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

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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.The National Heart, Lung and Blood…

Ethical review	Approved WMO
Status	Completed
Health condition type	Congenital cardiac disorders
Study type	Interventional

Summary

ID

NL-OMON46927

Source
ToetsingOnline

Brief title
Prevention of blood clots in children (2 to 8y) after Fontan procedure

Condition

- Congenital cardiac disorders

Synonym
single ventricle physiology, univentricular circulation

Research involving
Human

Sponsors and support

Primary sponsor: Janssen-Cilag
Source(s) of monetary or material Support: Janssen B.V.

Intervention

Keyword: Blood clots, Fontan, Pediatric, Rivaroxaban

Outcome measures

Primary outcome

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 outcome

Part A

To assess the safety and tolerability of rivaroxaban treatment.

Part B

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

Study description

Background summary

Rivaroxaban (JNJ-39039039; BAY 59-7939) is an oral anticoagulant. The mechanism of action of rivaroxaban is to selectively and directly inhibit Factor Xa (FXa), which plays a central role in the cascade of blood coagulation by mediating thrombin formation. Rivaroxaban does not require metabolic conversion or a cofactor to exert its activity. Rivaroxaban is marketed under the trade name XARELTO® and has been approved worldwide for the treatment of multiple thrombosis-mediated conditions.

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. 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. 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.

Study objective

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.
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. 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). 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. 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. 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.

Study design

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 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.

Intervention

Part A: Subjects are treated with Open-label Rivaroxaban BID, equivalent dose to 10mg once daily in adults.
Part B: 2/3 of the subjects are treated with Open-label Rivaroxaban BID, equivalent dose to 10mg once daily in adults. 1/3 of the subjects are treated with Open-label Aspirine (5mg/kg, QD)

Study burden and risks

For side effects of Rivaroxaban and ASA I refer to the informed consent form (Attachment C).
Side effects from the tests:
- Blood draw: Taking blood may cause bruising at the place where the needle goes into the skin. Fainting, and in rare cases infection, may occur.
- Echo: There is generally no risk with having an echo. The sticky patches used during the procedure may pull your skin or cause redness or itching.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Children (2-11 years)

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

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. Indication for anticoagulant or antiplatelet therapy other than current study.
6. Chronic use of nonsteroidal anti-inflammatory drugs (NSAIDs)
7. Platelet count <50 x 109/L at screening
8. Creatinine clearance (CrCl) <30 mL/min/1.73m2
9. Known clinically significant liver disease (eg, cirrhosis, acute hepatitis, chronic active hepatitis, or alanine aminotransferase (ALT) >3x upper limit of normal (ULN) with concurrent total bilirubin
>1.5x ULN with direct bilirubin >20% of the total at screening)
10. Known contraindication to ASA (subjects participating in Part B only)
11. Known allergies, hypersensitivity, or intolerance to rivaroxaban 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.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	01-10-2018
Enrollment:	6
Type:	Actual

Medical products/devices used

Product type:	Medicine

Brand name:	ASA
Generic name:	Acetylsalicylic acid
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Xarelto
Generic name:	Rivaroxaban
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	12-10-2016
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	12-04-2017
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	19-06-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	23-01-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	26-03-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO	

Date:	10-04-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	20-12-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	27-03-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	20-05-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	06-05-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2015-0202610-7-NL
CCMO	NL58318.078.16

Study results

Date completed: 16-07-2020

Results posted: 28-06-2021

First publication
25-04-2021

URL result
URL
Type
int
Naam
M2.2 Samenvatting voor de leek
URL

Internal documents
File