Document Type:	Statistical Analysis Plan
Official Title:	30-day, single-arm study of the safety, efficacy and the pharmacokinetic and pharmacodynamic properties of oral rivaroxaban in young children with various manifestations of venous thrombosis
NCT Number:	NCT02309411
Document Date:	28 Apr 2017

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

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

Bayer study drug	BAY 59-7939/rivaroxaban/Xarelto		
Clinical study phase:	II	**Date:**	28 Apr 2017
Study No.:	14374	**Version:**	2.0
Author:	PPD		

This Statistical Analysis Plan is produced on a word-processing system and bears no signatures.

The approval of the Statistical Analysis Plan is documented in a separate Signature Document.

[1] Title was modified via Protocol Amendment 4

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Abbreviations

ADS	Analysis dataset
AE	adverse event
AG	Aktiengesellschaft, joint stock company
ALT	alanine aminotransferase
anti-Xa	anti-factor Xa activity
aPTT	activated or adjusted partial thromboplastin time
AUC	Area under the curve
BAY	sponsor's reference number for drugs
b.i.d.	twice daily
CI	Confidence interval
CIAC	central independent adjudication committee
CRF	Case Report Form
CSR	Clinical Study Report
CT	computed tomography
dL	deciliter
DMC	data monitoring committee
DVT	deep vein thrombosis
eCRF	electronic case report form
e.g.	exempli gratia, for example
eGFR	estimated glomerular filtration rate
GCP	Good Clinical Practice
Hb	hemoglobin
HR	hazard ratio
IDMS	isotope dilution mass spectrometry
i.e.	id est, that is
ICH	International Committee on Harmonization
IEC	Independent Ethics Committee
INR	international normalized ratio
IRB	Institutional Review Board
ITT	Intent-to-treat
IxRS	interactive voice/web response system
LLOQ	Lower limit of quantification
LMWH	low molecular weight heparin
LOS	listing only set
MCMC	Monte Carlo Markov Chain
MedDRA	Medical Dictionary for Regulatory Activities
Mg	milligram
Min	minute
ml	milliliter
mmHg	millimeter of mercury
MR(I)	magnetic resonance (imaging)

NA	Not applicable
NI	non-inferiority
o.d.	once daily
PD	pharmacodynamics
PE	pulmonary embolism
PD	pharmacodynamics
PK	pharmacokinetic(s)
PPS	Per-protocol set
SAE	serious adverse event
PT	prothrombin time
SAP	statistical analysis plan
SoC	standard of care
TOSCA	Tools for Syntactic Corpus Analysis database system
UFH	unfractionated heparin
VKA	vitamin K antagonist
VTE	venous thromboembolism

1. Introduction

This SAP is based on the Clinical Study Protocol version 1.0 (04 Mar 2014), Global Amendment 1 (forming Integrated Protocol version 2.0, dated 02 Sep 2014), Local Amendment 2 (applicable to Japan only) to Clinical Study Protocol (21 Oct 2014), Local Amendment 3 (applicable to Canada only) to Clinical Study Protocol (28 Oct 2014), Global Amendment 4 (forming Integrated Protocol version 3.0, dated 14 Apr 2015), Local Amendment 5 (applicable to Canada only) to Clinical Study Protocol (16 Jun 2015).

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

For more details see Integrated Protocol, Section 1.

2. Study Objectives

The primary objective is:

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

The secondary objectives are:

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

3. Study Design

This is a single-arm, multicenter study evaluating the safety, efficacy and PK/PD profile of a 30-day treatment with age- and body weight-adjusted oral rivaroxaban in children aged between 6 months and < 6 years with various manifestations of symptomatic and asymptomatic venous thrombosis (Comparator arm was removed via Amendment 4; up to Protocol Amendment 4 it was an active-controlled randomized study).

The treatment period will be followed by a 30-day post study treatment period, regardless of the duration of study drug administration. After cessation of study treatment, it is at the investigator's discretion to continue with anticoagulants.

For further details see Integrated Protocol, Section 3.

3.1 Study population

Twenty children (10 per age group) are planned to be treated with rivaroxaban in total according to Protocol Amendment 4. Enrolment will start with the 2 to < 6 year age group, followed by the 6 months to < 2 year age group upon availability of the age and body weight

adapted dosing regimen for the age group 6 months to < 2 years (before Protocol Amendment 4 forty children; 20 per treatment group were planned to be enrolled and randomized to either rivaroxaban or standard of care).

Children who have been treated for at least 2 months or in case of catheter-related thrombosis, treated for at least 6 weeks with LMWH, fondaparinux and/or VKA for symptomatic or asymptomatic venous thrombosis will receive age- and body weight-adjusted rivaroxaban. Before first study treatment administration, the documented index thrombotic event will be confirmed by the central adjudication committee (CIAC) for the child to be eligible for the study. For further details see Integrated Protocol, Sections 3 and 4.

3.2 Treatment regimen

In this study, only rivaroxaban will be used after Protocol Amendment 4. Allocation to treatment will be done centrally by an interactive voice/web response system (IxRS; before Protocol Amendment 4 allocation was to be stratified by baseline presentation of venous thrombosis and it was to be done in a 1:1 ratio for rivaroxaban: standard of care, separately by age groups). The IxRS will initially restrict enrollment to children in the age group between 2 and less than 6 years. Once the age-and body weight adjusted dosing regimen has been confirmed for the age group 6 months to < 2 years, the IxRS will allow enrollment for this age group as well.

For further details see Integrated Protocol, Sections 3 and 5.

3.3 Outcomes

- The primary safety outcome is the composite of major bleeding and clinically relevant non major bleeding.
- Other safety outcomes:
    - all deaths
    - other vascular events (myocardial infarction, cerebrovascular accident, non-CNS systemic embolism).
- Efficacy outcomes:
    - Symptomatic recurrent VTE (composite of DVT and fatal or non-fatal PE)
    - Composite of symptomatic recurrent VTE and asymptomatic deterioration on appropriate imaging test

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

For further details see Sections 6.8, 6.11 and 6.14.2 of the Integrated Protocol as well.

4. General Statistical Considerations

4.1 General Principles

The statistical evaluation will be performed by using the software package SAS release 9.2 or higher (SAS Institute Inc., Cary, NC, USA) and other specialized software can be used for sensitivity analysis. All variables will be analyzed by descriptive statistical methods. The number of data available and missing data (nmiss), mean, standard deviation, minimum, quartiles, median, and maximum will be calculated for metric data. Frequency tables will be generated for categorical data.

As children were to be randomized also to standard of care before Protocol Amendment 4 comes into effect, data from these children will be presented separately in tables and listings where applicable.

The analysis datasets (ADS) standards for Xarelto will be applied.

4.2 Handling of Dropouts

For all children, visits are scheduled at regular time points (see study flow chart on Figure 1-1 of the Integrated Protocol and Local Amendments). Enrolled children who are not treated or those with premature discontinuation of study drug will at least be seen at the end of the study treatment period. During all contacts, the treatment and clinical course of the child will be evaluated. Children with suspected efficacy or safety outcomes will undergo confirmatory testing as per standard of care. Blood samples for PK/PD will be taken at defined time points (see study flow chart on Figure 1-1 of the Integrated Protocol).

For further details about collecting data from children who prematurely discontinue study medication see Integrated Protocol Sections 3 and 7.10.

4.3 Handling of Missing Data

All missing or partial data will be presented in the subject data listing as they are recorded on the Case Report Form (CRF).

The number of subjects who prematurely discontinue the study treatment and/or the study for any reason, as well as the reasons for premature discontinuation of study treatment will be reported for the treatment period. Days to end of study treatment and days to last visit will be listed for subjects who prematurely terminate study treatment.

Baseline characteristics will be summarized descriptively by non-completers (prematurely discontinuation the study treatment and/or the study respectively) versus completers.

The number of missing repeat imaging tests, number of missing laboratory values at baseline and at visit 4, number of missing weight values will be displayed by means of descriptive statistics for the rivaroxaban group and separately for children who randomized to standard of care before Protocol Amendment 4 comes into effect.

General rules

When appropriate, the following rules will be implemented so as not to exclude subjects from statistical analyses due to missing or incomplete data:

- **Index thrombosis**
  For cases where start month and year are reported but day is missing, impute it with the complete start date of pre-treatment or if no complete start date is available, with 15. For cases where months and/or year is missing impute it with the complete start date of pre-treatment or if no complete start date is available, no imputation will be done.
- **Start and stop dates for pre-treatment of index events**
  Missing start date will be imputed as max [(01, available month or 01, available year or IxRS year) and available complete date of index event]. Missing stop dates will be imputed as date of IxRS assignment.
- **Safety and efficacy clinical outcomes, adverse events**
  For cases where start month and year are reported but day is missing, impute the maximum of (date of IxRS assignment, first date of study medication, 01.month.year). For cases where only start year is reported, impute the maximum of (date of IxRS assignment, first date of study medication, 01.01.year), but not later than death date if the patient died.
- **Study medication start date**
  If the start day of study medication is missing then the start date will be imputed as the maximum of (date of IxRS assignment, 01.month.year). Otherwise if start month is also missing then the start date will be imputed with the date of IxRS assignment. If start date and time is recorded as earlier than IxRS assignment and cannot be clarified, date and time of IxRS assignment will be used for the statistical analysis.

Study medication stop date
If stop date is missing and there is an adverse event with action taken 'study medication discontinued permanently' then the stop date of study medication will be imputed by the start date of that adverse event.
Otherwise if the stop day is missing, but the stop month and stop year are available then the stop date will be imputed as minimum of [(15, month, year) and the last study visit date before the observational visit and death date]. If the stop day and month are missing then the stop date will be imputed as minimum of [the last study visit date before the observational visit and death date].

4.4 Interim Analyses and Data Monitoring

No interim analysis will be performed.

An independent Data Monitoring Committee (DMC) will monitor the children's safety and give recommendations to the steering committee. The DMC 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. For further details see also Section 6.14.3 of the Integrated Protocol .

4.5 Data Rules

4.5.1 Baseline laboratory values

Hemoglobin (Hb), platelets, creatinine, alanine aminotransferase (ALT), total and direct bilirubin prior to Visit 2 will be considered for the baseline. If a blood creatinine value is not available up to IxRS assignment, the value from the sample taken no later than 14 days after IxRS assignment will be considered. In case of more than one available lab value the non-missing value closest to IxRS assignment will be taken. If the estimated glomerular filtration rate (eGFR) was not calculated then it will be calculated depending on the blood creatinine measurement method with original Schwartz formula or with the updated Schwartz formula as given in the Integrated Protocol Appendix 17.2 if all other required measurements (gender, age, height) are available. For patients from Japan the formula recommended by the Japanese Society for Pediatric Nephrology will be used as given in the Local Protocol Amendment 2 for Japan.

As in this study there is no pre-dose PD sampling at Day 1, the 10-16 hr post dose PD value at Visit 4 will be used as comparison/reference value per subject.

4.5.2 Compliance

4.5.2.1 Rivaroxaban

Overall compliance will be calculated for the actual treatment period (final stop date minus start date + 1 day) as total volume of suspension taken divided by the total volume of suspension to be taken considering required dose (volume) given the weight of the child and b.i.d. regimen between the first intake and last intake dates in the main treatment period. The total volume of suspension taken will be derived as the sum of amount taken for each bottle dispensed. The amount administered from a bottle will be calculated as the difference between the dispensed and returned amount. If the difference would be negative then the amount administered will be 0 (the volume dispensed could be larger as nominal 45 mL). If the volume returned is missing, but the investigator stated in the CRF that the patient took all medications not returned then the amount of taken will be the amount of dispensed. If the amount administered is also given then this will be considered. If the volume of dispension taken by the patient cannot be determined for a bottle, because no bottle is returned and the amount administered is not stated, it will be assumed that the prescribed amount of study medication has been taken from the bottle unless the investigator commented it explicitly as non-compliance.

4.5.2.2 LMWH or Fondaparinux

This section is applicable only if a patient received LMWH or Fondaparinux as study medication before Protocol Amendment 4.

The visit compliance will be calculated as number of syringes administered divided by number of syringes to be administered between the two visits considering b.i.d. or o.d. regimen given the medication. In addition, Overall compliance will be calculated for the 30

days treatment period as total number of syringes administered divided by the total number of syringes to be administered considering b.i.d. or o.d. regimen between the first intake and last intake dates in the main treatment period.

4.5.2.3 Vitamin K antagonists

This section is applicable only if a patient received VKA as study medication before Protocol Amendment 4.

The Integrated Protocol states that at least one international normalized ratio (INR) measurement is required per two weeks. For calculation of compliance, the following rules will be applied:

The treatment period will be split up in periods of 14+5=19 days. If the last period is shorter than 15 days, the actual length relative to 19 days will be calculated, i.e. less than one (for example, if the subject stopped study medication on day 22, his 2nd period had a relative length of (22-19)/ 19=0.16). The number of these periods will be the denominator for the calculation of compliance including the last period which can be numerically less than one. Using the example above, the subject's denominator would be 1.16 (i.e. less than 2 full periods). If a subject received study medication for less than 19 days, the denominator will be one.

For the numerator it will be counted in how many periods INR measurements were done.

4.6 Blind Review

The results of the final data assessment will be documented in the final list of important deviations, validity findings and assignment to analysis set(s). Any changes to the statistical analysis prompted by the results of the review of study data will be documented in an amendment and, if applicable, in a supplement to this SAP.

5. Analysis Sets

5.1 Assignment of analysis sets

Final decisions regarding the assignment of subjects to analysis sets will be made during the review of study data and documented in the final list of important deviations, validity findings and assignment to analysis set(s) (see Section 4.6).

Full analysis set: This analysis set will include all enrolled children (except screening failures).

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

Per protocol set: This population includes all enrolled children who had at least 25 days study treatment. Children who discontinued study treatment earlier than 25 days due to an efficacy or bleeding outcome or due to death or due to a procedure defined in the study protocol or withrew consent will not be excluded from the per protocol set. Children with a calculated compliance less than 50% will be excluded from the per protocol set, calculated

compliance between 50% and less than 80% and greater than 120% is considered as minor protocol deviation. These definitions are considered as clarifications to the definitions in the study protocol. The per protocol set may also exclude other major protocol deviations. Further details will be specified in the in the Protocol Deviation Document and in the Validity Review Report.

In addition to the analysis population defined in the study protocol, the following population will be used as well.

All subjects with at least 1 PK sample in accordance with the PK sampling strategy will be included in the PK analysis (PK analysis set).

All subjects with at least 1 blood sample for clotting parameters in accordance with the PD sampling strategy will be included in the PD analysis (PD analysis set).

Listing only set: This population includes all screening failures.

6. Statistical Methodology

Treatment groups will be displayed as study medication administered.

6.1 Population characteristics

Summary statistics (arithmetic mean, standard deviation, median, minimum and maximum for quantitative variables) will be presented. Frequency tables for qualitative data will be provided. Descriptive statistics will be provided for all data combined and for each age cohort. Data from children received standard of care study treatment (i.e. randomized in the study before Protocol Amendment 4 coming into effect) will be summarized as separate treatment group.

6.1.1 Demography, medical history, populations for analysis

Age, sex, race, ethnicity, weight, height, body mass index, systolic and diastolic blood pressure at baseline will be described by appropriate summary statistics. Medical history findings will be summarized using Medical Dictionary for Regulatory Activities (MedDRA) Primary System Organ Class / High Level Term / Preferred Term.

6.1.2 Prior medication for treatment of index venous thrombosis

In the tabulation of prior medication of index event all anticoagulants will be tabulated that were categorized as prior medication. Type of initial treatment of the index event and duration of initial treatment will be summarized by descriptive statistics. If fondaparinux was categorized as LMWH pre-treatment of index thrombosis by the investigator, it will be grouped to fondaparinux for the purpose of tabulation. Duration of pre-treatment for the patients on rivaroxaban study medication will be calculated as min(start of rivaroxaban, stop date + 1 day) – start date. Duration of pre-treatment for patients randomized to standard of care study medication before Protocol Amendment 4 will be calculated as min(date of IxRS assignment, stop date + 1 day) – start date and summary statistics will be presented separately.

6.1.3 Description of the index venous thrombosis

Location(s) of index venous thrombosis as specified by the investigators and as adjudicated by the CIAC will be tabulated overall and by age group.

6.1.4 Concomitant medication

All concomitant medications will be displayed using WHO-DD, by first (anatomical main group) and second level of the ATC code (therapeutic main group).

6.1.4.1 Tabulation of concomitant antithrombotics started after stop of study medication

Concomitant antithrombotics that started on the stop day of study medication or later will be grouped first by the fourth level of their ATC codes (B01AA: Vitamin K antagonists, B01AB: Heparin group, B01AC: Platelet aggregation inhibitors excluding heparin, B01AD: Enzymes, B01AE: Direct thrombin inhibitors, B01AF: Direct factor Xa inhibitors, B01AX: Other antithrombotic agents) or if that is not available, by the third level (B01A: Antithrombotic agents). The second group will be the generic names that are reported using the codes for DRECNO where DSEQNO1=01 and DSEQNO2=001, except Certoparin, see below. The rows in the tables will be sorted first by ATC class (code order) then by generic name codes.

Note that certain medications can be coded by more than one DRECNO code. There are medications with same active ingredient, but different salt or ester component or with multiple ingredients may have different DRECNOs which may lead to tabulations of that active compound in different categories. If applicable, Certoparin sodium coded as DRECNO="016918" will be recoded to DRECNO="008896" and DSEQNO1="02" and DSEQNO2="017" to tabulate these medications under the drug name “CERTOPARIN SODIUM [HEPARIN-FRACTION, SODIUM SALT]”.

6.2 Bleeding analysis

All bleeding analyses will be performed on the safety analysis set based on the outcomes confirmed by the CIAC. Bleeding events that occurred during study treatment or within 2 days after stop of study medication (i.e. treatment-emergent) will be summarized. 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 by number of children at risk at start of study medication) will be presented for the primary safety outcome, for major bleedings, for all confirmed bleedings and components for pooled data and for each age stratum and by baseline presentation of venous thrombosis for the rivaroxaban group and for the standard of care group (randomized before Protocol Amendment 4) separately.

6.3 Efficacy

All efficacy analyses will be performed on the full analysis set population based on the outcomes confirmed by the CIAC. Incidence proportions will be calculated for the efficacy outcomes (see Section 3.3) overall and by age stratum for the rivaroxaban group and for the standard of care group (randomized before Protocol Amendment 4) separately. The analyses described above will include events up to the end of intended study treatment (30 days after study medication assignment) regardless of the actual stop date of study medication.
In addition if there is at least one confirmed recurrent event in the corresponding time period, the analyses described above will be performed counting only events that occurred during study treatment or within 2 days after stop of study medication (i.e. treatment-emergent) on the safety population as well.
Proportion of events that occurred more than 2 days after stop of study medication up to 30 days will be described (denominator: number of subjects entering the observational period) if there is at least one confirmed recurrent event in the corresponding time period.
In addition, all descriptive efficacy analyses will be performed on the per protocol population as a supportive analysis.

6.3.1 Sensitivity analysis to account for dropouts

Sensitivity analyses will be performed if at least one confirmed recurrent event occurred within the 30 days intended treatment period in order to evaluate the potential influence of dropouts on the incidence of the primary efficacy outcome for the treatment period up to visit 4. In these analyses subjects with premature termination before visit (no follow-up until Day 30) will be assumed as having hazard of recurrence of VTE (primary efficacy outcome) 1.5 times (scenario 1) and twice (scenario 2) as high as the hazard calculated including all patients within each treatment group assuming informative censoring. For this sensitivity analysis exponential distribution for the event rates (hazard) will be assumed and the analysis will be performed for the rivaroxaban treatment group. This method is an application of methods for informative missingness odds ratio (IMOR) by White et al (5).

- $t_j \sim \exp(h_{non\text{-}informative})$
  $P_{non\text{-}informative} = 1\text{-}e^{-(30 \cdot h_{non\text{-}informative})}$
  $h_{dropout} = h_{non\text{-}informative} \cdot IMHR$
  $P_{overall,\,j} = 1\text{-}e^{-(t_j \cdot h_{non\text{-}informative} + [30\text{-}t_j] \cdot h_{dropout})}$
  $P_{overall,\,mean} = mean(P_{overall,\,j})$
  where
  t_j: event times (or censoring) of patient *j*.
  $h_{non\text{-}informative}$: hazard of the primary efficacy outcome assuming non-informative censoring using all patients' data.
  $P_{non\text{-}informative}$: the cumulative event probability at Day 30 based on the exponential model.
  $h_{dropout}$: hazard of the primary efficacy outcome after dropping out.
  $P_{overall,\,j}$: cumulative event probability at Day 30 calculated based on mixture of $h_{non\text{-}informative}$ up to drop out and $h_{dropout}$ from drop out up to Day 30 using exponential model for patient *j*.
  $P_{overall,\,mean}$: mean of the cumulative event probability.
  IMHR: informative missingness hazard ratio.

- Prior for log hazard (non-informative censoring):
  $\log(h_{non\text{-}informative}) \sim dnorm(-6.6, 1/\sqrt{0.4})$.
- Priors (informative) for IMHR:
  IMHR ~ $\ln N(\mu, \sigma)$ where
  μ = scenario 1: $\ln(1.5) = 0.405$; scenario 2: $\ln(2) = 0.693$ and
  $\sigma = 1/\sqrt{10} = 0.316$.

The analysis will be done with an Bayesian Markov Chain Monte Carlo (MCMC) simulation approach (e.g. with OpenBUGS Version 3.2.3 or other). For an example code see Appendix, Section 9.2.

6.4 Pharmacokinetics / pharmacodynamics

Individual profiles and summary statistics overall and by weight groups will be provided for PK/PD data. 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.

6.5 Safety

6.5.1 Study drug exposure and compliance

The descriptive statistics in this section will be done for all data combined and for each age cohort.

6.5.1.1 Summary of treatment duration

The overall treatment duration will be summarized descriptively in the safety analysis set and in the per protocol analysis set.

6.5.1.2 Summary of compliance

Counts and percentages will be tabulated for the following compliance categories in the safety analysis set:
Missing, Compliance <50%, Compliance ≥50% to <80%, Compliance ≥80%.

The volume and type of fluid used to predilute the rivaroxaban oral suspension, as well as the volume and type of fluid taken after the study drug administration will be summarized by visit, overall and by age group.

6.5.1.3 Summary of INR measurements for the VKA treatment

This section is applicable only if a patient received VKA as study medication before Protocol Amendment 4. Proportion of patients with INR<2, within 2 to 3 INR inclusive and INR>3 will be summarized for the one month main treatment period using the observed INR values.

6.5.2 Adverse events

Individual listings of adverse events (including age, weight, height, gender, adverse event as reported, start, duration, severity and relation to study drug) will be provided. The incidence of treatment-emergent adverse events will be summarized by age group, using MedDRA preferred terms, grouped by primary system organ class. Time window for treatment-emergent events is defined as events occurring after start of study medication (for patients randomized to the standard of care group before Protocol Amendment 4 after IxRS assignment) until last intake of study medication plus 2 days. The incidences will be presented for all data combined and for each age cohort separately. Incidences of other vascular events and all deaths will be summarized, too.

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

6.5.3 Laboratory measurements

Descriptive statistics will be presented for Hb, platelets, ALT, total and direct bilirubin at visit 4 (Day 30) and for their changes to baseline. The descriptive statistics will be done for all data combined and for each age cohort. Additional lab data at visit 3 (Day 15) and their changes to baseline will be summarized for patients from Canada separately. For the calculation of the mean value an anti-Xa activity value below LLOQ will be substituted by one half of this limit. In tables showing desriptive statistics, where values below LLOQ are included in the calculation of mean values, these means will be marked. All other lab values including aPTT and PT with the qualifier '< i.e less than' will be considered for descriptive statistics with their values without the qualifier. All lab values with the qualifier '> i.e. greater than' will be considered for descriptive statistics with their values without the qualifier.

6.6 Pre-specified subgroup analysis

6.6.1 Analysis by baseline characteristics

The baseline, efficacy, bleeding and safety analyses will be done by age cohort and by baseline presentation of venous thrombosis as described in sections 6.1, 6.2, 6.3, 6.5.1.

6.7 Taste and texture questionnaire

Results for the taste-and-texture questionnaire in children older than 4 years who receive the oral suspension will be presented descriptively as counts and proportions of responses by questions.

7. Document history and changes in the planned statistical analysis

First draft of SAP was circulated with the Bayer team on 10 Dec 2014.

Version 1.0: 26 Jun 2015.

SAP Version 2.0 dated 28 Apr 2017 was prepared to provide the following edits. None of them are considered to change the primary efficacy analysis and other analyses as described, but includes additional analyses and further clarifications:

- There is a typo in the date of Version 1.0: it was finalized on 26 Jun 2015 and not in 2014.
- No by visit compliance will be calculated, because drug accountability data were not to be recorded at visit 3. The calculations of compliance were further specified.
- The definition of the per protocol set was updated based on the decisions of the blind review meetings: This population includes all enrolled children who had at least 25 days study treatment. Children who discontinued study treatment earlier than 25 days due to an efficacy or bleeding outcome or due to a procedure defined in the study protocol or withrew consent will not be excluded from the per protocol set. If a child died having less than 25 days study treatment, they will not be excluded form the per protocol set. Children with a calculated compliance less than 50% will be excluded from the per protocol set, calculated compliance between 50% and less than 80% and greater than 120% is considered as minor protocol deviation.
- Added PK analysis set and PD analysis set based on the decisions of the blind review meetings.
- Treatment groups will be displayed as study medication administered.
- Antithrombotics started after stop of study medication will be displayed only.
- Analysis of demographic, medical history and efficacy was further clarified, analysis of and PK/PD data by weigth was included.
- Sensitivity analysis as described in Section 6.3.1 will be done only if at least one confirmed recurrent event occurred within the 30 days intended treatment period.

8. References

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9. Appendix

9.1 Sample size and power considerations

A total of 20 children who took at least one dose of rivaroxaban study medication are planned to be enrolled in the study according to Global Amendment 4 to the Study Protocol. This sample size does not originate from a formal sample size calculation, but is based on a feasibility assessment. For observed incidences of safety and efficacy incidences see the results of the Einstein VTE treatment program in adults (1, 2, 3). Table 9-1 shows 95% exact confidence intervals (Blyth–Still–Casella interval; 6) for a range of potential incidence of safety and efficacy clinical outcomes (see Section 3.3 for outcomes in this study).

Table 9-1: 95% exact Blyth–Still–Casella confidence intervals around the estimated incidences for 20 patients.

Incidence	Blyth-Still-Casella confidence interval
0/20 (0%)	0.0% to 15.4%
1/20 (5%)	0.3% to 23.1%
2/20 (10%)	1.8% to 31.5%
3/20 (15%)	4.2% to 36.1%
4/20 (20%)	7.1% to 41.1%

This study with 20 children on rivaroxaban will allow for a description of the efficacy and safety outcomes as well as the PK and PD characteristics of rivaroxaban in the pediatric patient population.

9.2 Example OpenBUGS code for sensitivity analysis of the primary efficacy outcome

OpenBUGS model

```
Model { for (i in 1 : N) {
        # Survival times bounded below by censoring times, noninformative censoring
        t[i] ~ dexp(mu[i])C(t.cen[i],)
        mu[i] <- exp(alpha)
        im.alpha[i] <- alpha + log.IMHR
        lambda.1[i] <- -(t.obs[i] * exp(alpha) + (t.limit - t.obs[i]) * exp(im.alpha[i]))
        p.im1[i] <- 1 - exp(lambda.1[i])    }
        alpha ~ dnorm(-6.6, 0.4)
        exp.alpha <- exp(alpha)
    # IMHR = 2
    log.IMHR ~ dnorm(0.693, 10)
    # Results from informative censoring
    CDF.1 <- 1 - exp(-(t.limit * exp.alpha))
    p.mean.im1 <- sum(p.im1[])/N1       }
```

Openbugs node statistics

	mean	sd	MC_error	val2.5pc	median	val97.5pc	start	sample
CDF.1	0.07132	0.0552	0.003239	0.008807	0.05557	0.2108	1001	1000
alpha	-6.298	0.8361	0.05607	-8.129	-6.263	-4.842	1001	1000
p.mean.im1	0.09599	0.07443	0.004247	0.01128	0.07357	0.281	1001	1000