Title page

Study Protocol Title (incl. version no. and date):
Multicenter, open-label, active-controlled, randomized study to evaluate the efficacy and safety of age and body weight-adjusted rivaroxaban regimen compared to standard of care in children with acute venous thromboembolism

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

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

SAP (incl. Version no. and date): Additional SAP Version 1.0, dated 24 OCT 2019

Analysis purpose: Exploratory subgroup analysis for subjects with Cerebral Vein and Sinus Thrombosis

Clinical study phase: III  Date: 25 OCT 2019

Study No.: 14372  Version: 1.0

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This “Additional Statistical Analysis Plan” is produced on a word-processing system and bears no signatures.
1. Introduction

EINSTEIN-Jr phase 3 study was a multi-centre, open-label, randomised trial that compared the efficacy and safety of rivaroxaban with that of standard anticoagulants for the treatment of various manifestations of paediatric VTE. For details regarding the statistical analysis, see SAP version 3.0, dated 01 MAR 2019.

Since anticoagulant treatment of paediatric cerebral vein and sinus thrombosis (CVST) has not been prospectively evaluated in a randomized clinical trial setting (1), it was considered important to conduct a sub-study on EINSTEIN-Jr patients with baseline CVST by collection of additional relevant baseline and post-baseline data on the clinical course of the CVST during the 90-day main treatment period. The statistical analysis based on the data from the main study and from the sub-study of the CVST patients will be included in a separate technical report. This Statistical Analysis Plan (SAP) pre-specifies the analyses to be
performed on the patients with baseline CVST, including both the data from the main study as well as the additional data collected from the sub-study.

2. Population Characteristics

Summary statistics (arithmetic mean, standard deviation, median, minimum and maximum for quantitative variables) will be presented in total and by treatment group for the FAS. Frequency tables for qualitative data will be provided. No statistical tests will be performed to compare these characteristics across treatment groups.

2.1 Clinical characteristics

- Categorization by provoked or unprovoked 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).
  - Specific predisposing risk factors for CVST: Dural AV fistula, Hyperthyroidism, Inflammatory disease, Medication, Major head trauma, Paroxysmal Nocturnal Hemoglobinuria
- Parenchymal lesion(s) and the lesion type (Hemorrhagic, Non-hemorrhagic, or both)
- Clinical presentation of the CVST:
  - Coma
  - Dehydration
  - Epileptic seizure
  - Focal neurological deficits
  - Headache
  - Papilledema
  - Visual disturbances and its types (Decreased Vision, Diplopia)

2.2 Clinical course (post-baseline)

2.2.1 Clinical course during the three-month study period

The following clinical characteristics during the three-month study period will be summarized by treatment group:

- Duration in intensive care unit
- Duration of hospitalization
- Decompressive hemicraniectomy/craniotomy
- Hospitalization
- Intensive care unit
- Mechanical ventilation
• Shunting procedure

2.2.2 Clinical course at the three-month follow-up visit

The following clinical characteristics at the three-month follow-up visit will be summarized by treatment group to evaluate the clinical course of CVST:

• Ability to walk / move
• Decreased vision
• Death
• Epileptic seizure
• Focal neurological deficits
• Headache interfering with activities for greater than 2 weeks
• New cancer diagnosed
• Require help with activities of daily living

3. Efficacy

As for the main analysis defined in the SAP Version 3.0, the following efficacy variables will be considered:

• 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:
  o Composite of symptomatic recurrent VTE and major bleeding
  o 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
  o 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).
  o Normalization of thrombotic burden assessment on repeat imaging at the end of the main treatment period without confirmed symptomatic recurrent VTE
  o Fatal or non-fatal pulmonary embolism
  o Composite of symptomatic recurrent VTE and other clinically significant thrombosis

The above variables will be descriptively summarized as follows:
• Incidence proportions (number of children with outcome during the period divided by number of children at risk at the beginning of the period) and two-sided 95% exact confidence intervals for the frequency of outcomes (incidence proportions in the above analyses) by treatment group at the end of the main study treatment period

• Absolute risk differences (differences in incidence proportions) at the end of the main treatment period between rivaroxaban minus comparator and corresponding two-sided 95% exact confidence intervals

• Counts of composite of symptomatic recurrent VTE and thrombotic burden assessment at repeated imaging at the end of the main treatment period by treatment group

• Counts per imputation category for thrombotic burden assessment by treatment group – please see SAP Version 3.0 Section 4.3.4 for the imputation rules

• Functional dependency at the end of main treatment period using the modified Rankin Scale scores on a scale of 0-6 adapted for children and dichotomized as follows:
  o score of 0-2: favorable outcome
  o score of greater than 2: poor outcome.

  For further details, see CIAC charter in Section 6.

The following exploratory statistical models will be fitted:

• Proportional odds model for comparison of thrombotic burden assessment at the end of main treatment period between treatment groups

• Wilcoxon rank-sum test for comparison of the ordered categories of thrombotic burden assessment at the end of main treatment period

For details regarding the statistical methods, see SAP Version 3.0 Section 6.3.

4. Safety

4.1 Bleeding Analysis

All bleeding analyses will be performed on the safety analysis set based on the outcomes confirmed by the CIAC. As in the main Phase III study, the following safety outcomes related to bleeding will be considered:

• The principal safety outcome is the composite of overt major and clinically relevant non-major bleeding.

• Further safety outcomes
  o Major bleeding
  o Clinically relevant non-major bleeding
  o Trivial bleeding

The above variables will be descriptively summarized as follows:

• Incidences of all confirmed treatment-emergent bleedings up to the end of main treatment period by bleeding category
• Incidence rates of treatment-emergent Principal Safety outcome up to the end of main treatment period and two-sided 95% exact confidence intervals

• Absolute risk differences in incidences of treatment-emergent Principal Safety outcome for the main treatment period and the corresponding two-sided 95% exact confidence intervals

In addition, a listing will also be provided for clinically relevant non-major bleedings during the main treatment period.

5. Reference


6. Appendix

CIAC Charter for Modified Rankin Scale of CVST children in the EINSTEIN-Jr 14372 study.