardiovascular death, myocardial infarction, or stroke) after an acute coronary syndrome in adults with elevated cardiac biomarkers.

Rivaroxaban is currently being studied in pediatric subjects with VTE (see Section 1.1.4, Physiology-Based Pharmacokinetics). It has been well tolerated in a Phase 2 and Phase 3 study in pediatric subjects for the treatment and secondary prevention of VTE (studies ongoing).

For the most comprehensive nonclinical and clinical information regarding rivaroxaban, refer to the latest version of the Investigator's Brochure.[14]

The term "sponsor" used throughout this document refers to the entities listed in the Contact Information page(s), which will be provided as a separate document.

1.1. Background

1.1.1. Pediatric Patients with Single Ventricle Physiology – The Fontan Procedure - Scope of the Problem

The Fontan procedure has become the most common procedure performed for congenital heart disease (CHD) after the age of 2 years and is the final palliative surgery for children with single ventricle physiology.[10,19] Improvements in early outcomes have led to an increase in the number of patients surviving into adulthood after this palliative procedure.[15] 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, STS-CHSDB), Europe (EACTS Congenital Database) and Australia and New Zealand (Fontan Registry). Collectively, these registries reported about 1,460 Fontan procedures per year during 2007 to 2011, which captured the majority of the Fontan procedures performed in those regions.[3,16,31]

Thrombosis remains an important complication for patients with single ventricle physiology following the Fontan procedure; however, the true frequency of thrombotic events is not well known.[21,22] Several studies have estimated that the prevalence of thrombosis events occurring post-Fontan procedure ranges from 17% to 33%, with a reported mortality of 25% due to an

associated post-Fontan thromboembolism.[4,9,30] The risk of thrombotic complications is higher within 6 months after the Fontan procedure and the risk diminishes but persists over the first 2.5 years thereafter.[18]

1.1.2. Human Pharmacokinetics in Adults

Rivaroxaban is rapidly absorbed after oral administration, with peak plasma concentrations occurring approximately 2 to 4 hours postdose. Rivaroxaban is a low clearance drug (clearance is approximately 10 L/h or 0.14 L/h/kg) and does not undergo any relevant first-pass metabolism. The terminal elimination half-life of rivaroxaban ranges from 5 to 9 hours in healthy young male subjects and from 11 to 13 hours in healthy elderly subjects (aged 65 to 83 years). Due to the multiple elimination pathways of rivaroxaban, there are few clinically relevant drug-drug interactions.

In drug-drug interaction studies evaluating the concomitant use with drugs that are combined P-glycoprotein (P-gp) and cytochrome P450 3A4 (CYP3A4) inhibitors, increases in rivaroxaban exposure were observed. Similar increases in pharmacodynamic effects (ie, FXa inhibition and prothrombin time [PT] prolongation) were also observed. Significant increases in rivaroxaban exposure may increase bleeding risk.

In a drug interaction study, coadministration of rivaroxaban (20-mg single dose with food) with a drug that is a combined P-gp and strong CYP3A4 inducer (rifampicin titrated up to 600 mg once daily) led to an approximate decrease of 50% and 22% in area under the plasma concentration curve (AUC) and maximum plasma concentration (C_{max}), respectively. Similar decreases in PD effects were also observed. These decreases in exposure to rivaroxaban may decrease efficacy.

1.1.3. Efficacy and Safety Profile Based on Adult Clinical Studies

The efficacy and safety of rivaroxaban have been studied in several large clinical development programs for the prevention and treatment of multiple thrombosis-mediated conditions.

The highlights of relevant studies are:

- The pooled analysis of 4 studies comprising the RECORD program involving 12,729 subjects undergoing hip or knee arthroplasty demonstrated that rivaroxaban given at a dose of 10 mg once daily compared with enoxaparin given at a dose of 30 mg twice daily or 40 mg once daily for 30 days significantly reduced the risk of symptomatic VTE and mortality (0.8% absolute risk decrease). Rivaroxaban increased the risk of bleeding slightly compared with enoxaparin (0.2% absolute risk increase in major bleeding events).
- The ROCKET AF study involving 14,264 patients with NVAF at high risk of stroke demonstrated that rivaroxaban 20 mg once daily (15 once daily in subjects with an estimated glomerular filtration rate of 30 to 49 ml/min) compared with warfarin (target international normalized ratio [INR] 2.0 to 3.0) for a mean of 19 months was non inferior for the prevention of stroke or systemic embolism (hazard ratio 0.88; 95% confidence interval: 0.74 to 1.03), with a significant reduction in life-threatening, intracranial and fatal bleeding and a favorable effect on mortality, but more transfusions and hemoglobin decreases of >2 gm/dl.

- The EINSTEIN VTE treatment studies involving 9,447 subjects with VTE demonstrated that rivaroxaban 15 mg twice daily for 3 weeks followed by 20 mg once daily compared with initial low molecular-weight heparin (LMWH) followed by warfarin (INR 2.0 to 3.0) was associated with a similar or reduced risk of recurrent VTE with a similar or reduced rate of major bleeding during up to 12 months. Overall bleeding rates were similar with rivaroxaban compared to enoxaparin/ vitamin K antagonists (VKA), and showed a clinically important reduction in major bleeding risk.
- Rivaroxaban has been studied for reduction of the risk of thrombotic cardiovascular (CV) events in patients with acute coronary syndrome (ACS) (ST segment elevation myocardial infarction, non-ST-segment elevation myocardial infarction, or unstable angina) in combination with acetylsalicylic acid (ASA) alone or with ASA plus a thienopyridine (clopidogrel or ticlopidine) in the ATLAS program. The ATLAS ACS 2 TIMI 51 study randomized a total of 15,526 subjects and demonstrated that rivaroxaban 2.5 mg or 5 mg twice daily compared with placebo reduced the risk of CV death, MI, or stroke by 16% in patients with a recent ACS, most of whom (92%) were also receiving dual antiplatelet therapy. The incidences of all categories of treatment-emergent bleeding were consistently higher in subjects treated with rivaroxaban compared with placebo. The higher rates of bleeding with rivaroxaban were expected, since in this study rivaroxaban was compared to placebo on the background of standard antiplatelet therapy.
- The MAGELLaN study compared VTE prophylaxis with oral rivaroxaban 10 mg once daily for 35 days with enoxaparin 40 mg daily for 10 days in subjects who were hospitalized for a medical illness. The MAGELLaN study randomized 8,101 subjects and met both of its primary efficacy objectives (ie, for rivaroxaban versus enoxaparin/placebo noninferiority at Day 10, and superiority at Day 35). Although bleeding rates in MAGELLaN were low overall, the incidences of clinically relevant bleeding events were increased in rivaroxaban treated subjects compared to enoxaparin.

In addition to bleeding, other adverse reactions associated with rivaroxaban include nausea, fever, kidney and liver impairment, dyspepsia, allergic reactions including skin reactions, itching, rash, hives, swelling of face, lips, mouth, tongue, skin or throat, and cholestasis.

Postmarketing data gathered subsequently to the pivotal studies do not change the favorable benefit-risk assessment of rivaroxaban in the approved indications.

For the most comprehensive description of the safety profile of rivaroxaban, refer to the latest version of the Investigator's Brochure for rivaroxaban.[14]

1.1.4. Physiology-Based Pharmacokinetics

The rivaroxaban doses that are being tested in the pediatric VTE treatment studies were derived using Physiologically-based Pharmacokinetics (PBPK) modeling (ie, extrapolation of the known pharmacokinetic (PK) properties of the drug into the pediatric population by way of physiology based translational approaches).[6,7] The primary goal for dosing is to achieve in pediatric patients an equivalent exposure (as measured by AUC) to the 20 mg once daily dose regimen that has demonstrated effectiveness for treatment of VTE in adults. The term ‘equivalent exposure’ is used to indicate the achievement of a similar area under the plasma concentration curve from

0 to 24 hours (AUC_{0-24}) value between pediatric and adult subjects. For assessing dose linearity, pediatric doses that provide equivalent exposure to the rivaroxaban 10-mg once daily regimen in adults are also being evaluated in the Phase 1 study conducted by Bayer Healthcare. Based on the current knowledge of the coagulation system in the pediatric population, the expectation is that children will respond to FXa inhibition in a similar manner to adults. This hypothesis is supported by ex-vivo spiking experiments, which covered the entire rivaroxaban concentration in clinical studies ranging up to 500 ng/mL, and in which similar exposure-response relationships existed in healthy children and adults of different age groups (23 days to 23 months, 2 to 6 years, 7 to 11 years, 12 to 16 years, and adults).[1,2,25]

1.1.5. Efficacy and Safety Profile Based on Pediatric Clinical Studies

Rivaroxaban is currently being developed for the treatment of VTE in pediatric subjects (EINSTEIN Junior program). The VTE treatment pediatric clinical development program was designed in a comprehensive, staggered and stepwise approach to establish pediatric age-specific dosing recommendations and to explore the comparative safety and efficacy of rivaroxaban to the standard-of-care therapy in children from birth to <18 years. As of 29 March 2016, 223 pediatric subjects have received at least one dose of rivaroxaban in these pediatric trials.

The VTE treatment program is comprised of 7 studies of which 1 study has been completed, 5 are ongoing and 1 is planned to start in 2017.

- Two Phase 1 studies:
  - Study #12892 is a Phase 1 study in pediatric subjects from 6 months to 18 years of age, which recently completed enrollment. This Phase 1 study was designed to evaluate the safety profile of a single dose of rivaroxaban ready to use suspension and confirm the age- and body-weight adjusted pediatric dose recommendations equivalent to 10 and 20 mg single dose in adults derived from adult data and PBPK modeling.
  - Study #17992 is another Phase 1 single-dose study evaluating rivaroxaban granules for oral suspension formulation in pediatric subjects from 6 months to 12 years with previous thrombosis, currently starting enrollment.

  A total of 78 children have received a single dose of rivaroxaban in these Phase 1 studies.
- Two Phase 2 studies (Study #14373 and #14374) are enrolling pediatric subjects from 6 months to 18 years of age. Both studies investigate the safety, tolerability, effectiveness and pharmacokinetics and pharmacodynamics of a 30-day treatment of age- and body weight adjusted rivaroxaban. The pediatric dose targets an adult exposure of 20 mg in children with various manifestations of thrombosis.
  A total of 57 pediatric subjects have received rivaroxaban in these Phase 2 studies.
- Study #14372 is a Phase 3 study in pediatric subjects from 6 months to <18 years. It is a 3 to 12 month, open-label, active-controlled, randomized study of the safety, efficacy and the pharmacokinetic and pharmacodynamic properties of oral rivaroxaban in pediatric subjects with various manifestations of venous thrombosis. The study is currently enrolling the age cohort 12 to 18 years. A total of 87 subjects have received rivaroxaban.

- Study # 17618 is a Phase 1/2 7-day study of safety, efficacy and the pharmacokinetic and pharmacodynamic properties of oral rivaroxaban in pediatric subjects from birth to 6 months with catheter-related arterial or venous thrombosis. Pediatric subjects will be receiving an age- and body weight-adjusted dose of rivaroxaban (20 mg equivalent). Enrollment is currently starting, and 1 subject has received rivaroxaban.
- Study #17625 is a Phase 3 study in pediatric subjects from birth to 6 months planned to start in 2017.

In the ongoing rivaroxaban studies in pediatric subjects, rivaroxaban has been well tolerated; there have been no cases of drug-related death and no major bleeding events.

No recurrences of VTE have been observed during rivaroxaban treatment in phase 2 studies. In the Phase 3 study 14372 with a 2:1 randomization to the rivaroxaban and standard of care arm, there were 3 outcomes in the rivaroxaban arm (including 1 recurrence that occurred during the initial heparin treatment, ie, before rivaroxaban was started) and 1 outcome in the standard of care arm. The side effect profile of rivaroxaban has been similar to the side effect profile in adults. In summary, these data support a positive risk/benefit assessment.

1.2. Comparator Agent

Acetylsalicylic acid (ASA)

Acetylsalicylic acid is a nonsteroidal anti-inflammatory drug (NSAID). The mechanism of action of ASA is suppression of prostaglandins and thromboxanes production by irreversible inactivation of the cyclooxygenase enzyme required for prostaglandin and thromboxane synthesis.

Acetylsalicylic acid is indicated as a pain reliever for the temporary relief of minor aches and pains. It also has an antiplatelet effect and at lower doses can be used as a long-term treatment to help prevent heart attacks, strokes, and blood clot formation in patients at high risk of developing blood clots.

Adverse reactions associated with the use of ASA include allergic reactions, an increased risk of gastrointestinal bleeding, and Reye's syndrome.

Further information regarding low dose ASA can be found in the local approved product label.

1.3. Overall Rationale for the Study

Despite continuous improvements in the medical management of pediatric patients with CHD, the risk of thrombotic events remains an important complication for pediatric patients following the Fontan procedure.[21]

The National Heart, Lung and Blood Institute (NHLBI) convened a Working Group in 2012 to explore the issues related to thrombosis in children with CHD.[19] 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 both before and after the Fontan procedure were a top research priority. Therefore, there is an important unmet medical need for

additional therapies with well controlled studies upon which to base treatment decisions for thromboprophylaxis in children after the Fontan procedure.

There has been only 1 prospective study of anticoagulation prophylaxis in Fontan patients, which included 111 pediatric subjects that were randomized to treatment with ASA or heparin/warfarin for 2 years. The study did not reach the targeted recruitment goal of 242 subjects. Thrombotic events (venous and arterial) were the primary endpoints in the study. Results demonstrated a peak incidence of VTE in the first 6 months, and no significant difference in event rates between the treatment groups with thrombosis occurring in 21% of ASA-treated subjects and 24% of warfarin-treated subjects. The study found no difference in risk of thrombosis between subjects randomized to warfarin at the 2 years study endpoint. All of the thrombotic events in the study were venous events (no arterial events).[20] Although there was no difference between warfarin and ASA, the event rate supports the decision to include an active comparator for which there is a perceived equipoise.

To date, no consensus exists in the literature or in routine clinical practice as to the optimal type or duration of antithrombotic therapy for thromboprophylaxis after Fontan surgery and much of the data for pediatric recommendations is still extrapolated from adult data.[11,18] Current guidelines recommend the use of ASA, or unfractionated heparin followed by vitamin K antagonist (VKA) for thromboprophylaxis in pediatric subjects after the Fontan procedure.[12,11,18] While these recommendations are based on available literature and experts opinion and are routinely followed by pediatric hematologists and other health care providers, currently there are no anticoagulants approved for use in children for treatment or prophylaxis of thromboembolism in the United States or European Union . Instead, anticoagulants (namely, VKAs and heparins) are currently used off-label in children. Furthermore, there is a negligible amount of published data on the safety and efficacy of novel oral anticoagulation agents in children for whom anticoagulation is recommended.

This study aims to provide safety and efficacy information on the use of rivaroxaban, an oral anticoagulant, compared to ASA, an antiplatelet, in this population.

2. OBJECTIVES AND HYPOTHESIS

2.1. Objectives

Primary Objectives

Part A

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

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 pediatric subjects 2 to 8 years of age with single ventricle physiology who have completed the Fontan procedure within 4 months prior to enrollment.

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.

2.2. Hypothesis

Children with CHD who underwent a Fontan procedure will respond to FXa inhibition by rivaroxaban in a similar manner as seen in adults. This hypothesis is supported by ex vivo spiking experiments, which covered the entire rivaroxaban concentration in clinical studies ranging up to 500 ng/mL, and in which similar exposure-response relationships existed in healthy children and adults of different age groups (23 days to 23 months, 2 to 6 years, 7 to 11 years, 12 to 16 years, and adults).[1,2]

There is no statistical hypothesis testing for this study.

3. STUDY DESIGN AND RATIONALE

3.1. Overview of Study Design

This is a prospective, open-label, active-controlled, multicenter study designed to evaluate the PK and PK/PD profiles, safety, and efficacy of rivaroxaban for thromboprophylaxis in pediatric subjects 2 to 8 years of age with single ventricle physiology who have completed the Fontan procedure within 4 months prior to enrollment.

This study consists of 2 parts:

- Part A: This is the 12-month, non-randomized, open-label part of the study, which includes a 12-day Initial PK, PD, and Safety Assessment Period. An internal Data Review Committee (DRC) will assess before the subject returns for Day 12 the single- and multiple-dose rivaroxaban PK, PD, and the initial safety and tolerability data available from each subject, prior to the subject continuing in the study to complete the planned 12 months of open-label rivaroxaban therapy of Part A. Subjects in Part A will not participate in Part B.

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

Subjects Participating in Part A

Part A of the study will consist of an up to 21-day Screening Period, a 12-day Initial PK, PD, and Safety Assessment Period, a 12-month Open-Label Treatment Period, and a 30-day Follow-Up Contact (phone contact) (see Time and Events Schedule). Approximately 10 pediatric subjects are planned to be enrolled in Part A.

Parental informed consent/child assent (as appropriate, typically at age ≥7 years or as defined by local regulations) must be obtained prior to performing any study-specific procedures. The screening assessments will take place after the Fontan procedure and up to 21 days before the first dose of rivaroxaban. During the screening period, baseline laboratory blood testing will be done and a transthoracic echocardiogram will be performed to rule out thrombosis. Laboratory parameters obtained as part of the post-surgery standard-of-care may be used for screening if they have been done within 21 days prior to receiving the first dose of rivaroxaban. The most recent post-Fontan clinical laboratory results will be used for screening if there are multiple laboratory results. Subjects who do not meet all of the enrollment criteria for the study may be rescreened 1 additional time as long as enrollment is within 4 months of their Fontan procedure. Subjects who are rescreened will be assigned a new subject number, undergo the informed consent process, and then restart a new screening phase.

Subjects who meet all of the inclusion and none of the exclusion criteria will be enrolled and will receive the first dose of rivaroxaban oral suspension on Day 1 (on site). Rivaroxaban will be given twice daily for 12 days (+9 days). Pharmacokinetic and PD samples will be collected on Day 1 and Day 4 (+2 days) of rivaroxaban administration. An internal DRC will assess before the subject returns 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 are allowed to continue the 12-month treatment will also have PK and PD samples collected at Month 3 and Month 12. Safety and efficacy will be evaluated throughout the study. The assessment criteria will be described in the DRC charter.

Randomization in Part B of this study will begin once the cumulative data from the Initial PK, PD, and Safety Assessment Period in Part A are deemed acceptable by the IDMC. The decision tree of rivaroxaban exposure acceptability criteria will be described in the IDMC charter. The IDMC may stop enrollment into Part A and begin enrollment into Part B without changes, recommend to continue enrollment into Part A, or adjust the dose in Part B, depending on the results obtained.

Subjects Participating in Part B

For subjects randomized into Part B, there will be an up to a 21-day Screening Period, a 12-month Open-Label Treatment Period and a 30-day Follow-Up Contact (phone contact) (see Time & Events Schedule). Subjects who do not meet all of the enrollment criteria for the study may be rescreened 1 additional time as long as enrollment is within 4 months of their Fontan procedure. Subjects who are rescreened will be assigned a new subject number, undergo the informed consent process, and then restart a new screening phase. Approximately 90 subjects who meet all of the inclusion and none of the exclusion criteria will be randomly assigned in a 2:1 ratio to receive rivaroxaban oral suspension and ASA for 12 months.

Parental informed consent/child assent (as appropriate, typically at age ≥7 years or as defined by local regulations) must be obtained prior to performing any study-specific procedures. Subjects will undergo the same screening evaluations as in Part A. Eligible subjects will be enrolled and randomized on Day 1 and will receive their first dose of study drug on site at this visit. Pharmacokinetic and PD samples will be obtained on Day 1, Month 3, and Month 12 for subjects randomized to rivaroxaban only. Safety and efficacy will be evaluated throughout the study for all subjects.

Early Study Medication Discontinuation

For subjects in Part A and Part B who prematurely discontinue study drug for any reason, the Early Study Medication Discontinuation (ESMD) visit will be performed as soon as possible after discontinuation. A Follow-Up Contact (phone contact) will be performed 30 days following the last dose of study drug and at Month 12, the end of the planned treatment period. After cessation of the study drug, it is at the investigator's discretion to continue with other antiplatelet/anticoagulant therapy. Every attempt must be made to ensure the subject is not lost to follow up.

Note: An exception are subjects who are enrolled after local reading of the Screening transthoracic echocardiogram rules out thrombosis, and subsequently reported to have thrombosis after central reading by the core laboratory of the same transthoracic echocardiogram. These subjects will be withdrawn from the study when the result of the echocardiogram by the core laboratory becomes available. Subjects will be asked to return for the ESMD visit as soon as possible. They will not be required to have a repeat transthoracic echocardiogram as part of the ESMD. Subjects will go on to receive proper care according to the healthcare provider's judgment. They will be contacted by phone approximately 30 days (+/- 7 days) after last dose of study drug (Follow-Up Contact). An ESMD Month 12 follow up visit will not be required.

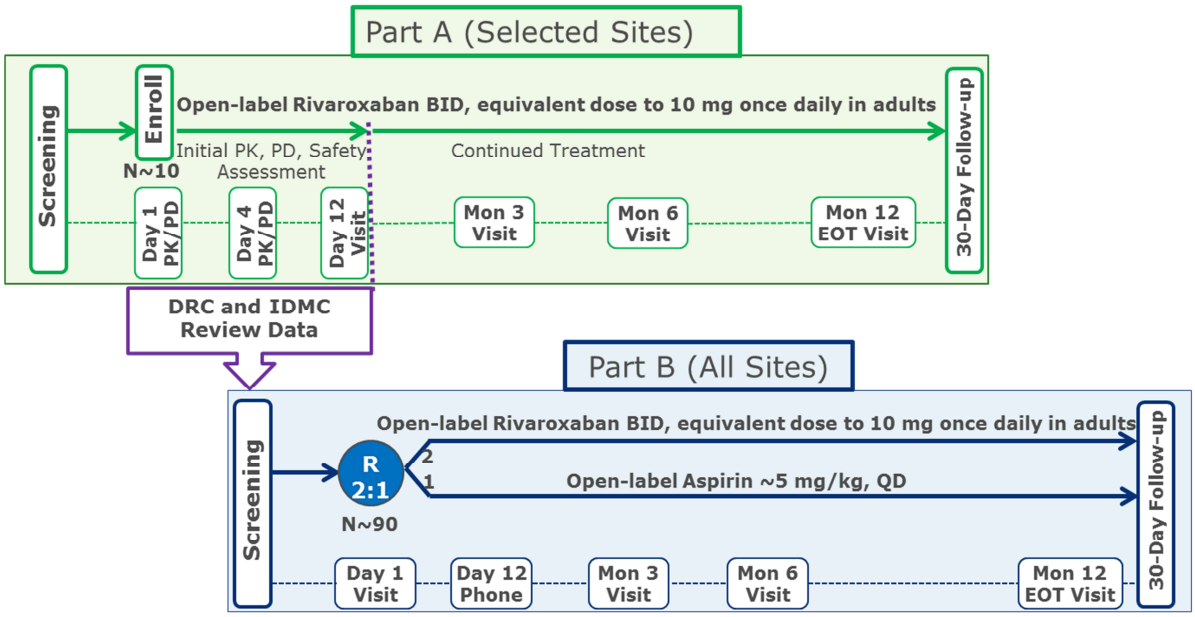
No interim analysis will be performed for this Study. An IDMC will monitor the subject's safety and give recommendations to the Executive Committee (EC). The IDMC has the responsibility to provide the EC and the sponsor with recommendations related to the protection of the pediatric subject's safety, including stopping recruitment and study treatment. For that purpose, the IDMC will regularly review all incidences of serious adverse events, thrombotic events and bleeding events. Organizational aspects, responsibilities, and processes will be described in the IDMC charter.

Committees and Advisors

An EC, an internal DRC, IDMC, a Central Independent Adjudication Committee (CIAC), Steering Committee (SC), and a Sponsor Committee, will be commissioned for this study. Refer to Section 9.7, Committees, for details.

A diagram of the study design is provided below in Figure 1.

Figure 1: Schematic Overview of Study 39039039CHD3001



Key: BID=twice daily, DRC= Data Review Committee, IDMC=Independent Data Monitoring Committee, PD= pharmacodynamics, PK= pharmacokinetic(s)

Note: An internal DRC will assess by Day 12 the PK, PD, and the safety data from each subject, prior to the subject continuing in the study to complete the planned 12 months of open-label rivaroxaban therapy.
Enrollment in Part A will end, and enrollment in Part B will start, once the cumulative data from all subjects in the Initial PK, PD, and Safety Assessment Period of Part A are deemed acceptable by the IDMC.

3.2. Study Design Rationale

Study Population

Young pediatric subjects who have recently completed the initial Fontan procedure were chosen for this study because they are a population with a high thrombotic risk and for whom there is scant evidence-based information regarding thromboprophylaxis. Much of the data for pediatric recommendations for thromboprophylaxis are still extrapolated from adult data. Alternative thromboprophylaxis strategies should be studied in the post-Fontan population in light of the high prevalence of thrombotic events, difficulties achieving consistent protection with current anticoagulant therapy, and the considerable residual risk that remains in children treated with warfarin or ASA. Results from this study would therefore fulfill an unmet medical need.

Two-Part Study

Because this is the first clinical study of rivaroxaban in pediatric post-Fontan subjects, 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 and compare them to those of ASA (Part B). Enrollment in Part B will begin once the cumulative data from the Initial PK, PD, and Safety Assessment Period in Part A are assessed by the IDMC.

Dose and Dosing Regimen, Treatment Period

Because patients with known thrombosis will not be allowed to be enrolled in this study, this population will more closely be similar to a prophylaxis population than a treatment population.

The rivaroxaban dose to be used in this study was determined via an adapted PBPK modeling approach based on previously established and validated rivaroxaban PBPK modeling, used for the VTE pediatric studies and adapted to reflect the special physiology of the pediatric post-Fontan population.[26,24] Rivaroxaban will be administered to the pediatric post-Fontan population as age- and body weight-adjusted dosing targeting exposure (as measured by AUC_{0-24} at steady state), matching that of rivaroxaban 10 mg total daily dose in adults that has been shown to be safe and effective for thromboprophylaxis in adult subjects after major orthopedic surgery (Phase 3 RECORD studies).[32]

The pediatric PBPK model was also used to compare once- or twice-daily dosing options. Twice-daily dosing was chosen because it provided both, a lower C_{max} that stayed completely within the adult reference range and a higher trough plasma concentration (C_{trough}) that was sufficiently high to not fall below the lower adult PBPK modeling range.

No relevant difference in C_{max} is expected between the first dosing day and steady state in the population targeted in this study.

These subjects will be followed for 1 year because thrombus formation is most significant immediately following the Fontan procedure and has been noted to peak within the first postoperative year in particular.[16,17]

PK and PD Sampling Scheme

Pharmacokinetic and PD samples will be drawn on Day 1 and Day 4 of rivaroxaban treatment in Part A with the main goal of obtaining initial assessment of rivaroxaban exposure. Pharmacokinetic and PD samples will also be drawn at Month 3 and Month 12, to further enrich and refine the initial PK/PD model and to evaluate any adjustment in dose made at Month 6 due to the subjects' weight gain.

Comparator Selection

Subjects in Part B are randomized to ASA as the appropriate comparator to allow for the evaluation of benefit/risk of rivaroxaban as a thromboprophylactic agent in pediatric subjects who have single-ventricle physiology and who have completed the Fontan procedure. This decision was made based on careful consideration of the literature, existing guidelines for the standard-of-care practice, and current clinical practice in many centers.

Current American College of Chest Physicians 2012 guidelines recommend ASA, or unfractionated heparin followed by warfarin for this patient population.[12] The American Heart Association, in a statement in 2013, suggested that long-term antiplatelet therapy for prevention of thrombosis is reasonable after the Fontan procedure and that prophylaxis with warfarin or LMWH may be reasonable after the Fontan procedure for patients with anatomic or hemodynamic risk factors.[11] However, controversy remains in clinical practice as to the optimal prevention strategy to be followed, as there are no evidence-based recommendations.[11,12] The only prospective, multicenter, randomized study published showed a similar cumulative risk for thrombosis between ASA (5 mg/kg/day) and heparin/warfarin treatment.[20] In a secondary analysis of this study, risk reduction was observed in a small subset of subjects in the warfarin group who had adequate INR levels and in those on ASA, compared with subjects in the warfarin group with a high prevalence of sub therapeutic INR measurements (<30% INR measurements within the target range).[18] These subjects had a significantly greater risk of thrombosis than those subjects who received ASA therapy alone. Because the factors associated with poorly controlled warfarin therapy in these subjects have not been identified yet, the authors of the study concluded that ASA might be the best current strategy to prevent thrombosis for this patient population.[18] Using ASA as the comparator in this study 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 Fontan procedure).

A new oral anticoagulant such as rivaroxaban, which demonstrated in studies in adults to be noninferior regarding efficacy but with more predictable and stable PK and easier to dose, may be a potential alternative to ASA or VKA treatment in the post-Fontan population.

Open-label and Randomization

Randomization will be used in Part B to minimize bias in the assignment of subjects to treatment groups, to increase the likelihood that known and unknown subject attributes (eg, demographic and baseline characteristics) are evenly balanced across treatment groups, and to enhance the validity of the descriptive comparisons between treatment groups. Open-label treatment will be used to allow for further evaluation of the PK and PK/PD profiles of rivaroxaban throughout the study.

Safety Assessments

As with any anticoagulant agent, the use of rivaroxaban is associated with an increased risk of bleeding events. Bleeding events will be assessed using the International Society on Thrombosis and Hemostasis (ISTH) classification to be consistent with the other rivaroxaban pediatric VTE treatment studies.[5,27] All bleeding events will be adjudicated by the CIAC.

Efficacy Assessment

The efficacy outcomes of any thrombotic event (venous or arterial), 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), are accepted, validated, clinical endpoints for the evaluation of thromboprohylaxis. All transthoracic echocardiograms will be taken under a standardized protocol and will be read in a blinded manner at a central laboratory to minimize inter-site variability and bias.

4. SUBJECT POPULATION

Screening for eligible subjects will be performed within 21 days before administration of the study drug.

The inclusion and exclusion criteria for enrolling subjects in this study are described in the following 2 subsections. If there is a question about the inclusion or exclusion criteria below, the investigator must consult with the appropriate sponsor representative and resolve any issues before enrolling a subject in the study. Waivers are not allowed.

For a discussion of the statistical considerations of subject selection, refer to Section 11.2, Sample Size Determination.

4.1. Inclusion Criteria

Each potential subject must satisfy all of the following criteria to be enrolled in the study.

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 enrollment

2. Considered to be clinically stable by the investigator and 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 must sign an informed consent form (ICF) and child assent will also be provided, if applicable, according to local requirements.

4.2. Exclusion Criteria

Any potential subject who meets any of the following criteria will be excluded from participating in the study.

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 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. Criterion modified per Amendment INT-2

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

   - A subject who has received 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 on 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 NSAIDs

7. Platelet count $<50 \times 10^9$/L at screening

8. Criterion modified per Amendment INT-2

8.1. Estimated glomerular filtration rate (eGFR) <30 mL/min/1.73m^2 (Attachment 3)

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

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

11.1. Known allergies, hypersensitivity, or intolerance to rivaroxaban, ASA or its excipients (Investigator's Brochure)[14]

12. Inability to cooperate with study procedures

13. Combined P-gp and strong 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 only

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

17. 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 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

NOTE: Investigators should ensure that all study enrollment criteria have been met at screening. If a subject's status changes (including laboratory results or receipt of additional medical records) after screening but before the first dose of study drug is given such that he or she no longer meets all eligibility criteria, then the subject should be excluded from participation in the study. Section 17.4, Source Documentation, describes the required documentation to support meeting

the enrollment criteria. Subjects who do not meet all of the enrollment criteria for the study may be rescreened 1 additional time as long as enrollment is within 4 months of their Fontan procedure. Subjects who are rescreened will be assigned a new subject number, undergo the informed consent process, and then restart a new screening phase.

Modification of an effective preexisting therapy should not be made for the explicit purpose of entering a subject into the study.

4.3. Prohibitions and Restrictions

Refer to Section 8, Prestudy and Concomitant Therapy, for details regarding prohibited and restricted therapy during the study.

5. TREATMENT ALLOCATION AND BLINDING

Subjects in Part A will not be randomized.

Treatment Allocation

Procedures for Randomization in Part B

Subjects will be randomly assigned to 1 of 2 treatment groups based on a computer-generated randomization schedule prepared before the study by or under the supervision of the sponsor. The randomization ratio will be 2:1 for rivaroxaban and ASA. The randomization will be balanced by using randomly permuted blocks. Based on this randomization code, the study drug will be packaged and labeled for each subject. Study drug code numbers will be preprinted on the study drug labels and assigned as subjects qualify for the study and are assigned to treatment.

The interactive web response system (IWRS) will assign a unique treatment code for each subject, which will dictate the treatment assignment and matching study drug kit for the subject. The requestor must use his or her own user identification and personal identification number when contacting the IWRS to receive the relevant subject details to uniquely identify the subject.

Blinding

As this is an open-label study, blinding procedures are not applicable.

6. DOSAGE AND ADMINISTRATION

Rivaroxaban: The rivaroxaban dose to be used in this study was determined via an adapted PBPK modeling approach.[26] Rivaroxaban will be administered twice daily in an open-label fashion as a 0.1% (1 mg/ml) oral suspension with target exposure (AUC_{0-24} at steady state) matching to that of rivaroxaban 10 mg total daily dose in adults (age- and body weight-adjusted dosing [see Table 1]). Because children with an estimated glomerular filtration rate below 30 mL/min/1.73 m^2 are excluded from the study, dose reduction for impaired renal function is not required. Rivaroxaban will be taken in the morning and in the evening (approximately 12 hours apart) at approximately the same times each day as described in the study booklet. Dose adjustment, due to increased body weight, will be made at Month 6 (both Part A and Part B).

Table 1: Dosing Table for Rivaroxaban Administration

Body weight [kg][a]	BID Dose[b] [mg or mL]	Total Daily Dose[c] [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) For subjects with body weight outside of the range provided in this table, please contact the sponsor for dosing information.
b) Oral suspension 0.1% (1 mg/mL)
c) Equivalent to exposure of 10 mg once daily in adults

ASA: Acetylsalicylic acid will be provided as 81-mg or 100-mg tablets according to local practice. Subjects randomized to ASA will receive approximately 5 mg/kg of ASA to a maximum of 1 whole tablet as a single daily dose as described in the study booklet. Tablets can be split in half, if necessary (eg. children weighing ≤10 kg), to meet the daily dose, and the dose must be documented. It is recommended that tablets are not split more than in half. Dose adjustments due to increased body weight, will be made at Month 6.

Temporary discontinuation of the study drug is allowed for events, such as intercurrent illnesses. In this case, standard clinical practice should be followed. See Section 10.2.1, Temporary Discontinuation of Study Treatment. All interruptions of study drug must be recorded in the eCRF.

Throughout the study, study drug will be dispensed at appropriate intervals (see the Time and Events Schedule) to ensure that subjects have adequate quantities of study drug between study visits. Study-site personnel will instruct parents/legally acceptable representatives on the proper administration and storage of study drug for at-home use.

Detailed instructions on the administration of the oral suspension will be provided in the study booklet.

Missed Dose

Rivaroxaban: is taken in a twice daily regimen. A missed morning dose should be taken immediately when it is noticed, any time during the calendar day, which could include taking it together with the evening dose. A missed evening dose should only be taken in the same evening. On the following day, the subject should continue with the regular twice daily regimen. A missed dose from a previous calendar day should not be taken.

ASA: if a dose of ASA is missed the subject should take the missed dose immediately when it is noticed within the same calendar day. On the following day, the subject should continue with the regular once daily regimen. A missed dose from a previous calendar day should not be taken.

Intentional stopping of study drug by the subject, unintentional stopping of study drug for more than 7 consecutive days, or temporary stopping of study drug as directed by the investigator or other physician will be documented. Study drug interruptions will be recorded in the eCRF.

Vomiting and/or Spitting After Dosing

If the subject immediately vomits and/or spits up the dose within 30 minutes after receiving a dose of study medicine (rivaroxaban or ASA), a second dose should be given. If the subject vomits more than 30 minutes after the first dose, a second dose must not be given to replace it. The parent should contact the study team if the subject spits up the dose or vomits after receiving the study medicine multiple times either the same day or on different days.

7. TREATMENT COMPLIANCE

The IWRS in Part A and Part B will keep track of study drug dispensed to the subjects.

The investigator or designated study-site personnel will maintain a log of all study drug dispensed and returned. Drug supplies for each subject will be inventoried and accounted for throughout the study.

8. PRESTUDY, CONCOMITANT AND POSTSTUDY THERAPY

Any previous anticoagulant/antiplatelet medication taken after the Fontan procedure and prior to first dose of study drug will be documented as prestudy therapy.

Concomitant medications include all medications received between the first dose and the last dose of study drug.

Any anticoagulant/antiplatelet medication initiated after the end of the study treatment period will also be documented on the concomitant medication eCRF page (see Section 9.1.5, Posttreatment Period [Follow-Up Contact]).

Concomitant therapies (prescription or over-the-counter medications, including vaccines, vitamins, herbal supplements) must be recorded throughout the study according to the Time and Events Schedule.

Prohibited Therapy

For All Subjects in the Study:

The use of any other antiplatelet, anticoagulant (other than study drug) taken concomitantly with study drug is prohibited.

Chronic NSAID therapy is prohibited during the study.

Modification of an effective preexisting therapy should not be made for the explicit purpose of entering a subject into the study.

The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered

For Subjects Receiving Rivaroxaban only:

Combined P-gp and strong CYP3A4 inhibitors (such as but not limited to ketoconazole, telithromycin, or protease inhibitors) use is prohibited within 4 days before enrollment, or during the study. Itraconazole use is prohibited within 7 days before enrollment or 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 is prohibited within 2 weeks before enrollment, or planned use during the study is prohibited.

Planned use of drugs that are moderate CYP3A4 inhibitors (such as erythromycin or fluconazole) are not allowed during the Initial PK, PD, and Safety Assessment Period of Part A only. However, they are allowed during the 12-month Open-Label Treatment Periods of Part A and Part B.

Allowed Therapy

Subjects can receive ASA during the screening period and up to 24 hours prior to the first dose of study drug at Day 1 Visit.

A subject who has received 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 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.

Occasional use of NSAID is allowed, but the lowest possible dosage and shortest duration should be selected.

9. STUDY EVALUATIONS

9.1. Study Procedures

9.1.1. Overview

The Time and Events Schedule summarizes the frequency and timing of PK, PD, safety, and efficacy measurements applicable to this study.

The study consists of 2 parts:

- Part A of the study has an up to 21-day Screening Period, a 12-Month Open-Label Treatment Period (which includes a 12-day Initial PK, PD, and Safety Assessment Period), and a 30-day Follow-up Contact
- Part B of the study has an up to 21-day Screening Period, a 12-Month Open-Label Treatment Period and a 30-day Follow-up Contact

For each subject in Part A, blood samples will be obtained at the timepoints noted in the Time and Events Schedule; the estimated amount of blood drawn in this study will be approximately 33 mL over 12 months (a maximum of approximately 3.5 mL on each blood draw, except for 1 blood draw each at the Month 3 and Month 12 visits, where 4.5 ml will be drawn). For details on the volumes and types of blood samples to be collected, see table in Attachment 1.

For each subject in Part B, blood samples will be obtained at the timepoints noted in the Time and Events Schedule; the estimated amount of blood drawn in Part B will be approximately 25 mL over a 12-month period (a maximum of approximately 3.5 ml on each blood draw, except for 1 blood draw at the Month 12 visit, where 4.3 ml will be drawn). For details, see table in Attachment 1.

9.1.2. Screening Period

Subjects Participating in Part A

Parental informed consent/child assent (as appropriate) must be obtained prior to performing any study-specific procedures. The screening assessments will take place after the Fontan procedure and up to 21 days before the first dose of study drug. During the screening period, baseline laboratory blood testing will be done and a transthoracic echocardiogram using a study-specific protocol (see Attachment 2) will be performed to rule out thrombosis. Laboratory parameters obtained as part of the standard-of-care may be used as baseline safety if conducted within 21 days prior to receiving the first dose of rivaroxaban. The most recent post-Fontan clinical laboratory results will be used for screening if there are multiple laboratory results. Subjects who do not meet all of the enrollment criteria for the study may be rescreened 1 additional time as long as enrollment is within 4 months of their Fontan procedure. Subjects who are rescreened will be assigned a new subject number, undergo the informed consent process, and then restart a new screening phase.

All screening activities must be completed before enrollment and the results must be available to the investigator for review to ensure that eligibility criteria are met. The IWRS will assign a unique subject identification number.

Subjects Participating in Part B

Parental informed consent/child assent (as appropriate) must be obtained prior to performing any study-specific procedures. Subjects will undergo the same screening evaluations as in Part A except for PT and aPTT testing which will be performed on Day 1 prior to first dose of study drug.

All screening activities related to establishing eligibility must be completed before randomization and the results must be available to the investigator for review to ensure that eligibility criteria are met. Subjects may be enrolled and randomized on the business day prior to Day 1 to facilitate logistics provided the investigator ensures that the subject meets all eligibility criteria prior to randomization. The first dose of study drug will be administered on site on Day 1 if the subject is still eligible.

9.1.3. Open-label Treatment Period

9.1.3.1. Part A

There will be up to 7 planned study visits and 1 telephone contact:

- Visit 1 - Screening visit (up to 21 days prior to the first dose of study drug)
- Visit 2-D1 – Enrollment and PK and PD sampling after first dose of study drug administered on site, dispense drug supply (Day 1)
- Visit 2-D4 – PK and PD sampling before and after the Day 4 dose of rivaroxaban (Day 4)
- Visit 2-D12 – Communicate to subject if rivaroxaban treatment will be continued. Physical examination and dispense 3-month drug supply (Day 12)
- Visit 3 – Physical examination, PK, PD, and dispense 3-month drug supply (Month 3)
- Visit 4 – Physical examination, transthoracic echocardiogram, adjustment of dose (if needed), and dispense 6-month drug supply (Month 6)
- Visit 5 - Physical examination, PK, PD, transthoracic echocardiogram, lab testing, final visit (Month 12)
- Phone call – Follow-Up Contact

Approximately 10 subjects are planned to be enrolled in Part A. Subjects will receive the first dose of rivaroxaban on Visit2/Day1 (on site). Any visit may take place while the subject is hospitalized.

On Day 1 and Day 4, blood samples for PK and PD assessments will be collected by venipuncture. Ideally, an intravenous line could be placed by an experienced pediatric phlebotomist on the days of multiple blood draws. For the detailed schedule see Section 9.2, Pharmacokinetics/Pharmacodynamics Evaluations.

Pharmacokinetic and PD (PT and aPTT tests) blood samples will be sent to the central laboratory after the collection of the last sample on Day 4 (ie, after the 6.0 to 8.0 hour sample). Results are anticipated to be available for DRC review 4 to 6 days after the samples are received by the central laboratory.

An internal DRC will review the subject's PK, PD and safety data obtained from the Initial PK, PD, and Safety Assessment Period prior to allowing the subject to continue on rivaroxaban therapy to complete the 12-month period. The sponsor will notify the investigator about the DRC decision prior to Visit 2-D12 (+ 9 days). At this visit, the subject will either be informed to continue on rivaroxaban in the 12-month Open-Label Treatment Period or be discontinued from the study.

Subjects who continue on in the Open-Label Treatment Period will have up to 3 more planned visits: after 3 months (Visit 3), after 6 months (Visit 4), and after 12 months (Visit 5/End of Study), and a Follow-Up Contact (phone contact) will be performed 30 days following the last dose of rivaroxaban.

Transthoracic echocardiograms will be obtained at screening, Month 6, and at the end of the study (Month 12) or ESMD (for details see Section 9.1.6, Transthoracic Echocardiograms). PK and PD blood samples will be collected at Month 3 and at Month 12. Safety and efficacy will be evaluated throughout the study.

Enrollment in Part A will end, and enrollment in Part B will start, once the cumulative data from the Initial PK, PD, and Safety Assessment Period are deemed acceptable by the IDMC. Assessment criteria will be described in the IDMC charter.

For Safety and Efficacy evaluations see Section 9.3, Safety Evaluations/Outcomes, and Section 9.4, Efficacy Evaluations/Outcomes, respectively.

9.1.3.2. Part B

Enrollment in Part B of this study will begin after enrollment in Part A ends. This recommendation will be made by the IDMC.

There will be up to 5 planned study visits and 2 phone contacts:

- Visit 1 – Screening visit (up to 21 days prior to the first dose of study drug)
- Visit 2 – enrollment, randomization, PK and PD sampling and first dose of study drug administration on site; dispensation of 3-month drug supply (Day 1)
- Phone call - after 12 days of the start of study drug
- Visit 3 – Physical examination, PK, PD, and dispense 3-month drug supply (Month 3)
- Visit 4 – Physical examination, transthoracic echocardiogram, adjustment of dose (if needed), and dispense 6-month drug supply (Month 6)
- Visit 5 – Physical examination, PK, PD, transthoracic echocardiogram, lab testing, final visit (Month 12)

- Phone call – Follow-Up Contact, 30 days after last study drug is taken.

Approximately 90 subjects are planned to be enrolled in Part B. Any visit may take place while the subject is hospitalized.

Subjects will be enrolled and randomized on Visit 2/Day 1 after meeting inclusion and exclusion criteria. Subjects may be enrolled and randomized on the business day prior to Day 1 to facilitate logistics provided the investigator ensures that the subject meets all eligibility criteria prior to randomization. The first dose of study drug will be administered on site on Day 1 if the subject is still eligible. Subjects will be contacted by phone at approximately 12 days (± 9 days) after the first dose to obtain safety and efficacy information after the start of study drug. Visits 3 and 4 are treatment visits and occur after 3 months and 6 months of therapy, respectively. Visit 5 is the end of study visit (Month 12). Transthoracic echocardiograms will be obtained at screening, at Month 6, and at the end of the study (Month 12), or ESMD visit (for details see Section 9.1.6, Transthoracic Echocardiograms). Safety and efficacy will be evaluated throughout the study.

For subjects randomized to rivaroxaban, blood samples for PK and PD evaluations will be collected. For details see Section 9.2, Pharmacokinetics/Pharmacodynamics Evaluations.

For Safety and Efficacy evaluations see Section 9.3, Safety Evaluations/Outcomes, and Section 9.4, Efficacy Evaluations/Outcomes, respectively.

9.1.4. Unscheduled Visits

Additional site visits may be added as necessary, at the discretion of the investigator.

9.1.5. Posttreatment Period (Follow-Up Contact)

In both Part A and Part B, all subjects will be contacted by phone at the following time periods:

1. Subjects who complete the 12-Month treatment period or subjects who are withdrawn from the study will receive 1 phone contact: Approximately 30 days (+/-7 days) after last dose taken (Follow-Up Contact). A review of safety and efficacy outcomes will be conducted at this contact and any concomitant medications will be recorded.
2. Subjects who permanently discontinue study drug early but continue in (are not withdrawn from) the study will receive 2 phone contacts: Approximately 30 days (+/- 7 days) after last dose taken (Follow-Up Contact) to review safety and efficacy outcomes and any concomitant medications; and at the end of the planned treatment period (ESMD 12 Month follow up) to determine their vital status and thrombotic events (no bleeding events).

Transition at End-of-Treatment

If at the end of study treatment a decision is made to continue a subject on an anticoagulant or ASA, the following guidelines are provided:

- Subjects who switch from rivaroxaban to heparin/LMWH/fondaparinux can switch at the time of the next scheduled dose.

- Subjects who switch from rivaroxaban to VKA need to continue rivaroxaban for 48 hours after the first dose of VKA. After 2 days of co-administration, an INR should be obtained prior to the next scheduled dose of rivaroxaban. Co-administration of rivaroxaban and VKA is advised to continue until the INR is ≥2.0.
- Subjects who switch from rivaroxaban to ASA can switch to ASA at the time of the next scheduled dose.

Any anticoagulant/antiplatelet medication initiated at the end of the study treatment period will be documented on the concomitant medication eCRF page.

9.1.6. Transthoracic Echocardiograms

Transthoracic echocardiograms will be obtained according to the timepoints noted in the Time and Events Schedule for the assessment of thrombotic events. For the Screening post-Fontan transthoracic echocardiogram, the Post-Fontan Echocardiographic Examination protocol in Attachment 2 is to be followed, and the following guidelines will be applicable:

- The subject is not to be enrolled if local reading of the Screening transthoracic echocardiogram confirms thrombosis. The subject's transthoracic echocardiogram will not need to be sent to the core laboratory.
- The subject may be enrolled if local reading of the Screening transthoracic echocardiogram rules out thrombosis and the remaining inclusion/exclusion criteria are satisfied. The Screening transthoracic echocardiogram is to be sent to the core laboratory for central reading.
- The subject will be withdrawn from the study if the subject is enrolled after local reading rules out thrombosis on the transthoracic echocardiogram and subsequently central reading by the core laboratory reports a thrombosis from the same transthoracic echocardiogram. The reasoning for the early withdrawal will be documented on the eCRF.

The core laboratory report will serve as the baseline for the comparison of the subsequent study transthoracic echocardiograms.

Investigators can image as often as medically necessary or as needed based on their institution's standard-of-care; however, protocol-based imaging must be performed according to the timepoints noted in the Time and Events Schedule. Echocardiograms will be sent to a core laboratory for blinded reading and to minimize inter-site variability and bias. During the course of the study, for subjects who prematurely discontinue study drug for any reason, the final echocardiogram will be performed as soon as possible after discontinuation at the ESMD visit. A detailed description of the echocardiogram core laboratory process will be provided in a separate manual. The Post-Fontan Echocardiographic Examination protocol is provided in Attachment 2.

9.2. Pharmacokinetics/Pharmacodynamics Evaluations

Blood samples for rivaroxaban PK and PD, including rivaroxaban plasma concentration, absolute PT, activated partial thromboplastin time (aPTT) and anti-FXa activity measurements will be taken from pediatric subjects enrolled in Part A and for subjects randomized to rivaroxaban in Part B at the timepoints noted in the Time and Events Schedule. Rivaroxaban

plasma concentration will be determined using the validated liquid chromatography/mass spectrometry/mass spectrometry (LC-MS/MS) method. The dosing, exact time of rivaroxaban administration and PK and PD blood sampling will be documented in the eCRF. The exact time must be documented even if PK and PD samples are taken outside of the prespecified time window.

Ideally, PK and PD blood samples will be collected by venipuncture by an experienced pediatric phlebotomist. A local anesthetic cream can be applied at the venipuncture site to decrease discomfort.

If blood samples are collected via an indwelling cannula, an appropriate amount (eg, 1 mL) of fluid slightly greater than the dead space volume of the lock will be removed from the cannula before each blood sample is taken (see Section 9.5, Sample Collection and Handling for more details).[8]

Detailed information about the handling and labeling of the samples will be provided in the laboratory manual.

Part A

Pharmacokinetic and PD blood samples will be collected on the first day of dosing (Visit 2/D1) between 0.5 to 1.5 hours and again between 1.5 to 4.0 hours postdose. Additional samples will be collected on Day 4 (Visit 2/D4), just prior to dose administration and again between 0.5 to 1.5 hours, 1.5 to 4.0 hours, and 6.0 to 8.0 hours postdose. Pharmacokinetic and PD samples will be sent to the central laboratory after the collection of the last sample on Day 4 (ie, the 6.0 to 8.0 hour sample).

Rivaroxaban plasma concentration will be determined using the validated LC-MS/MS method. The blood samples on Day 1 and Day 4 will be taken as specified in Table 2. See Attachment 1 for details.

Pharmacokinetic and PD samples will also be taken at Month 3 and Month 12. See the Time and Events Schedule and Attachment 1 for details.

If rivaroxaban is temporarily stopped, PK and PD blood samples should only be obtained if rivaroxaban administration has been restarted and sustained for at least 3 days.

Table 2: Sampling Schedule of the Initial PK, PD, and Safety Assessment Period (Day 1 and Day 4-6) (Part A)[a]

	Visit 2-D1/ Day 1		Visit 2-D4/ Day 4[b]			
	Postdose[c] 0.5-1.5 hours	Postdose[c] 1.5-4 hours[e]	Predose[c,d]	Postdose[c] 0.5-1.5 hours	Postdose[c] 1.5-4 hours[e]	Postdose[c] 6.0-8 hours
PK[f]	0.6 ml	0.6 ml	0.6 ml	0.6 ml	0.6 ml	0.6 ml
PD-1[g]	1.4 ml	1.4 ml	1.4 ml	1.4 ml	1.4 ml	1.4 ml
PD-2[h]	1.4 ml	1.4 ml	-	-	-	1.4 ml

D1=Day 1; D4=Day 4; PD=pharmacodynamics; PK=pharmacokinetics.

a) Subjects continuing in Part A will also have additional PK and PD assessments at Months 3 and 12. See Time and Events Schedule and Section 9.2, Pharmacokinetics/Pharmacodynamics Evaluations, for details.
b) Visit 2-D4 can be performed on Days 4, 5, or 6.
c) Sampling times are relative to morning dose.
d) Up to 3 hours predose.
e) Allow at least 30 minutes from the previous sample.
f) Blood volume per PK sample for rivaroxaban plasma concentration is approximately 0.6 mL; total blood volume for all PK samples is 3.6 mL (Day 1: 1.2 mL; Day 4: 2.4 mL); sites will send samples to the central laboratory on the day of collection for liquid chromatography/mass spectrometry/mass spectrometry (LC-MS/MS) determination.
g) PD-1 assessments will include prothrombin time (PT) and activated partial thromboplastin time (aPTT). Blood volume per PD-1 sample is approximately 1.4 mL; total blood volume for all PD-1 samples is 8.4 mL (Day 1: 2.8 mL; Day 4: 5.6 mL). Sites will send samples to the central laboratory after Day 4 of collection.
h) PD-2 assessment will be anti-FXa activity. Blood volume per PD-2 sample is approximately 1.4 mL; total blood volume for all PD-2 samples is 4.2 mL (Day 1: 2.8 mL; Day 4: 1.4 mL). Sites will send samples to the central laboratory.

Part B

Pharmacokinetic and PD samples will also be collected and analyzed for subjects randomized to rivaroxaban in Part B. Pharmacokinetic and PD blood samples will be collected on the first day of dosing (Visit 2/D1) before first dosing (PT and aPTT only), between 0.5 to 1.5 hours and again between 1.5 to 4.0 hours postdose. Additional samples will be collected at Month 3 and Month 12. Please see Time and Events Schedule and Attachment 1 for details.

If rivaroxaban was temporarily stopped, PK and PD blood samples for Month 3 and Month 12 should only be obtained if rivaroxaban administration has been restarted and sustained for at least 3 days prior to the sampling.

9.3. Safety Evaluations/Outcomes

9.3.1. Bleeding Events

The primary safety outcome will be major bleeding events, as defined below. Clinically relevant non-major bleeding events and trivial (minimal) bleeding will be secondary safety outcomes.

Bleeding events will be adjudicated by CIAC using the ISTH recommendations.[5,27] The following bleeding criteria are consistent across the rivaroxaban pediatric program:

Major bleeding is 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 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 is 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 is defined as any other overt bleeding event that does not meet criteria for clinically relevant non major bleeding.

9.3.2. Approach to the Subject with a Bleeding Event

If a subject has a serious bleed during study treatment, the following routine measures could be considered by the treating physician:

- Consider usual treatment for bleeding, including blood transfusion, and/or fresh frozen plasma if needed
- Consider that other causes besides thromboprophylaxis medication can be contributory to the seriousness of the bleeding event (eg, thrombocytopenia, and other coagulopathies; kidney and liver dysfunction; concomitant medications), and treat accordingly
- Delay the next ASA or rivaroxaban administration or temporarily discontinue treatment, if indicated

- If the subject is treated with rivaroxaban, a blood sample for PK and PD testing should be obtained

NOTE: Partial reversal of prothrombin time prolongation has been seen after administration of prothrombin complex concentrates (PCCs) in healthy volunteers. The use of other procoagulant reversal agents like activated prothrombin complex concentrate (APCC) or recombinant factor VIIa (rFVIIa) has not been evaluated.

If severe bleeding cannot be controlled, however, consider administration of one of the following procoagulants (both according to the dosages advised in the package insert):

- 4 factor concentrate
- Recombinant factor VIIa (NovoSeven®)

Protamine sulfate and vitamin K are not expected to affect the anticoagulant activity of rivaroxaban.

Any products administered to control bleeding should be entered in the CRF.

Parents/ legally acceptable representatives should call the study physician, if the subject has signs and symptoms of clinically significant bleeding, for example:

- bleeding (eg, nose or gum bleeding) that does not stop within 10 minutes
- coughing or throwing up blood
- dark-colored urine or black stools
- red or black-and-blue marks on the skin that get larger

If the subject has a bleeding incident, the parent/ legally acceptable representatives should consult the study physician in addition to their own cardiologist (if different) and always inform him/her of the date/time the subject took the last dose of anticoagulant medication. For severe bleeding, subjects should be moved to the nearest emergency room.

After resolution of the bleeding event, restarting study drug may be considered based on the clinical judgment of the investigator.

9.3.3. Other Safety Assessments

The safety and tolerability of rivaroxaban will also be evaluated by assessing other adverse events and clinical laboratory test values.

Any clinically relevant changes, including laboratory reports, occurring during the study must be recorded on the Adverse Event section of the eCRF. Any clinically significant abnormalities persisting at the end of the study/early withdrawal will be followed by the investigator until resolution or until a clinically stable endpoint is reached.

The study includes the evaluations of safety and tolerability according to the time points provided in the Time and Events Schedule.

Adverse Events

Adverse events will be reported by the parents/legally acceptable representatives for the duration of the study up to the Follow-Up Contact (30-days after last dose). Adverse events will be followed by the investigator as specified in Section 12, Adverse Event Reporting.

Clinical Laboratory Tests

The following tests results with reference ranges will be obtained at the visits specified in the Time and Events Schedule. Either hospital laboratory/local laboratory results or central laboratory results are acceptable at the time of study screening period. A central laboratory will be used during the rest of the study:

- Hematology Panel
  - hemoglobin
  - hematocrit
  - red blood cell (RBC) count[a]
  - white blood cell (WBC)[b] count
  - WBC differential[b]:
    - neutrophils
    - lymphocytes
    - monocytes
    - eosinophils
    - basophils
  - platelet count
- Serum chemistry
  - creatinine (eGFR will be calculated using the original or the modified Schwartz formula for pediatric population, see Attachment 3)[29]
  - liver function tests (ALT, aspartate aminotransferase [AST], total and direct bilirubin, alkaline phosphatase)
- PT, aPTT tests

[a] A RBC evaluation may include abnormalities in RBC count and/or RBC parameters (eg, reticulocyte count) and/or RBC morphology, which will then be reported by the laboratory

[b] A WBC evaluation may include any abnormal cells, which will then be reported by the laboratory. In addition, any other abnormal cells in a blood smear will also be reported.

9.4. Efficacy Evaluations/Outcomes

The primary efficacy outcome will be 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, pulmonary embolism).

Subjects who develop either a symptomatic or asymptomatic thrombotic event during the study must permanently discontinue the study drug. All thrombotic events and the primary cause of any death will be adjudicated by the CIAC. Transthoracic echocardiograms will be centrally read by an echocardiographic core laboratory. All available imaging results (eg, transthoracic or transesophageal echocardiograms, or MRIs), should be sent to the CIAC. Sites will be required to complete a worksheet, compile an adjudication package, and send it to the adjudication office within 6 weeks from occurrence of the event.

After cessation of the study drug, it is at the investigator's discretion to continue with other antithrombotic therapy. The investigator should document this therapy in the eCRF. Thrombotic events will not be reported as adverse events or serious adverse events, as they will be reported as efficacy outcomes, which will be documented in the eCRF.

9.5. Sample Collection and Handling

The actual dates and times of sample collection must be recorded in the eCRF or laboratory requisition form.

If blood samples are collected via an indwelling cannula, an appropriate amount (eg, 1 mL) of fluid slightly greater than the dead space volume of the lock will be removed from the cannula before each blood sample is taken. If a blood sample is taken from a central line, at least 3 mL of blood should be withdrawn prior to collecting study blood samples. Investigators should follow their institution's policy for discarding or re-infusing withdrawn blood. Heparin can be used to maintain catheter patency; however, before collecting PK/PD samples, the catheter needs to be flushed with saline and the first volume of (diluted) blood should be withdrawn, as described above.

Refer to the Time and Events Schedule for the timing and frequency of all sample collections.

Instructions for the collection, handling, storage, and shipment of samples are found in the laboratory manual that will be provided. Collection, handling, storage, and shipment of samples must be under the specified, and where applicable, controlled temperature conditions as indicated in the laboratory manual.

9.6. Study Booklet

Parents/legally acceptable representatives will receive a study booklet in Part A and Part B including information on:

- Instructions to return empty study drug packages and unused study drug
- Instructions on signs and symptoms of bleeding
- Instructions on how to report any adverse event occurring within the reporting period.

For the rivaroxaban treatment group:

- Rivaroxaban will be provided in a glass bottle with a child-resistant screw cap. An adaptor and a dosing pipette will be provided to support drug administration. Rivaroxaban should be stored according to the label.

For the ASA group:

- Acetylsalicylic acid will be provided in child-resistant packaging. The ASA tablets should be stored according to the local approved product label.

9.7. Committees

9.7.1. Executive Committee

The EC will provide overall academic leadership for the study and will oversee the conduct of the study and the publication of the results. In addition, the EC will receive recommendations from the IDMC and SC regarding modifications to the study and will decide whether to accept the recommendations. The EC will have 2 co-chairs and will consist of members of academic institutions and 1 member from the sponsor.

9.7.2. Independent Data Monitoring Committee

The IDMC will evaluate PK, PD, safety and efficacy data to ensure subject safety throughout the study. The IDMC will be 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 will provide the recommendation to the EC and Sponsor Committee to cease enrollment in Part A and to start enrollment directly into Part B. The IDMC will operate for both Part A and Part B. The decision tree of rivaroxaban exposure acceptability criteria will be described in the IDMC charter.

9.7.3. Data Review Committee

The DRC consists of members from the sponsor not directly involved in the conduct of the study, who will evaluate the PK and safety of each subject in Part A, and who will evaluate that information relative to the PBPK model predictions. The DRC will assess before the subject returns for Day 12 Visit 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 DRC will only operate during Part A.

9.7.4. Central Independent Adjudication Committee

The CIAC is comprised of specialist physicians as appropriate and necessary. Committee members do not directly enroll subjects in the study, are not involved in the study monitoring, and do not have direct operational responsibilities for the conduct of the study. Members will review all safety and efficacy outcomes that occur post-enrollment as they become available and adjudicate and classify the following events in a consistent and unbiased manner according to definitions in the CIAC charter while blinded to treatment assignment:

Safety and efficacy outcomes include bleeding events, any thrombotic event (venous or arterial), other vascular events as listed in Section 9.4, and deaths that occur during the study and the 30-day post study treatment period.

The CIAC procedures will be described in the CIAC charter. Adjudication results will be the basis for the final analyses.

9.7.5. Steering Committee

The SC will advise and assist the EC with regard to the scientific and operational aspects of the study. Details of the composition, roles, and responsibilities will be documented in the SC charter.

9.7.6. Sponsor Committee

The Sponsor Committee is responsible for communicating the IDMC recommendations within the Sponsor and identifying appropriate actions based on the recommendations of the IDMC.

10. SUBJECT COMPLETION/WITHDRAWAL

10.1. Completion

A subject will be considered to have completed the study if the subject completes:

- The Follow-Up Contact 30 days after the last dose of study drug taken for subjects who complete the 12 month treatment
- The ESMD Month 12 Follow-Up for subjects who discontinue the study drug prematurely

10.2. Discontinuation of Study Drug

If a subject's study drug must be discontinued before the end of the treatment regimen, this will not result in automatic withdrawal of the subject from the study.

10.2.1. Temporary Discontinuation of Study Drug

Study drug may be temporarily discontinued if the subject:

- Undergoes any surgical procedure, or has a medical condition that may require temporary interruption of the study drug, or use of prohibited therapy due to bleeding risk, or use of other antiplatelet or anticoagulant therapy
- Experiences a significant bleeding event
- Develops a platelet count <50,000/μL
- Has any serious adverse event possibly related to or exacerbated by study drug administration
- Requires a prohibited therapy on a temporary basis (see Section 8, Prestudy and Concomitant Therapy)

The investigator should consider stopping the study drug in pediatric subjects with elevated ALT values >5 x ULN and are increasing, or if ALT values remain unchanged at >5 x ULN with no change in total bilirubin for more than 2 weeks and are considered clinically relevant. In addition, investigators should also terminate the study drug in children with worsening clinical symptoms of liver injury and no other acceptable explanation.

The study drug can be resumed at any time when in the opinion of the investigator it is safe to do so. Otherwise the subject will be permanently discontinued from study drug.

10.2.2. Permanent Discontinuation of Study Drug

A subject's study treatment should be discontinued permanently if:

- The investigator believes that for safety reasons (eg, adverse event or persistent noncompliance) it is in the best interest of the subject to discontinue study treatment
- The subject has a thrombotic event
- The subject develops any condition that requires treatment with anticoagulant or antiplatelet therapy
- The subject has a major bleeding event, eg, intracranial bleeding (for definitions of major bleeding see Section 9.3.1, Bleeding Events)
- The subject, his or her parents/legally acceptable representatives request to discontinue the study drug permanently

For subjects in Part A and Part B who prematurely and permanently discontinue the study drug for any reason, the ESMD visit will be performed as soon as possible after discontinuation of the study drug. A Follow-Up phone contact will be performed 30 days following the last dose of the study drug. In addition, an ESMD Month 12 Follow-Up phone contact will be conducted at the end of the planned treatment period. This excludes subjects who are enrolled after local reading of the Screening transthoracic echocardiogram rules out thrombosis, and subsequently reported to have thrombosis after central reading by the core laboratory of the same transthoracic echocardiogram. These subjects will be withdrawn from the study when the result of the echocardiogram by the core laboratory becomes available. Subjects will be asked to return for

the ESMD visit as soon as possible. They will not be required to have a repeat transthoracic echocardiogram as part of the ESMD. Subjects will go on to receive proper care according to the healthcare provider's judgment. They will be contacted by phone approximately 30 days (+/- 7 days) after last dose of study drug (Follow-Up Contact). An ESMD Month 12 follow up visit will not be required.

10.3. Withdrawal from the Study

A subject will be withdrawn from the study for any of the following reasons:

- Lost to follow-up
- Withdrawal of consent/assent
- An internal DRC considers that the subject should not continue rivaroxaban treatment after the Initial PK, PD and Safety Assessment Period
- The core laboratory reports a thrombosis on the same Screening transthoracic echocardiogram that was ruled out by the local reader.
- Other – eg, termination of the study by the sponsor, closing of study sites

When a subject withdraws before completing the study, the reason for withdrawal is to be documented in the eCRF and in the source document. Study drug assigned to the withdrawn subject may not be assigned to another subject.

If a subject is withdrawn before the end of the study for reasons other than being lost to follow-up, the ESMD assessments should be obtained as soon as possible and a Follow-up phone contact will be performed approximately 30 days (+/-7 days) after last dose of study drug. This excludes subjects withdrawn after central reading by the core lab reports a thrombosis on Screening transthoracic echocardiogram. See Section 10.2, Discontinuation of Study Drug for more details.

If a subject is lost to follow-up, every reasonable effort must be made by the study site personnel to contact the subject and determine the reason for discontinuation/withdrawal. The measures taken to follow up must be documented.

Subjects who withdraw will not be replaced.

If a subject is unwilling or unable to return for follow-up visits in person or have follow-up contacts, the sites should collect as much follow-up visit information as possible, including contacting the subject or the subject's representative or health care professional, by telephone or by mail, to determine vital status and if an endpoint event has occurred, as agreed to by the subject and/or the subject's representative during the initial informed consent process. If applicable, vital status may be obtained by reviewing the subject's medical or public records unless this process is not allowed by local regulations.

11. STATISTICAL METHODS

Statistical analysis will be done by the sponsor or under the authority of the sponsor. A general description of the statistical methods to be used to analyze the PK, PK/PD, safety, and the efficacy data is outlined below. Specific details will be provided in the Statistical Analysis Plan (SAP), including, if necessary, censoring rules for time-to-event analyses and imputation rules for missing or partially missing dates.

The SAP will be finalized prior to first subject enrolled in the study.

Data from subjects participating in Part A of the study are planned to be combined with data from subjects in Part B of the study who were randomized to rivaroxaban. Summaries will also be provided based on data from: (a) randomized subjects only (rivaroxaban vs. ASA) from Part B, and (b) subjects participating in Part A only.

For both parts of the study, safety and efficacy results (adverse events, bleedings, and thrombotic events) will be summarized. All summaries will be presented using appropriate descriptive statistics for study variables including demographic and baseline characteristics. Descriptive statistics such as mean, median, standard deviation, minimum, and maximum will be used to summarize continuous variables. Counts and percentages will be used to summarize categorical variables.

The best available data for safety events will be used by the DRC and IDMC to review subjects in the Initial PK, PD, and Safety Assessment Period of Part A. The CIAC-adjudicated results will be used in the final analysis for all subjects.

No statistical hypothesis will be tested in this study.

11.1. Analysis Populations and Periods

11.1.1. Subject Information

Each summary or analysis involves the following 2 aspects: 1) analysis set, specifying the subjects to be included; and 2) analysis period, specifying the time window within which data will be included.

Key analysis sets and analysis periods are defined below.

11.1.2. Analysis Sets

Full Analysis Set: This analysis set consists of all subjects in Part A who receive at least 1 dose of study drug and all subjects in Part B who complete randomization and receive at least 1 dose of study drug.

Safety Analysis Set: This is the same as Full Analysis Set.

PK Analysis Set: All subjects who received at least 1 dose of study drug and have quantifiable rivaroxaban plasma concentrations will be included in the descriptive PK analysis.

PD Analysis Set: All subjects who received at least 1 dose of study drug and have quantifiable PT, aPTT, and anti-FXa activity values will be included in the descriptive PD analysis.

11.1.3. Analysis Periods

On-Treatment Period: This analysis period includes 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: This analysis period includes all data from first dose to end of treatment visit (Month 12 or ESMD visit).

11.2. Sample Size Determination

A total of at least 100 pediatric subjects overall are planned to be enrolled in this study. Due to the limited availability of the study population and the expected low event rates, this study is not powered to test a formal hypothesis for efficacy. The total sample size is based on regulatory feedback to obtain sufficient 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 subjects. Approximately 90 subjects will be enrolled into Part B of the study.

11.3. Pharmacokinetics/Pharmacodynamics Analyses

Descriptive statistics will be used to summarize rivaroxaban PK data for each time interval. Pharmacodynamic measurements, including PT, aPTT, and anti-FXa activity will be plotted against rivaroxaban plasma concentrations and will also be summarized by timepoint.

Rivaroxaban PK parameters including AUC_{0-24}, C_{max} after single dose and AUC_{0-24}, C_{max}, and minimum plasma concentration (C_{min}) at steady state will be derived through model-based methods. The PK/PD relationship will be quantified. Results from PK and PK/PD analyses will be reported separately from the Clinical Study Report. 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.

11.4. Safety Analyses

All safety analyses will be performed on the Safety Analysis Set (described in Section 11.1.2, Analysis Sets) and by treatment group as received.

Bleeding Events

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. Individual listings of major and clinically relevant non-major bleeding events will be provided. The bleeding events will be adjudicated by the CIAC.

Cumulative incidences and incidence rates over time based on time to the first bleeding event will be provided by treatment group using the Kaplan-Meier method.

Adverse Events

Overall safety will also be assessed by summarizing adverse events by treatment group.

The verbatim terms used in the eCRF by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent adverse events are adverse events with onset during the treatment period or that are a consequence of a pre-existing condition that has worsened since baseline. All reported adverse events will be included in the analysis. For each adverse event, the percentage of subjects who experience at least 1 occurrence of the given event will be summarized by treatment group. In addition, comparisons between treatment groups will be provided if appropriate.

Individual listings of adverse events (including treatment group, age, weight, height, gender, adverse event as reported, start, duration, severity, and relationship to the study drug) will be provided. The incidence of treatment-emergent adverse events will be summarized by treatment using MedDRA preferred terms grouped by primary system organ class.

Summaries, listings, datasets, or subject narratives may be provided, as appropriate, for those subjects who die, who discontinue treatment due to an adverse event, or who experience a severe or a serious adverse event. Additional summaries, listings, or subject narratives may be provided, as appropriate.

Clinical Laboratory Tests

This study will collect laboratory data at the timepoints specified in the Time and Events Schedule. Laboratory data will be summarized by treatment group.

11.5. Efficacy Analysis

Efficacy analyses will be performed on the Full Analysis Set, excluding subjects who start on study drug but are discontinued if central reading by the core laboratory reports thrombosis on the Screening transthoracic echocardiogram. These subjects will be included however in the safety analysis. Thrombotic events that occur during the Up-to-End-of-Treatment Period will be summarized by treatment received. Events that occur after Up-to-End-of-Treatment Period (after Month 12 or ESMD visit) will be summarized separately.

The efficacy outcomes will be adjudicated by CIAC.

The numbers and percentages of subjects with missing Follow-Up Contact (30-days after last dose) will be summarized. Details will be provided in the SAP.

12. ADVERSE EVENT REPORTING

Parents/legally acceptable representatives will receive a study booklet, specifying for both treatment groups important study-related information (see Section 9.6, Study Booklet).

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established Standard Operating Procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety information; all clinical studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

12.1. Definitions

12.1.1. Adverse Event Definitions and Classifications

Adverse Event

An adverse event is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An adverse event does not necessarily have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per International Conference on Harmonisation [ICH])

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Note: The sponsor collects adverse events starting with the signing of the ICF (refer to Section 12.3.1, All Adverse Events, for time of last adverse event recording).

Serious Adverse Event

A serious adverse event based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
  (The subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity

- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is Medically Important*

*Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

For the purposes of this study, efficacy outcome events (thrombotic events) will not be reported as adverse events or serious adverse events, as they will be reported as efficacy outcomes (See Section 12.3.1, All Adverse Events.).

Serious bleeding events will be considered serious adverse events and must be reported to the sponsor in an expedited manner as any other serious adverse events.

If a serious and unexpected adverse event occurs for which there is evidence suggesting a causal relationship between the study drug and the event, the event must be reported by the sponsor as a serious and unexpected suspected adverse reaction even if it is a component of the study endpoint.

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An adverse event is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For rivaroxaban, the expectedness of an adverse event will be determined by whether or not it is listed in the Investigator's Brochure.

Adverse Event Associated With the Use of the Drug

An adverse event is considered associated with the use of the drug if the attribution is possible, probable, or very likely by the definitions listed below in Section 12.1.2, Attribution Definitions.

12.1.2. Attribution Definitions

Not Related

An adverse event that is not related to the use of the drug.

Doubtful

An adverse event for which an alternative explanation is more likely, eg, concomitant drug(s), concomitant disease(s), or the relationship in time suggests that a causal relationship is unlikely.

Possible

An adverse event that might be due to the use of the drug. An alternative explanation, eg, concomitant drug(s), concomitant disease(s), is inconclusive. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded.

Probable

An adverse event that might be due to the use of the drug. The relationship in time is suggestive (eg, confirmed by dechallenge). An alternative explanation is less likely, eg, concomitant drug(s), concomitant disease(s).

Very Likely

An adverse event that is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, eg, concomitant drug(s), concomitant disease(s). The relationship in time is very suggestive (eg, it is confirmed by dechallenge and rechallenge).

12.1.3. Severity Criteria

An assessment of severity grade will be made using the following general categorical descriptors:

Mild: Awareness of symptoms that are easily tolerated, causing minimal discomfort and not interfering with everyday activities.

Moderate: Sufficient discomfort is present to cause interference with normal activity.

Severe: Extreme distress, causing significant impairment of functioning or incapacitation. Prevents normal everyday activities.

The investigator should use clinical judgment in assessing the severity of events not directly experienced by the subject (eg, laboratory abnormalities).

12.2. Special Reporting Situations

Safety events of interest on a sponsor study drug that may require expedited reporting and/or safety evaluation include, but are not limited to:

- Overdose of a sponsor study drug
- Suspected abuse/misuse of a sponsor study drug
- Accidental or occupational exposure to a sponsor study drug
- Any failure of expected pharmacologic action (ie, lack of effect) of a sponsor study drug
- Unexpected therapeutic or clinical benefit from use of a sponsor study drug
- Medication error involving product preparation or dose administration of a sponsor product (with or without subject/patient exposure to the sponsor study drug, eg, name confusion)

Special reporting situations should be recorded in the eCRF. Any special reporting situation that meets the criteria of a serious adverse event should be recorded on the serious adverse event page of the eCRF

12.3. Procedures

12.3.1. All Adverse Events

Adverse events should be reported by the subjects or their parents/legally acceptable representatives for the duration of the study.

For the purposes of this study, thrombotic events will be captured in the eCRF and in the database as efficacy outcomes only, and will not be reported as adverse events or serious adverse events, regardless of seriousness and severity, except for those thrombotic events that ended in death. All other thrombotic events will be exempted from expedited reporting.

Any serious adverse events other than thrombotic events will be reported to the sponsor in an expedited fashion according to Section 12.3.2, Serious Adverse Events.

All deaths (including those due to thrombotic causes) will be reported as serious adverse events.

All bleeding events will be collected on the eCRF as a bleeding event and as an adverse event or serious adverse event as appropriate. Serious bleeding events must be reported to the sponsor in an expedited manner as any other serious adverse events.

Certain adverse events are considered to be Adverse Events of Special Interest and should be reported as serious adverse events. These include:

- Suspected toxic effect on the bone marrow including severe thrombocytopenia (platelet count less than 50 x 10^9/L), severe neutropenia (white blood cell count less than 500/μL), pancytopenia, aplastic anemia
- 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

All adverse events and special reporting situations, whether serious or nonserious, will be reported from the time a signed and dated ICF is obtained until completion of the subject's last study-related procedure (ie, Follow-Up Contact [phone contact]).

Serious adverse events, including those spontaneously reported to the investigator within 30 days after the last dose of study drug, must be reported via facsimile (fax) when applicable using the Serious Adverse Event page of the eCRF. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

All adverse events, regardless of seriousness, severity, or presumed relationship to study drug, must be recorded using medical terminology in the source document and the eCRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper

respiratory infection"). Investigators must record in the eCRF their opinion concerning the relationship of the adverse event to study therapy. All measures required for adverse event management must be recorded in the source document and reported according to sponsor instructions.

The sponsor assumes responsibility for appropriate reporting of adverse events to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all suspected unexpected serious adverse reactions (SUSARs). The investigator (or sponsor where required) must report SUSARs to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB. A SUSAR will be reported to regulatory authorities unblinded. Participating investigators and IEC/IRB will receive a blinded SUSAR summary, unless otherwise specified.

For all studies with an outpatient phase, including open-label studies, parent/legally acceptable representative must be provided with a "wallet (study) card" and instructed to carry this card with them for the duration of the study indicating the following:

- Study number
- Statement, in the local language(s), that the subject is participating in a clinical study
- Investigator's name and 24-hour contact telephone number
- Local sponsor's name and 24-hour contact telephone number (for medical staff only)
- Site number
- Subject number
- Any other information that is required to do an emergency breaking of the blind

12.3.2. Serious Adverse Events

All serious adverse events occurring during the study must be reported to the appropriate sponsor contact person by study-site personnel within 24 hours of their knowledge of the event.

Information regarding serious adverse events will be transmitted to the sponsor using the Serious Adverse Event page of the eCRF, which must be completed and signed by a physician from the study site, and transmitted to the sponsor within 24 hours. The initial and follow-up reports of a serious adverse event should be transmitted electronically via facsimile (fax).

All serious adverse events that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available

- The event can be attributed to agents other than the study drug or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

Suspected transmission of an infectious agent by a medicinal product will be reported as a serious adverse event.

Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the course of a subject's participation in a study must be reported as a serious adverse event, except hospitalizations for the following:

- For the purposes of this study, thrombotic events will not be reported as serious adverse events, refer to Section 12.3.1, All Adverse Events for details.
- Hospitalizations not intended to treat an acute illness or adverse event (eg, social reasons such as pending placement in long-term care facility)
- Surgery or procedure planned before entry into the study (must be documented in the eCRF). Note: Hospitalizations that were planned before the signing of the ICF, and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered serious adverse events. Any adverse event that results in a prolongation of the originally planned hospitalization is to be reported as a new serious adverse event.

The cause of death of a subject in a study, whether or not the event is expected or associated with the study drug, is considered a serious adverse event.

12.4. Contacting Sponsor Regarding Safety

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding safety issues or questions regarding the study are listed on the Contact Information page(s), which will be provided as a separate document.

13. PRODUCT QUALITY COMPLAINT HANDLING

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, or reliability of a product, including its labeling or package integrity. A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information; all studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

13.1. Procedures

All initial PQCs must be reported to the sponsor by the study-site personnel within 24 hours after being made aware of the event.

If the defect is combined with a serious adverse event, the study-site personnel must report the PQC to the sponsor according to the serious adverse event reporting timelines (refer to Section 12.3.2, Serious Adverse Events). A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

13.2. Contacting Sponsor Regarding Product Quality

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding product quality issues are listed on the Contact Information page(s), which will be provided as a separate document.

14. STUDY DRUG INFORMATION

14.1. Physical Description of Study Drug(s)

Rivaroxaban will be used as a 0.1% oral suspension (strength 1 mg/mL). It will be manufactured and provided under the responsibility of the sponsor. Refer to the Investigator's Brochure for a list of excipients.[14]

The active comparator ASA used in this study is 81-mg or 100-mg ASA tablet. It will be provided under the responsibility of the sponsor to the study sites according to local regulations.

14.2. Packaging

Rivaroxaban will be provided in a glass bottle with a child-resistant screw cap. An adaptor and a dosing pipette will be provided to support drug administration.

Acetylsalicylic acid will be provided according to local approved product label in child-resistant packaging.

14.3. Labeling

Study drug labels will contain information to meet the applicable local regulatory requirements.

14.4. Preparation, Handling, and Storage

Rivaroxaban and ASA must be stored at room temperatures 77°F (25°C); excursions from 59° - 86°F (15° - 30°C) are allowed.

Rivaroxaban oral suspension should be stored according to the label.

The ASA tablets should be stored according to the label.

Refer to the pharmacy manual/study site investigational product and procedures manual for additional guidance on study drug preparation, handling, and storage.

14.5. Drug Accountability

The investigator is responsible for ensuring that all study drug received at the site is inventoried and accounted for throughout the study. The dispensing of study drug to the subject, and the return of study drug from the subject (if applicable), must be documented on the drug accountability form. Parents/legally acceptable representatives must be instructed to return all original containers, whether empty or containing study drug. The study drug administered to the subject must be documented on the drug accountability form. All study drug will be stored and disposed of according to the sponsor's instructions. Study-site personnel must not combine contents of the study drug containers.

Study drug must be handled in strict accordance with the protocol and the container label, and must be stored at the study site in a limited-access area or in a locked cabinet under appropriate environmental conditions. Unused study drug, and study drug returned by the subject's parents or legally acceptable representatives, must be available for verification by the sponsor's study site monitor during on-site monitoring visits. The return to the sponsor of unused study drug, or used returned study drug for destruction, will be documented on the drug return form. When the study site is an authorized destruction unit and study drug supplies are destroyed on-site, this must also be documented on the drug return form.

Study drug should be dispensed under the supervision of the investigator or a qualified member of the study-site personnel, or by a hospital/clinic pharmacist. Study drug will be supplied only to parents/legally acceptable representatives of subjects participating in the study. Returned study drug must not be dispensed again, even to the same subject. Study drug may not be relabeled or reassigned for use by other subjects. The investigator agrees neither to dispense the study drug from, nor store it at, any site other than the study sites agreed upon with the sponsor.

15. STUDY-SPECIFIC MATERIALS

The investigator will be provided with the following supplies:

- Investigator Brochure for rivaroxaban
- Pharmacy manual/study site investigational product manual
- Laboratory manual
- IWRS manual
- Electronic data capture (eDC) Manual/eDC Completion Guidelines
- Study booklet
- Subject wallet card
- Tablet splitter
- 60 mL BD™ syringes for reconstitution of rivaroxaban study medication
- Process for submitting outcome information to CIAC
- Transthoracic Echocardiogram Research Protocol and Core Laboratory Process

- Sponsor-approved subject recruiting materials
- Other tools, as applicable including the use of an iPad® (Part A only) to keep key subject information material easily available for the subject's parents or legally acceptable representatives for their use and reference. The subject study booklet will be available on the iPad.

16. ETHICAL ASPECTS

16.1. Study-Specific Design Considerations

The primary ethical consideration in this study is the use of young pediatric subjects who have recently completed the Fontan procedure with a high thrombotic risk and for whom there is scant evidence-based information regarding thromboprophylaxis. There is limited data on the optimal use of thromboprophylaxis for these children and the data are primarily extrapolated from clinical studies in adults. None of the current standards of care (ASA or warfarin) appear to have been very successful at mitigating the risk and incidence of post-Fontan thrombosis according to the small amount of data from few clinical studies and the cumulative years of practice.[12,11,23,20,18] Using ASA as the comparator in this study will allow a descriptive comparison of results across 2 different drug classes: antiplatelet (ASA) versus anticoagulant (rivaroxaban, which has demonstrated effectiveness in the adult population as a thromboprophylaxis agent). In combination with extrapolation from adult efficacy data, this study could support an alternative treatment in this population by providing PK, PD, safety, and supportive efficacy data.

Therefore, this study aims to assess the safety and efficacy of a novel oral anticoagulant that has been extensively studied and has demonstrated safety and efficacy for the prevention and treatment of multiple thrombosis-mediated conditions in adults, and thus far has been well tolerated in pediatric subjects. The study is designed with sufficient scientific rigor to meet its objectives while having close oversight of an IDMC, in addition to the sponsor, to protect subjects from experiencing unacceptably high levels of risk of harm or suffering. Further, the study risk/benefit consideration will be addressed, and reviewed, by an independent ethics review board before the conduct of the study. Due to the limited availability of subjects in this study population and the expected low event rate, formal hypothesis testing of the primary efficacy endpoint is not feasible.

Parents/legally acceptable representatives of potential subjects will be fully informed of the risks and requirements of the study, and during the study they will be given any new information that may affect their decision to continue participation. Parents/legally acceptable representatives and subjects 7 to 8 years of age will be told that their consent/assent to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled.

When referring to the signing of the ICF, the term legally acceptable representative refers to the legally appointed guardian of the child with authority to authorize participation in research. For each subject, his or her parent(s) (preferably both parents, if available) or a legally acceptable representative(s), as required by local regulations, must give written consent (permission)

according to local requirements after the nature of the study has been fully explained and before the performance of any study-related assessments. Assent must be obtained from children (minors) capable of understanding the nature of the study, typically subjects 7 years of age and older, depending on the institutional policies. For the purposes of this study, all references to subjects who have provided consent (and assent as applicable) refer to the subjects and his or her parent(s) or the subject's legally acceptable representative(s) who have provided consent/assent according to this process. Minors who assent to a study and later withdraw that assent should not be maintained in the study against their will, even if their parents/legally acceptable representatives still want them to participate.

Clinical Study with a New Study Drug

Thorough scientific evaluation of any promising treatment before market authorization is an ethical requirement. In the continuing search for medications with improved efficacy and safety profiles, it is necessary to fully investigate and understand new products before public exposure. Full investigation and study of a new product must always include the study of pediatric subjects if there is any reasonable belief that the treatment will benefit the pediatric population.

Rivaroxaban has been proven to have a positive benefit-risk profile in multiple thrombosis-mediated conditions. This study is being conducted in pediatric subjects 2 to 8 years of age with single ventricle physiology who have completed the Fontan procedure within 4 months prior to enrollment. The results of this study are expected to provide useful information on the PK, PK/PD, safety, and efficacy of rivaroxaban as well as the dosing guidelines for this pediatric patient population.

The daily, cumulative, and total blood volume to be collected from each subject in this study is within the range of maximum allowances for pediatric research set by hospitals routinely participating in pediatric clinical studies.[13] The total blood volume to be collected will be approximately 32.7 mL in Part A and 25 ml in Part B over a 12 month period (Attachment 1: Blood Volume). These estimates do not include any blood discarded due to blood drawing from peripheral or central lines, as these volumes may vary according to each site’s practice.

Safety of Dose

This is the first clinical study with rivaroxaban in pediatric subjects after the Fontan procedure; a potential risk will be the actual exposure to study drug at the planned dose in the studied population being inconsistent with the estimated exposure based on PBPK modeling, which can lead to adverse events including bleeding events, or lack of efficacy.

To ensure appropriate exposure to study drug, a staggered approach was chosen. In Part A of the study, in a small number of subjects, the single- and multiple-dose rivaroxaban PK will be evaluated as well as the initial safety and tolerability. The DRC will review the subject’s PK, PD, and safety data obtained from the Initial PK, PD, and Safety Assessment Period prior to allowing the subject to continue on rivaroxaban therapy to complete the 12-month period.

Enrollment and randomization into Part B of this study will only begin once the PK and safety results in the Initial PK, PD, and Safety Assessment Period for subjects in Part A are deemed acceptable by the IDMC.

Capacity to Provide Informed Consent

Only parent(s) (preferably both parents if available) or legally acceptable representative(s) who are fully able to understand the risks, benefits, potential adverse events, and alternatives to participation, will provide their consent voluntarily. Subjects 7 to 8 years of age may be asked for their voluntary assent; the investigator will determine each subject's capacity to provide informed assent.

Subjects of 7 to 8 years of age or their parents or legally acceptable representatives may withdraw their assent or consent, respectively at any time without having to give a reason.

16.2. Regulatory Ethics Compliance

16.2.1. Investigator Responsibilities

The investigator is responsible for ensuring that the study is performed in accordance with the protocol, current ICH guidelines on Good Clinical Practice (GCP), and applicable regulatory and country-specific requirements.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of study subjects are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the study data are credible.

16.2.2. Independent Ethics Committee or Institutional Review Board

Before the start of the study, the investigator (or sponsor where required) will provide the IEC/IRB with current and complete copies of the following documents (as required by local regulations):

- Final protocol and, if applicable, amendments
- Sponsor-approved ICF (and any other written materials to be provided to the subjects)
- Investigator's Brochure (or equivalent information) and amendments/addenda
- Sponsor-approved subject recruiting materials
- Information on compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- Investigator's curriculum vitae or equivalent information (unless not required, as documented by the IEC/IRB)
- Information regarding funding, name of the sponsor, institutional affiliations, other potential conflicts of interest, and incentives for subjects

- Any other documents that the IEC/IRB requests to fulfill its obligation

This study will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any, excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct), the ICF, applicable recruiting materials, and subject compensation programs, and the sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

During the study the investigator (or sponsor where required) will send the following documents and updates to the IEC/IRB for their review and approval, where appropriate:

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct)
- Revision(s) to ICF and any other written materials to be provided to subjects
- If applicable, new or revised subject recruiting materials approved by the sponsor
- Revisions to compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- New edition(s) of the Investigator's Brochure and amendments/addenda
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)
- Reports of adverse events that are serious, unlisted/unexpected, and associated with the study drug
- New information that may adversely affect the safety of the subjects or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the subjects
- Report of deaths of subjects under the investigator's care
- Notification if a new investigator is responsible for the study at the site
- Development Safety Update Report and Line Listings, where applicable
- Any other requirements of the IEC/IRB

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct), the amendment and applicable ICF revisions must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s).

At least once a year, the IEC/IRB will be asked to review and reapprove this study. The reapproval should be documented in writing (excluding the ones that are purely administrative, with no consequences for subjects, data, or study conduct).

At the end of the study, the investigator (or sponsor where required) will notify the IEC/IRB about the study completion (if applicable, the notification will be submitted through the head of investigational institution).

16.2.3. Informed Consent/Assent

Parents/legally acceptable representatives and subjects must give written consent/assent according to local requirements after the nature of the study has been fully explained. The ICF(s) must be signed before performance of any study-related activity. The ICF(s) and assent form that is/are used must be approved by both the sponsor and by the reviewing IEC/IRB and be in a language that the subject can read and understand. The informed consent/assent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.

Before enrollment in the study, the investigator or an authorized member of the study-site personnel must explain to parents/legally acceptable representatives of potential subjects and subjects the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Subjects and parents/legally acceptable representatives will be informed that their participation is voluntary and that they may withdraw consent/assent to participate at any time. They will be informed that choosing not to participate will not affect the care the subject will receive. Finally, they will be told that the investigator will maintain a subject identification register for the purposes of long-term follow up if needed and that their records may be accessed by health authorities and authorized sponsor personnel without violating the confidentiality of the subject, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the parent/legally acceptable representative and subjects are authorizing such access, and agrees to allow his or her study physician to recontact the subject for the purpose of obtaining consent/assent for additional safety evaluations, if needed.

The parent/legally acceptable representative and subjects will be given sufficient time to read the ICF and the opportunity to ask questions. After this explanation and before entry into the study, consent/assent should be appropriately recorded by means of the subject's parent/legally acceptable representative’s personally dated signature. After having obtained the consent/assent, a copy of the ICF must be given to the parent/legally acceptable representative of the subject.

If the subject or legally acceptable representative is unable to read or write, an impartial witness should be present for the entire informed consent/assent process (which includes reading and explaining all written information) and should personally date and sign the ICF after the oral consent/assent of the subject or legally acceptable representative is obtained.

Children (minors) or subjects who are unable to comprehend the information provided can be enrolled only after obtaining consent/assent of a legally acceptable representative. Assent must be obtained from children (minors) capable of understanding the nature of the study, typically subjects 7 years of age and older, depending on the institutional policies. Written assent should be obtained from subjects who are able to write. After having obtained the assent, a copy of the

assent form must be given to the subject, and to the subject's parent and/or legally acceptable representative.

16.2.4. Privacy of Personal Data

The collection and processing of personal data from subjects enrolled in this study will be limited to those data that are necessary to fulfill the objectives of the study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of subjects confidential.

The informed consent/assent obtained from the subject's parents/legally acceptable representatives includes explicit consent/assent for the processing of personal data and for the investigator/institution to allow direct access to his or her original medical records (source data/documents) for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. This consent/assent also addresses the transfer of the data to other entities and to other countries.

The subject's parents/legally acceptable representatives have the right to request through the investigator access to his or her personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

16.2.5. Country Selection

This study will only be conducted in those countries where the intent is to launch or otherwise help ensure access to the developed product, unless explicitly addressed as a specific ethical consideration in Section 16.1, Study-Specific Design Considerations.

17. ADMINISTRATIVE REQUIREMENTS

17.1. Protocol Amendments

Neither the investigator nor the sponsor will modify this protocol without a formal amendment by the sponsor. All protocol amendments must be issued by the sponsor, and signed and dated by the investigator. Protocol amendments must not be implemented without prior IEC/IRB approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazards to the subjects, in which case the amendment must be promptly submitted to the IEC/IRB and relevant competent authority. Documentation of amendment approval by the investigator and IEC/IRB must be provided to the sponsor. When the change(s) involves only logistic or administrative aspects of the study, the IRB (and IEC where required) only needs to be notified.

During the course of the study, in situations where a departure from the protocol is unavoidable, the investigator or other physician in attendance will contact the appropriate sponsor representative (see Contact Information page(s) provided separately). Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded in the eCRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

17.2. Regulatory Documentation

17.2.1. Regulatory Approval/Notification

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country, if applicable. A study may not be initiated until all local regulatory requirements are met.

17.2.2. Required Prestudy Documentation

The following documents must be provided to the sponsor before shipment of study drug to the study site:

- Protocol and amendment(s), if any, signed and dated by the principal investigator
- A copy of the dated and signed (or sealed, where appropriate per local regulations), written IEC/IRB approval of the protocol, amendments, ICF, any recruiting materials, and if applicable, subject compensation programs. This approval must clearly identify the specific protocol by title and number and must be signed (or sealed, where appropriate per local regulations) by the chairman or authorized designee.
- Name and address of the IEC/IRB, including a current list of the IEC/IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IEC/IRB, a general statement may be substituted for this list. If an investigator or a member of the study-site personnel is a member of the IEC/IRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study.
- Regulatory authority approval or notification, if applicable
- Signed and dated statement of investigator (eg, Form FDA 1572), if applicable
- Documentation of investigator qualifications (eg, curriculum vitae)
- Completed investigator financial disclosure form from the principal investigator, where required
- Signed and dated clinical study agreement, which includes the financial agreement
- Any other documentation required by local regulations

The following documents must be provided to the sponsor before enrollment of the first subject:

- Completed investigator financial disclosure forms from all subinvestigators
- Documentation of subinvestigator qualifications (eg, curriculum vitae)
- Name and address of any local laboratory conducting tests for the study, and a dated copy of current laboratory normal ranges for these tests, if applicable
- Local laboratory documentation demonstrating competence and test reliability (eg, accreditation/license), if applicable

17.3. Subject Identification, Enrollment, and Screening Logs

The investigator agrees to complete a subject identification and enrollment log to permit easy identification of each subject during and after the study. This document will be reviewed by the sponsor study-site contact for completeness.

The subject identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure subject confidentiality, no copy will be made. All reports and communications relating to the study will identify subjects by subject identification and date of birth. In cases where the subject is not enrolled into the study, the date seen and date of birth will be used.

The investigator must also complete a subject screening log, which reports on all subjects who were seen to determine eligibility for inclusion in the study.

17.4. Source Documentation

At a minimum, source documentations consistent in the type and level of detail with that commonly recorded at the study site as a basis for standard medical care, must be available for the following: subject identification, eligibility, and study identification; study discussion and date of signed informed consent/assent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all adverse events and follow-up of adverse events; concomitant medication; drug receipt/dispensing/return records; study drug administration information; and date of study completion and reason for early discontinuation of study drug or withdrawal from the study, if applicable.

The author of an entry in the source documents should be identifiable.

Specific details required as source data for the study and source data collection methods will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent document).

Inclusion and exclusion criteria not requiring documented medical history must be verified at a minimum by parent/legally acceptable representative interview or other protocol required assessment (eg, physical examination, laboratory assessment) and documented in the source documents.

An electronic source system may be utilized, which contains data traditionally maintained in a hospital or clinic record to document medical care (eg, electronic source documents) as well as the clinical study-specific data fields as determined by the protocol. This data is electronically extracted for use by the sponsor. If the electronic source system is utilized, references made to the eCRF in the protocol include the electronic source system but information collected through the electronic source system may not be limited to that found in the eCRF. Data in this system may be considered source documentation.

17.5. Case Report Form Completion

Case report forms are prepared and provided by the sponsor for each subject in electronic format. All data relating to the study must be recorded in eCRF. All eCRF entries, corrections, and alterations must be made by the investigator or authorized study-site personnel. The investigator must verify that all data entries in the eCRF are accurate and correct.

Electronic data capture will be used for this study. The study data will be transcribed by study-site personnel from the source documents onto an electronic eCRF, if applicable. Study-specific data will be transmitted in a secure manner to the sponsor.

Worksheets may be used for the capture of some data to facilitate completion of the eCRF. Any such worksheets will become part of the subject's source documentation. All data relating to the study must be recorded in eCRFs prepared by the sponsor. Data must be entered into eCRFs in English. The eCRF must be completed as soon as possible after a subject visit, and the forms should be available for review at the next scheduled monitoring visit.

The investigator must verify that all data entries in the eCRFs are accurate and correct.

All eCRF entries, corrections, and alterations must be made by the investigator or other authorized study-site personnel. If necessary, queries will be generated in the eDC tool.

If necessary, queries will be generated in the eDC tool. If corrections to a eCRF are needed after the initial entry into the eCRF, this can be done either of the following ways:

- Investigator and study site personnel can make corrections in the eDC tool at their own initiative or as a response to an auto query (generated by the eDC tool)
- Sponsor or sponsor delegate can generate a query for resolution by the investigator and study-site personnel.

17.6. Data Quality Assurance/Quality Control

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and study-site personnel before the study, and periodic monitoring visits by the sponsor, and direct transmission of clinical laboratory data from a central laboratory into the sponsor's data base. Written instructions will be provided for collection, handling, storage, and shipment of samples.

Guidelines for eCRF completion will be provided and reviewed with study-site personnel before the start of the study.

The sponsor will review eCRFs for accuracy and completeness during on-site monitoring visits and after transmission to the sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. After upload of the data into the study database they will be verified for accuracy and consistency with the data sources.

17.7. Record Retention

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all eCRFs and all source documents that support the data collected from each subject, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any study documents before having obtained written approval from the sponsor.

If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this study, the investigator/institution must permit access to such reports.

17.8. Monitoring

The sponsor will use a combination of monitoring techniques, central, remote, or on-site monitoring, to monitor this study. The sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study site visit log that will be kept at the study site. The first post-initiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will compare data entered into the eCRFs with the source documents (eg, hospital/clinic/physician's office medical records); a sample may be reviewed. The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the eCRF are known to the sponsor and study-site personnel and are accessible for verification by the sponsor study-site contact. If electronic records are maintained at the study site, the method of verification must be discussed with the study-site personnel.

Direct access to source documents (medical records) must be allowed for the purpose of verifying that the recorded data are consistent with the original source data. Findings from this review will be discussed with the study-site personnel. The sponsor expects that, during monitoring visits, the relevant study-site personnel will be available, the source documents will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the investigator on a regular basis during the study to provide feedback on the study conduct.

In addition to on-site monitoring visits, remote contacts can occur. It is expected that during these remote contacts, study-site personnel will be available to provide an update on the progress of the study at the site. Central monitoring will take place for data identified by the sponsor as requiring central review.

17.9. Study Completion/Termination

17.9.1. Study Completion/End of Study

The study is considered completed with the last scheduled study contact shown in the Time and Events Schedule for the last subject participating in the study. The final data from the study site will be sent to the sponsor (or designee) after completion of the final subject study contact at that study site, in the time frame specified in the Clinical Trial Agreement.

17.9.2. Study Termination

The sponsor reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IEC/IRB or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of subjects by the investigator
- Discontinuation of further study drug development

17.10. On-Site Audits

Representatives of the sponsor's clinical quality assurance department may visit the study site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection. Subject privacy must, however, be respected. The investigator and study-site personnel are responsible for being present and available for consultation during routinely scheduled study-site audit visits conducted by the sponsor or its designees.

Similar auditing procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a regulatory submission. The investigator should immediately notify the sponsor if he or she has been contacted by a regulatory agency concerning an upcoming inspection.

17.11. Use of Information and Publication

All information, including but not limited to information regarding rivaroxaban or the sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data, including research data, generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study, and will not use it for other purposes without the sponsor's prior written consent.

The investigator understands that the information developed in the study will be used by the sponsor in connection with the continued development of rivaroxaban, and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the sponsor with all data obtained in the study.

The results of the study will be reported in a Clinical Study Report generated by the sponsor and will contain data from all study sites that participated in the study as per protocol. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator. Results of analyses performed after

the Clinical Study Report has been issued will be reported in a separate report and will not require a revision of the Clinical Study Report. Study subject identifiers will not be used in publication of results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors guidelines, the sponsor shall have the right to publish such primary (multicenter) data and information without approval from the investigator. The investigator has the right to publish study site-specific data after the primary data are published. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and substudy approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual study site until the combined results from the completed study have been submitted for publication, within 12 months of the availability of the final data (tables, listings, graphs), or the sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, which state that the named authors must have made a significant contribution to the design of the study or analysis and interpretation of the data, provided critical review of the paper, and given final approval of the final version.

Registration of Clinical Studies and Disclosure of Results

The sponsor will register and disclose the existence of and the results of clinical studies as required by law.

REFERENCES

1. Attard C1, Monagle P, Kubitza D, Ignjatovic V. The in vitro anticoagulant effect of rivaroxaban in children. Thromb Res. 2012 Nov;130:804-807.
2. Attard A, Monagle P, Kubitza D, Ignjatovic, V. The in-vitro anticoagulant effect of rivaroxaban in neonates. Blood Coagulation and Fibrinolysis. 2014;25:237-240.
3. Australian and New Zealand Fontan Registry: Report 2014, July 2015.
4. Balling G, Vogt M, Kaemmerer H, Eicken A, Meisner H, Hess J. Intracardiac thrombus formation after the Fontan operation. J Thorac Cardiovasc Surg. 2000;119 (4 Pt 1):745-752.
5. Buller HR, Cohen AT, Davidson B, Decousus H, Gallus AS, Gent M, et al.. van Gogh Investigators, Idraparinux versus standard therapy for venous thromboembolic disease. N Engl J Med. 2007;357:1094-1104.
6. Coboeken K, Mueck W. PH-37113: Refined pediatric population physiologically-based pharmacokinetic (PBPK) model to explore BAY 59-7939 pharmacokinetics in children Bayer Pharma AG, 2013.
7. Coboeken K, Mueck W. PH-13148: Exploratory pediatric population physiologically-based pharmacokinetic (PBPK) analyses of BAY 59-7939. Bayer Health Care AG, 2010.
8. Cole M, Price L, Parry A, Picton S, Waters F, Marshall S, et al. A study to determine the minimum volume of blood necessary to be discarded from a central venous catheter before a valid sample is obtained in children with cancer. Pediatr Blood Cancer 2007;48(7):687-695.
9. Fyfe DA, Kline CH, Sade RM, Gillette PC. Transesophageal echocardiography detects thrombus formation not identified by transthoracic echocardiography after the Fontan operation. J Am Coll Cardiol. 1991;18 (7):1733-1737.
10. Gersony WM. Fontan operation after 3 decades: what we have learned. Circ. 2008;117:13-15.
11. Giglia TM, Massicotte PM, et.al . Prevention and treatment of thrombosis in pediatric and congenital heart disease: a scientific statement from the American Heart Association. Circ. 2013; 128:2622-2703.
12. Guyatt GH, Akl EA, et.al . Executive Summary: antithrombotic therapy and prevention of thrombosis, 9th ed. American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2012; 141(2) Suppl: 7S-47S.
13. Howie, SRC. Blood sample volumes in child health research: review of safe limits. Bulletin of the World Health Organization 2011;89:46-53. http://www.who.int/bulletin/volumes/89/1/10-080010/en/.
14. Investigator's Brochure BAY 59-7939. Document ID No. EDMS-ERI-44631052. J&JPRD (October 2015).
15. Iyengar AJ, Winlaw DS, Galati JC, Genties TL, Weintraub RG, Justo RN, et al. The Australia and New Zealand Fontan registry: description and initial results from the first population-based Fontan registry. Intern Med J. 2014;44(2):148-155.
16. Jacobs JP and Maruszewski B. World J Pediatr Congenit Heart Surg. 2013. 4:349-355.
17. Manlhiot C, Brandão LR, Kwok J, et al . Thrombotic complications and thromboprophylaxis across all three stages of single ventricle heart palliation. J Pediatr. 2012 Sep;161(3):513-519.
18. McCrindle BW, Manlhiot C, Cochrane A, Roberts R, Hughes, M, Szechtman B, et al for the Fontan Anticoagulation Study Group. Factors associated with thrombotic complications after the Fontan procedure. J Am Coll Cardiol. 2013 Jan 22;61(3):346-353.
19. McCrindle BW, Li JS, Manlhiot C, et al . Challenges and priorities for research: a report from the National Heart, Lung, and Blood Institute (NHLBI)/National Institutes of Health (NIH) Working Group on thrombosis in pediatric cardiology and congenital heart disease. Circ. 2014 Sep 30;130(14):1192-1203.
20. Monagle P, Cochrane A, Roberts R, Manlhiot C, Weintraub R, Szechtman B, et al; Fontan Anticoagulation Study Group. A multicenter, randomized trial comparing heparin/warfarin and acetylsalicylic acid as primary thromboprophylaxis for 2 years after the Fontan procedure in children. J Am Coll Cardiol. 2011 Aug 2;58(6):645-651.

21. Monagle P, Cochrane A, McCrindle B, Benson L, Williams W, Andrew M. Thromboembolic complications after Fontan procedures- the role of prophylactic anticoagulation. J Thorac Cardiovasc Surg. 1998 Mar; 115(3):493-498.

22. Monagle P, Karl TR. Thromboembolic problems after the Fontan operation. Semin Thora Cardiovasc Surg Pediatr Card Surg Annu. 2002;5: 36-47.

23. Potter BJ, Leong-Sit P, Fernandez SM, Feifer A, Mayer JE, Triedman JK, et al. Effect of aspirin and warfarin on thromboembolic events in patients with univentricular hearts and Fontan palliation. Int J Cardiol 2013;168:3040-3043.

24. Rychik J, Veldtman G, Rand E, Russo P, Rome JJ, Krok K, et al. The precarious state of the liver after a Fontan operation: summary of a multidisciplinary symposium. Pediatr Cardiol. 2012;33:1001-1012.

25. Samama M, et al . Evaluation of the anti-factor chromogenic assay for the measurement of rivaroxaban plasma concentrations using calibrators and controls. Thromb Haemost. 2012;107.

26. Schnizler, K. PH-38483: Physiology-based prediction of rivaroxaban pharmacokinetics in children with congenital heart disease after Fontan procedure, Bayer Pharma AG, 2015 .

27. Schulman S, Kearnon C. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. J Thromb Haemost. 2005;3:692- 694.

28. Schwartz GJ, Haycock GB, Edelmann CM, Jr., Spitzer A. A simple estimate of glomerular filtration rate in children derived from body length and plasma creatinine. Pediatr. 1976 Aug;58(2):259-263.

29. Schwartz GJ, Munoz A, Schneider MF, Mak RH, Kaskel F, Warady BA, et al. New equations to estimate GFR in children with CKD. J Am Soc Nephrol. 2009 Mar;20(3):629-637.

30. Stümper O, Sutherland GR, Geuskens R, Roelandt JR, Bos E, Hess J. Transesophageal echocardiography in evaluation and management after a Fontan procedure. J Am Coll Cardiol. 1991;17(5):1152-1160.

31. The Society of Thoracic Surgeons (STS) National Database. http://www.sts.org/nationaldatabase. Accessed on 30 June 2015

32. Turpie AGG, Lassen MR, Eriksson BI, et al . Rivaroxaban for the prevention of venous thromboembolism after hip or knee arthroplasty: pooled analysis of four studies. Thromb Haemost. 2011;105:444-453.

Attachment 1: Volume of Blood to be Collected

Volume of Blood to be Collected From Each Subject

Type of Sample	Volume per Sample (mL)	No. of Samples per Subject Part A/Part B	Total Volume of Blood (mL)[a] Part A/Part B
Safety Labs			
- Hematology[b]	1.2	2/2	2.4/2.4
- Serum chemistry[c]	1.1	3/2	3.3/2.2
- Baseline PT, aPTT	1.4	1/0	1.4/0
Pharmacokinetic samples	0.6	10/6	6.0/3.6
PD-1: PD samples (PT and aPTT tests)	1.4	10/7	14/9.8
PD-2: PD samples (anti-FXa assay)	1.4	4/5	5.6/7.0
Approximate Total			32.7/25

ALT= alanine aminotransferase; aPTT= activated partial thromboplastin time; AST= aspartate aminotransferase; CBC= complete blood count; FXa=Factor Xa; No.= number; PD= pharmacodynamics; PT= prothrombin time.

.

a. Calculated as number of samples multiplied by amount of blood per sample.
b. CBC with differential, platelet count;
c. Liver function tests (ALT, AST, total and direct bilirubin, alkaline phosphatase) and creatinine.

Notes:

Repeat or unscheduled samples may be taken for safety reasons or technical issues with the samples.
An indwelling intravenous cannula is recommended for blood sample collection.
Blood discarded due to blood drawing from peripheral or central lines are not included in this table.

Attachment 2: Post-Fontan Echocardiographic Examination protocol

Boston Children's Hospital: Echocardiographic Examination Protocol (Please see Technical Reference Manual for further details)

Status Post Fontan Operation

Inclusion: Patient having undergone a Fontan operation. This operation has been performed with various surgical modifications including: 1) direct anastomosis of the right atrium to the pulmonary artery; 2) valved or non-valved conduit from right atrium to right ventricle; 3) classic Glenn shunt (superior vena cava to transected right pulmonary artery) and conduit from inferior vena cava to left pulmonary artery; 4) bidirectional Glenn shunt plus intra-atrial conduit connection from the inferior vena cava to the right pulmonary artery; 5) bidirectional Glenn shunt plus extracardiac conduit connection from the inferior vena cava to the main pulmonary artery. **Optimal evaluation of the Fontan is achieved by knowledge of the specific type of connection that was performed. The individual performing the examination must find out the details of the operation before the examination.**

Blood pressure in arm and leg if status post Norwood or arch reconstruction.

Full examination of anatomy using 2D, color and spectral Doppler and 3-D evaluation when indicated.

Particular attention should be given to the following:

Subcostal

- The inferior vena cava (IVC) and intracardiac portion of Fontan with 2D, color, and pulsed Doppler. Visualization of Fontan fenestration and if present, pulsed Doppler with mean gradient measured
- Baffle leak
- Atrial septal defect (ASD) (pulmonary vein to atrioventricular [AV] valve pathway), rule out obstruction or restriction along entire pathway including pulmonary veins. If 2D or Doppler evidence of restriction, obtain mean gradient
- Rule out thrombus

Apical

- Fontan fenestration with pulsed Doppler and mean gradient
- Baffle leak
- Atrial Septal Defect (pulmonary vein to AV valve pathway) to exclude restriction. If 2D or Doppler evidence of restriction, obtain mean gradient.
- Atrioventricular valve regurgitation
- Aortic and/or pulmonary valve if present, including pulsed wave and continuous wave Doppler of outflow and assessment of regurgitation jet
- Rule out thrombus

Parasternal

- Aortic and/or pulmonary valve for regurgitation
- Aortic, neoaortic and ascending aorta measurements
- Assess for main pulmonary artery stump and any thrombus
- Assess a hypoplastic aortic root for flow, rule out thrombus
- Branch pulmonary arteries with 2D measurements, color, and pulsed Doppler
- Baffle in parasternal short axis, and long axis. Assess for thrombus
- Assess for pulmonary vein obstruction

Suprasternal

- Glenn shunt (superior vena cava down to cavopulmonary anastomosis if possible) with 2D and with color (color compare) and pulsed Doppler
- Branch pulmonary arteries with 2D measurements, color and pulsed Doppler
- Aortic arch

Full function protocol (systolic and diastolic) regardless of ventricular morphology

Attachment 3: Estimated glomerular filtration rate (eGFR)

- The original Schwartz formula: If serum creatinine (SCr) is measured with routine methods that have not been recalibrated to be traceable to isotope dilution mass spectrometry (IDMS) (eg, the traditional Jaffé reaction), the estimated glomerular filtration rate (eGFR) should be obtained from the original Schwartz formula:[28]

  eGFR (mL/min/1.73 m2) = k * height (cm) / SCr g/dL) where k is proportionality constant:

  k = 0.55 in children up to 13 years

- The updated Schwartz formula: If SCr is measured by an enzymatic creatinine method that has been calibrated to be traceable to IDMS, the updated Schwartz formula should be used to obtain the eGFR:[29]

  eGFR (mL/min/1.73 m^2) = 0.413 * height (cm) / SCr mg/dL

  The National Kidney Disease Education Program website

(http://www.nkdep.nih.gov/professionals/gfr_calculators/index.htm) offers electronic calculators of eGFR in the pediatric population based on the updated Schwartz formula. Serum creatinine in micromoles per liter, the value should be multiplied by 88.4 (1 mg/dL = 88.4 umol/L).

Attachment 4: Amendment 1 changes

Amendment 1 (7 April 2016)

This amendment is considered to be nonsubstantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union, in that it does not significantly impact the safety or physical/mental integrity of subjects, nor the scientific value of the study.

The overall reason for the amendment: The overall reason for the amendment is to address the feedback received from Investigators.

Applicable Section(s)	Description of Change(s)
Rationale: Clarification of study design, simplification of study conduct, to enhance enrollment and data collection and also to avoid scheduling difficulties (in response to comments from investigators in attendance.	
Synopsis Overview Of Study Design; Time And Events Schedule, Part A and Part B	The window of administering rivaroxaban for subjects in Part A and Part B for 12 days was increased from 6 days to 9 days, to allow for sufficient time to complete this visit/phone call.
Synopsis, Subject Population; Section 4.2 Exclusion Criteria	Exclusion criterion #1: Clarified that the screening transthoracic echocardiogram to rule out thrombosis needs to be post-Fontan. Exclusion criterion #4: Current chest-tube placement was deleted as an example of high risk for bleeding qualifying for exclusion. Exclusion criterion #6: Deleted 'Indication'. Exclusion criterion #7: To align with global practices, study participation exclusion limit of platelet counts at screening was changed from less than 100 x 10^9/L to less than 50 x 10^9/L.
Time And Events Schedule, Part A and B, Screening Period	Footnote regarding the screening period was added to also allow for local reading of the subjects' transthoracic echocardiogram to rule out thrombosis. In addition, if subject is enrolled, instruction was added to send the transthoracic echocardiogram also to the core laboratory. Clarification was provided that adverse event assessment includes a review of all ongoing and new adverse events. For Hematology, serum chemistry, PT, and aPTT testing at screening, clarification was added that either hospital laboratory, local laboratory results or central laboratory results are acceptable.
Section 1.1.5, Efficacy and Safety Profile Based on Pediatric Clinical Studies	The section was updated with a more current cut-off date on the status of enrollment and overall safety assessment.
Section 1.2, Comparator Agent	References to the PI and SmPC for ASA were replaced with reference to the local approved product label.
Synopsis, Section 6, Dosage and Administration	Minor edits for ASA tablet. Instructions were added regarding handling a missed morning and evening dose of rivaroxaban and ASA.
Section 9.1.2 Screening Period	Clarification was added that the screening visit will take place after the Fontan procedure.

Applicable Section(s)	Description of Change(s)
Synopsis, Overview Of Study Design, Early Study Medication Discontinuation; Section3.1.Overview of Study Design; Section 9.1.5. Posttreatment Period (Follow-Up Contact); Section 10.2.2. Permanent Discontinuation of Study Drug; Section 10.3. Withdrawal From the Study	Instructions were added regarding the follow-up of subjects who were reported by the core laboratory to have an event on the Screening transthoracic echocardiogram.
Section 9.1.6, Transthoracic Echocardiograms	For the Screening post-Fontan transthoracic echocardiogram, instructions were added to allow local reading to meet the inclusion criteria for enrollment and additional evaluation by the core laboratory if subject is enrolled.
Section 9.2. Pharmacokinetics/Pharmacodynamics Evaluations Part A	Procedure of sending blood samples to the central laboratory was simplified by limiting it to after the collection of the last sample on Day 4 only.
Section 9.3.2, Approach to the Subject with a Bleeding Event	Clarified that it is the treating physician who could consider the measures provided to treat a serious bleed. Clarifications for parents/ legally acceptable representatives were added if the subject has signs and symptoms of clinically significant bleeding.
Section 9.4. Efficacy Evaluations/Outcomes	Further clarification was added regarding the adjudication procedure by the CIAC and responsibility of sites to compile the adjudication package.
Section 9.6. Study Booklet	More information was added related to the packaging and storage of rivaroxaban and comparator ASA.
Section 10.2.2. Permanent Discontinuation of Study Drug	Persistent noncompliance was added as an example of safety reasons for study treatment discontinuation.
Section 10.3. Withdrawal From the Study	Additional reasons for withdrawing a subject from the study were added.
Section 11.5 Efficacy Analysis	To clarify the analysis set in which the efficacy analyses will be performed.
Section 12.3.2. Serious Adverse Events	To clarify the current company-wide clinical study conduct processes to transmit initial and follow-up reports of a serious adverse event.
Section 14.1. Physical Description of Study Drug(s)	Minor edits for ASA tablet.
Section 14.2, Packaging	Minor edits were made.
Section 14.4. Preparation, Handling, and Storage	Minor edits were made.
Section 15. Study-Specific Materials	Recruiting tools were edited to ‘Sponsor-approved subject recruiting materials’. Use of an iPAD was added to study management tools provided to the investigator.
Section 16.1 Study-Specific Design Considerations; Attachment 1, Volume of Blood to be Collected	Clarified that the blood volume estimates do not include any blood discarded, as these volumes may differ from site to site.

Applicable Section(s)	Description of Change(s)
Section 17.4. Source Documentation; Section 17.5. Case Report Form Completion; Section 17.9.1.Study Completion/End of Study	Changes were made to align wording with current company-wide clinical study conduct processes (use of electronic source system and CRFs).
Rationale: The collection of blood samples was further clarified and heparin flushes are to be allowed. Heparin flushes can be used except before PK/PD samples are drawn. These have to be performed with saline to avoid interference with PK/PD results.	
Section 9.2. Pharmacokinetics/Pharmacodynamics Evaluations; 9.5 Sample Collection and Handling	Explained procedure for blood sample collection via an indwelling cannula and central line in more detail and heparin flush was allowed, except before collecting PK/PD samples.
Throughout the protocol	Minor, consistency and logical clarifications were made throughout the document, which do not affect the overall study concept.
References	Addition of 2 references

INVESTIGATOR AGREEMENT

JNJ-39039039; BAY 59-7939 (rivaroxaban)
Clinical Protocol 39039039CHD3001 - Amendment INT-2

INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study drug, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____
(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____
(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): L. Miriam Pina

Institution: Janssen Research & Development

Signature: PPD Date: 7/28/2017
(Day Month Year)

Note: If the address or telephone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.

88

Approved, Date: 27 July 2017