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Official Title:	30-day, single-arm study of the safety, efficacy and the pharmacokinetic and pharmacodynamic properties of oral rivaroxaban in young children with various manifestations of venous thrombosis
NCT Number:	NCT02309411
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Cover page of the integrated protocol

30-day, single-arm study of the safety, efficacy and the pharmacokinetic and pharmacodynamic properties of oral rivaroxaban in young children with various manifestations of venous thrombosis[1]

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

- **Original protocol,** Version 1.0, dated 04 Mar 2014
- **Amendment 1** (global amendment described in Section 16.1) forming integrated protocol Version 2.0, dated 02 Sep 2014
- **Amendment 2** (local amendment Japan), dated 21 Oct 2014
- **Amendment 3** (local amendment Canada), dated 28 Oct 2014
- **Amendment 4** (global amendment described in Section 16.2**)** forming integrated protocol Version 3.0, dated 14 Apr 2015

This document integrates the original protocol and all global amendments.

[1] Title was modified via Amendment 4 (see Section 16.2.2.1)

Title page

30-day, single-arm study of the safety, efficacy and the pharmacokinetic and pharmacodynamic properties of oral rivaroxaban in young children with various manifestations of venous thrombosis[2]

EINSTEIN Junior Phase II-part B: oral rivaroxaban in young children with venous thrombosis

Test drug:	BAY 59-7939/rivaroxaban		
Clinical study phase:	II	Date:	14 Apr 2015
EudraCT no.:	2014-000566-22	Version no.:	3.0
Study no.:	BAY 59-7939/14374		
Sponsor:	**Bayer HealthCare AG, D-51368 Leverkusen, Germany**		

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The study will be conducted in compliance with the protocol, International Conference on Harmonization-Good Clinical Practice (ICH-GCP), and any applicable regulatory requirements.

[2] Title was modified via Amendment 4 (see Section 16.2.2.1)

Medically responsible person of Bayer

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

PPD

Date: May 11th 2015

Signature: PPD

Study center's principal investigator

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

Name:

Affiliation:

Date: _____ Signature: _____

Synopsis - amended

Title	30-day, single-arm study of the safety, efficacy and the pharmacokinetic and pharmacodynamic properties of oral rivaroxaban in young children with various manifestations of venous thrombosis.[3]
Short title	Einstein Junior Phase II-part B: Oral rivaroxaban in young children with venous thrombosis
Clinical study phase	II
Study objectives	The primary objective is: • to assess the incidence of major bleeding and clinically relevant non-major bleeding The secondary objectives are: • to assess the incidence of recurrent venous thromboembolism • to assess asymptomatic deterioration in the thrombotic burden on repeat imaging • to characterize the pharmacokinetic/pharmacodynamic profile of a 30-day treatment with oral rivaroxaban.
Experimental study drug	Rivaroxaban
Name of active ingredient	Rivaroxaban
Dose	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 [4]
Route of administration	Oral suspension
Duration of treatment	30 days
Comparator study drug	Not applicable[5]
Name of active ingredient	Not applicable[5]
Dose	Not applicable[5]
Route of administration	Not applicable[5]
Duration of treatment	Not applicable[5]

[3] Title was modified via Amendment 4 (see Section 16.2.2.1)
[4] Error in the dose frequency was corrected in amendment 1 (see Section 16.1.2.1)
[5] Comparator arm was removed via Amendment 4 (see Section 16.2.2.2)

Indication	Young children with documented venous thrombosis, including deep vein thrombosis of the lower extremity, caval vein thrombosis, right atrial thrombosis, pulmonary embolism, deep vein thrombosis of the upper extremity, subclavian vein thrombosis, jugular vein thrombosis, and cerebral vein and sinus thrombosis, mesenteric vein thrombosis, portal vein thrombosis, renal vein thrombosis or catheter-related thrombosis
Diagnosis and main criteria for inclusion	Children aged 6 months to < 6 years with documented symptomatic or asymptomatic venous thrombosis treated for at least 2 months or, in case of catheter-related thrombosis, treated for at least 6 weeks with LMWH, fondaparinux and/or VKA.[6] The imaging of the index thrombotic event will be confirmed by the central independent adjudication committee (CIAC).
Study design	Single-arm, multicenter study[7]
Methodology	Children will receive rivaroxaban according to an age- and body weight-adjusted regimen. The study treatment period is for a total of 30 days followed by an observational period of another 30 days. All suspected clinical study outcomes and baseline and repeat thrombosis imaging tests will be assessed by a CIAC. An independent data monitoring committee (DMC) will monitor the children's safety and give recommendations to the steering committee. [8]
Number of children	20 children (10 per age group) treated with rivaroxaban. [9]

[6] Inclusion criteria modified via Amendment 4 (see Section 16.2.2.2)
[7] Title was modified via Amendment 4 (see Section 16.2.2.1)
[8] Comparator arm was removed via Amendment 4 (see Section 16.2.2.2)
[9] Total number of subjects was reduced via Amendment 4 (see Section 16.2.2.2)

Inclusion/exclusion criteria	Inclusion 1. Children aged 6 months to < 6 years who have been treated for at least 2 months or, in case of catheter related thrombosis, for at least 6 weeks with LMWH, fondaparinux and/or VKA for documented symptomatic or asymptomatic venous thrombosis 2. Hemoglobin, platelets, creatinine, alanine aminotransferase (ALT) and bilirubin evaluated within 10 days prior to Visit 2[10] 3. Informed consent provided Exclusion 1. Active bleeding or high risk for bleeding contraindicating anticoagulant therapy 2. Symptomatic progression of venous thrombosis during preceding anticoagulant treatment 3. Planned invasive procedures, including lumbar puncture and removal of non-peripherally placed central lines during study treatment 4. An estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2 5. Hepatic disease which is associated with either: coagulopathy leading to a clinically relevant bleeding risk, or ALT > 5x upper level of normal (ULN) or total bilirubin > 2x ULN with direct bilirubin > 20% of the total 6. Platelet count < 50 x 10^9/L [11] 7. Hypertension defined as > 95th age percentile [12] 8. Life expectancy < 3 months 9. Concomitant use of strong inhibitors of both cytochrome P450 isoenzyme 3A4 (CYP3A4) and P-glycoprotein (P-gp), i.e. all human immunodeficiency virus protease inhibitors and the following azole-antimycotics agents: ketoconazole, itraconazole, voriconazole, posaconazole, if used systemically (fluconazole is allowed)

[10] Comparator arm was removed via Amendment 4 (see Section 16.2.2.2)
[11] Definition of thrombocytopenia adjusted via Amendment 4 (see Section 16.2.2.2)
[12] see Figure 1–1 and Table 1–1

Inclusion/exclusion criteria (continued)	10. Concomitant use of strong inducers of CYP3A4, i.e. rifampicin, rifabutin, phenobarbital, phenytoin and carbamazepine 11. Hypersensitivity or any other contraindication listed in the local labeling for the experimental treatment 12. Inability to cooperate with the study procedures 13. Previous enrollment to this study 14. Participation in a study with an investigational drug or medical device within 30 days prior to Visit 2. [13]
Primary outcome	Composite of major and clinically relevant non-major bleeding
Secondary outcome	Composite of all recurrent venous thromboembolism and asymptomatic deterioration on repeat imaging; results of pharmacokinetics (PK) / pharmacodynamics (PD).
Statistical Analysis Plan	The incidence of the composite of major and clinically relevant non-major bleeding and the incidence of symptomatic recurrent venous thromboembolism, and asymptomatic deterioration in the thrombotic burden on repeat imaging will be summarized descriptively. Quantitative data will be described by summary statistics and presented by age. Results of PK/PD analyses will be assessed descriptively. [14]

[13] Comparator arm was removed via Amendment 4 (see Section 16.2.2.2)
[14] Statistical Analysis Plan modified via Amendment 4 (see Section 16.2.2.2)

Figure 1–1: Flow chart

	Screen [a]	**Treatment period**			**30 day post study treatment contact**
Visit	**1**	**2**	**3**	**4**	**5**
Days	Day -60 to Day -10	Day 1	Day 15 ± 5 days	Day 30 ± 3 days	Day 60 ± 7 days
Obtain informed consent	•				
Check in-/exclusion criteria	•				
Obtain demographic data	•				
Check medical history	•	•			
Record anticoagulant medication	•	•			
Obtain height/length, and blood pressure	•				
Obtain body weight	•	•			
Check Hb, platelets, creatinine, ALT, bilirubin		•[b]			
Send baseline adjudication package	•				
Review the CIAC decision for index thrombotic event for final eligibility [c]		•			
Re-confirm in-/exclusion criteria [c]		•			
Provide patient details to IxRS	•				
Dispense study medication Instruct how to take study medication Provide study booklet Provide Rivaroxaban Oral Suspension Handling Guidelines to parents		• • • •			
Record all concomitant medication		•	•	•	•
Check for study outcomes [d]			•	•	•
Check adverse events		•	•	•	•
Check Hb, platelets, ALT, bilirubin				•	
Check drug accountability and compliance [e]			•	•	
Repeat imaging and send adjudication package				•	
Check if anticoagulant treatment continued after Visit 4					•
Complete eCRF	•	•	•	•	•
Pharmacokinetics and pharmacodynamics [f]	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
Time point (hours)		0.5-1.5 hr post dose / 2.5-4 hr post dose	2-8 hr post dose	10-16 hr post dose	
Obtain blood sample for pharmacokinetics [h]		• •	•	•	
Obtain blood sample for pharmacodynamics [i,j]		•	•	•	
Administer rivaroxaban at study site [k]		•	•		
Complete Taste-and-Texture Questionnaire [l]			•		

for footnotes please see following page

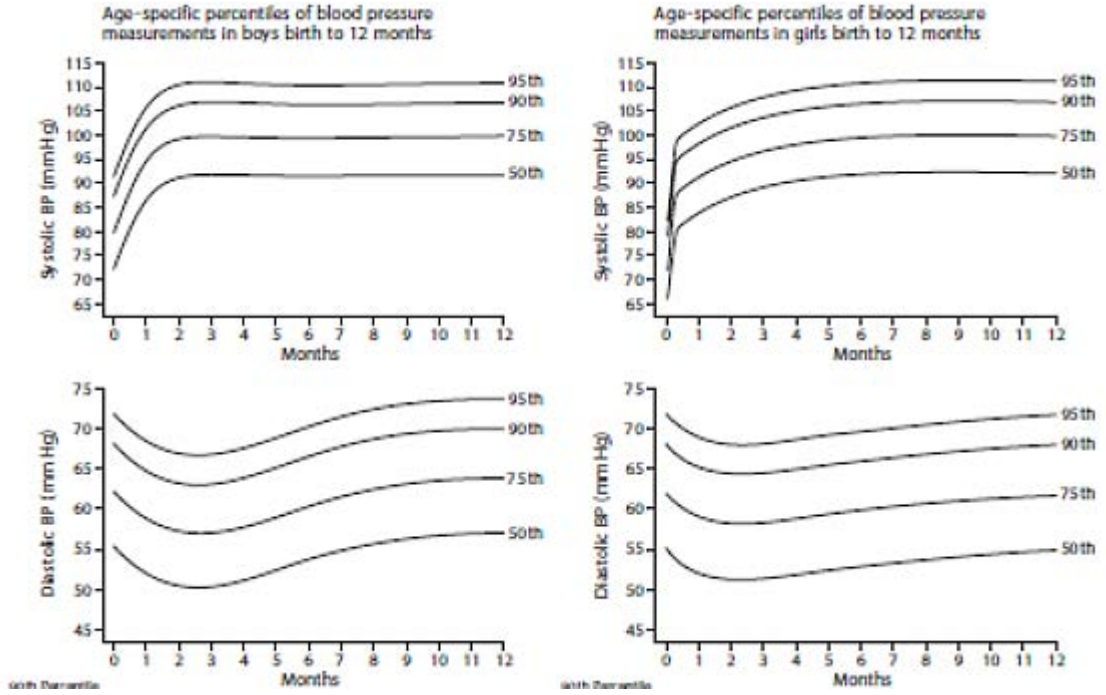
[a] The screening visit can be performed up to 60 days prior to Visit 2, but should not be less than 10 days prior to Visit 2. Please contact the adjudication office in case the available period prior to Visit 2 is less than 10 days.
[b] Results should be available within 10 days prior to Visit 2, if not obtain blood sample at visit 2.
[c] Done before the study drug intake.
[d] If suspected outcome occurred, the adjudication package needs to be compiled and sent to the adjudication office.
[f] The approximate total blood volume taken per child is 10 mL if blood taken via venipuncture, and 22 mL if blood taken via central venous line or peripheral catheter.
[g] PK/PD sampling only if the child received rivaroxaban for more than 3 days
[h] Blood volume per PK sample is 1.2 mL; total blood volume for all PK samples is 4.8 mL
[i] Blood volume per PD sample is 1.8 mL; total blood volume for all PD samples is 5.4 mL
[j] Always draw the pharmacodynamic sample as the last sample
[k] For switching from heparin, LMWH/fondaparinux, VKA see section 5.1.1
[l] Taste and texture questionnaire to be completed in part before and after the study drug intake (only children > 4 years old) [15]

eCRF: electronic case report form; Hb: Hemoglobin; INR: International normalized ratio; IxRS: interactive voice/web response system

[15] Flow chart modified via Amendment 4 (see Section 16.2.2.2)

Blood pressure levels for children

Figure 1–2: Age percentiles for blood pressure in children from birth to 12 months of age



Source: (15)

Table 1–1: Age and Height percentiles for blood pressure in children from 1 to 6 years of age

Boys

Age	Systolic blood pressure, mmHg							Diastolic blood pressure, mmHg						
	Percentile of height							Percentile of height						
	5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
1	98	99	101	103	104	106	106	54	54	55	56	57	58	58
2	101	102	104	106	108	109	110	59	59	60	61	62	63	63
3	104	105	107	109	110	112	113	63	63	64	65	66	67	67
4	106	107	109	110	112	114	115	66	67	68	69	70	71	71
5	108	109	110	112	114	115	116	69	70	71	72	73	74	74
6	109	110	112	114	115	117	117	72	72	73	74	75	76	76

Girls

Age	Systolic blood pressure, mmHg							Diastolic blood pressure, mmHg						
	Percentile of height							Percentile of height						
	5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
1	100	101	102	104	105	106	107	56	57	57	58	59	59	60
2	102	103	104	105	107	108	109	61	62	62	63	64	65	65
3	104	104	105	107	108	109	110	65	66	66	67	68	68	69
4	105	106	107	108	110	111	112	68	68	69	70	71	71	72
5	107	107	108	110	111	112	113	70	71	71	72	73	73	74
6	108	109	110	111	113	114	115	72	72	73	74	74	75	76

Shown are 95th percentiles for blood pressure. Source: (14)

Table of contents

List of tables

List of figures

List of abbreviations

ACCP	American College of Chest Physicians
AE	adverse event
AG	*Aktiengesellschaft*, joint stock company
ALT	alanine aminotransferase
anti-Xa	anti-factor Xa activity
aPTT	activated or adjusted partial thromboplastin time
BAY	sponsor's reference number for drugs
BHC	Bayer HealthCare
b.i.d.	twice daily
CCDS	Company Core Data Sheet
CIAC	central independent adjudication committee
CNS	Central nervous system
CRO	contract research organization
CT	computed tomography
CYP3A4	cytochrome P450 isoenzyme 3A4
dL	deciliter
DMC	data monitoring committee
DVT	deep vein thrombosis
eCRF	electronic case report form
e.g.	*exempli gratia*, for example
eGFR	estimated glomerular filtration rate
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trial (number)
FAS	full analysis set
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
Hb	Hemoglobin
IB	investigator's brochure
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceutical for Human Use
IDMS	isotope dilution mass spectrometry
i.e.	*id est*, that is
IEC	Independent Ethics Committee
INR	international normalized ratio
IRB	Institutional Review Board
IxRS	interactive voice/web response system
LLC	Liability Limited Company
LMWH	low molecular weight heparin
LOS	listing only set
MedDRA	Medical Dictionary for Regulatory Activities
mL	milliliter
mmHg	millimeters of mercury
MR(I)	Magnetic resonance (imaging)
NSAIDs	non-steroid anti-inflammatory drugs
o.d.	once daily
OMP	Ortho McNeil Pharmaceuticals, Inc.
PD	Pharmacodynamics
PE	pulmonary embolism
P-gp	P-glycoprotein
PK	pharmacokinetic(s)
PPS	per protocol set
RAVE	internet/web-based electronic data capture computer system

SAE	serious adverse event
SAP	statistical analysis plan
SAS	safety analysis set
SCr	serum creatinine
SID	child identification number
SUSAR	Suspected Unexpected Serious Adverse Reaction
TOSCA	Tools for Syntactic Corpus Analysis database system
u	Units
UFH	unfractionated heparin
ULN	upper limit of normal
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), bodyweight-adjusted subcutaneous low molecular weight heparin (LMWH), or bodyweight-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, this includes the requirement for intravenous or subcutaneous injection and monitoring of the activated partial thromboplastin time (aPTT). For VKA, this includes 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 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 venous thromboembolism. To accomplish this goal, it will be necessary to evaluate a pediatric age- and body weight adapted dosing regimen, and to address the safety and efficacy of rivaroxaban.[16]

The study will be initiated with the age group between 2 and less than 6 years. Once the age- and body weight adjusted dosing regimen has been finally confirmed for the age group between 6 months and less than 2 years in phase I, and approved by the data monitoring committee and steering committee, enrollment will be extended to this age group. Before enrollment of this age group is implemented and the interactive voice/web response system (IxRS) is activated, the investigators and their Institutional Review Boards (IRBs) will receive a formal notification, specifying the exposure results and safety outcomes.

In this phase II study, children with confirmed venous thrombosis will be treated for 30 days with the age- and body weight adapted rivaroxaban dosing regimen to achieve an exposure that is equivalent to the 20 mg rivaroxaban dose in adults.

[16] Comparator arm was removed via Amendment 4 (see Section 16.2.2.3)

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 venous thromboembolism (VTE) following elective hip or knee replacement surgery, for treatment and secondary prevention of deep-vein thrombosis (DVT) and pulmonary embolism (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 Various manifestations of venous thrombosis

Compared with adults, venous thrombosis is rare in children. Venous thrombosis in children is often provoked by a variety of risk factors and rarely is idiopathic in nature.[6] Expressions of venous thrombosis that usually require anticoagulant therapy include deep vein thrombosis of the lower extremity, caval vein thrombosis, renal vein thrombosis, right atrial thrombosis, pulmonary embolism, deep vein thrombosis of the upper extremity, subclavian vein thrombosis, jugular vein thrombosis, mesenteric vein thrombosis, portal vein thrombosis, and cerebral vein and sinus thrombosis.

A Canadian registry published in 1994 highlighted that central venous lines were the single most important predisposing cause of venous thrombosis in children (33%), whereas inherited coagulation disorders accounted for 9%. Venous thrombosis was associated with cancer (23%), congenital heart disease (15%), and trauma (15%).[7] The only randomized venous thrombosis treatment study in children (the REVIVE study) confirmed that cancer and infections followed by congenital heart disease were the most frequently reported risk factors.[8]

In the REVIVE study, children with cerebral vein and sinus thrombosis were at that time excluded due to lack of consensus on the need for anticoagulation. Risk factors for recurrent VTE in the European collaborative pediatric database on cerebral venous thrombosis include age at onset, absence of anticoagulant treatment, persistent venous occlusion, or presence of the prothrombin gene mutation.[9] The current treatment recommendation for cerebral vein and sinus thrombosis is therapeutic doses of anticoagulants.[10]

Currently, the recommendations for the initial treatment of various manifestations of venous thrombosis is activated partial thromboplastin time (aPTT) adjusted unfractionated heparin (UFH), body weight adjusted low molecular weight heparin (LMWH) or fondaparinux. For subsequent treatment, either INR titrated vitamin K antagonist (VKA) or body weight adjusted LMWH is recommended. For cases of catheter-related thrombosis, the current American College of Chest Physicians (ACCP) guidelines recommend a total duration of anticoagulation of between 6 weeks and 3 months [10].

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

Treatment with heparins and VKA is limited because of 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.

To carefully allow for the evaluation of rivaroxaban in children with thrombotic disease, it is mandatory to assess the efficacy and safety in a step-wise approach. Anticoagulant treatment for the acute episode of venous thrombosis is characterized by a high risk for recurrent thrombotic complications (although significantly reduced compared to no anticoagulant treatment) combined with a high risk for bleeding. Typically, these risks diminish considerably after the first month of anticoagulant treatment and remain stable thereafter. Therefore, we elected to evaluate the selected rivaroxaban dose regimen after the completion of a minimum period of 2 months or, in the case of catheter related thrombosis, treatment for at least 6 weeks with standard of care medication.[17] If this study reveals that the selected rivaroxaban dose regimen is safe and without evidence of loss of efficacy, subsequent studies might evaluate rivaroxaban also for the treatment in children with symptomatic VTE.

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 EINSTEIN PE [(11)] studies in adults, 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 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 (AEs) 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.

2. Study objectives

The primary objective is:

- to assess the incidence of major bleeding and clinically relevant non-major bleeding

The secondary objectives are:

- to assess the incidence of recurrent symptomatic venous thromboembolism
- to assess asymptomatic deterioration in the thrombotic burden on repeat imaging
- to characterize the pharmacokinetic/pharmacodynamic profile of a 30-day treatment with oral rivaroxaban.

[17] Section modified via Amendment 4 (see Section 16.2.2.4)

3. Study design - amended

This is a single-arm, multicenter study evaluating the safety, efficacy and PK/PD profile of a 30-day treatment with age- and body weight-adjusted oral rivaroxaban in children aged between 6 months and < 6 years with various manifestations of symptomatic and asymptomatic venous thrombosis.[18]

The study will be initiated with the age group between 2 and less than 6 years. Once the age- and body weight adjusted dosing regimen has been finally confirmed for the age group between 6 months and less than 2 years in phase I, and approved by the data monitoring committee and steering committee, enrollment will be extended to this age group. Before enrollment of this age group is implemented and the IxRS is activated, the investigators and their IRBs will receive a formal notification, specifying the exposure results and safety outcomes.

Study description

Children who have been treated for at least 2 months or in case of catheter-related thrombosis, treated for at least 6 weeks with LMWH, fondaparinux and/or VKA for symptomatic or asymptomatic venous thrombosis will receive age- and body weight-adjusted rivaroxaban. Before first study treatment administration, the documented index thrombotic event will be confirmed by the central adjudication committee (CIAC) for the child to be eligible for the study.

Allocation to treatment will be done centrally by an interactive voice/web response system (IxRS). The investigator will provide the IxRS with study center identification, the child's date of birth (day, month and year), gender, weight and clinical presentation.

Please refer to the IxRS manual for further details.

The IxRS will initially restrict enrollment to children in the age group between 2 and less than 6 years. Once the age-and body weight adjusted dosing regimen has been confirmed for the age group 6 months to < 2 years, the IxRS will allow enrollment for this age group as well.

Children will receive rivaroxaban for a total of 30 days.[18]

The treatment period will be followed by a 30-day post study treatment period, regardless of the duration of study drug administration. After cessation of study treatment, 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 symptomatic recurrent venous thromboembolism and asymptomatic deterioration in thrombotic burden on repeat imaging. All suspected recurrent VTEs, asymptomatic deterioration 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. The Data Monitoring Committee (DMC) will monitor the children's safety during the study and give recommendations to the steering committee.

For all children, visits are scheduled at regular time points (see Figure 1–1). Enrolled children who are not treated or those with premature discontinuation of study drug will at least be seen

[18] Comparator arm was removed via Amendment 4 (see Section 16.2.2.5)

at the end of the study treatment period.[19] 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 Figure 1–1).

4. Study population

4.1 Planned number of children - amended

Twenty children (10 per age group) are planned to be treated with rivaroxaban. Enrolment will start with the 2 to < 6 year age group, followed by the 6 months to < 2 year age group upon availability of the age and body weight adapted dosing regimen for the age group 6 months to < 2 years.[20]

4.2 Inclusion criteria - amended

1. Children aged between 6 months to < 6 years who have been treated for at least 2 months or, in case of catheter related thrombosis, for at least 6 weeks with LMWH, fondaparinux and/or VKA for documented symptomatic or asymptomatic venous thrombosis
2. Hemoglobin, platelets, creatinine and alanine aminotransferase (ALT) and bilirubin evaluated within 10 days prior to Visit 2
3. Informed consent provided. [21]

4.3 Exclusion criteria - amended

1. Active bleeding or high risk for bleeding contraindicating anticoagulant therapy
2. Symptomatic progression of venous thrombosis during preceding anticoagulant treatment
3. Planned invasive procedures, including lumbar puncture and removal of non-peripherally placed central lines during study treatment.
4. An estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2
5. Hepatic disease which is associated either: with coagulopathy leading to a clinically relevant bleeding risk, or ALT > 5x upper level of normal (ULN), or total bilirubin > 2x ULN with direct bilirubin > 20% of the total.
6. Platelet count < 50 x 10^9/L[22]
7. Hypertension defined as > 95th age percentile
8. Life expectancy < 3 months
9. Concomitant use of strong inhibitors of both CYP3A4 and P-gp, i.e. all human immunodeficiency virus protease inhibitors and the following azole-antimycotics agents: ketoconazole, itraconazole, voriconazole, posaconazole, if used systemically (fluconazole is allowed)

[19] Comparator arm was removed via Amendment 4 (see Section 16.2.2.5)
[20] Total number of subjects was reduced via Amendment 4 (see Section 16.2.2.6)
[21] Inclusion criteria modified via Amendment 4 (see Section 16.2.2.7)
[22] Definition of thrombocytopenia adjusted via Amendment 4 (see Section 16.2.2.8)

10. Concomitant use of strong inducers of CYP3A4, i.e. rifampicin, rifabutin, phenobarbital, phenytoin and carbamazepine
11. Hypersensitivity or any other contraindication listed in the local labeling for the experimental treatment
12. Inability to cooperate with the study procedures
13. Previous participation in this study
14. Participation in a study with an investigational drug or medical device within 30 days prior to Visit 2. [23]

4.4 Concomitant medication - amended

Concomitant medications include either continuation of a treatment started before Visit 2, or addition of a new treatment during the study. Non-steroidal anti-inflammatory drugs (NSAIDs) and antiplatelet agents are strongly discouraged since they increase the risk for bleeding in patients treated with anticoagulants. However, if such medication is indicated, the lowest possible dosage should be selected.

Central venous lines and peripheral catheters that are used in this study should only be flushed with saline. Heparin flushes are not allowed.

Concomitant use of strong inhibitors of both CYP3A4 and P-gp, i.e. all human immunodeficiency virus protease inhibitors and azole-antimycotics agents (i.e. ketoconazole, itraconazole, voriconazole, posaconazole; concomitant treatment with fluconazole is allowed), if used systemically, is not allowed, as well as concomitant use of strong inducers of CYP3A4 (i.e. rifampicin, rifabutin, phenobarbital, phenytoin, carbamazepine).

Any previous anticoagulant medication taken within 90 days prior to Visit 2 will be documented. Anticoagulant use after the study treatment period will also be documented. [24]

5. Treatment regimen - amended

5.1 Treatment - amended

In this study, only rivaroxaban will be used. [25],[26]

5.1.1 Rivaroxaban - amended

Age- and body weight-adjusted rivaroxaban will be administered twice daily (12 hours apart) as oral suspension based on the results from the phase I study (12892).[25]

A Taste- and-Texture Questionnaire, using a visual analog scale, will be used to determine the acceptance of the oral suspension in children older than 4 years.

Rivaroxaban will be taken in the morning and in the evening within 2 hours after a meal. If a rivaroxaban dose was missed, the child should take rivaroxaban immediately to ensure intake

[23] Comparator arm was removed via Amendment 4 (see Section 16.2.2.8)
[24] Concomitant medication instructions modified via Amendment 4 (see Section 16.2.2.9)
[25] Section title modified via Amendment 4 (see Section 16.2.2.10 and Section 16.2.2.12)
[26] Comparator arm was removed via Amendment 4 (see Section 16.2.2.11)

of the maximum daily dose per day. In this case, two oral suspension doses may be taken at once. The child should continue with the regular twice daily intake as recommended on the following day.

Instructions on how to prepare the rivaroxaban oral suspension are provided in the Rivaroxaban 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 manual. The training will be documented.[27]

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

Table 5–1: Rivaroxaban dosing schedule

Age group	Body weight [kg]		Oral suspension dose (b.i.d.)	Maximum daily dose
	Min	Max		
≥ 6 months to < 6 years	3	<4	0.7 mg	1.4 mg
	4	<5	0.9 mg	1.8 mg
	5	<6	1.4 mg	2.8 mg
	6	<7	1.8 mg	3.6 mg
	7	<8	2.2 mg	4.4 mg
	8	<9	3.2 mg	6.4 mg
	9	<10	3.2 mg	6.4 mg
	10	<12	3.4 mg	6.8 mg
	12	<14	4.0 mg	8.0 mg
	14	<16	4.0 mg	8.0 mg
	16	<20	4.0 mg	8.0 mg
	20	<30	5.0 mg	10.0 mg
	30	<40	7.5 mg	15.0 mg
	40	<50	7.5 mg	15.0 mg

5.1.1.1 Switching from VKA to rivaroxaban - amended

If a child is on VKA therapy and has a supra-therapeutic INR (> 3.0), rivaroxaban administration should be delayed. In case of an INR between 2.5 to 3.0, the first rivaroxaban dose should be delayed to the next day. If the INR is below 2.5, the first rivaroxaban dose can be taken at Visit 2. VKA therapy must be stopped before rivaroxaban treatment commences.[28]

5.1.1.2 Switching from heparin/fondaparinux to rivaroxaban - amended

If the child received heparin treatment before study treatment with rivaroxaban, rivaroxaban administration should be planned 4 hours after stopping the infusion of UFH, 6 - 12 hours

[27] Instructions about the oral suspension administration were adjusted and information about the Rivaroxaban Oral Suspension Handling Guidelines were added in Amendment 1 (see Section 16.1.2.2)

[28] Section modified via Amendment 4 (see Section 16.2.2.13)

after the last injection of LMWH with a twice-daily regimen, or 12 - 24 hours after the last injection of fondaparinux or LMWH with a once-daily regimen.[29] Heparin/fondaparinux treatment cannot be continued after the start of rivaroxaban treatment in these children.

5.1.1.3 Switching from rivaroxaban to heparin/fondaparinux - amended

Children who switch from rivaroxaban to heparin /fondaparinux can switch at the time of the next scheduled dose. [30]

5.1.1.4 Switching from rivaroxaban to VKA - amended

Children who switch from rivaroxaban to VKA need to continue rivaroxaban for 48 hours after the first dose of VKA. After 2 days of co-administration, an INR should be obtained prior to the next scheduled dose of rivaroxaban. Co-administration of rivaroxaban and VKA is advised to continue until the INR is ≥ 2.0.[30]

5.1.2 Comparator group - amended

This single-arm study does not include comparator treatment.[31]

5.2 Subject identification - amended

Upon signing the informed consent, each child will be assigned unique 9-digit child 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.[31]

5.3 Duration of study treatment

Children will receive study treatment for a period of 30 days.

5.4 Formulation and dose

5.4.1 Rivaroxaban - amended

Rivaroxaban will be provided by Bayer as a 0.1% (1mg/ml) suspension. [32] Rivaroxaban will be dosed according to body weight groups (see Table 5–1). Since children with a glomerular filtration rate below 30 mL/min/1.73 m^2 are excluded from the study, a dose adaptation is not indicated.

[29] Section modified via Amendment 4 (see Section 16.2.2.14)
[30] Addition of switch from rivaroxaban to standard of care via Amendment 4 (see Section 16.2.2.15 and Section 16.2.2.16)
[31] Comparator arm was removed via Amendment 4 (see Section 16.2.2.17 and Section 16.2.2.18)
[32] Section modified via Amendment 4 (see Section 16.2.2.19)

5.4.2 Comparator - amended

This single-arm study does not include comparator treatment.[33]

5.5 Packaging, labeling, and storage - amended

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

All study medication will be labeled according to local law and legislation. Also, 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.

All study medication need to be stored at the investigational site according to the labeled storage advice and in accordance with Good Clinical Practice (GCP) and Good Manufacturing Practice (GMP) requirements. Rivaroxaban oral suspension should not be frozen and should be stored at a temperature not exceeding 25°C. The study drug is to be 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 study medication via IxRS and will use the study medication only for this study and in accordance with this protocol. Receipt, distribution, return and destruction (if any) of the study medication must be properly documented according to specified procedures.[33]

5.6 Treatment assignment - amended

Not applicable.[33]

5.7 Dosage and administration - amended

Rivaroxaban will be dosed according to body weight as oral 0.1% suspension.[33]

5.8 Treatment compliance - amended

5.8.1 Rivaroxaban

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 study medication should be kept securely in the original containers in a designated locked container until retrieved or dispensed. [33]

[33] Comparator arm was removed via Amendment 4 (see Section 16.2.2.20, 16.2.2.21, 16.2.2.22, 16.2.2.23 and 16.2.2.24)

6. Study Procedures

6.1 Study visits - amended

The study has 5 planned visits (see Figure 1–1).

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 venous thrombosis. This visit will take place 60 to 10 days before Visit 2.

Visit 2 is the first study drug administration day and will be a hospital visit. Eligible children will receive rivaroxaban for 30 days.

Visit 3 and Visit 4 are the treatment and end of treatment visits, respectively. These visits will be hospital visits which will take place at Day 15 ± 5 days, and Day 30 ± 3 days, respectively. At visit 2, 3 and 4, PK/PD blood samples will be drawn. At Visit 4, the study medication will be stopped. After cessation of study treatment, 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 60 ± 7 days. This visit will be the last study visit.

In children who prematurely discontinue study medication, visit 5 will take place 30 ± 7 days after premature discontinuation. [34]

6.2 Visit 1 - Screening visit at 60 to 10 days before Visit 2 - amended

The parents/legal guardians will be given explanation about the study and will be given sufficient time to consider participation of their child in the study. Parents/legal guardians who are willing to have their child participating 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, height/length, blood pressure and anticoagulant medication will be collected.

The images of the index venous 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.

Adverse events will not be collected between visit 1 and visit 2. Since hemoglobin, platelet counts, creatinine and liver function 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, and bilirubin within 10 days prior to Visit 2 is an inclusion criterion for this study (see section 4.2).[34]

[34] Section modified via Amendment 4 (see Section 16.2.2.25 and 16.2.2.26)

6.3 Visit 2 - Treatment visit at Day 1 - amended

If the CIAC confirmed the qualifying venous thrombotic event, then re-confirm eligibility. If results for hemoglobin, platelets, creatinine, ALT, bilirubin were not available within 10 days prior to Visit 2, obtain blood sample. If the child still meets the inclusion criteria and does not meet any of the exclusion criteria, the child can receive rivaroxaban.

- If a child is on VKA therapy and has a supra-therapeutic INR (> 3.0), the first administration of rivaroxaban should be delayedVKA therapy should be stopped and the timing of the administration of the first rivaroxaban dose will depend on the INR (see also section 5.1.1.1).

If the INR is between 2.5 to 3.0, the first rivaroxaban dose should be delayed to the next day. If the INR is below 2.5, the first rivaroxaban dose should be taken at Visit 2.

- Collect body weight
- Provide instructions how to take the study drug and give the study booklet and the Rivaroxaban Oral Suspension Handling Guidelines to parents
- Administer first dose of rivaroxaban oral suspension
- Document the volume and type of fluid used to predilute the rivaroxaban oral suspension, as well as the volume and type of fluid taken after the study drug administration.
- Document the exact time of drug intake and the time and type of meal (e.g. breast feeding, baby bottle, porridge, breakfast, lunch, snack, dinner) the child took 2 hours before, during and after study drug administration.
- At 0.5-1.5 hr after drug intake, collect only a PK blood sample
- At 2.5-4 hr after drug intake, collect a PK blood sample followed by the PD blood sample.[35]
- Check for adverse events
- Record all concomitant medication
- Update eCRF.
- Instruct to 1) document in the study booklet the exact time of the last dose taken on the day prior to Visit 3, 2) the exact time and type of meal the child took 2 hours before, during and after study drug administration, 3) the volume and type of fluid used to predilute the rivaroxaban oral suspension and 4) the volume and type of fluid taken after the study drug administration.
- Instruct that on the day of visit 3, rivaroxaban should not be taken in the morning and medication should be brought to the hospital. [36],[37]

[35] Instructions about how to administer the oral suspension were adjusted in Amendment 1 (see Section 16.1.2.3)

[36] Section modified via Amendment 1 (see Section 16.1.2.3)

[37] Section modified via Amendment 4 (see Section 16.2.2.27)

6.4 Visit 3 - Treatment visit at Day 15 (+/- 5 days) - amended

- 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.
- Administer the next rivaroxaban dose and document the volume and type of fluid used to predilute the rivaroxaban oral suspension, as well as the volume and type of fluid taken after the study drug administration.
- Document the exact time of drug intake and type of meal the child took 2 hours before, during and after drug administration
- Complete the Taste-and-Texture Questionnaire for children older than 4 years
- At 2 – 8 hr after drug intake, 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
- Update eCRF.
- Inform that on the day before visit 4
  - the evening dose of rivaroxaban should be taken as late as possible (i.e. closely before the child goes to bed) and medication should not be taken on the day of visit 4
  - 1) to document in the study booklet the exact time of the last dose taken on the day before Visit 4, 2) the exact time and type of meal the child took 2 hours before, during and after study drug administration, 3) the volume and type of fluid used to predilute the rivaroxaban oral suspension and 4) the volume and type of fluid taken after the study drug administration. [38], [39]

If a child discontinues study treatment 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.

[38] Section modified via Amendment 1 (see Section 16.1.2.4)

[39] Section modified via Amendment 4 (see Section 16.2.2.28)

6.5 Visit 4 - End of study treatment visit at Day 30 (+/- 3 days) - amended

No study medication should 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.
- Obtain blood sample for hemoglobin, platelets, ALT and bilirubin
- document the exact time of drug intake on the day prior to visit 4 and document the volume and type of fluid used to predilute the rivaroxaban oral suspension, as well as the volume and type of fluid taken after the study drug administration
- document the time and type of meal the child took 2 hours before, during and after study drug administration on the day prior to Visit 4.
- at 10 – 16 hr after last drug intake, collect the 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.
- Update eCRF
- Repeat imaging with ultrasound should be obtained if applicable. If repeat imaging can be done with MRI or MR angiography, this should be done only if sedation and/or general anesthesia are not required. Other modalities of imaging, e.g. CT (angiography) scan or contrast angiography, will be obtained only if the repeat test was planned independently of the study. A repeat imaging adjudication package needs to be compiled and sent to the adjudication office.

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, or for hemoglobin, platelets, ALT or bilirubin, is required.[40], [41]

[40] Section modified via Amendment 1 (see Section 16.1.2.5)

[41] Section modified via Amendment 4 (see Section 16.2.2.29)

6.6 Visit 5 - 30 day post treatment contact at Day 60 (+/- 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 60 ± 7 days in children who completed the study treatment.

However, in children who prematurely discontinue study medication, this visit will take place 30 ± 7 days after premature discontinuation.

- 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.

6.7 Unscheduled visits

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

6.8 Safety outcomes

The primary 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, or
    - 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 or
- impairment of activities of daily life (such as loss of school days or hospitalization).

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 - amended

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.[42]

6.10 Management of bleeding in children - amended

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 the PK/PD sample.

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

- recombinant factor VIIa (NovoSeven®)
- 4-factor concentrate.

Protamine sulfate and vitamin K are not expected to affect the anticoagulant activity of rivaroxaban.[43]

6.11 Efficacy outcome

The efficacy outcome will be symptomatic recurrence of venous thrombosis or asymptomatic deterioration.

Symptomatic recurrence of venous thrombosis or asymptomatic deterioration should be documented using the appropriate imaging test.

6.12 PK/PD assessments - amended

Blood samples will be taken for PK and PD measurements.[44] 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:

1) PK/PD samples at visit 2,
2) PK/PD sample at visit 3, and
3) PK/PD sample at visit 4.

[42] Comparator arm was removed via Amendment 4 (see Section 16.2.2.30)
[43] Section modified via Amendment 4 (see Section 16.2.2.31)
[44] Section modified via Amendment 4 (see Section 16.2.2.32)

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.

If rivaroxaban was temporarily stopped at the time of a study visit (e.g. if treatment was temporarily stopped prior to visit 3), sampling of blood for PK/PD analysis according to this visit's schedule should be postponed until rivaroxaban treatment has been restarted and sustained for at least 3 days.

If a blood sample is taken from a central line, 3 mL of blood should be discarded.[16] In children from 6 months to 1 year old, it might not be possible to withdraw blood from central venous line due to the amount of blood required especially at visit 2. In this case, it is advised to withdraw blood from a peripheral catheter. If a blood sample is taken from a peripheral catheter, fluid is to be withdrawn from the line until all is removed and blood is sampled. An anesthetic cream can be applied to minimize pain from drawing of blood from a vein. Central venous lines and peripheral catheters that are used in this study should only be flushed with saline.

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 pooled and analyzed using population approaches to estimate the PK/PD profile of rivaroxaban. Details for the population PK/PD analysis will be described in a separate evaluation plan.

6.13 Study booklet - amended

Parents/children will receive a booklet with the following information:

- The local medical contact person and emergency telephone number
- The visit schedule provided by the IxRS, including dates of telephone and/or hospital visits
- Instructions to keep empty medication packages and unused study medication.
- How to take rivaroxaban
- Calendar to track the date and time of food and study drug intake as well as the volume of fluid taken. [45]

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:

[45] Comparator arm was removed via Amendment 4 (see Section 16.2.2.33)

- 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 and ancillary studies.

6.14.2 Central independent adjudication committee (CIAC)

All index venous thrombotic events, and all suspected recurrent venous 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 (SAEs), recurrent venous 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 - amended

Full analysis set (FAS): This analysis set will include all enrolled children.

Safety analysis set (SAS): This analysis set will include all enrolled children who received at least one dose of study medication.

Per protocol set (PPS): This population includes all enrolled children who completed the 30-day treatment period. The PPS may also exclude major protocol deviations. Further details will be specified in the Statistical Analysis Plan.

Listing only set (LOS): This population includes all screening failures.[46]

7.3 Demographic and other baseline characteristics - amended

Summary statistics (arithmetic mean, standard deviation, median, minimum and maximum for quantitative variables) will be presented by age group. Frequency tables for qualitative data will be provided. Medical history findings will be summarized using Medical Dictionary for Regulatory Activities (MedDRA) terms.[47]

7.4 Safety analysis - amended

All safety analyses will be performed on the SAS population. The analysis will primarily focus on bleeding that occurred during or within 2 days after stop of study treatment. 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 descriptively. 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 descriptively for the original data as well as for the difference to baseline. Frequency tables will be provided for qualitative data. [48]

7.5 Efficacy analysis - amended

All efficacy analyses will be performed on the FAS population. The occurrence of recurrent venous thromboembolism and asymptomatic deterioration in thrombotic burden will be summarized by age group.[49]

7.6 PK/PD analysis

PK/PD modeling, using population approaches will be used to describe the pharmacokinetics of rivaroxaban, including potential influence of relevant co-variables, and to relate anticoagulant parameters of rivaroxaban with plasma concentrations. Details will be given in a separate detailed PK/PD evaluation plan.

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[46] Comparator arm was removed via Amendment 4 (see Section 16.2.2.34)
[47] Section was modified via Amendment 4 (see Section 16.2.2.35)
[48] Comparator arm was removed via Amendment 4 (see Section 16.2.2.36)
[49] Section was modified via Amendment 4 (see Section 16.2.2.37)

7.7 Interim analyses

No interim analysis will be performed.

7.8 Determination of sample size - amended

A total of 20 children who took at least one dose of study medication are planned to be enrolled in the study.[50] The sample size does not originate from a formal sample size calculation, but is based on a feasibility assessment because of the very low incidence of venous thrombosis in children, and on the pharmacokinetic moderate inter-individual variability of rivaroxaban. Based on past experience in obtaining parental consent in this indication, it is estimated that fewer than 10% of eligible children can be enrolled in this study.

7.9 Adverse events (AE) - amended

Individual listings of adverse events (including age, weight, height, gender, adverse event as reported, start, duration, severity and relation to study drug) will be provided. The incidence of treatment-emergent adverse events will be summarized by age group using MedDRA preferred terms grouped by primary system organ class.[51]

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.

[50] Total number of subjects reduced via Amendment 4 (see Section 16.2.2.38)
[51] Section modified via Amendment 4 (see Section 16.2.2.39)

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 would be 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, e.g. the child while on a bike is struck by an automobile when there is no indication that the drug caused disorientation that may have caused the event. 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 procedure

The assessment of a possible causal relationship between the AE and protocol-required procedure is based on the presence of a reasonable relationship.

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), and 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 reaction/s (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 (recurrent venous thrombosis) 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 AEs of special safety interest - amended

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

- Concurrent elevations of ALT > 5x ULN and total bilirubin > 2x ULN
- Liver injury
- A platelet count below $50x10^9$/L.[52]

7.10 Premature discontinuation of study medication

Children prematurely discontinue study medication

- at their own request or at the request of their parents/legally acceptable 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 30-day treatment period. If study medication is permanently discontinued, further treatment is at the investigator's discretion.

If the child or 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 the child/parent/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.

[52] Definition of thrombocytopenia was adjusted via Amendment 4 (see Section 16.2.2.40)

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 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.

9. Premature termination of the study

The investigator has the right to terminate 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:

- If the risk-benefit ratio becomes unacceptable due to, for example,
  - safety or efficacy findings from this study
  - results of parallel clinical studies.
- If 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:

- closures should occur only after consultation between involved parties
- 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 destructed 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 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 Child information and consent

All relevant study information will be summarized in an integrated child information sheet, and informed consent form provided by Bayer or the study center. A sample child information and informed consent form is provided as a document separate to this protocol. Consent will be asked from parent(s) or legal guardian.

The investigator or designee will explain all relevant aspects of the study to the parent(s)/legal guardian(s) and the child, if applicable, 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 parent(s)/legal guardian(s) and the child, if applicable, 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 parent(s)/legal guardian(s) agree to sign and date the informed consent and have done so. Then the investigator or designee will sign and date the form. The parent(s)/legal guardian(s) 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 guardians will be revised whenever important new information become available that may be relevant to the child's consent, or if there is an amendment to the protocol that necessitates a change to the content of the child information and/or the written informed consent form. The investigator will inform the parents/legal guardian of changes in a timely manner and will ask the parents/legal guardians to confirm participation in the study by signing the revised informed consent form. Revised informed consent and the child information sheet must receive the IEC's/IRB's approval before implementation.

11. Investigators and other study participants

The study coordinating investigator is

Dr Guy A. Young, M.D., Director, Hemostasis and Thrombosis Center, Children's Hospital of Los Angeles, PPD USA.

Key personnel will be listed in the study file.

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

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 country 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 study 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, the children/parents/legal guardians 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.

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10. Monagle P, Chan A, Goldemberg N, Ichord R, Journeycake J, Nowak-Gottl U, Vesely S. Antithrombotic therapy in neonates and children: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (9th Edition). Chest 2012;144: e737S-e801S887S-968S.

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16. Protocol amendments

16.1 Amendment 1

Amendment 1 is the first global amendment dated 02 Sep 2014.

16.1.1 Overview of changes

16.1.1.1 Modification 1: Correction of erroneous dosing information

The dosing for this study and information on the adult study were wrong in the previous version of the protocol and were corrected.

Affected protocol sections: Synopsis

16.1.1.2 Modification 2: Adjustment of suspension information

In the phase I study (#12892) the rivaroxaban oral suspension showed an unexpected PK profile which differed from the one of the standard tablet formulation. It was observed that the unexpected PK profile of the rivaroxaban oral suspension is due to a pH dependent precipitation of one of the ingredients in the formulation leading to a slow release of rivaroxaban. Data from phase I study (#12892) have shown that pre-diluting the suspension prior to administration helps to restore a tablet-like profile. The team decided to provide a high level summary of the rivaroxaban oral suspension preparation. The detailed instruction for preparation and administration is specified in the Rivaroxaban Oral Suspension Guidelines.

Affected protocol sections: Section 5.1.1 Rivaroxaban group, Section 6.3 Visit 2 - Randomization visit at Day 1, Section 6.4 Visit 3 - Treatment visit at Day 15 (+/- 5 days), Section 6.5 Visit 4 - End of study treatment visit at Day 30 (+/- 3 days)

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 <u>underlined</u> in the "new text". Corrections of typing errors or omissions are not highlighted in this amendment.

16.1.2.1 Synopsis

This section was changed as a result of Modifications 1 and 2.

Old text:

[...]

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

[...]

New text:

[...]

Dose	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

[...]

Old text:

[…]

Figure 1-1: Flow chart

	Screen [a]	Treatment period			30 day post study treatment contact
Visit	1	2	3	4	5
Days	Day -60 to Day -10	Day 1	Day 15 ± 5 days	Day 30 ± 3 days	Day 60 ± 7 days
Obtain informed consent	•				
Check in-/exclusion criteria	•				
Obtain demographic data	•				
Check medical history	•	•			
Record anticoagulant medication	•	•			
Obtain height/length, and blood pressure	•				
Obtain body weight	•	•			
Check Hb, platelets, creatinine, ALT, bilirubin		•[b]			
Send baseline adjudication package	•				
Review the CIAC decision for index thrombotic event for final eligibility [c]		•			
Re-confirm in-/exclusion criteria [c]		•			
Provide patient details to IxRS	•				
Randomize patient using IxRS		•			
Dispense study medication Instruct how to take study medication Provide study booklet		• • •			

[…]

New text:

[…]

Figure 1-1: Flow chart

	Screen [a]	Treatment period			30 day post study treatment contact
Visit	1	2	3	4	5
Days	Day -60 to Day -10	Day 1	Day 15 ± 5 days	Day 30 ± 3 days	Day 60 ± 7 days
Obtain informed consent	•				
Check in-/exclusion criteria	•				
Obtain demographic data	•				
Check medical history	•	•			
Record anticoagulant medication	•	•			
Obtain height/length, and blood pressure	•				
Obtain body weight	•	•			
Check Hb, platelets, creatinine, ALT, bilirubin		•[b]			
Send baseline adjudication package	•				
Review the CIAC decision for index thrombotic event for final eligibility [c]		•			
Re-confirm in-/exclusion criteria [c]		•			
Provide patient details to IxRS	•				
Randomize patient using IxRS		•			
Dispense study medication Instruct how to take study medication Provide study booklet Provide Rivaroxaban Oral Suspension Handling Guidelines to parents		• • • •			

[…]

16.1.2.2 Section 5.1.1 Rivaroxaban group

This section was changed as a result of Modification 2.

Old text:

[…]

~~The administration of the oral suspension should be immediately followed by the intake of up to 240 mL of liquid.~~ A Taste and Texture Questionnaire, using a visual analog scale, will be used to determine the acceptance of the oral suspension in children older than 4 years.

New text:

[…]

A Taste- and- Texture Questionnaire, using a visual analog scale, will be used to determine the acceptance of the oral suspension in children older than 4 years.

[…]

Old text:

[…]

Instructions on how to handle rivaroxaban oral suspension can be found in the oral suspension handling guidelines.

[…]

New Text:

[…]

Instructions on how to prepare the rivaroxaban oral suspension are provided in the Rivaroxaban 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 manual. The training will be documented.

[…]

16.1.2.3 Section 6.3 *Visit 2 - Randomization visit at Day 1*

This section was changed as a result of Modification 2.

Old text:

[…]

- Provide instructions how to take the study drug and give the study booklet
- Administer the assigned study drug
- In children allocated to rivaroxaban,
  - administer the first rivaroxaban dose ~~as instructed in the oral suspension handling guidelines.~~
  - document the exact time of drug intake and the time and type of meal (~~i.e.~~ breakfast, lunch, snack, dinner) the child took 2 hours before and after study drug administration.
  - at 0.5-1.5 hr after drug intake, collect only a PK blood sample

- at 2.5-4 hr after drug intake, collect a PK blood sample followed by the PD blood sample.

- Check for adverse events
- Record all concomitant medication
- Instruct that on the day of visit 3, rivaroxaban should not be taken in the morning and medication should be brought to the hospital
- ~~Update eCRF.~~

[…]

New text:

[…]

- Provide instructions how to take the study drug and give the study booklet and the Rivaroxaban Oral Suspension Handling Guidelines to parents
- Administer the assigned study drug
- In children allocated to rivaroxaban,
  - administer the first rivaroxaban dose and document the volume and type of fluid used to predilute the rivaroxaban oral suspension, as well as the volume and type of fluid taken after the study drug administration.
  - document the exact time of drug intake and the time and type of meal (e.g. breast feeding, baby bottle, porridge, breakfast, lunch, snack, dinner) the child took 2 hours before, during and after study drug administration.
  - at 0.5-1.5 hr after drug intake, collect only a PK blood sample
  - at 2.5-4 hr after drug intake, collect a PK blood sample followed by the PD blood sample.
- Check for adverse events
- Record all concomitant medication
- Update eCRF.
- In children allocated to rivaroxaban, instruct to 1) document in the study booklet the exact time of the last dose taken on the day prior to Visit 3, 2) the exact time and type of meal the child took 2 hours before, during and after study drug administration, 3) the volume and type of fluid used to predilute the rivaroxaban oral suspension and 4) the volume and type of fluid taken after the study drug administration.
- Instruct that on the day of visit 3, rivaroxaban should not be taken in the morning and medication should be brought to the hospital

[…]

16.1.2.4 Section 6.4 *Visit 3 - Treatment visit at Day 15 (+/- 5 days)*

This section was changed as a result of Modification 2.

Old text:

[…]

- In children randomized to rivaroxaban
  - administer the next rivaroxaban dose ~~immediately followed by the intake of up to 240 mL of liquid and record the type and volume of fluid taken~~.
  - document the exact time of drug intake and type of meal ~~(i.e. breakfast, lunch, snack, dinner)~~ the child took 2 hours before and after drug administration
  - ~~record the volume of fluid taken after study medication.~~
  - complete the Taste and Texture Questionnaire for children older than 4 years
  - at 2 – 8 hr after drug intake, 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
- In children allocated to rivaroxaban, inform that on the day before visit 4
  - the evening dose of rivaroxaban should be taken as late as possible (i.e. closely before the child goes to bed) and medication should not be taken on the day of visit 4
  - ~~Instruct to~~ document the exact time of drug intake on the day prior to Visit 4 ~~and~~ the time and type of meal (i.e. breakfast, lunch, snack, dinner) the child took 2 hours before and after study drug administration
  - ~~Record the type and volume of fluid taken after study medication.~~
- ~~Update eCRF.~~

New text:

[…]

- In children randomized to rivaroxaban
  - administer the next rivaroxaban dose and document the volume and type of fluid used to predilute the rivaroxaban oral suspension, as well as the volume and type of fluid taken after the study drug administration.
  - document the exact time of drug intake and type of meal the child took 2 hours before, during and after drug administration
  - complete the Taste-and-Texture Questionnaire for children older than 4 years
  - at 2 – 8 hr after drug intake, 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
- Update eCRF.
- In children allocated to rivaroxaban, inform that on the day before visit 4
  - the evening dose of rivaroxaban should be taken as late as possible (i.e. closely before the child goes to bed) and medication should not be taken on the day of visit 4
  - 1) to document in the study booklet the exact time of the last dose taken on the day before Visit 4, 2) the exact time and type of meal the child took 2 hours before, during and after study drug administration, 3) the volume and type of fluid used to predilute the rivaroxaban oral suspension and 4) the volume and type of fluid taken after the study drug administration.

16.1.2.5 Section 6.5 Visit 4 - End of study treatment visit at Day 30 (+/- 3 days)

This section was changed as a result of Modification 2.

Old text:

[...]

- In children randomized to rivaroxaban
  - document the exact time of drug intake on the day prior to visit 4 and the time and type of meal ~~(i.e breakfast, lunch, snack, dinner)~~ the child took 2 hours before, during and after study drug administration
  - ~~record the type and volume of fluid taken after study medication~~

[...]

New text:

[…]

- In children randomized to rivaroxaban
  - document the exact time of drug intake on the day prior to visit 4 and document the volume and type of fluid used to predilute the rivaroxaban oral suspension, as well as the volume and type of fluid taken after the study drug administration
  - document the time and type of meal the child took 2 hours before, during and after study drug administration on the day prior to Visit 4.

[…]

16.2 Amendment 4

Amendment 4 is the second global amendment dated 14 Apr 2015.

16.2.1 Overview of changes

16.2.1.1 Change 1: Minor clarifications for consistency

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

Affected sections: Synopsis, Section 4.3: Exclusion criteria, Section 4.4: Concomitant medication, Section 5.4.1: Rivaroxaban, Section 6.3. Visit 2 - Treatment visit at Day 1 Section 6.4: Visit 3 - Treatment visit at Day 15 (+/- 5 days)

16.2.1.2 Change 2: Comparator arm was removed

The comparator arm was originally included in an attempt to provide a calibrator group for the assessment of safety and efficacy of rivaroxaban. However, the sample size is considered too small to support meaningful comparison of rivaroxaban vs. standard of care with regard to safety and efficacy. Therefore, the comparator arm was removed. All information regarding the comparator arm was deleted in the protocol.

After implementation of the amendment, no further children will be treated with comparator. However, all data from children treated with comparator prior to this amendment will be analyzed as planned and reported in the CSR.

Affected sections: Title page, Synopsis, Section 1: Introduction, Section 1.3: Rationale of the study and risk-benefit assessment, Section 3: Study design, Section 4.2: Inclusion criteria, Section 4.3: Exclusion criteria, Section 4.4: Concomitant medication, Section 5: Treatment regimens, Section 5.1: Treatment, Section 5.1.1: Rivaroxaban , Section 5.1.1.1: Switching from VKA to rivaroxaban, Section 5.1.1.2: Switching from heparin/fondaparinux

to rivaroxaban, Section 5.1.2: Comparator group, Section 5.2: Subject identification, Section 5.4.2: Comparator, Section 5.5: Packaging, labeling, and storage, Section 5.6: Treatment assignment, Section 5.7: Dosage and administration, Section 5.8: Treatment compliance, Section 6.1: Study visits, Section 6.2: Visit 1 - Screening visit at 60 to 10 days before Visit 2, Section 6.3. Visit 2 - Treatment visit at Day 1, Section 6.4: Visit 3 - Treatment visit at Day 15 (+/- 5 days), Section 6.5: Visit 4 - End of study treatment visit at Day 30 (+/- 3 days), Section 6.9: Recommendations before and after invasive procedures and surgical intervention, Section 6.10: Management of bleeding in children, Section 6.12: PK/PD assessments, Section 6.13: Study booklet, Section 7.2: Analysis sets, Section 7.3: Demographic and other baseline characteristics, Section 7.4: Safety analysis, Section 7.5: Efficacy analysis, Section 7.9: Adverse events (AE)

16.2.1.3 Change 3: Total number of subjects was reduced

As described in Change 2 (Section 16.3.1.2), the comparator arm was removed. Therefore, no further children need to be enrolled for this arm. This reduces the required total number of enrolled children from 40 to 20. The planned number of children treated with rivaroxaban (10 per age group) remains unchanged.

Affected sections: Synopsis, Section 4.1: Planned number of children, Section 7.8: Determination of sample size

16.2.1.4 Change 4: Modification of inclusion criterion 1

Inclusion criterion 1 was changed to enable enrollment of children who are on long-term anticoagulant treatment. The text indicating that children need to be on their last month of intended anticoagulant treatment was removed.

Affected sections: Synopsis, Section 3: Study design, Section 4.2: Inclusion criteria

16.2.1.5 Change 5: Addition of switch from rivaroxaban to standard of care

Change 4 (Section 16.2.1.4) implements that children can now be enrolled and treated with rivaroxaban during long-term anticoagulant treatment. Switching from one anticoagulant regimen to another occurs frequently in daily clinical practice. With the approval of rivaroxaban for various thrombosis conditions in adults, there is now considerable experience for switching patients on and off rivaroxaban therapy. Instructions on how to safely handle the switch form heparin/fondaparinux and VKA to rivaroxaban and vice versa are available in the protocol.

Affected sections: New Section 5.1.1.3: Switching from rivaroxaban to heparin/fondaparinux, New Section 5.1.1.4: Switching from rivaroxaban to VKA

16.2.1.6 Change 6: Modification of exclusion criterion 6

Clinical practice supports the administration of anticoagulants with platelet counts of 50x109/L and even lower. [8] Therefore, the platelet count threshold for exclusion of children was adjusted from $<100x10^9$/L to $<50x10^9$/L.

Affected sections: Synopsis, Section 4.3: Exclusion criteria, Section 7.9.9: AEs of special safety interest

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 Amendment Change 2.

Old text:	30-day, ~~open-label, active-controlled, randomized~~ study of the safety, efficacy and the pharmacokinetic and pharmacodynamic properties of oral rivaroxaban in young children with various manifestations of venous thrombosis
New text:	30-day, single-arm study of the safety, efficacy and the pharmacokinetic and pharmacodynamic properties of oral rivaroxaban in young children with various manifestations of venous thrombosis

16.2.2.2 Synopsis

This section was modified based on Amendment Changes 1, 2, 3, 4 and 6

Old text:

Title	30-day, ~~open-label, active-controlled, randomized~~ study of the safety, efficacy and the pharmacokinetic and pharmacodynamic properties of oral rivaroxaban in young children with various manifestations of venous thrombosis.
	[…]
Comparator study drug	~~Children continue to receive the anticoagulant treatment regimen they have received prior to randomization~~
Name of active ingredient	~~Low molecular weight heparin (LMWH), fondaparinux or vitamin K antagonist (VKA)~~

Dose	~~As per standard of care~~
Route of administration	~~As per standard of care~~
Duration of treatment	~~30 days~~
	[…]
Diagnosis and main criteria for inclusion	Children aged 6 months to < 6 years with documented symptomatic or asymptomatic venous thrombosis treated for at least 2 months or, in case of catheter-related thrombosis, treated for at least 6 weeks with LMWH, fondaparinux and/or VKA ~~and who are entering the last month of intended anticoagulant treatment~~. The imaging of the index thrombotic event will be confirmed by the central independent adjudication committee (CIAC).
Study design	~~Open label, active controlled~~, multicenter~~, randomized~~ study
Methodology	Children ~~randomized to rivaroxaban~~ will receive an age- and body weight-adjusted regimen. ~~Children randomized to comparator continue to receive the same treatment regimen they received prior to randomization.~~ All suspected clinical study outcomes and baseline and repeat thrombosis imaging tests will be assessed by a CIAC ~~blinded to treatment allocation.~~ An independent data monitoring committee (DMC) will monitor the children's safety and give recommendations to the steering committee.
Number of children	~~40~~ children (~~20~~ per ~~treatment~~ group)
Inclusion/ exclusion criteria	Inclusion 1. Children aged 6 months to < 6 years who have been treated for at least 2 months or, in case of catheter related thrombosis, for at least 6 weeks with LMWH, fondaparinux and/or VKA for documented symptomatic or asymptomatic venous thrombosis ~~and who will enter their last month of intended anticoagulant treatment~~ 2. Hemoglobin, platelets, creatinine, alanine aminotransferase (ALT) and bilirubin evaluated within 10 days prior to ~~randomization~~ 3. […] Exclusion […] 6. Platelet count < ~~100~~ x 10^9/L […] 9. Concomitant use of strong inhibitors of both cytochrome P450 isoenzyme 3A4 (CYP3A4) and P-glycoprotein (P-gp), i.e. all human immunodeficiency virus protease inhibitors and the following azole-antimycotics agents: ketoconazole, itraconazole, voriconazole, posaconazole, if used systemically 10. […] 11. Hypersensitivity or any other contraindication listed in the local labeling for the ~~comparator treatment or~~ experimental- treatment 12. […] 13. Previous ~~randomization~~ to this study 14. Participation in a study with an investigational drug or medical device within 30 days prior to ~~randomization.~~

	[…]
Statistical Analysis Plan	The incidence of the composite of major and clinically relevant non-major bleeding and the incidence of symptomatic recurrent venous thromboembolism, and asymptomatic deterioration in the thrombotic burden on repeat imaging will be summarized ~~by treatment~~. Quantitative data will be described by summary statistics and presented by ~~treatment~~. Results of PK/PD analyses will be assessed ~~using population PK/PD methodology~~.

New text:

Title	30-day, single-arm study of the safety, efficacy and the pharmacokinetic and pharmacodynamic properties of oral rivaroxaban in young children with various manifestations of venous thrombosis.
	[…]
Comparator study drug	Not applicable
Name of active ingredient	Not applicable
Dose	Not applicable
Route of administration	Not applicable
Duration of treatment	Not applicable
	[…]
Diagnosis and main criteria for inclusion	Children aged 6 months to < 6 years with documented symptomatic or asymptomatic venous thrombosis treated for at least 2 months or, in case of catheter-related thrombosis, treated for at least 6 weeks with LMWH, fondaparinux and/or VKA. The imaging of the index thrombotic event will be confirmed by the central independent adjudication committee (CIAC).
Study design	Single-arm, multicenter study
Methodology	Children will receive rivaroxaban according to an age- and body weight-adjusted regimen. All suspected clinical study outcomes and baseline and repeat thrombosis imaging tests will be assessed by a CIAC An independent data monitoring committee (DMC) will monitor the children's safety and give recommendations to the steering committee.
Number of children	20 children (10 per age group) treated with rivaroxaban.
Inclusion/ exclusion criteria	Inclusion 1. Children aged 6 months to < 6 years who have been treated for at least 2 months or, in case of catheter related thrombosis, for at least 6 weeks with LMWH, fondaparinux and/or VKA for documented symptomatic or asymptomatic venous thrombosis 2. Hemoglobin, platelets, creatinine, alanine aminotransferase (ALT) and bilirubin evaluated within 10 days prior to Visit 2 3. […] Exclusion […] 6. Platelet count < 50 x 10^9/L […] 9. Concomitant use of strong inhibitors of both cytochrome P450 isoenzyme 3A4

	(CYP3A4) and P-glycoprotein (P-gp), i.e. all human immunodeficiency virus protease inhibitors and the following azole-antimycotics agents: ketoconazole, itraconazole, voriconazole, posaconazole, if used systemically (fluconazole is allowed) 10. […] 11. Hypersensitivity or any other contraindication listed in the local labeling for the experimental treatment 12. […] 13. Previous enrollment to this study 14. Participation in a study with an investigational drug or medical device within 30 days prior to Visit 2.
	[…]
Statistical Analysis Plan	The incidence of the composite of major and clinically relevant non-major bleeding and the incidence of symptomatic recurrent venous thromboembolism, and asymptomatic deterioration in the thrombotic burden on repeat imaging will be summarized descriptively. Quantitative data will be described by summary statistics and presented by age. Results of PK/PD analyses will be assessed descriptively.

Old text:

Figure 1-1: Flow chart

	Screen [a]	Treatment period			30 day post study treatment contact
Visit	1	2	3	4	5
Days	Day -60 to Day -10	Day 1	Day 15 ± 5 days	Day 30 ± 3 days	Day 60 ± 7 days
[…]					
Provide patient details to IxRS	•				
~~Randomize patient using IxRS~~		•			
[…]					
Pharmacokinetics and pharmacodynamics [f]		**~~Rivaroxaban group only~~** [g]			
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
[…]					
		~~Comparator group only~~			
~~INR adjusted VKA~~		~~At least 1 INR per 2 weeks~~			

[a] The screening visit can be performed up to 60 days prior to ~~randomization~~, but should not be less than 10 days prior to ~~randomization.~~ Please contact the adjudication office in case the available period prior to ~~randomization~~ is less than 10 days.

[b] Results should be available within 10 days prior to ~~randomization~~, if not obtain blood sample at visit 2.

[e] ~~VKA compliance will be ensured by minimum of 1 INR per 2 weeks.~~

[...]

New text:

Figure 1-1: Flow chart

	Screen [a]	Treatment period	30 day post study treatment contact		
Visit	1	2	3	4	5
Days	Day -60 to Day -10	Day 1	Day 15 ± 5 days	Day 30 ± 3 days	Day 60 ± 7 days
[…]					
Provide patient details to IxRS	•				
[…]					
Pharmacokinetics and pharmacodynamics [f]	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
[…]					

[a] The screening visit can be performed up to 60 days prior to Visit 2, but should not be less than 10 days prior to Visit 2. Please contact the adjudication office in case the available period prior to Visit 2 is less than 10 days.

[b] Results should be available within 10 days prior to Visit 2, if not obtain blood sample at visit 2.

[e] This footnote was removed via Amendment 4.

[…]

16.2.2.3 Section 1: Introduction

This section was modified based on Amendment Change 2.

Old text: The goal of the rivaroxaban pediatric program is to make rivaroxaban available to children for treatment and secondary prevention of venous thromboembolism. To accomplish this goal, it will be necessary to evaluate a pediatric age- and body weight adapted dosing regimen, and to address the safety and efficacy of rivaroxaban ~~versus the standard of care.~~

New text: The goal of the rivaroxaban pediatric program is to make rivaroxaban available to children for treatment and secondary prevention of venous thromboembolism. To accomplish this goal, it will be necessary to evaluate a pediatric age- and body weight adapted dosing regimen, and to address the safety and efficacy of rivaroxaban.

16.2.2.4 Section 1.3: Rationale of the study and risk-benefit assessment

This section was modified based on Amendment Change 2

Old text:	[…] Therefore, we elected to evaluate the selected rivaroxaban dose regimen after the completion of a minimum period of 2 months or, in the case of catheter related thrombosis, treatment for at least 6 weeks with ~~comparator.~~ […]
New text:	[…] Therefore, we elected to evaluate the selected rivaroxaban dose regimen after the completion of a minimum period of 2 months or, in the case of catheter related thrombosis, treatment for at least 6 weeks with standard of care medication. […]

16.2.2.5 Section 3: Study design

This section was modified based on Amendment Change 2 and 4.

Old text:	This is ~~an open-label, active-controlled~~, multicenter~~, randomized~~ study evaluating the safety, efficacy and PK/PD profile of a 30-day treatment with age- and body weight-adjusted oral rivaroxaban in children aged between 6 months and < 6 years with various manifestations of symptomatic and asymptomatic venous thrombosis. Children who have been treated for at least 2 months or in case of catheter-related thrombosis, treated for at least 6 weeks -with LMWH, fondaparinux and/or VKA for symptomatic or asymptomatic venous thrombosis will ~~be randomized to~~ receive ~~either~~ age- and body weight-adjusted rivaroxaban~~, or comparator (i.e. LMWH, fondaparinux or VKA), for their last month of intended anticoagulant~~ treatment~~. Before randomization~~, the documented index thrombotic event will be confirmed by the central adjudication committee (CIAC) for the child to be eligible for the study. Allocation to treatment will be done centrally by an interactive voice/web response system (IxRS). ~~Allocation will be stratified by baseline presentation of venous thrombosis, i.e~~. ~~a) lower extremity DVT, caval vein thrombosis, upper extremity DVT, subclavian thrombosis, right atrial thrombosis and pulmonary embolism, and catheter-related thrombosis, *or*~~ ~~b) cerebral vein and sinus thrombosis, jugular vein thrombosis, mesenteric vein thrombosis, portal vein thrombosis and renal vein thrombosis.~~ ~~After randomization, children~~ will receive ~~either~~ rivaroxaban~~, or comparator~~ for a total of 30 days. For all children, visits are scheduled at regular time points (see Figure 1-1). ~~Randomized~~ children who are not treated or those with premature discontinuation of study drug 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 Figure 1-1).
New text:	This is a single-arm, multicenter study evaluating the safety, efficacy and PK/PD profile of a 30-day treatment with age- and body weight-adjusted oral rivaroxaban in children aged between 6 months and < 6 years with various manifestations of symptomatic and asymptomatic venous thrombosis.

Children who have been treated for at least 2 months or in case of catheter-related thrombosis, treated for at least 6 weeks with LMWH, fondaparinux and/or VKA for symptomatic or asymptomatic venous thrombosis will receive age- and body weight-adjusted rivaroxaban. Before first study treatment administration, the documented index thrombotic event will be confirmed by the central adjudication committee (CIAC) for the child to be eligible for the study.

Allocation to treatment will be done centrally by an interactive voice/web response system (IxRS). The investigator will provide the IxRS with study center identification, the child's date of birth (day, month and year), gender, weight and clinical presentation.

Please refer to the IxRS manual for further details.

Children will receive rivaroxaban for a total of 30 days.

For all children, visits are scheduled at regular time points (see Figure 1-1). Enrolled children who are not treated or those with premature discontinuation of study drug 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 Figure 1-1).

16.2.2.6 Section 4.1: Planned number of children

This section was modified based on Amendment Change 3.

Old text:	~~Forty~~ children (~~20~~ per ~~treatment~~ group) are planned to be ~~enrolled in the study, of whom twenty will be in the 2 to < 6 year age group and twenty in the 6 months to < 2 year age group~~. Enrolment will start with the 2 to < 6 year age group, followed by the 6 months to < 2 year age group upon availability of the age and body weight adapted dosing regimen for the age group 6 months to < 2 years.
New text:	Twenty children (10 per age group) are planned to be treated with rivaroxaban. Enrolment will start with the 2 to < 6 year age group, followed by the 6 months to < 2 year age group upon availability of the age and body weight adapted dosing regimen for the age group 6 months to < 2 years.

16.2.2.7 Section 4.2: Inclusion criteria

This section was modified based on Amendment Change 2 and 4.

Old text:	1. Children aged between 6 months to < 6 years who have been treated for at least 2 months or, in case of catheter related thrombosis, for at least 6 weeks with LMWH, fondaparinux and/or VKA for documented symptomatic or asymptomatic venous thrombosis ~~and who will enter their last month of intended anticoagulant treatment~~ 2. Hemoglobin, platelets, creatinine and alanine aminotransferase (ALT) and bilirubin evaluated within 10 days prior to ~~randomization~~ […]
New text:	1. Children aged between 6 months to < 6 years who have been treated for at least 2 months or, in case of catheter related thrombosis, for at least 6 weeks with LMWH, fondaparinux and/or VKA for documented symptomatic or asymptomatic venous thrombosis 2. Hemoglobin, platelets, creatinine and alanine aminotransferase (ALT) and bilirubin evaluated within 10 days prior to Visit 2 […]

16.2.2.8 Section 4.3: Exclusion criteria

This section was modified based on Amendment Change 1, 2 and 6.

Old text:	[…] 6. Platelet count < ~~100~~ x 10^9/L […] 9. Concomitant use of strong inhibitors of both CYP3A4 and P-gp, i.e. all human immunodeficiency virus protease inhibitors and the following azole-antimycotics agents: ketoconazole, itraconazole, voriconazole, posaconazole, if used systemically 10. […] 11. Hypersensitivity or any other contraindication listed in the local labeling for the ~~comparator treatment or~~ experimental treatment 12. […] 13. Previous ~~randomization to~~ this study 14. Participation in a study with an investigational drug or medical device within 30 days prior to ~~randomization~~.
New text:	[…] 6. Platelet count < 50 x 10^9/L […] 9. Concomitant use of strong inhibitors of both CYP3A4 and P-gp, i.e. all human immunodeficiency virus protease inhibitors and the following azole-antimycotics agents: ketoconazole, itraconazole, voriconazole, posaconazole, if used systemically (fluconazole is allowed) 10. […] 11. Hypersensitivity or any other contraindication listed in the local labeling for the experimental treatment 12. […] 13. Previous participation in this study 14. Participation in a study with an investigational drug or medical device within 30 days prior to Visit 2.

16.2.2.9 Section 4.4: Concomitant medication

This section was modified based on Amendment Change 1 and 2.

Old text:	Concomitant medications include either continuation of a treatment started before ~~study randomization~~, or addition of a new treatment during the study. Non-steroidal anti-inflammatory drugs (NSAIDs) and antiplatelet agents are strongly discouraged since they increase the risk for bleeding in patients treated with ~~heparins, fondaparinux and/or VKA or rivaroxaban.~~ However, if such medication is indicated, the lowest possible dosage should be selected. Concomitant use of strong inhibitors of both CYP3A4 and P-gp, i.e. all human immunodeficiency virus protease inhibitors and azole-antimycotics agents (i.e. ketoconazole, itraconazole, voriconazole, posaconazole; concomitant treatment with fluconazole is allowed), if used systemically, is not allowed, as well as concomitant use of strong inducers of CYP3A4 (i.e. rifampicin, rifabutin, phenobarbital, phenytoin, carbamazepine). Any previous anticoagulant medication taken within 90 days prior to ~~randomization~~ will be documented. Anticoagulant use after the study treatment period will also be documented.
New text:	Concomitant medications include either continuation of a treatment started before Visit 2, or addition of a new treatment during the study. Non-steroidal anti-inflammatory drugs (NSAIDs) and antiplatelet agents are strongly discouraged since they increase the risk for bleeding in patients treated with anticoagulants. However, if such medication is indicated, the lowest possible dosage should be selected. Concomitant use of strong inhibitors of both CYP3A4 and P-gp, i.e. all human immunodeficiency virus protease inhibitors and azole-antimycotics agents (i.e. ketoconazole, itraconazole, voriconazole, posaconazole; concomitant treatment with fluconazole is allowed), if used systemically, is not allowed, as well as concomitant use of strong inducers of CYP3A4 (i.e. rifampicin, rifabutin, phenobarbital, phenytoin, carbamazepine). Any previous anticoagulant medication taken within 90 days prior to Visit 2 will be documented. Anticoagulant use after the study treatment period will also be documented.

16.2.2.10 Section 5: Treatment regimens

This section was modified based on Amendment Change 2.

Old text:	**5. Treatment ~~groups and~~ regimen~~s~~**
New text:	**5. Treatment regimen**

16.2.2.11 Section 5.1: Treatment

This section was modified based on Amendment Change 2.

Old text:	**5.1: ~~Method of treatment allocation~~** ~~Allocation to treatment will be done centrally by an interactive voice/web response system (IxRS). Allocation will be stratified by baseline presentation of venous thrombosis i.e.~~ ~~a) lower extremity DVT, caval vein thrombosis, upper extremity DVT, subclavian thrombosis, right atrial thrombosis, pulmonary embolism and catheter related thrombosis and~~ ~~b) cerebral vein and sinus thrombosis, jugular vein thrombosis, mesenteric vein thrombosis, portal vein thrombosis and renal vein thrombosis.~~ ~~Study treatment allocation will be done in a 1:1 ratio (rivaroxaban: standard of care), and will be done separately for the 2 to < 6 years age group and the 6 months to < 2 years age group.~~ ~~The investigator will provide the IxRS with study center identification, the child's date of birth (month and year), gender, weight and clinical presentation.~~ ~~Procedures for treatment assignment through the IxRS are specified in the IxRS manual.~~
New text:	**5.1 Treatment** In this study, only rivaroxaban will be used.

16.2.2.12 Section 5.1.1: Rivaroxaban

This section was modified based on Amendment Change 2.

Old text:	**5.1.1 Rivaroxaban ~~group~~**
New text:	**5.1.1 Rivaroxaban**

16.2.2.13 Section 5.1.1.1: Switching from VKA to rivaroxaban

This section was modified based on Amendment Change 2.

Old text:	If a child is on VKA therapy and has a supra-therapeutic INR (> 3.0), ~~randomization into the study~~ should be delayed. In case of an INR between 2.5 to 3.0, ~~randomization can be done and, if allocated to rivaroxaban,~~ the first rivaroxaban dose should be delayed to the next day. If the INR is below 2.5, ~~randomization can be done and if allocated to rivaroxaban,~~ the first rivaroxaban dose can be taken ~~on the day of randomization.~~ VKA therapy ~~cannot~~ be ~~continued after randomization, if allocated to~~ rivaroxaban.
New text:	If a child is on VKA therapy and has a supra-therapeutic INR (> 3.0), rivaroxaban administration should be delayed. In case of an INR between 2.5 to 3.0, the first rivaroxaban dose should be delayed to the next day. If the INR is below 2.5, the first rivaroxaban dose can be taken at Visit 2. VKA therapy must be stopped before rivaroxaban treatment commences.

16.2.2.14 Section 5.1.1.2: Switching from heparin/fondaparinux to rivaroxaban

This section was modified based on Amendment Change 2.

Old text:	If the child received heparin treatment before ~~randomization, randomization~~ 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, or 12 - 24 hours after the last injection of fondaparinux or LMWH with a once-daily regimen. Heparin/fondaparinux treatment cannot be continued after the start of rivaroxaban treatment in these children.
New text:	If the child received heparin treatment before study treatment with rivaroxaban, rivaroxaban administration 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, or 12 - 24 hours after the last injection of fondaparinux or LMWH with a once-daily regimen. Heparin/fondaparinux treatment cannot be continued after the start of rivaroxaban treatment in these children

16.2.2.15 New Section 5.1.1.3: Switching from rivaroxaban to heparin/fondaparinux

This section was modified based on Amendment Change 5.

New text:	**5.1.1.3: Switching from rivaroxaban to heparin/fondaparinux** Children who switch from rivaroxaban to heparin /fondaparinux can switch at the time of the next scheduled dose.

16.2.2.16 New Section 5.1.1.4: Switching from rivaroxaban to VKA

This section was modified based on Amendment Change 5.

New text:	**5.1.1.4: Switching from rivaroxaban to VKA** Children who switch from rivaroxaban to VKA need to continue rivaroxaban for 48 hours after the first dose of VKA. After 2 days of co-administration, an INR should be obtained prior to the next scheduled dose of rivaroxaban. Co-administration of rivaroxaban and VKA is advised to continue until the INR is ≥ 2.0.

16.2.2.17 Section 5.1.2: Comparator group

This section was modified based on Amendment Change 2.

Old text:	~~Children randomized to the comparator group will continue with the anticoagulant treatment that was planned prior to study randomization. Thus, children who received heparins/ fondaparinux before randomization, continue with it after randomization. Children, who received VKA before randomization, continue with VKA after randomization. VKA dosages will be adjusted to maintain the INR within the therapeutic range (target 2.5, range 2.0 - 3.0). VKA therapy will be administered according to local guidelines. If a VKA dose was missed, it can only be taken the same day. Double dosing on a single day is not allowed.~~
New text:	This single-arm study does not include comparator treatment.

16.2.2.18 Section 5.2: Subject identification

This section was modified based on Amendment Change 2.

Old text:	SID numbers will have to be used in sequence and no number should be skipped or substituted. ~~At Visit 2, Day 1, children will be assigned a unique randomization number by IxRS that will allow subsequent identification of treatment allocation.~~
New text:	SID numbers will have to be used in sequence and no number should be skipped or substituted.

16.2.2.19 Section 5.4.1: Rivaroxaban

This section was modified based on Amendment Change 1.

Old text:	Rivaroxaban will be provided by Bayer as a 0.1% suspension. Rivaroxaban will be dosed according to body weight groups (see Table 5-1). Since children with a glomerular filtration rate below 30 mL/min/1.73 m^2 are excluded from the study, a dose adaptation is not indicated.
New text:	Rivaroxaban will be provided by Bayer as a 0.1% (1mg/ml) suspension. Rivaroxaban will be dosed according to body weight groups (see Table 5-1). Since children with a glomerular filtration rate below 30 mL/min/1.73 m^2 are excluded from the study, a dose adaptation is not indicated.

16.2.2.20 Section 5.4.2: Comparator

This section was modified based on Amendment Change 2.

Old text:	~~Comparator will be used according to approved formulations~~
New text:	This single-arm study does not include comparator treatment.

16.2.2.21 Section 5.5: Packaging, labeling, and storage

This section was modified based on Amendment Change 2.

Old text:	~~Comparator will be supplied from local commercial resources and provided by sites. If required by local regulations, Bayer will purchase the comparator from local sources, and label and distribute to investigative centers.~~ […] ~~Comparator provided by sites will be documented in the hospital/pharmacy records.~~

16.2.2.22 Section 5.6: Treatment assignment

This section was modified based on Amendment Change 2.

Old text: ~~After randomization, the randomization number of the child will be recorded on the corresponding electronic case report form (eCRF). Subject identification number will have to be recorded on the label of the study medication.~~

~~In case LMWH, fondaparinux and/or VKA is provided by sites, the compound's name, dose, quantity and batch number or a copy of the prescription must be included in the child's files.~~

New text: Not applicable.

16.2.2.23 Section 5.7: Dosage and administration

This section was modified based on Amendment Change 2.

Old text: ~~Comparator treatment consists of locally used anticoagulants for VTE treatment, specified in Table 5-2.~~

~~**Table 5-2: Overview of comparator treatment**~~

~~Generic name~~	~~Dosage~~
~~Warfarin~~	~~INR 2.0-3.0~~
~~Acenocoumarol~~	~~INR 2.0-3.0~~
~~Phenprocoumon~~	~~INR 2.0-3.0~~
~~Enoxaparin~~	~~1 mg/kg b.i.d.~~
~~Fondaparinux~~	~~0.1 mg/kg o.d.~~
~~Tinzaparin~~	~~2-12 mo 250 u/kg o.d.~~
	~~1- 5 yrs 240 u/kg o.d.~~
	~~5-10 yrs 200 u/kg o.d.~~
~~Dalteparin~~	~~129 ± 43 u/kg/dose o.d.~~

~~b.i.d. : twice daily; o.d.: once daily; u:units~~

~~Source: (10)~~

~~The comparator list above is not all-inclusive.~~

New text: Rivaroxaban will be dosed according to body weight as oral 0.1% suspension.

16.2.2.24 Section 5.8: Treatment compliance

This section was modified based on Amendment Change 2.

Old text:

~~5.8.2 Vitamin K antagonists~~

~~Compliance with VKA treatment will only be ensured by the use of INR, with a minimum of 1 INR per 2 weeks. The date of first and last intake with specifications of the brand and all INR values and the actual measurement dates will be documented. This information will be obtained directly from the child's file or transmitted by the INR monitoring physician or laboratory.~~

~~5.8.3 Low molecular weight heparin/fondaparinux~~

~~Instruction will be given to return all unused syringes at Visit 3, Visit 4 and, if applicable, at the premature discontinuation visit. Compliance will be evaluated by counting remaining syringes. All non-dispensed syringes should be kept securely in the original containers in a designated locked container until retrieved or dispensed.~~

16.2.2.25 Section 6.1: Study visits

This section was modified based on Amendment 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 venous thrombosis. This visit will take place 60 to 10 days before ~~the last month of intended anticoagulation treatment~~.

Visit 2 is the ~~randomization visit~~ and will be a hospital visit. Eligible children will ~~be randomized to~~ 30 days ~~of anticoagulation with study medication (day 1).~~

Visit 3 and Visit 4 are the treatment and end of treatment visits, respectively. These visits will be hospital visits which will take place at Day 15 ± 5 days, and Day 30 ± 3 days, respectively. At visit 2, 3 and 4, PK/PD blood ~~sampling~~ will be ~~done in the rivaroxaban group only~~. At Visit 4, the study medication will be stopped. After cessation of study treatment, it is at the investigator's discretion to continue with anticoagulation, as needed. Repeat imaging will be obtained if applicable.

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 venous thrombosis. This visit will take place 60 to 10 days before Visit 2.

Visit 2 is the first study drug administration day and will be a hospital visit. Eligible children will receive rivaroxaban for 30 days.

Visit 3 and Visit 4 are the treatment and end of treatment visits, respectively. These visits will be hospital visits which will take place at Day 15 ± 5 days, and Day 30 ± 3 days, respectively. At visit 2, 3 and 4, PK/PD blood samples will be drawn. At Visit 4, the study medication will be stopped. After cessation of study treatment, it is at the investigator's discretion to continue with anticoagulation, as needed. Repeat imaging will be obtained if applicable.

16.2.2.26 Section 6.2: Visit 1 - Screening visit at 60 to 10 days before Visit 2

This section was modified based on Amendment Change 2.

Old text:	Adverse events will not be collected between visit 1 and visit 2. Since hemoglobin, platelet counts, creatinine and liver function 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, and bilirubin within 10 days prior to ~~randomization~~ is an inclusion criterion for this study (see section 4.2).
New text:	Adverse events will not be collected between visit 1 and visit 2. Since hemoglobin, platelet counts, creatinine and liver function 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, and bilirubin within 10 days prior to Visit 2 is an inclusion criterion for this study (see section 4.2)

16.2.2.27 Section 6.3. Visit 2 - Treatment visit at Day 1

This section was modified based on Amendment Change 1 and 2.

Old text: **6.3. Visit 2 - ~~Randomization~~ visit at Day 1**

If the CIAC confirmed the qualifying venous thrombotic event, then re-confirm eligibility. If results for hemoglobin, platelets, creatinine, ALT, bilirubin were not available within 10 days prior to ~~randomization~~, obtain blood sample. If the child still meets the inclusion criteria and does not meet any of the exclusion criteria, the child can ~~be randomized~~.

- If a child is on VKA therapy and has a supra-therapeutic INR (> 3.0), ~~randomization into the study should be delayed. In case~~ of ~~an INR below 3.0, randomization can be done. If randomized to VKA, treatment with VKA should continue. If randomized to~~ rivaroxaban~~,~~ ~~VKA~~ should be stopped and the timing of the administration of the first rivaroxaban dose will depend on the INR (see also section 5.1.1.1).

If the INR is below 2.5, the first rivaroxaban dose should be taken ~~on the day of randomization~~.

[…]

- Administer ~~the assigned study drug~~
- ~~In children allocated to rivaroxaban,~~
- ~~administer the first rivaroxaban dose and document~~ the volume and type of fluid used to predilute the rivaroxaban oral suspension, as well as the volume and type of fluid taken after the study drug administration.
- ~~document~~ the exact time of drug intake and the time and type of meal (e.g. breast feeding, baby bottle, porridge, breakfast, lunch, snack, dinner) the child took 2 hours before, during and after study drug administration.
- ~~at~~ 0.5-1.5 hr after drug intake, collect only a PK blood sample
- ~~at~~ 2.5-4 hr after drug intake, collect a PK blood sample followed by the PD blood sample.

[…]

- ~~In children allocated to rivaroxaban, instruct~~ to 1) document in the study booklet the exact time of the last dose taken on the day prior to Visit 3, 2) the exact time and type of meal the child took 2 hours before, during and after study drug administration, 3) the volume and type of fluid used to predilute the rivaroxaban oral suspension and 4) the volume and type of fluid taken after the study drug administration.

[…]

New text: **6.3. Visit 2 - Treatment visit at Day 1**

If the CIAC confirmed the qualifying venous thrombotic event, then re-confirm eligibility. If results for hemoglobin, platelets, creatinine, ALT, bilirubin were not available within 10 days prior to Visit 2, obtain blood sample. If the child still meets the inclusion criteria and does not meet any of the exclusion criteria, the child can receive rivaroxaban.

- If a child is on VKA therapy and has a supra-therapeutic INR (> 3.0), the first administration of rivaroxaban should be delayedVKA therapy should be stopped and the timing of the administration of the first rivaroxaban dose will depend on the INR (see also section 5.1.1.1).

If the INR is below 2.5, the first rivaroxaban dose should be taken at Visit 2.

[…]

- Administer first dose of rivaroxaban oral suspension
- Document the volume and type of fluid used to predilute the rivaroxaban oral suspension, as well as the volume and type of fluid taken after the study drug administration.
- Document the exact time of drug intake and the time and type of meal (e.g. breast feeding, baby bottle, porridge, breakfast, lunch, snack, dinner) the child took 2 hours before, during and after study drug administration.
- At 0.5-1.5 hr after drug intake, collect only a PK blood sample
- At 2.5-4 hr after drug intake, collect a PK blood sample followed by the PD blood sample.

[…]

- Instruct to 1) document in the study booklet the exact time of the last dose taken on the day prior to Visit 3, 2) the exact time and type of meal the child took 2 hours before, during and after study drug administration, 3) the volume and type of fluid used to predilute the rivaroxaban oral suspension and 4) the volume and type of fluid taken after the study drug administration.

[…]

16.2.2.28 Section 6.4: Visit 3 - Treatment visit at Day 15 (+/- 5 days)

This section was modified based on Amendment Change 1 and 2.

Old text: […]

- ~~In children randomized to rivaroxaban~~
- ~~administer~~ the next rivaroxaban dose and document the volume and type of fluid used to predilute the rivaroxaban oral suspension, as well as the volume and type of fluid taken after the study drug administration.
- ~~document~~ the exact time of drug intake and type of meal the child took 2 hours before, during and after drug administration
- ~~complete~~ the Taste-and-Texture Questionnaire for children older than 4 years
- ~~at~~ 2 – 8 hr after drug intake, collect a post-dose PK blood sample followed by the PD blood sample
- ~~document~~ the exact time of blood sampling for PK/PD.

[…]

- ~~In children allocated to rivaroxaban, inform~~ that on the day before visit 4

[…]

New text: […]

- Administer the next rivaroxaban dose and document the volume and type of fluid used to predilute the rivaroxaban oral suspension, as well as the volume and type of fluid taken after the study drug administration.
- Document the exact time of drug intake and type of meal the child took 2 hours before, during and after drug administration
- Complete the Taste-and-Texture Questionnaire for children older than 4 years
- At 2 – 8 hr after drug intake, collect a post-dose PK blood sample followed by the PD blood sample
- Document the exact time of blood sampling for PK/PD.

[…]

- Inform that on the day before visit 4

[…]

16.2.2.29 Section 6.5: Visit 4 - End of study treatment visit at Day 30 (+/- 3 days)

This section was modified based on Amendment Change 2.

Old text: […]

- ~~In children randomized to rivaroxaban~~

[…]

16.2.2.30 Section 6.9: Recommendations before and after invasive procedures and surgical intervention

This section was modified based on Amendment Change 2.

Old text:	~~For the comparator please follow the respective product label.~~

16.2.2.31 Section 6.10: Management of bleeding in children

This section was modified based on Amendment Change 2.

Old text:	• ~~Delay the next LMWH, fondaparinux, VKA or rivaroxaban administration or discontinue treatment, if indicated~~ • ~~If the child is treated with VKA, consider vitamin K administration~~ • ~~If the child is treated with LMWH, consider protamine sulfate administration~~ • […] • ~~If the child is treated with rivaroxaban, obtain~~ the PK/PD sample~~.~~
New text:	• […] • Obtain the PK/PD sample.

16.2.2.32 Section 6.12: PK/PD assessments

This section was modified based on Amendment Change 2.

Old text:	Blood samples will be taken for PK and PD measurements~~ from children randomized to rivaroxaban~~. 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:
New text:	Blood samples will be taken for PK and 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:

16.2.2.33 Section 6.13: Study booklet

This section was modified based on Amendment Change 2.

Old text:	Parents/children will receive a booklet with the following information ~~for both treatment groups~~: […] ~~For the rivaroxaban treatment group~~ […] ~~For the comparator group~~ • ~~How to use comparator~~ • ~~The planned dates of blood collections for the next INR control, if VKA is used~~ • ~~Instruction to insert the INR values (if available).~~
New text:	Parents/children will receive a booklet with the following information: […]

16.2.2.34 Section 7.2: Analysis sets

This section was modified based on Amendment Change 2.

Old text:	Full analysis set (FAS): This analysis set will include all ~~randomized~~ children. Safety analysis set (SAS): This analysis set will include all ~~randomized~~ children who received at least one dose of study medication. Per protocol set (PPS): This population includes all ~~randomized~~ children who completed the 30-day treatment period. The PPS may also exclude major protocol deviations. Further details will be specified in the Statistical Analysis Plan.
New text:	Full analysis set (FAS): This analysis set will include all enrolled children. Safety analysis set (SAS): This analysis set will include all enrolled children who received at least one dose of study medication. Per protocol set (PPS): This population includes all enrolled children who completed the 30-day treatment period. The PPS may also exclude major protocol deviations. Further details will be specified in the Statistical Analysis Plan.

16.2.2.35 Section 7.3: Demographic and other baseline characteristics

This section was modified based on Amendment Change 2.

Old text:	Summary statistics (arithmetic mean, standard deviation, median, minimum and maximum for quantitative variables) will be presented by ~~treatment~~. Frequency tables for qualitative data will be provided. Medical history findings will be summarized using Medical Dictionary for Regulatory Activities (MedDRA) terms.
New text:	Summary statistics (arithmetic mean, standard deviation, median, minimum and maximum for quantitative variables) will be presented by age group. Frequency tables for qualitative data will be provided. Medical history findings will be summarized using Medical Dictionary for Regulatory Activities (MedDRA) terms.

16.2.2.36 Section 7.4: Safety analysis

This section was modified based on Amendment Change 2.

Old text:	Individual listings of major and clinically relevant non-major bleeding will be provided. The incidence of bleeding will be summarized ~~by treatment.~~ 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 ~~by treatment for~~ the original data as well as for the difference to baseline. Frequency tables will be provided for qualitative data.
New text:	Individual listings of major and clinically relevant non-major bleeding will be provided. The incidence of bleeding will be summarized descriptively. 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 descriptively for the original data as well as for the difference to baseline. Frequency tables will be provided for qualitative data.

16.2.2.37 Section 7.5: Efficacy analysis

This section was modified based on Amendment Change 2.

Old text:	All efficacy analyses will be performed on the FAS population. The occurrence of recurrent venous thromboembolism and asymptomatic deterioration in thrombotic burden will be summarized by ~~treatment~~.
New text:	All efficacy analyses will be performed on the FAS population. The occurrence of recurrent venous thromboembolism and asymptomatic deterioration in thrombotic burden will be summarized by age group.

16.2.2.38 Section 7.8: Determination of sample size

This section was modified based on Amendment Change 3.

Old text:	A total of ~~40~~ children who took at least one dose of study medication are planned to be enrolled in the study. The sample size does not originate from a formal sample size calculation, but is based on a feasibility assessment because of the very low incidence of venous thrombosis in children, and on the pharmacokinetic moderate inter-individual variability of rivaroxaban. Based on past experience in obtaining parental consent in this indication, it is estimated that fewer than 10% of eligible children can be enrolled in this study.
New text:	A total of 20 children who took at least one dose of study medication are planned to be enrolled in the study. The sample size does not originate from a formal sample size calculation, but is based on a feasibility assessment because of the very low incidence of venous thrombosis in children, and on the pharmacokinetic moderate inter-individual variability of rivaroxaban. Based on past experience in obtaining parental consent in this indication, it is estimated that fewer than 10% of eligible children can be enrolled in this study.

16.2.2.39 Section 7.9: Adverse events (AE)

This section was modified based on Amendment Change 2.

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

16.2.2.40 Section 7.9.9: AEs of special safety interest

This section was modified based on Amendment Change 6.

Old text:	[…] • A platelet count below ~~100~~ x 10^9/L.
New text:	[…] • A platelet count below 50 x 10^9/L.

17. Appendices

17.1 Methods and measurements

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.

17.2 Estimated glomerular filtration rate

If serum creatinine (SCr) is measured with routine methods that have not been recalibrated to be traceable to isotope dilution mass spectrometry (IDMS) (e.g. the traditional Jaffé reaction), the eGFR should be obtained from the original Schwartz formula: [12]

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

Where k is proportionality constant:

k = 0.55 in children up to 13 years of age

k = 0.70 in boys >13 years and <18 years of age (not in girls; because of the presumed increase in male muscle mass, the constant remains 0.55 for girls)

If SCr is measured by an enzymatic creatinine method that has been calibrated to be traceable to IDMS, the updated Schwartz formula should be used to obtain the eGFR: [13]

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

The National Kidney Disease Education Program website (http://www.nkdep.nih.gov/professionals/gfr_calculators/index.htm) offers electronic calculators of eGFR in the pediatric population based on the updated Schwartz formula.

Note: To express SCr in micromoles per liter, the value should be multiplied by 88.4 (1 mg/dL = 88.4 μmol/L).