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Cover page of the integrated protocol

7-day study of the safety, efficacy and the pharmacokinetic and pharmacodynamic properties of oral rivaroxaban in children from birth to less than 6 months with arterial or venous thrombosis

EINSTEIN Junior Phase I/II in children from birth to less than 6 months

This protocol version is an integration of the following documents / sections:

- **Original protocol**, Version 1.0, dated 11 Nov 2014
- **Amendment 1** (described in Section [16.1](#))
forming integrated protocol Version 2.0, dated 21 Jul 2015
- **Amendment 2** applicable to Canada only, dated 22 Sep 2015
- **Amendment 3** applicable to Turkey only, dated 22 Mar 2016
- **Amendment 4** (described in Section [16.2](#))
forming integrated protocol Version 3.0, dated 10 May 2016
- **Amendment 5** (described in Section [16.3](#))
forming integrated protocol Version 4.0, dated 15 Nov 2016
- **Amendment 6** applicable to Turkey only, dated 15 Nov 2016

This document integrates the original protocol and all global amendments.

Title page - amended

Study title

7-day study of the safety, efficacy and the pharmacokinetic and pharmacodynamic properties of oral rivaroxaban in children from birth to less than 6 months with arterial or venous thrombosis ¹

EINSTEIN Junior Phase I/II in children from birth to less than 6 months

Test drug: BAY 59-7939/ Rivaroxaban

Clinical study phase: I/II Date: 15 Nov 2016

Registration: 2014-002385-74 Version no.: 4.0

Sponsor's study no.: 17618

Sponsor: Non-US territory: Bayer AG, D-51368 Leverkusen, Germany
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The study will be conducted in compliance with the protocol, ICH-GCP and any applicable regulatory requirements.

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¹ The study population was modified via Amendment 4 (see Section 16.2.2.1)

² The sponsor information was changed via Amendment 5 (see Section 16.3.2.1)

³ The medical expert was changed via Amendments 4 and 5 (see Section 16.2.2.1 and 16.3.2.1)



Signature of Bayer's medically responsible person

The signatory agrees to the content of the final clinical study protocol as presented.

Name: PPD

Role:

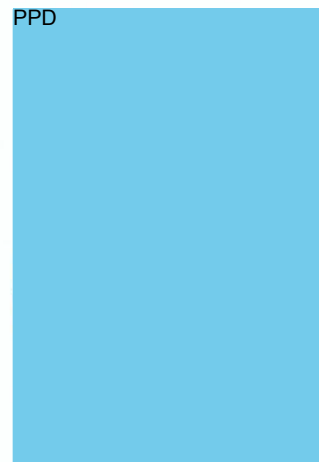
PPD

Date:

November 16th 2016

Signature:

PPD



Signature of the investigator

The signatory agrees to the content of the final clinical study protocol as presented.

Name:

Affiliation:

Date:

Signature:

Signed copies of this signature page are stored in the sponsor's study file and in the respective center's investigator site file.

Synopsis - amended

Title	7-day study of the safety, efficacy and the pharmacokinetic and pharmacodynamic properties of oral rivaroxaban in children from birth to less than 6 months with arterial or venous thrombosis ⁴
Short title	EINSTEIN Junior Phase I/II in children from birth to less than 6 months
Clinical study phase	I/II
Study objectives	<p>The primary objective is:</p> <ul style="list-style-type: none"> to characterize the pharmacokinetic/pharmacodynamic profile of a 7-day treatment with oral rivaroxaban <p>The secondary objectives are:</p> <ul style="list-style-type: none"> to assess the incidence of major bleeding and clinically relevant non-major bleeding, to assess the incidence of symptomatic recurrent thromboembolism and to assess asymptomatic deterioration in the thrombotic burden on repeat imaging
Test drug/ active ingredient	Rivaroxaban
Dose(s)	Age- and body weight-adjusted three times daily dosing of rivaroxaban to achieve a similar exposure as that observed in adults treated for venous thromboembolism (VTE) with 20 mg rivaroxaban once daily ⁵
Route of administration	Oral suspension
Duration of treatment	7 days
Indication	Children from birth to less than 6 months with documented symptomatic or asymptomatic arterial or venous thrombosis ⁶
Diagnosis and main criteria for inclusion /exclusion	<p>Children from birth to less than 6 months with documented symptomatic or asymptomatic arterial or venous thrombosis who have been treated with anticoagulant therapy for at least five days. ⁷</p> <p>Inclusion</p> <ol style="list-style-type: none"> Children from birth to less than 6 months with documented symptomatic or asymptomatic venous or arterial thrombosis who have been treated with anticoagulant therapy for at least 5 days. ⁸ Gestational age at birth of at least 37 weeks. Hemoglobin, platelets, creatinine, alanine aminotransferase (ALT) and total and direct bilirubin assessed within 10 days prior to enrollment.

⁴ The study population was modified via Amendment 4 (see Section 16.2.2.2)

⁵ The dosing was changed from b.i.d. to t.i.d. via Amendment 5 (see Section 16.3.2.2)

⁶ The study population was modified via Amendment 4 (see Section 16.2.2.2)

⁷ This section was modified via Amendment 4 (see Section 16.2.2.2)

⁸ Inclusion criterion 1 was changed via Amendment 4 (see Section 16.2.2.2)

	<ol style="list-style-type: none"> 4. Oral feeding/nasogastric/gastric feeding for at least 10 days. 5. Informed consent provided. 6. Body weight >2600 g. ⁹ <p>Exclusion</p> <ol style="list-style-type: none"> 1. Active bleeding or high risk for bleeding contraindicating anticoagulant therapy, including history of intra-ventricular bleeding 2. Symptomatic progression of thrombosis during preceding anticoagulant treatment 3. Planned invasive procedures, including lumbar puncture and removal of non-peripherally placed central lines during study treatment 4. Hepatic disease which is associated with either: coagulopathy leading to a clinically relevant bleeding risk, or alanine aminotransferase (ALT) > 5x upper level of normal (ULN) or total bilirubin (TB) > 2x ULN with direct bilirubin > 20% of the total 5. Creatinine > 1.5 times of normal 6. Uncontrolled hypertension defined as > 95th percentile^a ¹⁰ 7. History of gastrointestinal disease or surgery associated with impaired absorption 8. Platelet count <100 x 10⁹/L 9. Concomitant use of strong inhibitors of both cytochrome P450 isoenzyme 3A4 (CYP3A4) and P-glycoprotein (P-gp), e.g. all human immunodeficiency virus protease inhibitors and the following azole-antimycotics agents: ketoconazole, itraconazole, voriconazole, posaconazole, if used systemically (fluconazole is allowed) ¹¹ 10. Concomitant use of strong inducers of CYP3A4, e.g. rifampicin, rifabutin, phenobarbital, phenytoin and carbamazepine ¹² 11. Indication for anticoagulant therapy other than current thrombosis 12. An indication for continued antiplatelet therapy or non-steroid anti-inflammatory drug (NSAID) therapy. Incidental use is allowed. ¹³ 13. Hypersensitivity to rivaroxaban or its excipients 14. Participation in a study with an investigational drug or medical device within 30 days prior to enrollment. <p>^a See Appendix 17.1.2</p>
Study design	Non-randomized, open label, multicenter, combined single and multiple dose study

⁹ Inclusion criterion 6 was added via Amendment 1 (see Section 16.1.2.1)

¹⁰ Exclusion criterion 6 was modified via Amendment 4 (see Section 16.2.2.2)

¹¹ Exclusion criterion 9 was modified via Amendment 1 (see Section 16.1.2.1)

¹² Exclusion criterion 10 was modified via Amendment 1 (see Section 16.1.2.1)

¹³ Exclusion criterion 12 was modified via Amendment 4 (see Section 16.2.2.2)

Methodology	<p>Children with confirmed arterial or venous thrombosis who have been treated with anticoagulant therapy for at least five days.¹⁴</p> <p>Children will receive an age- and body weight-adjusted rivaroxaban regimen using an oral suspension (1 mg/mL) for a total of 7 days followed by an observational period of another 30 days. Rivaroxaban will be administered three times daily.¹⁵</p> <p>An ultrasound will be performed at day 1 and 8 of rivaroxaban treatment to document asymptomatic changes. In addition, children will be monitored for the occurrence of symptomatic recurrent thrombosis and bleedings. All suspected clinical study outcomes and baseline and repeat ultrasound imaging tests will be assessed by a Central Independent Adjudication Committee (CIAC).</p> <p>An independent data monitoring committee (DMC) will monitor the children's safety and give recommendations to the steering committee.</p>
Number of subjects	At least 8 children will be included.
Primary outcome	Results of pharmacokinetics (PK) / pharmacodynamics (PD) (prothrombin time, activated partial thromboplastin time and anti-factor Xa activity)
Secondary outcomes	Composite of major and clinically relevant non-major bleeding. Composite of all symptomatic recurrent thromboembolism and asymptomatic deterioration in thrombotic burden on repeat imaging.
Plan for statistical analysis	The incidence of the composite of major and clinically relevant non-major bleeding and the incidence of symptomatic recurrent thromboembolism, and asymptomatic deterioration in thrombotic burden on repeat imaging will be summarized. Quantitative data will be described by summary statistics. Results of PK/PD analyses will be provided.

¹⁴ This section was changed via Amendment 4 (see Section 16.2.2.2)

¹⁵ The dosing was changed from b.i.d. to t.i.d. via Amendment 5 (see Section 16.3.2.2)

Table 1: Flow chart: study visits ¹⁶

	Screen ^a	Treatment period			30 day post study treatment contact
Visit	1	2	3	4	5
Days	Day -10 to Day 1	Day 1	Day 3	Day 8	Day 37+ 7 days
Obtain informed consent	•				
Check in-/exclusion criteria	•				
Obtain demographic data	•				
Check medical history	•	•			
Record anticoagulant medication	•	•			
Obtain blood pressure	•				
Obtain body weight	•	•	•		
Check Hb, platelets, creatinine, ALT, total and direct bilirubin	• ^b				
Obtain ALT, total and direct bilirubin				•	
Re-confirm in-/exclusion criteria		•			
Obtain INR, if receiving VKA ^f		•			
Enroll patient		•			
Dispense study medication Instruct how to administer the study medication Provide study booklet Provide rivaroxaban oral suspension handling guidelines		• ^c			
Record all concomitant medication		•	•	•	•
Collect baseline imaging ^d	•				
Repeat ultrasound imaging ^d		•		• ^e	
Check for study outcomes ^d			•	•	•
Check adverse events		•	•	•	•
Check drug accountability and compliance				•	
Check if anticoagulant treatment continued after Visit 4					•
Complete eCRF	•	•	•	•	•

ALT = alanine aminotransferase, eCRF = electronic case report form, Hb = hemoglobin; INR= international normalized ratio, VKA= vitamin K antagonist

^a The screening visit can be performed up to 10 days prior to inclusion into the study.

^b Hb, platelets, creatinine, ALT, total and direct bilirubin results should be available within 10 days prior to inclusion into the study. If results are not available, obtain blood sample.

^c If child discharged from the hospital.

^d Compile adjudication package and send it to the adjudication office.

^e Repeat ultrasound can be obtained on Day 8 ± 1.

^f INR should be below 2.5 before starting rivaroxaban (see Section 5.1.1.3).

¹⁶ The study flow chart was modified via Amendment 1 (see Section 16.1.2.1)

Table 2: Flow chart: pharmacokinetics and pharmacodynamics ¹⁷

PK and PD ^a	Visit 1	Visit 2						Visit 3						Visit 4
Rivaroxaban treatment days	Screen day -10 to day 1	Treatment day 1			Treatment day 2			Treatment day 3			Treatment day 4 to 7			Day 8
Rivaroxaban administration		1 st dose	2 nd dose	3 rd dose	1 st dose	2 nd dose	3 rd dose	1 st dose	2 nd dose	3 rd dose	1 st dose	2 nd dose	3 rd dose	
PK/PD time points		0.5 to 3 hr post dose	7 to 8hr post dose					0.5 to 3 hr post dose	7 to 8hr post dose					10-16 hr after last dose at day 7
Obtain blood sample for PK ^b		•	•					•	•					
Obtain blood sample for PD ^c			•					•						• ^d

hr = hour(s), PD = pharmacodynamics, PK = pharmacokinetics

^a The approximate total blood volume taken per child for PK/PD is 6.6 mL. Always draw the PD sample as the last sample.

^b Blood volume per PK sample is approximately 0.6 mL; total blood volume for all PK samples is 2.4 mL.

^c Blood volume per PD sample is approximately 1.4 mL; total blood volume for all PD samples is 4.2 mL.

^d If continued treatment with anticoagulants is necessary, administer the anticoagulant after last sample is taken for rivaroxaban.

¹⁷ The PK/PD flow chart was changed via Amendment 5 (see Section 16.3.2.2)

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List of abbreviations

AE	adverse event	IEC	independent ethics committee
ALT	alanine aminotransferase	INR	international normalized ratio
aPTT	activated partial thromboplastin time	IRB	Institutional Review Board
anti-Xa	anti-factor Xa activity	LMWH	low molecular weight heparin
AUC	area under the curve	MedDRA	Medical Dictionary for Regulatory Activities
b.i.d.	twice daily	mmHg	millimeters of mercury
CCDS	company core data sheet	NSAID	non-steroid anti-inflammatory drug
CIAC	central independent adjudication committee	PD	pharmacodynamics
CNS	central nervous system	PE	pulmonary embolism
CRO	contract research organization	P-gp	P-glycoprotein
CV	coefficient of variation	PK	pharmacokinetic
CYP3A4	cytochrome P450 isoenzyme 3A4	SAE	serious adverse event
dL	deciliter	SAP	statistical analysis plan
DMC	data monitoring committee	SID	subject identification number
DVT	deep vein thrombosis	SUSAR	Suspected Unexpected Serious Adverse Reaction
eCRF	electronic case report form	TB	total bilirubin
EudraCT	European Union Drug Regulating Authorities Clinical Trial	t.i.d.	three times daily
GCP	good clinical practice	TOSCA	Tool for Syntactic Corpus Analysis
GMP	good manufacturing practice	U	units
Hb	hemoglobin	UFH	unfractionated heparin
IB	investigator's brochure	ULN	upper limit of normal
ICH	International Conference on Harmonization	VKA	vitamin K antagonist
		VTE	venous thromboembolism

1. Introduction - amended

The classical management of venous thromboembolism (VTE) in adults consists of an initial treatment with adjusted-dose intravenous unfractionated heparin (UFH), body weight-adjusted subcutaneous low molecular weight heparin (LMWH), or body weight-adjusted subcutaneous fondaparinux followed by long-term treatment with a vitamin K antagonist (VKA).⁽¹⁾ VKA therapy should be continued for at least three months. The dose of VKA needs to be adjusted to maintain the international normalized ratio (INR) in the therapeutic range (target 2.5, range 2.0-3.0). This therapeutic approach has also been adopted for VTE treatment in children.

Treatment with heparins and VKA has several unsatisfying aspects. For heparins, these include the requirement for intravenous or subcutaneous injection and monitoring of the activated partial thromboplastin time (aPTT). For VKA, these include a slow onset and offset of action, a narrow therapeutic window requiring frequent INR monitoring, and subsequent dose adjustments, caused by food and drug interactions.⁽²⁾ An oral anticoagulant drug that requires no monitoring of its effect, with a rapid onset of action and a high benefit-risk ratio is of considerable interest not only for adults, but especially for the pediatric population.

Rivaroxaban has been extensively studied in the adult population with symptomatic deep vein thrombosis (DVT) and pulmonary embolism (PE). In two dose finding studies,^(3,4) various rivaroxaban dosages were evaluated and compared to standard of care: LMWH and VKA. As a result of these dose finding studies, a rivaroxaban regimen was selected that consisted of 15 mg twice daily treatment for the initial 3 week acute treatment, followed by 20 mg once daily for long-term treatment. Subsequently, this fixed dose rivaroxaban regimen was evaluated in a large phase III study and was compared to body weight-adjusted LMWH and INR titrated VKA in patients with symptomatic deep vein thrombosis. The results demonstrated clear non-inferiority for the primary efficacy outcome and a similar safety profile in terms of the occurrence of major bleeding and clinically relevant non-major bleeding.⁽⁵⁾

The goal of the rivaroxaban pediatric program is to make rivaroxaban available to children for treatment and secondary prevention of VTE. To accomplish this goal, an age- and body weight adjusted dosing regimen has been developed and is being evaluated in a phase III program in children from 6 months to less than 18 years.

Children between birth and less than 6 months will be evaluated within separate studies because of distinct differences in the coagulation system, presentation of venous thrombosis and treatment requirements.

In this phase I/II study, children with confirmed symptomatic or asymptomatic arterial or venous thrombosis will be treated for 7 days with the age- and body weight-adjusted rivaroxaban three times daily dosing regimen to achieve a similar exposure as that observed in adults treated for VTE with 20 mg rivaroxaban once daily.¹⁸

¹⁸ This section was modified via Amendment 4 and 5 (see Sections 16.2.2.3 and 16.3.2.3)

1.1 Rivaroxaban

Rivaroxaban is an oral, highly selective direct factor Xa inhibitor. Inhibition of factor Xa interrupts the intrinsic and extrinsic pathway of the blood coagulation cascade, inhibiting both thrombin formation and development of thrombi. Rivaroxaban is widely approved for the prevention of VTE following elective hip or knee replacement surgery, for treatment and secondary prevention of DVT and PE, for the primary and secondary prevention of stroke and systemic non-central nervous system (CNS) embolism in non-valvular atrial fibrillation, and for the prevention of atherothrombotic events after an acute coronary syndrome.

1.2 Venous or arterial thrombosis - amended ¹⁹

Compared with adults, thrombosis is rare in children and often is a secondary complication of primary underlying medical conditions or of the use of central lines.⁽⁶⁾

In neonates who have a central line, a high risk of thrombotic events has been observed. Canadian prospective registries estimated an incidence of thrombosis of 24 per 10,000 neonatal admissions, whereas for older children (>1 month old), the incidence is about 5.3 per 10,000 hospital admissions.^(7,8)

A Canadian registry published in 1994 in children aged 1 month to 18 years reported that thrombosis was associated with the use of central venous lines in 33%, with cancer in 23%, with congenital heart disease in 15%, with trauma in 15%, with inherited thrombophilia in 9%, and with infection in 7.5%.⁽⁸⁾ Multiple co-existing risk factors were often present and 39.4% and 35% of children had 2 or 3 concomitant risk factors, respectively.⁽⁸⁾

In 1995, another Canadian registry reported that, except for spontaneous renal vein thrombosis, 89% of thromboses in neonates were associated with the use of central venous or arterial lines. Most of the cases involved the superior caval vein, inferior caval vein, right atrium or femoral veins. Less commonly affected were the brachiocephalic, subclavian, jugular and iliac veins. Arterial thrombosis typically affected the aorta or the iliac and femoral arteries.⁽⁷⁾

1.3 Rationale of the study and risk-benefit assessment - amended

Treatment options are limited to heparins and VKA, which are cumbersome to manage due to the requirement for daily subcutaneous or intravenous injections and regular blood sampling for laboratory monitoring followed by dose adaptations. In children, the availability of an oral anticoagulant treatment that does not require subcutaneous or intravenous injections and regular blood sampling for laboratory monitoring, as is the case in adults, would be desirable.

In adults, rivaroxaban is administered orally and is characterized by stable and predictable pharmacokinetics and, therefore, does not require laboratory monitoring with subsequent dose adjustments. In the Phase III EINSTEIN DVT and PE studies in adults,⁽⁹⁾ rivaroxaban was non-inferior to standard of care with enoxaparin followed by VKA treatment. In the pooled analysis, the incidence of the primary efficacy outcome (the composite of symptomatic

¹⁹ The heading was modified via Amendment 4 (see Section 16.2.2.4)

recurrent DVT, non-fatal and fatal PE) was lower on rivaroxaban than on enoxaparin/VKA treatment, with a similar incidence of clinically relevant bleeding. The comparison against placebo in patients studied for extended treatment of VTE (EINSTEIN extension study) demonstrated clear superiority for rivaroxaban against placebo in all efficacy analyses and across all subgroups. Rivaroxaban was well tolerated and the safety profile, including adverse events and observed laboratory abnormalities, was comparable to enoxaparin/VKA treatment.

As a consequence, the expectation is that the selected rivaroxaban age- and body-weight adjusted dose regimen in children will be safe and efficacious without the need for frequent blood sampling to monitor the anticoagulant activity.

To carefully allow for the evaluation of rivaroxaban in neonates and children younger than 6 months with confirmed symptomatic or asymptomatic arterial or venous thrombosis, we elected to evaluate the selected rivaroxaban dose regimen first in children that have been treated with anticoagulant therapy for at least five days. If this study reveals that the selected rivaroxaban dose regimen results in a similar exposure as that observed with 20 mg rivaroxaban in adults, and safety and efficacy is confirmed, a subsequent study will evaluate the selected rivaroxaban dose regimen for the acute and continued treatment of VTE. ²⁰

2. Study objectives

The primary objective is:

- to characterize the pharmacokinetic/pharmacodynamic profile of a 7-day treatment with oral rivaroxaban

The secondary objectives are:

- to assess the incidence of major bleeding and clinically relevant non-major bleeding
- to assess the incidence of symptomatic recurrent thromboembolism and
- to assess asymptomatic deterioration in the thrombotic burden on repeat imaging

3. Study design - amended

This is a non-randomized, open label, multicenter study evaluating the safety, efficacy and PK/PD profile of a 7-day treatment with age- and body weight-adjusted oral rivaroxaban in neonates and infants younger than 6 months with symptomatic or asymptomatic arterial or venous thrombosis. ²¹

²⁰ This section was modified via Amendment 4 (see Section 16.2.2.5)

²¹ This section was modified via Amendment 4 (see Section 16.2.2.6)

3.1 Study description - amended

Neonates and infants aged less than 6 months who pass the screen of in- and exclusion criteria, who have been treated for at least five days with heparin and /or VKA for confirmed symptomatic or asymptomatic arterial or venous thrombosis are eligible for the study. Study treatment consists of a 7-day treatment with an age- and body weight-adjusted three times daily oral rivaroxaban dosing to achieve a similar exposure as that observed in adults treated for venous thromboembolism (VTE) with 20 mg rivaroxaban once daily. Rivaroxaban will be provided as granules for preparation of an oral suspension (1 mg/mL after re-suspension) using a t.i.d. regimen with 8-hour intervals. ²²

An ultrasound will be performed before starting rivaroxaban at treatment day 1 and after the end of rivaroxaban treatment at day 8. The last dose of rivaroxaban treatment will be followed by a 30-day post study treatment period, regardless of the duration of study drug administration. After cessation of rivaroxaban, it is at the investigator's discretion to continue with anticoagulants. The principal safety outcome is the combination of major and clinically relevant non-major bleeding. The efficacy outcome is the composite of all symptomatic recurrent thromboembolism and asymptomatic deterioration in thrombotic burden on repeat imaging. All suspected recurrent thromboembolism, asymptomatic deterioration in thrombotic burden on repeat imaging, deaths, as well as all episodes of bleeding will be evaluated by a CIAC. Adjudication results will be the basis for the final analyses. ²³

For all children, visits are scheduled at regular time points (see [Table 1](#)). Enrolled children who are not treated or those with premature discontinuation of rivaroxaban will at least be seen at the end of the study treatment period. During all contacts, the treatment and clinical course of the child will be evaluated. Children with suspected efficacy or safety outcomes will undergo confirmatory testing as per standard of care. Blood samples for PK/PD will be taken at defined time points (see [Table 2](#)).

An Independent Data Monitoring Committee (DMC) will monitor the children's safety during the study and give recommendations to the steering committee.

²² The dosing was changed to t.i.d. via Amendment 5 (see Section [16.3.2.4](#))

²³ This section was modified via Amendment 4 (see Section [16.2.2.7](#))

4. Study population

4.1 Planned number of children

At least eight children are planned to be enrolled in the study.

4.2 Inclusion criteria - amended

1. Children from birth to less than 6 months with documented symptomatic or asymptomatic venous or arterial thrombosis who have been treated with anticoagulant therapy for at least 5 days. ²⁴
2. Gestational age at birth of at least 37 weeks.
3. Hemoglobin, platelets, creatinine, ALT and total and direct bilirubin assessed within 10 days prior to enrollment.
4. Oral feeding/nasogastric/gastric feeding for at least 10 days.
5. Informed consent provided.
6. Body weight >2600 g. ²⁵

4.3 Exclusion criteria - amended

1. Active bleeding or high risk for bleeding contraindicating anticoagulant therapy, including history of intra-ventricular bleeding.
2. Symptomatic progression of thrombosis during preceding anticoagulant treatment.
3. Planned invasive procedures, including lumbar puncture and removal of non-peripherally placed central lines during study treatment.
4. Hepatic disease which is associated with either: coagulopathy leading to a clinically relevant bleeding risk, or alanine aminotransferase (ALT) > 5x upper level of normal (ULN) or total bilirubin (TB) > 2x ULN with direct bilirubin > 20% of the total.
5. Creatinine >1.5 times of normal.
6. Uncontrolled hypertension defined as >95th percentile. ²⁶
7. History of gastrointestinal disease or surgery associated with impaired absorption.
8. Platelet count <100 x 10⁹/L.
9. Concomitant use of strong inhibitors of both cytochrome P450 isoenzyme 3A4 (CYP3A4) and P-glycoprotein (P-gp), e.g. all human immunodeficiency virus protease

²⁴ Inclusion criterion 1 was modified via Amendment 4 (see Section 16.2.2.8)

²⁵ Inclusion criterion 6 was added via Amendment 1 (see Section 16.1.2.2)

²⁶ Exclusion criterion 6 was modified via Amendment 4 (see Section 16.2.2.9)

inhibitors and the following azole-antimycotics agents: ketoconazole, itraconazole, voriconazole, posaconazole, if used systemically (fluconazole is allowed).²⁷

10. Concomitant use of strong inducers of CYP3A4, e.g. rifampicin, rifabutin, phenobarbital, phenytoin and carbamazepine.²⁸
11. Indication for anticoagulant therapy other than current thrombosis.
12. An indication for continued antiplatelet therapy or non-steroid anti-inflammatory drug (NSAID) therapy. Incidental use is allowed.²⁹
13. Hypersensitivity to rivaroxaban or its excipients.
14. Participation in a study with an investigational drug or medical device within 30 days prior to enrollment

4.4 Concomitant medication - amended

Concomitant medications include either continuation of a treatment started before study enrollment, or addition of a new treatment during the study. An indication for the continued use of NSAIDs or antiplatelet agents is an exclusion criterion since they increase the risk for bleeding in patients treated with anticoagulants. However, incidental use is allowed.³⁰

Concomitant use of strong inhibitors of both CYP3A4 and P-gp is not allowed, as well as concomitant use of strong inducers of CYP3A4.

Any anticoagulant medication taken for the current thrombosis prior to study entry will be documented. Anticoagulant use after the study treatment period will also be documented.

5. Treatment groups and regimens

5.1 Method of treatment allocation

5.1.1 Rivaroxaban regimen - amended

Age- and body weight-adjusted rivaroxaban will be administered three times daily approximately 8 hours apart as oral suspension. The oral suspension will be administered immediately before or (early) during feeding.³¹

Originally, the study started with a b.i.d. regimen. Rivaroxaban was well tolerated in the 5 children treated according to the b.i.d. regimen and there were no bleeding events. Furthermore, no symptomatic recurrent venous thromboembolic complications occurred. Repeat imaging of the thrombosis in two children with a persistent thrombosis at the start of

²⁷ Exclusion criterion 9 was modified via Amendment 1 (see Section 16.1.2.3)

²⁸ Exclusion criterion 10 was modified via Amendment 1 (see Section 16.1.2.3)

²⁹ Exclusion criterion 12 was modified via Amendment 4 (see Section 16.2.2.9)

³⁰ This section was modified via Amendment 4 (see Section 16.2.2.10)

³¹ Throughout the complete section t.i.d. dosing was introduced via Amendment 5 (see Section 16.3.2.5)

rivaroxaban treatment showed normalization and substantial regression of the thrombosis, respectively, after the 7-day treatment with rivaroxaban.

However, PK results of the first 5 children enrolled with the b.i.d. regimen indicate lower rivaroxaban exposure ($AUC_{ss,24h}$) and C_{trough} concentrations than initially expected by the PK model. Based on these observations, the Data Monitoring Committee recommended to change the dosing regimen from a b.i.d. (approx. 12-hour intervals) to a t.i.d. (approx. 8-hour intervals) schedule applying the same individual doses previously administered twice daily. This recommendation was endorsed by the steering committee.

Following implementation of Amendment 5, children will be dosed according to the t.i.d. schedule (according to [Table 3](#)). The 50% increase of the total daily dose will increase the exposure, and the shortening of the dosing interval from 12 to 8 hours (t.i.d. schedule) aims to increase the C_{trough} concentrations.

If a rivaroxaban individual dose was missed, the t.i.d. administration schedule with approx. 8-hour intervals should be resumed without compensating for the missed dose.

Instructions on how to handle rivaroxaban oral suspension are provided in the oral suspension handling guidelines, which will be issued separately from the protocol. Parents will be instructed and trained to prepare the suspension according to the guidelines, if applicable. The training will be documented.

The body weight-adjusted rivaroxaban dosing schedule is provided in [Table 3](#).³²

Table 3: Rivaroxaban dosing schedule

Body weight [kg]		Oral suspension dose (t.i.d.)*	Total daily dose
Min	Max	[mg]	[mg]
2.6	<3	0.5	1.5
3	<4	0.6	1.8
4	<5	0.9	2.7
5	<6	1.2	3.6
6	<7	1.6	4.8
7	<8	1.9	5.7
8	<9	2.5	7.5
9	<10	2.7	8.1
10	<12	2.9	8.7

* to be administered every 8 hours

5.1.1.1 Switching from heparin to rivaroxaban

If the child received heparin treatment before enrollment, enrollment should be planned 4 hours after stopping the infusion of UFH, 6 - 12 hours after the last injection of LMWH with a twice-daily regimen, 12 - 24 hours after the last injection of LMWH with a once-daily

³² The dosing table was added via Amendment 1 (see Section [16.1.2.4](#))

regimen. Heparin treatment cannot be continued after the start of rivaroxaban treatment in these children.

5.1.1.2 Switching from rivaroxaban to heparin

Children who switch from rivaroxaban to heparin can switch at the time the next rivaroxaban dose would have been scheduled.

5.1.1.3 Switching from VKA to rivaroxaban - amended

If a child is on VKA therapy and has a supra-therapeutic INR (> 3.0), enrollment into the study should be delayed. In case of an INR between 2.5 to 3.0, enrollment can be done and the first rivaroxaban dose should be delayed to the next day. If the INR is below 2.5, enrollment can be done and the first rivaroxaban dose can be taken on the day of enrollment. VKA therapy cannot be continued after enrollment.

Children who switch from VKA to rivaroxaban should avoid using both drugs at therapeutic doses simultaneously. Rivaroxaban can be started only if the INR is < 2.5 . ³³

5.1.1.4 Switching from rivaroxaban to VKA

Children who switch from rivaroxaban to VKA need to switch to heparin and VKA at the time the next rivaroxaban dose would have been scheduled. Thereafter, heparin needs to be co-administered with VKA until the INR is ≥ 2.0 .

5.2 Subject identification

After the parents/ legal representative sign the informed consent form, each child will be assigned by the site staff a unique 9-digit subject identification (SID) number for unambiguous identification. The first 2 digits represent the country number, the next 3 digits represent the center number, and the last 4 digits represent a sequential number assigned to each child. SID numbers will have to be used in sequence and no number should be skipped or substituted. All enrolled subjects must be listed on the site enrollment log.

5.3 Duration of study treatment

Children will receive study treatment for a period of 7 days.

5.4 Formulation and dose

5.4.1 Rivaroxaban - amended

Rivaroxaban will be provided as granules for preparation of a 0.1% oral suspension (1 mg/mL). Rivaroxaban will be dosed according to body weight. Since children with renal impairment will be excluded from the study, a dose adaptation is not indicated. ³⁴

³³ Text was modified via Amendment 1 (see Section 16.1.2.5)

³⁴ This section was modified via Amendment 4 (see Section 16.2.2.12)

5.5 Packaging, labeling, and storage - amended

Rivaroxaban will be provided by Bayer and labeled according to local law and regulations.

A system of numbering in accordance with Good Manufacturing Practice (GMP) will be used, ensuring that each dose of study medication can be traced back to the respective bulk ware of the ingredients. A complete record of batch numbers and expiry dates of all study medication provided by Bayer, as well as the labels, will be maintained in the study file. Rivaroxaban granules for oral suspension need to be stored at the investigational site according to the labeled storage advice and in accordance with Good Clinical Practice (GCP) and GMP requirements. Rivaroxaban granules for oral suspension should not be frozen and should be stored at a temperature not exceeding 25°C and kept in a secure area (e.g. locked cabinet). Complete records of batch numbers and expiry dates can be found in the Bayer study file. The responsible site personnel will confirm receipt of rivaroxaban as described in the study drug guidance document and will use rivaroxaban only for this study and in accordance with this protocol. Receipt, distribution, return and destruction (if any) of rivaroxaban must be properly documented according to specified procedures. ³⁵

5.6 Treatment assignment

All subjects will receive an age- and body weight-adjusted rivaroxaban dosing.

5.7 Dose and administration

Rivaroxaban will be dosed according to body weight as oral 0.1% suspension (1 mg/mL).

Instruction will be given to return all unused study drug including packaging, if applicable, at visit 3, visit 4, and, if applicable, at the premature discontinuation visit. Compliance will be evaluated by measuring remaining suspension. All non-used rivaroxaban should be kept securely in the original containers in a designated locked storage area until retrieved or dispensed.

6. Study procedures

6.1 Study visits - amended

The study has 5 planned visits (see [Table 1](#)).

Visit 1 is a screening visit and will be a hospital visit. This visit is to identify potential eligibility of children who are treated with anticoagulants for confirmed symptomatic or asymptomatic arterial or venous thrombosis. This visit will take place 1 to 10 days before inclusion into the study. Visit 2 is the first treatment visit and will be a hospital visit. Eligible children will start 7 days of anticoagulation with rivaroxaban (day 1). ³⁶

³⁵ This section was modified via Amendment 4 (see Section [16.2.2.13](#))

³⁶ This section was modified via Amendment 4 (see Section [16.2.2.14](#))

Visit 3 and visit 4 are treatment and end of treatment visits, respectively. These visits will be hospital visits which will take place at day 3 and day 8, respectively.

PK/PD blood sampling will be done at visit 2, 3 and 4. ALT, total and direct bilirubin will be measured at visit 4.

Rivaroxaban will be stopped at day 7. After cessation of study treatment with rivaroxaban, it is at the investigator's discretion to continue with anticoagulation, as needed. Repeat imaging will be obtained, if applicable.

Visit 5 is the 30-day post treatment contact visit and will be a hospital visit or a telephone contact. It will take place at day 37 + 7 days. This visit will be the last study visit.

6.2 Visit 1 – Screening visit at 1 to 10 days before Visit 2 - amended

The parents/legal representative will be given explanation about the study and will be given sufficient time to consider participation of their child in the study. Parents/legal representative who are willing to have their child participate in the study will be asked to sign an informed consent form.

Screening will only be performed after having received informed consent. Children who pass the screen of inclusion and exclusion criteria can be enrolled into the study.

Then demographic data, medical history, weight, blood pressure and anticoagulant medication will be collected. ³⁷

Children are not eligible for enrollment into the study, if the mother is treated with strong inhibitors of both cytochrome P450 isoenzyme 3A4 (CYP3A4) and P-glycoprotein (P-gp), or with strong inducers of CYP3A4, and is breastfeeding the child.

The images of the index thrombotic event need to be collected and the adjudication package needs to be completed and sent to the central adjudication office for their assessment. ³⁸

Adverse events will not be collected between visit 1 and visit 2. Since hemoglobin, platelet count, creatinine, ALT, total and direct bilirubin tests are performed as part of routine clinical practice in children treated with anticoagulants, recent results will be available and, therefore, a blood sample is not required as part of the study screening assessments. Availability of results for hemoglobin, platelets, creatinine, ALT, total and direct bilirubin within 10 days prior to enrollment is an inclusion criterion for this study.

6.3 Visit 2 – Treatment visit at Day 1 - amended

If the child still meets the inclusion criteria and does not meet any of the exclusion criteria, the child can be enrolled. If results for hemoglobin, platelets, creatinine, ALT and total and direct bilirubin were not available within 10 days prior to enrollment, obtain a blood sample.

³⁷ The blood pressure measurement was added via Amendment 1 (see Section 16.1.2.6)

³⁸ This section was modified via Amendment 4 (see Section 16.2.2.15)

For children receiving VKA, the INR should be obtained. INR should be below 2.5 before starting rivaroxaban. ³⁹

The following assessments and procedures have to be performed on visit 2:

- Collect body weight.
- Provide instructions on how to administer the study drug and give the study booklet and the rivaroxaban oral suspension handling guidelines to parents, if applicable.
- Administer the first rivaroxaban dose according to the oral suspension handling guidelines. ⁴⁰
- Document the exact time of rivaroxaban intake and the type (e.g., breast milk, formula, porridge, or pureed food) and estimated volume of fluid (e.g. breast milk and formula) or food (e.g. porridge or pureed food) rivaroxaban was administered with. ⁴¹
- In case rivaroxaban is administered together with porridge or pureed food, encourage the child to drink a typical serving of liquid thereafter (e.g., breast milk, formula, water, juice) and document the type of liquid and the estimated volume.
- At 0.5-3 hr after rivaroxaban, collect only a PK blood sample.
- At 7-8 hr after rivaroxaban intake, collect a PK blood sample followed by the PD sample.
- Document the exact time of each blood sampling for PK/PD.
- Obtain ultrasound and prepare an adjudication package to be sent to the adjudication office. In case other diagnostic tests were performed to visualize the clot, these should be sent as well.
- Check for adverse events.
- Record all concomitant medication including anticoagulant medication for the current thrombosis.
- Update eCRF.

6.4 Visit 3 – Treatment visit at Day 3 - amended

The following assessments and procedures have to be performed on visit 3:⁴²

- Check for potential study outcomes. If a suspected study outcome occurred, an adjudication package needs to be compiled and sent to the adjudication office.
- Check for adverse events.

³⁹ This section was modified via Amendment 1 and 5 (see Section 16.1.2.7 and 16.3.2.6)

⁴⁰ Bullet was modified via Amendment 4 (see Section 16.2.2.16)

⁴¹ Bullet was modified via Amendment 1 (see Section 16.1.2.7)

⁴² This section was modified via Amendment 4 (see Section 16.2.2.17)

- Collect body weight and if needed adjust the dosage of rivaroxaban.
- Administer the next dose of rivaroxaban according to the oral suspension handling guidelines. ⁴³
- Document the exact time of rivaroxaban intake and the type (e.g. breast milk, formula, porridge, or pureed food) and estimated volume of food rivaroxaban was administered with.
- In case rivaroxaban is administered together with porridge or pureed food, encourage the child to drink a typical serving of liquid thereafter (e.g., breast milk, formula, water, juice) and document the type of liquid and the estimated volume.
- At 0.5-3 hr after rivaroxaban, collect a PK blood sample followed by the PD blood sample.
- At 7-8 hr after rivaroxaban intake, collect only a PK blood sample.
- Document the exact time of blood sampling for PK/PD.
- Check changes in concomitant medications.
- Instruct to document in the study booklet
 - the exact time of the last dose of rivaroxaban on the day prior to visit 4,
 - the type (e.g. breast milk, formula, porridge, or pureed food) and estimated volume of fluid (e.g. breast milk and formula) or food (e.g. porridge or pureed food) rivaroxaban was administered with, ⁴⁴
 - In case rivaroxaban is administered together with porridge or pureed food, parents should document the type and estimated volume of liquid (e.g., breast milk, formula, water, juice) that the child took thereafter.
- Update eCRF.

⁴³ Bullet was modified via Amendment 4 (see Section 16.2.2.17)

⁴⁴ Bullet was modified via Amendment 1 (see Section 16.1.2.8)

If a child discontinues rivaroxaban permanently before visit 3, visit 3 will still need to take place:

- Check for potential study outcomes. If a suspected study outcome occurred, an adjudication package needs to be compiled and sent to the adjudication office.
- Check for adverse events. If an adverse event occurred, update the eCRF.
- Perform drug accountability and assess compliance.
- Check changes in (concomitant) medications.
- No blood sampling for PK/PD is required.

6.5 Visit 4 – Day 8 - amended

The following assessments and procedures have to be performed on visit 4: ⁴⁵

- Rivaroxaban should not be taken anymore.
- Check for potential study outcomes. If a suspected study outcome occurred, an adjudication package needs to be compiled and sent to the adjudication office.
- Check for adverse events.
- Document
 - the exact time of the last dose of rivaroxaban on the day prior to visit 4,
 - the type (e.g. breast milk, formula, porridge, or pureed food) and estimated volume of fluid (e.g. breast milk and formula) or food (e.g. porridge or pureed food) rivaroxaban was administered with. ⁴⁶
 - In case rivaroxaban was administered together with porridge or pureed food, parents should document the type and estimated volume of liquid (e.g., breast milk, formula, water, juice) that the child took thereafter.
- At 10-16 hr after last rivaroxaban intake, collect ALT, total and direct bilirubin sample, followed by the PD blood sample. If continued treatment with anticoagulants is necessary, administer the anticoagulant after this sample is taken.
- Document the exact time of blood sampling for PD.
- Repeat ultrasound and prepare an adjudication package to be sent to the adjudication office. The repeat ultrasound can be performed on day 8 ± 1 . In case other diagnostic tests were performed to visualize the clot, these should be sent as well.
- Perform drug accountability and assess compliance.
- Check changes in concomitant medications.

⁴⁵ This section was modified via Amendment 4 and 5 (see Section 16.2.2.18 and 16.3.2.8)

⁴⁶ Bullet was modified via Amendment 1 (see Section 16.1.2.9)

- Update eCRF

If a child discontinues study treatment permanently before visit 4, visit 4 will still need to take place:

- Check for potential study outcomes. If a suspected study outcome occurred, an adjudication package needs to be compiled and sent to the adjudication office.
- Check for adverse events. If an adverse event occurred, update the eCRF.
- Perform drug accountability and assess compliance.
- Check changes in (concomitant) medications.
- No blood sampling for PK/PD is required.

6.6 Visit 5 – 30 day post treatment contact at Day 37 (+ 7 days)

This visit or telephone contact is to document what happens to children during the 30-day post study treatment period. Therefore, this visit or telephone contact will take place at day 37 + 7 days in children who completed the study treatment.

The following assessments and procedures have to be performed on visit 5:

- Check for potential study outcomes. If a suspected study outcome occurred, an adjudication package needs to be compiled and sent to the adjudication office.
- Check for adverse events. If an adverse event occurred, update the eCRF.
- Check for changes in (concomitant) medications.
- Document if anticoagulant treatment was continued or stopped after visit 4.
- Update eCRF.

6.7 Unscheduled visits

If deemed necessary, it is at the investigator's discretion to arrange additional visits.

6.8 Safety outcomes

The principal safety outcome is the composite of major bleeding and clinically relevant non-major bleeding. Other safety outcomes include all deaths and other vascular events (myocardial infarction, cerebrovascular accident, non-CNS systemic embolism).

The CIAC will classify bleeding as:

Major bleeding which 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

- occurring in a critical site, e.g. 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 child such as pain

All other overt bleeding episodes not meeting the criteria for clinically relevant bleeding will be classified as trivial bleed.

6.9 Recommendations before and after invasive procedures and surgical intervention

If an invasive procedure or surgical intervention is required, rivaroxaban should be stopped at least 24 hours before the intervention, if possible and based on the clinical judgment of the physician. If the procedure cannot be delayed, the increased risk of bleeding should be assessed against the urgency of the intervention. Rivaroxaban should be restarted after the invasive procedure or surgical intervention within 24 hours, provided the clinical situation allows and adequate hemostasis has been established.

6.10 Management of bleeding in children

If a child has a serious bleed during study treatment, the following routine measures could be considered:

- Consider usual treatment for bleeding, including blood transfusion, and/or fresh frozen plasma.
- Obtain PK/PD blood sample.
- If bleeding cannot be controlled, consider administration of one of the following procoagulants:
 - 4-factor prothrombin complex concentrate
 - recombinant factor VIIa (NovoSeven[®])
- Protamine sulfate and vitamin K are not expected to affect the anticoagulant activity of rivaroxaban.

6.11 Efficacy outcome

The efficacy outcome will be the composite of all symptomatic recurrent thromboembolism and asymptomatic deterioration in thrombotic burden on repeat imaging.

6.12 PK/PD assessment - amended

Blood samples will be taken for PK/PD measurements. The number and volume of PK/PD blood samples represents the minimum amount of blood needed for adequate analysis (sparse sampling approach). The following blood samples will be taken: ⁴⁷

- two post-dose PK samples at visit 2
- one post-dose PD sample at visit 2
- two post-dose PK sample at visit 3
- one post-dose PD sample at visit 3
- one post-dose PD sample at visit 4

The exact time of rivaroxaban dosing and PK/PD blood sampling will be documented in the eCRF. If, for any reason, PK/PD samples are taken outside of the pre-specified time window, the exact time that the sample was taken should be recorded and not the time of the time window.

The use of low dose heparin and tissue plasminogen activator to maintain catheter patency is acceptable. However before collecting PK/PD samples, the catheters need to be flushed with saline. In addition, if PK/PD samples are drawn through a central line, a small amount of blood needs to be drawn and discarded, before collecting the PK/PD sample in order to avoid dilution of the PK/PD sample with saline that remains in the central line.

The prothrombin time, activated partial thromboplastin time and anti-factor Xa activity (anti Xa) will be used to assess the pharmacodynamic effects after administration of the study drug.

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

The data obtained from the blood samples taken will be analyzed.

6.13 Study booklet

Parents will receive a booklet with the following information:

- The local medical contact person and emergency telephone number
- The visit schedule, including dates of telephone and/or hospital visits
- Instructions to keep empty, partially used, and unused bottles of study medication
- Instructions on signs and symptoms of bleeding
- How to take rivaroxaban

⁴⁷ This section was modified via Amendment 5 (see Section [16.3.2.9](#))

6.14 Study committees

6.14.1 Steering committee

The steering committee has the overall scientific responsibility of the study. Its tasks and responsibilities are:

- To facilitate and approve the final protocol
- To help select the investigators network
- To support and organize the national logistics in the initiation and conduct of the study
- To ensure a scientifically sound and safe conduct of the study
- To decide on the DMC recommendations
- To guarantee the integrity of data collection and analyses
- To monitor progress of study enrollment
- To assist in the analysis and presentation of the results
- To decide on the publication and presentation policy of final results

6.14.2 Central independent adjudication committee (CIAC)

All index venous or arterial thrombotic events, and all suspected recurrent thromboembolic events, asymptomatic deterioration in the thrombotic burden on repeat imaging, bleeding, other vascular events and deaths that occur after visit 2 including the 30-day post treatment period will be evaluated by a CIAC, which will be provided with all relevant documentation related to the events. The procedures followed by the CIAC will be described in an adjudication manual. Adjudication results will be the basis for the final analyses.

6.14.3 Data monitoring committee (DMC)

This committee has the responsibility to provide the steering committee with recommendations related to the protection of the children's safety, including stopping recruitment and study treatment. For that purpose, the DMC will regularly review all incidences of serious adverse events, recurrent venous or arterial thromboembolic events and bleeding. Organizational aspects, responsibilities, and processes will be described in the DMC charter.

7. Statistical and analytical methods

7.1 General considerations

The plan described in the following sections will be detailed in a statistical analysis plan (SAP). The SAP will accommodate protocol amendments or unexpected issues in study execution or data that affect planned analyses. Any revision will be clearly identified in the final SAP, issued prior to data base lock. If not stated otherwise, the following statistical specifications will apply.

7.2 Analysis sets

Full analysis set:	This analysis set will include all children from whom informed consent was obtained.
Safety analysis set:	This analysis set will include all children who received at least one dose of rivaroxaban.
Per protocol analysis set:	This population includes all children who completed the 7-day treatment period or had an efficacy or bleeding outcome before. This analysis set may exclude major protocol deviations.
Listing only set:	This population includes all screening failures.

7.3 Demographic and other baseline characteristics

Summary statistics (arithmetic mean, standard deviation, median, minimum and maximum for quantitative variables) will be presented. Frequency tables for qualitative data will be provided. Medical history findings will be summarized using Medical Dictionary for Regulatory Activities (MedDRA) terms.

7.4 Safety analysis

All safety analyses will be performed on the safety population. The analysis will primarily focus on bleeding that occurred during or within 2 days after stop of rivaroxaban. Bleeding events observed later will be described separately. Individual listings of major and clinically relevant non-major bleeding will be provided. The incidence of bleeding will be summarized. If a sufficient number of bleeding events is observed, factors which potentially influence the occurrence of bleeding will be assessed by appropriate statistical procedures. Quantitative data will be described by the summary statistics and will be presented for the original data as well as for the difference to baseline. Frequency tables will be provided for qualitative data.

7.5 Efficacy analysis

All efficacy analyses will be performed on the full analysis set population. The incidence of symptomatic recurrent venous thromboembolism and asymptomatic deterioration in thrombotic burden on repeat imaging will be summarized.

7.6 PK/PD analysis

PK/PD modeling, using population approaches will be used to describe the pharmacokinetics of rivaroxaban, and to relate anticoagulant parameters of rivaroxaban with plasma concentrations.

7.7 Interim analyses

No interim analysis will be performed.

7.8 Determination of sample size

At least 8 children are planned to be enrolled in the study. For the area under the curve (AUC), a geometric coefficient of variation (geom. CV) of about 40% was observed in adults, and was also observed in study 12892 in the age group 12 to 18 years (n=9). In the age cohort 6 to <12 years, an even smaller geometric coefficient of variation was observed. Although it is expected from the model that the variability will be higher in neonates and infants, the exact numbers remain unclear. The sample size of 8 subjects will yield an exploratory 90% confidence interval for the geometric mean AUC-estimate between 50% and 200% of the estimate, provided the geometric coefficient of variation does not exceed 138%, which would be more than a tripling of the variability observed in adolescents. If the geometric coefficient of variation will be 80%, the exploratory 90% confidence interval for the geometric mean AUC-estimate would be located between 62% and 161% of the estimate.

7.9 Adverse events

Individual listings of adverse events (including age, gender, adverse event as reported, time to adverse event after study drug intake, duration, intensity, relation to study drug, action taken and outcome) will be provided.

7.9.1 Definitions

7.9.1.1 Adverse event (AE)

An AE is any untoward medical occurrence in a subject administered with a pharmaceutical product and does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, whether or not considered related to the drug. AE associated with the use of a drug, whether or not considered drug related, includes AE occurring in the course of the use of a drug, from an overdose whether accidental or intentional, from drug abuse, from drug withdrawal, or if there is a reasonable possibility that the event occurred purely as a result of participation in the study, even if it is not related to the drug.

The clinical manifestation of any failure of expected pharmacological action is not recorded as an AE, if it is already reflected as an outcome captured in the eCRF, except if the event fulfills the criteria for a “serious” AE.

A surgical procedure or intervention that was planned prior to visit 2 should not be recorded as an AE. Conditions, including abnormal physical examination findings, symptoms, and diseases will be recorded as medical history if they started before visit 2 and no symptoms or treatment are present until visit 2, or symptoms or treatment are present after visit 2 at unchanged intensity.

If the condition started or deteriorated after administration of study drug at visit 2, it will be documented as adverse event.

7.9.1.2 Serious adverse event (SAE)

An SAE is any untoward medical occurrence that at any dose is resulting in death, is life-threatening (i.e. the patient was at risk of death at the time of the event), requires hospitalization or prolongation of existing hospitalization unless the admission results in a hospital stay of less than 12 hours, is pre-planned, or is not associated with an AE (i.e. social hospitalization for purposes of respite care), results in persistent or significant disability/incapacity. In addition, SAE is a congenital anomaly or a birth defect or an important medical event, including associated invasive treatment, as judged by the investigator. For reporting of a SAE, local regulations take precedence if more stringent definitions are applicable.

7.9.1.3 Unexpected AEs

An unexpected AE is any adverse drug event whose specificity or severity is not consistent with the investigator brochure (or package inserts for marketed products). Also, reports which add significant information on specificity or severity of an already documented AE constitute unexpected AEs. For example, an event more specific or more severe than described in the investigator brochure would be considered "unexpected".

Specific examples: 1) acute renal failure as a labeled adverse event with a subsequent new report of interstitial nephritis and 2) hepatitis with a first report of fulminant hepatitis.

7.9.2 Relationship of AE to the study drug

The assessment of the causal relationship between an AE and the use of medication is a clinical decision based on all available information at the time of the completion of the eCRF and is based on whether there was a "reasonable causal relationship" to the medication.

An assessment of "no" would include the existence of a clear alternative explanation, e.g. mechanical bleeding at surgical site, or non-plausibility. An assessment of "yes" indicates that there is a reasonable suspicion that the AE is associated with the use of the drug. Factors in assessing the relationship of the AE to study treatment include the temporal sequence from drug administration (the event should occur after the drug is given) and the length of time from drug exposure, recovery on drug discontinuation (de-challenge), and recurrence on drug re-introduction (re-challenge), underlying, concomitant, or intercurrent diseases should be evaluated in the context of the natural history and course of any disease the child may have, concomitant medication or treatment and, finally, the pharmacology and pharmacokinetics of study treatment.

7.9.3 Causal relationship to protocol-required procedures

The assessment of a possible causal relationship between the AE and protocol-required procedures is based on the question whether there was a "reasonable causal relationship" to protocol-required procedure(s). Possible answers are "yes" or "no".

7.9.4 Intensity of an AE, action taken and outcome

The intensity of an AE is assessed as mild (usually transient in nature and generally not interfering with normal activities), moderate (sufficiently discomforting to interfere with normal activities), or severe (prevents normal activities).

Any action on study treatment to resolve the AE is to be documented as either: study drug withdrawn, interrupted, dose not changed, not applicable or unknown. Other specific treatment(s) of AEs will be documented as: none, remedial drug therapy or other. The outcome of the AE is to be documented as: recovered/resolved, recovering/resolving, recovered/resolved with sequelae, not recovered/not resolved, fatal or unknown.

7.9.5 Assessments and documentation of adverse events

Complications that occur during the screening period between visit 1 and visit 2 will not be reported as AEs, because no study medication or study related procedures are required during this period, but may be documented in the medical history, if applicable.

After study drug intake at visit 2, documentation of AEs must be supported by an entry in the subject's file. A laboratory test abnormality considered clinically relevant, e.g. causing the subject to withdraw from the study, requiring treatment or causing apparent clinical manifestations, or judged relevant by the investigator, should be reported as an AE. Each event should be described in detail along with start and stop dates, severity, relationship to study drug, action taken and outcome.

When assigning the cause of death, "death" should not be recorded as an AE on the AE page. Instead, "death" is the outcome of underlying AE(s).

7.9.6 Reporting of serious adverse events

All investigators will be thoroughly instructed and trained on all relevant aspects of the reporting obligations for SAEs. This information, including all relevant contact details, is summarized in the investigator site file and will be updated as needed.

SAEs occurring after study drug intake at visit 2 until 1 month after the last dose must be reported within 24 hours of the investigator's awareness. Reports should be as complete as possible, and must be followed up until resolution or stabilization. When required, and according to local law and regulations, SAEs must be reported to the ethics committee and regulatory authorities.

If reported, SAEs occurring after the protocol-defined observation period will be processed by Bayer according to all applicable regulations.

Bayer will inform all investigational sites about the occurrence of suspected unexpected serious adverse reactions (SUSARs) according to all applicable regulations.

7.9.7 Study specific exceptions to the (S)AE reporting

AEs between visit 1 and visit 2 will not need to be reported. The efficacy outcomes (symptomatic recurrent thromboembolism and asymptomatic deterioration in thrombotic burden on repeat imaging) will not be reported as (S)AE. Transfer of children to a rehabilitation unit as a standard practice will not be considered as a prolonged hospitalization and should not be reported as a SAE. However, if this transfer is part of treatment of a medical complication, it should be considered as prolonged hospitalization and the event should be reported as a SAE. To collect additional information about clinically important laboratory abnormalities, any laboratory abnormality that required cessation of the study drug will be captured as a SAE.

7.9.8 Expected AEs

The applicable reference document is the most current version of the investigator's brochure (IB) / Company Core Data Sheet (CCDS). Overview listings of frequent events that have occurred so far in the clinical development are shown in the current IB. If relevant new safety information is identified, it will be integrated into an update of the IB and distributed. The expectedness of AEs will be determined by Bayer according to the applicable reference document and according to all local regulations.

7.9.9 Adverse events of special safety interest

The following AEs are considered as AEs of special safety interest:

- Concurrent elevations of alanine aminotransferase (ALT) > 5x ULN and total bilirubin > 2x ULN with direct bilirubin > 20% of the total.
- A platelet count below $100 \times 10^9/L$.
- Allergic skin reactions, allergic systemic reactions

7.10 Premature discontinuation of study medication

Children prematurely discontinue study medication

- at the request of parents/legal representative without the need to provide a reason.
- if, in the investigator's opinion, study medication should be stopped for any reason.
- In case of symptomatic efficacy outcome for which anticoagulant or fibrinolytic therapy is indicated.
- at the (exceptional) request of Bayer.

If study medication is temporarily discontinued, it can be restarted as long as the total treatment duration does not exceed the intended 7-day treatment period. If study medication is permanently discontinued, further treatment is at the investigator's discretion.

If parents/legal representative indicate to stop study medication, the investigator will ask to continue with study visits as planned, only with the aim to collect potential study outcomes and AEs. If parents/legal representative indicate that they no longer authorize the investigator to continue to obtain outcome data, this will be respected and documented in the source records.

In all children who prematurely discontinue study treatment for other reasons than withdrawal of the informed consent, study visits will take place as planned only with the reason to collect potential study outcomes and AEs. A special effort will be made to collect data from children who did not complete all study visits.

7.11 Appropriateness of procedures / measurements

The diagnostic methods to document safety and efficacy outcomes are standard methods in clinical practice and are used and generally recognized as reliable, accurate and relevant.

8. Data handling and quality assurance

For all data entered into the eCRF, source documentation should be available at the site. A source document checklist will be used to identify the source data for all data points collected.

In accordance with GCP and Bayer's procedures, monitors will review the protocol, study requirements, and responsibilities with the site staff, including identification and documentation of source data items. Bayer personnel will monitor the site to verify that data are authentic, accurate, complete and that the safety and rights of participating children are being protected. In addition, they will assess if the study is conducted in accordance with the latest version of the protocol and study agreements. The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents.

8.1 Data processing

The data collection tool for this study will be a validated electronic system called RAVE and data will be entered into a validated database or data system (Tools for Syntactic Corpus Analysis [TOSCA]). Study data management will be performed in accordance with applicable Bayer's standards. This is applicable for data recorded on eCRF as well as for data from other study sources. Internationally recognized and accepted dictionaries will be used for data coding.

8.2 Audit and inspection

Bayer's (or a designated contract research organization's [CRO's]) quality assurance unit may conduct an audit to ensure compliance with GCP and regulatory requirements. The investigator/institution will be informed verbally at the closing meeting of the audit outcome. In addition, inspections by regulatory health authority representatives, ethic committees, and/or institutional review boards might occur and the site will notify Bayer immediately.

The investigator/institution agrees to allow the auditor or inspector direct access to all relevant documents and allocate time to the auditor/inspector to discuss any findings. Audits and inspections may occur at any time during or after completion of the study.

8.3 Archiving

Study documents will be archived safely and securely in such a way that they are readily available upon authorities' request. Patient and related hospital files will be archived according to local regulations and in accordance with the maximum period of time permitted by the hospital, institution or private practice. If the archiving procedures do not meet the minimum timelines required by Bayer, alternative arrangements will be made to ensure the availability of the source documents for the required period. The investigator/institution will notify Bayer if a change in archival arrangements occurs. The investigator site file will not be destroyed without Bayer's approval. The investigator's contract will contain all regulations relevant for the study center.

8.4 Missing data

Counts and proportion of missing data of baseline and post-baseline measurements will be displayed.

9. Premature termination of the study

The investigator has the right to stop participating in the study at any time.

Bayer has the right to close this study or study sites at any time, which may be due but not limited to the following reasons: 1) The risk-benefit ratio becomes unacceptable due to, for example, safety or efficacy findings from this study or results of parallel clinical studies. 2) Study conduct (e.g. recruitment rate; dropout rate; data quality; protocol compliance) does not suggest a proper completion of the trial within a reasonable time frame. For any of the above closures, the following applies: 1) closures should occur only after consultation between involved parties, 2) all affected institutions must be informed, as applicable, according to local law.

All study materials will be returned to Bayer, except documentation that has to remain stored at the site. This documentation can only be destroyed with approval from Bayer.

10. Ethical and legal aspects

10.1 Ethical and legal conduct of the study

The procedures set out in this protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that Bayer and the investigator abide by GCP guidelines and under the guiding principles detailed in the Declaration of Helsinki. The study will also be carried out in keeping with applicable local law(s) and regulation(s).

Documented approval from appropriate Independent Ethics Committees (IECs)/Institutional Review Boards (IRBs) will be obtained for all participating centers/countries before start of the study, according to GCP, local laws, regulations and organizations. When necessary, an extension, amendment or renewal of the IEC/IRB approval must be obtained and also forwarded to Bayer. The responsible unit (e.g. IEC/IRB, head of the study center/medical institution) must supply Bayer, upon request, a list of the IEC/IRB members involved in the vote and a statement to confirm that the IEC/IRB is organized and operates according to GCP and applicable laws and regulations.

Strict adherence to all specifications laid down in this protocol is required for all aspects of study conduct; the investigator may not modify or alter the procedures described in this protocol.

Modifications to the study protocol will not be implemented by either Bayer or the investigator without agreement by both parties. However, the investigator or Bayer may implement a deviation from, or a change of the protocol to eliminate an immediate hazard to the trial children without prior IEC/IRB/Bayer approval/favorable opinion. As soon as possible, the implemented deviation or change, the reasons for it and if appropriate the proposed protocol amendment should be submitted to the IEC/IRB/head of medical

institution/Bayer. Any deviations from the protocol must be explained and documented by the investigator.

For each participating EU country, the end of the study according to the EU Clinical Trial Directive will be reached when the last visit of the last subject for all centers in the respective country has occurred.

The end of the study as a whole will be reached as soon as the end of the study according to the above definition has been reached in all participating countries (EU and non-EU).

10.2 Consent

All relevant study information will be summarized in an integrated informed consent form provided by Bayer or the study center. A sample informed consent form is provided as a document separate to this protocol. Consent will be asked from the parents or legal representative.

The investigator or designee will explain all relevant aspects of the study to the parents/legal representative prior to entry into the study (i.e. before any examinations and procedures associated with the selection for the study are performed or any study-specific data is recorded on study-specific forms).

The parents/legal representative will have ample time and opportunity to ask questions and will be informed about the right to withdraw from the study at any time without any disadvantage and without having to provide reasons for their decision.

The child can only enter the study if the parents/legal representative agree to sign and date the informed consent and have done so. Then the investigator or designee will sign and date the form. The parents/legal representative will receive a copy of the signed and dated form(s).

The signed informed consent will remain in the investigator site file or, if locally required, in the patient's note/file of the medical institution. If informed consent is obtained on the date that study specific procedures are performed, the study record or child's clinical record must clearly show that informed consent was obtained prior to these procedures.

The informed consent form and any other written information provided to the parents/legal representative will be revised whenever important new information becomes available that may be relevant to the consent, or if there is an amendment to the protocol that necessitates a change to the written informed consent form. The investigator will inform the parents/legal representative of changes in a timely manner and will ask the parents/legal representative to confirm participation in the study by signing the revised informed consent form. Revised informed consent must receive the IEC's/IRB's approval before implementation.

11. Investigators and other study personnel

The principal investigator of each site must sign the protocol signature sheet before recruitment may start at the respective center. Likewise, all protocol amendments/integrated protocols must be signed and dated by the principal investigator before coming into effect at the respective center. A complete list of all participating centers and their investigators, as well as all required signature documents, will be maintained in the Bayer study file.

If required by local law, local co-sponsors will be nominated; they will be identified on the respective country-specific signature pages.

12. Publication policy and use of data

Bayer is committed to publication of the results of every study it performs. The steering committee will be responsible for the publication and presentation strategy. All publications will be based on data released or agreed by Bayer, verified by the steering committee. The study protocol has been made publicly available on the internet at www.clinicaltrials.gov.

13. Insurance for children

Bayer maintains clinical trial insurance coverage for this study in accordance with the laws and regulations of the countries in which the study is performed.

14. Confidentiality

All records identifying the child will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available.

Children's names will not be supplied to Bayer. Only the child's subject identification (SID) number will be recorded in the eCRF. If the child's name appears on any other document, it will be anonymized. Study data stored in a computer will be handled in accordance with local data protection laws. As part of the informed consent process, parents/legal representative will be informed in writing that representatives of Bayer, IEC/IRB, or regulatory authorities may inspect their medical records to verify collected information and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws. If the results of the study are published, the child's identity will remain confidential. The investigator will maintain a list to enable children to be identified.

15. Reference list

1. Kearon C, Akl EA, Comerota AJ, Prandoni P, Bounameaux H, Goldhaber SZ, et al. Antithrombotic Therapy for VTE Disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012 Feb;141(2 Suppl):e419S-494S.
2. Ageno W, Gallus AS, Wittkowsky A, Crowther M, Hylek EM, Palareti G; American College of Chest Physicians. Oral anticoagulant therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012 Feb;141(2 Suppl):e44S-88S.
3. Agnelli G, Gallus A, Goldhaber SZ, Hass S, Huisman MV, Hull RD, et al. Treatment of proximal deep-vein thrombosis with the oral direct factor Xa inhibitor rivaroxaban (BAY 59-7039): the ODIXa-DVT (Oral Direct Factor Xa Inhibitor BAY 59-7939 in Patients With Acute Symptomatic Deep-Vein Thrombosis) study. Circulation 2007 Jul 10; 116(2):180-7.
4. Buller HR, Lensing AW, Prins MH, Agnelli G, Cohen A, Gallus AS, et al. A dose ranging study evaluating once-daily oral administration of the factor Xa inhibitor rivaroxaban in the treatment of patients with acute symptomatic deep vein thrombosis: the Einstein-DVT Dose-Ranging Study. Blood 2008 Sep 15; 112(6):2242-7.
5. The EINSTEIN investigators. Oral Rivaroxaban for Symptomatic Venous Thromboembolism. N Engl J Med 2010; 363: 2499-2510.
6. Chalmers EA. Epidemiology of venous thromboembolism in neonates and children. Thromb Res 2006;118(1):3-12.
7. Schmidt B, Andrew M. Neonatal thrombosis: report of a prospective Canadian and international registry. Pediatrics. 1995;96(5 pt 1): 939-943
8. Andrew M, David M, Adams M, Ali K, Anderson R, Barnard D, et al. Venous thromboembolic complications (VTE) in children: first analyses of the Canadian Registry of VTE. Blood 1994;83 (5):1251-1257.
9. Report of the Second Task Force on Blood Pressure Control in Children. Pediatrics 1987; 79(1):1-25.

16. Protocol amendments

16.1 Amendment 1

16.1.1 Overview of changes

Amendment 1 is the first global amendment dated 21 Jul 2015.

16.1.1.1 Change 1: Addition of minimum body weight for inclusion

A minimum body weight for inclusion to the study was added to inclusion criterion 6.

Rationale:

The minimum body weight of 2600 g was added as inclusion criterion based on a Steering Committee recommendation. This will ensure that the total volume of blood collected in the course of the study does not exceed the total volume allowed by respective guidelines.

Affected sections: [Synopsis](#), [Section 4.2 Inclusion criteria](#)

16.1.1.2 Change 2: Addition of examples for concomitant medication excluding study participation

Examples for concomitant medication were added to exclusion criteria 9 and 10.

Rationale:

Examples were added for consistency with other rivaroxaban pediatric studies. It is now specified that fluconazole is an allowed antimycotic drug.

Affected sections: [Synopsis](#), [Section 4.3 Exclusion criteria](#)

16.1.1.3 Change 3: Addition of blood pressure measurement at screening

The blood pressure measurement was added at Visit 1 in the study flow chart and the visit description at screening.

Rationale:

The addition of the blood pressure measurement to the flow chart highlights the requirement to check for exclusion criterion 6 and ensures consistency with the inclusion/exclusion criteria and description of the screening visit.

Affected section: [Synopsis](#), [Section 6.2 Visit 1 – Screening visit at 1 to 10 days before Visit 2](#)

16.1.1.4 Change 4: Minor clarifications for consistency

Minor, consistency and logical clarifications were made throughout the document.

Rationale:

Changes were made to ensure consistency throughout the document. These changes do not affect the overall study concept.

Affected sections: [Synopsis](#), [Section 5.1.1 Rivaroxaban regimen](#)

16.1.1.5 Change 5: Addition of INR measurement at Visit 2

The INR measurement was added at Visit 2 in the study flow charts and the visit description at screening.

Rationale:

Children who switch from VKA to rivaroxaban should avoid using both drugs at therapeutic doses simultaneously. Rivaroxaban can be started only if the INR is below 2.5. Therefore, the INR has to be collected before rivaroxaban is started.

Affected section: [Synopsis](#), [Section 5.1.1.3 Switching from VKA to rivaroxaban](#)

16.1.1.6 Change 6: Addition of body-weight adjusted dosing table

A body weight-adjusted dosing Table for rivaroxaban oral suspension was added.

Rationale:

After confirmation of the age- and body weight-adjusted dosing regimen for the age group between 6 months and less than 2 years in the phase I study 12892 and approval by the data monitoring committee and steering committee, the dosing schedule/regimen for the present study 17618 was added.

Affected section: [Section 5.1.1 Rivaroxaban regimen](#)

16.1.1.7 Change 7: Replacement of CIAC confirmation for enrollment

The text of visit 2 was change in order to enroll children without prior CIAC confirmation if they meet the inclusion criteria and do not meet any of the exclusion criteria.

Rationale:

It was decided that a CIAC evaluation to confirm enrollment of a child to the study is not required. If children meet the inclusion criteria and do not meet any of the exclusion criteria, they can be enrolled without further CIAC confirmation. This is in line with other studies in the rivaroxaban pediatric program.

Affected section: [Section 6.3 Visit 2 – Treatment visit at Day 1](#)

16.1.1.8 Change 8: Clarification of recording food and fluid intake together with rivaroxaban

The recording of estimated food and fluid volumes that are given together with rivaroxaban was further specified.

Rationale:

The new wording considers liquid meals but also solid meals, which should be accompanied by fluid intake.

Affected section: [Section 6.3 Visit 2 – Treatment visit at Day 1](#), [Section 6.4 Visit 3 – Treatment visit at Day 3](#), [Section 6.5 Visit 4 – Day 8](#)

16.1.2 Changes to the protocol text

In this section, all affected protocol sections are detailed; the sequence of the sections follows the structure of the original protocol. In the display of modifications, the “old text” refers to the protocol version preceding this amendment. Deletions are ~~crossed-out~~ in the “old text”. Additions are underlined in the “new text”. Corrections of typing errors or omissions are not highlighted in this amendment.

16.1.2.1 Synopsis

This section was modified via Changes 1, 2, 3, 4 and 5.

Old text:

[...]

	[...]
Diagnosis and main criteria for inclusion /exclusion	Inclusion
	[...]
	5. Informed consent provided.
	[...]
	Exclusion
	[...]
	9. Concomitant use of strong inhibitors of both cytochrome P450 isoenzyme 3A4 (CYP3A4) and P-glycoprotein (P-gp)
	10. Concomitant use of strong inducers of CYP3A4
	[...]
	[...]

[...]

New text:

[...]

	[...]
Diagnosis and main criteria for inclusion /exclusion	<p>Inclusion</p> <p>[...]</p> <p>5. Informed consent provided.</p> <p>6. <u>Body weight >2600 g.</u></p> <p>[...]</p> <p>Exclusion</p> <p>[...]</p> <p>9. Concomitant use of strong inhibitors of both cytochrome P450 isoenzyme 3A4 (CYP3A4) and P-glycoprotein (P-gp), <u>e.g. all human immunodeficiency virus protease inhibitors and the following azole-antimycotics agents: ketoconazole, itraconazole, voriconazole, posaconazole, if used systemically (fluconazole is allowed)</u></p> <p>10. Concomitant use of strong inducers of CYP3A4, <u>e.g. rifampicin, rifabutin, phenobarbital, phenytoin and carbamazepine</u></p> <p>[...]</p>
	[...]

[...]

Old text:

[...]

Table 1: Flow chart: study visits

	Screen ^a	Treatment period			30 day post study treatment contact
Visit	1	2	3	4	5
Days	Day -10 to Day 1	Day 1	Day 3	Day 8	Day 37+ 7 days
[...]					
Record anticoagulant medication	•	•			
Obtain body weight	•	•	•		
Check Hb, platelets, creatinine, ALT, total and direct bilirubin		• ^b			
Obtain ALT, total and direct bilirubin				•	
Re-confirm in-/exclusion criteria		•			
[...]					

ALT = alanine aminotransferase, eCRF = electronic case report form, Hb = hemoglobin

^a The screening visit can be performed up to 10 days prior to inclusion into the study.

^b Hb, platelets, creatinine, ALT, total and direct bilirubin results should be available within 10 days prior to inclusion into the study. If results are not available, obtain blood sample.

^c If child discharged from the hospital.

^d Compile adjudication package and send it to the adjudication office.

^e Repeat ultrasound can be obtained on Day 8 ± 1.

[...]

New text:

[...]

Table 1: Flow chart: study visits

	Screen ^a	Treatment period			30 day post study treatment contact
Visit	1	2	3	4	5
Days	Day -10 to Day 1	Day 1	Day 3	Day 8	Day 37+ 7 days
[...]					
Record anticoagulant medication	•	•			
Obtain blood pressure	•				
Obtain body weight	•	•	•		
Check Hb, platelets, creatinine, ALT, total and direct bilirubin	• ^b				
Obtain ALT, total and direct bilirubin				•	
Re-confirm in-/exclusion criteria		•			
Obtain INR, if receiving VKA ^f		•			
[...]					

ALT = alanine aminotransferase, eCRF = electronic case report form, Hb = hemoglobin, INR= international normalized ratio, VKA= vitamin K antagonist

^a The screening visit can be performed up to 10 days prior to inclusion into the study.

^b Hb, platelets, creatinine, ALT, total and direct bilirubin results should be available within 10 days prior to inclusion into the study. If results are not available, obtain blood sample.

^c If child discharged from the hospital.

^d Compile adjudication package and send it to the adjudication office.

^e Repeat ultrasound can be obtained on Day 8 ± 1.

^f INR should be below 2.5 before starting rivaroxaban (see Section 5.1.1.3).

[...]

16.1.2.2 Section 4.2 Inclusion criteria

This section was modified via Change 1.

Old text: [...]

4. Oral feeding/nasogastric/gastric feeding for at least 10 days.
5. Informed consent provided.

[...]

New text: [...]

4. Oral feeding/nasogastric/gastric feeding for at least 10 days.
5. Informed consent provided.
6. Body weight >2600 g.

[...]

16.1.2.3 Section 4.3 Exclusion criteria

This section was modified via Change 2.

Old text: [...]

9. Concomitant use of strong inhibitors of both cytochrome P450 isoenzyme 3A4 (CYP3A4) and P-glycoprotein (P-gp).
10. Concomitant use of strong inducers of CYP3A4.

[...]

New text: [...]

9. Concomitant use of strong inhibitors of both cytochrome P450 isoenzyme 3A4 (CYP3A4) and P-glycoprotein (P-gp), e.g. all human immunodeficiency virus protease inhibitors and the following azole-antimycotics agents: ketoconazole, itraconazole, voriconazole, posaconazole, if used systemically (fluconazole is allowed).
10. Concomitant use of strong inducers of CYP3A4, e.g. rifampicin, rifabutin, phenobarbital, phenytoin and carbamazepine.

[...]

16.1.2.4 Section 5.1.1 Rivaroxaban regimen

This section was modified via Change 4 and 6.

Old text: [...]

If a rivaroxaban dose was missed, the child should take rivaroxaban immediately to ensure intake of the ~~maximum~~ daily dose per day. In this case, two oral suspension doses may be taken at once. Thereafter, the child should continue with the regular b.i.d. rivaroxaban administrations.

Instructions on how to handle rivaroxaban oral suspension are provided in the oral suspension handling guidelines, which will be issued separately from the protocol. Parents will be instructed and trained to prepare the suspension according to the guidelines, if applicable. The training will be documented.

~~Once the age- and body weight-adjusted dosing regimen has been confirmed for the age group between 6 months and less than 2 years in the phase I study 12892 and approved by the data monitoring committee and steering committee, the dosing schedule/regimen for the present study 17618 (age group birth to less than 6 months) will be made available through an administrative amendment. The investigators and ethics committees/IRBs will receive the administrative amendment well in advance with an opportunity for evaluation before permission will be given to start enrolling children in this age group.~~

[...]

New text: [...]

If a rivaroxaban dose was missed, the child should take rivaroxaban immediately to ensure intake of the total daily dose per day. In this case, two oral suspension doses may be taken at once. Thereafter, the child should continue with the regular b.i.d. rivaroxaban administrations.

[...]

The body weight-adjusted rivaroxaban dosing schedule is provided in Table 5–1.

Table 3: Rivaroxaban dosing schedule

Body weight [kg]		Oral suspension dose (b.i.d.)	Total daily dose
Min	Max	[mg]	[mg]
<u>2.6</u>	<u><3</u>	<u>0.5</u>	<u>1.0</u>
<u>3</u>	<u><4</u>	<u>0.6</u>	<u>1.2</u>
<u>4</u>	<u><5</u>	<u>0.9</u>	<u>1.8</u>
<u>5</u>	<u><6</u>	<u>1.2</u>	<u>2.4</u>
<u>6</u>	<u><7</u>	<u>1.6</u>	<u>3.2</u>
<u>7</u>	<u><8</u>	<u>1.9</u>	<u>3.8</u>
<u>8</u>	<u><9</u>	<u>2.5</u>	<u>5.0</u>
<u>9</u>	<u><10</u>	<u>2.7</u>	<u>5.4</u>
<u>10</u>	<u><12</u>	<u>2.9</u>	<u>5.8</u>
<u>12</u>	<u><20</u>	<u>3.2</u>	<u>6.4</u>

[...]

16.1.2.5 Section 5.1.1.3 Switching from VKA to rivaroxaban

This section was modified via Change 5.

New text: [...]

Children who switch from VKA to rivaroxaban should avoid using both drugs at therapeutic doses simultaneously. Rivaroxaban can be started only if the INR is < 2.5.

[...]

16.1.2.6 Section 6.2 Visit 1 – Screening visit at 1 to 10 days before Visit 2

This section was modified via Change 3.

Old text: [...]

Then demographic data, medical history, weight and anticoagulant medication will be collected.

[...]

New text: [...]

Then demographic data, medical history, weight, blood pressure and anticoagulant medication will be collected.

[...]

16.1.2.7 Section 6.3 Visit 2 – Treatment visit at Day 1

This section was modified via Changes 7 and 8.

Old text: [...]

~~If the CIAC confirmed the qualifying thrombotic event, then reconfirm eligibility. If results for hemoglobin, platelets, creatinine, ALT and total and direct bilirubin were not available within 10 days prior to enrollment, obtain a blood sample. If the child still meets the inclusion criteria and does not meet any of the exclusion criteria, the child can be enrolled.~~

The following assessments and procedures have to be performed on visit 2:

[...]

- Document the exact time of rivaroxaban intake and the type (e.g., breast milk, formula, porridge, or pureed food) and estimated volume of food rivaroxaban was administered with.

[...]

New text: [...]

If the child still meets the inclusion criteria and does not meet any of the exclusion criteria, the child can be enrolled. If results for hemoglobin, platelets, creatinine, ALT and total and direct bilirubin were not available within 10 days prior to enrollment, obtain a blood sample. For children receiving VKA, the INR should be obtained. INR should be below 2.5 before starting rivaroxaban.

The following assessments and procedures have to be performed on visit 2:

[...]

- Document the exact time of rivaroxaban intake and the type (e.g., breast milk, formula, porridge, or pureed food) and estimated volume of fluid (e.g. breast milk and formula) or food (e.g. porridge or pureed food) rivaroxaban was administered with.

[...]

16.1.2.8 Section 6.4 Visit 3 – Treatment visit at Day 3

This section was modified via Change 8.

Old text: [...]

- Instruct to document in the study booklet
 - the exact time of the last dose of rivaroxaban on the day prior to visit 4,
 - the volume and type of liquid (e.g., breast milk, formula, water, juice) used to predilute the rivaroxaban oral suspension,
 - the type (e.g. breast milk, formula, porridge, or pureed food) and estimated volume of food rivaroxaban was administered with,

[...]

New text: [...]

- Instruct to document in the study booklet
 - the exact time of the last dose of rivaroxaban on the day prior to visit 4,
 - the volume and type of liquid (e.g., breast milk, formula, water, juice) used to predilute the rivaroxaban oral suspension,
 - the type (e.g. breast milk, formula, porridge, or pureed food) and estimated volume of fluid (e.g. breast milk and formula) or food (e.g. porridge or pureed food) rivaroxaban was administered with,

[...]

16.1.2.9 Section 6.5 Visit 4 – Day 8

This section was modified via Change 8.

Old text: [...]

- Document
 - the exact time of the last dose of rivaroxaban on the day prior to visit 4,
 - the volume and type of liquid (e.g., breast milk, formula, water, juice) used to predilute the rivaroxaban oral suspension,
 - the type (e.g. breast milk, formula, porridge, or pureed food) and estimated volume of food rivaroxaban was administered with.

[...]

New text: [...]

- Document
 - the exact time of the last dose of rivaroxaban on the day prior to visit 4,
 - the volume and type of liquid (e.g., breast milk, formula, water, juice) used to predilute the rivaroxaban oral suspension,
 - the type (e.g. breast milk, formula, porridge, or pureed food) and estimated volume of fluid (e.g. breast milk and formula) or food (e.g. porridge or pureed food) rivaroxaban was administered with.

[...]

16.2 Amendment 4

16.2.1 Overview of changes

Amendment 4 is the second global amendment dated 10 May 2016.

16.2.1.1 Change 1: Replacement of Medical Expert details

The Medical Expert and the contact details were updated on the Title page.

Rationale:

The responsible Medical Expert for this study has changed and details on the title page were updated accordingly.

Affected sections: [Title page](#)

16.2.1.2 Change 2: Modification of study population

The study population was extended by removing the requirement of having a “catheter-related” arterial or venous thrombosis.

Rationale:

The original study protocol focused on children with catheter-related arterial or venous thrombosis, as this type of thrombosis – based on the limited amount of literature available – was considered to be the most prevalent form of thrombosis in the age range birth to 6 months. However, feedback from investigators indicates, that children with other forms of thrombosis requiring anticoagulant therapy should be included into the study as well. Through this change, the study will not only collect PK/PD, safety and efficacy data in catheter-related arterial or venous thrombosis, but in all kind of arterial or venous thrombosis requiring anticoagulant therapy.

Affected sections: [Title page](#); [Synopsis](#); [Section 1. Introduction](#); [Section 1.2 Venous or arterial thrombosis](#); [Section 1.3 Rationale of the study and risk-benefit assessment](#); [Section 3. Study design](#); [Section 3.1 Study description](#); [Section 4.2 Inclusion criteria](#); [Section 6.1 Study visits](#)

16.2.1.3 Change 3: Modification of inclusion criterion 1

Inclusion criterion 1 was changed.

Rationale:

Current guidelines recommend anticoagulant therapy for 6 weeks in case of catheter-related thrombosis. However, in current practice, many neonates and young infants are treated for a shorter period of time. Therefore, the minimum time of initial heparinization before start of rivaroxaban treatment is reduced from at least 2 weeks to at least 5 days in order to accommodate for shorter treatment durations.

Affected sections: [Synopsis](#); [Section 4.2 Inclusion criteria](#)

16.2.1.4 Change 4: Clarification of exclusion criterion 6

In exclusion criterion 6, the word uncontrolled was added.

Rationale:

Children with a antihypertensive therapy leading to normal blood pressure values (ie. < 95th percentile) are allowed to be enrolled in the study.

Affected sections: [Synopsis](#); [Section 4.3 Exclusion criteria](#)

16.2.1.5 Change 5: Clarification of exclusion criterion 12

In exclusion criterion 12, it was clarified that children should not have an indication for continued antiplatelet or NSAID therapy. However, incidental use is allowed.

Rationale:

Children should not have an indication requiring continued antiplatelet or NSAID therapy at the time rivaroxaban treatment is started. Incidental doses of an antiplatelet or NSAID treatment may be given during the 7-day treatment course with rivaroxaban.

Affected sections: [Synopsis](#); [Section 4.3 Exclusion criteria](#); [Section 4.4 Concomitant medication](#)

16.2.1.6 Change 6: Change of oral suspension formulation

The rivaroxaban formulation was changed from “ready-to-use” suspension to “granules for oral suspension”.

Rationale:

The study started with the rivaroxaban “ready-to-use” oral suspension, which requires a dilution step during preparation of individual doses. As this dilution step is putting an additional burden on parents of sick children and may introduce a potential source of handling errors, the formulation in this study will be replaced by the “granules for oral suspension” formulation, which was recently developed, and is currently investigated in a phase I study in children aged 6 months to 12 years (# 17992), after the formulation had been tested in a relative bioavailability in adults. PK data obtained from 16 children (thereof, 5 children aged 6 months to 2 years) after administration of the resuspended granules for oral suspension are in line with predictions by the pediatric physiologically-based PK (PBPK) model. The granules for oral suspension formulation does not require dilution of individual doses, and is the preferred formulation for the phase III program.

Affected sections: [Synopsis](#); [Section 3.1 Study description](#); [Section 5.1.1 Rivaroxaban regimen](#); [Section 5.5 Packaging, labeling, and storage](#); [Section 6.3 Visit 2 – Treatment visit at Day 1](#); [Section 6.4 Visit 3 – Treatment visit at Day 3](#); [Section 6.5 Visit 4 – Day 8](#)

16.2.1.7 Change 7: Clarification of CIAC assessment

The process for assessment of the index event by the CIAC was clarified.

Rationale:

The CIAC will assess the index event; however, inclusion of child into the study does not depend on the outcome of the assessment.

Affected sections: [Section 6.2 Visit 1 – Screening visit at 1 to 10 days before Visit 2](#)

16.2.1.8 Change 8: Change of drug accountability and compliance assessment procedure

At visit 3 (day 3) drug accountability and compliance will be not be assessed.

Rationale:

Due to the small dose volumes and the limited accuracy of measuring the remaining volume after 3 days of dosing, it was decided to measure the volume only after completion of treatment.

Affected sections: [Synopsis](#); [Section 6.4 Visit 3 – Treatment visit at Day 3](#)

16.2.1.9 Change 9: Timing of rivaroxaban administration in relation to feeding

With the introduction of the granules for oral suspension formulation, rivaroxaban should be administered immediately before or (early) during feeding.

Rationale:

The properties of the granules formulation allows for rivaroxaban administration immediately before or early during feeding. This timing is also more consistent with instructions in case of administrations through a gastric or nasogastric tube. This should be suitable to reduce the risk of children refusing drug intake. In addition, drug administration before or early during feeding should lower the risk that all or part of the suspensions is spit out (with the usual burp after feeding).

Affected section: [Section 5.1.1 Rivaroxaban regimen](#)

16.2.2 Changes to the protocol text

In this section, all affected protocol sections are detailed; the sequence of the sections follows the structure of the original protocol. In the display of modifications, the “old text” refers to the protocol version preceding this amendment. Deletions are ~~crossed out~~ in the “old text”. Additions are underlined in the “new text”. Corrections of typing errors or omissions are not highlighted in this amendment.

16.2.2.1 Title page

This section was modified based on Changes 1 and 2.

Old text:

[...]

7-day study of the safety, efficacy and the pharmacokinetic and pharmacodynamic properties of oral rivaroxaban in children from birth to less than 6 months with ~~catheter-related~~ arterial or venous thrombosis

[...]

PPD	PPD	
PPD		at Bayer
PPD	Bayer HealthCare Pharmaceuticals	
PPD	PPD	
PPD	PPD	Brazil
	Telephone:	PPD
	Email:	PPD

[...]

New text:

[...]

7-day study of the safety, efficacy and the pharmacokinetic and pharmacodynamic properties of oral rivaroxaban in children from birth to less than 6 months with arterial or venous thrombosis

[...]

PPD	PPD	
PPD	PPD	
PPD	PPD	
PPD	PPD	
	Telephone:	PPD
	Email:	PPD

[...]

16.2.2.2 Synopsis

This section was modified based on Changes 2, 3, 4 and 5.

Old text:

[...]

Title	7-day study of the safety, efficacy and the pharmacokinetic and pharmacodynamic properties of oral rivaroxaban in children from birth to less than 6 months with catheter-related arterial or venous thrombosis
[...]	
Indication	Children from birth to less than 6 months with documented symptomatic or asymptomatic catheter-related arterial or venous thrombosis
Diagnosis and main criteria for inclusion /exclusion	<p>Children from birth to less than 6 months with documented symptomatic or asymptomatic catheter-related arterial or venous thrombosis who have been treated with anticoagulant therapy for at least two weeks.</p> <p>Inclusion</p> <ol style="list-style-type: none"> Children from birth to less than 6 months with documented symptomatic or asymptomatic catheter-related venous or arterial thrombosis who have been treated with anticoagulant therapy for at least two weeks. <p>[...]</p> <p>Exclusion</p> <ol style="list-style-type: none"> [...] Creatinine > 1.5 times of normal Hypertension defined as > 95th percentile^a <p>[...]</p> <ol style="list-style-type: none"> Indication for anticoagulant therapy other than current thrombosis Indication for antiplatelet therapy or non-steroid anti-inflammatory drug (NSAID) therapy [...]
[...]	
Methodology	Children with confirmed catheter-related arterial or venous thrombosis who have been treated with anticoagulant therapy for at least two weeks .
[...]	[...]
[...]	

[...]

New text:

[...]

Title	7-day study of the safety, efficacy and the pharmacokinetic and pharmacodynamic properties of oral rivaroxaban in children from birth to less than 6 months with arterial or venous thrombosis
[...]	
Indication	Children from birth to less than 6 months with documented symptomatic or asymptomatic arterial or venous thrombosis
Diagnosis and main criteria for inclusion /exclusion	<p>Children from birth to less than 6 months with documented symptomatic or asymptomatic arterial or venous thrombosis who have been treated with anticoagulant therapy for at least <u>five days</u>.</p> <p>Inclusion</p> <ol style="list-style-type: none"> 1. Children from birth to less than 6 months with documented symptomatic or asymptomatic venous or arterial thrombosis who have been treated with anticoagulant therapy for at least <u>five days</u>. [...] <p>Exclusion</p> <ol style="list-style-type: none"> 4. [...] 5. Creatinine > 1.5 times of normal 6. <u>Uncontrolled</u> hypertension defined as > 95th percentile^a [...] 11. Indication for anticoagulant therapy other than current thrombosis 12. <u>An</u> indication for <u>continued</u> antiplatelet therapy or non-steroid anti-inflammatory drug (NSAID) therapy. <u>Incidental use is allowed</u>. 13. [...]
[...]	
Methodology	<p>Children with confirmed arterial or venous thrombosis who have been treated with anticoagulant therapy for at least <u>five days</u>.</p> <p>[...]</p>
[...]	

[...]

16.2.2.3 Section 1. Introduction

This section was modified based on Change 2.

Old text:

[...]

In this phase I/II study, children with confirmed symptomatic or asymptomatic ~~catheter-related~~ arterial or venous thrombosis will be treated for 7 days with the age- and body weight-adjusted rivaroxaban twice daily dosing regimen to achieve a similar exposure as that observed in adults treated for VTE with 20 mg rivaroxaban once daily.

[...]

New text:

[...]

In this phase I/II study, children with confirmed symptomatic or asymptomatic arterial or venous thrombosis will be treated for 7 days with the age- and body weight-adjusted rivaroxaban twice daily dosing regimen to achieve a similar exposure as that observed in adults treated for VTE with 20 mg rivaroxaban once daily.

[...]

16.2.2.4 Section 1.2 Venous or arterial thrombosis

This section was modified based on Change 2.

Old text:

[...]

1.2 ~~Catheter-related~~ venous or arterial thrombosis

[...]

New text:

[...]

1.2 Venous or arterial thrombosis

[...]

16.2.2.5 Section 1.3 Rationale of the study and risk-benefit assessment

This section was modified based on Change 2.

Old text:

[...]

To carefully allow for the evaluation of rivaroxaban in neonates and children younger than 6 months with confirmed symptomatic or asymptomatic ~~catheter-related~~ arterial or venous thrombosis, we elected to evaluate the selected rivaroxaban dose regimen first in children that have been treated with anticoagulant therapy for at least ~~two weeks~~. If this study reveals that the selected rivaroxaban dose regimen results in a similar exposure as that observed with 20 mg rivaroxaban in adults, and safety and efficacy is confirmed, a subsequent study will evaluate the selected rivaroxaban dose regimen for the acute and continued treatment of VTE.

[...]

New text:

[...]

To carefully allow for the evaluation of rivaroxaban in neonates and children younger than 6 months with confirmed symptomatic or asymptomatic arterial or venous thrombosis, we elected to evaluate the selected rivaroxaban dose regimen first in children that have been treated with anticoagulant therapy for at least five days. If this study reveals that the selected rivaroxaban dose regimen results in a similar exposure as that observed with 20 mg rivaroxaban in adults, and safety and efficacy is confirmed, a subsequent study will evaluate the selected rivaroxaban dose regimen for the acute and continued treatment of VTE.

[...]

16.2.2.6 Section 3. Study design

This section was modified based on Change 2.

Old text:

[...]

This is a non-randomized, open label, multicenter study evaluating the safety, efficacy and PK/PD profile of a 7-day treatment with age- and body weight-adjusted oral rivaroxaban in neonates and infants younger than 6 months with symptomatic or asymptomatic ~~catheter-related~~ arterial or venous thrombosis.

[...]

New text:

[...]

This is a non-randomized, open label, multicenter study evaluating the safety, efficacy and PK/PD profile of a 7-day treatment with age- and body weight-adjusted oral rivaroxaban in neonates and infants younger than 6 months with symptomatic or asymptomatic arterial or venous thrombosis.

[...]

16.2.2.7 Section 3.1 Study description

This section was modified based on Changes 2 and 6.

Old text:

[...]

Neonates and infants aged less than 6 months who pass the screen of in- and exclusion criteria ~~and who have been treated for at least 2 weeks with heparin and /or VKA for confirmed symptomatic or asymptomatic catheter-related~~ arterial or venous thrombosis are eligible for the study. Study treatment consists of a 7-day treatment with an age- and body weight-adjusted twice daily oral rivaroxaban dosing to achieve a similar exposure as that observed in adults treated for venous thromboembolism (VTE) with 20 mg rivaroxaban once daily. Rivaroxaban will be provided as an oral suspension (1 mg/mL) using a b.i.d. regimen with 12-hour intervals.

[...]

New text:

[...]

Neonates and infants aged less than 6 months who pass the screen of in- and exclusion criteria, who have been treated for at least five days with heparin and /or VKA for confirmed symptomatic or asymptomatic arterial or venous thrombosis are eligible for the study. Study treatment consists of a 7-day treatment with an age- and body weight-adjusted twice daily oral rivaroxaban dosing to achieve a similar exposure as that observed in adults treated for venous thromboembolism (VTE) with 20 mg rivaroxaban once daily. Rivaroxaban will be provided as granules for preparation of an oral suspension (1 mg/mL after re-suspension) using a b.i.d. regimen with 12-hour intervals.

[...]

16.2.2.8 Section 4.2 Inclusion criteria

This section was modified based on Changes 2 and 3.

Old text:

[...]

1. Children from birth to less than 6 months with documented symptomatic or asymptomatic ~~catheter-related~~ venous or arterial thrombosis who have been treated with anticoagulant therapy for at least ~~two weeks~~.

[...]

New text:

[...]

1. Children from birth to less than 6 months with documented symptomatic or asymptomatic venous or arterial thrombosis who have been treated with anticoagulant therapy for at least five days.

[...]

16.2.2.9 Section 4.3 Exclusion criteria

This section was modified based on Changes 4 and 5.

Old text:

[...]

6. Hypertension defined as >95th percentile.
[...]
12. Indication for antiplatelet therapy or non-steroid anti-inflammatory drug (NSAID) therapy.

[...]

New text:

[...]

6. Uncontrolled hypertension defined as >95th percentile.

[...]

12. An indication for continued antiplatelet therapy or non-steroid anti-inflammatory drug (NSAID) therapy. Incidental use is allowed.

[...]

16.2.2.10 Section 4.4 Concomitant medication

This section was modified based on Change 5.

Old text:

[...]

Concomitant medications include either continuation of a treatment started before study enrollment, or addition of a new treatment during the study. An indication for the use of NSAIDs or antiplatelet agents is an exclusion criterion since they increase the risk for bleeding in patients treated with anticoagulants.

[...]

New text:

[...]

Concomitant medications include either continuation of a treatment started before study enrollment, or addition of a new treatment during the study. An indication for the continued use of NSAIDs or antiplatelet agents is an exclusion criterion since they increase the risk for bleeding in patients treated with anticoagulants. However, incidental use is allowed.

[...]

16.2.2.11 Section 5.1.1 Rivaroxaban regimen

This section was modified based on Change 9.

Old text:

Age- and body weight-adjusted rivaroxaban will be administered twice daily (approximately 12 hours apart) as oral suspension. Rivaroxaban will be taken in the morning and evening during ~~or directly after~~ feeding.

[...]

New text:

[...]

Age- and body weight-adjusted rivaroxaban will be administered twice daily (approximately 12 hours apart) as oral suspension. Rivaroxaban will be taken in the morning and evening immediately before or (early) during feeding.

16.2.2.12 Section 5.4.1 Rivaroxaban

This section was modified based on Change 6.

Old text:

[...]

Rivaroxaban will be provided as a 0.1% suspension (1 mg/mL). Rivaroxaban will be dosed according to body weight. Since children with renal impairment will be excluded from the study, a dose adaptation is not indicated.

[...]

New text:

[...]

Rivaroxaban will be provided as granules for preparation of a 0.1% oral suspension (1 mg/mL). Rivaroxaban will be dosed according to body weight. Since children with renal impairment will be excluded from the study, a dose adaptation is not indicated.

[...]

16.2.2.13 Section 5.5 Packaging, labeling, and storage

This section was modified based on Change 6.

Old text:

[...]

A system of numbering in accordance with Good Manufacturing Practice (GMP) will be used, ensuring that each dose of study medication can be traced back to the respective bulk ware of the ingredients. A complete record of batch numbers and expiry dates of all study medication provided by Bayer, as well as the labels, will be maintained in the study file. Rivaroxaban ~~needs~~ to be stored at the investigational site according to the labeled storage advice and in accordance with Good Clinical Practice (GCP) and GMP requirements. Rivaroxaban oral

suspension should not be frozen and should be stored at a temperature not exceeding 25°C and kept in a secure area (e.g. locked cabinet).

[...]

New text:

[...]

A system of numbering in accordance with Good Manufacturing Practice (GMP) will be used, ensuring that each dose of study medication can be traced back to the respective bulk ware of the ingredients. A complete record of batch numbers and expiry dates of all study medication provided by Bayer, as well as the labels, will be maintained in the study file. Rivaroxaban granules for oral suspension need to be stored at the investigational site according to the labeled storage advice and in accordance with Good Clinical Practice (GCP) and GMP requirements. Rivaroxaban granules for oral suspension should not be frozen and should be stored at a temperature not exceeding 25°C and kept in a secure area (e.g. locked cabinet).

[...]

16.2.2.14 Section 6.1 Study visits

This section was modified based on Change 2.

Old text:

[...]

Visit 1 is a screening visit and will be a hospital visit. This visit is to identify potential eligibility of children who are treated with anticoagulants for confirmed symptomatic or asymptomatic ~~catheter-related~~ arterial or venous thrombosis. This visit will take place 1 to 10 days before inclusion into the study. Visit 2 is the first treatment visit and will be a hospital visit. Eligible children will start 7 days of anticoagulation with rivaroxaban (day 1).

[...]

New text:

[...]

Visit 1 is a screening visit and will be a hospital visit. This visit is to identify potential eligibility of children who are treated with anticoagulants for confirmed symptomatic or asymptomatic arterial or venous thrombosis. This visit will take place 1 to 10 days before inclusion into the study. Visit 2 is the first treatment visit and will be a hospital visit. Eligible children will start 7 days of anticoagulation with rivaroxaban (day 1).

[...]

16.2.2.15 Section 6.2 Visit 1 – Screening visit at 1 to 10 days before Visit 2

This section was modified based on Change 7.

Old text:

[...]

The images of the index thrombotic event need to be collected and the adjudication package needs to be completed and sent to the central adjudication office. ~~The CIAC will assess the images and will inform the investigator about their decision.~~

[...]

New text:

[...]

The images of the index thrombotic event need to be collected and the adjudication package needs to be completed and sent to the central adjudication office for their assessment.

[...]

16.2.2.16 Section 6.3 Visit 2 – Treatment visit at Day 1

This section was modified based on Change 6.

Old text:

[...]

- Provide instructions on how to administer the study drug and give the study booklet and the rivaroxaban oral suspension handling guidelines to parents, if applicable.
- Administer the first rivaroxaban dose according to the oral suspension handling guidelines ~~and document the volume and type of liquid (e.g., breast milk, formula, water, or juice) used to predilute the rivaroxaban oral suspension.~~
- Document the exact time of rivaroxaban intake and the type (e.g., breast milk, formula, porridge, or pureed food) and estimated volume of fluid (e.g. breast milk and formula) or food (e.g. porridge or pureed food) rivaroxaban was administered with.

[...]

New text:

[...]

- Provide instructions on how to administer the study drug and give the study booklet and the rivaroxaban oral suspension handling guidelines to parents, if applicable.
- Administer the first rivaroxaban dose according to the oral suspension handling guidelines.
- Document the exact time of rivaroxaban intake and the type (e.g., breast milk, formula, porridge, or pureed food) and estimated volume of fluid (e.g. breast milk and formula) or food (e.g. porridge or pureed food) rivaroxaban was administered with.

[...]

16.2.2.17 Section 6.4 Visit 3 – Treatment visit at Day 3

This section was modified based on Change 6.

Old text:

[...]

- Administer the next dose of rivaroxaban according to the oral suspension handling guidelines ~~and document the volume and type of liquid (e.g., breast milk, formula, water, or juice) used to predilute the rivaroxaban oral suspension.~~
- Document the exact time of rivaroxaban intake and the type (e.g. breast milk, formula, porridge, or pureed food) and estimated volume of food rivaroxaban was administered with.
- In case rivaroxaban is administered together with porridge or pureed food, encourage the child to drink a typical serving of liquid thereafter (e.g., breast milk, formula, water, juice) and document the type of liquid and the estimated volume.
- At 2–8 hr after rivaroxaban, collect a post-dose PK blood sample followed by the PD blood sample.
- Document the exact time of blood sampling for PK/PD.
- ~~Perform drug accountability and assess compliance.~~
- Check changes in concomitant medications.
- Inform that on the day before visit 4, the evening dose of rivaroxaban should be taken as late as possible.

- Instruct to document in the study booklet
 - the exact time of the last dose of rivaroxaban on the day prior to visit 4,
 - ~~the volume and type of liquid (e.g., breast milk, formula, water, juice) used to predilute the rivaroxaban oral suspension;~~
 - the type (e.g. breast milk, formula, porridge, or pureed food) and estimated volume of fluid (e.g. breast milk and formula) or food (e.g. porridge or pureed food) rivaroxaban was administered with,

[...]

New text:

[...]

- Administer the next dose of rivaroxaban according to the oral suspension handling guidelines.
- Document the exact time of rivaroxaban intake and the type (e.g. breast milk, formula, porridge, or pureed food) and estimated volume of food rivaroxaban was administered with.
- In case rivaroxaban is administered together with porridge or pureed food, encourage the child to drink a typical serving of liquid thereafter (e.g., breast milk, formula, water, juice) and document the type of liquid and the estimated volume.
- At 2–8 hr after rivaroxaban, collect a post-dose PK blood sample followed by the PD blood sample.
- Document the exact time of blood sampling for PK/PD.
- Check changes in concomitant medications.
- Inform that on the day before visit 4, the evening dose of rivaroxaban should be taken as late as possible.
- Instruct to document in the study booklet
 - the exact time of the last dose of rivaroxaban on the day prior to visit 4,
 - the type (e.g. breast milk, formula, porridge, or pureed food) and estimated volume of fluid (e.g. breast milk and formula) or food (e.g. porridge or pureed food) rivaroxaban was administered with,

[...]

16.2.2.18 Section 6.5 Visit 4 – Day 8

This section was modified based on Change 6.

Old text:

[...]

- Document
 - the exact time of the last dose of rivaroxaban on the day prior to visit 4,
 - ~~the volume and type of liquid (e.g., breast milk, formula, water, juice) used to predilute the rivaroxaban oral suspension,~~

[...]

New text:

[...]

- Document
 - the exact time of the last dose of rivaroxaban on the day prior to visit 4,

[...]

16.3 Amendment 5

16.3.1 Overview of changes

Amendment 5 is the third global amendment dated 15 Nov 2016.

16.3.1.1 Change 1: Change Medical Expert's name

The surname of the sponsor's Medical Expert we updated.

Rational:

The surname of the sponsor's Medical Expert changed during the course of the study and was adjusted accordingly.

Affected sections: [Title page](#)

16.3.1.2 Change 2: Change of sponsorship information

The sponsor was changed from Bayer Healthcare AG to Bayer AG for non-US territory and sponsor information for Bayer Healthcare Pharmaceuticals Inc. was added for US-territory.

Rational:

Bayer HealthCare AG merged with Bayer AG, an affiliated company within the Bayer Group, effective as of 1st July 2016. Thereby, Bayer HealthCare AG ceased to exist and Bayer AG became its legal successor and automatically took over all of the Bayer HealthCare AG's

rights, obligations and liabilities by law. As a result of the above mentioned merger, Bayer AG assumes the role of the sponsor.

Affected sections: [Title page](#)

16.3.1.3 Change 3: Modification of dosing regimen

The total daily dose will be increased by 50% for all body weight groups. This will be achieved by three times daily administration of the same individual dose previously used with the b.i.d. schedule.

Rationale:

Rivaroxaban was well tolerated in the 5 children treated according to the b.i.d. regimen and there were no bleeding events. Furthermore, no symptomatic recurrent venous thromboembolic complications occurred. Repeat imaging of the thrombosis in two children with a persistent thrombosis at the start of rivaroxaban treatment showed normalization and substantial regression of the thrombosis, respectively, after the 7-day treatment with rivaroxaban.

However, PK results of the first 5 children enrolled with the b.i.d. regimen indicate lower rivaroxaban exposure ($AUC_{ss,24h}$) and C_{trough} concentrations than initially expected by the PK model.

Based on these observations the Data Monitoring Committee in its meeting on September 19, 2016, identified an efficacy concern. The DMC clarified that “the efficacy concern the committee identified was related to the potential for the low levels to be associated with thrombotic events, not related to any observed events in the patients treated to date.” The DMC recommended to change the dosing regimen from a b.i.d. (approx. 12-hour intervals) to a t.i.d. (approx. 8-hour intervals) schedule, applying the same individual doses previously administered twice daily. This recommendation was endorsed by the steering committee.

The 50% increase of the total daily dose aims to elevate the exposure to the lower end of the adult reference range. The shortening of the dosing interval from 12 hours (b.i.d. schedule) to 8 hours (t.i.d. schedule) aims to increase the C_{trough} concentrations to match the adult reference range which will allow to extrapolate safety and efficacy from the adult VTE treatment population.

The change from b.i.d. to t.i.d. schedule requires an adaptation of PK/PD sampling timepoints and instructions for administration of rivaroxaban.

The original protocol included dosing information for children with body weight of 12 to < 20 kg. This specific dosing information was deleted as this body weight group does not apply to children aged younger than 6 months.

Affected sections: [Synopsis](#), [Section 1 Introduction](#), [Section 3.1 Study description](#), [Section 5.1.1 Rivaroxaban regimen](#), [Section 6.3 Visit 2 – Treatment visit at Day 1](#), [Section 6.4 Visit 3 – Treatment visit at Day 3](#), [Section 6.5 Visit 4 – Day 8](#), [Section 6.12 PK/PD assessment](#)

16.3.1.4 Change 4: Provision of additional imaging tests for adjudication

Investigators are asked to also submit diagnostic tests other than ultrasound for evaluation of repeat imaging by the Central Independent Adjudication Committee, if available.

Rationale:

Repeat imaging will provide valuable efficacy information. The protocol requires repeat ultrasound imaging before start and after completion of the 7-day rivaroxaban treatment. If other imaging tests (e.g., CT, MRI) are planned and conducted independently of the study protocol, these imaging tests may support the evaluation of the status of the thrombosis and should therefore be submitted for adjudication, in addition to the ultrasound imaging required by the protocol.

Affected sections: [Section 6.3 Visit 2 – Treatment visit at Day 1](#); [Section 6.5 Visit 4 – Day 8](#)

16.3.2 Changes to the protocol text

In this section, all affected protocol sections are detailed; the sequence of the sections follows the structure of the original protocol. In the display of modifications, the “old text” refers to the protocol version preceding this amendment. Deletions are ~~crossed out~~ in the “old text”. Additions are underlined in the “new text”. Corrections of typing errors or omissions are not highlighted in this amendment.

16.3.2.1 Title page

This section was modified based on Changes 1 and 2.

Old text:

[...]

~~Please note that Bayer HealthCare AG merges with Bayer AG, an affiliated company within the Bayer Group, effective as of 1st July 2016. Thereby, Bayer HealthCare AG ceases to exist and Bayer AG becomes its legal successor and automatically takes over all of the Bayer HealthCare AG's rights, obligations and liabilities by law. As a result of the above mentioned merger, Bayer AG assumes the role of the sponsor for these trials. Detailed information on the merger will be provided in due time.~~

[...]

Bayer HealthCare AG, D-51368 Leverkusen, Germany

[...]

PPD

PPD

Telephone: PPD

Email: PPD

[...]

New text:

[...]

Non-US territory: Bayer AG, D-51368 Leverkusen, Germany

US territory: Bayer Healthcare Pharmaceuticals Inc.,
100 Bayer Boulevard, P.O. Box 915,
Whippany NJ 07981-0915, USA

[...]

PPD

PPD

Telephone:

PPD

Email:

PPD

[...]

16.3.2.2 Synopsis

This section was modified based on Change 3.

Old text:

[...]

Dose(s)

Age- and body weight-adjusted ~~twice~~ daily dosing of rivaroxaban to achieve a similar exposure as that observed in adults treated for venous thromboembolism (VTE) with 20 mg rivaroxaban once daily

[...]

Methodology

Children with confirmed arterial or venous thrombosis who have been treated with anticoagulant therapy for at least five days.
Children will receive an age- and body weight-adjusted rivaroxaban regimen using an oral suspension (1 mg/mL) for a total of 7 days followed by an observational period of another 30 days. Rivaroxaban will be administered ~~twice~~ daily.
An ultrasound will be performed at day 1 and 8 of rivaroxaban treatment to document asymptomatic changes. In addition, children will be monitored for the occurrence of symptomatic recurrent thrombosis and bleedings.
All suspected clinical study outcomes and baseline and repeat ultrasound imaging tests will be assessed by a Central Independent Adjudication Committee (CIAC).

An independent data monitoring committee (DMC) will monitor the children's safety and give recommendations to the steering committee.

[...]

Table 2: Flow chart: pharmacokinetics and pharmacodynamics

Pharmacokinetics and pharmacodynamics (PK/PD) ^a	Visit 1	Visit 2				Visit 3				Visit 4
Rivaroxaban treatment days	Screen day -10 to day 1	Treatment day 1		Treatment day 2		Treatment day 3		Treatment day 4 to 7		Day 8
Rivaroxaban administration		1 st dose	2 nd dose	1 st dose	2 nd dose	1 st dose	2 nd dose	1 st dose	2 nd dose	
PK/PD time points		0.5 to 1.5 hr post dose	2-4 hr post dose			2-8 hr post dose				10-16 hr after last dose at day 7
Obtain blood sample for PK ^b		•	•			•				•
Obtain blood sample for PD ^c			•			•				•
hr = hour(s), PD = pharmacodynamics, PK = pharmacokinetics ^a The approximate total blood volume taken per child for PK/PD is 6.6 mL. Always draw the PD sample as the last sample. ^b Blood volume per PK sample is approximately 0.6 mL; total blood volume for all PK samples is 2.4 mL. ^c Blood volume per PD sample is approximately 1.4 mL; total blood volume for all PD samples is 4.2 mL.										

New text:

[...]

Dose(s)

Age- and body weight-adjusted three times daily dosing of rivaroxaban to achieve a similar exposure as that observed in adults treated for venous thromboembolism (VTE) with 20 mg rivaroxaban once daily

[...]

Methodology	<p>Children with confirmed arterial or venous thrombosis who have been treated with anticoagulant therapy for at least five days.</p> <p>Children will receive an age- and body weight-adjusted rivaroxaban regimen using an oral suspension (1 mg/mL) for a total of 7 days followed by an observational period of another 30 days. Rivaroxaban will be administered <u>three times</u> daily.</p> <p>An ultrasound will be performed at day 1 and 8 of rivaroxaban treatment to document asymptomatic changes. In addition, children will be monitored for the occurrence of symptomatic recurrent thrombosis and bleedings.</p> <p>All suspected clinical study outcomes and baseline and repeat ultrasound imaging tests will be assessed by a Central Independent Adjudication Committee (CIAC).</p> <p>An independent data monitoring committee (DMC) will monitor the children's safety and give recommendations to the steering committee.</p>
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[...]

Table 2: Flow chart: pharmacokinetics and pharmacodynamics

PK and PD ^a	Visit 1	Visit 2						Visit 3						Visit 4
Rivaroxaban treatment days	Screen day -10 to day 1	Treatment day 1			Treatment day 2			Treatment day 3			Treatment day 4 to 7			Day 8
Rivaroxaban administration		1 st dose	2 nd dose	3 rd dose	1 st dose	2 nd dose	3 rd dose	1 st dose	2 nd dose	3 rd dose	1 st dose	2 nd dose	3 rd dose	
PK/PD time points		0.5 to 3 hr post dose	7 to 8 hr post dose					0.5 to 3 hr post dose	7 to 8 hr post dose					10-16 hr after last dose at day 7
Obtain blood sample for PK ^b		•	•					•	•					
Obtain blood sample for PD ^c			•					•						• ^d

hr = hour(s), PD = pharmacodynamics, PK = pharmacokinetics

^a The approximate total blood volume taken per child for PK/PD is 6.6 mL. Always draw the PD sample as the last sample.

^b Blood volume per PK sample is approximately 0.6 mL; total blood volume for all PK samples is 2.4 mL.

^c Blood volume per PD sample is approximately 1.4 mL; total blood volume for all PD samples is 4.2 mL.

^d If continued treatment with anticoagulants is necessary, administer the anticoagulant after last sample is taken for rivaroxaban.

16.3.2.3 Section 1 Introduction

This section was modified based on Change 3.

Old text:

[...]

In this phase I/II study, children with confirmed symptomatic or asymptomatic arterial or venous thrombosis will be treated for 7 days with the age- and body weight-adjusted rivaroxaban ~~twice~~ daily dosing regimen to achieve a similar exposure as that observed in adults treated for VTE with 20 mg rivaroxaban once daily.

[...]

New text:

[...]

In this phase I/II study, children with confirmed symptomatic or asymptomatic arterial or venous thrombosis will be treated for 7 days with the age- and body weight-adjusted rivaroxaban three times daily dosing regimen to achieve a similar exposure as that observed in adults treated for VTE with 20 mg rivaroxaban once daily.

[...]

16.3.2.4 Section 3.1 Study description

This section was modified based on Change 3.

Old text:

[...]

Neonates and infants aged less than 6 months who pass the screen of in- and exclusion criteria, who have been treated for at least five days with heparin and /or VKA for confirmed symptomatic or asymptomatic arterial or venous thrombosis are eligible for the study. Study treatment consists of a 7-day treatment with an age- and body weight-adjusted ~~twice~~ daily oral rivaroxaban dosing to achieve a similar exposure as that observed in adults treated for venous thromboembolism (VTE) with 20 mg rivaroxaban once daily. Rivaroxaban will be provided as granules for preparation of an oral suspension (1 mg/mL after re-suspension) using a ~~b.i.d.~~ regimen with ~~12~~-hour intervals.

[...]

New text:

[...]

Neonates and infants aged less than 6 months who pass the screen of in- and exclusion criteria, who have been treated for at least five days with heparin and /or VKA for confirmed symptomatic or asymptomatic arterial or venous thrombosis are eligible for the study. Study treatment consists of a 7-day treatment with an age- and body weight-adjusted three times daily oral rivaroxaban dosing to achieve a similar exposure as that observed in adults treated for venous thromboembolism (VTE) with 20 mg rivaroxaban once daily. Rivaroxaban will be provided as granules for preparation of an oral suspension (1 mg/mL after re-suspension) using a t.i.d. regimen with 8-hour intervals.

[...]

16.3.2.5 Section 5.1.1 Rivaroxaban regimen

This section was modified based on Change 3.

Old text:

[...]

Age- and body weight-adjusted rivaroxaban will be administered ~~twice~~ daily (approximately 12 hours apart) as oral suspension. ~~Rivaroxaban will be taken in the morning and evening immediately before or (early) during feeding.~~

If a rivaroxaban dose was missed, the child should ~~take rivaroxaban immediately to ensure intake of the total daily dose per day. In this case, two oral suspension doses may be taken at once. Thereafter, the child should continue with the regular b.i.d. rivaroxaban administrations.~~

[...]

Table 3: Rivaroxaban dosing schedule

Body weight [kg]		Oral suspension dose (b.i.d.)	Total daily dose
Min	Max	[mg]	[mg]
2.6	<3	0.5	1.0
3	<4	0.6	1.2
4	<5	0.9	1.8
5	<6	1.2	2.4
6	<7	1.6	3.2
7	<8	1.9	3.8
8	<9	2.5	5.0
9	<10	2.7	5.4
10	<12	2.9	5.8
12	<20	3.2	6.4

[...]

New text:

[...]

Age- and body weight-adjusted rivaroxaban will be administered three times daily approximately 8 hours apart as oral suspension. The oral suspension will be administered immediately before or (early) during feeding.

Originally, the study started with a b.i.d. regimen. Rivaroxaban was well tolerated in the 5 children treated according to the b.i.d. regimen and there were no bleeding events. Furthermore, no symptomatic recurrent venous thromboembolic complications occurred.

Repeat imaging of the thrombosis in two children with a persistent thrombosis at the start of rivaroxaban treatment showed normalization and substantial regression of the thrombosis, respectively, after the 7-day treatment with rivaroxaban.

However, PK results of the first 5 children enrolled with the b.i.d. regimen indicate lower rivaroxaban exposure ($AUC_{ss,24h}$) and C_{trough} concentrations than initially expected by the PK model. Based on these observations, the Data Monitoring Committee recommended to change the dosing regimen from a b.i.d. (approx. 12-hour intervals) to a t.i.d. (approx. 8-hour intervals) schedule applying the same individual doses previously administered twice daily. This recommendation was endorsed by the steering committee.

Following implementation of Amendment 5, children will be dosed according to the t.i.d. schedule (according to Table 3). The 50% increase of the total daily dose will increase the exposure, and the shortening of the dosing interval from 12 to 8 hours (t.i.d. schedule) aims to increase the C_{trough} concentrations.

If a rivaroxaban individual dose was missed, the t.i.d. administration schedule with approx. 8-hour intervals should be resumed without compensating for the missed dose.

[...]

Table 3: Rivaroxaban dosing schedule

Body weight [kg]		Oral suspension dose (t.i.d.)	Total daily dose
Min	Max	[mg]	[mg]
2.6	<3	0.5	<u>1.5</u>
3	<4	0.6	<u>1.8</u>
4	<5	0.9	<u>2.7</u>
5	<6	1.2	<u>3.6</u>
6	<7	1.6	<u>4.8</u>
7	<8	1.9	<u>5.7</u>
8	<9	2.5	<u>7.5</u>
9	<10	2.7	<u>8.1</u>
10	<12	2.9	<u>8.7</u>

* to be administered every 8 hours

[...]

16.3.2.6 Section 6.3 Visit 2 – Treatment visit at Day 1

This section was modified based on Change 3.

Old text:

[...]

- At 0.5-~~1.5~~ hr after rivaroxaban, collect only a PK blood sample.
- At ~~2.0~~-4 hr after rivaroxaban intake, collect a PK blood sample followed by the PD sample.
- Document the exact time of each blood sampling for PK/PD.
- Obtain ultrasound and prepare an adjudication package to be sent to the adjudication office.

[...]

New text:

[...]

- At 0.5-3 hr after rivaroxaban, collect only a PK blood sample.
- At 7-8 hr after rivaroxaban intake, collect a PK blood sample followed by the PD sample.
- Document the exact time of each blood sampling for PK/PD.
- Obtain ultrasound and prepare an adjudication package to be sent to the adjudication office. In case other diagnostic tests were performed to visualize the clot, these should be sent as well.

[...]

16.3.2.7 Section 6.4 Visit 3 – Treatment visit at Day 3

This section was modified based on Change 3.

Old text:

[...]

- At ~~2-8~~ hr after rivaroxaban, collect a ~~post-dose~~ PK blood sample followed by the PD blood sample.
- Document the exact time of blood sampling for PK/PD.
- Check changes in concomitant medications.
- ~~Inform that on the day before visit 4, the evening dose of rivaroxaban should be taken as late as possible.~~

[...]

New text:

[...]

- At 0.5-3 hr after rivaroxaban, collect a PK blood sample followed by the PD blood sample.
- At 7-8 hr after rivaroxaban intake, collect only a PK blood sample.
- Check changes in concomitant medications.

[...]

16.3.2.8 Section 6.5 Visit 4 – Day 8

This section was modified based on Change 3.

Old text:

[...]

- At 10-16 hr after last rivaroxaban intake, ~~collect the PK blood sample followed by the PD blood sample~~, collect ALT, total and direct bilirubin sample.
- Document the exact time of blood sampling for ~~PK~~/PD.
- Repeat ultrasound and prepare an adjudication package to be sent to the adjudication office. The repeat ultrasound can be performed on day 8 ± 1 .

[...]

New text:

[...]

- At 10-16 hr after last rivaroxaban intake, collect ALT, total and direct bilirubin sample, followed by the PD blood sample. If continued treatment with anticoagulants is necessary, administer the anticoagulant after this sample is taken.
- Document the exact time of blood sampling for PD.
- Repeat ultrasound and prepare an adjudication package to be sent to the adjudication office. The repeat ultrasound can be performed on day 8 ± 1 . In case other diagnostic tests were performed to visualize the clot, these should be sent as well.

[...]

16.3.2.9 Section 6.12 PK/PD assessment

This section was modified based on Change 3.

Old text:

[...]

- two post-dose PK samples at visit 2
- one post-dose PD sample at visit 2
- one post-dose ~~PK~~/PD sample at visit 3
- one post-dose ~~PK~~/PD sample at visit 4

[...]

New text:

[...]

- two post-dose PK samples at visit 2
- one post-dose PD sample at visit 2
- two post-dose PK sample at visit 3
- one post-dose PD sample at visit 3
- one post-dose PD sample at visit 4

[...]

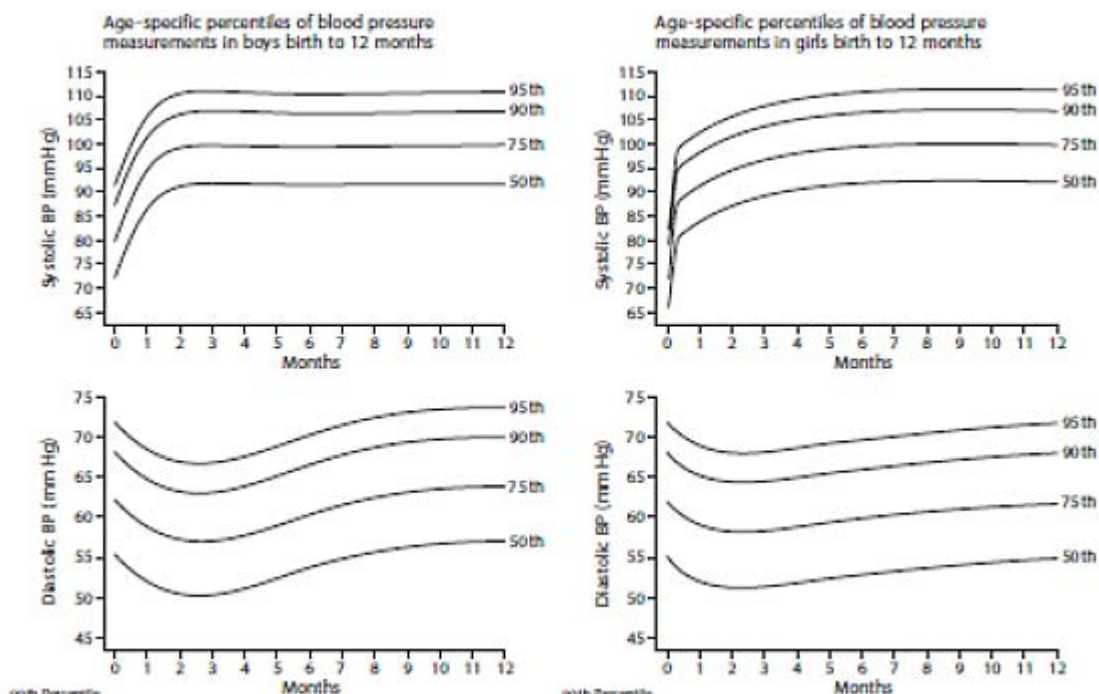
17. Appendices

17.1.1 Bioanalytics and pharmacokinetics

Rivaroxaban concentrations in plasma will be measured by a validated high-performance liquid chromatography assay with tandem mass spectrometric detection. Quality control and calibration samples will be analyzed concurrently with study samples. The results of quality check samples will be reported together with concentrations in unknown samples in the clinical study report. Concentrations are calculated from the chromatographic raw data in accordance with current Bayer guidelines. Only values above the lower limit of quantification are used to determine pharmacokinetic parameters.

Rivaroxaban (BAY 59-7939, JNJ-39039039) is being co-developed under a collaboration and license agreement between Bayer HealthCare AG and Ortho McNeil Pharmaceuticals, Inc. dated 01 Oct 2005. As determined by the parties, both Bayer HealthCare AG and Janssen Pharmaceuticals Inc. (successor in interest to Ortho McNeil Pharmaceuticals, Inc.) may use affiliated corporate entities to conduct this clinical study. With regard to Janssen Pharmaceuticals Inc., such affiliates may include Janssen Research & Development, LLC (formerly Johnson & Johnson Pharmaceutical Research & Development LLC), Janssen Scientific Affairs, LLC, and Janssen-Cilag International N.V. The term “sponsor” or “designee” is used to represent these various legal entities that have been identified to perform various clinical study services; the actual sponsor or designee is identified on the Contact Information page that accompanies this protocol.

17.1.2 Age percentiles for blood pressure in children



Source: 9