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

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

Bayer study drug BAY 59-7939/rivaroxaban/Xarelto

Clinical study phase: III **Date:** 01 Mar 2019

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Abbreviations

ADS	Analysis dataset
AE	adverse event
AESI	adverse event of special interest
AG	Aktiengesellschaft, joint stock company
ALT	alanine aminotransferase
BAY	sponsor's reference number for drugs
b.i.d.	twice daily
CIAC	central independent adjudication committee
CKD	chronic kidney disease
C_{max}	maximum drug concentration in measured matrix,
$C_{max,ss}$	maximum drug concentration at steady state during a dosage interval
CSR	Clinical Study Report
CT	computed tomography
C_{trough}	drug concentration in measured matrix at the end of the dosing interval,
CVC	central venous catheter
CVST	cerebral vein and sinus thrombosis
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
IEC	Independent Ethics Committee
INR	international normalized ratio
IRB	Institutional Review Board
ITT	Intent-to-treat
IxRS	interactive voice/web response system
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)
NI	non-inferiority
o.d.	once daily
PD	Pharmacodynamics
PE	pulmonary embolism
PK	pharmacokinetic(s)
SAE	serious adverse event
SAP	statistical analysis plan
SOC	standard of care
t_{\max}	time to reach $C_{\max,ss}$
UFH	unfractionated heparin
VKA	vitamin K antagonist
VTE	venous thromboembolism

1. Introduction

This SAP is based on the following study protocol versions:

- 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 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 forming integrated protocol Version 3.0, dated 20 Sep 2016
- Amendment 9 (local amendment Canada), dated 20 Dec 2016
- Amendment 10 forming integrated protocol Version 4.0, dated 11 Jan 2017
- Amendment 11 (local amendment Japan), dated 07 Mar 2017
- Amendment 12 forming integrated protocol version 5.0, dated 27 Sep 2017.
- Amendment 13 (local amendment Japan), dated 14 Nov 2017
- Amendment 14 (local amendment Turkey), dated 19 Dec 2017
- Amendment 15 (local amendment Japan), dated 10 Jan 2018
- Amendment 16 (local amendment Spain), dated 03 Apr 2018

- Amendment 17 (local amendment Germany), dated 04 May 2018

“The goal of the rivaroxaban pediatric program is to make rivaroxaban available to children for treatment and secondary prevention of venous thromboembolism (VTE). It is anticipated that similar exposure in children, as compared to adults, will result in a similar safety and efficacy profile in children.” (study protocol, Section 1).

For more details see study protocol, Section 1.

2. Study Objectives

According to the study protocol version 5.0, Section 2:

The efficacy objectives are:

- To assess the incidence of symptomatic recurrent VTE
- To assess the incidence of symptomatic recurrent VTE and asymptomatic deterioration on repeat imaging at the end of main treatment period

The safety objective is:

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

Other objectives are:

- To characterize the pharmacokinetic (PK) / pharmacodynamics (PD) profile of rivaroxaban

Note that the main treatment period is Month 1, Day 30 ± 7 , for children from birth to <2 years with CVC-VTE (central venous catheter venous thromboembolism), for other children Month 3, Day 90 ± 7 .

3. Study Design

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

Children aged birth to <18 years with confirmed acute VTE who received 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. Randomization can be done during the first 9 days of initial treatment and will be in a 2 (rivaroxaban): 1 (comparator) fashion. Note that comparator can also mean comparator administered with standard of care.

After randomization, all children, except those aged < 2 years with CVC-VTE, will receive either study medication with 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 will be made by the investigator to stop study treatment or to continue for an additional 3 months. In children who completed 6 months of treatment, the decision will 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 will be 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 will be at the investigator's discretion to continue with anticoagulants.

In children aged < 2 years with CVC-VTE, the main study treatment period is 1 month. After that, it is at the discretion of the investigator 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 month.

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 further details see study protocol version 5.0, Section 3.

3.1 Study population

At least 170 children are needed for this study, 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 < 0.5 years.

Children aged birth to < 18 years with confirmed VTE who receive initial treatment with therapeutic dosages of UFH, LMWH or fondaparinux and require anticoagulant therapy for at least 90 days will be included. However, for children with CVC-VTE who are younger than 2 years, the required minimum duration of anticoagulant therapy is at least 30 days.

For further details, see study protocol version 5.0, Section 4.

For further sample size and power consideration, see Appendix, section [9.1](#).

3.2 Treatment groups and regimens

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 (comparator) fashion and it will be stratified by two types of baseline presentation of venous thrombosis as diagnosed by the investigator and entered in the IxRS (for more details see section 5.1 of the study protocol) for each age group, separately.

All children randomized to the rivaroxaban group before implementation of protocol amendment 10 received tablets in the 12 to < 18 years age group. Rivaroxaban was provided with the option of tablets or oral suspension for the 6 to < 12 years age group, and as oral suspension for children younger than 6 years.

According to protocol amendment 10, children with body weight of ≥ 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, although

children with body weight between 20 and <30 kg enrolled prior to protocol amendment 8 will receive rivaroxaban o.d. 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. For further details regarding dosing, see section 5.1.1 and Appendix 4 of the study protocol version 5.0. Children randomized to the comparator group will continue with UFH, LMWH or fondaparinux or may switch to VKA therapy.

For further details, see study protocol version 5.0, Section 5.

3.3 Outcomes

- The primary efficacy outcome is composite of symptomatic recurrent VTE;
- The secondary efficacy outcome is the composite of symptomatic recurrent VTE and asymptomatic deterioration in thrombotic burden on repeat imaging at the end of the main treatment period
- Further efficacy outcomes:
 - Composite of symptomatic recurrent VTE and major bleeding
 - Composite of symptomatic recurrent VTE and asymptomatic deterioration and no change in thrombotic burden assessment on repeat imaging at the end of the main treatment period
 - Composite of symptomatic recurrent VTE and thrombotic burden assessment at repeated imaging at the end of the main treatment period (symptomatic recurrent VTE, asymptomatic deterioration, no relevant change, uncertain, improved, normalized).
 - Normalization of thrombotic burden assessment on repeat imaging at the end of the main treatment period without confirmed symptomatic recurrent VTE
 - Fatal or non-fatal pulmonary embolism
 - Composite of symptomatic recurrent VTE and other clinically significant thrombosis
- The principal safety outcome is the composite of overt major and clinically relevant non-major bleeding.
- Further safety outcomes
 - Death
 - Other vascular events (arterial thrombotic complications i.e. myocardial infarction, ischemic stroke, cerebrovascular accident, non-CNS systemic embolism)
 - Major bleeding
 - Clinically relevant non-major bleeding

- Trivial bleeding

For further details, see sections 6.10 and 6.13 of the study protocol version 5.0

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 using other statistical software as applicable. 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.

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 (for all children except children aged < 2 years with CVC-VTE, see study flow chart on Table 0-1 of the study protocol version 5.0, for children aged < 2 years with CVC-VTE, see study flow chart on 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 study treatment period. Children who prematurely discontinue study drug will be seen at the end of the intended study treatment period (for children from birth to < 2 years with CVC-VTE at Month 1, for other children 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 (for all children except children aged < 2 years with CVC-VTE see study flow chart on Table 0-1 of the study protocol, for children aged < 2 years with CVC-VTE see study flow chart on Table 0-2 of the study protocol).

For further details about collecting data from children who prematurely discontinue study medication see study protocol version 5.0 section 7.10.

4.3 Handling of Missing Data

4.3.1 General Rules

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 missing values including laboratory values at baseline and post-baseline visits, number of missing weight values and missing values in other relevant variables will be displayed by means of descriptive statistics by treatment group to explore potential missing data imbalance in these variables.

For PK/PD data, individual listings of the subjects with missing data will be provided by age groups, regimen and formulation. All subjects with unscheduled visits will be also be listed for all visits separately for PK and PD data. Duplicate records identified by PCTRTV will not be analyzed.

4.3.2 Descriptive analyses for premature discontinuations

The number of subjects who prematurely discontinue study treatment and/or the study for any reason, as well as the reasons for premature discontinuation of study treatment and study by treatment group will be reported for the main treatment period, extended treatment period and intended treatment period. The denominators will be number of patients in the Safety set for the main treatment period and number of patients who entered the extended treatment period respectively for calculating the percentages of subjects who discontinue.

Baseline characteristics will be summarized descriptively by completers (defined in Section 4.5.3) versus non-completers. For details on baseline characteristics, please see Section 6.1.1.

4.3.3 Imputing partial and completely missing dates

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

- **Efficacy and Safety outcomes**

If there is no evidence from the incomplete event date that the event occurred definitely earlier than start of study medication/randomization then for cases where start month and year are reported but day is missing, impute the maximum of (date of randomization, first date of study medication, 01.month.year). For cases where only start year is reported, impute the maximum of (date of randomization, first date of study medication, 01.01.year). For events with complete missing date impute the maximum of (date of randomization, first date of study medication).

- **Adverse events**

A missing or partial start date for an adverse event will be imputed with the same rules as above for efficacy and safety outcomes

- **Start and stop date of study medication from the exposure dataset for subjects who took study medication**

Start date

If the start day of study medication is missing in the rivaroxaban arm, then the start date will be imputed as the maximum of (date of randomization, 01.month.year). Otherwise, if start month is also missing, then the start date will be imputed with the date of randomization.

In the comparator arm, the start date will simply be the randomization date.

Stop date

If stop date is missing or partial and there is an adverse event with action taken 'drug withdrawn', then the stop date of study medication will be imputed by the start date of that adverse event. Otherwise the stop date will be imputed with the latest of (date of last study medication dispense, start date of the study medication period, 1st day of the

stop month if month and year are available, 1st June if stop year is available only), but not later than the death date if the patient died.

- **Stop date of initial treatment**

If the stop date of initial treatment is missing due to subject withdrawal, then the stop date will not be imputed and simply be indeterminate.

- **Stop date of any anticoagulant therapy including those started within 7 days after the actual stop of main study treatment period**

For anticoagulants that started within 7 days after the actual stop of main study treatment period, a missing stop date will be imputed with the start date of the subsequent anticoagulant, if administered. Otherwise, if other anticoagulant was not administered subsequently, the stop date will be imputed with the latest of (stop date of study medication + 1, start date of the anticoagulant+1, 1st day of the stop month, if month and year are available, 1st June, if stop year is available only), but not later than the death date, if the patient died. Anticoagulants that started within 7 days after the actual stop of main study treatment period and reported by the investigator as “continued after study” do not have a stop date. In such cases, the stop date will be imputed with the last contact date for calculations.

4.3.4 Imputation rules for thrombus burden assessment if repeated imaging was not performed or done outside of time window

Table 4–1 shows thrombus burden assessment categories from the CIAC and categorization, if repeated imaging was not performed or done out of time window. Table 4–2 summarizes the categorization after imputation. The analysis will be performed based on that order of the categories. The CIAC will select the relevant repeated imaging by patient in case of multiple imaging at the end of the main treatment period.

Table 4–1. Overview of repeated imaging categories from the CIAC and the imputation rules for if repeated imaging was not performed or done out of time window

Repeat imaging	Status of anticoagulant therapy	Thrombus burden assessment categories
Performed in time window, assessment is either normalized, improved, unchanged or deteriorated*	Not applicable	Accept adjudication outcome
Performed before time window, assessment is either normalized, improved, unchanged or deteriorated*	If any anticoagulation** stopped at the time of imaging (+ 7 days)	Accept adjudication outcome
Performed before time window, assessment is either normalized, improved, unchanged or deteriorated*	If any anticoagulation** continued for >7 days after repeat imaging	Classify outcome as “uncertain”
Performed after time window, assessment is either normalized, improved, unchanged or deteriorated*	Not applicable	Classify as “uncertain”
Not performed or assessment is not evaluable	If any anticoagulation** stopped before main treatment time window&	Classify as “uncertain”
Not performed or assessment is not evaluable	If any anticoagulation** stopped during main treatment time window&	Classify as “improved”
Not performed or assessment is not evaluable	If any anticoagulation** is continued after main treatment time window&	Classify as “uncertain”
Confirmed symptomatic recurrent venous thromboembolism+	Not applicable	Classify as “recurrent VTE”

*Time window for repeat imaging relative to randomization: Day 90±21 (or Day 30±7 for children with CVC-VTE younger than 2 years).

**Any anticoagulation defined as anticoagulant therapy with either study medication or non-study anticoagulation with either direct factor Xa inhibitors, direct thrombin inhibitors, unfractionated or low molecular weight heparin (except mucopolysaccharide polysulfuric acid ester), fondaparinux, or a vitamin K antagonist. Non-study anticoagulant therapy counted if started within 7 days after stop of study medication with a duration of at least 7 days (subsequent therapies will also be considered).

&Time window for stop of study medication relative to randomization: Day 83-97 (or Day 23-37 for children with CVC-VTE younger than 2 years).

+regardless of availability of repeat imaging, up to the upper limit of the end of main treatment time window, see section 4.5.3.

Table 4–2. Categorization of the thrombus burden assessment at the repeated imaging after imputation

Category	Source
Normalized	Adjudication by the CIAC
Improved	Adjudication by the CIAC or derived by algorithm
Uncertain	Derived by algorithm
Unchanged	Adjudication by the CIAC
Deteriorated including recurrent VTE	Adjudication by the CIAC

Note: The analysis will be performed based on the above order of the categories.

4.3.5 Imputation rules for missing baseline body weight

For subjects whose weights have not been recorded at baseline, the following imputation strategy will be implemented:

- If available, the weight recorded in the study drug exposure form will be used
- For subjects with any recorded dose of enoxaparin, the baseline weight will be calculated based on the total daily enoxaparin dose divided by 1.5 if a once daily regimen was used and divided by 2.0 if a twice-daily regimen was used
- For all other subjects, the weight recorded at any other visit will be used.

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 VTEs and bleedings. Organizational aspects, responsibilities, and processes will be described in the DMC charter.

4.5 Data Rules

4.5.1 Baseline laboratory values

Hemoglobin (Hb), platelets, creatinine, alanine aminotransferase (ALT), total and direct bilirubin taken for the screening visit (visit 1) will be considered for the baseline. If a blood creatinine value is not available up to randomization, the value from the sample taken no later than 14 days after randomization will be considered. In case of more than one available lab value the non-missing value closest to randomization will be taken. If the estimated glomerular filtration rate (eGFR) was not calculated, 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 study protocol version 5.0 Appendix 17.2, if all other required measurements (gender, age, height) are available. In children younger than 1 year, serum creatinine levels will be considered instead of eGFR.

4.5.2 Compliance

4.5.2.1 Rivaroxaban

For the tablet formulation, the visit compliance will be calculated as number of tablets taken divided by number of tablets to be taken between the two visits considering b.i.d. or o.d. regimen. In addition, overall compliance will be calculated for the main treatment period as total number of tablets taken divided by the total number of tablets to be taken between the first intake and last intake dates in the main treatment period.

For the suspension formulation, the visit compliance will be calculated as volume of suspension taken divided by volume of suspension to be taken between the two visits considering required dose (volume) given the weight of the child and o.d., b.i.d. or t.i.d regimen. In addition, overall compliance will be calculated for the main treatment period as total volume of suspension taken divided by the total volume of suspension to be taken between the first intake and last intake dates in the main treatment period.

4.5.2.2 LMWH or Fondaparinux

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 main treatment period as total number of syringes administered divided by the total number of syringes to be administered between the first intake and last intake dates in the main treatment period for those countries where study medication provided centrally (France, Italy, Poland, Belgium, Spain, Japan, Austria, Russia, Turkey). In all other countries, LMWH or fondaparinux study medication is supplied locally, i.e. no drug accountability will be available, but the parents' statement about compliance will be entered as comment.

4.5.2.3 Vitamin K antagonists

The study protocol states that at least one international normalized ratio (INR) measurement is required per two weeks, if the INR is stable in therapeutic range (INR 2 to 3). If the INR is out of therapeutic range, INR monitoring should be performed more frequently per investigators' discretion. 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 19 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 80, his 5th period had a relative length of $(80-4*19)/19=0.21$). 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 4.21 (i.e. less than 5 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.

4.5.3 Time definitions for the time to event analyses

Individual intended end of main study treatment period

According to the protocol version 5.0, the following time window limit per patient will be applied as follows based on predefined main treatment duration

All children except children aged < 2 years with CVC-VTE

- a) If the last treatment visit day was less than 90-7=83 then events up to Day 83 will be considered.
- b) If the last treatment visit day was between Day 83 and Day 97, then events up to the visit day will be considered.
- c) If the last treatment visit day was later than Day 97, then events up to Day 97 will be considered.

Children aged < 2 years with CVC-VTE

- a) If the last treatment visit day was less than 30-7=23, then events up to Day 23 will be considered.
- b) If the last treatment visit day was between Day 23 and Day 37, then events up to the visit day will be considered.
- c) If the last treatment visit day was later than Day 37, then events up to Day 37 will be considered.

Main treatment period completer: patient who was on study medication until the lower limit of the scheduled main treatment period or who had the last treatment visit or last vital status collected not earlier than the end of main treatment, as given in under a), b) or c) in the respective scenarios.

For an event contributing to the following time-to-event variables, the time windows are defined in [Table 4-3](#):

- symptomatic recurrent VTE
- composite of overt major and clinically relevant non-major bleeding.
- composite of symptomatic recurrent VTE and major bleeding
- composite of symptomatic recurrent VTE and other clinically significant thrombosis

Table 4–3. Time to event and time to censoring

	Event or censoring up to the end of the main treatment period	On Treatment Treatment-emergent event or censoring up to two days after last intake of study medication, but not later than the end of the main treatment period	On Treatment Treatment-emergent event or censoring up to two days after last intake of study medication
Reference date	Randomization ²	Randomization ²	Randomization ²
Subjects with an event of interest	Events occurring until <i>the end of main treatment period</i> ¹ described above calculated per subject.	Events occurring up to two days after last intake of study medication, but not later than <i>the end of main treatment limit</i> ¹ per subject.	Events occurring up to 2 days after stop of medication
Censoring date for subjects without an event of interest	Minimum of - [last visit date of the subject] - [<i>end of main treatment limit</i> ¹]	Minimum of - [last visit date of the subject] - [<i>end of main treatment limit</i> ¹] - [days up to last study treatment +2 days]	Minimum of - [last visit date of the subject] - [days up to last study treatment +2 days]

- 1) For end of main treatment limit, see definitions above in this section. If a subject died due to another reason, the censoring date cannot be later than death date.
- 2) Bleeding events with onset on the day of randomization are considered only if the investigator stated that the event was related to study medication.

4.6 Validity Review

The results of the Validity Review Meeting will be documented in the Validity Review Report and may comprise decisions and details relevant for statistical evaluation. Any relevant changes to the statistical analysis prompted by the results of the validity review meeting might be documented in an amendment or, if applicable, in a supplement to this SAP.

5. Analysis Sets

Final decisions regarding the assignment of subjects to analysis sets will be made during the Validity Review Meeting and documented in the Validity Review Report (see section 4.6).

Full analysis set (FAS): this population will include all randomized children.

Safety analysis set (SAF): this population will include all randomized children who received at least one dose of study medication.

Per-protocol set (PPS): this population will include all FAS children without major protocol deviations. The detailed list of these deviations will be finalized prior to database lock and included in the protocol deviation document and SAP.

Listing-only set (LoS): this population includes all screening failures, i.e. all children with valid informed consent who were not randomized.

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)

6. Statistical Methodology

6.1 Population characteristics

Summary statistics (arithmetic mean, standard deviation, median, minimum and maximum for quantitative variables) will be presented in total and by treatment. Frequency tables for qualitative data will be provided. Medical history findings will be summarized using Medical Dictionary for Regulatory Activities (MedDRA) Primary System Organ Class / High Level Term. Concomitant medication will be displayed using WHO-DD. No statistical tests will be performed to compare these characteristics across treatment groups.

6.1.1 Demographic and Baseline Characteristics

The following baseline characteristics will be summarized overall and by age groups, weight groups (seven level grouping), formulation assignment and presentation of index event (subgroups are defined in Section 6.6):

Demographics

- Sex
- Race
- Ethnicity
- Weight
- Height
- BMI (<25 kg/m², 25-35 kg/m², >35 kg/m²)
- Kidney function – for details see section 6.1.2

Clinical characteristics

- Classification of index event (confirmed; unconfirmed/unknown)
- Presentation of index event by location (split by all CVST, CVC-VTE, non-CVC-VTE) – for details see section 6.1.3
- Was the index event a recurrent episode of venous thrombosis? (yes; no)
- Was the index event symptomatic? (yes; no; unconfirmed/unknown)
- Risk factors (provoked thrombosis by persistent risk factor, provoked thrombosis by persistent and transient risk factors, provoked thrombosis by transient risk factor, unprovoked, unconfirmed/unknown)

A substudy will be conducted on patients with baseline CVST. The details will be discussed in a separate technical document.

- **Initial treatment**

Type of initial treatment of the index event will be summarized by the following:

- Overview of initial treatment with UFH, LMWH or fondaparinux and thrombolytic drugs and/or thrombectomy

Initial anticoagulant or thrombolytic treatment by medication type. The duration of initial treatment up to the start of study medication will be summarized by descriptive statistics in the treatment arm only.

6.1.2 Summaries of kidney function

Descriptive statistics will be provided for serum creatinine levels in mg/dL for all data combined and for each age cohort. Number of patients aged ≥ 1 year will be summarized by the following categories of kidney function based on the estimated GFR (for formulas, see the study protocol):

- normal kidney function (≥ 80 mL/min/1.73m²)
- mild kidney dysfunction (50 to <80 mL/min/1.73m²)
- moderate kidney dysfunction (30 to <50 mL/min/1.73m²)
- severe kidney dysfunction (< 30 mL/min/1.73m²)

In children < 1 year, since the GFR cannot be accurately calculated and comparable GFR categories do not exist, the following categories based on creatinine would be merged into those based on the estimated GFR as follows [15]:

- the <90 th percentile group for creatinine into the eGFR >80 ml/min/1.73m² (normal kidney function)
- the 90-97.5th percentile group for creatinine into the eGFR 50-80 ml/min/1.73m² (mild kidney dysfunction)

- >97.5th percentile group for creatinine into the eGFR 30-50 ml/min/1.73m² (moderate kidney dysfunction)

The percentiles depend on the age at which creatinine was measured and are given in the appendix, [Table 9–2](#), taken from [15].

6.1.3 Description of the index venous thrombosis

The CIAC will categorize the index venous thrombosis of each patient to one of the following location groups:

- Lower extremity
- Caval vein
- Portal vein
- Renal vein
- Right side of the heart
- Lung
- Upper extremity
- Jugular vein
- Cerebral vein or sinus
- Mesenteric vein

Moreover, the CIAC will specify whether the relevant index venous thrombosis was catheter-related or non-catheter related.

Using the categorizations by CIAC and the above locations, there will be three main groups:

- CVST,
- CVC-VTE,
- non-CVC-VTE.

Index event locations of subjects with unconfirmed/unknown index events will be listed.

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 Anticoagulants that were prolonged or started after the main treatment period

Any anticoagulant therapy with either study medication or non-study medication with either direct factor Xa inhibitors, direct thrombin inhibitors, UFH, or LMWH (except mucopolysaccharide polysulfuric acid ester), fondaparinux, or a VKA will be considered. Non-study anticoagulant therapy will be counted, if it started within 7 days after end of main treatment. Subsequent therapies will also be considered.

Number of subjects who had any anticoagulant treatment within 7 days after end of main treatment period with a duration of at least 7 days will be displayed by treatment group.

Subjects for whom the investigator stopped the main study treatment up to the main treatment end visit and did not start any concomitant anticoagulant will not be considered as having extended anticoagulation, even if the main study treatment visit took place later than defined in the study protocol.

6.2 Study drug exposure and compliance

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

6.2.1 Summary of treatment duration

The overall treatment duration (date of last study medication-date of randomization+1 day) up to the end of the extended treatment period (mean, SD, minimum, quartiles, median, maximum) as well as the cumulative durations will be summarized by treatment group in the safety analysis set and in the per protocol analysis set.

6.2.2 Summary of compliance

The compliance calculation is based on tablet counts or on the volume of suspension taken for the rivaroxaban group, and on number of syringes of LMWH administered or on the frequency of INR measurements during VKA treatment in the comparator group. Due to this fundamental differences, the actual percentage compliance values are not fully comparable between the 2 treatment groups. Hence, only the following compliance categories will be compared between treatment groups in the per protocol set and safety analysis set: Missing, Compliance <50%, Compliance \geq 50% to <80%, Compliance \geq 80%.

6.2.3 Summary of INR measurements for the VKA treatment

The INR values will be described (mean – SD) biweekly for the main treatment period. Proportion of patients with average INR<2, within 2 to 3 INR inclusive and INR>3 will be summarized biweekly using the observed INR values during the main treatment period (2 day window inclusive). Multiple INR measurements observed on the same day will be first averaged, and the average value for the day will contribute to the patient-specific average. The time intervals will be specified using the day of measurement relative to the first VKA dose after initial treatment.

6.3 Efficacy

All efficacy analyses will be performed on the FAS, SAF and PPS populations based on the outcomes specified in section 3.3 and confirmed by the CIAC. Incidence proportions will be calculated for the efficacy outcomes by treatment group at the end of the main treatment period for the combined data over all children and by classification of index event. Cumulative incidences (time to first event; Kaplan-Meier, Kalbfleisch and Prentice, 7) will be calculated for the primary efficacy outcome and for the composite of all symptomatic recurrent VTE and major bleeding by treatment group at the end of the main study treatment period for pooled data over all children. Kaplan-Meier estimates beyond 1 month are applicable for those children who are planned to be treated for 3 months in the main treatment

period. In addition, incidence proportions will be calculated for each age stratum, weight group (seven level grouping), dosing formulation assignment at the end of the main treatment period for SAF and PPS populations and by presentation of index event (for children <2 years with CVC-VTE separately as well). Incidence proportions will be calculated for the primary outcome by treatment group for each age stratum, and pooled data excluding children <2 years with CVC-VTE in the extended study treatment period at 6, 9 and 12 months. Counts of composite of symptomatic recurrent VTE and thrombotic burden assessment at repeated imaging at the end of the main treatment period will be reported by classification and presentation of index event. The counts will also be calculated for subjects with anticoagulants that were prolonged after the main treatment period versus subjects that without any anticoagulants after the main treatment period. Incidence proportions in the extended treatment period for children <2 years with CVC-VTE will be presented separately at 2 and 3 months. Denominators will be the number of patients at risk at the start of the respective period.

Two-sided 95% confidence intervals for the frequency efficacy outcomes will be calculated by applying the method of Blyth-Still-Casella [13, 14]. For time-to-event analyses, the censoring mechanism will be assumed to be non-informative. The analyses described above will include events up to the end of study periods per subject regardless of the actual stop date of study medication. For details of time to event and time to censoring see section 4.5.3. Events that occurred more than 2 days after stop of study medication up to 30 days will be listed.

For further subgroups and pools see section 6.7.

6.3.1 Statistical models

Although the study is not designed to test a hypothesis regarding comparing incidences of outcomes between rivaroxaban versus comparator with standard of care, exploratory stratified (strata: CVST, CVC-VTE, non-CVC-VTE) Cox proportional hazards models will be fitted for the primary efficacy outcome and for the composite of all symptomatic recurrent VTE and major bleeding. In addition, Cox proportional hazards models will be fitted separately for the subgroups CVST, CVC-VTE and non-CVC-VTE for the primary efficacy outcome and for the composite of all symptomatic recurrent VTE and major bleeding. As it is expected that in some strata the number of events will be low, Firth's penalized maximum likelihood estimation will be used to reduce bias in the parameter estimates. Point estimates for hazard ratios, confidence intervals (obtained with profile-likelihood function) and p-values for the treatment effect will be reported. No hazard ratio will be calculated if no event occurred in a treatment group.

Logistic regression models will be fitted for the binary secondary and other efficacy outcomes (composite of symptomatic recurrent VTE and asymptomatic deterioration in thrombotic burden on repeat imaging, composite of symptomatic recurrent VTE and asymptomatic deterioration and no change in thrombotic burden assessment on repeat imaging, normalization of thrombotic burden assessment on repeat imaging; for more details see section 3.3) for the main treatment period to compare incidences between treatment groups.

In addition, absolute risk differences (differences in incidence proportions) for the primary, secondary and further efficacy (composite of symptomatic recurrent VTE and major bleeding; composite of symptomatic recurrent VTE and asymptomatic deterioration and no change in thrombotic burden assessment on repeat imaging at the end of the main treatment period; normalization of thrombotic burden assessment on repeat imaging at the end of the main treatment period without confirmed symptomatic recurrent VTE; composite of symptomatic recurrent VTE and other clinically significant thrombosis) outcomes for the main treatment period will be calculated between rivaroxaban minus comparator overall, by age group, weight group (seven level grouping), dosing formulation assignment and by presentation of index event (for children <2 years with CVC-VTE separately as well) with unstratified exact method using the standardized test statistic and inverting a two-sided test [9] as exploratory analysis. The software StatXact will be used for the calculation of the exact confidence intervals.

The ordered categories of thrombotic burden assessment at the end of main treatment period after imputations as described in section 4.3.4 will be compared between treatment groups with the nonparametric test by van Elteren [11, 12] for stratified ordinal response data (this test is an extension of Wilcoxon's rank-sum test). Strata will be presentation of index event (CVST, CVC-VTE, non-CVC-VTE). In addition, the thrombotic burden assessment at the end of main treatment period will be compared between treatment groups by fitting proportional odds models:

$$\text{logit}(\pi_j) = \ln\left(\frac{\pi_j}{1-\pi_j}\right) = \alpha_j + \beta x$$

where

α_j are 4 intercepts comparing 4 ordered categories of thrombotic burden assessment at the end of the main treatment period comparing with the selected baseline;

x is the matrix for the factors treatment group, presentation of index event (3 groups) for the subjects;

β is the corresponding log odds ratio parameters to be estimated.

One can compare the treatment groups by calculating odds ratios using different cutpoints, for example normalized versus not normalized, normalized+improved versus the rest etc, see cutpoints in section 4.3.4. The constraint placed on the proportional odds is that the odds ratio for treatment groups is constant over the cutpoints [10] i.e. the model can be interpreted as "average up" over all possible cutpoint models to maximize the amount of information one can get out of the data. The result from the proportional odds model is the odds ratio of improving of the thrombotic burden between the rivaroxaban and comparator treatment groups. If the proportional odds assumption is likely violated ($p < 0.10$), the odds ratios for different cutpoints will be presented. Subjects with not available, not evaluable or out of time window will be listed including location of the index venous thrombosis and its imaging method(s) together with their imputed assessment according to section 4.3.4.

6.3.2 Sensitivity analysis to account for dropouts

Sensitivity analyses will be performed in order to evaluate the potential influence of dropouts on the incidence of the primary efficacy outcome for the main treatment period including

patients having scheduled 3 months of study treatment (i.e. except children <2 years with CVC-VTE where the main treatment period is 1 months). In these analyses subjects with premature termination before the end of intended main treatment period (no follow-up until Month 3 defined as Day 83, until Month 1 as Day 23, see section 4.5.3) 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 each treatment group separately. This method is an application of methods for informative missigness odds ratio (IMOR) by White et al [8].

- $t_{j,i} \sim \exp(h_{\text{non-informative},i})$
 $P_{\text{non-informative},j,i} = 1 - e^{-t_{j,i} \cdot h_{\text{non-informative},i}}$
 $h_{\text{dropout},i} = h_{\text{non-informative},i} \cdot \text{IMHR}$
 $P_{\text{dropout},j,i} = 1 - e^{-([83-t_{j,i}] \cdot h_{\text{dropout},i})}$
 $P_{\text{overall},j,i} = \min(1, P_{\text{non-informative},j,i} + P_{\text{dropout},j,i})$
 $P_{\text{overall,mean},i} = \text{mean}(P_{\text{overall},j,i})_i$

where

$t_{j,i}$: event times (or censoring) of patient j in treatment group i .

$h_{\text{non-informative},i}$: hazard of the primary efficacy outcome assuming non-informative censoring using all patients' data in treatment group i .

$P_{\text{non-informative},j,i}$: the cumulative event probability at Day 83 or at censoring calculated based on the exponential model for patient j in treatment group i .

$h_{\text{dropout},i}$: hazard of the primary efficacy outcome after dropping out in treatment group i .

$P_{\text{dropout},j,i}$: the assumed worse case (defined in scenarios) cumulative event probability at from censoring up to Day 83 calculated from the exponential model for patient j in treatment group i .

$P_{\text{overall,mean},i}$: mean of the cumulative event probability in treatment group i .

IMHR: informative missingness hazard ratio.

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

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. Profiles and summary statistics for PK/PD data, by dosing regimen (OD, BID, TID) and by combination of dosing regimen and age groups (birth to <2

years, birth to < 0.5 years, 0.5 years to <2 years, 2 to <6 years, 6 to <12 years, 12 to <18 years), by combination of dosing regimen and formulation (tablet, suspension), by combination of dosing regimen and weight groups (>12 kg, between 6 and 12 kg and below 6 kg), by combination of dosing regimen, age groups, and formulation, and by combination of weight categories, dosing regimen and formulation will be provided. For PK parameters, additionally, summary statistics by age groups and by combination of age groups and formulation will be provided, i.e. pooling of dosing regimens. Number of subjects valid in all three of PK, PD and PPS analysis sets will be tabulated by age groups (birth to <2 years, birth to <0.5 years, 0.5 years to <2 years, 2 to <6 years, 6 to <12 years, 12 to <18 years). Note that PK validity assessment will be performed according to the “Guidance document for PK validity in Phase II/III trials”.

Japanese patients will be included in the PK/PD modeling and the influence of ethnicity will be investigated.

Pharmacokinetic data

The concentration-times courses of rivaroxaban will be tabulated separated by regimen and per age group for each sampling interval. The following statistics will be calculated for each of the sampling intervals: arithmetic mean, standard deviation and coefficient of variation (CV), geometric mean, geometric standard deviation (re-transformed standard deviation of the logarithms) and CV, minimum, median, maximum value and the number of measurements. Means for any interval will only be calculated if at least 2/3 of the individual data were measured and were above the lower limit of quantification (LLOQ). For the calculation of the mean value a data point below LLOQ will be substituted by one half of this limit. In tables showing mean values, where values below LLOQ are included in the calculation of mean values, these means will be marked.

Individual and geometric mean concentration vs time curves of rivaroxaban (using the actual sampling times for individual plots and the planned sampling intervals for mean plots) will be plotted using both linear and semilogarithmic scale.

If applicable, pharmacokinetic characteristics derived via popPK modeling (t_{max} excluded) will be summarized by the statistics mentioned above. t_{max} will be described utilizing minimum, maximum and median as well as frequency counts.

Comparisons with reference data will be graphically sketched.

Pharmacodynamic data

Results for pharmacodynamic data will be displayed using appropriate summary statistics and figures.

In addition, the PK/PD relationship in the age groups will be investigated in an exploratory manner and compared to the adult reference data. Comparisons with reference data will be graphically sketched. The relationships between PT and anti-Xa with rivaroxaban concentrations will be explored by regression methods including analysis of potential effects of age and/or weight effects enriched by data from other pediatric trials as appropriate and may be reported separately.

In case of any finding, further explorative investigations may be done.

6.5 Safety

6.5.1 Adverse events

Individual listings of adverse events (AEs) will be provided. The incidence of treatment-emergent AEs will be summarized by treatment, using MedDRA preferred terms, grouped by primary system organ class. Time window for treatment-emergent events is defined as events occurring after randomization until last intake of study medication plus 2 days. The incidences will be presented for each age cohort separately and for the following time points:

- Post-randomization AEs up to the end of the main treatment period
- Treatment-emergent AEs up to the end of the main treatment period
- All post-randomization AEs
- All treatment-emergent AEs
- Post-randomization AEs started after the end of main treatment period
- Treatment-emergent AEs started after the end of main treatment period
- AEs started more than 2 days after stop of study medication up to 30 days

For the purpose of AE documentation, study drug is defined as either rivaroxaban or comparator, as allocated starting from randomization up to the end of study treatment visit.

6.5.2 Adverse events of special interest

The incidences of the AEs of special interest (AESI) - 1) liver-related AEs, 2) Thrombocytopenia, 3) allergic skin reactions and allergic systemic reactions, will be flagged by the sponsor's medical experts as "potential" and "suspected or confirmed" AESI by medical review. Also, subjects with concurrent elevations of ALT > 5x ULN and total bilirubin > 2x ULN, subjects with platelet count below $50 \times 10^9/L$ will be counted. The incidences will then be displayed by treatment group for the following time periods:

- Post-randomization AEs up to the end of the main treatment period
- Treatment-emergent AEs up to the end of the main treatment period
- All post-randomization AEs
- All treatment-emergent AEs
- Post-randomization AEs started after the end of main treatment period
- Treatment-emergent AEs started after the end of main treatment period
- AEs started more than 2 days after stop of study medication up to 30 days

For more details, see Appendix [9.3](#).

6.5.3 Laboratory

Descriptive statistics will be presented for Hb, platelets, ALT, total and direct bilirubin at visit 4 (at visit 2 for children with CVC-VTE) and for their changes to baseline. Unscheduled visits will be included for the summary statistics tables if the patient did not have end of

treatment visit, and the unscheduled visit was around the planned EoT visit (for example, ± 3 week).

In addition, number of subjects with treatment-emergent high and treatment-emergent low laboratory abnormalities by laboratory category and treatment will be displayed. The numerator will be the number of subjects with at least one high laboratory assessment after the start of treatment who had a normal or lower than normal laboratory assessment at baseline in the treatment-emergent high laboratory abnormalities table. Similarly for the treatment-emergent low laboratory abnormalities table. The descriptive statistics will be done for all data combined and for each age cohort. In addition, all laboratory data will be listed by patient.

6.5.4 Bleeding analysis

All bleeding analyses will be performed on the safety analysis set based on the outcomes confirmed by the CIAC and categorized into one of the following bleeding sites:

- Gastrointestinal tract
- Nasal
- Oral Cavity
- Skin
- Injection site
- Genital
- Urinary tract
- Conjunctival
- Intra-articular
- Respiratory tract
- Intramuscular – without compartment syndrome
- Intracranial
- Other
- Unknown

For details, see Appendix 9.5.

All bleeding events that occurred during study treatment or within 2 days after stop of study medication (i.e. treatment-emergent) 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, Kalbfleisch and Prentice, 7) will be calculated for the primary safety outcome by treatment group at the end of the main study treatment period (for children <2 years with CVC-VTE separately as well). Incidence proportions for the principal safety outcome will be reported overall by classification of index event. Incidence proportions will also be calculated for each age stratum, weight group (seven level grouping), dosing

formulation assignment, summaries of kidney function at the end of the main study treatment period and by presentation of index event as well (for children <2 years with CVC-VTE separately as well). For details of time to event and time to censoring see section 4.5.3.

In addition, incidence proportions will be calculated by treatment group for each age stratum, and overall in the extended study treatment period at 2 and 3 months (for the children <2 years with CVC-VTE) 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. Two-sided 95% confidence intervals for the frequency of bleeding outcomes will be calculated by applying the method of Blyth-Still-Casella [13, 14].

Incidence proportions of other bleeding outcomes and components including duration and intensity of menstrual bleeding, any new action taken based on the menstrual bleeding questionnaire per on-treatment visit will be presented descriptively. The last menstrual bleeding start date, whether the menarche occurred before start of anticoagulation and new action taken related to menstrual bleeding (e.g., change in contraceptive therapy, blood transfusion, prohemostatic drug / antifibrinolytic drug, other concomitant medications or referral to gynecologist) will also be listed.

6.5.4.1 Statistical models

For comparing incidences of outcomes between rivaroxaban versus comparator, stratified (strata: CVST, CVC-VTE, non-CVC-VTE) Cox proportional hazards models will be fitted for the time to principal safety outcome as an exploratory analysis as described for efficacy in Section 6.3.1. As with the efficacy outcomes, Cox proportional hazards models will be fitted separately for the subgroups CVST, CVC-VTE and non-CVC-VTE.

As it is expected that in some strata the number of events will be low, Firth's penalized maximum likelihood estimation will be used to reduce bias in the parameter estimates. Point estimates for hazard ratios, confidence intervals (obtained with profile-likelihood function) and p-values for the treatment effect will be obtained. No hazard ratio will be calculated if no event occurred in a treatment group.

In addition, absolute risk differences (differences in incidence proportions) for the principal safety outcome at the end of the main treatment period will be calculated between rivaroxaban minus comparator with standard of care overall, by age group, weight group (seven level grouping), dosing formulation assignment and by presentation of index event (for children <2 years with CVC-VTE separately as well) with unstratified exact method using the standardized test statistic and inverting a two-sided test [9] as exploratory analysis. The software StatXact will be used for the calculation of the exact confidence intervals.

6.6 Taste-and-texture questionnaire

Results for the taste-and-texture questionnaire in children 4 to < 18 years who receive the oral suspension will be presented descriptively as counts and proportions of responses by questions overall and by age groups.

6.7 Pre-specified subgroup analysis

Analysis by baseline and clinical characteristics The efficacy, bleeding and safety outcomes, including appropriate confidence intervals, at the end of the main treatment period will be described by the following subgroups.

- Age (birth to <2 years; (birth to <0.5 years; 0.5 to <2 years); 2 to <6 years; 6 to <12 years; 12 to <18 years)
- Body weight
Three level grouping: <6 kg; 6 to 12 kg; >12 kg
Seven level grouping: 0<5 kg; 5 to 10 kg; 10 to 20 kg; 20 to 30 kg; 30 to 40 kg; 40 to 50 kg; >50 kg
- Gender (male; female)
- Presentation of index event (CVST; CVC-VTE; non-CVC-VTE)
- Was the index event a recurrent episode of venous thrombosis? (yes; no)
- Risk factors (provoked thrombosis by persistent risk factor, provoked thrombosis by persistent and transient risk factors, provoked thrombosis by transient risk factor, unprovoked, unconfirmed/unknown)
- Dosing formulation assignment (rivaroxaban tablets, rivaroxaban oral suspension, comparator) for SAF and PPS populations
- Presence of catheter (only at baseline, at baseline and end of main treatment, no)

6.8 Extrapolation of data obtained in adult patients with VTE treated with rivaroxaban to the setting of treatment of VTE with rivaroxaban in children

To allow extrapolation of efficacy from adults to the pediatric population [16, 17, 18], the following conditions are considered. First, the pediatric 20 mg-equivalent rivaroxaban dose regimens should result in similar achieved drug exposure in children as observed in adults who received the approved therapeutic dose of 20 mg once-daily. Second, the clinical course of VTE (i.e. incidences of symptomatic recurrent VTE, major bleeding and mortality) should be similar in children and adults. Finally, the response to rivaroxaban therapy as compared to standard anticoagulation should be similar in children and adults.

To document the similarity between adults and children in clinical course of VTE and the relative efficacy and safety, the following analyses will be done for the primary efficacy outcome, composite of primary efficacy outcome and major bleeding, composite of major and clinically relevant nonmajor bleeding:

- 1) Assessment of the incidences and the corresponding two-sided 95% confidence intervals by treatment group
- 2) Assessment of the relative treatment effects (hazard ratio and their 95, 90, 80, 50% confidence intervals)

These analyses will be done for the FAS but also for the subgroup of children with non-CVC-VTE (excluding those with CVC-VTE and CVST).

The upper margin of the 95% CI of the rivaroxaban versus comparator hazard ratio will be used for comparison with the non-inferiority margin as established for the Einstein DVT and PE program. In that program, a non-inferiority margin of 2.0 was accepted for the individual Einstein DVT and PE studies whereas a non-inferiority margin of 1.75 was accepted for the pooled Einstein DVT and PE data.

7. Document history and changes in the planned statistical analysis

- First draft of SAP was circulated with the Bayer team on 30 SEP 2014.
- Version 1.0 was released on 03 Dec 2014.
- SAP Version 2.0 dated 13 Feb 2019 was prepared to provide the following edits. None of them are considered to change the primary efficacy analysis and other analyses as described in the study protocol and its amendments and in the SAP version 1.0 dated 03 Dec 2014.
 - Referred all study protocol versions/amendments up to date
 - Although the initial description of the program referred to treatment with “age and body weight” adjusted rivaroxaban regimen, in reality rivaroxaban dose adjustments based on age never took place. Since pediatric rivaroxaban regimens are entirely based on body weight, we refer in this document, including the title, to “body weight –adjusted” rivaroxaban regimens
 - The assessment of repeated imaging at visit contains a further category ‘normalized’ which was added in section 3.3. Imputation rules for thrombus burden assessment if repeated imaging was not performed or it was done outside of time window was included in section 4.3.
 - Different main and extended treatment periods for children aged < 2 years with catheter-related thrombosis were considered.
 - The sample size was increased to at least 170 children due to the extended age group from birth to 0.5 years.
 - Descriptive analysis of the menstrual bleeding questionnaire was included.
 - Van Elteren test and proportional odds model to compare change in thrombus burden categories at the end of main treatment period between treatment groups was defined.
 - Subgroup analyses and calculation of confidence intervals for frequencies were included.
 - Calculation of compliance for the VKA comparator treatment will be based on 19 days periods as done in other studies.
 - Concomitant antithrombotics will be categorized based on Drug Groupings (DGs, both Standardized DGs and Bayer DGs, related to WHODrug Version 2018sep and requested updates).
 - A section with detailed time definitions for the time to event analyses was included.
- SAP Version 3.0 dated 01 Mar 2019 was prepared to provide the following edits. None of them are considered to change the primary efficacy analysis and other analyses as

described in the study protocol and its amendments and in the SAP version 1.0 dated 03 Dec 2014 or SAP version 2.0 dated 13 Feb 2019.

- Subgroup for index event classification
- Bleeding site groupings
- Reference to analysis for Japanese patients was removed, because such analysis will be performed separately.

8. References

1. The EINSTEIN investigators. Oral Rivaroxaban for Symptomatic Venous Thromboembolism. *N Engl J Med* 2010; 363: 2499-2510.
2. Buller HR, Prins MH, Lensing AW, Decousus H, Jacobson BF, Minar E, et al. Oral Rivaroxaban for the treatment of symptomatic pulmonary embolism. *N.Engl J Med* 2012; 366 (14):1287-97.
3. Prins MH, Lensing AWA. Derivation of the non-inferiority margin for the evaluation of direct oral anticoagulants in the treatment of venous thromboembolism. *Thromb J* 2013; 11: 13. DOI: 10.1186/1477-9560-11-13
4. Massicotte P, Julian JA, Gent M, et al. An open-label randomized controlled trial of low molecular weight heparin compared to heparin and coumadin for the treatment of venous thromboembolic events in children: the REVIVE trial. *Thromb Res* 2003; 109: 85-92. DOI:10.1016/S0049-3848(03)00059-8.
5. Jung,Sin-Ho; Kang, Sun J.; McCall, Linda M.; Blumenstein, Brent. 2005. 'Sample Sizes Computation for Two-Sample Noninferiority Log-Rank Test', *J. of Biopharmaceutical Statistics*, Volume 15, pages 969-979.
6. Hintze, J. (2011). *PASS 11*. NCSS, LLC. Kaysville, Utah, USA. www.ncss.com.
7. Kalbfleisch JD, Prentice RL. *The Statistical Analysis of Failure Time Data*. Wiley Series in Probability and Statistics, 2. Edition – 2002.
8. White IR, Welton NJ, Wood AM, Ades AE, Higgins JP. Allowing for uncertainty due to missing data in meta-analysis—Part 2: Hierarchical models. *Stat Med*. 2008; 27: 728-45.
9. Agresti A, MinY. On small-sample confidence intervals for parameters in discrete distributions. *Biometrics* 2001; 57: 963-971.
10. Hosmer DW, Lemeshow S. *Special Topics, in Applied Logistic Regression*, 2nd Edition, John Wiley & Sons, Inc., Hoboken, NJ, USA, 2000. doi: 10.1002/0471722146.ch8.
11. van Elteren PH. On the combination of independent two-sample tests of Wilcoxon. *Bulletin of the International Statistical Institute*. 1960, 37: 351-361.
12. Dmitrienko A, Molenberghs G, Chuang-Stein C, Offen W. *Analysis of Clinical Trials Using SAS: A Practical Guide*, Cary, NC: SAS Institute Inc, 2005.
13. Blyth C, Still H. Binomial confidence intervals. *Journal of American Statistical Association* 1983; 78:108-116.

14. Casella G. Refining binomial confidence intervals. *Canadian Journal of Statistics* 1986; 14:113-129.
15. Boer DP, de Rijke YB, Hop WC, et al. *Pediatr Nephrol.* 2010; Reference values for serum creatinine in children younger than 1 year of age; 25:2107–2113.
16. Lensing AWA et al. Rivaroxaban versus standard anticoagulation for acute venous thromboembolism in childhood. Design of the EINSTEIN-Jr phase III study. *Throm J* 2018; 16:34. Doi: 10.1186/s12959-018-0188-y.
17. Reflection paper on the use of extrapolation in the development of medicines for paediatrics. 7 October 2018, EMA/189724/2018.
18. Dunne J, Rodriguez WJ, Murphy MD, Beasley BN, Burckart GJ, Filie JD, et al. Extrapolation of adult data and other data in pediatric drug-development programs. *Pediatrics.* 2011;128:e1242–9.

9. Appendix

9.1 Sample size and power considerations

The sample size of 170 children does not originate from a formal sample size calculation, but is based on a feasibility assessment. In order to show non-inferiority (NI) of rivaroxaban versus comparator regarding symptomatic recurrent VTE, one would use a non-inferiority margin of 2.0 on the hazard ratio scale, as it was derived for the VTE treatment studies in adults and one would apply similar statistical model appropriate for time to event data (Einstein DVT and PE studies; see 1, 2, 3). A non-inferiority logrank test with an overall number of patients of 90 having outcome event achieves 90% power at a one-sided 0.05 significance level to show non-inferiority with a margin of hazard ratio of 2.0 when the actual hazard ratio is 1.0. In the REVIVE randomized controlled clinical trial in pediatric population (Massicotte et al., 4) under reviparin-sodium (LMWH), 2/36 patients (5.6%) had recurrent VTE or death and 4/40 patients (10.0%) receiving UFH/VKA over 3 months. Based on this incidence data and assuming a dropout rate of only 0.01 in both treatment group Table 9-1 shows the number of subjects to be randomized to show non-inferiority (margin: 2.0) based on the required number of events to be observed.

Table 9–1. Number of subjects to be randomized depending on the hazard rate of the recurrent VTE.

Hazard rate (in both groups)	N _{rivaroxaban}	N _{comparator}	N _{total}
0.05	613	1247	1860
0.07	442	900	1342
0.09	347	707	1054
0.10	314	639	953

Note: The calculations are based on the NI margin of 2.0 (HR), one-sided 0.05 significance level, 90% power, actual HR of 1.0, proportion of dropouts of 0.01 in both groups.

The calculations were performed based on methods by Jung et al. (5) with the statistical software PASS 11 (6). Such large sample sizes are assessed as not feasible for pediatric studies in this indication. However, this study with at least 150 children 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 to account for Dropout

OpenBUGS model

```

model
{
  for (i in 1 : N) {
    # Survival times bounded below by censoring times:
    t[i] ~ dexp(mu)C(t.cen[i],)
    p.imhr2[i] <- min(1,(1 - exp(-(t.obs[i] * mu)) + 1 - exp(-((t.limit - t.obs[i]) * mu * IMHR2))))
  }
  mu <- exp(alpha);
  alpha ~ dnorm(-6.6, 0.4)
  IMHR2 ~ dlnorm (0.693, 10)
  CDF <- 1 - exp(-(t.limit * mu))
  p.mean.imhr2 <- mean(p.imhr2[])
}

```

OpenBUGS node statistics

	mean	sd	MC_error	val2.5pc	median	val97.5pc	start	sample
CDF	0.07934	0.03257	0.002	0.03089	0.07445	0.1573	30001	30000
IMHR2	2.1	0.6788	0.004	1.069	2.0	3.714	30001	30000
Alpha	-6.997	0.439	0.027	-7.88	-6.978	-6.184	30001	30000
Mu	0.001004	4.33E-04	2.656E-5	3.78E-04	9.32E-04	0.002062	30001	30000
p.mean.imhr2	0.1132	0.05039	0.003	0.04112	0.1047	0.2365	30001	30000

9.3 Adverse events of special interest

9.3.1 Potential treatment-emergent AESIs

Adverse events screened will be reviewed and flagged by the sponsor’s medical experts whether they fulfill the criteria of liver-related or thrombocytopenia or allergic reactions AESI to classify for full or partial narrative.

- The SMQ for liver-related AEs is:
SMQ Drug related hepatic disorders – comprehensive search: 20000006 excluding sub-SMQ Liver-related coagulation and bleeding disturbances: 20000015
- The SMQ for Haematopoietic thrombocytopenia (SMQ) is: 20000031
- The SMQs for allergic skin reactions and allergic systemic reactions are: Anaphylactic reaction (2 - narrow scope only) (SMQ code='20000021'), SMQ Severe cutaneous adverse reactions (2 - narrow scope only) (SMQ code='20000020'), SMQ Hypersensitivity (2 - narrow scope only) (SMQ code='20000214), SMQ Angioedema (2 - narrow scope only) (SMQ code='20000024')

Additional adverse event fulfilling the criteria of AESI may also be flagged during medical review. The incidences of these adverse events using MedDRA SOC and PT will be displayed by treatment group.

9.3.2 Suspected or confirmed AESIs

The incidences of the suspected or confirmed AESIs will be derived from flagging those identified for full narratives during medical review and which had already been flagged as a potential AESI requiring partial narrative.

9.4 Reference values for kidney function classification

The reference values are from the publication of Boer et al. [15].

Table 9–2. Reference values for serum creatinine in different subgroups

Group	Creatinine _{predicted} ^a	2.5th percentile ^b	10th percentile ^b	90th percentile ^b	97.5th percentile ^b	n ^c
Day 1	55	37	43	70	81	5
Day 2	47	32	36	60	69	13
Day 3	42	29	33	54	62	12
Day 4	39	27	31	50	58	9
Day 5	37	25	29	48	55	8
Day 6	36	24	28	46	53	7
Day 7	34	23	27	44	51	13
Week 2	31	21	24	40	46	15
Week 3	28	19	22	36	41	15
Week 4	25	17	20	32	37	15
Month 2	22	15	17	29	33	65
Month 3	20	14	16	26	30	69
Month 4–6	20	14	16	26	30	65
Month 7–9	20	14	16	26	30	65
Month 10–12	21	15	17	27	32	65

Values are given as micromoles per litre (µmol/L). To express serum creatinine values in milligrams per decilitre (mg/dL) divide by 88.4

^a Creatinine_{predicted} expresses predicted median values by our formula

^b 2.5th, 10th, 90th and 97.5th percentiles are the percentiles predicted from the model

^c n is the number of included patients

9.5 Bleeding site categorization

Table 9–3. Bleeding site grouping of confirmed bleedings

Bleeding Site Grouping	Individual Bleeding Site as adjudicated
Gastrointestinal tract	Gastrointestinal tract - esophageal Gastrointestinal tract - gastric Gastrointestinal tract - large intestine / colon Gastrointestinal tract - rectal - non-hemorrhoidal
Nasal	Nasal
Oral Cavity/Gingival	Gastrointestinal tract - oral cavity Gastrointestinal tract – gingival
Skin	Skin (other than injection site) - petechiae Skin (other than injection site) - ecchymosis Skin (other than injection site) – hematoma Skin (other than injection site) - surgical site Leg Finger Upper limb Skin, other Ear Umbilical Other – ostomy bag Other - stoma
Injection site	Injection / blood sampling site Skin (other than injection site) - percutaneous instrumentation site
Genital	Genital - ovarian Genital - uterine Genital - vaginal
Urinary tract	Urinary bladder Urethra Kidney
Conjunctival	Eye - conjunctival
Intra-articular	Intra-articular
Respiratory tract	Respiratory tract – pleural Respiratory tract - tracheal
Intramuscular – without compartment syndrome	Intramuscular - without compartment syndrome
Intracranial	Intracranial - subdural
Unknown	Undetermined



Title page

Study Protocol Title (incl. version no. and date): 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

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

Global Protocol Amendment 12 forming integrated protocol version 5.0, dated 27 SEP 2017

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[Analysis purpose:] Additional Analyses

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Abbreviations

BAY	sponsor's reference number for drugs
BMI	body mass index
CIAC	central independent adjudication committee
CVC	central venous catheter
CVST	cerebral vein and sinus thrombosis
eGFR	estimated glomerular filtration rate
FAS	full analysis set
LMWH	low molecular weight heparin
mg	Milligram
min	Minute
ml	Milliliter
PK	pharmacokinetic(s)
SAP	statistical analysis plan
UFH	unfractionated heparin
VKA	vitamin K antagonist
VTE	venous thromboembolism

1. Introduction

This SAP Supplement 2.0 is based on the SAP version 3.0. The purpose of this SAP Supplement 2.0 is to define further analyses and include clarifications or alterations of analyses specified on the original SAP. Sections 2.1, 2.3, 2.6, 2.7 specify further analyses while the rest of the sections are clarifications or alterations to the analyses specified in SAP version 3.0. None of the additional analyses detailed in this document are considered to change the primary efficacy analysis and other analyses as described in the study protocol and its amendments and in the SAP version 3.0 dated 01 Mar 2019.

2. Description of additional analyses and clarifications

2.1 Study medication

2.1.1 Treatment Duration up to the end of main treatment period

In addition to the analyses specified in Section 6.2.1 of the original SAP, the duration of the study treatment in the main treatment period will be summarized separately for (i) children aged < 2 years with CVC-VTE, (ii) all other children - overall, by treatment and age groups by calculating number of data available and missing data, mean, standard deviation, minimum, quartiles, median, and maximum.

For each subject, the main treatment period for this analysis is defined as the period starting on the day of randomization and stopping either on the day of the last intake of study medication or on Day 97 (Day 37 for children < 2 years with CVC-VTE), whichever comes earlier.

2.1.2 Rivaroxaban study treatment up to the end of main treatment period

Number of subjects in the rivaroxaban arm will be presented by dosing formulation assignment (tablet versus suspension) overall and by age group.

2.1.3 Comparator study treatment up to the end of main treatment period

Number of subjects in the comparator arm will be presented by the following main categories overall and by age group:

- LMWH/Fondaparinux (UFH) only
- VKA

2.2 Intended duration of main treatment for subjects with CVC-VTE and <2years who were enrolled before Protocol Amendment 12

Subjects with CVC-VTE and <2 years who were enrolled before Protocol Amendment 12 will be considered similar to such subjects enrolled after Protocol Amendment 12. This means that the main treatment duration, for the purpose of analysis of key end points, will be 1 month. After that, there may be two consecutive optional extension periods of 1 month duration each. Treatment beyond 3 months will be considered as part of the second extension period.

2.3 Imputation rules for thrombus burden assessment if repeated imaging was not performed or done outside of time window

The SAP Version 3 defined imputation rules for thrombotic burden at repeated imaging based on the availability of the assessment, relative time to randomization and presence/timing of anticoagulant treatment, see more details in Table 4-1 of section 4.3.4 of the SAP version 3.0. The following modifications will be applied to the status of anticoagulation therapy outlined in Table 4-1 of the original SAP version 3.0.

Table 2–1. Overview of repeated imaging categories from the CIAC and the imputation rules for if repeated imaging was not performed or done out of time window

Repeat imaging	Status of anticoagulant therapy	Thrombus burden assessment categories
Performed in time window, assessment is either normalized, improved, unchanged or deteriorated*	Not applicable	Accept adjudication outcome
Performed before time window, assessment is either normalized, improved, unchanged or deteriorated*	If any anticoagulation** stopped up to 7 days after repeat imaging	Accept adjudication outcome
Performed before time window, assessment is either normalized, improved, unchanged or deteriorated*	If any anticoagulation** continued for >7 days after repeat imaging	Classify outcome as “uncertain”
Performed after time window, assessment is either normalized, improved, unchanged or deteriorated*	Not applicable	Classify as “uncertain”
Not performed or assessment is not evaluable	If any anticoagulation** stopped before main treatment time window (or no anticoagulation recorded)&	Classify as “uncertain”
Not performed or assessment is not evaluable	If any anticoagulation** stopped during main treatment time window&	Classify as “improved”
Not performed or assessment is not evaluable	If any anticoagulation** is continued after main treatment time window&	Classify as “uncertain”
Confirmed symptomatic recurrent venous thromboembolism+	Not applicable	Classify as “recurrent VTE”

*Time window for repeat imaging relative to randomization: Day 90±21 (or Day 30±7 for children with CVC-VTE younger than 2 years).

**Any anticoagulation defined as anticoagulant therapy with either study medication or non-study anticoagulation with either direct factor Xa inhibitors, direct thrombin inhibitors, unfractionated or low molecular weight heparin (except mucopolysaccharide polysulfuric acid ester), fondaparinux, or a vitamin K antagonist. Non-study anticoagulant therapy counted if started within 7 days after stop of study medication with a duration of at least 7 days (subsequent therapies will also be considered).

&Time window for stop of anticoagulation relative to randomization: Day 83-97 (or Day 23-37 for children with CVC-VTE younger than 2 years).

+regardless of availability of repeat imaging, up to the upper limit of the end of main treatment time window, see section 4.5.3 from SAP Version 3.0.

In addition to that, the original results of the adjudication will be cross-tabulated with the imputed categories and counts (%) per each cross-tabulation categories will be presented.

2.4 Compliance

Overall compliance for the main treatment period will be calculated taking into account dose interruptions; for the total duration of exposure interruptions will be excluded. Visit

compliance will not be calculated as it cannot be estimated reliably and it has no relevance. For further details of the methods of calculation, see SAP version 3.0 Section 4.5.2. Subjects who took both VKA and LMWH/Fondaparinux, compliance will be calculated for both periods separately and the overall compliance will be a weighted average by duration of treatment. For subjects on LMWH/Fondaparinux treatment and did not have study medication dispensed by the site or dispensed but not returned, compliance will not be calculated and “not available” will be displayed in the tables. This category will also include subjects whose medication was dispensed in the main treatment period but returned in the extended treatment period.

The above compliance calculation will also done for the overall study period.

2.5 Analysis sets

2.5.1 Per-protocol set (PPS)

This population included all FAS (i.e. randomized) children without major protocol deviations. The detailed list of these deviations were finalized prior to database lock and included in the protocol deviation document and validity review report. Further details of the deviations will not be added here; please see the above documents for more details.

2.5.2 Amended population for the PK analysis

Four rivaroxaban subjects who had at least one valid rivaroxaban concentration measurement were excluded by error from the PK analysis set and one subject without rivaroxaban concentration measurement was included by error in the PK analysis set. In the PK validity assessment performed according to the “Guidance document for PK validity in Phase II/III trials” (see SAP version 3.0), all concentrations invalid for PK were individually flagged so that the exclusion of invalid PK data via these flags is assured. Based on this and in agreement with the original SAP, only subjects with at least 1 PK sample in accordance with the PK sampling strategy will be included in the PK analysis (including Population PK analysis). This will be documented in a Note to File.

2.6 Pediatric risk factors for thrombosis

The CIAC performed a standardized assessment of the clinical characteristics of each individual subject with a confirmed thrombosis to determine risk categories for VTE. For further details see section 6.1.1 of the SAP version 3.0.

The following 12 categories, as adjudicated, will be considered as distinct risk factor for the calculation of the number of risk factors per patient

- Active cancer
- Family history of venous thrombosis
- Known inherited thrombophilia
- Acquired thrombophilia

- Major congenital venous anomaly
- Major organ disease
- Central venous catheter
- Major infectious disease
- Major surgery or major trauma
- Morbid Obesity
- Prolonged immobilization
- Use of estrogens or progestins

As per the SAP Version 3.0, the number of subjects having each of the above risk factors will be tabulated. In addition to that, number of subjects having one, two or more than two risk factors will be presented overall, by treatment and age groups. The risk factors will be presented overall in the full analysis set and in the safety analysis set as well as by age groups

2.7 Additional Efficacy and Safety Analyses

The stratified Cox proportional hazard models for time to event outcomes, the logistic regression models for binary outcomes and the proportional odds model fitted for ordered categorical outcome of the thrombus burden assessment at repeated imaging as specified in the SAP Version 3.0 are considered as generalized linear models, which allows for response variables that have error distribution models other than a normal distribution (1). Although the number of subjects with primary and secondary efficacy outcomes, principal safety outcomes are relatively low, according to Vittinghoff et al. (2) and Lin et al. (3) models even with 5-9 events per predictor variable provide reasonably conservative confidence intervals and p-values. The following analyses will be performed in addition to the efficacy and safety analyses specified in the SAP Version 3.0:

Efficacy Analysis:

Cox proportional hazards models will be fitted for the composite of symptomatic recurrent VTE and other clinically significant thrombosis overall and separately for the subgroups CVST, CVC-VTE and non-CVC-VTE up to the end of the main treatment period. As it is expected that in some strata the number of events will be low, Firth's penalized maximum likelihood estimation will be used to reduce bias in the parameter estimates. Point estimates for hazard ratios, confidence intervals (obtained with profile-likelihood function) and p-values for the treatment effect will be reported.

Safety Analysis:

Exact confidence intervals for the incidences by treatment group and absolute risk differences (differences in incidence proportions between treatment groups) and their exact confidence intervals will be calculated at the end of the main treatment period for the following safety outcomes:

- Death

- Major bleeding

3. Document history and changes in the planned statistical analysis

- First draft of SAP Supplement was circulated with the Bayer team on 03 APR 2019.
- Version 1.0 was released on 08 APR 2019.
- SAP Supplement Version 2.0 dated 03 MAY 2019 was prepared to provide the following edits. None of them are considered to change the primary efficacy analysis and there is no substantial change to other analyses as described in the study protocol and its amendments, SAP Version 3.0 or SAP Supplement version 1.0 dated 08 APR 2019.
 - Clarifications to imputation rules for thrombus burden assessment if repeated imaging was not performed or done outside of time window from Section 4.3.4 of SAP Version 3.0
 - ‘Morbid Obesity’, as adjudicated, to be considered a pediatric risk factor instead of ‘BMI > 35 kg/m²’ calculated from the data
 - Added note to the appropriateness of the confidence intervals and p-values calculated from the Cox proportional hazards and logistic regression models.

4. References

1. McCullagh P, Nelder JA. Generalized Linear Models. 2nd Edition, Chapman and Hall, London, 1989.
2. Vittinghoff E, McCulloch CE. Relaxing the Rule of Ten Events per Variable in Logistic and Cox Regression. *Am J Epidemiol* 2007;165:710-8.
3. Lin IF, Chang WP, Liao YN. Shrinkage methods enhanced the accuracy of parameter estimation using Cox models with small number of events. *J Clin Epidemiol*. 2013; 66:743-51. doi: 10.1016/j.jclinepi.2013.02.002.