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<b>Official Title:</b>	Multicenter, open-label, active-controlled, randomized study to evaluate the efficacy and safety of body weight-adjusted rivaroxaban regimen compared to standard of care in children with acute venous thromboembolism
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## Cover page of the integrated protocol

**Multicenter, open-label, active-controlled, randomized study to evaluate the efficacy and safety of an age-and body weight-adjusted rivaroxaban regimen compared to standard of care in children with acute venous thromboembolism**

EINSTEIN Junior Phase III: oral rivaroxaban in children with venous thrombosis

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

- **Original protocol**, Version 1.0, dated 12 Mar 2014
- **Amendment 1** (local amendment Japan), dated 21 Oct 2014
- **Amendment 2** (local amendment Canada), dated 28 Oct 2014
- **Amendment 3** (local amendment Germany), dated 02 Dec 2014
- **Amendment 4** (described in Section [16.1](#))  
forming integrated protocol Version 2.0, dated 21 Jul 2015
- **Amendment 5** (local amendment Canada), dated 21 Jul 2015
- **Amendment 6** (local amendment Japan), dated 28 Jul 2015
- **Amendment 7** (local amendment Canada), dated 20 Oct 2015
- **Amendment 8** (described in Section [16.2](#))  
forming integrated protocol Version 3.0, dated 20 Sep 2016
- **Amendment 9** (local amendment Canada), dated 20 Dec 2016
- **Amendment 10** (described in Section [16.3](#))  
forming integrated protocol Version 4.0, dated 11 Jan 2017
- **Amendment 11** (local amendment Japan), dated 07 Mar 2017
- **Amendment 12** (described in Section [16.4](#))  
forming integrated protocol version 5.0, dated 27 SEP 2017

This document integrates the original protocol and all global amendments.

**Multicenter, open-label, active-controlled, randomized study to evaluate the efficacy and safety of an age-and body weight-adjusted rivaroxaban regimen compared to standard of care in children with acute venous thromboembolism**

EINSTEIN Junior Phase III: oral rivaroxaban in children with venous thrombosis

Test drug: BAY 59-7939/rivaroxaban  
Clinical study phase: III 27 SEP 2017  
EudraCT no.: 2014-000565-47 Version no.: 5.0  
Study no.: BAY 59-7939/14372  
Sponsor: Non-US territory: Bayer 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.

**Confidential**

The information provided in this document is strictly confidential and is intended solely for the guidance of this study. Reproduction or disclosure of this document -whether in part or in full- to parties not associated with this study or its use for any other purpose, without the prior written consent of Bayer AG is not permitted. <sup>1</sup>

Throughout this document, symbols indicating proprietary names (®, TM) are not displayed. Hence, the appearance of product names without these symbols does not imply that these names are not protected.

<sup>1</sup> The sponsor information was changed via Amendment 8 (see Section 16.2.2.1)

<sup>2</sup> The non-emergency medical and protocol issues contact was changed via Amendment 8 (see Section 16.2.2.1)

<sup>3</sup> The non-emergency medical and protocol issues contact was changed via Amendment 12 (see Section 16.4.2.1)



**Medically responsible person of Bayer agrees to the content of the final clinical study protocol as presented.**

PPD 

Global Clinical Leader

PPD 

Date: 02 OCTOBER, 2017 Signature:



**Study center's principal investigator agrees to the content of the final clinical study protocol as presented.**

Name:

Affiliation:

Date:

Signature:

Rivaroxaban (BAY-59-7939, JNJ-39039039) is being co-developed under a collaboration and license agreement between Bayer AG and Ortho McNeil Pharmaceuticals, Inc. (OMP) dated 01 Oct 2005. <sup>PPD</sup>

The term "sponsor" or "designee" is used to represent these various legal entities that have been identified to perform various clinical study services; the actual sponsor or designee is identified on the Contact Information page that accompanies this protocol. <sup>4</sup>

<sup>4</sup> The sponsor name was changed via Amendment 8 (see Section 16.2.2.2)

## Synopsis

<b>Title</b>	Multicenter, open-label, active-controlled, randomized study to evaluate the efficacy and safety of an age-and body weight-adjusted rivaroxaban regimen compared to standard of care in children with acute venous thromboembolism.
<b>Short title</b>	EINSTEIN Junior Phase III: oral rivaroxaban in children with venous thrombosis
<b>Clinical study phase</b>	III
<b>Study objectives</b>	<p>The primary efficacy objective is:</p> <ul style="list-style-type: none"> <li>To assess the incidence of symptomatic recurrent venous thromboembolism.</li> </ul> <p>The secondary efficacy objective is:</p> <ul style="list-style-type: none"> <li>To assess the incidence of symptomatic recurrent venous thromboembolism and asymptomatic deterioration on repeat imaging.</li> </ul> <p>The principal safety objective is:</p> <ul style="list-style-type: none"> <li>To assess the incidence of overt major and clinically relevant non-major bleeding.</li> </ul> <p>An additional objective is:</p> <ul style="list-style-type: none"> <li>To characterize the pharmacokinetic / pharmacodynamic profile of rivaroxaban.</li> </ul>
<b>Experimental study drug</b>	Rivaroxaban
<b>Name of active ingredient</b>	Rivaroxaban
<b>Dose</b>	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 once daily.
<b>Route of administration</b>	Oral tablets or oral suspension
<b>Comparator study drug</b>	Subcutaneous low molecular weight heparin (LMWH), subcutaneous fondaparinux, intravenous unfractionated heparin (UFH) and/or oral vitamin K antagonist (VKA) <sup>5</sup>
<b>Dose</b>	As per standard of care
<b>Indication</b>	Children aged birth to < 18 years 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, cerebral vein and sinus thrombosis, mesenteric vein thrombosis, portal vein thrombosis, renal vein thrombosis, or catheter-related thrombosis. <sup>6</sup>

<sup>5</sup> The missing comparator “unfractionated heparin” was added in the synopsis for consistency throughout the protocol via Amendment 4 (see Section 16.1.2.1).

<sup>6</sup> The indication was modified via Amendment 12 to include children aged from birth to < 18 years (see Section 16.4.2.2)

<b>Diagnosis and main criteria for inclusion</b>	Children aged birth to < 18 years with acute venous thromboembolism confirmed by diagnostic imaging. <sup>7</sup>
<b>Study design</b>	Open-label, active-controlled, multicenter, randomized study
<b>Methodology</b> <sup>8</sup>	<p>Children aged birth to &lt; 18 years with confirmed venous thromboembolism who receive initial treatment with therapeutic dosages of unfractionated heparin (UFH), low molecular weight heparin (LMWH), or fondaparinux are potentially eligible for the study.</p> <p>Initial treatment with UFH, LMWH or fondaparinux will be administered for at least 5 days.</p> <ul style="list-style-type: none"> <li>• Randomization can be done during the first 9 days of initial treatment and will be in a 2 (rivaroxaban): 1 (standard of care [SOC]) fashion. Children randomized to rivaroxaban will start rivaroxaban the day following the last administration of initial therapy with UFH, LMWH, or fondaparinux but with a minimal duration of initial therapy of 5 days and a maximum duration of 9 days.</li> <li>• The first administration of rivaroxaban will be started: 4 hours after discontinuation of UFH</li> <li>• 12 hours after discontinuation of LMWH with a b.i.d. regimen, and</li> <li>• 24 hours after discontinuation of fondaparinux or LMWH with an o.d. regimen</li> </ul> <p>Children randomized to SOC can continue UFH, LMWH, or fondaparinux or can switch to vitamin K antagonist (VKA) therapy. If VKA therapy is planned it can be initiated any time after randomization. Initial therapy with UFH, LMWH, or fondaparinux can be stopped after a minimum of 5 days and only if the international normalized ratio (INR) is above 2 on two separate occasions, 24 hours apart.</p> <p>In children randomized to rivaroxaban in whom VKA therapy was already initiated before randomization, VKA therapy should be stopped and the switch to rivaroxaban should be made as described in Section 5.1.1.3.</p> <p>The main study treatment period is for a total of 3 months at which time the diagnostic imaging test, which was obtained at baseline, will be repeated, if clinically feasible. However, in children younger than 2 years with catheter-related thrombosis, the main study treatment period is for a total of 1 month at which time the repeat imaging will be performed. In all children, except those &lt; 2 years with catheter-related thrombosis, the decision is made to stop study treatment at 3 months or to continue for an additional 3 months. In children who completed 6 months of treatment, the decision is made to stop study treatment or to continue for an additional 3 months. Then, in children who completed 9 months of treatment, the decision is made to stop study treatment or to continue for an additional 3 months. In children &lt; 2 years with catheter-related thrombosis, the decision is made to stop study treatment at 1</p>

<sup>7</sup> Diagnosis and main criteria for diagnosis was modified via Amendment 12 to include children from birth (see Section 16.4.2.2)

<sup>8</sup> Methodology section in Synopsis was modified via Amendment 12 to include children from birth and to highlight different treatment duration in children <2 with catheter related thrombosis ( see Section 16.4.2.2)

	<p>month or to continue for an additional month. Then, in children who completed 2 months of treatment, the decision is made to stop study treatment or to continue for an additional month.</p> <p>Regardless of the duration of study treatment (&lt;3, 3, 6, 9 or 12 months), an additional 1-month post-treatment observational period will be completed for all children. All suspected clinical study outcomes and baseline and repeat thrombosis imaging tests will be assessed by a central independent adjudication committee (CIAC) blinded to treatment allocation. An independent Data Monitoring Committee (DMC) will monitor the children's safety and give recommendations to the steering committee.<sup>9</sup></p>
<p><b>Number of children</b></p>	<p>At least 170 children are needed for this study, of whom 80 in the age group 12 to &lt; 18 years, 30 in the age group 6 to &lt; 12 years, 20 in the age group 2 to &lt; 6 years, and 20 in the age group birth to &lt; 2 years, with at least 12 aged birth to &lt; 6 months.<sup>10</sup></p>
<p><b>Inclusion/exclusion criteria</b></p>	<p>Inclusion<sup>11</sup></p> <ol style="list-style-type: none"> <li>1. Children aged birth to &lt; 18 years with confirmed venous thromboembolism who receive initial treatment with therapeutic dosages of UFH, LMWH or fondaparinux and require anticoagulant therapy for at least 90 days. However, children aged birth to &lt; 2 years with catheter-related thrombosis require anticoagulant therapy for at least 30 days.</li> <li>2. Informed consent provided and, if applicable, child assent provided</li> <li>3. For children younger than 6 months:             <ul style="list-style-type: none"> <li>- Gestational age at birth of at least 37 weeks.</li> <li>- Oral feeding/nasogastric/gastric feeding for at least 10 days.</li> <li>- Body weight <math>\geq</math>2600 g.</li> </ul> </li> </ol> <p>Exclusion<sup>12</sup></p> <ol style="list-style-type: none"> <li>1. Active bleeding or bleeding risk contraindicating anticoagulant therapy</li> <li>2. An estimated glomerular filtration rate (eGFR) &lt; 30 mL/min/1.73 m<sup>2</sup> (in children younger than 1 year, serum creatinine results above 97.5<sup>th</sup> percentile excludes participation, see Table 17-1)</li> <li>3. Hepatic disease which is associated with either: coagulopathy leading to a clinically relevant bleeding risk, or alanine aminotransferase (ALT) &gt; 5x upper level of normal (ULN) or total bilirubin (TB) &gt; 2x ULN with direct bilirubin &gt; 20% of the total</li> <li>4. Platelet count &lt; 50 x 10<sup>9</sup>/L</li> <li>5. Sustained uncontrolled hypertension defined as systolic and/or</li> </ol>

9 The methodology section in the synopsis was modified via Amendment 8 (see Section 16.2.2.3)

10 The number of children was modified via Amendment 12 (see Section 16.4.2.2)

11 Inclusion criterion 1 was modified and criterion 3 was added via Amendment 12 ( see Section 16.4.2.2)

12 Exclusion criteria 1, 5, 7, and 8 were modified via Amendment 8 (see Section 16.2.2.3)



	<p>diastolic blood pressure &gt; 95<sup>th</sup> age percentile (See <a href="#">Appendix 3</a>)<sup>13</sup></p> <ol style="list-style-type: none"> <li>6. Life expectancy &lt; 3 months</li> <li>7. Concomitant use of strong inhibitors of both cytochrome P450 isoenzyme 3A4 (CYP3A4) and P-glycoprotein (P-gp), including but not limited to all human immunodeficiency virus protease inhibitors and the following azole-antimycotics agents: ketoconazole, itraconazole, voriconazole, posaconazole, if used systemically (fluconazole is allowed)<sup>13</sup></li> <li>8. Concomitant use of strong inducers of CYP3A4, including but not limited to rifampicin, rifabutin, phenobarbital, phenytoin and carbamazepine</li> <li>9. Childbearing potential without proper contraceptive measures, pregnancy or breast feeding</li> <li>10. Hypersensitivity or any other contraindication listed in the local labeling for the comparator treatment or experimental treatment</li> <li>11. Inability to cooperate with the study procedures</li> <li>12. Previous assignment to treatment during this study<sup>13</sup></li> <li>13. Participation in a study with an investigational drug or medical device within 30 days prior to randomization</li> </ol>
<b>Primary efficacy outcome</b>	The composite of all symptomatic recurrent venous thromboembolism.
<b>Secondary efficacy outcome</b>	The composite of all symptomatic recurrent venous thromboembolism and asymptomatic deterioration on repeat imaging.
<b>Principal safety outcome</b>	The composite of overt major and clinically relevant non-major bleeding.
<b>Other outcomes</b>	Results of pharmacokinetics (PK)/ pharmacodynamics (PD) analyses
<b>Primary efficacy outcome analysis</b>	Incidence proportions and cumulative incidences will be calculated for the primary efficacy outcome at the end of the main study treatment period. <sup>14</sup>
<b>Secondary efficacy outcome analysis</b>	Incidence proportions and cumulative incidences will be calculated for the secondary efficacy outcome at the end of the main study treatment period. <sup>15</sup>

<sup>13</sup> Exclusion criterion 5, 7 and 12 were modified for consistency throughout the protocol and minor clarification via Amendment 4 (see Section [16.1.2.1](#)).

<sup>14</sup> Primary efficacy outcome analysis was modified via Amendment 12 (see Section [16.4.2.2](#))

<sup>15</sup> Secondary efficacy outcome analysis was modified via Amendment 12 (see Section [16.4.2.2](#))

<b>Other efficacy outcome analysis</b>	Incidence proportions will be calculated for the primary efficacy outcome in the extended treatment period at 3 as well as 6, 9 and 12 months (see study flow charts). <sup>16</sup>
<b>Principal safety outcome analysis</b>	Incidence proportions and cumulative incidences will be calculated for the principal safety outcome at the end of the main study treatment period. <sup>17</sup>
<b>Other safety outcome analysis</b>	Incidence proportions will be calculated for the principal safety outcome in the extended treatment period at 3 as well as 6, 9 and 12 months (see study flow charts). <sup>18</sup>

<sup>16</sup> Other efficacy outcome analysis was modified via Amendment 12 (see Section 16.4.2.2)

<sup>17</sup> Principal safety outcome analysis was modified via Amendment 12 (see Section 16.4.2.2)

<sup>18</sup> Other safety outcome analysis was modified via Amendment 12 (see Section 16.4.2.2)

**Table 0–1 Flow chart for all children except children aged < 2 years with catheter related thrombosis (see Table 2)** <sup>19 20</sup>

Visit	Main Treatment period						Extended treatment period with blocks of 3 months			30-day post study treatment
	1	1a	2	3	4	5	6	7	8	
Days	Before random.	After random.	2+1 days after start t.i.d.rivaroxaban <sup>p</sup>	Day 30 ± 7 days	Day 60 ± 7 days	Day 90 ± 7 days	Day 180 ± 7 days	Day 270 ± 7 days	Day 360 ± 7 days	30 ± 7 days After last visit
Contact	Visit	Visit	Visit	Visit	Visit	Visit	Visit	Visit	Visit	Visit or phone
Obtain informed consent/child assent	•									
Check in-/exclusion criteria	•									
Obtain demographic data	•									
Check medical history	•									
Record concomitant medication/anticoagulants	•									
Obtain height/length/body weight/blood pressure	•									
Check Hb, platelets, creatinine, ALT, total and direct bilirubin	• <sup>a</sup>									
Perform urine pregnancy test, if applicable	•									
Randomize patient using IxRS <sup>b</sup>		•								
Dispense study medication		•		•	•	• <sup>c</sup>	• <sup>c</sup>	• <sup>c</sup>		
Dispense additional supplies (devices for oral suspension)		•		•	•	• <sup>c</sup>	• <sup>c</sup>	• <sup>c</sup>		
Instruct how to take study medication <sup>n</sup>		•								
Send baseline adjudication package		•								
Check for adverse events		•	•	•	•	•	•	•	•	•
Check for device-related adverse events <sup>o</sup>		•	•	•	•	•	•	•	•	
Obtain body weight				• <sup>d</sup>	• <sup>d</sup>	• <sup>d</sup>	• <sup>d</sup>	• <sup>d</sup>		
Assess duration and intensity of menstruation, if applicable <sup>21</sup>				•	•	•	•	•	•	
Check for study outcomes <sup>e</sup>			•	•	•	•	•	•	•	•
Check study drug accountability and compliance				•	•	•	•	•	•	
Check changes in concomitant medication			•	•	•	•	•	•	•	•
Obtain Hb, platelets, ALT, total and direct bilirubin						•				
Repeat imaging and send adjudication package <sup>f</sup>						•				
Perform post-thrombotic syndrome assessment <sup>m</sup>						•	•	•	•	
Complete eCRF	•	•	•	•	•	•	•	•	•	•
<b>Comparator group only</b>										
If INR-adjusted VKA <sup>g</sup>										1 INR per 2 weeks

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19 The study flow chart was modified via Amendment 8 (see Section 16.2.2.3) and Amendment 10 (see Section 16.3.2.1)

20 The study flow chart was modified via Amendment 12 (see Section 16.4.2.2)

21 Assessment of menstrual bleeding was added from visit 1 to visit 7 via Amendment 4 (see Section 16.1.2.1).

**Table 0-1 Flow chart (continued)**

Visit	Main Treatment period						Extended treatment period with blocks of 3 months			30-day post study treatment
	1		1a	2	3	4	5	6	7	8
Days	Before random	After random	2+1 days after start t.i.d. rivaroxaban <sup>p</sup>	Day 30 ± 7 days	Day 60 ± 7 days	Day 90 ± 7 days	Day 180 ± 7 days	Day 270 ± 7 days	Day 360 ± 7 days	30 ± 7 days After last visit
Contact	Visit	Visit	Visit	Visit	Visit	Visit	Visit	Visit	Visit	Visit or phone
<b>Pharmacokinetics (PK) and pharmacodynamics (PD) for rivaroxaban using o.d. regimen<sup>h</sup></b>										
If suspension, complete pre-dosing Taste-and-Texture questionnaire in children 4 to < 18 years				•						
Administer rivaroxaban at study site				•	•					
Take up to 240 mL of liquid immediately after dosing				•	•					
If suspension, complete post-dosing Taste-and-Texture questionnaire in children 4 to < 18 years				•						
Obtain PK blood sample <sup>i</sup>				•	•	•	•			
Obtain PD blood sample <sup>j,k</sup>				•	•	•	•			
Time point for PK/PD blood sample (hours)				0.5-1.5hr post dose	2.5-4hr post dose	2-8hr post dose	20-24 hr after dose on previous day			
<b>Pharmacokinetics (PK) and pharmacodynamics (PD) for rivaroxaban using b.i.d. regimen<sup>h</sup></b>										
If suspension, complete pre-dosing Taste-and-Texture questionnaire in children 4 to < 18 years				•						
Administer rivaroxaban at study site				•	•					
Take up to 240 mL of liquid immediately after dosing				•	•					
If suspension, then complete post-dosing Taste-and-Texture questionnaire in children 4 to < 18 years				•						
Obtain PK blood sample <sup>i</sup>				•	•	•	•			
Obtain PD blood sample <sup>j,k</sup>				• <sup>l</sup>	•	•	•			
Time point for PK/PD blood sample (hours) if dosing continues beyond Day 90				0.5-1.5hr post dose	2.5-4hr post dose	2-8hr post dose	10-16 hr after last evening dose, give next dose after PK/PD samples			
Time point for PK/PD blood sample (hours) if dosing does not continue beyond Day 90				0.5-1.5hr post dose	2.5-4hr post dose	2-8hr post dose	10-16 hr after last evening dose			

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**Table 0-1 Flow chart (continued)**

Visit	Main Treatment period						Extended treatment period with blocks of 3 months			30-day post study treatment
	1	1a	2	3	4	5	6	7	8	
Days	Before random	After random.	2+1 days after start t.i.d rivaroxaban <sup>p</sup>	Day 30 ± 7 days	Day 60 ± 7 days	Day 90 ± 7 days	Day 180 ± 7 days	Day 270 ± 7 days	Day 360 ± 7 days	30 ± 7 days After last visit
Contact	Visit	Visit	Visit	Visit	Visit	Visit	Visit	Visit	Visit	Visit or phone
<b>Pharmacokinetics (PK) and pharmacodynamics (PD) for rivaroxaban using t.i.d. regimen<sup>h</sup></b>										
Administer rivaroxaban at study site			•	•	•					
Take up to 120 mL of liquid immediately after dosing			•	•	•					
Obtain PK blood sample <sup>l</sup>			•	• <sup>q</sup>	• <sup>q</sup>	•				
Obtain PD blood sample <sup>j,k</sup>				• <sup>q</sup>	•	•				
Time point for PK/PD blood sample (hours) if dosing continues beyond Day 90			0.5-3hr post dose	7-8hr post dose	0.5-3hr post dose	7-8hr post dose	2-6hr post dose	10-16hr after last evening dose, give next dose after PD sample		
Time point for PK/PD blood sample (hours) if dosing does not continue beyond Day 90			0.5-3hr post dose	7-8hr post dose	0.5-3hr post dose	7-8hr post dose	2-6hr post dose	10-16hr after last evening dose		

Footnotes:

- <sup>a</sup> Blood sample should be obtained within a maximum of 5 days prior to randomization.
- <sup>b</sup> Randomization can be done during the first 9 days of initial therapy with UFH, LMWH or fondaparinux.
- <sup>c</sup> If study treatment is continued, provide study medication
- <sup>d</sup> Adjust dosage of study medication, if change in body weight. Additional visits can be planned to accommodate dose adjustment of study medication, if applicable.
- <sup>e</sup> If suspected outcome occurred, the adjudication package needs to be compiled and sent to the adjudication office.
- <sup>f</sup> After the main study treatment period of 3 months, the diagnostic imaging test which was obtained at baseline will be repeated, if clinically feasible.
- <sup>g</sup> VKA compliance will be ensured by minimum of 1 INR per 2 weeks.
- <sup>h</sup> The approximate total blood volume taken per child for PK/PD is 12 mL if blood taken via venipuncture (for t.i.d. regimen it is 7.2 mL), and up to 24 mL if blood taken via central venous line or peripheral catheter (see Section 6.14).
- <sup>i</sup> Blood volume per PK sample is approximately 1.2 mL (for t.i.d. regimen it is 0.6 mL); total blood volume for all PK samples is 4.8 mL for o.d. and b.i.d. regimen and 3 mL for t.i.d. regimen.
- <sup>j</sup> Blood volume per PD sample is approximately 1.8 mL (for t.i.d. regimen it is 1.4 mL); total blood volume for all PD samples is 7.2 mL for o.d. and b.i.d. regimen and 4.2 mL for t.i.d. regimen.
- <sup>k</sup> Always draw the PD sample as the last sample.
- <sup>l</sup> PD sample will not be collected at 0.5-1.5 hr after rivaroxaban intake for children < 6 years. Please note that this is different than in children <2 years with catheter related thrombosis
- <sup>m</sup> Only in children ≥12 years with lower or upper extremity DVT
- <sup>n</sup> In addition, provide Rivaroxaban Oral Suspension Handling Instructions, if applicable, and Study Booklet
- <sup>o</sup> Only applicable for children treated with oral suspension
- <sup>p</sup> Only in children treated with rivaroxaban t.i.d. regimen. If visit 1a falls on a weekend and cannot take place, the visit must be scheduled for the following Monday.
- <sup>q</sup> Visit 2 will be modified for children weighing < 3250 grams. The PK and PD samples taken 0.5 to 3 hours post-dose will be taken on a dosing day within the visit window (total volume to be drawn is 2.0 mL), and the 7-8 hour post-dose PK sample (total volume to be drawn is 0.6 ml) may be taken on the following dosing day within the visit window. This modification may only occur in children weighing less than 3250 kg at the time of visit 2.

o.d. = once daily dosing  
b.i.d. = twice daily dosing  
t.i.d. = three times daily dosing  
eCRF = electronic case report form;  
IxRS = interactive voice/ web response system  
PTS = post-thrombotic syndrome

**Table 0–2 Flow chart for children aged < 2 years with catheter related thrombosis <sup>22</sup>**

Visit	Main Treatment period				Extended treatment period with blocks of 30 days		30-day post study treatment
	1	1a	2	3	4	8	
Days	Before random.	After random.	2+1 days after start t.i.d. rivaroxaban <sub>m</sub>	Day 30 ± 7 days	Day 60 ± 7 days	Day 90 ± 7 days	30 ± 7 days After last visit <sup>t</sup>
Contact	Visit	Visit	Visit	Visit	Visit	Visit	Visit
Obtain informed consent	•						
Check in-/exclusion criteria	•						
Obtain demographic data	•						
Check medical history	•						
Record concomitant medication/anticoagulants	•						
Obtain height/length/body weight/blood pressure	•						
Check Hb, platelets, creatinine, ALT, total and direct bilirubin	• <sup>a</sup>						
Randomize patient using IxRS <sub>b</sub>		•					
Dispense study medication		•		•	• <sup>c</sup>	• <sup>c</sup>	
Dispense additional supplies (devices for oral suspension)		•		•	• <sup>c</sup>	• <sup>c</sup>	
Instruct how to take study medication <sup>l</sup>		•					
Send baseline adjudication package		•					
Check for adverse events		•	•	•	•	•	•
Check for device-related adverse events		•	•	•	•	•	
Obtain body weight				• <sup>d</sup>	• <sup>d</sup>	• <sup>d</sup>	
Check for study outcomes <sup>e</sup>			•	•	•	•	•
Check study drug accountability and compliance				•	•	•	
Check changes in concomitant medication			•	•	•	•	•
Obtain Hb, platelets, ALT, total and direct bilirubin				•			
Repeat imaging and send adjudication package <sup>f</sup>				•			
Complete eCRF	•	•	•	•	•	•	•
<b>Comparator group only</b>							
If INR-adjusted VKA <sup>g</sup>	1 INR per 2 weeks						

22 The flow chart for children <2 years with catheter related thrombosis was added via Amendment 12 (see Section 16.4.2.2)

**Table 0-2 Flow chart for children < 2 years of age with catheter related thrombosis (continued)**

Visit	Main Treatment period				Extended treatment period with blocks of 30 days		30-day post study treatment
	1		1a	2	3	4	8
Days	Before random	After random.	2+1 days after start t.i.d rivaroxaban <sub>m</sub>	Day 30 ± 7 days	Day 60 ± 7 days	Day 90 ± 7 days	30 ± 7 days After last visit <sup>f</sup>
Contact	Visit	Visit	Visit	Visit	Visit	Visit	Visit
<b>Pharmacokinetics (PK) and pharmacodynamics (PD) for rivaroxaban using b.i.d. regimen<sup>h</sup></b>							
Administer rivaroxaban at study site				•		•	
Take up to 240 mL of liquid immediately after dosing				•		•	
Obtain PK blood sample <sup>i</sup>				•	•	•	
Obtain PD blood sample <sup>j,k</sup>					•	•	• <sup>o</sup>
Time point for PK/PD blood sample (hours)				10-16hr after last evening dose, give next dose after PK sample	0.5-1.5hr post dose	2.5-4hr post dose	2-8hr post dose
<b>PK and PD for rivaroxaban using t.i.d. regimen<sup>h</sup></b>							
Administer rivaroxaban at study site			•		•	•	
Take up to 120 mL of liquid immediately after dosing			•		•	•	
Obtain PK blood sample <sup>i</sup>			•	•	• <sup>o</sup>	• <sup>o</sup>	•
Obtain PD blood sample <sup>j,k</sup>					• <sup>o</sup>	•	• <sup>n</sup>
Time point for PK/PD blood sample (hours)			0.5-3hr post dose	7-8hr post dose	0.5-3hr post dose	7-8hr post dose	2-6hr post dose

Footnotes:

- <sup>a</sup> Blood sample should be obtained within a maximum of 5 days prior to randomization.
- <sup>b</sup> Randomization can be done during the first 9 days of initial therapy with UFH, LMWH or fondaparinux.
- <sup>c</sup> If study treatment is continued, provide study medication
- <sup>d</sup> Adjust dosage of study medication and treatment regimen, if change in body weight. Additional visits can be planned to accommodate dose adjustment of study medication, if applicable.
- <sup>e</sup> If suspected outcome occurred, the adjudication package needs to be compiled and sent to the adjudication office.
- <sup>f</sup> After the main study treatment period of 1 month, the diagnostic imaging test which was obtained at baseline will be repeated, if clinically feasible.
- <sup>g</sup> VKA compliance will be ensured by minimum of 1 INR per 2 weeks.
- <sup>h</sup> The approximate total blood volume taken per child for PK/PD is 12 mL for b.i.d. and 7.2 mL for t.i.d. if blood taken via venipuncture, and up to 24 mL if blood taken via central venous line or peripheral catheter (see Section 6.14).
- <sup>i</sup> Blood volume per PK sample is approximately 1.2 mL for b.i.d. and 0.6 mL for t.i.d.; total blood volume for all PK samples is 4.8 mL for b.i.d. and 3 mL for t.i.d.
- <sup>j</sup> Blood volume per PD sample is approximately 1.8 mL for b.i.d. and 1.4 mL for t.i.d.; total blood volume for all PD samples is 7.2 mL for b.i.d. and 4.2 mL for t.i.d. Always draw the PD sample as the last sample.
- <sup>k</sup>
- <sup>l</sup> In addition, provide Rivaroxaban Oral Suspension Handling Instructions, and Study Booklet
- <sup>m</sup> Only in children treated with rivaroxaban t.i.d. regimen. If visit 1a falls on a weekend and cannot take place, the visit must be scheduled for the following Monday.
- <sup>n</sup> Visit 8 cannot be conducted by phone in children who are aged < 2 with catheter-related thrombosis, as a PD sample must be collected at this visit. If the patient is started on another anticoagulant during the 30 day post study treatment period, the PD sample needs to be taken at least 8 hours after last dose of rivaroxaban and before initiation of a new anticoagulant.
- <sup>o</sup> Visit 2 will be modified for children weighing < 3250 grams. The PK and PD samples taken 0.5 to 3 hours post-dose will be taken on a dosing day within the visit window (total volume to be drawn is 2.0 mL), and the 7-8 hour post-dose PK sample (total volume to be drawn is 0.6 ml) may be taken on the following dosing day within the visit window. This modification may only occur in children weighing less than 3250 kg at the time of visit 2.

o.d. = once daily dosing

b.i.d. = twice daily dosing

t.i.d. = three times daily dosing

eCRF = electronic case report form;

IxRS = interactive voice/ web response system

PTS = post-thrombotic syndrome



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## Abbreviations

ACCP	American College of Chest Physicians	LOS	listing only set
AE	adverse event	MedDRA	Medical Dictionary for Regulatory Activities
ALT	alanine aminotransferase	MR	Magnetic resonance
anti-Xa	anti-factor Xa activity	MRI	magnetic resonance imaging
aPTT	activated partial thromboplastin time	NSAIDs	non-steroid anti-inflammatory drugs
b.i.d.	twice daily	o.d.	once daily
CCDS	Company Core Data Sheet	PD	pharmacodynamics
CIAC	Central independent adjudication committee	PE	pulmonary embolism
CNS	central nervous system	P-gp	P-glycoprotein
CT	computed tomography	PK	pharmacokinetic(s)
CYP3A4	cytochrome P450 isoenzyme 3A4	PP	polypropylene
DMC	data monitoring committee	PPS	per protocol set
DVT	deep vein thrombosis	PTC	Product Technical Complaint
eCRF	electronic case report form	SAE	serious adverse event
eGFR	estimated glomerular filtration rate	SAP	statistical analysis plan
EU	European Union	s.c.	subcutaneously
GCP	Good Clinical Practice	SCr	serum creatinine
GMP	Good Manufacturing Practice	SID	child identification number
HDPE	High density polyethylene	SOC	Standard of care
IB	investigator's brochure	SUSAR	suspected unexpected serious adverse reactions
ICH	International Conference on Harmonization	TB	total bilirubin
IDMS	isotope dilution mass spectrometry	t.i.d.	three times daily
IEC	Independent Ethics Committee	TOSCA	Tools for Syntactic Corpus Analysis
INN	International non-proprietary name	U	Units
INR	international normalized ratio	UFH	unfractionated heparin
IRB	Institutional Review Board	ULN	upper limit of normal
IxRS	interactive voice/web response system	US	United States
LDD	Liquid Dosing Devices	VKA	vitamin K antagonist
LMWH	low molecular weight heparin	VTE	venous thromboembolism



## 1. Introduction

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).<sup>[1]</sup> 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.<sup>[2]</sup> 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,<sup>[3,4]</sup> 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 two large phase III studies and was compared to body weight adjusted LMWH and INR titrated VKA in patients with symptomatic deep vein thrombosis and pulmonary thromboembolism. The pooled analysis demonstrated clear non-inferiority for the primary efficacy outcome and an improved safety profile in terms of the occurrence of major bleeding in adults.<sup>[5]</sup>

The goal of the rivaroxaban pediatric program is to make rivaroxaban available to children for treatment and secondary prevention of venous thromboembolism. It is anticipated that similar exposure in children, as compared to adults, will result in a similar safety and efficacy profile in children. To accomplish this goal, an age- and body weight-adjusted dosing regimen is being evaluated in a phase II program in children aged 6 months to 18 years with various manifestations of venous thrombosis. These children will receive rivaroxaban during the last month of their regular anticoagulant treatment.

In phase II, enrollment of children aged 6 months to less than 18 years has been completed. Rivaroxaban was well tolerated, no recurrent venous thromboembolism and/or major bleeding were observed and PK/PD results were in the expected range for children weighing more than 12 kg.<sup>23 24</sup>

23 Section was modified via Amendment 8 (see Section 16.2.2.4)

24 The Paragraph was modified via Amendment 12 (see Section 16.4.2.3)

The study will be initiated with children in the age group between 12 and less than 18 years since the age-and body weight adjusted dosing regimen has been confirmed for this age group in the phase II study 14373 and was approved by the data monitoring committee and steering committee. The dosing schedule/regimen for this age group is available in [Appendix 4](#).

Once the age-and body weight adjusted dosing regimen has been confirmed for the age group between 6 and less than 12 years in the phase II study 14373 and approved by the data monitoring committee and steering committee, the dosing schedule/regimen for this age group will be made available through an administrative amendment. The investigators and ethics committees/IRBs will receive the administrative amendment well in advance with an opportunity for evaluation before permission will be given to start enrolling children in this age group.

Once the age-and body weight adjusted dosing regimen has been confirmed for the age group between 2 and less than 6 years in the phase II study 14374 and approved by the data monitoring committee and steering committee, the dosing schedule/regimen for this age group will be made available through an administrative amendment. The investigators and ethics committees/IRBs will receive the administrative amendment well in advance with an opportunity for evaluation before permission will be given to start enrolling children in this age group.

Once the age-and body weight adjusted dosing regimen has been confirmed for the age group between 6 months and less than 2 years in the phase II study 14374 and approved by the data monitoring committee and steering committee, the dosing schedule/regimen for this age group will be made available through an administrative amendment. The investigators and ethics committees/IRBs will receive the administrative amendment well in advance with an opportunity for evaluation before permission will be given to start enrolling children in this age group.

The age-and body weight adjusted dosing regimen has now been established for all children aged birth to less than 18 years from data collected in the phase I/II studies and has been approved by the data monitoring committee and steering committee. [Table 17–2](#) specifies the dosing regimen for each age group.<sup>25</sup>

## 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.

<sup>25</sup> The paragraph was added via Amendment 12 ( see Section [16.4.2.3](#))

## 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.<sup>[6]</sup> Expressions of venous thrombosis that usually requires 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%).<sup>[7]</sup> 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.<sup>[8,9]</sup>

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.<sup>[9]</sup> The current treatment recommendation for cerebral vein and sinus thrombosis is therapeutic doses of anticoagulants.<sup>[10]</sup>

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. The American College of Chest Physicians (ACCP) management guidelines for children with secondary VTE (i.e., VTE that occurred in association with a risk factor) in whom the risk factor has resolved recommend anticoagulant therapy for 3 months. In children who have ongoing risk factors, guidelines suggest continued anticoagulant therapy beyond 3 months. For children with idiopathic VTE, the recommendation is anticoagulant therapy for 6 to 12 months. For catheter-related thrombosis, the guidelines recommend a total duration of anticoagulation of between 6 weeks and 3 months.<sup>[9]</sup>

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

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.

Type of anticoagulant drug, dose and duration of treatment for VTE in children is primarily derived from adult data. The majority of the recommendations for dosing in children are

based on Grade 2 level of evidence.<sup>[10]</sup> Therefore, there is a medical need for additional clinical studies that address the efficacy and safety of anticoagulants treatment in children.

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 studies in adults,<sup>[11]</sup> 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 and observed laboratory abnormalities, was comparable to enoxaparin/VKA treatment.

## 2. Study objectives

The efficacy objectives are:

- To assess the incidence of symptomatic recurrent venous thromboembolism
- To assess the incidence of symptomatic recurrent venous thromboembolism and asymptomatic deterioration on repeat imaging.

The safety objective is:

- To assess the incidence of overt major and clinically relevant non-major bleeding.

Other objectives are:

- To characterize the pharmacokinetic/pharmacodynamic profile of rivaroxaban.

## 3. Study design

This is a multicenter, open-label, active-controlled, randomized study to evaluate the efficacy and safety of an age- and body weight-adjusted rivaroxaban regimen in children with acute venous thromboembolism.

The study will be initiated with children in the age group between 12 and less than 18 years since the age- and body weight adjusted dosing regimen has been confirmed for this age group in the phase II study 14373 and was approved by the data monitoring committee and steering committee. The dosing schedule/regimen for this age group is available in [Appendix 4](#) (update: for oral suspension this is implemented through Amendment 8).

Once the age-and body weight adjusted dosing regimen has been confirmed for the age group between 6 and less than 12 years in the phase II study 14373 and approved by the data monitoring committee and steering committee, the dosing schedule/regimen for this age group will be made available through an administrative amendment (For tablet, this was implemented through Amendment 4<sup>26</sup>; update: for oral suspension this is implemented through Amendment 8).<sup>27</sup> The investigators and ethics committees/IRBs will receive the administrative amendment well in advance with an opportunity for evaluation before permission will be given to start enrolling children in this age group.

Once the age-and body weight adjusted dosing regimen has been confirmed for the age group between 2 and less than 6 years in the phase II study 14374 and approved by the data monitoring committee and steering committee, the dosing schedule/regimen for this age group will be made available through an administrative amendment (update: implemented through Amendment 8). The investigators and ethics committees/IRBs will receive the administrative amendment well in advance with an opportunity for evaluation before permission will be given to start enrolling children in this age group.

Once the age-and body weight adjusted dosing regimen has been confirmed for the age group between 6 months and less than 2 years in the phase II study 14374 and approved by the data monitoring committee and steering committee, the dosing schedule/regimen for this age group will be made available through an administrative amendment (update: implemented through Amendment 8). The investigators and ethics committees/IRBs will receive the administrative amendment well in advance with an opportunity for evaluation before permission will be given to start enrolling children in this age group.<sup>28</sup>

The age-and body weight adjusted dosing regimen has now been established for all children aged birth to less than 18 years from data collected in the phase I/II studies and has been approved by the data monitoring committee and steering committee. [Table 17–2](#) specifies the dosing regimen for each age group.<sup>29</sup>

Amendment 8 introduced a single consistent body weight adjusted dosing schedule/regimen for children aged 6 months to < 18 years and body weight  $\geq 12$ kg (see [Table 17–2](#)).<sup>30</sup> Age dependency is implicitly considered in this table as certain body weights are connected (through standard growth charts) with certain ages (with some variability, excluding extreme obesity) as well as with anatomical and physiological differences that affect the absorption, distribution, metabolism, and excretion (ADME) processes at different ages.<sup>31</sup>

26 The tablet dosing regimen for children from 6 to <12 years was included via Amendment 4 (see Section 16.1.2.2).

27 The oral suspension was implemented via Amendment 8 (see Section 16.2.2.5)

28 Information of start of enrollment in cohorts 6 months to less years 2 years and 2 to less than 6 years was added via Amendment 8 (Section 16.2.2.5)

29 The paragraph was added via Amendment 12 (see Section 16.4.2.4)

30 A dosing regimen for children with body weight between 6 and less than 12 kg was added via Amendment 10 (see Section 16.3.2.2)

31 A single consistent body weight adjusted dosing schedule/regimen for children aged 6 months to < 18 years was introduced via Amendment 8 (see Section 16.2.2.5)

Amendment 10 introduced dosing information and a new **three times daily** dosing schedule for children with body weight between 6 and <12 kg. This new dosing regimen is based on an exploratory PopPK model, that considers all rivaroxaban PK data available from children below 2 years dosed in our phase I and phase II studies. As less data are available for younger children (e.g., due to sparse sampling), the model predictions have a higher level of uncertainty for children with lower body weight. The Steering Committee therefore recommended to evaluate PK around the expected  $C_{max}$  and at  $C_{trough}$  as soon as the steady state is achieved (day 2+1 after start of rivaroxaban treatment; Visit 1a).

The PK samples obtained at Visit 1a will be shipped and analyzed for each child individually and will allow to determine whether the plasma concentrations are in the adult reference range. The results will be provided to the investigator/site and discussed in a timely manner, i.e. within approximately 1 to 2 weeks after sample collection. Up to now, the predictions from the exploratory PopPK model are confirmed by the data from children enrolled in this weight group.

Amendment 12 opened enrollment to children aged birth to < 6 months and introduced dosing information for children with a body weight between 2.6 and 6 kg. This new dosing regimen is based on data from all studies in children younger than 2 years, as well as an exploratory PopPK model, that considers all rivaroxaban PK data available from all children younger than 2 years. As the exploratory model is based on limited data (e.g., limited number of subjects, sparse sampling), the model predictions had a higher level of uncertainty for these children. However, observed data from this study (14372) and data from the phase I/II study (17618) that is enrolling children of this weight category, have confirmed the predictions from the exploratory PopPK model in all children dosed t.i.d thus far in both studies.<sup>32</sup>

## Study description<sup>33</sup>

Children aged birth to < 18 years with confirmed acute venous thromboembolism who receive initial treatment with therapeutic dosages of unfractionated heparin (UFH), low molecular weight heparin (LMWH), or fondaparinux are potentially eligible for the study. Initial treatment with UFH, LMWH or fondaparinux will be administered for at least 5 days (day 1-5).

Randomization can be done during the first 9 days of initial treatment and will be in a 2 (rivaroxaban): 1 (standard of care [SOC]) fashion. Children randomized to rivaroxaban will start rivaroxaban the day following the last administration of initial therapy with UFH, LMWH, or fondaparinux but with a minimal duration of initial therapy of 5 days and a maximum duration of 9 days.

The first administration of rivaroxaban will be started:

- 4 hours after discontinuation of UFH
- 12 hours after discontinuation of LMWH with a b.i.d. regimen, and

<sup>32</sup> The paragraph was added via Amendment 12 ( see Section 16.4.2.4)

<sup>33</sup> The study description was modified to include children in younger cohort 8 from birth) and to highlight different treatment duration for children <2 years with catheter related thrombosis (see Section 16.4.2.4)

- 24 hours after discontinuation of fondaparinux or LMWH with an o.d. regimen.

Children randomized to standard of care can continue UFH, LMWH, or fondaparinux or can switch to VKA therapy. If VKA therapy is planned, it can be initiated any time after randomization. Initial therapy with UFH, LMWH, or fondaparinux can be stopped after a minimum of 5 days and only if the INR is above 2 on two separate occasions, 24 hours apart. In children randomized to rivaroxaban in whom VKA therapy was already initiated before randomization, VKA therapy should be stopped and the switch to rivaroxaban should be made as described in Section 5.1.1.3.<sup>34</sup> After randomization, children will receive either rivaroxaban or comparator for a main study treatment period of 3 months. After the main study treatment period of 3 months, the diagnostic imaging test which was obtained at baseline will be repeated, if clinically feasible. However, in children younger than 2 years with catheter-related thrombosis, the main study treatment period is for a total of 1 month at which time the repeat imaging will be performed.

In all children, except those aged < 2 years with catheter-related thrombosis, the decision is made to stop study treatment at 3 months or to continue for an additional 3 months. In children who completed 6 months of treatment, the decision is made to stop study treatment or to continue for an additional 3 months. Then, in children who completed 9 months of treatment, the decision is made to stop study treatment or to continue for an additional 3 months. In children < 2 years with catheter-related thrombosis, the decision is made to stop study treatment at 1 month or to continue for an additional month. Then, in children who completed 2 months of treatment, the decision is made to stop study treatment or to continue for an additional month.

Regardless of the duration of study treatment (<3, 3, 6, 9 or 12 months), an additional 1-month post-treatment observational period will be completed for all children. After cessation of study treatment, it is at the investigator's discretion to continue with anticoagulants.

The primary efficacy outcome is symptomatic recurrent venous thromboembolism. The secondary efficacy outcome is the composite of all symptomatic recurrent venous thromboembolism and asymptomatic deterioration in thrombotic burden on repeat imaging. The principal safety outcome is the composite of overt major and clinically relevant non-major bleeding. All suspected clinical study outcomes and baseline and repeat thrombosis imaging tests will be assessed by a central independent adjudication committee (CIAC) blinded to treatment allocation. An independent data monitoring committee (DMC) will monitor the children's safety and give recommendations to the steering committee.

For all children, visits are scheduled at regular time points (see [Table 0-1](#) and [Table 0-2](#)). Randomized children who have not received the study drug will be seen (visit or phone contact) at the end of the respective main study treatment period. Children who prematurely discontinue study drug will be seen at the end of the intended study treatment period at month <3, 3, 6, 9 or 12. During all contacts, the treatment and clinical course of the child will be evaluated. Children with suspected efficacy or safety outcomes will undergo confirmatory

<sup>34</sup> This paragraph was added via Amendment 8 (see Section 16.2.2.5)

testing as per standard of care. Blood samples for PK/PD will be taken at defined time points (see [Table 0–1](#) and [Table 0–2](#)).

In children 12 years or older with DVT of the lower or upper extremity, the incidence of the post-thrombotic syndrome will be assessed at month 3, 6, 9 and 12 months, if applicable, using the Villalta Score.<sup>[17], 35</sup>

The reason why children did not pass the screen of in- and exclusion criteria after obtaining informed consent/child assent will be documented.

## 4. Study population

### 4.1 Planned number of children<sup>36</sup>

At least 170 children are needed for this study, of whom 80 in the age group 12 to < 18 years, 30 in the age group 6 to < 12 years, 20 in the age group 2 to < 6 years, and 20 in the age group birth to < 2 years, with at least 12 aged birth to < 6 months.

### 4.2 Inclusion criteria

1. Children aged birth to < 18 years with confirmed venous thromboembolism who receive initial treatment with therapeutic dosages of UFH, LMWH or fondaparinux and require anticoagulant therapy for at least 90 days. However, children aged birth to < 2 years with catheter-related thrombosis require anticoagulant therapy for at least 30 days.<sup>37</sup>
2. Informed consent provided and, if applicable, child assent provided
3. For children younger than 6 months:
  - Gestational age at birth of at least 37 weeks.
  - Oral feeding/nasogastric/gastric feeding for at least 10 days.
  - Body weight  $\geq 2600$  g<sup>38</sup>

### 4.3 Exclusion criteria

1. Active bleeding or bleeding risk contraindicating anticoagulant therapy<sup>39</sup>
2. An estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m<sup>2</sup> (in children younger than 1 year, serum creatinine results above 97.5<sup>th</sup> percentile excludes participation, see [Table 17–1](#)).<sup>40</sup>
3. 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.

35 The post-thrombotic syndrome assessment was added Amendment 8 (see Section [16.2.2.5](#))

36 The planned number of children was increased via Amendment 12 (see Section [16.4.2.5](#))

37 The inclusion criterion was modified via Amendment 12 to include children from birth (see Section [16.4.2.6](#))

38 The inclusion criterion 3 was added via Amendment 12 (see Section [16.4.2.6](#))

39 Exclusion criteria 1, 5, 7 and 8 were modified via Amendment 8 (see Section [16.2.2.6](#))

40 The exclusion criterion 2 was modified via Amendment 12 to instruct that serum creatinine value should be used instead of eGRF for children <1 year (see Section [16.4.2.7](#))



4. Platelet count  $< 50 \times 10^9/L$ .
5. Sustained uncontrolled hypertension defined as systolic and/or diastolic blood pressure  $> 95^{\text{th}}$  age percentile <sup>39,41</sup>
6. Life expectancy  $< 3$  months
7. Concomitant use of strong inhibitors of both CYP3A4 and P-gp, including but not limited to all human immunodeficiency virus protease inhibitors and the following azole-antimycotics agents: ketoconazole, itraconazole, voriconazole, posaconazole, if used systemically (fluconazole is allowed). For exceptions, see Section 4.4. <sup>39</sup>
8. Concomitant use of strong inducers of CYP3A4, including but not limited to rifampicin, rifabutin, phenobarbital, phenytoin, and carbamazepine <sup>39</sup>
9. Childbearing potential without proper contraceptive measures, pregnancy or breast feeding
10. Hypersensitivity or any other contraindication listed in the local labeling for the comparator treatment or experimental treatment
11. Inability to cooperate with the study procedures
12. Previous assignment to treatment during this study
13. Participation in a study with an investigational drug or medical device within 30 days prior to randomization

#### **4.4 Concomitant medication**

Non-steroid 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 vitamin K antagonist (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 (including but not limited to ketoconazole, itraconazole, voriconazole, posaconazole), if used systemically, is not allowed, as well as concomitant use of strong inducers of CYP3A4 (including but not limited to rifampicin, rifabutin, phenobarbital, phenytoin, carbamazepine). Concomitant treatment with fluconazole is allowed. <sup>42</sup>

### **5. Treatment groups and regimens**

#### **5.1 Method of treatment allocation**

Allocation to treatment will be done centrally by an interactive voice /web response system (IxRS). Allocation will be done in a 2 (rivaroxaban) to 1 (standard of care) fashion.

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41 Exclusion criterion 5, 7 and 12 was modified for minor clarification via Amendment 4 (see Section 16.1.2.3)

42 Concomitant use of strong inhibitors of both CYP3A4 and P-gp was modified via Amendment 8 (Section 16.2.2.7)

The investigator will provide the IxRS with study center identification, the child's date of birth (day, month and year)<sup>43</sup>, gender, weight and clinical presentation. Allocation will be stratified by baseline presentation of venous thrombosis for each age group, separately, 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.

Specific procedures for treatment assignment through IxRS are contained in the IxRS manual.

### 5.1.1 Rivaroxaban group<sup>44</sup>

The body weight adjusted dosing schedule for children aged birth to < 18 years is provided in Appendix 4 (see Section 17.4).<sup>45</sup>

Children with body weight of  $\geq 20$  kg will receive rivaroxaban tablets or oral suspension. Children with body weight of < 20 kg will receive rivaroxaban as oral suspension.

Children with body weight of  $\geq 30$  kg will be treated according to a once daily (o.d.) regimen, irrespective of whether they receive rivaroxaban tablets or oral suspension. Children with body weight between 12 and < 30 kg will receive rivaroxaban twice daily (b.i.d) with a dosing intervals of approximately 12 hours. Children with body weight below 12 kg will receive rivaroxaban three times daily (t.i.d.) with dosing interval of approximately 8 hours.

Dosing regimen, including dosing frequency, will be adjusted if the child's body weight changes during the study (Table 17-2).

With a once daily regimen, rivaroxaban will be taken in the morning during or within 2 hours after breakfast. With a twice daily regimen the morning dose will be taken during or within 1 hour after breakfast and the evening dose will be taken during or within 1 hour after dinner. With a three times daily regimen, the morning, afternoon and night doses should be taken during or within 30 minutes after feeding.

Each rivaroxaban dose should be immediately followed by the intake of one typical serving of up to 240 mL of liquid (o.d. or b.i.d regimen) or 120 mL (t.i.d. regimen). This volume will depend on age and may range from for example 20 mL in children aged 6 months up to 240 mL in adolescents.<sup>46</sup>

#### Use of oral suspension

Oral suspension is available for use in children aged birth to < 18 years.

At Visit 2, the Taste-and-Texture Questionnaire, using a three point scale, will be applied to determine the acceptance of the oral suspension in children from 4 to < 18 years. The pre-

43 A clarification was added that the day of birth has to be collected via Amendment 4 (see Section 16.1.2.4)

44 The section was modified via Amendment 12 to include children from birth ( see Section 16.4.2.8)

45 This section was modified via Amendment 8 (see Section 16.2.2.8)

46 A dosing regimen for children with body weight between 6 and less than 12 kg was added via Amendment 10 (see Section 16.3.2.3)

dose part of this questionnaire needs to be completed before rivaroxaban suspension is taken, the post-dose part of this questionnaire needs to be completed after rivaroxaban suspension dose is taken and up to 240 mL of liquid has been taken.

Instructions on how to handle rivaroxaban oral suspension can be found in the Rivaroxaban Oral Suspension Handling Instructions.

### **Handling of missed doses**<sup>47</sup>

If rivaroxaban is taken with an o.d. regimen, a missed dose should be taken immediately when it is noticed, but only on the same day. Double dosing on a single day is not allowed.

If rivaroxaban is taken with a b.i.d. regimen, a missed morning dose should be taken immediately when it is noticed, and it may be taken together with the evening dose. A missed evening dose can only be taken at the same evening.

If rivaroxaban is taken with a t.i.d. regimen, the t.i.d. administration schedule with approximately 8-hour intervals should be resumed at the next scheduled dose without compensating for the missed dose.

On the following day, the child should continue with the regular o.d., b.i.d. or t.i.d. regimen.<sup>46</sup>

#### **5.1.1.1 Switching from heparin/fondaparinux to rivaroxaban**

For switching from heparin/fondaparinux to rivaroxaban, the pharmacological activity of UFH, LMWH and fondaparinux should be taken into account. The first administration of rivaroxaban should be planned 1) 4 hours after stopping the infusion of UFH, 2) 12 hours after the last injection of LMWH with a twice-daily regimen, or 3) 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.

#### **5.1.1.2 Switching from rivaroxaban to heparin/fondaparinux**

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

#### **5.1.1.3 Switching from rivaroxaban to VKA and vice-versa**

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  $\geq 2.0$ .

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

### **5.1.2 Comparator group**

Children randomized to the comparator group will continue with UFH, LMWH or fondaparinux or may switch to VKA therapy. VKA dosages will be adjusted to maintain the

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<sup>47</sup> Missed dose handling was added via Amendment 4 (see Section 16.1.2.5).

INR within the therapeutic range (target 2.5, range 2.0 - 3.0). UFH, LMWH or fondaparinux can be discontinued once the INR is above 2.0 on two separate occasions, 24 hours apart.

## 5.2 Subject identification

Upon signing the informed consent/assent as per local requirements, each child will be assigned unique 9-digit child identification (SID) number by IxRS 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.

At Visit 1, Day 1, children will be assigned a unique randomization number by IxRS that will allow subsequent identification of treatment allocation.

## 5.3 Duration of study treatment<sup>48</sup>

In all children, except those aged < 2 years with catheter-related thrombosis, the main study treatment period is 3 months. After that, it is up to the discretion of the treating physician to stop study treatment or to continue for an additional 3 months.

In children who completed 6 months of treatment, the decision can be made to stop study treatment or to continue for an additional 3 months. Then, in children who completed 9 months of treatment, the decision can be made to stop study treatment or to continue for an additional 3 months. Thereafter, no prolongation of study treatment can take place.

In children aged < 2 years with catheter-related thrombosis, the main study treatment period is 1 month. After that, it is up to the discretion of the treating physician to stop study treatment or to continue for an additional 1 month.

In children who completed 2 months of treatment, the decision can be made to stop study treatment or to continue for an additional 1 months. Thereafter, no prolongation of study treatment can take place.

Children who turn 2, 6, 12 or 18 years after randomization can continue their treatment regimen.<sup>49</sup> Specifically children who turn 18 years after randomization are allowed to continue participation for the entire elected study treatment duration of 3, 6, 9 or 12 months.

Children randomized last into the study will have a minimal study treatment duration of 3 months, except children aged < 2 years with catheter-related thrombosis, who will have a minimal study treatment duration of 1 month.<sup>50</sup>

<sup>48</sup> The section was modified via Amendment 12 to highlight different treatment duration for children <2 years with catheter related thrombosis (see Section 16.4.2.9)

<sup>49</sup> Information for children who turn 2, 6, 12 or 18 was included (see Section 16.1.2.5)

<sup>50</sup> Information on minimal study treatment duration was added via Amendment 8 (see Section 16.2.2.9)

## 5.4 Formulation and dose

### 5.4.1 Rivaroxaban

Rivaroxaban will be provided by Bayer as immediate-release film-coated tablets, and as a granules for oral suspension formulation (0.1% suspension as finally administered drug product), see [Table 5–1](#). Rivaroxaban will be dosed according to body weight groups as detailed in the dosing schedules/regimens associated with this protocol. Since children with an estimated glomerular filtration rate below 30 mL/min/1.73 m<sup>2</sup> (in children younger than 1 year, serum creatinine results above 97.5<sup>th</sup> percentile, see [Table 17–1](#)) are excluded from the study, dose reduction for impaired renal function is not required.<sup>51 52</sup>

**Table 5–1 Identity of test drug**

International non-proprietary name (INN)	Rivaroxaban	
Substance code number	BAY 59-7939	
Formulation	Film-coated tablets	Granules for oral suspension
Composition	Active ingredient: rivaroxaban / BAY 59-7939 micronized Excipients: microcrystalline cellulose, croscarmellose sodium, hypromellose, lactose monohydrate, magnesium stearate, and sodium lauryl sulfate Film-coating: hypromellose, macrogol, titanium dioxide, and ferric oxide red or ferric oxide yellow	Active ingredient: rivaroxaban / BAY 59-7939 micronized Excipients: microcrystalline cellulose and carmellose sodium, xanthan gum, citric acid anhydrous, sodium benzoate, flavor sweet and creamy, hypromellose 5 cP, sucralose, mannitol
Type of packaging and content	Type of packaging: plastic bottle high density polyethylene (HDPE) white opaque, closed with white screw cap polypropylene (PP) with sealing inserter and childproof lock	Type of packaging: brown glass bottle type 3 closed with PP screw cap childproof lock
Strength of rivaroxaban	Tablets of 5.0, 10.0, 15.0 and 20.0 mg	1 mg per ml

### 5.4.2 Comparator

Comparator will be used according to approved formulations.

## 5.5 Packaging, labeling, and storage<sup>53</sup>

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

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 it to the sites.

51 Oral suspension information was updated via Amendment 8 (see Section [16.2.2.10](#))

52 Paragraph was modified via Amendment 12 to highlight that for children <1 year the serum creatinine value should be used instead of eGFR (see Section [16.4.2.10](#))

53 A minor modification was done in the Section to remove redundancy (see Section [16.4.2.11](#))

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. Comparator provided by sites will be documented in the hospital/pharmacy records.

All study medication needs to be stored at the site according to the labeled storage advice in accordance with Good Clinical Practice (GCP) and GMP requirements. The study drug is to be kept in a secure area. 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.

## 5.6 Treatment assignment

After randomization, the randomization number will be recorded on the corresponding electronic case report form (eCRF). The subject identification number will have to be recorded on the label of the study medication.

In case UFH, LMWH, fondaparinux and/or VKA is provided locally, the compound's name, dose, quantity and batch number, or a copy of the prescription has to be included in the child's files.

## 5.7 Dosage and administration

Comparator treatment consists of locally used anticoagulants, 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.
	5 yr	240 u/kg o.d.
	5-10 yr	200 u/kg o.d.
	10-16 yr	175 u/kg o.d.
Dalteparin	129 ± 43 u/kg/dose o.d.	
UFH	aPTT 1.5-2.5 prolongation	

b.i.d.: twice daily; o.d.: once daily; u: units; this comparator list is not all-inclusive.<sup>[10]</sup>

## **5.8 Study treatment delivery and compliance assessment<sup>54</sup>**

A 1-month supply of drug will be given at visits 1, 2, and 3, if applicable. In children who continue study treatment for an additional 3 months, (not applicable to children aged < 2 years with catheter-related thrombosis) study drug will be supplied at visit 4 covering a 3-month period. In children who continue the study for a third and a fourth cycle of 3 months; study drug will be supplied at visits 5 and 6.

All used and unused medication and additional supplies will be returned at all study visits. All non-used study medication will be kept securely in a designated locked container.

### **5.8.1 Rivaroxaban**

Compliance will be evaluated by counting remaining rivaroxaban tablets or measuring remaining suspension.

### **5.8.2 Vitamin K antagonists**

Compliance with VKA treatment will be evaluated 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, 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. The time in therapeutic range (INR 2 to 3) will be calculated.

### **5.8.3 Low molecular weight heparin/fondaparinux**

Compliance will be evaluated by counting remaining syringes.

## **5.9 Devices for preparation and administration of rivaroxaban oral suspension**

The rivaroxaban granules for oral suspension will be suspended with water. In order to measure the appropriate volume of water, parents will be provided with 100 ml syringes.

In addition, parents will be provided with Liquid Dosing Devices (LDDs; dosing pipettes) for precise, accurate and reproducible measuring of the rivaroxaban oral suspension dose volume and for administration to the child.

Both supplies, the syringe and the LDDs, are class 1 devices with measuring function, which is considered a low risk class.

The syringes and LDDs will be provided to the parents together with the rivaroxaban oral suspension as additional supplies. The use of these supplies is described in the Rivaroxaban Oral Suspension Handling Instructions. Any device malfunction or defect, or any use error by site personnel or parents will be assessed during study visits (see Section 7.9.10).

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<sup>54</sup> The section was modified via Amendment 12 (see Section 16.4.2.12)

## 6. Study Procedures

### 6.1 Study visits

The study has 4 to 9 planned visits, depending on the elected study duration and dosing.<sup>55</sup>

### 6.2 Visit 1 - Randomization Visit

The parents/legal guardians and children will be given an explanation about the study and will be given sufficient time to consider their participation in the study and to ask any questions. Afterwards, informed consent and/or assent will be obtained (see Section 10.2). If the child passes the screen of inclusion and exclusion criteria, the child can be randomized.<sup>56</sup> Then,

- Obtain demographics and relevant medical history
- Record all medication, including anticoagulant medication given for the current thrombosis
- Obtain height/length, body weight and blood pressure
- If results for hemoglobin, platelets, creatinine, ALT, total and direct bilirubin were not available within 5 days prior to randomization, obtain blood sample
- Perform a urine pregnancy test, if applicable
- Randomization can be done during the first 9 days of initial treatment and will be in a 2 (rivaroxaban): 1 (standard of care [SOC]) fashion. Children randomized to rivaroxaban will start rivaroxaban the day following the last administration of initial therapy with UFH, LMWH, or fondaparinux but with a minimal duration of initial therapy of 5 days and a maximum duration of 9 days.
- Dispense study medication and additional supplies (devices for oral suspension)<sup>57</sup>
- Provide instructions on how to take the study drug and give the study booklet. If child will take rivaroxaban oral suspension, provide the Rivaroxaban Oral Suspension Handling Instructions. Train parents/child on the preparation and administration of the oral suspension and on the use of the liquid dosing device.
- The first administration of rivaroxaban will be started:
  - 4 hours after discontinuation of UFH
  - 12 hours after discontinuation of LMWH with a b.i.d. regimen, and
  - 24 hours after discontinuation of fondaparinux or LMWH with an o.d. regimen
- Check for adverse events and device-related adverse events

<sup>55</sup> The section was modified via Amendment 12 (see Section 16.4.2.13)

<sup>56</sup> This section was updated via Amendment 8 (see Section 16.2.2.14)

<sup>57</sup> Dispense of study medication was listed for consistency with the study flow chart via Amendment 4 (see Section 16.1.2.6).



- Instruct that on the day of the next scheduled visit (visit 1a for t.i.d. regimen or visit 2 for o.d. or b.i.d. regimen), rivaroxaban should not be taken at home and that all used and unused medication/supplies should be returned to the hospital<sup>58</sup>
- Update eCRF
- Collect images of the index venous thrombotic event, prepare the adjudication package and send it to the central adjudication office.

### 6.3 Visit 1a (2+1 days after start t.i.d. rivaroxaban)

This visit will only be performed for children in the rivaroxaban t.i.d. group. If this visit falls on a weekend and cannot take place, the visit must be scheduled for the following Monday.

- Check for potential study outcomes. If a suspected study outcome occurred, an adjudication package will be compiled and sent to the adjudication office.
- Administer the next rivaroxaban dose immediately followed by the intake of up to 120 mL of liquid.
- Document the volume and type of liquid taken.
- Document the exact time of rivaroxaban intake as well as the time and type of meal (i.e. breakfast, lunch, dinner) the child took during or within 30 minutes after rivaroxaban.<sup>59</sup>
- At 0.5-3 hours and at 7-8 hours after the rivaroxaban intake:
  - Collect a PK blood sample
  - Document the exact time of blood sampling for PK.
- Check for changes in concomitant medications
- Check for adverse events and device-related adverse events
- Instruct that on the day of visit 2, rivaroxaban should not be taken at home and that all used and unused medication/supplies should be returned to the hospital
- Update eCRF<sup>60</sup>

<sup>58</sup> This section was changed to implement new dosing regimen for children with body weight between 6 and less than 12 kg via Amendment 10 (see Section 16.3.2.4)

<sup>59</sup> The bullet was modified according to Amendment 12 ( see Section 16.4.2.14)

<sup>60</sup> This section was added to implement new dosing regimen for children with body weight between 6 and less than 12 kg via Amendment 10 (see Section 16.3.2.5)

#### 6.4 Visit 2 at Day 30 ( $\pm 7$ days)<sup>61</sup>

- Check for potential study outcomes. If a suspected study outcome occurred, an adjudication package will be compiled and sent to the adjudication office.<sup>62</sup>
- Assess duration and intensity of menstruation, if applicable.<sup>63</sup>
- In children randomized to rivaroxaban:
  - In case rivaroxaban is provided as tablet:
    - Administer the next rivaroxaban dose immediately followed by up to 240 ml of liquid.
  - In case rivaroxaban is provided as oral suspension:
    - Complete the pre-dose part of the Taste- and-Texture Questionnaire only for children from 4 to < 18 years
    - Administer the next rivaroxaban dose immediately followed by up to 240 ml (o.d. or b.i.d.) or up to 120ml (t.i.d.) of liquid.
    - Complete the post-dose part of the Taste- and-Texture Questionnaire only for children from 4 to < 18 years
- Document the volume and type of liquid taken
- Document the exact time of rivaroxaban intake as well as time and type of meal (i.e. breakfast, lunch, dinner) the child took in relation to rivaroxaban.

<sup>61</sup> The section was modified via Amendment 12 ( see Section 16.4.2.15)

<sup>62</sup> This section was updated via Amendment 8 (see Section 16.2.2.15)

<sup>63</sup> Assessment of time and intensity of menstruation was included via Amendment 4 (see Section 16.1.2.7).

- Blood sampling for o.d. or b.i.d. regimen (tablet and oral suspension):
  - At 0.5-1.5 hours and at 2.5-4 hours after this rivaroxaban intake, collect the PK blood sample
  - In children 6 years or older, collect a PD blood sample after the PK blood sample at both time points
  - In children < 2years with catheter related thrombosis receiving the b.i.d. regimen, a PK sample will also be collected at 10-16h after last evening dose of rivaroxaban, but before the first morning dose.
  - In children < 6 years receiving rivaroxaban b.i.d, no PD sample will be collected after the PK sample at 0.5-1.5 hours, but a PD sample will be taken after the PK sample at 2.5-4 hours
- Blood sampling for t.i.d. regimen (oral suspension):
  - At 0.5-3 hours after this rivaroxaban intake collect the PK sample, followed by the PD blood sample
  - At 7-8 hours after this rivaroxaban intake collect the PK blood sample
  - Visit 2 will be modified for children weighing < 3250 grams. The PK and PD samples taken 0.5 to 3 hours post-dose will be taken on a dosing day within the visit window (total volume to be drawn is 2.0 mL), and the 7-8 hour post-dose PK sample (total volume to be drawn is 0.6 ml) may be taken on the following dosing day within the visit window. This modification may only occur in children weighing less than 3250 kg at the time of visit 2.
- Document the exact time of rivaroxaban dosing and blood sampling for PK/PD<sup>64</sup>
- Perform drug accountability and assess compliance
- Obtain body weight and adjust the rivaroxaban dose, if applicable.
- Dispense study medication and additional supplies (devices for oral suspension)<sup>65</sup>
- Check for changes in concomitant medications
- Check for adverse events and device-related adverse events
- Instruct that on the day of visit 3, rivaroxaban should not be taken at home and that all used and unused medication/supplies should be returned to the hospital
- Update eCRF
- If a child discontinued study drug permanently before visit 2, visit 2 will still need to take place, but no blood sampling for PK/PD is required.

<sup>64</sup> This section was changed to implement new dosing regimen for children with body weight between 6 and less than 12 kg via Amendment 10 (see Section 16.3.2.6)

<sup>65</sup> Dispense of study medication was listed for consistency with the study flow chart via Amendment 4 (see Section 16.1.2.6).

**Following procedures are applicable only to children <2 years of age with catheter related thrombosis:**

- Obtain safety blood sample for hemoglobin, platelets, ALT, total and direct bilirubin.
- Repeat imaging with ultrasound, if applicable. If repeat imaging can be done with magnetic resonance imaging (MRI) or MR angiography, this should be done only if sedation and/or general anesthesia are not required. Other modalities of imaging, e.g. computed tomography (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.
- After the main 30 day study treatment period in children aged < 2 years with catheter related thrombosis, the decision is made to stop study treatment or to continue for an additional 30 days. If study treatment is stopped, the 30-day post study treatment visit (Visit 8) will be scheduled. If study treatment is continued for 30 days, a visit (Visit 3) will be schedule at day 60 ± 7 days.

**6.5 Visit 3 at Day 60 (± 7 days)<sup>66</sup>**

- Check for potential study outcomes. If a suspected study outcome occurred, an adjudication package needs to be compiled and sent to the adjudication office.<sup>67</sup>
- Assess duration and intensity of menstruation, if applicable.<sup>68</sup>
- In children randomized to rivaroxaban (tablet or oral suspension):
  - Administer the next rivaroxaban dose immediately followed by the intake of up to 240 mL (o.d. and b.i.d. regimen) or up to 120 mL (t.i.d. regimen) of liquid.
  - Document the volume and type of liquid taken.
  - Document the exact time of rivaroxaban intake as well as the time and type of meal (i.e. breakfast, lunch, dinner) the child took in relation to rivaroxaban.
  - If rivaroxaban is given using an o.d. or b.i.d. regimen, at 2-8 hours after the rivaroxaban intake, collect a PK blood sample followed by the PD blood sample.
  - If rivaroxaban is given using a t.i.d. regimen, at 2-6 hours after the rivaroxaban intake, collect a PK blood sample followed by the PD blood sample
  - Document the exact time of blood sampling for PK/PD.

<sup>66</sup> The Section was updated via Amendment 12 (see Section 16.4.2.16)

<sup>67</sup> This section was updated via Amendment 8 (see Section 16.2.2.16)

<sup>68</sup> Assessment of time and intensity of menstruation was included via Amendment 4 (see Section 16.1.2.6).

- Provide instructions for the day before visit 4
  - If rivaroxaban is given using an o.d. regimen, take rivaroxaban on the day before visit 4 at noon immediately followed by the intake of up to 240 ml of liquid
  - If rivaroxaban is given using a b.i.d. regimen, take rivaroxaban as late as possible in the evening on the day before visit 4 immediately followed by the intake of up to 240ml of liquid
  - If rivaroxaban is given using a t.i.d. regimen, take rivaroxaban night dose before visit 4 as scheduled, immediately followed by the intake of up to 120 ml of liquid
  - Document the volume and type of liquid taken
  - Document the exact time of rivaroxaban intake as well as the time and type of meal (i.e. breakfast, lunch, dinner) the child took in relation to rivaroxaban.<sup>69</sup>
- Perform drug accountability and assess compliance
- Obtain body weight and adjust the rivaroxaban dose, if applicable.
- Dispense study medication and additional supplies (devices for oral suspension)<sup>70</sup>
- Check changes in concomitant medications
- Check for adverse events and device-related adverse events
- Instruct that on the day of visit 4, all used and unused medication/supplies should be returned to the hospital
- Update eCRF
- If a child discontinued study drug permanently before visit 3, visit 3 will still need to take place, but no blood sampling for PK/PD is required.

**Following procedures are applicable only to children <2 years of age with catheter related thrombosis:**

- If study treatment is stopped, the 30-day post study treatment visit will be scheduled. If study treatment is continued for an additional 30 days, a visit (Visit 4) will be schedule at day 90 ± 7 days. If study treatment is stopped, the 30-day post study treatment visit will be scheduled

<sup>69</sup> This section was changed to implement new dosing regimen for children with body weight between 6 and less than 12 kg via Amendment 10 (see Section 16.3.2.7)

<sup>70</sup> Dispense of study medication was listed for consistency with the study flow chart via Amendment 4 (see Section 16.1.2.6).

## 6.6 Visit 4 at Day 90 ( $\pm 7$ days)<sup>71</sup>

- Check for potential study outcomes. If a suspected study outcome occurred, an adjudication package needs to be compiled and sent to the adjudication office.<sup>72</sup>
- Assess duration and intensity of menstruation, if applicable.<sup>73</sup>
- Obtain body weight if the child continues in the study for an additional 3 months and adjust the rivaroxaban dose, if applicable.
- In case child continues study treatment, instruct that on the day of visit 5, all used and unused medication/supplies should be returned to the hospital.
- In children randomized to rivaroxaban:
  - Document the exact time of rivaroxaban intake on the day prior to visit 4 and time and type of meal the child took in relation to rivaroxaban as well as the volume and type of liquid taken.
  - If rivaroxaban is given using an o.d. regimen, collect the blood sample for hemoglobin, platelets, ALT, total and direct bilirubin, followed by PK blood sample and finally the PD blood sample at 20-24h after rivaroxaban was taken on the previous day
  - If rivaroxaban is given using a b.i.d. regimen, collect the blood sample for hemoglobin, platelets, ALT, total and direct bilirubin, followed by PK blood sample and finally the PD blood sample at 10 to 16 hours after the last evening dose (in all children except those aged < 2 years with catheter related thrombosis).
  - If rivaroxaban is given using a t.i.d. regimen, collect hemoglobin, platelets, ALT, total and direct bilirubin, followed by the PD blood sample 10 to 16 hours after the last evening dose (in all children except those aged < 2 years with catheter related thrombosis).
  - If dosing continues beyond visit 4/day 90, give next dose after PD sample (in all children except those aged < 2 years with catheter related thrombosis)
  - Document the exact time of blood sampling for PK/PD.<sup>74</sup>
- Perform drug accountability and assess compliance
- Dispense study medication and additional supplies (devices for oral suspension)<sup>75</sup>
- Check changes in concomitant medications

<sup>71</sup> The section was updated via Amendment 12 (see Section 16.4.2.17)

<sup>72</sup> This section was updated via Amendment 8 (see Section 16.2.2.17)

<sup>73</sup> Assessment of time and intensity of menstruation was included via Amendment 4 (see Section 16.1.2.6).

<sup>74</sup> This section was changed to implement new dosing regimen for children with body weight between 6 and less than 12 kg via Amendment 10 (see Section 16.3.2.8)

<sup>75</sup> Dispense of study medication was listed for consistency with the study flow chart via Amendment 4 (see Section 16.1.2.6).

- Repeat imaging with ultrasound, if applicable. If repeat imaging can be done with magnetic resonance imaging (MRI) or MR angiography, this should be done only if sedation and/or general anesthesia are not required. Other modalities of imaging, e.g. computed tomography (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.
- Check for adverse events and device-related adverse events
- Perform post-thrombotic syndrome assessment (only for children  $\geq 12$  years and with lower or upper extremity DVT)
- Update eCRF

After the main 3-month study treatment period in all children except those aged  $< 2$  years with catheter related thrombosis, the decision is made to stop study treatment or to continue for an additional 3 months. If study treatment is stopped, the 30-day post study treatment visit will be scheduled. If study treatment is continued for 3 months, a visit (Visit 5) will be schedule at day  $180 \pm 7$  days. If study treatment is stopped, the 30-day post study treatment visit will be scheduled. If study treatment is continued for an additional 3 months, a visit (Visit 6) will be schedule at day  $270 \pm 7$  days. If study treatment is stopped, the 30-day post study treatment visit will be scheduled. If study treatment is continued for an additional 3 months, a visit (Visit 7) will be schedule at day  $360 \pm 7$  days.

- If a child discontinued study drug permanently before visit 4, visit 4 will still need to take place, but no blood sampling for PK/PD is required.

#### **6.7 Visit 5, Visit 6, and Visit 7 at Day 180, Day 270, Day 360 ( $\pm 7$ days)**

- Check for potential study outcomes. If a suspected study outcome occurred, adjudication package needs to be compiled and sent to the adjudication office.<sup>76</sup>
- Assess duration and intensity of menstruation, if applicable.<sup>77</sup>
- Obtain body weight at visits 5 and 6, if the child continues in the study for an additional 3 months. Adjust the rivaroxaban dose, if applicable.
- Check for adverse events and device-related adverse events.
- Perform post-thrombotic syndrome assessment (only for children  $\geq 12$  years and with lower or upper extremity DVT).
- Perform drug accountability and assess compliance.
- Dispense study medication and additional supplies (devices for oral suspension).<sup>78</sup>
- Check changes in concomitant medications.

<sup>76</sup> This section was updated via Amendment 8 (see Section 16.2.2.18)

<sup>77</sup> Assessment of time and intensity of menstruation was included via Amendment 4 (see Section 16.1.2.6).

<sup>78</sup> Dispense of study medication was listed, if applicable, for consistency with the study flow chart via Amendment 4 (see Section 16.1.2.6).

- Instruct that on the day of visits (visit 6 and visit 7, if applicable), all used and unused medication/supplies should be returned to the hospital.
- Update eCRF
- If a child discontinued study drug permanently before visit 5, 6, or 7, these visits will still need to take place.

## **6.8 Visit 8, 30-day post study treatment contact (30 days $\pm$ 7 days after last visit)<sup>79</sup>**

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 (telephone contact cannot be conducted in children who are aged  $< 2$  with catheter-related thrombosis) will take place 30 days  $\pm$  7 after the last visit of the patient. In children who prematurely discontinue study medication, this visit will take place 30  $\pm$ 7 days after premature discontinuation.<sup>80</sup>

- Check for potential study outcomes. If a suspected study outcome occurred, an adjudication package needs to be compiled and sent to the adjudication office.
- Check for adverse events.
- Document if anticoagulant treatment was continued or interrupted after stopping study medication.
- Update eCRF.

### **Following procedures are applicable only to children $< 2$ years of age with catheter related thrombosis:**

- This visit cannot occur by telephone
- Check changes in concomitant medications
- Obtain PD blood sample
  - If the patient is started on another anticoagulant during the 30 day post study treatment period, the PD sample needs to be taken at least 8 hours after last dose of rivaroxaban and before initiation of a new anticoagulant.

## **6.9 Unscheduled visits**

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

<sup>79</sup> The Section was updated via Amendment 12 ( see Section 16.4.2.18).

<sup>80</sup> This section was corrected via Amendment 8 (see Section 16.2.2.19).



## 6.10 Safety outcomes

The primary safety outcome is the composite of overt 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.

## 6.11 Recommendations before and after invasive procedures and surgical intervention

If an invasive procedure or surgical intervention is required, rivaroxaban should be stopped at least 24 hours before the intervention, if possible and based on the clinical judgment of the physician.

If the procedure cannot be delayed, the increased risk of bleeding should be assessed against the urgency of the intervention.

Rivaroxaban should be restarted after the invasive procedure or surgical intervention within 24 hours, provided the clinical situation allows and adequate hemostasis has been established.

For the comparator please follow the respective product label.

## 6.12 Management of bleeding in children

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

- 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
- Consider usual treatment for bleeding, including blood transfusion, and/or fresh frozen plasma
- If the child is treated with rivaroxaban, 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):

- 4-factor concentrate
- recombinant factor VIIa (NovoSeven<sup>®</sup>)

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

## 6.13 Efficacy outcomes

The primary efficacy outcome will be the composite of all symptomatic recurrent venous thromboembolism as confirmed by the CIAC. The secondary efficacy outcome will be the composite of all symptomatic recurrent venous thromboembolism and asymptomatic deterioration on repeat imaging,<sup>[3],[10]</sup> as assessed by the CIAC.

## 6.14 PK/PD assessments<sup>81</sup>

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

Blood samples will be taken for PK and PD measurements from children randomized to rivaroxaban.

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<sup>81</sup> The Section was updated via Amendment 12 (see Section 16.4.2.19)

The following blood samples will be taken in children without catheter related thrombosis and with

- **o.d. (children with body-weight > 30 kg) or b.i.d. (children with body weight 12-30 kg) regimen:**
  - two post-dose PK/PD samples at visit 2 (no PD sample at 0.5-1.5 hours for children < 6 years)
  - one post-dose PK/PD sample at visit 3, and
  - one pre-dose PK/PD sample at visit 4.
- **t.i.d. regimen (children with body-weight < 12 kg) :**
  - two post-dose PK samples at visit 1a
  - two post-dose PK samples at visit 2
  - one post-dose PD sample at visit 2, and
  - one post-dose PK/PD sample at visit 3, and
  - one pre-dose PD sample at visit 4.<sup>82</sup>

The following blood samples will be taken in children aged < 2 years with catheter related thrombosis and

- **b.i.d regimen (children with body weight  $\geq 12$  kg):**
  - one pre-dose PK sample at visit 2
  - two post-dose PK/PD samples at visit 2, and
  - one post-dose PK/PD sample at visit 3, if occurs, and
  - one PD sample at visit 8
- **t.i.d regimen (children with body weight <12 kg)**
  - two post-dose PK sample at visit 1a, and
  - two post-dose PK sample at visit 2
  - one post-dose PD sample at visit 2, and
  - one post-dose PK/PD sample at visit 3, if occurs, and
  - one PD sample at visit 8

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.

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<sup>82</sup> Blood samples were added for new dosing regimen for children with body weight between 6 and less than 12 kg via Amendment 10 (see Section 16.3.2.9)

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

If a blood sample is taken from a central line, it is recommended to discard 3 mL of blood. For small children a smaller volume can be discarded and sites can follow their own practical standard.<sup>[16]</sup> At visit 3, in children from 6 months to 1 year, it is advised to withdraw blood from a peripheral catheter rather than a central venous line to limit the volume of required blood. If a blood sample is taken from a peripheral catheter, fluid has to be withdrawn until all fluid is removed. For venipunctures, an anesthetic cream can be applied. Heparin can be used to maintain catheter patency; however, before collecting PK/PD samples, the catheter needs to be flushed with saline. A first volume of (diluted) blood should be discarded, as usual.<sup>83</sup>

Detailed information about the handling and labeling of the samples will be provided in the laboratory manual. To estimate the PK/PD profile of rivaroxaban, results will be pooled and analyzed using population approaches. Details for the population PK/PD analysis will be described in a separate evaluation plan

## 6.15 Study booklet

Parents/children will receive a booklet/patient card, specifying for both treatment groups:

- The local medical contact person and local emergency telephone number
- The dates of hospital visits and telephone calls, if applicable
- Instructions to return empty medication packages and unused study medication
- Instructions on signs and symptoms of bleeding.

For the rivaroxaban treatment group:

- How to take rivaroxaban
- Calendar to track the date, time and type of food and study drug intake as well as the volume of liquid taken

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).

## 6.16 Study committees

### 6.16.1 Steering committee

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

- To facilitate and approve the final protocol

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<sup>83</sup> Catheter flushes with heparin are added as allowed via Amendment 4 (see Section 16.1.2.12)

- 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 monitor progress of study enrollment
- To assist in the analysis and presentation of the results
- To decide on the publication and presentation policy of final results.

### **6.16.2 Central independent adjudication committee (CIAC)**

All index venous thrombotic events, and all suspected recurrent venous thromboembolic events, asymptomatic deterioration of the thrombotic burden on repeat imaging, bleeding, other vascular events and deaths that occur during the study and the 30-day post study treatment period, will be evaluated by a CIAC. For all index events and study outcomes, the requirement to complete a worksheet and to compile an adjudication package and to send it to adjudication office within 2 weeks from randomization or occurrence of the event, respectively. The CIAC procedures will be described in an adjudication manual. Adjudication results will be the basis for the final analyses.

### **6.16.3 Data monitoring committee (DMC)**

This committee has the responsibility to provide the steering committee and the sponsor with recommendations related to the protection of the children's safety, including stopping recruitment and study treatment. For that purpose, the DMC will regularly review all incidences of serious adverse events, recurrent venous thromboembolic events and bleedings. 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. Any revision will be clearly identified in the final SAP, issued prior to data base lock. All efforts will be taken to avoid missing data in important baseline characteristics and post baseline data. Missing data proportions will be reported.

### **7.2 Analysis sets**

Full analysis set: this population will include all randomized children. Safety analysis set: this population will include all randomized children who received at least one dose of study medication. Per-protocol set: the per-protocol set may exclude subjects with major protocol deviations. The detailed list of these deviations will be finalized prior to database lock and included in the protocol deviation document, the approved final list of important deviations,

validity findings and assignment to analysis set(s).<sup>84</sup> Listing only set (LOS): this population includes all screening failures.

### 7.3 Demographic and other baseline characteristics

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

### 7.4 Bleeding analysis<sup>85</sup>

All safety analyses will be performed on the safety analysis set. All bleeding events that occurred during study treatment or within 2 days after stop of study medication will be summarized by treatment group. Bleeding events observed more than 2 days after stop of study medication will be described separately. Individual listings of major and clinically relevant non-major bleeding events will be provided.

Incidence proportions (number of children with outcome during the period divided by number of children at risk at the beginning of the period) and cumulative incidences (time to first event; Kaplan-Meier) will be calculated for the primary safety outcome by treatment group at the end of the main study treatment period for pooled data. Incidence proportions will be calculated for each age stratum at the end of the main study treatment period as well. In addition, incidence proportions will be calculated by treatment group for each age stratum and pooled data overall in the extended study treatment period at 2 and 3 months (for the children <2 years with catheter related thrombosis) and at 6, 9 and 12 months (for the other groups). Denominators in this case will be the number of patients at risk at the start of the respective period.

Incidence proportions of other bleeding outcomes and components including duration and intensity of menstrual bleeding will be presented descriptively.<sup>86</sup>

### 7.5 Efficacy analysis<sup>87</sup>

All efficacy analyses will be performed on the full analysis set population based on the outcomes confirmed by the CIAC. Incidence proportions and cumulative incidences (time to first event; Kaplan-Meier) will be calculated for the primary and secondary efficacy outcomes by treatment group at the end of the main study treatment period for pooled data. In addition, incidence proportions will be calculated for each age stratum at the end of the main study treatment period. Incidence proportions will be calculated for the primary outcomes by treatment group for each age stratum and pooled data overall in the extended study treatment period at 2 and 3 months (for the children <2 years with catheter related thrombosis) and, at 6,

<sup>84</sup> The description for the major protocol deviation documentation was corrected via Amendment 10 (see Section 16.3.2.10)

<sup>85</sup> The Section was updated via Amendment 12 (see Section 16.4.2.20)

<sup>86</sup> Duration and intensity of menstruation was included via Amendment 4 (see Section 16.1.2.13)

<sup>87</sup> The Section was updated and subgroup analysis added according to Amendment 12 (see Section 16.4.2.21)

9 and 12 months (for the other groups). Denominators will be the number of patients at risk at the start of the respective period.

Data of post-thrombotic syndrome assessment in children  $\geq 12$  years with lower or upper extremity DVT will be presented descriptively. Duration of treatment for the main treatment period (up to month 3) and the overall treatment duration will be summarized descriptively by treatment group.

Results for the Taste-and-Texture Questionnaire in children 4 to  $< 18$  years who receive the oral suspension will be presented descriptively.<sup>88</sup>

### **Subgroup analysis**

Demographic and other baseline characteristics, as well as efficacy, safety and PK/PD data will be summarized for the main treatment period (up to the month 3 visit) for each age group and for combinations of age groups.

## **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 relation of anticoagulant parameters of rivaroxaban with plasma concentrations. Details will be given in a separate PK/PD evaluation plan.

## **7.7 Interim analyses**

No interim analysis will be performed.

## **7.8 Determination of sample size<sup>89</sup>**

At least 170 children 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.

## **7.9 Adverse events**

Individual listings of adverse events 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.

For the purpose of adverse event (AE) documentation, study drug is defined as either rivaroxaban or standard of care as allocated starting from randomization up to the end of study treatment visit.

### **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

<sup>88</sup> Statistical analysis of Taste- and Texture questionnaire and PTS was added via Amendment 8 (see Section 16.2.2.20)

<sup>89</sup> The minimum number of children was increased via Amendment 12 (see Section 16.4.2.22)

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 the study 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 randomization. If the condition started or deteriorated after randomization, it will be documented as adverse event.

### **7.9.1.2 Serious adverse event (SAE)**

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

### **7.9.1.3 Unexpected AEs**

An unexpected AE is any adverse drug event whose specificity or severity is not consistent with the investigator brochure or package inserts for marketed products. Also, reports which add significant information on specificity or severity of an already documented AE constitute unexpected AEs, e.g. 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 study drug 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 study drug. 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 study 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 study drug. Factors in assessing the relationship of the AE to study drug include the temporal sequence from drug administration (the event should occur after the study drug is given) and the length of time from study drug



exposure, recovery on study drug discontinuation (de-challenge), and recurrence on study 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 drug.

### **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 drug 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 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**

After randomization, 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 randomization up to 1 month after the last study drug administration 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**

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 needs to be reported only for rivaroxaban study treatment and will be determined by Bayer according to the applicable reference document and according to all local regulations.

### **7.9.9 AEs of special interest**

The following AEs are of special interest:

- Concurrent elevations of ALT > 5x ULN and total bilirubin > 2x ULN
- A platelet count below  $50 \times 10^9/L$
- Allergic skin reactions, allergic systemic reactions.

### **7.9.10 Adverse events related to devices used for preparation and administration of rivaroxaban oral suspension**

#### **7.9.10.1 Definitions**

##### **7.9.10.1.1 Incident**

An "Incident" is any malfunction or deterioration in the characteristics and / or performance of a device, as well as any inadequacy in the labeling or the instructions for use which, directly or indirectly, led, might lead to or might have led to the death of a patient, or user or of other persons or to a serious deterioration in their state of health.

Any event which meets all three basic reporting criteria (A, B and C) is considered an "Incident". The criteria are as follows:

- A) An adverse device event has occurred. Typical adverse events in the context of device could be among others:
- Malfunction or deterioration in the characteristics or performance, or
  - Degradation / destruction of the device, or
  - Inappropriate therapy (e.g., underdosing or overdosing).

- B) The device is suspected to be a contributory cause of the “*Incident*”.
- C) The event led, or might have led, to death or serious deterioration in state of health of a patient, or user, or other person.

#### **7.9.10.1.2 Other Reportable Incident**

An “*Other Reportable Incident*” is any incident that did not lead to death or serious deterioration in health, but it might do if it occurred again under less fortunate circumstances or without intervention of healthcare personnel. This may include cases without any medical event reported.

#### **7.9.10.1.3 Other Event**

An “*Other Event*” is any device related case that does not fulfill all the three basic “*Incident*” criteria A-C listed in the definition of an “*Incident*” above.

#### **7.9.10.1.4 Product Technical Complaint (PTC)**

A PTC is any report received (written, electronic or verbal communication) about a potential or alleged failure of a product in its quality (including the identity, durability, reliability, safety, efficacy or performance) or suspect counterfeit. The complaint may or may not represent a potential risk to the patient.

#### **7.9.10.2 Device Malfunction or Failure and Medical Device Reporting**

Any device complaint, malfunction, or failure including use errors will be recorded by the clinical/investigational site, including all relevant device information using the clinical investigations device complaint form, and forwarded within 24 hours to the sponsor or sponsor’s designee for evaluation and investigation, regardless of whether or not a medical event was associated with the device malfunction or failure.

There are three different situations, in which a medical device complaint form might need to be filled out by the investigator:

- a) When an AE is recorded, the investigator needs to check if a device malfunction or failure might be associated with the recorded AE.
- b) When a device malfunction or device failure occurs, the investigator needs to assess whether an AE might have occurred in relation to the device.
- c) When a device malfunction, device failure, or use error occurs, without any associated AE, this also needs to be captured in the form and immediately forwarded to the sponsor for investigation.

The details of the malfunction and medical circumstances will be captured on a Device Complaint Form filled out by the investigator and then returned to the sponsor or sponsor’s designee. The final determination of reportability is made by the sponsor and not the clinical/investigational site based on the medical circumstances surrounding the event.

#### **Investigator’s notification of the sponsor**

All investigators will be instructed and trained on all relevant aspects of the investigator’s reporting obligations for device incidents and serious public health threats. This information,

including all relevant contact details, is summarized in the investigator site file. This information will be updated as needed.

The manufacturer will inform the sponsor about necessary trend reports and will provide the required documentation after completing the respective investigation and statistical analysis. The sponsor will then notify the authorities of any trend reports according to all applicable regulations.

All devices that have malfunctioned or failed will be collected and returned to the sponsor or sponsor's designee. Malfunctioned or failed devices should be:

- provided with a failure description („What went wrong“),
- free of sources for contamination such as drug residues,
- clearly marked as already used at patients and shall include corresponding warning symbols on packaging.

## **7.10 Premature discontinuation of study drug**

Children prematurely discontinue study drug

- 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 drug should be stopped for any reason.
- at the (exceptional) request of Bayer.

If study drug is temporarily discontinued, it can be restarted. If study drug is permanently discontinued, further treatment is at the investigator's discretion.

If the child or parents/legal representatives withdraws consent to treatment with study drug (including comparator), 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 representatives state to the investigator that they no longer authorize to continue to obtain outcome data, this will be respected and documented in the source records, and no further study data will be collected.

In all children who prematurely discontinue study drug for other reasons than withdrawal of informed consent, study visits will take place as planned to collect potential study outcomes and AEs.

## **7.11 Pregnancies**

The investigator must report to the sponsor any pregnancy occurring in a study subject, or in the study subject's partner, during the subject's participation in this study. The report should be submitted within the same timelines as an SAE, although a pregnancy per se is not considered an SAE. The outcome of the pregnancy should be followed up carefully, and any outcome of the mother or child should be reported. For the pregnancy of a study subject's partner, all efforts should be made to obtain similar information on course and

outcome, subject to the partner's consent. For all reports, the forms provided are to be used.

### **7.12 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, and 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) 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 participation in the study at any time.

Bayer has the right to close this study or study sites at any time, which may be due but not limited to the following reasons:

- 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 European Union (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, an informed consent and an informed assent form provided by Bayer or the study center. A sample child information and informed consent and assent form are provided as documents separate to this protocol. Consent will be asked from the parent(s)/ legal guardian(s) and, if appropriate as determined by local regulation, age and individual child capability, will be asked from the child, according to country-specific regulations.

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.

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) voluntarily agree to sign and date the informed consent and the child provides informed consent or assent, as appropriate and determined by local regulation, age and individual child capability, and have done so. Then the investigator or designee will sign and date the forms. The parent(s)/legal guardian(s) and the child, if applicable, will receive a copy of the signed and dated form(s).

The signed informed consent and the assent form will remain in the investigator site file or, if locally required, in the child's file.

The informed consent/assent form and any other written information provided to the child/parents/legal guardians will be revised whenever important new information becomes 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/assent form. The investigator will inform the child/parents/legal guardian of changes in a timely manner and will ask the parents/legal guardians and the child, if applicable, to confirm participation in the study by signing the revised informed consent, and, if applicable, will ask the child to provide informed assent as documented on the revised assent form. Revised informed consent/assent form and the child information sheet must receive the IEC's/IRB's approval before implementation.

In the event that informed consent is obtained on the date that baseline study procedures are performed, the study record or subject's clinical record must clearly show that informed consent was obtained prior to these procedures.

## **11. Investigators and other study participants**

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 at [www.clinicaltrials.gov](http://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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## 16. Protocol amendments

### 16.1 Amendment 4

#### 16.1.1 Overview of changes

Amendment 4 is the first global amendment dated 21 Jul 2015.

##### 16.1.1.1 Modification 1: Minor clarifications for consistency

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

*Rationale:*

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

*Affected protocol section:*

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<sup>90</sup> A reference was added via Amendment 8 (see Section 16.2.2.22)

<sup>91</sup> A reference was added via Amendment 12 (see Section 16.4.2.23)

Synopsis, Section 4.3 Exclusion criteria, Section 5.1 Method of treatment allocation, Section 6.3 Visit 2 at Day 30 ( $\pm 7$  days), Section 6.4 Visit 3 at Day 60 ( $\pm 7$  days), Section 6.5 Visit 4 at Day 90 ( $\pm 7$  days), Section 6.6 Visit 5, Visit 6, and Visit 7 at Day 180, Day 270, Day 360 ( $\pm 7$  days),

#### **16.1.1.2 Modification 2: Implementation of dosing regimen for children from 6 to <12 years**

The dosing schedule/regimen for the age group from 6 to <12 years was included.

*Rationale:*

The body weight adjusted dosing regimen was confirmed for the age group between 6 and less than 12 years in the phase II study (14373). Therefore, the dosing schedule/regimen for this age group was included.

*Affected protocol section:*

Section 3 Study design, Section 5.1.1 Rivaroxaban group, New Section 17.5 Appendix 5: Dosing table for children from 6 to <12 years

#### **16.1.1.3 Modification 3: Inclusion of menstruation intensity assessments**

The protocol was adjusted throughout to reflect that the intensity of menstruation has to be assessed from visit 2 to visit 7.

*Rationale:*

For sufficient evaluation of the occurrence of menorrhagia during the study treatment period, the intensity of menstruation has to be assessed.

*Affected protocol section:*

Synopsis, Section 6.3 Visit 2 at Day 30 ( $\pm 7$  days), Section 6.4 Visit 3 at Day 60 ( $\pm 7$  days), Section 6.5 Visit 4 at Day 90 ( $\pm 7$  days), Section 6.6 Visit 5, Visit 6, and Visit 7 at Day 180, Day 270, Day 360 ( $\pm 7$  days),

#### **16.1.1.4 Modification 4: Addition of information on how to treat children turning 2, 6, 12 or 18 years**

Information was provided on continuing age- and body-weight adjusted treatment in children who turn 2, 6, 12 and 18.

*Rationale:*

In this study, children are allocated to age cohorts from 6 months to <2 years, 2 to <6 years, 6 to <12 years, and 12 to <18 years. If a child turns to the next highest age- group, a rule had to be implemented how to proceed with the treatment. Children will continue treatment according to age- and body weight dependent dosing of their inclusion age cohort.

*Affected protocol section:*

[Section 5.3 Duration of study treatment](#)

#### **16.1.1.5 Modification 5: Addition of allowing heparin flushes for catheters**

Heparins flushes were added to maintain catheter patency.

*Rationale:*

Heparin flushes are more effective to maintain the peripheral catheter patency than saline flushes. Therefore, it was decided to allow heparin flushes except for flushes before PK/PD samples. These have to be performed with saline to avoid biased PK/PD results.

*Affected protocol section:*

[Section 6.13 PK/PD assessments](#)

#### **16.1.1.6 Modification 6: Addition of instructions on how to take rivaroxaban with an o.d. and b.i.d. regimen in children aged 6 to < 12 years**

Instructions for rivaroxaban administration with an o.d. and b.i.d. regimen for children aged 6 to < 12 years were added.

*Rationale:*

The addition of the dosing table for children aged 6 to < 12 years required instructions on how to administer rivaroxaban on an o.d. and b.i.d. regimen, respectively.

*Affected sections:* [Section 5.1.1 Rivaroxaban group](#)

#### **16.1.1.7 Modification 7: Addition of handling instructions for missed doses**

Instructions for handling of missed doses are provided for o.d. and bid dosing in children aged 6 to < 12 years.

*Rationale:*

With the implementation of the dosing regimen for children from 6 to < 12 years handling of missed doses needed to be clarified. Rather than adding these instructions to the section “6 to < 12 years age group”, the respective text was deleted in the description of the age cohort “12 to < 18 years age group”, and a new paragraph, applicable to all age groups was added.

*Affected sections:* [Section 5.1.1 Rivaroxaban group](#)

## 16.1.2 Changes to the protocol text

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

### 16.1.2.1 Synopsis

This section was changed based on Modifications 1 and 3.

*Old text:*

<b>Comparator study drug</b>	Subcutaneous low molecular weight heparin (LMWH), subcutaneous fondaparinux and/or oral vitamin K antagonist (VKA)
	[...]
<b>Inclusion/exclusion criteria</b>	<p>[...]</p> <p>5. Hypertension defined as &gt; 95th age percentile <sup>a</sup></p> <p>6. [...]</p> <p>7. 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</p> <p>[...]</p> <p>12. Participation in a study with an investigational drug or medical device within 30 days prior to randomization</p> <p><sup>a</sup>See Appendix 3</p>

*New text:*

<b>Comparator study drug</b>	Subcutaneous low molecular weight heparin (LMWH), subcutaneous fondaparinux, <u>intravenous unfractionated heparin (UFH)</u> and/or oral vitamin K antagonist (VKA)
	[...]
<b>Inclusion/exclusion criteria</b>	<p>5. Hypertension defined as <u>systolic and/or diastolic blood pressure</u> <math>\geq</math> 95<sup>th</sup> age percentile <u>(See Appendix 3)</u></p> <p>6. [...]</p> <p>7. 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 <u>(fluconazole is allowed)</u></p> <p>[...]</p> <p>12. <u>Previous assignment to treatment during this study</u></p> <p>13. Participation in a study with an investigational drug or medical device within 30 days prior to randomization</p>

Old text:

**Table 1-1 Flow chart**

Visit	Main Treatment period				Extended treatment period with blocks of 3 months			30-day post study treatment	
	1	2	3	4	5	6	7	8	
Days	Before random.	After random.	Day 30 ± 7 days	Day 60 ± 7 days	Day 90 ± 7 days	Day 180 ± 7 days	Day 270 ± 7 days	Day 360 ± 7 days	30 ± 7 days After last visit
Contact	Visit	Visit	Visit	Visit	Visit	Visit	Visit	Visit	Visit or phone
[...]									
Obtain body weight <sup>d</sup>					● <sup>d</sup>	● <sup>d</sup>	● <sup>d</sup>		
Check for study outcomes <sup>e</sup>			●	●	●	●	●	●	●

[...]

New text:

**Table 1-1 Flow chart**

Visit	Main Treatment period				Extended treatment period with blocks of 3 months			30-day post study treatment	
	1	2	3	4	5	6	7	8	
Days	Before random.	After random.	Day 30 ± 7 days	Day 60 ± 7 days	Day 90 ± 7 days	Day 180 ± 7 days	Day 270 ± 7 days	Day 360 ± 7 days	30 ± 7 days After last visit
Contact	Visit	Visit	Visit	Visit	Visit	Visit	Visit	Visit	Visit or phone
[...]									
Obtain body weight <sup>d</sup>					● <sup>d</sup>	● <sup>d</sup>	● <sup>d</sup>		
<u>Assess duration and intensity of menstruation, if applicable</u>			●	●	●	●	●	●	
Check for study outcomes <sup>e</sup>			●	●	●	●	●	●	●

[...]

### 16.1.2.2 Section 3 Study design

This section was changed based on Modification 4.

Old text: [...]

Once the age-and body weight adjusted dosing regimen has been confirmed for the age group between 6 and less than 12 years in the phase II study 14373 and approved by the data monitoring committee and steering committee, the dosing schedule/regimen for this age group will be made available through an administrative amendment. The investigators and ethics committees/IRBs will receive the administrative amendment well in advance with an opportunity for evaluation before permission will be given to start enrolling children in this age group.

[...]

*New text:* [...]

Once the age-and body weight adjusted dosing regimen has been confirmed for the age group between 6 and less than 12 years in the phase II study 14373 and approved by the data monitoring committee and steering committee, the dosing schedule/regimen for this age group will be made available through an administrative amendment (For tablet, this was implemented through Amendment 4). The investigators and ethics committees/IRBs will receive the administrative amendment well in advance with an opportunity for evaluation before permission will be given to start enrolling children in this age group.

[...]

### 16.1.2.3 Section 4.3 Exclusion criteria

This section was changed based on Modification 1.

*Old text:* [...]

5. Hypertension defined as > 95th age percentile
6. Life expectancy < 3 months
7. 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. For exceptions, see section 4.4.

[...]

*New text:* [...]

5. Hypertension defined as systolic and/or diastolic blood pressure > 95th age percentile
6. Life expectancy < 3 months
7. 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). For exceptions, see section 4.4.

[...]

### 16.1.2.4 Section 5.1 Method of treatment allocation

This section was changed based on Modification 1.

*Old text:* [...]

The investigator will provide the IxRS with study center identification, the child's date of birth (month and year), gender, weight and clinical presentation. Allocation will be stratified by baseline presentation of venous thrombosis for each age group, separately, i.e.

[...]

*New text:* [...]

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. Allocation will be stratified by baseline presentation of venous thrombosis for each age group, separately, i.e.

[...]



### 16.1.2.5 Section 5.1.1 Rivaroxaban group

This section was changed based on Modifications 1, 2, 6 and 7.

*Old text:* **12 to < 18 years age group**

Rivaroxaban will be dosed according to the dosing schedule/regimen for the 12 to < 18 years age group (see Appendix 4).

Tablets will be taken once daily in the morning within 2 hours after breakfast and immediately followed by the intake of up to 240 mL of liquid. ~~If a rivaroxaban tablet dose was missed, it can only be taken the same day. Double dosing of tablets on a single day is not allowed.~~

**6 to < 12 years age group**

The dosing schedule/regimen will become available as an administrative amendment to this protocol once it has been confirmed for this age group in the phase II study 14373 and approved by the data monitoring committee and steering committee.

~~The dosing schedule/regimen will specify whether rivaroxaban tablet should be given using a once daily or twice daily regimen. Oral suspension will be given using a twice daily regimen.~~

Rivaroxaban tablets and oral suspension will be immediately followed by the intake of up to 240 mL of liquid.

**2 to < 6 years age group**

Rivaroxaban will be provided as oral suspension. The dosing schedule/regimen will become available as an administrative amendment to this protocol once it has been confirmed for this age group in the phase II study 14374 and approved by the data monitoring committee and steering committee.

~~Oral suspension will be given using a twice daily regimen and~~ will be immediately followed by the intake of up to 240 mL of liquid.

**6 months to < 2 years age group**

Rivaroxaban will be provided as oral suspension. The dosing schedule/regimen will become available as an administrative amendment to this protocol once the age-and body weight adjusted dosing regimen has been confirmed for this age group in the phase II study 14374 and approved by the data monitoring committee and steering committee.

~~Oral suspension will be given using a twice daily regimen and~~ will be immediately followed by the intake of up to 240 mL of liquid.

**Use of oral suspension**

Oral suspension will not be used in the 12 to < 18 years age group. It can be used in children aged 6 to < 12 years, and will be used in all children aged 6 months to < 6 years. Oral suspension ~~will always be taken twice daily and~~ should be immediately followed by the intake of up to 240 mL of liquid. The Taste and Texture Questionnaire, using a visual analog scale, will be applied to determine the acceptance of the oral suspension in children from 4 to < 12 years. The pre-dose part of this questionnaire needs to be completed before rivaroxaban suspension is taken, the post-dose part of this questionnaire needs to be completed after rivaroxaban suspension dose is taken and up to 240 mL of liquid has been taken.

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

*New text:* **12 to < 18 years age group**

Rivaroxaban will be dosed according to the dosing schedule/regimen for the 12 to < 18 years age group (see Appendix 4).

Tablets will be taken once daily in the morning within 2 hours after breakfast and immediately followed by the intake of up to 240 mL of liquid

**6 to < 12 years age group**

Rivaroxaban will be provided with the option of tablets or oral suspension. The dosing schedule/regimen for rivaroxaban tablet is provided in Appendix 5 (implemented through Amendment 4). The dosing schedule/regimen for rivaroxaban oral suspension will become available as an administrative amendment to this protocol once it has been confirmed for this age group in the phase II study 14373 and approved by the data monitoring committee and steering committee.

With an o.d. regimen, rivaroxaban will be taken in the morning within 2 hours after breakfast. With a b.i.d regimen the morning dose will be Rivaroxaban tablets taken within 2 hours after breakfast and the evening dose will be taken within 2 hours after dinner. Each rivaroxaban dose should be immediately followed by the intake of up to 240 mL of liquid.

**2 to < 6 years age group**

Rivaroxaban will be provided as oral suspension. The dosing schedule/regimen will become available as an administrative amendment to this protocol once it has been confirmed for this age group in the phase II study 14374 and approved by the data monitoring committee and steering committee.

Oral suspension will be immediately followed by the intake of up to 240 mL of liquid.

**6 months to < 2 years age group**

Rivaroxaban will be provided as oral suspension. The dosing schedule/regimen will become available as an administrative amendment to this protocol once the age-and body weight adjusted dosing regimen has been confirmed for this age group in the phase II study 14374 and approved by the data monitoring committee and steering committee.

Oral suspension will be immediately followed by the intake of up to 240 mL of liquid.

**Use of oral suspension**

Oral suspension will not be used in the 12 to < 18 years age group. It can be used in children aged 6 to < 12 years, and will be used in all children aged 6 months to < 6 years. Oral suspension should be immediately followed by the intake of up to 240 mL of liquid. The Taste and Texture Questionnaire, using a visual analog scale, will be applied to determine the acceptance of the oral suspension in children from 4 to < 12 years. The pre-dose part of this questionnaire needs to be completed before rivaroxaban suspension is taken, the post-dose part of this questionnaire needs to be completed after rivaroxaban suspension dose is taken and up to 240 mL of liquid has been taken.

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

**Handling of missed doses**

If rivaroxaban is taken with an o.d. regimen, a missed dose should be taken immediately when it is noticed, but only on the same day. Double dosing on a single day is not allowed.

If rivaroxaban is taken with a b.i.d. regimen, a missed morning dose should be taken immediately when it is noticed, and it may be taken together with the evening dose. A missed evening dose can only be taken at the same evening.

On the following day, the child should continue with the regular o.d. or b.i.d. regimen.

### 16.1.2.6 Section 5.3 Duration of study treatment

This section was changed based on Modification 1.

*Old text:* [...]

Thereafter, no prolongation of study treatment can take place. ~~Children~~ who turn 18 years after randomization are allowed to continue participation for the entire elected study treatment duration of 3, 6, 9 or 12 months.

[...]

*New text:* [...]

Thereafter, no prolongation of study treatment can take place. Children who turn 2, 6, 12 or 18 years after randomization can continue their treatment regimen. Specifically children who turn 18 years after randomization are allowed to continue participation for the entire elected study treatment duration of 3, 6, 9 or 12 months.

[...]

### 16.1.2.7 Section 6.2 Visit 1 - Randomization Visit

This section was changed based on Modification 1.

*Old text:* [...]

The parents/legal guardians and children will be given an explanation about the study and will be given sufficient time to consider their participation in the study and to ask any questions. Afterwards, informed consent and/or assent will be obtained (see section 10.2). If the child passes the screen of inclusion and exclusion criteria, the child can be randomized. Then,

- Provide instructions how to take the study drug and give the study booklet

[...]

*New text:* [...]

The parents/legal guardians and children will be given an explanation about the study and will be given sufficient time to consider their participation in the study and to ask any questions. Afterwards, informed consent and/or assent will be obtained (see section 10.2). If the child passes the screen of inclusion and exclusion criteria, the child can be randomized. Then,

- Provide instructions on how to take the study drug and give the study booklet
- Dispense study medication

[...]

### 16.1.2.8 Section 6.3 Visit 2 at Day 30 ( $\pm 7$ days)

This section was changed based on Modifications 1 and 3.

*Old text:* [...]

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

[...]

*New text:* [...]

- Check for potential study outcomes. If a suspected study outcome occurred, an adjudication package will be compiled and sent to the adjudication office. Assess duration and intensity of menstruation, if applicable.
- Dispense study medication

[...]

### 16.1.2.9 Section 6.4 Visit 3 at Day 60 ( $\pm 7$ days)

This section was changed based on Modifications 1 and 3.

*Old text:* [...]

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

[...]

*New text:* [...]

- Check for potential study outcomes. If a suspected study outcome occurred, an adjudication package needs to be compiled and sent to the adjudication office. Assess duration and intensity of menstruation, if applicable.
- Dispense study medication

[...]

#### **16.1.2.10 Section 6.5 Visit 4 at Day 90 ( $\pm$ 7 days)**

This section was changed based on Modifications 1 and 3.

*Old text:* [...]

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

[...]

*New text:* [...]

- Check for potential study outcomes. If a suspected study outcome occurred, an adjudication package needs to be compiled and sent to the adjudication office. Assess duration and intensity of menstruation, if applicable.
- Dispense study medication

[...]

#### **16.1.2.11 Section 6.6 Visit 5, Visit 6, and Visit 7 at Day 180, Day 270, Day 360 ( $\pm$ 7 days)**

This section was changed based on Modifications 1 and 3.

*Old text:* [...]

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

[...]

*New text:* [...]

- Check for potential study outcomes. If a suspected study outcome occurred, adjudication package needs to be compiled and sent to the adjudication office. Assess duration and intensity of menstruation, if applicable.
- Dispense study medication, if applicable.

[...]

#### 16.1.2.12 Section 6.13 PK/PD assessments

This section was changed based on Modifications 5.

*Old text:* [...]

For venipunctures, an anesthetic cream can be applied. ~~Central venous lines and peripheral catheters should only be flushed with saline. Heparin flushes are not allowed.~~

[...]

*New text:* [...]

For venipunctures, an anesthetic cream can be applied. Heparin can be used to maintain catheter patency; however, before collecting PK/PD samples, the catheter needs to be flushed with saline. A first volume of (diluted) blood should be discarded, as usual.

[...]

#### 16.1.2.13 Section 7.4 Bleeding analysis

This section was changed based on Modifications 3.

*Old text:* [...]

Incidence proportions of other bleeding outcomes and components will be presented descriptively.

[...]

*New text:* [...]

Incidence proportions of other bleeding outcomes and components including duration and intensity of menstrual bleeding will be presented descriptively.

[...]

#### 16.1.2.14 New Section 17.5 Appendix 5: Dosing table for children from 6 to <12 years

This section was added based on Modifications 4.

*New text:*

#### Appendix 5: Dosing table for children from 6 to <12 years

**Table 17-2 Body weight-adjusted rivaroxaban dosing schedule for children aged 6 to < 12 years**

<u>Body weight (kg)</u>		<u>20 mg equivalent</u>		
<u>Min</u>	<u>Max</u>	<u>o.d. Dose</u>	<u>b.i.d. Dose</u>	<u>Total Daily Dose</u>
<u>12</u>	<u>&lt;20<sup>a</sup></u>		=	=
<u>20</u>	<u>&lt;30</u>		<u>5 mg</u>	<u>10 mg</u>
<u>30</u>	<u>&lt;50</u>	<u>15 mg</u>		<u>15 mg</u>
	<u>≥ 50</u>	<u>20 mg</u>		<u>20 mg</u>

<sup>a</sup> Children with body weight below 20 kg can only receive oral suspension.

## 16.2 Amendment 8

Amendment 8 is the second global amendment dated 20 Sep 2016.

### 16.2.1 Overview of changes

#### 16.2.1.1 Modification 1: Change of sponsorship information

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

*Rational:*

PPD



*Affected sections:*

Title page; Study center's principal investigator agrees to the content of the final clinical study protocol as presented.

### **16.2.1.2 Modification 2: Change of non-emergency medical and protocol issues contact**

The non-emergency medical and protocol issues contact was updated.

*Rational:*

The update of the contact details for non-emergency medical and protocol issues reflect the change of the responsible Study Medical Expert.

*Affected sections:*

[Title page](#)

### **16.2.1.3 Modification 3: Extension of the randomization timeframe**

The timeframe in which randomization can be done was extended from day 1-5 to day 1-9 of the initial treatment.

*Rational:*

Children with venous thrombosis are often referred by their doctors to expert centers for institution of continued anticoagulation following initial heparinization. The original time window limited randomization to day 1-5. Therefore, children referred on days 6-9 were not eligible for the study, although they could have started study medication on day 6-9 as required by the study protocol. The extension of the time window for randomization from day 1-5 to day 1-9 will therefore potentially increase the number of children who can be considered for the study without changing the start day of study medication.

*Affected sections:*

[Synopsis; Section 3 Study design, Section 6.2 Visit 1 – Randomization Visit](#)



#### **16.2.1.4 Modification 4: Addition of information for switch from VKA to rivaroxaban**

Children who were randomized to rivaroxaban and in whom VKA therapy was already initiated before randomization, VKA therapy should be stopped and the switch to rivaroxaban should be made as described in Section [5.1.1.3](#).

*Rational:*

This modification clarifies the procedure for children randomized to rivaroxaban, who have already started VKA therapy prior to randomization.

*Affected sections:*

[Synopsis](#); [Section 3 Study design](#)

#### **16.2.1.5 Modification 5: Update of exclusion criterion 1**

In exclusion criterion 1 “high risk for bleeding contraindicating anticoagulant therapy” was modified to read “bleeding risk contraindicating anticoagulant therapy”.

*Rational:*

The modified wording specifies that patients should be excluded from the study if any bleeding risk contraindicates anticoagulant therapy.

*Affected section:*

[Synopsis](#), [Section 4.3 Exclusion criteria](#)

#### **16.2.1.6 Modification 6: Clarification of exclusion criterion 5**

In exclusion criterion 5 it was clarified that children with sustained uncontrolled hypertension should be excluded from the study.

*Rational:*

The modification clarifies, that children with an antihypertensive therapy leading to normal blood pressure values (i.e. < 95th percentile) are allowed to be enrolled in the study. In

addition, it is clarified, that children should only be excluded from the study, if there is a sustained increase of blood pressure with continued measurement of values beyond the 95th age percentile. Individual blood pressure value(s) beyond the 95th percentile do not require exclusion of a child.

*Affected section:*

Synopsis; [Section 4.3 Exclusion criteria](#)

#### **16.2.1.7 Modification 7: Clarification of concomitant medication in exclusion criteria 7 and 8**

The modification indicates that the drugs listed are considered strong inhibitors of both CYP3A4 and P-gp, and of strong inducers of CYP3A4, respectively, but that the lists are not limited to the drugs mentioned.

*Rational:*

Additional drugs with these properties may become available. Therefore, it is indicated that the lists provided may not be exhaustive.

*Affected section:*

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

#### **16.2.1.8 Modification 8: Addition of body weight assessment at Visits 2 and 3**

The collection of body weight was added for Visits 2 and 3.

*Rationale:*

The body weight will be obtained additionally at Visit 2 and 3 to assess if an adjustment of the rivaroxaban dose is required for the child.

*Affected section:*

Synopsis; [Section 6.3 Visit 2 at Day 30 \( \$\pm\$  7 days\)](#); [Section 6.4 Visit 3 at Day 60 \( \$\pm\$  7 days\)](#)

### **16.2.1.9 Modification 9: Addition of post-thrombotic syndrome assessment**

The assessment of the incidence of post-thrombotic syndrome was added for children of  $\geq 12$  years with lower or upper extremity DVT at Visit 4, 5, 6 and 7.

*Rationale:*

Post-thrombotic syndrome is an important sequelae of deep vein thrombosis. Therefore, the exploratory assessment of the incidence of post-thrombotic syndrome will be included using the Villalta Score in children 12 years and older with DVT of the lower or upper extremity at month 3, 6, 9 and 12 months.

*Affected section:*

Synopsis; Section 3 Study design; Section 6.5 Visit 4 at Day 90 ( $\pm 7$  days); Section 6.5.1 Visit 5, Visit 6, and Visit 7 at Day 180, Day 270, Day 360 ( $\pm 7$  days); Section 7.5 Efficacy analysis; Section 15. References

### **16.2.1.10 Modification 10: Age range for assessment of oral suspension Taste- and- Texture**

The upper range for children completing the Taste- and Texture questionnaire was changed from  $<12$  to  $< 18$  years.

*Rationale:*

The oral suspension will be made available to children of all age groups, including adolescents. Therefore, the Taste- and Texture questionnaire will need to be completed by children from 4 to less than 18 years.

*Affected section:*

Synopsis; Section 7.5 Efficacy analysis

### **16.2.1.11 Modification 11: Introduction of additional supplies for preparation and administration of oral suspension**

Additional supplies will be provided to prepare, measure and administer the rivaroxaban oral suspension. These supplies include a syringe for measurement of 100 mL of water and liquid

dosing devices for measurement of the dose volume. The use of the supplies is described in the Rivaroxaban Oral Suspension Handling Instructions.

*Rational:*

The supplies are required for precise and accurate volume measurement during preparation of the suspension and for dose administration.

*Affected section:*

Synopsis; Section 5.9 Devices for preparation and administration of rivaroxaban oral suspension; Section 6.2 Visit 1 – Randomization Visit; Section 6.3 Visit 2 at Day 30 ( $\pm 7$  days); Section 6.4 Visit 3 at Day 60 ( $\pm 7$  days); Section 6.5 Visit 4 at Day 90 ( $\pm 7$  days); Section 6.5.1 Visit 5, Visit 6, and Visit 7 at Day 180, Day 270, Day 360 ( $\pm 7$  days)

**16.2.1.12 Modification 12: Start of enrollment in cohorts 6 months to less than 2 years and 2 to less than 6 years**

The age cohorts 6 months to less than 2 years and 2 to less than 6 years were opened. In this context, the structure of age cohort specific dosing and regimen instructions was resolved and replaced by a consistent description applicable for children aged 6 months to less than 18 years. In addition, a single dosing table was included, that provides the body weight dependent dosing and regimen (o.d. vs. b.i.d) irrespective of the formulation used (tablet, oral suspension) applicable for all age groups.

*Rationale:*

Opening of the age cohorts 6 months to less than 2 years and 2 to less than 6 years was anticipated in the original protocol. After review of phase II data from study 14374, the DMC recommended opening the two age cohorts.

Amendment 8 introduces a single consistent body weight adjusted dosing schedule/regimen for children aged 6 months to < 18 years. Age dependency is implicitly considered in this table as certain body weights are connected with certain ages through standard growth charts (with some variability, excluding extreme obesity).

*Affected sections:*

Synopsis; Section 3 Study design; Section 5.1.1 Rivaroxaban group; Section 17.4 Appendix 4: Dosing table for children from 6 months to 18 years; Section 17.5 Appendix 5: Dosing table for children from 6 to <12 years

### **16.2.1.13 Modification 13: Introduction of oral suspension**

The oral suspension formulation is now provided for VTE treatment in children of all age cohorts.

*Rationale:*

This change was anticipated in the original protocol. <sup>PPD</sup> [REDACTED] Based on a health authority request, the oral suspension will be provided to children of all age cohorts.

*Affected section:*

[Section 3 Study design](#); [Section 5.1.1 Rivaroxaban group](#); [Section 17.4 Appendix 4: Dosing table for children from 6 months to 18 years](#); [Section 17.5 Appendix 5: Dosing table for children from 6 to <12 years](#)

### **16.2.1.14 Modification 14: Update of phase II results**

The information from the phase II studies described in the protocol was updated.

*Rationale:*

New information on the rivaroxaban pediatric phase II studies became available and was updated accordingly.

*Affected section:*

[Section 1. Introduction](#)

### **16.2.1.15 Modification 15: Minor clarifications for consistency**

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

*Rationale:*

Changes were made to ensure consistency within the protocol and with the associated documents (Study Booklet, Rivaroxaban Oral Suspension Handling Instructions). These changes do not affect the overall study concept.

*Affected section:*

Section 1. Introduction; Section 3 Study design; Section 6.2 Visit 1 – Randomization Visit; Section 6.3 Visit 2 at Day 30 ( $\pm 7$  days); Section 6.4 Visit 3 at Day 60 ( $\pm 7$  days); Section 6.5 Visit 4 at Day 90 ( $\pm 7$  days); Section 6.5.1 Visit 5, Visit 6, and Visit 7 at Day 180, Day 270, Day 360 ( $\pm 7$  days); Section 6.7 30-day post study treatment contact (30 days  $\pm 7$  days after last visit)

### **16.2.1.16 Modification 16: Treatment duration for children randomized last into the study**

It is clarified that children randomized towards the end of the planned study duration will have a minimal study treatment duration of 3 months.

*Rationale:*

The study outcome parameters focus on the 3-month study period. In order to collect the required information from the planned number of children, especially in the younger age cohorts, children included towards the end of the study period will have a minimum study treatment duration of 3 months, however, they may not be offered the 3-month extension periods, or not all of them.

*Affected section:*

Section 5.3 Duration of study treatment

### **16.2.1.17 Modification 17: Update of rivaroxaban oral suspension information**

Information regarding the rivaroxaban oral suspension formulation, including reference to storage condition, is updated.

*Rationale:*

Originally, it was intended to introduce a rivaroxaban ready-to-use suspension, however, based on results from phase I studies, an improved formulation, the “granules for oral suspension” will be introduced in phase III. Therefore, the respective information is exchanged.

*Affected section:*

Section 5.4.1 Rivaroxaban; Section 6.2 Visit 1 – Randomization Visit; Section 6.3 Visit 2 at Day 30 ( $\pm$  7 days); Section 6.4 Visit 3 at Day 60 ( $\pm$  7 days); Section 6.5 Visit 4 at Day 90 ( $\pm$  7 days); Section 6.5.1 Visit 5, Visit 6, and Visit 7 at Day 180, Day 270, Day 360 ( $\pm$  7 days)

### **16.2.1.18 Modification 18: Addition for statistical analysis of Taste- and Texture questionnaire and PTS**

Details of the statistical analysis for evaluation of the Taste- and- Texture Questionnaire and on for evaluation of the PTS assessment were added.

*Rationale:*

The information was missing and had to be added.

*Affected section:*

Section 7.5 Efficacy analysis

### **16.2.1.19 Modification 19: Reporting of device-related adverse events**

Detailed information on the reporting of device-related AEs were added.

*Rationale:*

Adverse events may be related to device incidents. Therefore, it will be assessed whether an AE is related the use of a device, e.g. the syringe used for measuring the volume of water or the liquid dosing device.

*Affected section:*

Synopsis; Section 5.9 Devices for preparation and administration of rivaroxaban oral suspension; Section 7.9.10 Adverse events related to devices used for preparation and administration of rivaroxaban oral suspension

### **16.2.1.20 Modification 20: Addition of calculation constants for eGFR calculation**

Constants for calculation of the eGFR in younger children were added.

*Rationale:*

Due to the enrollment of children as young as 6 months of age the respective constants for calculation of the eGFR were added to cover the entire age range of the study.

*Affected sections:*

Section 6.2 Visit 1 – Randomization Visit; Section 6.3 Visit 2 at Day 30 ( $\pm$  7 days); Section 6.4 Visit 3 at Day 60 ( $\pm$  7 days); Section 6.5 Visit 4 at Day 90 ( $\pm$  7 days); Section 6.5.1 Visit 5, Visit 6, and Visit 7 at Day 180, Day 270, Day 360 ( $\pm$  7 days); Section 17.2 Appendix 2: Estimated glomerular filtration rate

## **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 changed based on modifications 1 and 2.

*Old text:*

[...]

Sponsor: Bayer ~~HealthCare~~ AG, D-51368 Leverkusen, Germany

PPD ~~medical expert at Bayer  
Bayer HealthCare Pharmaceuticals  
Avenida Domingos Jorge 1100, prédio 9503, 2º andar  
04779-900, São Paulo, SP - Brazil  
Telephone: PPD  
Email: PPD~~

[...]

*New text:*

[...]

Sponsor: Non-US territory: Bayer AG, D-51368 Leverkusen, Germany  
US territory: Bayer Healthcare Pharmaceuticals Inc.,  
100 Bayer Boulevard, P.O. Box 915,  
Whippany NJ 07981-0915, USA

PPD Aprather Weg/Gebäude 402  
42113, Wuppertal, Germany  
Telephone: PPD  
Email: PPD

[...]

**16.2.2.2 Study center's principal investigator agrees to the content of the final clinical study protocol as presented.**

This section was changed based on modification 1.

*Old text:*

[...]

Rivaroxaban (BAY-59-7939, JNJ-39039039) is being co-developed under a collaboration and license agreement between Bayer HealthCare AG (BHC) and Ortho McNeil Pharmaceuticals, Inc. (OMP) dated 01 Oct 2005.

[...]

*New text:*

[...]

Rivaroxaban (BAY-59-7939, JNJ-39039039) is being co-developed under a collaboration and license agreement between Bayer AG and Ortho McNeil Pharmaceuticals, Inc. (OMP) dated 01 Oct 2005.

[...]

### 16.2.2.3 Synopsis

This section was changed based on modifications 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 and 19.

*Old text:*

[...]

[...]	
<b>Methodology</b>	<p>[...]</p> <ul style="list-style-type: none"> <li>Randomization can be done during the first 5 days of initial treatment and will be in a 2 (rivaroxaban): 1 (standard of care [SOC]) fashion. Children randomized to rivaroxaban will start rivaroxaban the day following the last administration of initial therapy with UFH, LMWH, or fondaparinux but with a minimal duration of initial therapy of 5 days and a maximum duration of 9 days.</li> </ul> <p>Regardless of the duration of study treatment (3, 6, 9 or 12 months), an additional 1-month post-treatment observational period will be completed for all children. All suspected clinical study outcomes and baseline and repeat thrombosis imaging tests will be assessed by a central independent adjudication committee (CIAC) blinded to treatment allocation. An independent Data Monitoring Committee (DMC) will monitor the children's safety and give recommendations to the steering committee.</p> <p>[...]</p>
	[...]
<b>Inclusion/exclusion criteria</b>	<p>[...]</p> <p>Exclusion</p> <ol style="list-style-type: none"> <li>Active bleeding or <del>high risk for</del> bleeding contraindicating anticoagulant therapy [...]</li> <li><del>Hypertension</del> defined as systolic and/or diastolic blood pressure &gt; 95<sup>th</sup> age percentile (See Appendix 3) [...]</li> <li>Concomitant use of strong inhibitors of both cytochrome P450 isoenzyme 3A4 (CYP3A4) and P-glycoprotein (P-gp), <del>i.e.</del> all human immunodeficiency virus protease inhibitors and the followingazole-antimycotics agents: ketoconazole, itraconazole, voriconazole, posaconazole, if used systemically (fluconazole is allowed)</li> <li>Concomitant use of strong inducers of CYP3A4, <del>i.e.</del> rifampicin, rifabutin, phenobarbital, phenytoin and carbamazepine [...]</li> <li>Previous assignment to treatment during this study</li> <li>Participation in a study with an investigational drug or medical device within 30 days prior to randomization</li> </ol>

**Table 1 Flow chart**

Visit	Main Treatment period					Extended treatment period with blocks of 3 months			30-day post study treatment
	1	2	3	4	5	6	7	8	
Days	Before random.	After random.	Day 30 ± 7 days	Day 60 ± 7 days	Day 90 ± 7 days	Day 180 ± 7 days	Day 270 ± 7 days	Day 360 ± 7 days	30 ± 7 days After last visit
Contact	Visit	Visit	Visit	Visit	Visit	Visit	Visit	Visit	Visit or phone
[...]									
Dispense study medication		•	•	•	• <sup>c</sup>	• <sup>c</sup>	• <sup>c</sup>		
Instruct how to take study medication		•							
[...]									
Obtain body weight <sup>d</sup>					• <sup>d</sup>	• <sup>d</sup>	• <sup>d</sup>		
If suspension, complete pre-dosing Taste-and-Texture questionnaire in children 4 to < 12 years			•						
[...]									
If suspension, <del>then</del> complete post-dosing Taste-and-Texture questionnaire in children 4 to < 12 years			•						
[...]									
If suspension, complete pre-dosing Taste-and-Texture questionnaire in children 4 to < 12 years			•						
[...]									
If suspension, then complete post- dosing Taste-and-Texture questionnaire in children 4 to < 12 years			•						
[...]									

[...]

<sup>b</sup> Randomization can be done during the first 5 days of initial therapy with UFH, LMWH or fondaparinux.

[...]

[...]

*New text:*

[...]

[...]	
<b>Methodology</b>	<p>[...]</p> <ul style="list-style-type: none"> <li>Randomization can be done during the first <u>9</u> days of initial treatment and will be in a 2 (rivaroxaban): 1 (standard of care [SOC]) fashion. Children randomized to rivaroxaban will start rivaroxaban the day following the last administration of initial therapy with UFH, LMWH, or fondaparinux but with a minimal duration of initial therapy of 5 days and a maximum duration of 9 days.</li> </ul> <p>[...]</p> <p><u>In children randomized to rivaroxaban in whom VKA therapy was already initiated before randomization, VKA therapy should be stopped and the switch to rivaroxaban should be made as described in Section 5.1.1.3.</u></p> <p>[...]</p> <p>Regardless of the duration of study treatment (3, 6, 9 or 12 months), an additional 1-month post-treatment observational period will be completed for all children. All suspected clinical study outcomes and baseline and repeat thrombosis imaging tests will be assessed by a central independent adjudication committee (CIAC) blinded to treatment allocation. An independent Data Monitoring Committee (DMC) will monitor the children's safety and give recommendations to the steering committee.</p>
[...]	[...]
<b>Inclusion/exclusion criteria</b>	<p>[...]</p> <p>Exclusion</p> <ol style="list-style-type: none"> <li>Active bleeding or bleeding <u>risk</u> contraindicating anticoagulant therapy</li> </ol> <p>[...]</p> <ol style="list-style-type: none"> <li><u>Sustained uncontrolled hypertension</u> defined as systolic and/or diastolic blood pressure &gt; 95<sup>th</sup> age percentile (See Appendix 3)</li> </ol> <p>[...]</p> <ol style="list-style-type: none"> <li>Concomitant use of strong inhibitors of both cytochrome P450 isoenzyme 3A4 (CYP3A4) and P-glycoprotein (P-gp), <u>including but not limited to</u> all human immunodeficiency virus protease inhibitors and the following azole-antimycotics agents: ketoconazole, itraconazole, voriconazole, posaconazole, if used systemically (fluconazole is allowed)</li> <li>Concomitant use of strong inducers of CYP3A4, <u>including but not limited to</u> rifampicin, rifabutin, phenobarbital, phenytoin and carbamazepine</li> </ol> <p>[...]</p> <ol style="list-style-type: none"> <li>Previous assignment to treatment during this study</li> <li>Participation in a study with an investigational drug or medical device within 30 days prior to randomization</li> </ol>
[...]	

**Table 1 Flow chart**

Visit	Main Treatment period					Extended treatment period with blocks of 3 months			30-day post study treatment
	1	2	3	4	5	6	7	8	
Days	Before random.	After random.	Day 30 ± 7 days	Day 60 ± 7 days	Day 90 ± 7 days	Day 180 ± 7 days	Day 270 ± 7 days	Day 360 ± 7 days	30 ± 7 days After last visit
Contact	Visit	Visit	Visit	Visit	Visit	Visit	Visit	Visit	Visit or phone
[...]									
Dispense study medication		•	•	•	• <sup>c</sup>	• <sup>c</sup>	• <sup>c</sup>		
Dispense additional supplies (devices for oral suspension)		•	•	•	• <sup>c</sup>	• <sup>c</sup>	• <sup>c</sup>		
Instruct how to take study medication <sup>n</sup>		•							•
[...]									
Check for device-related adverse events <sup>o</sup>		•	•	•	•	•	•	•	
Obtain body weight	•	•	• <sup>d</sup>	• <sup>d</sup>	• <sup>d</sup>	• <sup>d</sup>	• <sup>d</sup>		
[...]									
Perform post-thrombotic syndrome assessment <sup>m</sup>					•	•	•	•	
[...]									
If suspension, complete pre-dosing Taste-and-Texture questionnaire in children 4 to < 18 years			•						
[...]									
If suspension, complete post-dosing Taste-and-Texture questionnaire in children 4 to < 18 years			•						
[...]									
If suspension, complete pre-dosing Taste-and-Texture questionnaire in children 4 to < 18 years			•						
[...]									
If suspension, then complete post-dosing Taste-and-Texture questionnaire in children 4 to < 18 years			•						
[...]									

[...]

<sup>b</sup> Randomization can be done during the first 9 days of initial therapy with UFH, LMWH or fondaparinux.

<sup>m</sup> Only in children ≥12 years with lower or upper extremity DVT

<sup>n</sup> In addition, provide Rivaroxaban Oral Suspension Handling Instructions, if applicable, and Study Booklet

<sup>o</sup> Only applicable for children treated with oral suspension

[...]

IxRS = interactive voice/ web response system

PTS = post-thrombotic syndrome

[...]

[...]

#### 16.2.2.4 Section 1. Introduction

This section was changed based on modifications 14 and 15.

*Old text:*

[...]

~~Enrollment for children from 12 to less than 18 years has been completed. Rivaroxaban was well tolerated, compliance with rivaroxaban was optimal, no recurrent venous thromboembolism and/or major bleeding were observed and PK/PD results confirmed a similar exposure as in adults receiving 20 mg of rivaroxaban once daily. Therefore, as in adults, there is no need for monitoring the anticoagulant activity of rivaroxaban in children from 12 to less than 18 years.~~

[...]

*New text:*

[...]

In phase II, enrollment of children from 2 to less than 18 years has been completed. Rivaroxaban was well tolerated, compliance with rivaroxaban was optimal, no recurrent venous thromboembolism and/or major bleeding were observed and PK/PD results confirmed a similar exposure as in adults receiving 20 mg of rivaroxaban once daily. Therefore, as in adults, there is no need for monitoring the anticoagulant activity of rivaroxaban in children.

[...]

#### 16.2.2.5 Section 3 Study design

This section was changed based on modifications 3, 4, 9, 12, 13 and 15.

*Old text:*

[...]

<p>The study will be initiated with children in the age group between 12 and less than 18 years since the age-and body weight adjusted dosing regimen has been confirmed for this age group in the phase II study 14373 and was approved by the data monitoring committee and steering committee. The dosing schedule/regimen for this age group is available in Appendix 4.</p>
--

Once the age-and body weight adjusted dosing regimen has been confirmed for the age group between 6 and less than 12 years in the phase II study 14373 and approved by the data monitoring committee and steering committee, the dosing schedule/regimen for this age group will be made available through an administrative amendment (For tablet, this was implemented through Amendment 4). The investigators and ethics committees/IRBs will receive the administrative amendment well in advance with an opportunity for evaluation before permission will be given to start enrolling children in this age group.

Once the age-and body weight adjusted dosing regimen has been confirmed for the age group between 2 and less than 6 years in the phase II study 14374 and approved by the data monitoring committee and steering committee, the dosing schedule/regimen for this age group will be made available through an administrative amendment. The investigators and ethics committees/IRBs will receive the administrative amendment well in advance with an opportunity for evaluation before permission will be given to start enrolling children in this age group.

Once the age-and body weight adjusted dosing regimen has been confirmed for the age group between 6 months and less than 2 years in the phase II study 14374 and approved by the data monitoring committee and steering committee, the dosing schedule/regimen for this age group will be made available through an administrative amendment. The investigators and ethics committees/IRBs will receive the administrative amendment well in advance with an opportunity for evaluation before permission will be given to start enrolling children in this age group.

[...]

## Study description

[...]

Randomization can be done during the first 5 days of initial treatment and will be in a 2 (rivaroxaban): 1 (standard of care [SOC]) fashion. Children randomized to rivaroxaban will start rivaroxaban the day following the last administration of initial therapy with UFH, LMWH, or fondaparinux but with a minimal duration of initial therapy of 5 days and a maximum duration of 9 days.

[...]

*New text:*

[...]

The study will be initiated with children in the age group between 12 and less than 18 years since the age-and body weight adjusted dosing regimen has been confirmed for this age group in the phase II study 14373 and was approved by the data monitoring committee and steering committee. The dosing schedule/regimen for this age group is available in Appendix 4 (update: for oral suspension this is implemented through Amendment 8).



Once the age-and body weight adjusted dosing regimen has been confirmed for the age group between 6 and less than 12 years in the phase II study 14373 and approved by the data monitoring committee and steering committee, the dosing schedule/regimen for this age group will be made available through an administrative amendment (For tablet, this was implemented through Amendment 4; update: for oral suspension this is implemented through Amendment 8). The investigators and ethics committees/IRBs will receive the administrative amendment well in advance with an opportunity for evaluation before permission will be given to start enrolling children in this age group.

Once the age-and body weight adjusted dosing regimen has been confirmed for the age group between 2 and less than 6 years in the phase II study 14374 and approved by the data monitoring committee and steering committee, the dosing schedule/regimen for this age group will be made available through an administrative amendment (update: implemented through Amendment 8). The investigators and ethics committees/IRBs will receive the administrative amendment well in advance with an opportunity for evaluation before permission will be given to start enrolling children in this age group.

Once the age-and body weight adjusted dosing regimen has been confirmed for the age group between 6 months and less than 2 years in the phase II study 14374 and approved by the data monitoring committee and steering committee, the dosing schedule/regimen for this age group will be made available through an administrative amendment (update: implemented through Amendment 8). The investigators and ethics committees/IRBs will receive the administrative amendment well in advance with an opportunity for evaluation before permission will be given to start enrolling children in this age group.

Amendment 8 introduced a single consistent body weight adjusted dosing schedule/regimen for children aged 6 months to < 18 years (see Table 4; dosing table available for children with a body weight of  $\geq$  12 kg). Age dependency is implicitly considered in this table as certain body weights are connected (through standard growth charts) with certain ages (with some variability, excluding extreme obesity) as well as with anatomical and physiological differences that affect the absorption, distribution, metabolism, and excretion (ADME) processes at different ages.

[...]

### **Study description**

[...]

Randomization can be done during the first 9 days of initial treatment and will be in a 2\_(rivaroxaban): 1 (standard of care [SOC]) fashion. Children randomized to rivaroxaban will start rivaroxaban the day following the last administration of initial therapy with UFH, LMWH, or fondaparinux but with a minimal duration of initial therapy of 5 days and a maximum duration of 9 days.

[...]

In children randomized to rivaroxaban in whom VKA therapy was already initiated before randomization, VKA therapy should be stopped and the switch to rivaroxaban should be made as described in Section 5.1.1.3.

[...]

In children 12 years or older with DVT of the lower or upper extremity, the incidence of the post-thrombotic syndrome will be assessed at month 3, 6, 9 and 12 months, if applicable, using the Villalta Score.<sup>[17]</sup>

[...]

### 16.2.2.6 Section 4.3 Exclusion criteria

This section was changed based on modifications 5, 6 and 7.

*Old text:*

[...]

1. Active bleeding or ~~high risk for~~ bleeding contraindicating anticoagulant therapy
5. Hypertension defined as systolic and/or diastolic blood pressure > 95th age percentile
7. 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). For exceptions, see section 4.4.
8. Concomitant use of strong inducers of CYP3A4, ~~i.e.~~ rifampicin, rifabutin, phenobarbital, phenytoin and carbamazepine

[...]

*New text:*

[...]

1. Active bleeding or bleeding risk contraindicating anticoagulant therapy
5. Sustained uncontrolled hypertension defined as systolic and/or diastolic blood pressure > 95th age percentile
7. Concomitant use of strong inhibitors of both CYP3A4 and P-gp, including but not limited to all human immunodeficiency virus protease inhibitors and the following azole-antimycotics agents: ketoconazole, itraconazole, voriconazole, posaconazole, if used systemically (fluconazole is allowed). For exceptions, see Section 4.4.
8. Concomitant use of strong inducers of CYP3A4, including but not limited to rifampicin, rifabutin, phenobarbital, phenytoin, and carbamazepine

[...]

#### 16.2.2.7 Section 4.4 Concomitant medication

This section was changed based on modification 7.

*Old text:*

[...]

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), if used systemically, is not allowed, as well as concomitant use of strong inducers of CYP3A4 (~~i.e.~~ rifampicin, rifabutin, phenobarbital, phenytoin, carbamazepine). Concomitant treatment with fluconazole is allowed.

[...]

*New text:*

[...]

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

[...]

#### 16.2.2.8 Section 5.1.1 Rivaroxaban group

This section was changed based on modifications 12 and 13.

*Old text:*

[...]

##### ~~12 to <18 years age group~~

~~Rivaroxaban will be dosed according to the dosing schedule/regimen for the 12 to <18 years age group (see Appendix 4).~~

~~Tablets will be taken once daily in the morning within 2 hours after breakfast and immediately followed by the intake of up to 240 mL of liquid.~~

### **6 to < 12 years age group**

Rivaroxaban will be provided with the option of tablets or oral suspension.

The dosing schedule/regimen for rivaroxaban tablet is provided in Appendix 5 (implemented through Amendment 4). The dosing schedule/regimen for rivaroxaban oral suspension will become available as an administrative amendment to this protocol once it has been confirmed for this age group in the phase II study 14373 and approved by the data monitoring committee and steering committee.

With an ~~o.d.~~ regimen, rivaroxaban will be taken in the morning within 2 hours after breakfast. With a ~~b.i.d~~ regimen the morning dose will be taken within 2 hours after breakfast and the evening dose will be taken within 2 hours after dinner. Each rivaroxaban dose should be immediately followed by the intake of ~~up to 240 mL of liquid.~~

### **2 to < 6 years age group**

Rivaroxaban will be provided as oral suspension. The dosing schedule/regimen will become available as an administrative amendment to this protocol once it has been confirmed for this age group in the phase II study 14374 and approved by the data monitoring committee and steering committee.

Oral suspension will be immediately followed by the intake of up to 240 mL of liquid.

### **6 months to < 2 years age group**

Rivaroxaban will be provided as oral suspension. The dosing schedule/regimen will become available as an administrative amendment to this protocol once the age and body weight adjusted dosing regimen has been confirmed for this age group in the phase II study 14374 and approved by the data monitoring committee and steering committee.

Oral suspension will be immediately followed by the intake of up to 240 mL of liquid.

Oral suspension will not be used in the ~~12 to < 18 years age group.~~ It can be used in children aged 6 to < 12 years, and will be used in all children aged 6 months to < 6 years. Oral suspension should be immediately followed by the intake of up to 240 mL of liquid. The Taste-and-Texture Questionnaire, using a ~~visual analog~~ scale, will be applied to determine the acceptance of the oral suspension in children from 4 to < 12 years. The pre-dose part of this questionnaire needs to be completed before rivaroxaban suspension is taken, the post-dose part of this questionnaire needs to be completed after rivaroxaban suspension dose is taken and up to 240 mL of liquid has been taken.

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

[...]

*New text:*

[...]

The body weight adjusted dosing schedule for children aged 6 months to < 18 years is provided in Appendix 4 (see Section 17.4).

Children with body weight of  $\geq$  20 kg will receive rivaroxaban tablets or oral suspension.

Children with body weight of < 20 kg will receive rivaroxaban as oral suspension.

Children with body weight of  $\geq$  30 kg will be treated according to a once daily (o.d.) regimen, irrespective of whether they receive rivaroxaban tablets or oral suspension. Children with body weight < 30 kg will receive rivaroxaban twice daily (b.i.d).

With a once daily regimen, rivaroxaban will be taken in the morning during or within 2 hours after breakfast. With a twice daily regimen the morning dose will be taken during or within 2 hours after breakfast and the evening dose will be taken during or within 2 hours after dinner.

Each rivaroxaban dose should be immediately followed by the intake of one typical serving of up to 240 mL of liquid. This volume will depend on age and may range from for example 20 mL in children aged 6 months up to 240 mL in adolescents

#### **Use of oral suspension**

Oral suspension is available for use in children aged 6 months to < 18 years.

At Visit 2, the Taste-and-Texture Questionnaire, using a three point scale, will be applied to determine the acceptance of the oral suspension in children from 4 to < 18 years. The pre-dose part of this questionnaire needs to be completed before rivaroxaban suspension is taken, the post-dose part of this questionnaire needs to be completed after rivaroxaban suspension dose is taken and up to 240 mL of liquid has been taken.

Instructions on how to handle rivaroxaban oral suspension can be found in the [Rivaroxaban Oral Suspension Handling Instructions](#).

[...]

#### **16.2.2.9 Section 5.3 Duration of study treatment**

This section was changed based on modification 16.

*Old text:*

[...]

Specifically children who turn 18 years after randomization are allowed to continue participation for the entire elected study treatment duration of 3, 6, 9 or 12 months.

[...]

*New text:*

[...]

Specifically children who turn 18 years after randomization are allowed to continue participation for the entire elected study treatment duration of 3, 6, 9 or 12 months.

Children randomized last into the study will have a minimal study treatment duration of 3 months.

[...]

### 16.2.2.10 Section 5.4.1 Rivaroxaban

This section was changed based on modification 17.

*Old text:*

[...]

Rivaroxaban will be provided by Bayer as immediate-release film-coated tablets, and as a 0.1% suspension (1 mg/mL), see ~~Table 5-1~~. Rivaroxaban will be dosed according to ~~age- and~~ body weight groups as detailed in ~~age-group specific~~ dosing schedules/regimens associated with this protocol. Since children with an estimated glomerular filtration rate below 30 mL/min/1.73 m<sup>2</sup> are excluded from the study, dose reduction for impaired renal function is not required.

**Table 2 Identity of test drug**

International non-proprietary name (INN)	Rivaroxaban	
Substance code number	BAY 59-7939	
Formulation	Film-coated tablets	Oral suspension-0.1%
Composition	Film-coating: hypromellose, macrogol, titanium dioxide, and ferric oxide red or ferric oxide yellow	Excipients: microcrystalline cellulose, carmellose sodium, xanthan gum, citric acid anhydrous, sodium benzoate, flavor sweet and creamy, sucralose, and water for injection
Type of packaging and content	Type of packaging: plastic bottle high density polyethylene (HDPE) white opaque, closed with white screw cap polypropylene (PP) with sealing inserter and childproof lock	Type of packaging: brown glass bottle type 3 with adapter polyethylene for plastic dosing pipette-closed with PP screw cap childproof lock
Strength of rivaroxaban	Tablets of 5.0, <del>7.5</del> , 10.0, 15.0 and 20.0 mg	1 mg per ml

*New text:*

[...]

Rivaroxaban will be provided by Bayer as immediate-release film-coated tablets, and as a granules for oral suspension formulation (0.1% suspension as finally administered drug product), see Table 2. Rivaroxaban will be dosed according to body weight groups as detailed in the dosing schedules/regimens associated with this protocol. Since children with an estimated glomerular filtration rate below 30 mL/min/1.73 m<sup>2</sup> are excluded from the study, dose reduction for impaired renal function is not required.

**Table 2 Identity of test drug**

<b>International non-proprietary name (INN)</b>	<b>Rivaroxaban</b>	
Substance code number	BAY 59-7939	
Formulation	Film-coated tablets	Granules for oral suspension
Composition	Film-coating: hypromellose, macrogol, titanium dioxide, and ferric oxide red or ferric oxide yellow	Excipients: microcrystalline cellulose <u>and</u> carmellose sodium, xanthan gum, citric acid anhydrous, sodium benzoate, flavor sweet and creamy, <u>hypromellose 5 cP, sucralose, mannitol</u>
Type of packaging and content	Type of packaging: plastic bottle high density polyethylene (HDPE) white opaque, closed with white screw cap polypropylene (PP) with sealing inserter and childproof lock	Type of packaging: brown glass bottle type 3 closed with PP screw cap childproof lock
Strength of rivaroxaban	Tablets of 5.0, 10.0, 15.0 and 20.0 mg	1 mg per ml

### 16.2.2.11 Section 5.5 Packaging and labeling, and storage

This section was changed based on modification 17.

*Old text:*

[...]

All study medication ~~need~~ to be stored at the site according to the labeled storage advice in accordance with Good Clinical Practice (GCP) and GMP requirements. ~~Rivaroxaban oral suspension should not be frozen and should be stored at a temperature not exceeding 25°C. Rivaroxaban tablets should be stored at room temperature but not above 30°C.~~ The study drug is to be kept in a secure area. Complete records of batch numbers and expiry dates can be found in the 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.

[...]

*New text*

## **5.5 Packaging an labeling, and storage**

[...]

All study medication needs to be stored at the site according to the labeled storage advice in accordance with Good Clinical Practice (GCP) and GMP requirements. The study drug is to be kept in a secure area. Complete records of batch numbers and expiry dates can be found in the 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.

### **16.2.2.12 Section 5.8 Study treatment delivery and compliance assessment**

This section was changed based on modification 17.

*Old text:*

[...]

All ~~empty packaging~~ and unused ~~study drug~~ will be returned at all study visits. All non-used study medication will be kept securely in a designated locked container.

*New text*

[...]

All used and unused medication and additional supplies will be returned at all study visits. All non-used study medication will be kept securely in a designated locked container.

### **16.2.2.13 Section 5.9 Devices for preparation and administration of rivaroxaban oral suspension**

This section was added based on Modification 19.

*New text:*

#### **5.9 Devices for preparation and administration of rivaroxaban oral suspension**

The rivaroxaban granules for oral suspension will be suspended with water. In order to measure the appropriate volume of water, parents will be provided with 100 ml syringes.

In addition, parents will be provided with Liquid Dosing Devices (LDDs; dosing pipettes) for precise, accurate and reproducible measuring of the rivaroxaban oral suspension dose volume and for administration to the child.



Both supplies, the syringe and the LDDs, are class 1 devices with measuring function, which is considered a low risk class.

The syringes and LDDs will be provided to the parents together with the rivaroxaban oral suspension as additional supplies. The use of these supplies is described in the Rivaroxaban Oral Suspension Handling Instructions. Any device malfunction or defect, or any use error by site personnel or parents will be assessed during study visits (see Section 7.9.10).

#### 16.2.2.14 Section 6.2 Visit 1 – Randomization Visit

This section was changed based on modifications 9, 11, 17, and 19.

*Old text:*

[...]

The parents/legal guardians and children will be given an explanation about the study and will be given sufficient time to consider their participation in the study and to ask any questions. Afterwards, informed consent and/or assent will be obtained (see ~~section~~ 10.2). If the child passes the screen of inclusion and exclusion criteria, the child can be randomized. Then,

[...]

- Randomization can be done during the first 5 days of initial treatment and will be in a 2 (rivaroxaban): 1 (standard of care [SOC]) fashion. Children randomized to rivaroxaban will start rivaroxaban the day following the last administration of initial therapy with UFH, LMWH, or fondaparinux but with a minimal duration of initial therapy of 5 days and a maximum duration of 9 days.
- [...]
- Provide instructions on how to take the study drug and give the study booklet
- [...]
- Dispense study medication
- [...]
- Check for adverse events
- Instruct that on the day of visit 2, rivaroxaban should not be taken at home and medication should be brought to the hospital
- [...]
- Collect images of the index venous thrombotic event, prepare the adjudication package and send it to the central adjudication office. ~~Visit 2 at Day 30 (± 7 days)~~

[...]

*New text:*

[...]

The parents/legal guardians and children will be given an explanation about the study and will be given sufficient time to consider their participation in the study and to ask any questions. Afterwards, informed consent and/or assent will be obtained (see Section 10.2). If the child passes the screen of inclusion and exclusion criteria, the child can be randomized. Then,

[...]

- Randomization can be done during the first 9 days of initial treatment and will be in a 2 (rivaroxaban): 1 (standard of care [SOC]) fashion. Children randomized to rivaroxaban will start rivaroxaban the day following the last administration of initial therapy with UFH, LMWH, or fondaparinux but with a minimal duration of initial therapy of 5 days and a maximum duration of 9 days.
- [...]
- Dispense study medication and additional supplies (devices for oral suspension)
- Provide instructions on how to take the study drug and give the study booklet. If child will take rivaroxaban oral suspension, provide the Rivaroxaban Oral Suspension Handling Instructions. Train parents/child on the preparation and administration of the oral suspension and on the use of the liquid dosing device.
- [...]
- Check for adverse events and device-related adverse events
- Instruct that on the day of visit 2, rivaroxaban should not be taken at home and that all used and unused medication/supplies should be returned to the hospital
- [...]
- Collect images of the index venous thrombotic event, prepare the adjudication package and send it to the central adjudication office.

[...]

#### **16.2.2.15 Section 6.3 Visit 2 at Day 30 ( $\pm$ 7 days)**

This section was changed based on modifications 8, 9, 11, 17, and 19.

*Old text:*

- Check for potential study outcomes. If a suspected study outcome occurred, an adjudication package will be compiled and sent to the adjudication office.
- Assess duration and intensity of menstruation, if applicable.
  - In case rivaroxaban is provided as tablet:

- [...]
- Document the volume of fluid taken
- Document the exact time of rivaroxaban intake and type of meal (i.e. breakfast, lunch, dinner) the child took 2 hours before and after rivaroxaban.
- In case rivaroxaban is provided as oral suspension:
  - Complete the pre-dose part of the Taste- and-Texture-Questionnaire only for children from 4 to < 12
  - [...]
  - Document the volume of fluid taken
  - Complete the post-dose part of the Taste- and-Texture-Questionnaire only for children from 4 to < 12
  - Document the exact time of rivaroxaban intake and type of meal (i.e. breakfast, lunch, dinner) the child took 2 hours before and after rivaroxaban.
- [...]
  - Dispense study medication
  - [...]
  - Check for adverse events
  - [...]
  - Instruct that on the day of visit 3, rivaroxaban should not be taken at home and medication should be brought to the hospital

[...]

*New text:*

[...]

- Check for potential study outcomes. If a suspected study outcome occurred, an adjudication package will be compiled and sent to the adjudication office.
- Assess duration and intensity of menstruation, if applicable.
- In case rivaroxaban is provided as tablet:
  - [...]
  - Document the volume and type of fluid taken
  - Document the exact time of rivaroxaban intake as well as time and type of meal (i.e. breakfast, lunch, dinner) the child took within 2 hours before and 2 hours after rivaroxaban.

- In case rivaroxaban is provided as oral suspension:
  - Complete the pre-dose part of the Taste- and-Texture Questionnaire only for children from 4 to < 18 years
  - [...]
  - Document the volume and type of fluid taken
  - Complete the post-dose part of the Taste- and-Texture Questionnaire only for children from 4 to < 18 years
  - Document the exact time of rivaroxaban intake as well as the time and type of meal (i.e. breakfast, lunch, dinner) the child took within 2 hours before and 2 hours after rivaroxaban.
- [...]
- Obtain body weight and adjust the rivaroxaban dose, if applicable.
- Dispense study medication and additional supplies (devices for oral suspension)
- [...]
- Check for adverse events and device-related adverse events
- [...]
- Instruct that on the day of visit 3, rivaroxaban should not be taken at home and that all used and unused medication/supplies should be returned to the hospital

[...]

#### **16.2.2.16 Section 6.4 Visit 3 at Day 60 ( $\pm$ 7 days)**

This section was changed based on modifications 8, 9, 11, 17, and 19.

*Old text:*

- Check for potential study outcomes. If a suspected study outcome occurred, an adjudication package needs to be compiled and sent to the adjudication office. Document the volume of fluid taken.
- Assess duration and intensity of menstruation, if applicable.
- In children randomized to rivaroxaban (tablet or oral suspension):

- [...]
  - Document the volume of fluid taken
    - Document the exact time of rivaroxaban intake and type of meal (i.e. breakfast, lunch, dinner) the child took 2 hours before and after rivaroxaban-
  - At 2-8 hours after the rivaroxaban intake (tablet or suspension):
    - [...]
  - If rivaroxaban is given using an o.d. regimen:
    - Take rivaroxaban on the day before visit 4 at noon immediately followed by the intake of up to 240ml of liquid
    - Document the volume of fluid taken
    - Document the exact time of rivaroxaban intake and type of meal (i.e. breakfast, lunch, dinner) the child took 2 hours before and after rivaroxaban If rivaroxaban is given using a b.i.d. regimen:
  - If rivaroxaban is given using a b.i.d regimen:
    - Take rivaroxaban as late as possible in the evening on the day before visit 4 immediately followed by the intake of up to 240ml of liquid
    - Document the volume of fluid taken
    - Document the exact time of rivaroxaban intake and type of meal (i.e. breakfast, lunch, dinner) the child took 2 hours before and after rivaroxaban
    - [...]
    - Dispense study medication
    - [...]
  - Check for adverse events
- [...]

*New text:*

- Check for potential study outcomes. If a suspected study outcome occurred, an adjudication package needs to be compiled and sent to the adjudication office.
- Assess duration and intensity of menstruation, if applicable.
- In children randomized to rivaroxaban (tablet or oral suspension):
  - [...]
  - Document the volume and type of fluid taken.
  - Document the exact time of rivaroxaban intake as well as the time and type of meal (i.e. breakfast, lunch, dinner) the child took within 2 hours before and 2 hours after rivaroxaban.

- At 2-8 hours after the rivaroxaban intake (tablet or suspension):
- [...]
- If rivaroxaban is given using an o.d. regimen:
  - Take rivaroxaban on the day before visit 4 at noon immediately followed by the intake of up to 240ml of liquid
  - Document the volume and type of fluid taken
  - Document the exact time of rivaroxaban intake as well as the time and type of meal (i.e. breakfast, lunch, dinner) the child took within 2 hours before and 2 hours after rivaroxaban.
- If rivaroxaban is given using a b.i.d. regimen:
  - Take rivaroxaban as late as possible in the evening on the day before visit 4 immediately followed by the intake of up to 240ml of liquid
  - Document the volume and type of fluid taken
  - Document the exact time of rivaroxaban intake as well as the time and type of meal (i.e. breakfast, lunch, dinner) the child took within 2 hours before and 2 hours after rivaroxaban.
- [...]
- Obtain body weight and adjust the rivaroxaban dose, if applicable.
- Dispense study medication and additional supplies (devices for oral suspension)
- [...]
- Check for adverse events and device-related adverse events
- Instruct that on the day of visit 4, all used and unused medication/supplies should be returned to the hospital

[...]

#### **16.2.2.17 Section 6.5 Visit 4 at Day 90 (± 7 days)**

This section was changed based on modifications 9, 11, 17 and 19.

*Old text:*

[...]

- Check for potential study outcomes. If a suspected study outcome occurred, an adjudication package needs to be compiled and sent to the adjudication office.
- [...]
  - Document the exact time of rivaroxaban intake on the day prior to visit 4 and time and type of meal the child took 2 hours before and 2 hours after rivaroxaban as well as the volume of liquid taken .
- [...]

- Dispense study medication
- Check for adverse events

[...]

*New text:*

[...]

- Check for potential study outcomes. If a suspected study outcome occurred, an adjudication package needs to be compiled and sent to the adjudication office.
- In case child continues study treatment, instruct that on the day of visit 5, all used and unused medication/supplies should be returned to the hospital.
  - Document the exact time of rivaroxaban intake on the day prior to visit 4 and time and type of meal the child took within 2 hours before and 2 hours after rivaroxaban as well as the volume and type of liquid taken.
- [...]
- Dispense study medication and additional supplies (devices for oral suspension)
- Check for adverse events and device-related adverse events
- Perform post-thrombotic syndrome assessment (only for children  $\geq 12$  years and with lower or upper extremity DVT)

[...]

#### **16.2.2.18 Section 6.5.1 Visit 5, Visit 6, and Visit 7 at Day 180, Day 270, Day 360 ( $\pm 7$ days)**

This section was changed based on modifications 9, 11, 17, and 19.

*Old text:*

[...]

- Check for potential study outcomes. If a suspected study outcome occurred, adjudication package needs to be compiled and sent to the adjudication office.
- [...]
- Check for adverse events-
- [...]
- Dispense study medication, ~~if applicable.~~

[...]

*New text:*

[...]

- Check for potential study outcomes. If a suspected study outcome occurred, adjudication package needs to be compiled and sent to the adjudication office.
- [...]
- Check for adverse events and device-related adverse events.
- Perform post-thrombotic syndrome assessment (only for children  $\geq 12$  years and with lower or upper extremity DVT).
- [...]
- Dispense study medication and additional supplies (devices for oral suspension).
- [...]
- Instruct that on the day of visits (visit 6 and visit 7, if applicable), all used and unused medication/supplies should be returned to the hospital.

[...]

#### **16.2.2.19 Section 6.7 30-day post study treatment contact (30 days $\pm$ 7 days after last visit)**

This section was changed based on modification 15.

*Old text:*

[...]

- Check for adverse events.
- Document if anticoagulant treatment was continued or interrupted after stopping study medication.
- Update eCRF.

*New text:*

[...]

- Check for adverse events.
- Document if anticoagulant treatment was continued or interrupted after stopping study medication.



- Update eCRF.

#### **16.2.2.20 Section 7.5 Efficacy analysis**

This section was changed based on modifications 10 and 18.

*New text:*

[...]

Data of post-thrombotic syndrome assessment in children  $\geq 12$  years with lower or upper extremity DVT will be presented descriptively. Duration of treatment for the main treatment period (up to month 3) and the overall treatment duration will be summarized descriptively by treatment group.

Results for the Taste-and-Texture Questionnaire in children 4 to  $< 18$  years who receive the oral suspension will be presented descriptively.

[...]

#### **16.2.2.21 Section 7.9.10 Adverse events related to devices used for preparation and administration of rivaroxaban oral suspension**

This section was added based on modification 19.

*New text:*

#### **7.9.10 Adverse events related to devices used for preparation and administration of rivaroxaban oral suspension**

##### **7.9.10.1 Definitions**

##### **7.9.10.1.1 Incident**

An “Incident” is any malfunction or deterioration in the characteristics and / or performance of a device, as well as any inadequacy in the labeling or the instructions for use which, directly or indirectly, led, might lead to or might have led to the death of a patient, or user or of other persons or to a serious deterioration in their state of health.

Any event which meets all three basic reporting criteria (A, B and C) is considered an “Incident”. The criteria are as follows:

- A) An adverse device event has occurred. Typical adverse events in the context of device could be among others:
- Malfunction or deterioration in the characteristics or performance, or
  - Degradation / destruction of the device, or

- Inappropriate therapy (e.g., underdosing or overdosing).
- B) The device is suspected to be a contributory cause of the “Incident”.
- C) The event led, or might have led, to death or serious deterioration in state of health of a patient, or user, or other person.

#### **7.9.10.1.2 Other Reportable Incident**

An “Other Reportable Incident” is any incident that did not lead to death or serious deterioration in health, but it might do if it occurred again under less fortunate circumstances or without intervention of healthcare personnel. This may include cases without any medical event reported.

#### **7.9.10.1.3 Other Event**

An “Other Event” is any device related case that does not fulfill all the three basic “Incident” criteria A-C listed in the definition of an “Incident” above.

#### **7.9.10.1.4 Product Technical Complaint (PTC)**

A PTC is any report received (written, electronic or verbal communication) about a potential or alleged failure of a product in its quality (including the identity, durability, reliability, safety, efficacy or performance) or suspect counterfeit. The complaint may or may not represent a potential risk to the patient.

#### **7.9.10.2 Device Malfunction or Failure and Medical Device Reporting**

Any device complaint, malfunction, or failure including use errors will be recorded by the clinical/investigational site, including all relevant device information using the clinical investigations device complaint form, and forwarded within 24 hours to the sponsor or sponsor’s designee for evaluation and investigation, regardless of whether or not a medical event was associated with the device malfunction or failure.

There are three different situations, in which a medical device complaint form might need to be filled out by the investigator:

- a) When an AE is recorded, the investigator needs to check if a device malfunction or failure might be associated with the recorded AE.
- b) When a device malfunction or device failure occurs, the investigator needs to assess whether an AE might have occurred in relation to the device.
- c) When a device malfunction, device failure, or use error occurs, without any associated AE, this also needs to be captured in the form and immediately forwarded to the sponsor for investigation.

The details of the malfunction and medical circumstances will be captured on a Device Complaint Form filled out by the investigator and then returned to the sponsor or sponsor’s designee. The final determination of reportability is made by the sponsor and not the clinical/investigational site based on the medical circumstances surrounding the event.

#### **Investigator’s notification of the sponsor**

All investigators will be instructed and trained on all relevant aspects of the investigator's reporting obligations for device incidents and serious public health threats. This information, including all relevant contact details, is summarized in the investigator site file. This information will be updated as needed.

The manufacturer will inform the sponsor about necessary trend reports and will provide the required documentation after completing the respective investigation and statistical analysis. The sponsor will then notify the authorities of any trend reports according to all applicable regulations.

All devices that have malfunctioned or failed will be collected and returned to the sponsor or sponsor's designee. Malfunctioned or failed devices should be:

- provided with a failure description („What went wrong“),
- free of sources for contamination such as drug residues,
- clearly marked as already used at patients and shall include corresponding warning symbols on packaging.

#### **16.2.2.22 Section 15. References**

A new reference was added based on modification 9.

*New text:*

[...]

17. Kahn SR, Partsch H, Vedantham S, et al. Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Definition of post-thrombotic syndrome of the leg for use in clinical investigations: a recommendation for standardization. J Thromb Haemost 2009;7:879-83.

### 16.2.2.23 Section 17.2 Appendix 2: Estimated glomerular filtration rate

This section was changed based on modification 20.

*Old text:*

[...]

eGFR (mL/min/1.73 m<sup>2</sup>) = k \* height (cm) / SCr (g/dL) where k is proportionality constant:

[...]

k = 0.55 in children up to 13 years

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

[...]

*New text:*

[...]

eGFR (mL/min/1.73 m<sup>2</sup>) = k \* height (cm) / SCr (mg/dL) where k is proportionality constant:

[...]

Where k is proportionality constant:

k = 0.33 in pre-term infants up to 1 year

k = 0.45 in full-term infants up to 1 year

k = 0.55 in children 1 year to 13 years

k = 0.55 in girls > 13 and < 18 years

k = 0.70 in boys > 13 and < 18 years

[...]

### 16.2.2.24 Section 17.4 Appendix 4: Dosing table for children from 6 months to 18 years

This section was changed based on modification 12 and 13.

*Old text:*

#### 17.4 Appendix 4: Dosing table for children from ~~12~~ to 18 years

**Table 4** Body weight-adjusted rivaroxaban dosing schedule for children aged ~~12~~ to < 18 years

Body weight (kg)		<del>20 mg equivalent</del>
Min	Max	<del>o.d. Dose</del>
20	<30	<del>10 mg</del>
30	<40	<del>15 mg</del>
40	<50	<del>15 mg</del>
50	<100	<del>20 mg</del>
	≥ 100	<del>20 g</del>

*New text:*

#### 17.4 Appendix 4: Dosing table for children from 6 months to 18 years

**Table 4** Body weight-adjusted rivaroxaban dosing schedule for children aged 6 months to < 18 years

Body weight (kg)		Formulation	o.d. Dose	<u>b.i.d. Dose</u>	<u>Total Daily Dose</u>
Min	Max				
<u>12</u> *	<u>&lt;20</u>	<u>Oral suspension</u>		<u>5 mg</u>	<u>10 mg</u>
20	<30	<u>Tablet or oral suspension</u>		<u>5 mg</u>	<u>10 mg</u>
<u>30</u>	<u>&lt;50</u>	<u>Tablet or oral suspension</u>	<u>15 mg</u>		<u>15 mg</u>
	<u>≥ 50</u>	<u>Tablet or oral suspension</u>	<u>20 mg</u> **		<u>20 mg</u> **

\* At present, only children with body weight of ≥12 kg can be enrolled.

\*\* 15 mg in Japan

### 16.2.2.25 Section 17.5 Appendix 5: Dosing table for children from 6 to <12 years

This section was removed based on modification 12 and 13.

### ~~17.5 Appendix 5: Dosing table for children from 6 to <12 years~~

~~Table 4 — Body weight adjusted rivaroxaban dosing schedule for children aged 6 to < 12 years~~

Body weight (kg)		20 mg equivalent		
Min	Max	e.d. Dose	b.i.d. Dose	Total Daily Dose
12	<20 <sup>a</sup>		-	-
20	<30		5 mg	10 mg
30	<50	15 mg		15 mg
	≥ 50	20 mg		20 mg

<sup>a</sup>Children with body weight below 20 kg can only receive oral suspension.

### 16.3 Amendment 10

Amendment 10 is the third global amendment dated 11 Jan 2017.

#### 16.3.1 Overview of changes

##### 16.3.1.1 Modification 1: Addition of Visit 1a for rivaroxaban PK assessment

A visit was added to be scheduled 2+1 days after start of rivaroxaban treatment for children treated according to a t.i.d. regimen.

*Rationale:* Amendment 10 introduced dosing information and a new **three times daily** dosing schedule for children with body weight between 6 and <12 kg. This new dosing regimen is based on an exploratory PopPK model, that considers all rivaroxaban PK data available from children below 2 years dosed in our phase I and phase II studies. As less data are available for younger children (e.g., due to sparse sampling), the model predictions have a higher level of uncertainty for children with lower body weight. The Steering Committee therefore recommended to evaluate PK around the expected  $C_{max}$  and at  $C_{trough}$  as soon as the steady state is achieved (day 2+1 after start of rivaroxaban treatment; Visit 1a).

The PK samples obtained at Visit 1a will be shipped and analyzed for each child individually and will allow to determine whether the plasma concentrations are in the adult reference range. The results will be provided to the investigator/site and discussed in a timely manner, i.e. within approximately 1 to 2 weeks after sample collection.

*Affected sections:* [Synopsis](#); [Section 6.2 Visit 1 - Randomization Visit](#); [Section 6.3 Visit 1a \(2+1 days after start t.i.d. rivaroxaban\)](#)

##### 16.3.1.2 Modification 2: Addition of dosing regimen for children with body weight between 6 and less than 12 kg

The dosing table was extended and now includes dosing information for children with body weight of 6 kg to 12 kg. Children with body weight between 6 and less than 12 kg will be treated according to a three times daily (t.i.d.) schedule with a time interval of approximately 8 hours between individual doses.

*Rationale:* The dosing in children in general is aiming to target the adult exposure. Exposure was investigated in phase I and phase II studies and an attempt was made to provide a better match from one study to the next. The result from phase I and phase II studies have demonstrated that in children with body weight below 12 kg, plasma concentrations after 10 to 12 hours were lower than expected, indicating that the clearance is higher than expected in these children. No signals of an impaired safety or efficacy profile was obtained in phase II studies.

An exploratory PopPK model was established for children below 2 years to establish the dosing regimen. This model suggests that children with a body weight below 12 kg require three times daily dosing to provide  $C_{through}$  values in the adult reference range.

The Steering Committee agreed to the extension of the dosing regimen for children with body weight from 6 kg and less than 12 kg based on these model predictions.

*Affected sections:* [Synopsis](#); [Section 3. Study design](#); [Section 5.1.1 Rivaroxaban group](#); [Section 6.2 Visit 1 - Randomization Visit](#); [Section 6.3 Visit 1a \(2+1 days after start t.i.d. rivaroxaban\)](#); [Section 6.4 Visit 2 at Day 30 \( \$\pm\$  7 days\)](#); [Section 6.5 Visit 3 at Day 60 \( \$\pm\$  7 days\)](#); [Section 6.6 Visit 4 at Day 90 \( \$\pm\$  7 days\)](#); [Section 6.14 PK/PD assessments](#)

### **16.3.1.3 Modification 3: Correction of erroneous description for major protocol deviation documentation**

The document for collection of protocol deviations was corrected to “approved final list of important deviations, validity findings and assignment to analysis set(s)”.

*Rationale:* The protocol erroneously described that protocol deviations will be collected in the SAP. This information had to be corrected to refer to the approved final list of important deviations, validity findings and assignment to analysis set(s).

*Affected sections:* [Section 7.2 Analysis sets](#)



## **16.3.2 Changes to the protocol text**

### **16.3.2.1 Synopsis**

This section was changed based on modifications 1 and 2.

*New text:*

*[see next page]*

**Table 0-1 Flow chart**

Visit	Main Treatment period						Extended treatment period with blocks of 3 months			30-day post study treatment
	1	1a	2	3	4	5	6	7	8	
Days	Before random.	After random.	2+1 days after start t.i.d.rivaroxaban <sup>p</sup>	Day 30 ± 7 days	Day 60 ± 7 days	Day 90 ± 7 days	Day 180 ± 7 days	Day 270 ± 7 days	Day 360 ± 7 days	30 ± 7 days After last visit
Contact	Visit	Visit	Visit	Visit	Visit	Visit	Visit	Visit	Visit	Visit or phone
Obtain informed consent/child assent	•									
Check in-/exclusion criteria	•									
Obtain demographic data	•									
Check medical history	•									
Record concomitant medication/anticoagulants	•									
Obtain height/length/body weight/blood pressure	•									
Check Hb, platelets, creatinine, ALT, total and direct bilirubin	• <sup>a</sup>									
Perform urine pregnancy test, if applicable	•									
Randomize patient using IxRS <sup>b</sup>		•								
Dispense study medication		•		•	•	• <sup>c</sup>	• <sup>c</sup>	• <sup>c</sup>		
Dispense additional supplies (devices for oral suspension)		•		•	•	• <sup>c</sup>	• <sup>c</sup>	• <sup>c</sup>		
Instruct how to take study medication <sup>n</sup>		•								
Send baseline adjudication package		•								
Check for adverse events		•	•	•	•	•	•	•	•	•
Check for device-related adverse events <sup>o</sup>		•	•	•	•	•	•	•	•	
Obtain body weight				• <sup>d</sup>	• <sup>d</sup>	• <sup>d</sup>	• <sup>d</sup>	• <sup>d</sup>		
Assess duration and intensity of menstruation, if applicable				•	•	•	•	•	•	
Check for study outcomes <sup>e</sup>			•	•	•	•	•	•	•	•
Check study drug accountability and compliance			•	•	•	•	•	•	•	
Check changes in concomitant medication			•	•	•	•	•	•	•	•
Obtain Hb, platelets, ALT, total and direct bilirubin						•				
Repeat imaging and send adjudication package <sup>f</sup>						•				
Perform post-thrombotic syndrome assessment <sup>m</sup>						•	•	•	•	
Complete eCRF	•	•	•	•	•	•	•	•	•	•
<b>Comparator group only</b>										
If INR-adjusted VKA <sup>g</sup>										1 INR per 2 weeks

continued on next page

**Table 1 Flow chart (continued)**

Visit	Main Treatment period						Extended treatment period with blocks of 3 months			30-day post study treatment
	1		1a	2	3	4	5	6	7	8
Days	Before random	After random.	2+1 days after start t.i.d. rivaroxaban <sup>p</sup>	Day 30 ± 7 days	Day 60 ± 7 days	Day 90 ± 7 days	Day 180 ± 7 days	Day 270 ± 7 days	Day 360 ± 7 days	30 ± 7 days After last visit
Contact	Visit	Visit	Visit	Visit	Visit	Visit	Visit	Visit	Visit	Visit or phone
<b>Pharmacokinetics (PK) and pharmacodynamics (PD) for rivaroxaban using o.d. regimen<sup>h</sup></b>										
If suspension, complete pre-dosing Taste-and-Texture questionnaire in children 4 to < 18 years				•						
Administer rivaroxaban at study site				•	•					
Take up to 240 mL of liquid immediately after dosing				•	•					
If suspension, complete post-dosing Taste-and-Texture questionnaire in children 4 to < 18 years				•						
Obtain PK blood sample <sup>i</sup>				•	•	•	•			
Obtain PD blood sample <sup>j,k</sup>				•	•	•	•			
Time point for PK/PD blood sample (hours)				0.5-1.5hr post dose	2.5-4hr post dose	2-8hr post dose	20-24 hr after dose on previous day			
<b>Pharmacokinetics (PK) and pharmacodynamics (PD) for rivaroxaban using b.i.d. regimen<sup>h</sup></b>										
If suspension, complete pre-dosing Taste-and-Texture questionnaire in children 4 to < 18 years				•						
Administer rivaroxaban at study site				•	•					
Take up to 240 mL of liquid immediately after dosing				•	•					
If suspension, then complete post- dosing Taste-and-Texture questionnaire in children 4 to < 18 years				•						
Obtain PK blood sample <sup>i</sup>				•	•	•	•			
Obtain PD blood sample <sup>j,k</sup>				• <sup>l</sup>	•	•	•			
Time point for PK/PD blood sample (hours) if dosing continues beyond Day 90				0.5-1.5hr post dose	2.5-4hr post dose	2-8hr post dose	10-16 hr after last evening dose, give next dose after PK/PD samples			
Time point for PK/PD blood sample (hours) if dosing does not continue beyond Day 90				0.5-1.5hr post dose	2.5-4hr post dose	2-8hr post dose	10-16 hr after last evening dose			

continued on next page

Visit	Main Treatment period						Extended treatment period with blocks of 3 months			30-day post study treatment
	1		1a	2	3	4	5	6	7	8
Days	Before random	After random.	2+1 days after start t.i.d rivaroxaban <sup>p</sup>	Day 30 ± 7 days	Day 60 ± 7 days	Day 90 ± 7 days	Day 180 ± 7 days	Day 270 ± 7 days	Day 360 ± 7 days	30 ± 7 days After last visit
Contact	Visit	Visit	Visit	Visit	Visit	Visit	Visit	Visit	Visit	Visit or phone

*Pharmacokinetics (PK) and pharmacodynamics (PD) for rivaroxaban using t.i.d. regimen<sup>h</sup>*

Administer rivaroxaban at study site			•	•	•					
Take up to 120 mL of liquid immediately after dosing			•	•	•					
Obtain PK blood sample <sup>l</sup>			•	•	•	•				
Obtain PD blood sample <sup>j,k</sup>				•	•	•				
Time point for PK/PD blood sample (hours) if dosing continues beyond Day 90			0.5-3hr post dose	7-8hr post dose	0.5-3hr post dose	7-8hr post dose	2-6hr post dose	10-16hr after last evening dose, give next dose after PD sample		
Time point for PK/PD blood sample (hours) if dosing does not continue beyond Day 90			0.5-3hr post dose	7-8hr post dose	0.5-3hr post dose	7-8hr post dose	2-6hr post dose	10-16hr after last evening dose		

**Table 1 Flow chart (continued)**

Footnotes:

- <sup>a</sup> Blood sample should be obtained within a maximum of 5 days prior to randomization.
- <sup>b</sup> Randomization can be done during the first 9 days of initial therapy with UFH, LMWH or fondaparinux.
- <sup>c</sup> If study treatment is continued, provide study medication
- <sup>d</sup> Adjust dosage of study medication, if change in body weight. Additional visits can be planned to accommodate dose adjustment of study medication, if applicable.
- <sup>e</sup> If suspected outcome occurred, the adjudication package needs to be compiled and sent to the adjudication office.
- <sup>f</sup> After the main study treatment period of 3 months, the diagnostic imaging test which was obtained at baseline will be repeated, if clinically feasible
- <sup>g</sup> VKA compliance will be ensured by minimum of 1 INR per 2 weeks.
- <sup>h</sup> The approximate total blood volume taken per child for PK/PD is 12 mL if blood taken via venipuncture, and 24 mL if blood taken via central venous line or peripheral catheter.
- <sup>i</sup> Blood volume per PK sample is approximately 1.2 mL; total blood volume for all PK samples is 4.8 mL for o.d. and b.i.d. regimen and 6 mL for t.i.d. regimen.
- <sup>j</sup> Blood volume per PD sample is approximately 1.8 mL; total blood volume for all PD samples is 7.2 mL for o.d. and b.i.d. regimen and 5.4 for t.i.d. regimen.
- <sup>k</sup> Always draw the pharmacodynamics sample as the last sample.
- <sup>l</sup> PD sample will not be collected at 0.5-1.5 hr after rivaroxaban intake for children < 6 years
- <sup>m</sup> Only in children ≥12 years with lower or upper extremity DVT
- <sup>n</sup> In addition, provide Rivaroxaban Oral Suspension Handling Instructions, if applicable, and Study Booklet
- <sup>o</sup> Only applicable for children treated with oral suspension
- <sup>p</sup> Only in children treated with rivaroxaban t.i.d. regimen. If visit 1a falls on a weekend and cannot take place, the visit must be scheduled for the following Monday.
- o.d. = once daily dosing  
b.i.d. = twice daily dosing  
t.i.d. = three times daily dosing  
eCRF = electronic case report form;  
IxRS = interactive voice/ web response system  
PTS = post-thrombotic syndrome

### 16.3.2.2 Section 3. Study design

This section was changed based on modifications 2.

*Old text:*

[...]

Age dependency is implicitly considered in this table as certain body weights are connected (through standard growth charts) with certain ages (with some variability, excluding extreme obesity) as well as with anatomical and physiological differences that affect the absorption, distribution, metabolism, and excretion (ADME) processes at different ages.

[...]

*New text:*

[...]

Age dependency is implicitly considered in this table as certain body weights are connected (through standard growth charts) with certain ages (with some variability, excluding extreme obesity) as well as with anatomical and physiological differences that affect the absorption, distribution, metabolism, and excretion (ADME) processes at different ages.

Amendment 10 introduced dosing information and a new three times daily dosing schedule for children with body weight between 6 and <12 kg. This new dosing regimen is based on an exploratory PopPK model, that considers all rivaroxaban PK data available from children below 2 years dosed in our phase I and phase II studies. As less data are available for younger children (e.g., due to sparse sampling), the model predictions have a higher level of uncertainty for children with lower body weight. The Steering Committee therefore recommended to evaluate PK around the expected C<sub>max</sub> and at C<sub>trough</sub> as soon as the steady state is achieved (day 2+1 after start of rivaroxaban treatment; Visit 1a).

The PK samples obtained at Visit 1a will be shipped and analyzed for each child individually and will allow to determine whether the plasma concentrations are in the adult reference range. The results will be provided to the investigator/site and discussed in a timely manner, i.e. within approximately 1 to 2 weeks after sample collection.

[...]

### 16.3.2.3 Section 5.1.1 Rivaroxaban group

This section was changed based on modification 2.

*New text:*

[...]

Children with body weight of  $\geq 30$  kg will be treated according to a once daily (o.d.) regimen, irrespective of whether they receive rivaroxaban tablets or oral suspension. Children with body weight between 12 and  $< 30$  kg will receive rivaroxaban twice daily (b.i.d) with a dosing intervals of approximately 12 hours. Children with body weight below 12 kg will receive rivaroxaban three times daily (t.i.d.) with dosing interval of approximately 8 hours.

Dosing regimen, including dosing frequency, will be adjusted if the child's body weight changes during the study (Table 4).

With a once daily regimen, rivaroxaban will be taken in the morning during or within 2 hours after breakfast. With a twice daily regimen the morning dose will be taken during or within 2 hours after breakfast and the evening dose will be taken during or within 2 hours after dinner. With a three times daily regimen, the morning, afternoon and night doses should be taken during or within 2 hours after feeding.

Each rivaroxaban dose should be immediately followed by the intake of one typical serving of up to 240 mL of liquid (o.d. or b.i.d regimen) or 120mL (t.i.d. regimen). This volume will depend on age and may range from for example 20 mL in children aged 6 months up to 240 mL in adolescents.

[...]

If rivaroxaban is taken with a t.i.d. regimen, the t.i.d. administration schedule with approximately 8-hour intervals should be resumed at the next scheduled dose without compensating for the missed dose.

On the following day, the child should continue with the regular o.d., b.i.d. or t.i.d. regimen.

### 16.3.2.4 Section 6.2 Visit 1 - Randomization Visit

This section was changed based on modifications 1 and 2.

*Old text:*

[...]

- Instruct that on the day of ~~visit 2~~, rivaroxaban should not be taken at home and that all used and unused medication/supplies should be returned to the hospital

[...]

*New text:*

[...]

- Instruct that on the day of the next scheduled visit (visit 1a for t.i.d. regimen or visit 2 for o.d. or b.i.d. regimen), rivaroxaban should not be taken at home and that all used and unused medication/supplies should be returned to the hospital

[...]

### **16.3.2.5 Section 6.3 Visit 1a (2+1 days after start t.i.d. rivaroxaban)**

This section was introduced based on modification 1 and 2.

*New text:*

This visit will only be performed for children in the rivaroxaban t.i.d. group. If this visit falls on a weekend and cannot take place, the visit must be scheduled for the following Monday.

- Check for potential study outcomes. If a suspected study outcome occurred, an adjudication package will be compiled and sent to the adjudication office.
- Administer the next rivaroxaban dose immediately followed by the intake of up to 120 mL of liquid.
- Document the volume and type of liquid taken.
- Document the exact time of rivaroxaban intake as well as the time and type of meal (i.e. breakfast, lunch, dinner) the child took within 2 hours before and 2 hours after rivaroxaban.
- At 0.5-3 hours and at 7-8 hours after the rivaroxaban intake:
  - Collect a PK blood sample
  - Document the exact time of blood sampling for PK.
- Check for changes in concomitant medications
- Check for adverse events and device-related adverse events
- Instruct that on the day of visit 2, rivaroxaban should not be taken at home and that all used and unused medication/supplies should be returned to the hospital
- Update eCRF

### 16.3.2.6 Section 6.4 Visit 2 at Day 30 ( $\pm$ 7 days)

This section was changed based on modification 2.

*Old text:*

[...]

- In case rivaroxaban is provided as tablet:
  - Administer the next rivaroxaban dose immediately followed by up to 240 ml of liquid.
  - ~~• Document the volume and type of fluid taken~~
  - ~~• Document the exact time of rivaroxaban intake as well as time and type of meal (i.e. breakfast, lunch, dinner) the child took within 2 hours before and 2 hours after rivaroxaban.~~
- In case rivaroxaban is provided as oral suspension:
  - Complete the pre-dose part of the Taste- and-Texture Questionnaire only for children from 4 to < 18 years
  - Administer the next rivaroxaban dose immediately followed by up to 240 ml of liquid.
  - ~~• Document the volume and type of fluid taken~~
  - Complete the post-dose part of the Taste- and-Texture Questionnaire only for children from 4 to < 18 years
  - ~~• Document the exact time of rivaroxaban intake as well as the time and type of meal (i.e. breakfast, lunch, dinner) the child took within 2 hours before and 2 hours after rivaroxaban.~~
- At 0.5-1.5 and at 2.5-4 hours after this rivaroxaban intake (~~tablet or suspension~~):
  - ~~• Collect the PK blood sample in all children~~
  - In children 6 years or older, collect a PD blood sample after the PK blood sample at both time points
  - In children < 6 years, no PD sample will be collected after the PK sample at 0.5-1.5 hr, but a PD sample will be taken after the PK sample at 2.5-4 hours
  - Document the exact time of blood sampling for PK/PD.

[...]



*New text:*

[...]

- In case rivaroxaban is provided as tablet:
  - Administer the next rivaroxaban dose immediately followed by up to 240 ml of liquid.
- In case rivaroxaban is provided as oral suspension:
  - Complete the pre-dose part of the Taste- and-Texture Questionnaire only for children from 4 to < 18 years
  - Administer the next rivaroxaban dose immediately followed by up to 240 ml (o.d. or b.i.d.) or up to 120 ml (t.i.d.) of liquid.
  - Complete the post-dose part of the Taste- and-Texture Questionnaire only for children from 4 to < 18 years
- Document the volume and type of liquid taken
- Document the exact time of rivaroxaban intake as well as time and type of meal (i.e. breakfast, lunch, dinner) the child took within 2 hours before and 2 hours after rivaroxaban.
- Blood sampling for o.d. or b.i.d. regimen (tablet and oral suspension):
  - At 0.5-1.5 hours and at 2.5-4 hours after this rivaroxaban intake, collect the PK blood sample
  - In children 6 years or older, collect a PD blood sample after the PK blood sample at both time points
  - In children < 6 years, no PD sample will be collected after the PK sample at 0.5-1.5 hours, but a PD sample will be taken after the PK sample at 2.5-4 hours
- Blood sampling for t.i.d. regimen (oral suspension):
  - At 0.5-3 hours after this rivaroxaban intake collect the PK sample, followed by the PD blood sample
  - At 7-8 hours after this rivaroxaban intake collect the PK blood sample
- Document the exact time of blood sampling for PK/PD

[...]

### 16.3.2.7 Section 6.5 Visit 3 at Day 60 ( $\pm$ 7 days)

This section was changed based on modification 2.

*Old text:*

[...]

- In children randomized to rivaroxaban (tablet or oral suspension):
  - Administer the next rivaroxaban dose immediately followed by the intake of up to 240 mL of liquid.
  - Document the volume and type of ~~fluid~~ taken.
  - Document the exact time of rivaroxaban intake as well as the time and type of meal (i.e. breakfast, lunch, dinner) the child took within 2 hours before and 2 hours after rivaroxaban.
- ~~At 2-8 hours after the rivaroxaban intake (tablet or suspension):~~
  - ~~Collect a PK blood sample followed by the PD blood sample.~~
  - ~~Document the exact time of blood sampling for PK/PD.~~
  - ~~Give instructions how to handle rivaroxaban the day before visit 4:~~
  - ~~If rivaroxaban is given using an o.d. regimen:~~
    - ~~Take rivaroxaban on the day before visit 4 at noon immediately followed by the intake of up to 240ml of liquid~~
    - ~~Document the volume and type of fluid taken~~
    - ~~Document the exact time of rivaroxaban intake as well as the time and type of meal (i.e. breakfast, lunch, dinner) the child took within 2 hours before and 2 hours after rivaroxaban.~~
  - ~~If rivaroxaban is given using a b.i.d. regimen:~~
    - ~~Take rivaroxaban as late as possible in the evening on the day before visit 4 immediately followed by the intake of up to 240 ml of liquid~~
    - Document the volume and type of ~~fluid~~ taken
    - Document the exact time of rivaroxaban intake as well as the time and type of meal (i.e. breakfast, lunch, dinner) the child took within 2 hours before and 2 hours after rivaroxaban.

[...]

*New text:*

[...]

- In children randomized to rivaroxaban (tablet or oral suspension):
  - Administer the next rivaroxaban dose immediately followed by the intake of up to 240 mL (o.d. and b.i.d. regimen) or up to 120 mL (t.i.d. regimen) of liquid.
  - Document the volume and type of liquid taken.
  - Document the exact time of rivaroxaban intake as well as the time and type of meal (i.e. breakfast, lunch, dinner) the child took within 2 hours before and 2 hours after rivaroxaban.
  - If rivaroxaban is given using an o.d. or b.i.d. regimen, at 2-8 hours after the rivaroxaban intake, collect a PK blood sample followed by the PD blood sample.
  - If rivaroxaban is given using a t.i.d. regimen, at 2-6 hours after the rivaroxaban intake, collect a PK blood sample followed by the PD blood sample.
  - Document the exact time of blood sampling for PK/PD.
  - Provide instructions for the day before visit 4
    - If rivaroxaban is given using an o.d. regimen, take rivaroxaban on the day before visit 4 at noon immediately followed by the intake of up to 240 ml of liquid
    - If rivaroxaban is given using a b.i.d. regimen, take rivaroxaban as late as possible in the evening on the day before visit 4 immediately followed by the intake of up to 240 ml of liquid
    - If rivaroxaban is given using a t.i.d. regimen, take rivaroxaban night dose before visit 4 as scheduled, immediately followed by the intake of up to 120 ml of liquid
    - Document the volume and type of liquid taken
    - Document the exact time of rivaroxaban intake as well as the time and type of meal (i.e. breakfast, lunch, dinner) the child took within 2 hours before and 2 hours after rivaroxaban.

[...]

### 16.3.2.8 Section 6.6 Visit 4 at Day 90 ( $\pm$ 7 days)

This section was changed based on modification 2.

*Old text:*

[...]

- In children randomized to rivaroxaban:
  - Document the exact time of rivaroxaban intake on the day prior to visit 4 and time and type of meal the child took within 2 hours before and 2 hours after rivaroxaban as well as the volume and type of liquid taken.
  - If rivaroxaban is given using an o.d. regimen:
    - Collect the PK blood sample 20-24h after rivaroxaban was taken on the previous day, ~~followed by the PD blood sample~~
    - ~~Document the exact time of blood sampling for PK/PD.~~
  - If rivaroxaban is given using a b.i.d. regimen:
    - Collect the PK blood sample 10 to 16 hours after the last evening dose, ~~followed by the PD blood sample~~
    - If dosing continues beyond visit 4/day 90, give next dose after ~~PK/PD~~ samples
    - Document the exact time of blood sampling for PK/PD.
  - ~~Obtain hemoglobin, platelets, ALT, total and direct bilirubin~~

[...]

*New text:*

[...]

- In children randomized to rivaroxaban:
  - Document the exact time of rivaroxaban intake on the day prior to visit 4 and time and type of meal the child took within 2 hours before and 2 hours after rivaroxaban as well as the volume and type of liquid taken.
  - If rivaroxaban is given using an o.d. regimen, collect the blood sample for hemoglobin, platelets, ALT, total and direct bilirubin, followed by PK blood sample and finally the PD blood sample at 20-24h after rivaroxaban was taken on the previous day
  - If rivaroxaban is given using a b.i.d. regimen, collect the blood sample for hemoglobin, platelets, ALT, total and direct bilirubin, followed by PK blood sample and finally the PD blood sample at 10 to 16 hours after the last evening dose

- If rivaroxaban is given using a t.i.d. regimen, collect hemoglobin, platelets, ALT, total and direct bilirubin, followed by the PD blood sample 10 to 16 hours after the last evening dose
- If dosing continues beyond visit 4/day 90, give next dose after PD sample
- Document the exact time of blood sampling for PK/PD.

[...]

### 16.3.2.9 Section 6.14 PK/PD assessments

This section was changed based on modification 2.

*New text:*

[...]

Blood samples will be taken for PK and PD measurements from children randomized to rivaroxaban.

The following blood samples will be taken in children with o.d. or b.i.d. regimen:

- two post-dose PK/PD samples at visit 2 (no PD sample at 0.5-1.5 hours for children < 6 years)
- one post-dose PK/PD sample at visit 3, and
- one pre-dose PK/PD sample at visit 4.

The following blood samples will be taken in children with t.i.d. regimen:

- two post-dose PK samples at visit 1a
- two post-dose PK samples at visit 2
- one post-dose PD sample at visit 2, and
- one post-dose PK/PD sample at visit 3, and
- one pre-dose PD sample at visit 4.

[...]

### 16.3.2.10 Section 7.2 Analysis sets

This section was changed based on modification 3.

*Old text:*

[...]

The detailed list of these deviations will be finalized prior to database lock and included in the protocol deviation document ~~and SAP.~~

[...]

*New text:*

[...]

The detailed list of these deviations will be finalized prior to database lock and included in the protocol deviation document, the approved final list of important deviations, validity findings and assignment to analysis set(s).

[...]

## 16.4 Amendment 12

Amendment 12 is the fourth global amendment dated 27 SEP 2017.

### 16.4.1 Overview of changes

#### 16.4.1.1 **Modification 1: Introducing new dosing information for children with body weight between 2.6 and <6 kg, and inclusion of children aged birth to 6 months**

*Rationale:* Amendment 12 introduced new dosing information for children with body weight between 2.6 and <6 kg. This new dosing regimen is based on data from all studies in children younger than 2 years, as well as an exploratory PopPK model, that considers all rivaroxaban PK data available from all children younger than 2 years. As the exploratory model is based on limited data (e.g., limited number of subjects, sparse sampling), the model predictions had a higher level of uncertainty for these children. However, observed data from this study (14372) and data from the phase I/II study (17618) that is enrolling children aged < 6 months (including those 2.6 and <6 kg), have confirmed the predictions from the exploratory PopPK model in all children dosed t.i.d thus far in both studies. Therefore, the Steering Committee with concurrence from the DMC recommended dosing for children < 6 kg.

This additional dosing information facilitates enrollment of children from birth to < 6 months. This age group was added to a revised cohort for children from birth to aged < 2 years. A single cohort from birth to aged < 2 years generally shares common risk factors for thrombosis, distribution of thrombus (with catheter-related thrombosis predominating), a different standard of care treatment regimen (< 90 days of treatment is common) and

rivaroxaban treatment regimen (most will require t.i.d. dosing). Lastly, to conform to treatment guidelines and clinical practice, a main study treatment duration of 30 days was added for those < 2 years with catheter-related thrombosis.

*Affected sections:* [Synopsis](#); [Section 1 Introduction](#); [Section 3 Study design](#); [Section 4.1 planned number of children](#); [Section 4.2 Inclusion criteria](#); [Section 4.3 Exclusion criteria](#); [Section 5.1.1 Rivaroxaban group](#); [Section 5.3 Duration of study treatment](#); [Section 5.4.1 Rivaroxaban](#); [Section 5.8 Study treatment and compliance assessment](#); [Section 6.1 Study visits](#); [Section 6.3 Visit 1a \(2+1 days after start t.i.d rivaroxaban\)](#); [Section 6.4 Visit 2 at Day 30 \(± 7 days\)](#); [Section 6.5 Visit 3 at Day 60 \(± 7 days\)](#); [Section 6.6 Visit 4 at Day 90 \(± 7 days\)](#); [Section 6.8 Visit 8, 30 day post study treatment contact \(30 days ± 7 days after last visit\)](#); [Section 6.14 PK/PD assessments](#); [Section 7.4 Bleeding analysis](#); [Section 7.5 Efficacy analysis](#); [Section 7.8 Determination of sample size](#); [Section 15 References](#); [Section 17.2 Appendix 2: Estimated glomerular filtration rate](#); [Section 17.4 Appendix 4: Dosing table for children from birth to 18 years](#)

#### 16.4.1.2 Modification 2: Minor clarifications for consistency

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

*Rationale:* Changes were made to ensure correctness and consistency and to remove redundancy within the protocol. These changes do not affect the overall study concept.

*Affected sections:* [Title page](#); [Section 5.5 Packaging, labeling and storage](#)

#### 16.4.2 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.

##### 16.4.2.1 Title page

The section was changed based on modification 2.

*Old text:*

PPD

~~Aprather Weg/Gebäude 402  
42113, Wuppertal, Germany~~

~~Telephone: PPD~~

~~Email: PPD~~

*New text:*

PPD  
Bayer U.S. LLC  
Pharmaceuticals,  
Pharmaceuticals study medical Experts  
100 Bayer Boulevard  
P.O. Box 915  
Whippany, NJ 07981  
United States  
 Tel: PPD  
 E-mail: PPD

### 16.4.2.2 Synopsis

The section was changed based on modification 1.

*Old text:*

<b>Indication</b>	Children aged <del>6 months</del> to < 18 years 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, cerebral vein and sinus thrombosis, mesenteric vein thrombosis, portal vein thrombosis, renal vein thrombosis, or catheter-related thrombosis.
<b>Diagnosis and main criteria for inclusion</b>	Children aged <del>6 months to</del> < 18 years with acute venous thromboembolism confirmed by diagnostic imaging.

[...]

<b>Methodology</b>	<p>Children aged <del>6 months to</del> &lt; 18 years with confirmed venous thromboembolism who receive initial treatment with therapeutic dosages of unfractionated heparin (UFH), low molecular weight heparin (LMWH), or fondaparinux are potentially eligible for the study.</p> <p>[...]</p> <p>The main study treatment period is for a total of 3 months at which time the diagnostic imaging test, which was obtained at baseline, will be repeated, if clinically feasible.</p> <p>[...]</p> <p>The main study treatment period is for a total of 3 months at which time the diagnostic imaging test, which was obtained at baseline, will be repeated, if clinically feasible. <del>After the main study treatment period of 3 months,</del> the decision is made to stop study treatment or to continue for an additional 3 months. In children who completed 6 months of treatment, the decision is made to stop study treatment or to continue for an additional 3 months. Then, in children who completed 9 months of treatment, the decision is made to stop study treatment or to continue for an additional 3 months.</p>
--------------------	--



	<p>[...]</p> <p>Regardless of the duration of study treatment (3, 6, 9 or 12 months), an additional 1-month post-treatment observational period will be completed for all children. [...]</p>
<b>Number of children</b>	<p>At least 150 children are needed for this study, of whom 80 in the age group 12 to &lt; 18 years, 30 in the age group 6 to &lt; 12 years, 20 in the age group 2 to &lt; 6 years, and 20 in the age group <del>6 months</del> to &lt; 2 years.</p>
<b>Inclusion/exclusion criteria</b>	<p>Inclusion</p> <ol style="list-style-type: none"> <li>1. Children aged <del>6 months to</del> &lt; 18 years with confirmed venous thromboembolism who receive initial treatment with therapeutic dosages of UFH, LMWH or fondaparinux and require anticoagulant therapy for at least 90 days. [...]</li> <li>2. Informed consent provided and, if applicable, child assent provided</li> </ol> <p>Exclusion</p> <p>[...]</p> <ol style="list-style-type: none"> <li>2. An estimated glomerular filtration rate (eGFR) &lt; 30 mL/min/1.73 m<sup>2</sup></li> </ol> <p>[...]</p>

[...]

<b>Primary efficacy outcome analysis</b>	<p>Incidence proportions and cumulative incidences will be calculated for the primary efficacy outcome at the end of <del>month 3</del>.</p>
<b>Secondary efficacy outcome analysis</b>	<p>Incidence proportions and cumulative incidences will be calculated for the secondary efficacy outcome at the end of <del>month 3</del>.</p>
<b>Other efficacy outcome analysis</b>	<p>Incidence proportions will be calculated for the primary efficacy outcome at 6, 9 and 12 months.</p>
<b>Principal safety outcome analysis</b>	<p>Incidence proportions and cumulative incidences will be calculated for the principal safety outcome at the end of <del>month 3</del>.</p>
<b>Other safety outcome analysis</b>	<p>Incidence proportions will be calculated for the principal safety outcome at 6, 9 and 12 months.</p>

[...]

**Table 0-1 Flow chart**

Visit	Main Treatment period						Extended treatment period with blocks of 3 months			30-day post study treatment
	1	1a	2	3	4	5	6	7	8	
Days	Before random	After random	2+1 days after start t.i.d rivaroxaban <sup>p</sup>	Day 30 ± 7 days	Day 60 ± 7 days	Day 90 ± 7 days	Day 180 ± 7 days	Day 270 ± 7 days	Day 360 ± 7 days	30 ± 7 days After last visit
Contact	Visit	Visit	Visit	Visit	Visit	Visit	Visit	Visit	Visit	Visit or phone

**Pharmacokinetics (PK) and pharmacodynamics (PD) for rivaroxaban using t.i.d. regimen<sup>h</sup>**

Obtain PK blood sample <sup>i</sup>			•	•	•	•	•				
Obtain PD blood sample <sup>j,k</sup>					•		•	•			
Time point for PK/PD blood sample (hours) if dosing continues beyond Day 90			0.5-3hr post dose	7-8hr post dose	0.5-3hr post dose	7-8hr post dose	2-6hr post dose	10-16hr after last evening dose, give next dose after PD sample			

Footnotes:

[...]

<sup>h</sup> The approximate total blood volume taken per child for PK/PD is 12 mL if blood taken via venipuncture, and up to 24 mL if blood taken via central venous line or peripheral catheter (see Section 6.14).

<sup>i</sup> Blood volume per PK sample is approximately 1.2 mL, total blood volume for all PK samples is 4.8 mL for o.d. and b.i.d. regimen and 6 mL for t.i.d. regimen.

<sup>j</sup> Blood volume per PD sample is approximately 1.8 mL ; total blood volume for all PD samples is 7.2 mL for o.d. and b.i.d. regimen and 5.4 for t.i.d. regimen.

<sup>k</sup> Always draw the pharmacodynamics sample as the last sample.

<sup>l</sup> PD sample will not be collected at 0.5-1.5 hr after rivaroxaban intake for children < 6 years

[...]

Not applicable as Table 0-2 was added via this Amendment (Amendment 12)

*New text:*

<b>Indication</b>	Children aged <u>birth</u> to < 18 years 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, cerebral vein and sinus thrombosis, mesenteric vein thrombosis, portal vein thrombosis, renal vein thrombosis, or catheter-related thrombosis.
<b>Diagnosis and main criteria for inclusion</b>	Children aged <u>birth to</u> < 18 years with acute venous thromboembolism confirmed by diagnostic imaging.

[...]

<b>Methodology</b>	Children aged <u>birth to</u> < 18 years with confirmed venous thromboembolism who receive initial treatment with therapeutic dosages of unfractionated heparin (UFH), low molecular weight heparin (LMWH), or fondaparinux are potentially eligible for the study. [...] The main study treatment period is for a total of 3 months at which time the diagnostic imaging test, which was obtained at baseline, will be repeated, if clinically feasible. <u>However, in children younger than 2 years with catheter-related thrombosis, the main study treatment period is</u>
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	<p><u>for a total of 1 month at which time the repeat imaging will be performed. In all children, except those &lt; 2 years with catheter-related thrombosis, the decision is made to stop study treatment at 3 months or to continue for an additional 3 months. In children who completed 6 months of treatment, the decision is made to stop study treatment or to continue for an additional 3 months. Then, in children who completed 9 months of treatment, the decision is made to stop study treatment or to continue for an additional 3 months. In children &lt; 2 years with catheter-related thrombosis, the decision is made to stop study treatment at 1 month or to continue for an additional month. Then, in children who completed 2 months of treatment, the decision is made to stop study treatment or to continue for an additional month.</u></p> <p>Regardless of the duration of study treatment (&lt;u&gt;3, 3, 6, 9 or 12 months), an additional 1-month post-treatment observational period will be completed for all children. [...]</p>
<p><b>Number of children</b></p>	<p>At least <u>170</u> children are needed for this study, of whom 80 in the age group 12 to &lt; 18 years, 30 in the age group 6 to &lt; 12 years, 20 in the age group 2 to &lt; 6 years, and 20 in the age group <u>birth to &lt; 2 years, with at least 12 aged birth to &lt; 6 months.</u></p>
<p><b>Inclusion/exclusion criteria</b></p>	<p>Inclusion</p> <ol style="list-style-type: none"> <li>1. Children aged <u>birth to &lt; 18 years</u> with confirmed venous thromboembolism who receive initial treatment with therapeutic dosages of UFH, LMWH or fondaparinux and require anticoagulant therapy for at least 90 days. <u>However, children aged birth to &lt; 2 years with catheter-related thrombosis require anticoagulant therapy for at least 30 days.</u></li> <li>2. Informed consent provided and, if applicable, child assent provided</li> <li>3. <u>For children younger than 6 months:</u> <ul style="list-style-type: none"> <li>- <u>Gestational age at birth of at least 37 weeks.</u></li> <li>- <u>Oral feeding/nasogastric/gastric feeding for at least 10 days.</u></li> <li>- <u>Body weight &gt;2600 g.</u></li> </ul> </li> </ol> <p>Exclusion</p> <ol style="list-style-type: none"> <li>2. An estimated glomerular filtration rate (eGFR) &lt; 30 mL/min/1.73 m<sup>2</sup> <u>(in children younger than 1 year, serum creatinine results above 97.5<sup>th</sup> percentile excludes participation, see Table 17-1)</u></li> </ol>

[...]

<b>Primary efficacy outcome analysis</b>	Incidence proportions and cumulative incidences will be calculated for the primary efficacy outcome at the end of <u>the main study treatment period</u> .
<b>Secondary efficacy outcome analysis</b>	Incidence proportions and cumulative incidences will be calculated for the secondary efficacy outcome at the end of <u>the main study treatment period</u> .
<b>Other efficacy outcome analysis</b>	Incidence proportions will be calculated for the primary efficacy outcome <u>in the extended treatment period at 3 as well as 6, 9 and 12 months (see study flow charts)</u> .
<b>Principal safety outcome analysis</b>	Incidence proportions and cumulative incidences will be calculated for the principal safety outcome at the end of <u>the main study treatment period</u> .
<b>Other safety outcome analysis</b>	Incidence proportions will be calculated for the principal safety outcome <u>in the extended treatment period at 3 as well as 6, 9 and 12 months (see study flow charts)</u> .

[...]

**Table 0-1: Flow chart for all children except children aged < 2 years with catheter related thrombosis (see Table 2)**

Visit	Main Treatment period						Extended treatment period with blocks of 3 months			30-day post study treatment
	1		1a	2	3	4	5	6	7	8
Days	Before random	After random.	2+1 days after start t.i.d rivaroxaban <sup>p</sup>	Day 30 ± 7 days	Day 60 ± 7 days	Day 90 ± 7 days	Day 180 ± 7 days	Day 270 ± 7 days	Day 360 ± 7 days	30 ± 7 days After last visit
Contact	Visit	Visit	Visit	Visit	Visit	Visit	Visit	Visit	Visit	Visit or phone

**Pharmacokinetics (PK) and pharmacodynamics (PD) for rivaroxaban using t.i.d. regimen<sup>h</sup>**

Obtain PK blood sample <sup>i</sup>			•	•	• <sup>q</sup>	• <sup>q</sup>	•					
Obtain PD blood sample <sup>j,k</sup>					• <sup>q</sup>		•	•				
Time point for PK/PD blood sample (hours) if dosing continues beyond Day 90			0.5-3hr post dose	7-8hr post dose	0.5-3hr post dose	7-8hr post dose	2-6hr post dose	10-16hr after last evening dose, give next dose after PD sample				

Footnotes:

[...]

<sup>h</sup> The approximate total blood volume taken per child for PK/PD is 12 mL if blood taken via venipuncture (for t.i.d. regimen it is 7.2 mL), and up to 24 mL if blood taken via central venous line or peripheral catheter (see Section 6.14).

<sup>i</sup> Blood volume per PK sample is approximately 1.2 mL (for t.i.d. regimen it is 0.6 mL); total blood volume for all PK samples is 4.8 mL for o.d. and b.i.d. regimen and 3 mL for t.i.d. regimen.

<sup>j</sup> Blood volume per PD sample is approximately 1.8 mL (for t.i.d. regimen it is 1.4 mL); total blood volume for all PD samples is 7.2 mL for o.d. and b.i.d. regimen and 4.2 mL for t.i.d. regimen.

<sup>k</sup> Always draw the PD sample as the last sample.

<sup>l</sup> PD sample will not be collected at 0.5-1.5 hr after rivaroxaban intake for children < 6 years. Please note that this is different than in children < 2 years with catheter related thrombosis

<sup>q</sup> Visit 2 will be modified for children weighing < 3250 grams. The PK and PD samples taken 0.5 to 3 hours post-dose will be taken on a dosing day within the visit window (total volume to be drawn is 2.0 mL), and the 7-8 hour post-dose PK sample (total volume to be drawn is 0.6 ml) may be taken on the following dosing day within the visit window. This modification may only occur in children weighing less than 3250 kg at the time of visit 2

[...]

**Table 0-2 Flow chart for children aged < 2 years with catheter related thrombosis**

Visit	Main Treatment period				Extended treatment period with blocks of 30 days		30-day post study treatment
	1	1a	2	3	4	8	
Days	Before random.	After random.	2+1 days after start t.i.d. rivaroxaban <sup>m</sup>	Day 30 ± 7 days	Day 60 ± 7 days	Day 90 ± 7 days	30 ± 7 days After last visit <sup>f</sup>
Contact	Visit	Visit	Visit	Visit	Visit	Visit	Visit
Obtain informed consent	•						
Check in-/exclusion criteria	•						
Obtain demographic data	•						
Check medical history	•						
Record concomitant medication/anticoagulants	•						
Obtain height/length/body weight/blood pressure	•						
Check Hb, platelets, creatinine, ALT, total and direct bilirubin	• <sup>a</sup>						
Randomize patient using IxRS <sup>b</sup>		•					
Dispense study medication		•		•	• <sup>c</sup>	• <sup>c</sup>	
Dispense additional supplies (devices for oral suspension)		•		•	• <sup>c</sup>	• <sup>c</sup>	
Instruct how to take study medication <sup>l</sup>		•					
Send baseline adjudication package		•					
Check for adverse events		•	•	•	•	•	•
Check for device-related adverse events		•	•	•	•	•	
Obtain body weight				• <sup>d</sup>	• <sup>d</sup>	• <sup>d</sup>	
Check for study outcomes <sup>e</sup>			•	•	•	•	•
Check study drug accountability and compliance				•	•	•	
Check changes in concomitant medication			•	•	•	•	•
Obtain Hb, platelets, ALT, total and direct bilirubin				•			
Repeat imaging and send adjudication package <sup>f</sup>				•			
Complete eCRF	•	•	•	•	•	•	•
<b>Comparator group only</b>							
If INR-adjusted VKA <sup>g</sup>	1 INR per 2 weeks						

**Table 0-2 Flow chart for children < 2 years of age with catheter related thrombosis (continued)**

Visit	Main Treatment period					Extended treatment period with blocks of 30 days		30-day post study treatment
	1		1a	2		3	4	8
Days	Before random	After random	2+1 days after start t.i.d rivaroxaban <sup>m</sup>	Day 30 ± 7 days		Day 60 ± 7 days	Day 90 ± 7 days	30 ± 7 days After last visit <sup>f</sup>
Contact	Visit	Visit	Visit	Visit		Visit	Visit	Visit
<b>Pharmacokinetics (PK) and pharmacodynamics (PD) for rivaroxaban using b.i.d. regimen<sup>h</sup></b>								
Administer rivaroxaban at study site				●		●		
Take up to 240 mL of liquid immediately after dosing				●		●		
Obtain PK blood sample <sup>1</sup>				●	●	●		
Obtain PD blood sample <sup>j,k</sup>					●	●		● <sup>o</sup>
Time point for PK/PD blood sample (hours)				10-16hr after last evening dose, give next dose after PK sample	0.5-1.5hr post dose	2.5-4hr post dose	2-8hr post dose	
<b>PK and PD for rivaroxaban using t.i.d. regimen<sup>h</sup></b>								
Administer rivaroxaban at study site			●	●		●		
Take up to 120 mL of liquid immediately after dosing			●	●		●		
Obtain PK blood sample <sup>1</sup>			●	●	● <sup>o</sup>	● <sup>o</sup>		
Obtain PD blood sample <sup>j,k</sup>					● <sup>o</sup>	●		● <sup>n</sup>
Time point for PK/PD blood sample (hours)			0.5-3hr post dose	7-8hr post dose	0.5-3hr post dose	7-8hr post dose	2-6hr post dose	

Footnotes:

- <sup>a</sup> Blood sample should be obtained within a maximum of 5 days prior to randomization.
- <sup>b</sup> Randomization can be done during the first 9 days of initial therapy with UFH, LMWH or fondaparinux.
- <sup>c</sup> If study treatment is continued, provide study medication
- <sup>d</sup> Adjust dosage of study medication and treatment regimen, if change in body weight. Additional visits can be planned to accommodate dose adjustment of study medication, if applicable.
- <sup>e</sup> If suspected outcome occurred, the adjudication package needs to be compiled and sent to the adjudication office.
- <sup>f</sup> After the main study treatment period of 1 month, the diagnostic imaging test which was obtained at baseline will be repeated, if clinically feasible.
- <sup>g</sup> VKA compliance will be ensured by minimum of 1 INR per 2 weeks.
- <sup>h</sup> The approximate total blood volume taken per child for PK/PD is 12 mL for b.i.d. and 7.2 mL for t.i.d. if blood taken via venipuncture, and up to 24 mL if blood taken via central venous line or peripheral catheter (see Section 6.14).
- <sup>i</sup> Blood volume per PK sample is approximately 1.2 mL for b.i.d. and 0.6 mL for t.i.d.; total blood volume for all PK samples is 4.8 mL for b.i.d. and 3 mL for t.i.d.
- <sup>j</sup> Blood volume per PD sample is approximately 1.8 mL for b.i.d. and 1.4 mL for t.i.d.; total blood volume for all PD samples is 7.2 mL for b.i.d. and 4.2 mL for t.i.d.
- <sup>k</sup> Always draw the PD sample as the last sample.
- <sup>l</sup> In addition, provide Rivaroxaban Oral Suspension Handling Instructions, and Study Booklet
- <sup>m</sup> Only in children treated with rivaroxaban t.i.d. regimen. If visit 1a falls on a weekend and cannot take place, the visit must be scheduled for the following Monday.
- <sup>n</sup> Visit 8 cannot be conducted by phone in children who are aged < 2 with catheter-related thrombosis, as a PD sample must be collected at this visit. If the patient is started on another anticoagulant during the 30 day post study treatment period, the PD sample needs to be taken at least 8 hours after last dose of rivaroxaban and before initiation of a new anticoagulant.
- <sup>o</sup> Visit 2 will be modified for children weighing < 3250 grams. The PK and PD samples taken 0.5 to 3 hours post-dose will be taken on a dosing day within the visit window (total volume to be drawn is 2.0 mL), and the 7-8 hour post-dose PK sample (total volume to be drawn is 0.6 ml) may be taken on the following dosing day within the visit window. This modification may only occur in children weighing less than 3250 kg at the time of visit 2.

o.d. = once daily dosing  
b.i.d. = twice daily dosing  
t.i.d. = three times daily dosing  
eCRF = electronic case report form;  
IxRS = interactive voice/ web response system  
PTS = post-thrombotic syndrome

### 16.4.2.3 Section 1 Introduction

The section was changed based on modification 1.

*Old text:*

[...]

In phase II, enrollment of children ~~from 2~~ to less than 18 years has been completed. Rivaroxaban was well tolerated, ~~compliance with rivaroxaban was optimal~~, no recurrent venous thromboembolism and/or major bleeding were observed and PK/PD results ~~confirmed a similar exposure as in adults receiving 20 mg of rivaroxaban once daily. Therefore, as in adults, there is no need for monitoring the anticoagulant activity of rivaroxaban in children.~~

[...]

Once the age-and body weight adjusted dosing regimen has been confirmed for the age group between 6 months and less than 2 years in the phase II study 14374 and approved by the data monitoring committee and steering committee, the dosing schedule/regimen for this age group will be made available through an administrative amendment. The investigators and ethics committees/IRBs will receive the administrative amendment well in advance with an



opportunity for evaluation before permission will be given to start enrolling children in this age group.

*New text:*

In phase II, enrollment of children aged 6 months to less than 18 years has been completed. Rivaroxaban was well tolerated, no recurrent venous thromboembolism and/or major bleeding were observed and PK/PD results were in the expected range for children weighing more than 12 kg.

[...]

The age-and body weight adjusted dosing regimen has now been established for all children aged birth to less than 18 years from data collected in the phase I/II studies and has been approved by the data monitoring committee and steering committee. Table 17-2 specifies the dosing regimen for each age group.

#### 16.4.2.4 Section 3 Study design

The section was changed based on modification 1.

*Old text:*

[...]

Once the age-and body weight adjusted dosing regimen has been confirmed for the age group between 6 months and less than 2 years in the phase II study 14374 and approved by the data monitoring committee and steering committee, the dosing schedule/regimen for this age group will be made available through an administrative amendment (update: implemented through Amendment 8). The investigators and ethics committees/IRBs will receive the administrative amendment well in advance with an opportunity for evaluation before permission will be given to start enrolling children in this age group.

[...]

The PK samples obtained at Visit 1a will be shipped and analyzed for each child individually and will allow to determine whether the plasma concentrations are in the adult reference range. The results will be provided to the investigator/site and discussed in a timely manner, i.e. within approximately 1 to 2 weeks after sample collection.

[...]

#### Study description

Children aged ~~6 months~~ to < 18 years with confirmed acute venous thromboembolism who receive initial treatment with therapeutic dosages of unfractionated heparin (UFH), low molecular weight heparin (LMWH), or fondaparinux are potentially eligible for the study. Initial treatment with UFH, LMWH or fondaparinux will be administered for at least 5 days (day 1- 5).

[...]

After randomization, children will receive either rivaroxaban or comparator for a main study treatment period of 3 months. After the main study treatment period of 3 months, the diagnostic imaging test which was obtained at baseline will be repeated, if clinically feasible ~~and~~ the decision is made to stop study treatment or to continue for an additional 3 months. In children who completed 6 months of treatment, the decision is made to stop study treatment or to continue for an additional 3 months. Then, in children who completed 9 months of treatment, the decision is made to stop study treatment or to continue for an additional 3 months. -Regardless of the duration of study treatment (3, 6, 9 or 12 months), an additional 1-month post-treatment observational period will be completed for all children. After cessation of study treatment, it is at the investigator's discretion to continue with anticoagulants.

[...]

For all children, visits are scheduled at regular time points (see Table 0-1). Randomized children who have not received the study drug will be seen (visit or phone contact) at the end of the respective study treatment period ~~at month 3~~. Children who prematurely discontinue study drug will be seen at the end of the intended study treatment period at month 3, 6, 9 or 12. During all contacts, the treatment and clinical course of the child will be evaluated. Children with suspected efficacy or safety outcomes will undergo confirmatory testing as per standard of care. Blood samples for PK/PD will be taken at defined time points (see ~~Table 0-4~~).

[...]

*New text:*

[...]

Once the age-and body weight adjusted dosing regimen has been confirmed for the age group between 6 months and less than 2 years in the phase II study 14374 and approved by the data monitoring committee and steering committee, the dosing schedule/regimen for this age group will be made available through an administrative amendment (update: implemented through Amendment 8). The investigators and ethics committees/IRBs will receive the administrative amendment well in advance with an opportunity for evaluation before permission will be given to start enrolling children in this age group.

The age-and body weight adjusted dosing regimen has now been established for all children aged birth to less than 18 years from data collected in the phase I/II studies and has been approved by the data monitoring committee and steering committee. Table 17-2 specifies the dosing regimen for each age group.

[...]

The PK samples obtained at Visit 1a will be shipped and analyzed for each child individually and will allow to determine whether the plasma concentrations are in the adult reference range. The results will be provided to the investigator/site and discussed in a timely manner, i.e. within approximately 1 to 2 weeks after sample collection. Up to now, the predictions from the exploratory PopPK model are confirmed by the data from children enrolled in this weight group.

Amendment 12 opened enrollment to children aged birth to < 6 months and introduced dosing information for children with a body weight between 2.6 and 6 kg. This new dosing regimen is based on data from all studies in children younger than 2 years, as well as an exploratory PopPK model, that considers all rivaroxaban PK data available from all children younger than 2 years. As the exploratory model is based on limited data (e.g., limited number of subjects, sparse sampling), the model predictions had a higher level of uncertainty for these children. However, observed data from this study (14372) and data from the phase I/II study (17618) that is enrolling children of this weight category, have confirmed the predictions from the exploratory PopPK model in all children dosed t.i.d thus far in both studies.

### Study description

Children aged birth to < 18 years with confirmed acute venous thromboembolism who receive initial treatment with therapeutic dosages of unfractionated heparin (UFH), low molecular weight heparin (LMWH), or fondaparinux are potentially eligible for the study. Initial treatment with UFH, LMWH or fondaparinux will be administered for at least 5 days (day 1-5).

[...]

After randomization, children will receive either rivaroxaban or comparator for a main study treatment period of 3 months. After the main study treatment period of 3 months, the diagnostic imaging test which was obtained at baseline will be repeated, if clinically feasible. However, in children younger than 2 years with catheter-related thrombosis, the main study treatment period is for a total of 1 month at which time the repeat imaging will be performed.

In all children, except those aged < 2 years with catheter-related thrombosis, the decision is made to stop study treatment at 3 months or to continue for an additional 3 months. In children who completed 6 months of treatment, the decision is made to stop study treatment or to continue for an additional 3 months. Then, in children who completed 9 months of treatment, the decision is made to stop study treatment or to continue for an additional 3 months. In children < 2 years with catheter-related thrombosis, the decision is made to stop study treatment at 1 month or to continue for an additional month. Then, in children who completed 2 months of treatment, the decision is made to stop study treatment or to continue for an additional month.

Regardless of the duration of study treatment (≤3, 3, 6, 9 or 12 months), an additional 1-month post-treatment observational period will be completed for all children. After cessation of study treatment, it is at the investigator's discretion to continue with anticoagulants.

[...]

For all children, visits are scheduled at regular time points (see Table 0–1 and Table 0–2). Randomized children who have not received the study drug will be seen (visit or phone contact) at the end of the respective main study treatment period. Children who prematurely discontinue study drug will be seen at the end of the intended study treatment period at month ≤3, 3, 6, 9 or 12. During all contacts, the treatment and clinical course of the child will be evaluated. Children with suspected efficacy or safety outcomes will undergo confirmatory

testing as per standard of care. Blood samples for PK/PD will be taken at defined time points (see Table 0–1 and Table 0–2).

[...]

#### **16.4.2.5 Section 4.1 planned number of children**

The section was changed based on modification 1.

*Old text:*

At least 150 children are needed for this study, of whom 80 in the age group 12 to < 18 years, 30 in the age group 6 to < 12 years, 20 in the age group 2 to < 6 years, and 20 in the age group ~~6 months~~ to < 2 years.

*New text:*

At least 170 children are needed for this study, of whom 80 in the age group 12 to < 18 years, 30 in the age group 6 to < 12 years, 20 in the age group 2 to < 6 years, and 20 in the age group birth to < 2 years, with at least 12 aged birth to < 6 months.

#### **16.4.2.6 Section 4.2 Inclusion criteria**

The section was changed based on modification 1.

*Old text:*

1. Children aged ~~6 months to~~ < 18 years with confirmed venous thromboembolism who receive initial treatment with therapeutic dosages of UFH, LMWH or fondaparinux and require anticoagulant therapy for at least 90 days.
2. Informed consent provided and, if applicable, child assent provided

*New text:*

1. Children aged birth to < 18 years with confirmed venous thromboembolism who receive initial treatment with therapeutic dosages of UFH, LMWH or fondaparinux and require anticoagulant therapy for at least 90 days. However, children aged birth to < 2 years with catheter-related thrombosis require anticoagulant therapy for at least 30 days.
2. Informed consent provided and, if applicable, child assent provided
3. For children younger than 6 months:
  - Gestational age at birth of at least 37 weeks.
  - Oral feeding/nasogastric/gastric feeding for at least 10 days.
  - Body weight  $\geq$ 2600 g

#### **16.4.2.7 Section 4.3 Exclusion criteria**

The section was changed based on modification 1.

*Old text:*

2. An estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m<sup>2</sup>

*New text:*

2. An estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m<sup>2</sup> (in children younger than 1 year, serum creatinine results above 97.5<sup>th</sup> percentile excludes participation, see Table 17-1).

#### **16.4.2.8 Section 5.1.1 Rivaroxaban group**

The section was changed based on modification 1.

*Old text:*

The body weight adjusted dosing schedule for children aged ~~6 months~~ to < 18 years is provided in Appendix 4 (see Section 17.4).

[...]

Dosing regimen, including dosing frequency, will be adjusted if the child's body weight changes during the study (~~Table 17-1~~).

With a once daily regimen, rivaroxaban will be taken in the morning during or within 2 hours after breakfast. With a twice daily regimen the morning dose will be taken during or within ~~2~~ hours after breakfast and the evening dose will be taken during or within ~~2~~ hours after dinner. With a three times daily regimen, the morning, afternoon and night doses should be taken during or within ~~2 hours~~ after feeding.

[...]

#### **Use of oral suspension**

Oral suspension is available for use in children aged ~~6 months~~ to < 18 years.

*New text:*

The body weight adjusted dosing schedule for children aged birth to < 18 years is provided in Appendix 4 (see Section 17.4).<sup>22</sup>

[...]

Dosing regimen, including dosing frequency, will be adjusted if the child's body weight changes during the study (Table 17-2).

With a once daily regimen, rivaroxaban will be taken in the morning during or within 2 hours after breakfast. With a twice daily regimen the morning dose will be taken during or within 1 hour after breakfast and the evening dose will be taken during or within 1 hour after dinner. With a three times daily regimen, the morning, afternoon and night doses should be taken during or within 30 minutes after feeding.

[...]

### Use of oral suspension

Oral suspension is available for use in children aged birth to < 18 years.

[...]

#### 16.4.2.9 Section 5.3 Duration of study treatment

The section was changed based on modification 1.

*Old text:*

The main study treatment period is 3 months. After that, it is up to the discretion of the treating physician to stop study treatment or to continue for an additional 3 months.

In children who completed 6 months of treatment, the decision can be made to stop study treatment or to continue for an additional 3 months. Then, in children who completed 9 months of treatment, the decision can be made to stop study treatment or to continue for an additional 3 months. Thereafter, no prolongation of study treatment can take place.

Children who turn 2, 6, 12 or 18 years after randomization can continue their treatment regimen.<sup>92</sup> Specifically children who turn 18 years after randomization are allowed to continue participation for the entire elected study treatment duration of 3, 6, 9 or 12 months.

Children randomized last into the study will have a minimal study treatment duration of 3 months.

*New text:*

In all children, except those aged < 2 years with catheter-related thrombosis, the main study treatment period is 3 months. After that, it is up to the discretion of the treating physician to stop study treatment or to continue for an additional 3 months.

In children who completed 6 months of treatment, the decision can be made to stop study treatment or to continue for an additional 3 months. Then, in children who completed 9 months of treatment, the decision can be made to stop study treatment or to continue for an additional 3 months. Thereafter, no prolongation of study treatment can take place.

In children aged < 2 years with catheter-related thrombosis, the main study treatment period is 1 month. After that, it is up to the discretion of the treating physician to stop study treatment or to continue for an additional 1 month.

In children who completed 2 months of treatment, the decision can be made to stop study treatment or to continue for an additional 1 months. Thereafter, no prolongation of study treatment can take place.

Children who turn 2, 6, 12 or 18 years after randomization can continue their treatment regimen. Specifically children who turn 18 years after randomization are allowed to continue participation for the entire elected study treatment duration of 3, 6, 9 or 12 months.

Children randomized last into the study will have a minimal study treatment duration of 3 months, except children aged < 2 years with catheter-related thrombosis, who will have a minimal study treatment duration of 1 month.

#### **16.4.2.10 Section 5.4.1 Rivaroxaban**

The section was changed based on modification 1.

*Old text:*

Rivaroxaban will be provided by Bayer as immediate-release film-coated tablets, and as a granules for oral suspension formulation (0.1% suspension as finally administered drug product), see Table 5–1. Rivaroxaban will be dosed according to body weight groups as detailed in the dosing schedules/regimens associated with this protocol Since children with an estimated glomerular filtration rate below 30 mL/min/1.73 m<sup>2</sup> are excluded from the study, dose reduction for impaired renal function is not required.

[...]

*New text:*

Rivaroxaban will be provided by Bayer as immediate-release film-coated tablets, and as a granules for oral suspension formulation (0.1% suspension as finally administered drug product), see Table 5–1. Rivaroxaban will be dosed according to body weight groups as detailed in the dosing schedules/regimens associated with this protocol Since children with an estimated glomerular filtration rate below 30 mL/min/1.73 m<sup>2</sup> (in children younger than 1 year, serum creatinine results above 97.5<sup>th</sup> percentile, see Table 17–1) are excluded from the study, dose reduction for impaired renal function is not required.

#### **16.4.2.11 Section 5.5 Packaging, labeling and storage**

The section was changed based on modification 2.

*Old text:*

[...]

All study medication needs to be stored at the site according to the labeled storage advice in accordance with Good Clinical Practice (GCP) and GMP requirements. The study drug is to be kept in a secure area. ~~Complete records of batch numbers and expiry dates can be found in the study file.~~

[...]

*New text:*

[...]

All study medication needs to be stored at the site according to the labeled storage advice in accordance with Good Clinical Practice (GCP) and GMP requirements. The study drug is to be kept in a secure area.

[...]

#### **16.4.2.12 Section 5.8 Study treatment and compliance assessment**

*Old text:*

A 1-month supply of drug will be given at visits 1, 2, and 3, if applicable. In children who continue study treatment for an additional 3 months, study drug will be supplied at visit 4 covering a 3-month period. In children who continue the study for a third and a fourth cycle of 3 months; study drug will be supplied at visits 5 and 6.

[...]

*New text:*

A 1-month supply of drug will be given at visits 1, 2, and 3, if applicable. In children who continue study treatment for an additional 3 months, (not applicable to children aged < 2 years with catheter-related thrombosis) study drug will be supplied at visit 4 covering a 3-month period. In children who continue the study for a third and a fourth cycle of 3 months; study drug will be supplied at visits 5 and 6.

[...]

#### **16.4.2.13 Section 6.1 Study visits**

The section was changed based on modification 1.

*Old text:*

The study has ~~5~~ to 8 planned visits, depending on the elected study duration.

*New text:*

The study has 4 to 9 planned visits, depending on the elected study duration and dosing.

#### **16.4.2.14 Section 6.3 Visit 1a (2+1 days after start t.i.d rivaroxaban)**

The section was changed based on modification 1.

*Old text:*

[...]

- Document the exact time of rivaroxaban intake as well as the time and type of meal (i.e. breakfast, lunch, dinner) the child took within ~~2 hours before and 2 hours~~ after rivaroxaban.

[...]

*New text:*

[...]

- Document the exact time of rivaroxaban intake as well as the time and type of meal (i.e. breakfast, lunch, dinner) the child took during or within 30 minutes after rivaroxaban.

[...]



#### 16.4.2.15 Section 6.4 Visit 2 at Day 30 ( $\pm$ 7 days)

The section was changed based on modification 1.

*Old text:*

[...]

- Document the exact time of rivaroxaban intake as well as time and type of meal (i.e. breakfast, lunch, dinner) the child took ~~within 2 hours before and 2 hours after~~ rivaroxaban.

[...]

- In children < 6 years, no PD sample will be collected after the PK sample at 0.5-1.5 hours, but a PD sample will be taken after the PK sample at 2.5-4 hours

[...]

- Blood sampling for t.i.d. regimen (oral suspension):

[...]

- Document the exact time of blood sampling for PK/PD

[...]

*New text:*

- Document the exact time of rivaroxaban intake as well as time and type of meal (i.e. breakfast, lunch, dinner) the child took in relation to rivaroxaban.

[...]

- In children < 2years with catheter related thrombosis receiving the b.i.d. regimen, a PK sample will also be collected at 10-16h after last evening dose of rivaroxaban, but before the first morning dose.
- In children < 6 years receiving rivaroxaban b.i.d., no PD sample will be collected after the PK sample at 0.5-1.5 hours, but a PD sample will be taken after the PK sample at 2.5-4 hours

[...]

- Blood sampling for t.i.d. regimen (oral suspension):

[...]

- Visit 2 will be modified for children weighing < 3250 grams. The PK and PD samples taken 0.5 to 3 hours post-dose will be taken on a dosing day within the visit window (total volume to be drawn is 2.0 mL), and the 7-8 hour post-dose PK sample (total volume to be drawn is 0.6 ml) may be taken on the following dosing day within the visit window. This modification may only occur in children weighing less than 3250 kg at the time of visit 2.

[...]

- Document the exact time of rivaroxaban dosing and blood sampling for PK/PD  
[...]

**Following procedures are applicable only to children <2 years of age with catheter related thrombosis:**

- Obtain safety blood sample for hemoglobin, platelets, ALT, total and direct bilirubin.
- Repeat imaging with ultrasound, if applicable. If repeat imaging can be done with magnetic resonance imaging (MRI) or MR angiography, this should be done only if sedation and/or general anesthesia are not required. Other modalities of imaging, e.g. computed tomography (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.
- After the main 30 day study treatment period in children aged < 2 years with catheter related thrombosis, the decision is made to stop study treatment or to continue for an additional 30 days. If study treatment is stopped, the 30-day post study treatment visit (Visit 8) will be scheduled. If study treatment is continued for 30 days, a visit (Visit 3) will be schedule at day 60 ± 7 days.

**16.4.2.16 Section 6.5 Visit 3 at Day 60 (± 7 days)**

The section was changed based on modification 1.

*Old text:*

[...]

- Document the exact time of rivaroxaban intake as well as the time and type of meal (i.e. breakfast, lunch, dinner) the child took ~~within 2 hours before and 2 hours after~~ rivaroxaban.

[...]

- Provide instructions for the day before visit 4

[...]

- Document the exact time of rivaroxaban intake as well as the time and type of meal (i.e. breakfast, lunch, dinner) the child took ~~within 2 hours before and 2 hours after~~ rivaroxaban.

[...]

*New text:*

- Document the exact time of rivaroxaban intake as well as the time and type of meal (i.e. breakfast, lunch, dinner) the child took in relation to rivaroxaban

[...]

- Provide instructions for the day before visit 4

[...]

- Document the exact time of rivaroxaban intake as well as the time and type of meal (i.e. breakfast, lunch, dinner) the child took in relation to rivaroxaban.

[...]

**Following procedures are applicable only to children <2 years of age with catheter related thrombosis:**

- If study treatment is stopped, the 30-day post study treatment visit will be scheduled. If study treatment is continued for an additional 30 days, a visit (Visit 4) will be schedule at day 90 ± 7 days. If study treatment is stopped, the 30-day post study treatment visit will be scheduled

**16.4.2.17 Section 6.6 Visit 4 at Day 90 (± 7 days)**

The section was changed based on modification 1.

*Old text:*

- In children randomized to rivaroxaban:
  - Document the exact time of rivaroxaban intake on the day prior to visit 4 and time and type of meal the child took ~~within 2 hours before and 2 hours after~~ rivaroxaban as well as the volume and type of liquid taken.

[...]

- If rivaroxaban is given using a b.i.d. regimen, collect the blood sample for hemoglobin, platelets, ALT, total and direct bilirubin, followed by PK blood sample and finally the PD blood sample at 10 to 16 hours after the last evening dose
- If rivaroxaban is given using a t.i.d. regimen, collect hemoglobin, platelets, ALT, total and direct bilirubin, followed by the PD blood sample 10 to 16 hours after the last evening dose
- If dosing continues beyond visit 4/day 90, give next dose after PD sample

[...]

After the main 3-month study treatment period, the decision is made to stop study treatment or to continue for an additional 3 months. If study treatment is stopped, the 30-day post study treatment visit will be scheduled.

[...]

*New text:*

- In children randomized to rivaroxaban:
  - Document the exact time of rivaroxaban intake on the day prior to visit 4 and time and type of meal the child took in relation to rivaroxaban as well as the volume and type of liquid taken.

[...]

- If rivaroxaban is given using a b.i.d. regimen, collect the blood sample for hemoglobin, platelets, ALT, total and direct bilirubin, followed by PK blood sample and finally the PD blood sample at 10 to 16 hours after the last evening dose (in all children except those aged < 2 years with catheter related thrombosis).
- If rivaroxaban is given using a t.i.d. regimen, collect hemoglobin, platelets, ALT, total and direct bilirubin, followed by the PD blood sample 10 to 16 hours after the last evening dose (in all children except those aged < 2 years with catheter related thrombosis).
- If dosing continues beyond visit 4/day 90, give next dose after PD sample (in all children except those aged < 2 years with catheter related thrombosis)

[...]

After the main 3-month study treatment period in all children except those aged < 2 years with catheter related thrombosis, the decision is made to stop study treatment or to continue for an additional 3 months.

#### **16.4.2.18 Section 6.8 Visit 8, 30 day post study treatment contact (30 days ± 7 days after last visit)**

The section was changed based on modification 1.

*Old text:*

##### **Section 6.8 30 day post study treatment contact (30 days ± 7 days after last visit)**

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 30 days ± 7 after the last visit of the patient.

*New text:*

##### **Section 6.8 Visit 8, 30 day post study treatment contact (30 days ± 7 days after last visit)**

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 (telephone contact cannot be conducted in children who are aged < 2 with catheter-related thrombosis) will take place 30 days ± 7 after the last visit of the patient.

[...]

**Following procedures are applicable only to children <2 years of age with catheter related thrombosis:**

- This visit cannot occur by telephone
- Check changes in concomitant medications
- Obtain PD blood sample
  - If the patient is started on another anticoagulant during the 30 day post study treatment period, the PD sample needs to be taken at least 8 hours after last dose of rivaroxaban and before initiation of a new anticoagulant.

**16.4.2.19 Section 6.14 PK/PD assessments**

The section was changed based on modification 1.

*Old text:*

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

Blood samples will be taken for PK and PD measurements from children randomized to rivaroxaban.

- The following blood samples will be taken in children with **o.d. or b.i.d. regimen:**
  - [...]
- The following blood samples will be taken in children with **t.i.d. regimen:**
  - [...]

[...]

If a blood sample is taken from a central line, 3 mL of blood ~~should be discarded.~~

[...]

*New text:*

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

Blood samples will be taken for PK and PD measurements from children randomized to rivaroxaban.

The following blood samples will be taken in children without catheter related thrombosis and with

- **o.d. (children with body-weight > 30 kg) or b.i.d. (children with body weight 12-30 kg) regimen:**
  - [...]
- **t.i.d. regimen (children with body-weight < 12 kg) :**

- [...]

The following blood samples will be taken in children aged < 2 years with catheter related thrombosis and

- **b.i.d regimen (children with body weight  $\geq 12$  kg):**
  - one pre-dose PK sample at visit 2
  - two post-dose PK/PD samples at visit 2, and
  - one post-dose PK/PD sample at visit 3, if occurs, and
  - one PD sample at visit 8
- **t.i.d regimen (children with body weight <12 kg)**
  - two post-dose PK sample at visit 1a, and
  - two post-dose PK sample at visit 2
  - one post-dose PD sample at visit 2, and
  - one post-dose PK/PD sample at visit 3, if occurs, and
  - one PD sample at visit 8

[...]

If a blood sample is taken from a central line, it is recommended to discard 3 mL of blood. For small children a smaller blood volume can be discarded and sites can follow their own practical standard.

#### 16.4.2.20 Section 7.4 Bleeding analysis

The section was changed based on modification 1.

*Old text:*

[...]

Incidence proportions (number of children with outcome during the period divided by number of children at risk at the beginning of the period) and cumulative incidences (time to first event; Kaplan-Meier) will be calculated for the primary safety outcome by treatment group at ~~3 months~~ for pooled data. Incidence proportions will be calculated for each age stratum at ~~3 months~~ as well. In addition, incidence proportions will be calculated by treatment group and overall at 6, 9 and 12 months. Denominators in this case will be the number of patients at risk at the start of the respective period. ~~Incidences will be calculated for 3 to 6 month study period, 6 to 9 month study period, and 9 to 12 month period, separately.~~

[...]

*New text*

[...]

Incidence proportions (number of children with outcome during the period divided by number of children at risk at the beginning of the period) and cumulative incidences (time to first event; Kaplan-Meier) will be calculated for the primary safety outcome by treatment group at the end of the main study treatment period for pooled data. Incidence proportions will be calculated for each age stratum at the end of the main study treatment period as well. In addition, incidence proportions will be calculated by treatment group for each age stratum and pooled data overall in the extended study treatment period at 2 and 3 months (for the children <2 years with catheter related thrombosis) and at 6, 9 and 12 months (for the other groups). Denominators in this case will be the number of patients at risk at the start of the respective period.

[...]

#### 16.4.2.21 Section 7.5 Efficacy analysis

The section was changed based on modification 1.

*Old text:*

All efficacy analyses will be performed on the full analysis set population based on the outcomes confirmed by the CIAC. Incidence proportions and cumulative incidences (time to first event; Kaplan-Meier) will be calculated for the primary and secondary efficacy outcomes by treatment group at ~~3 months~~ for pooled data. In addition, incidence proportions will be calculated for each age stratum at ~~3 months~~. Incidence proportions will be calculated for the primary outcomes by treatment group and overall at 6, 9 and 12 months. Denominators will be the number of patients at risk at the start of the respective period. ~~Incidencees will be calculated for the 3 to 6 month study period, 6 to 9 month study period, and 9 to 12 month study period, separately.~~

[...]

*New text:*

All efficacy analyses will be performed on the full analysis set population based on the outcomes confirmed by the CIAC. Incidence proportions and cumulative incidences (time to first event; Kaplan-Meier) will be calculated for the primary and secondary efficacy outcomes by treatment group at the end of the main study treatment period for pooled data. In addition, incidence proportions will be calculated for each age stratum at the end of the main study treatment period. Incidence proportions will be calculated for the primary outcomes by treatment group for each age stratum and pooled data overall in the extended study treatment period at 2 and 3 months (for the children <2 years with catheter related thrombosis) and, at 6, 9 and 12 months (for the other groups). Denominators will be the number of patients at risk at the start of the respective period.

[...]

### **Subgroup analysis**

Demographic and other baseline characteristics, as well as efficacy, safety and PK/PD data will be summarized for the main treatment period (up to the month 3 visit) for each age group and for combinations of age groups.

#### **16.4.2.22 Section 7.8 Determination of sample size**

The section was changed based on modification 1.

*Old text:*

At least 150 children 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.

*New text:*

At least 170 children 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.

#### **16.4.2.23 Section 15 References**

The section was changed based on modification 1.

*Old text:*

Not applicable.

*New text:*

18. Boer DP, Rijke YB, Hop WC et al. Reference values for serum creatinine in children younger than 1 year of age. *Pediatr Nephrol* 2010;25:2107-2113.

#### **16.4.2.24 Section 17.2 Appendix 2: Estimated glomerular filtration rate**

The section was changed based on modification 1.

*Old text:*

Not applicable.

*New text:*

[...]

For children younger than 1 year, the serum creatinine levels provided in Table 17-1 are used instead of eGFR < 30 mL/min/1.73m<sup>2</sup> to evaluate the eligibility regarding to the exclusion criterion 2 in Section 4.3. A serum creatinine above the 97.5th percentile excludes participation in the study.



**Table 17–1: Serum creatinine 97.5<sup>th</sup> percentile in children aged < 1<sup>[18]</sup>**

Age Group	Serum creatinine (micromol/L)
Week 2	46
Week 3	41
Week 4	37
Month 2	33
Month 3	30
Month 4-6	30
Month 7-9	30
Month 10-12	32

**16.4.2.25 Section 17.4 Appendix 4: Dosing table for children from birth to 18 years**

The section was changed based on modification 1.

*Old text:*

**Section 17.4 Appendix 4: Dosing table for children from 6 to 18 years**

[...]

**Table 17–2: Body weight-adjusted rivaroxaban dosing schedule for children aged 6 months to < 18 years**

Body weight (kg)		Formulation	o.d. Dose	b.i.d. Dose	t.i.d. Dose	Total Daily Dose
Min	Max					
5	<6	Oral suspension			1.8 mg	5.4 mg
6*	<7	Oral suspension			1.6 mg	4.8 mg

[...]

*New text:*

**Section 17.4 Appendix 4: Dosing table for children from birth to 18 years**

[...]



**Table 17–2: Body weight-adjusted rivaroxaban dosing schedule for children aged birth to < 18 years**

Body weight (kg)		Formulation	o.d. Dose	b.i.d. Dose	t.i.d. Dose	Total Daily Dose
Min	Max					
<u>2.6</u>	<u>&lt;3</u>	<u>Oral suspension</u>			<u>0.8 mg</u>	<u>2.4 mg</u>
<u>3</u>	<u>&lt;4</u>	<u>Oral suspension</u>			<u>0.9 mg</u>	<u>2.7 mg</u>
<u>4</u>	<u>&lt;5</u>	<u>Oral suspension</u>			<u>1.4 mg</u>	<u>4.2 mg</u>
<u>5</u>	<u>&lt;6</u>	<u>Oral suspension</u>			<u>1.6 mg</u>	<u>4.8 mg</u>
<u>6*</u>	<u>&lt;7</u>	<u>Oral suspension</u>			<u>1.6 mg</u>	<u>4.8 mg</u>

[...]

## 17. Appendices

### 17.1 Appendix 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 Appendix 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:<sup>[12]</sup>

$eGFR \text{ (mL/min/1.73 m}^2\text{)} = k * \text{height (cm)} / \text{SCr (mg/dL)}$  where k is proportionality constant:<sup>92</sup>

Where k is proportionality constant:

k = 0.33 in pre-term infants up to 1 year

k = 0.45 in full-term infants up to 1 year

k = 0.55 in children 1 year to 13 years

k = 0.55 in girls > 13 and < 18 years

k = 0.70 in boys > 13 and < 18 years

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:<sup>[13]</sup>

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

The National Kidney Disease Education Program website

([http://www.nkdep.nih.gov/professionals/gfr\\_calculators/index.htm](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. SCr in micromoles per liter, the value should be multiplied by 88.4 (1 mg/dL = 88.4 umol/L).

<sup>92</sup> eGFR calculation was updated via Amendment 8 (see Section 16.2.2.23)

For children younger than 1 year, the serum creatinine levels provided in [Table 17–1](#) are used instead of eGFR < 30 mL/min/1.73m<sup>2</sup> to evaluate the eligibility regarding to the exclusion criterion 2 in Section 4.3. A serum creatinine above the 97.5<sup>th</sup> percentile excludes participation in the study.<sup>93</sup>

**Table 17–1 Serum creatinine 97.5<sup>th</sup> percentile in children aged < 1** <sup>[18]</sup> <sup>94</sup>

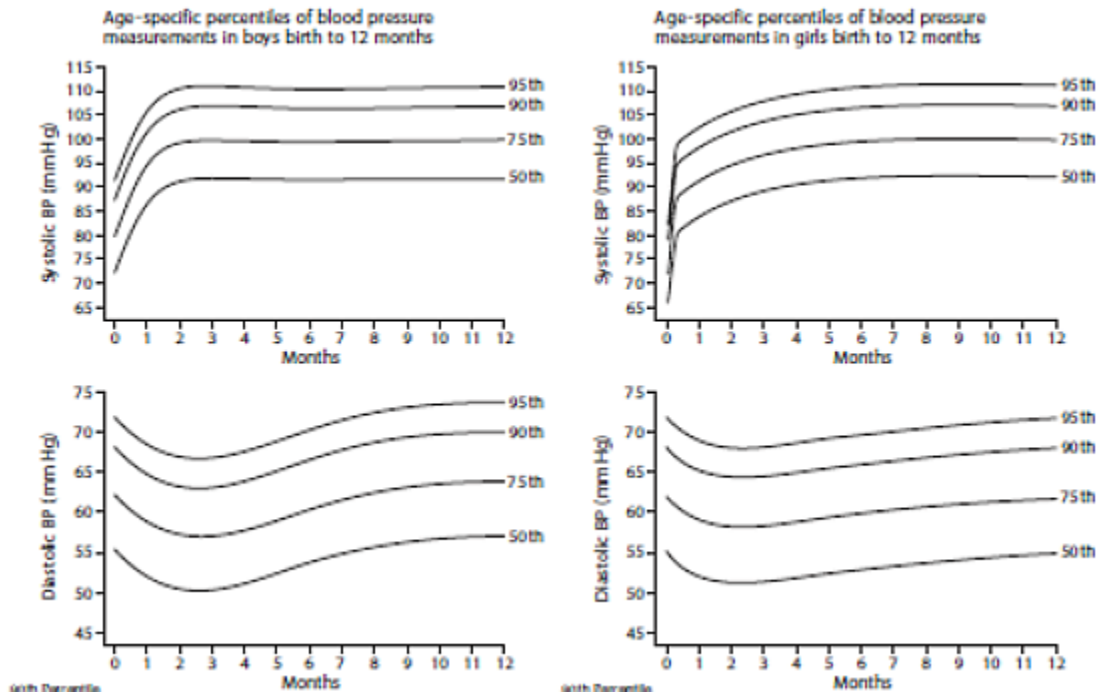
Age Group	Serum creatinine (micromol/L)
Week 2	46
Week 3	41
Week 4	37
Month 2	33
Month 3	30
Month 4-6	30
Month 7-9	30
Month 10-12	32

<sup>93</sup> Text added via Amendment 12 (see Section [16.4.2.24](#))

<sup>94</sup> Table 17-1 and guidance that serum creatinine level should be used instead of eGFR for children <1 year when evaluating eligibility and were added via Amendment 12 (see Section [16.4.2.24](#))

### 17.3 Appendix 3: Reference values for blood pressure in children

**Figure 1** Age-specific percentiles of blood pressure in children from birth to 12 months



Source: Report of the Second Task Force on Blood Pressure Control in Children .Pediatrics 1987; 79(1):1 25. <sup>15</sup>

**Figure 2 95<sup>th</sup> blood pressure percentiles by age and height percentiles in children from 1 to 17 years**

Boys														
Age	Systolic blood pressure, mmHg							Diastolic blood pressure, mmHg						
	Percentile of height							Percentile of height						
	5 <sup>th</sup>	10 <sup>th</sup>	25 <sup>th</sup>	50 <sup>th</sup>	75 <sup>th</sup>	90 <sup>th</sup>	95 <sup>th</sup>	5 <sup>th</sup>	10 <sup>th</sup>	25 <sup>th</sup>	50 <sup>th</sup>	75 <sup>th</sup>	90 <sup>th</sup>	95 <sup>th</sup>
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
7	110	111	113	115	117	118	119	74	74	75	76	77	78	78
8	111	112	114	116	118	119	120	75	76	77	78	79	79	80
9	113	114	116	118	119	121	121	76	77	78	79	80	81	81
10	115	116	117	119	121	122	123	77	78	79	80	81	81	82
11	117	118	119	121	123	124	125	78	78	79	80	81	82	82
12	119	120	122	123	125	127	127	78	79	80	81	82	82	83
13	121	122	124	126	128	129	130	79	79	80	81	82	83	83
14	124	125	127	128	130	132	133	80	80	81	82	83	84	84
15	126	127	129	131	133	134	135	81	81	82	83	84	85	85
16	129	130	132	134	135	137	137	82	83	83	84	85	86	87
17	131	132	134	136	138	139	140	84	85	86	87	87	88	89

(continued)

**Figure 2 95<sup>th</sup> blood pressure percentiles by age and height percentiles in children from 1 to 17 years**

Girls														
Age	Systolic blood pressure, mmHg							Diastolic blood pressure, mmHg						
	Percentile of height							Percentile of height						
	5th	10th	25th	50th	75th	90 <sup>th</sup>	95th	5th	10th	25th	50th	75th	90 <sup>th</sup>	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
7	110	111	112	113	115	116	116	73	74	74	75	76	76	77
8	112	112	114	115	116	118	118	75	75	75	76	77	78	78
9	114	114	115	117	120	121	122	77	77	77	78	79	80	80
10	116	116	117	119	120	121	122	77	77	77	78	79	80	80
11	118	118	119	121	122	123	124	78	78	78	79	80	81	81
12	119	120	121	123	124	125	126	79	79	79	80	81	82	82
13	121	122	123	124	126	127	128	80	80	80	81	82	83	83
14	123	123	125	126	127	129	129	81	81	81	82	83	84	84
15	124	125	126	127	129	130	131	82	82	82	83	84	85	85
16	125	126	127	129	130	131	132	82	82	83	84	85	85	86
17	125	126	127	129	130	131	132	82	83	83	84	85	85	86

Shown are 95<sup>th</sup> percentiles for blood pressure <sup>14</sup>

## 17.4 Appendix 4: Dosing table for children from birth to 18 years

**Table 17–2 Body weight-adjusted rivaroxaban dosing schedule for children aged birth to < 18 years** <sup>95</sup> <sup>96</sup>

Body weight (kg)		Formulation	o.d. Dose	b.i.d. Dose	t.i.d. Dose	Total Daily Dose
Min	Max					
2.6	<3	Oral suspension			0.8 mg	2.4 mg
3	<4	Oral suspension			0.9 mg	2.7 mg
4	<5	Oral suspension			1.4 mg	4.2 mg
5	<6	Oral suspension			1.6 mg	4.8 mg
6	<7	Oral suspension			1.6 mg	4.8 mg
7	<8	Oral suspension			1.8 mg	5.4 mg
8	<9	Oral suspension			2.4 mg	7.2 mg
9	<10	Oral suspension			2.8 mg	8.4 mg
10	<12	Oral suspension			3.0 mg	9 mg
12	<20	Oral suspension		5 mg		10 mg
20	<30	Tablet or oral suspension		5 mg		10 mg
30	<50	Tablet or oral suspension	15 mg			15 mg
	≥ 50	Tablet or oral suspension	20 mg **			20 mg **

\*\* 15 mg in Japan

Note: Dosing regimen, including dosing frequency, will be adjusted if the child's body weight changes during the study.

95 The dosing table was updated via Amendment 8 (see Sections 16.2.2.23 and 16.2.2.24)

96 The dosing table was updated via Amendment 12 ( see Section 16.4.2.25)