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

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

Bayer study drug	BAY 59-7939/rivaroxaban/Xarelto		
Clinical study phase:	I/II	**Date:**	09 Feb 2016
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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.

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Abbreviations

ADS	Analysis dataset
AE	adverse event
AUC	Area under the curve
BAY	sponsor's reference number for drugs
CV	Coefficient of variation
DMC	data monitoring committee
DVT	deep vein thrombosis
eGFR	estimated glomerular filtration rate
Hb	hemoglobin
i.e.	id est, that is
IxRS	interactive voice/web response system
MedDRA	Medical Dictionary for Regulatory Activities

mg	milligram
min	minute
ml	milliliter
PD	pharmacodynamics
PD	pharmacodynamics
PK	pharmacokinetic(s)
SAP	statistical analysis plan

1. Introduction

This SAP is based on the integrated clinical study protocol version 2.0 (21 Jul 2015) and its local amendment 2 for Canada dated 22 September 2015.

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

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

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

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

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

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

2. Study Objectives

The primary objective is:

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

The secondary objectives are:

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

3. Study Design

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

At least 8 children are planned to be enrolled in the study.

Study treatment consists of a 7-day treatment with an age- and body weight-adjusted twice daily oral rivaroxaban dosing to achieve a similar exposure as that observed in adults treated for venous thromboembolism (VTE) with 20 mg rivaroxaban once daily. Rivaroxaban will be provided as an oral suspension (1 mg/mL) using a b.i.d. regimen with 12-hour intervals in the morning and evening during or directly after feeding. If a rivaroxaban dose was missed, the child should take rivaroxaban immediately to ensure intake of the total daily dose per day. In this case, two oral suspension doses may be taken at once. The last dose of rivaroxaban treatment will be followed by a 30-day post study treatment period, regardless of the duration of study drug administration.

The principal safety outcome is the combination of major and clinically relevant non-major bleeding. The efficacy outcome is the composite of all symptomatic recurrent thromboembolism and asymptomatic deterioration in thrombotic burden on repeat imaging. All suspected recurrent thromboembolism, asymptomatic deterioration in thrombotic burden on repeat imaging, deaths, as well as all episodes of bleeding will be evaluated by a CIAC. Adjudication results will be the basis for the final analyses.

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

Table 2: Flow chart: pharmacokinetics and pharmacodynamics

Pharmacokinetics and pharmacodynamics (PK/PD)[a]	**Visit 1**	**Visit 2**					**Visit 3**				**Visit 4**
Rivaroxaban treatment days	**Screen day -10 to day 1**	**Treatment day 1**			**Treatment day 2**		**Treatment day 3**		**Treatment day 4 to 7**		**Day 8**
Rivaroxaban administration		**1st dose**		**2nd dose**	**1st dose**	**2nd dose**	**1st dose**	**2nd dose**	**1st dose**	**2nd dose**	
PK/PD time points		0.5 to 1.5 hr post dose	2-4 hr post dose				2-8 hr post dose				10-16 hr after last dose at day 7
Obtain blood sample for PK [b]		•	•				•				•
Obtain blood sample for PD [c]			•				•				•

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

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

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

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

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). All variables will be analyzed by descriptive statistical methods. The number of data available and missing data, mean, standard deviation, minimum, median, and maximum will be calculated for metric data if not otherwise specified. Frequency tables will be generated for categorical data.

Summary statistics will be presented for the subjects under active treatment, data of subjects which did not receive any study medication will be listed only

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

4.2 Handling of Missing Data

Missing data will not be estimated by specific methods for imputation of data. Possible impact of missing values on the analysis will be discussed in the clinical study report.

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

4.3 Interim Analyses and Data Monitoring

No interim analysis will be performed.

A data monitoring committee (DMC) has the responsibility to provide the steering committee with recommendations related to the protection of the children's safety, including stopping recruitment and study treatment. For that purpose, the DMC will regularly review all incidences of serious adverse events, recurrent venous or arterial thromboembolic events and bleeding, and PK/PD results.

4.4 Data Rules

All reported medication intake by the children that stopped at least one day before the date of first study drug intake will be considered as previous medication, otherwise as concomitant medication.

Baseline is defined as the last observation prior to the first dose of study medication.

Arithmetic means will be calculated and used for tables and figures in case of repeated measurements for the same subject, timepoint, laboratory, and laboratory test.

In case of laboratory measurements from different laboratories with different normal ranges, ULN-normalized values will be calculated and used for tables and figures, if applicable. In case of missing upper limit of normal information, values will be listed only.

Phase I pool reference data for rivaroxaban plasma concentration, PT, and aPTT measurements to be used are given in

/by-sasp/patdb/projects/597939/xa_ph1_reports/stat/test_epbka/pip/pip_data.sas7bdat,

and by the corresponding high dose age groups of the Phase I pediatric study 12892 in

/by-sasp/patdb/projects/597939/12892/dm/prod/data/ad.

4.5 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

5.1 Assignment of 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 0).

Full analysis set: This analysis set will include all children from whom informed consent was obtained.

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

Per protocol analysis set: This population includes all children who completed the 7 day treatment period or had an efficacy or bleeding outcome before. This analysis set may exclude major protocol deviations.

Listing only set (LoS): this population includes all screening failures.

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 Demographic and other baseline characteristics

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

6.2 Safety analysis

Adverse events

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

Safety parameters

Quantitative data (hematology, blood chemistry, pulse rate) will be described by the following summary statistics: arithmetic mean, standard deviation, median, minimum and maximum. These summary statistics will be presented for the original data, as well as for the difference to baseline. Frequency tables will be provided for qualitative data. Laboratory data outside the reference range will be listed and flagged with 'L' for low and 'H' for high. Additional tables with all abnormal values will be presented.

Graphical displays of individual data as well as mean values with standard deviation will be included.

6.3 Efficacy analysis

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

6.4 PK/PD analysis

Pharmacokinetic data

The concentration-times courses of rivaroxaban will be tabulated 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.

Comparison with reference data will be graphically sketched.

Pharmacodynamic data

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

If applicable, the pharmacodynamic data will be analyzed for any relationship to C_{max} and C_{trough}. In addition, the PK/PD relationship will be investigated in an exploratory manner and compared to the reference data.

Comparison with reference data will be graphically sketched.

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

7. Document history and changes in the planned statistical analysis

Not applicable.

8. References

Not applicable.