



## Clinical trial results:

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

#### Summary

|                          |                   |
|--------------------------|-------------------|
| EudraCT number           | 2011-004539-30    |
| Trial protocol           | AT DE IT NL       |
| Global end of trial date | 01 September 2016 |

#### Results information

|                                |                                                          |
|--------------------------------|----------------------------------------------------------|
| Result version number          | v2                                                       |
| This version publication date  | 17 November 2017                                         |
| First version publication date | 17 March 2017                                            |
| Version creation reason        | • Correction of full data set<br>EMA results maintenance |

#### Trial information

##### Trial identification

|                       |                  |
|-----------------------|------------------|
| Sponsor protocol code | BAY59-7939/14373 |
|-----------------------|------------------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01684423 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |                                                                    |
|------------------------------|--------------------------------------------------------------------|
| Sponsor organisation name    | Bayer AG                                                           |
| Sponsor organisation address | Kaiser-Wilhelm-Allee, D-51368 Leverkusen, Germany,                 |
| Public contact               | Therapeutic Area Head, Bayer AG, clinical-trials-contact@bayer.com |
| Scientific contact           | Therapeutic Area Head, Bayer AG, clinical-trials-contact@bayer.com |

Notes:

#### Paediatric regulatory details

|                                                                      |                     |
|----------------------------------------------------------------------|---------------------|
| Is trial part of an agreed paediatric investigation plan (PIP)       | Yes                 |
| EMA paediatric investigation plan number(s)                          | EMA-000430-PIP01-08 |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No                  |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | Yes                 |

Notes:

## Results analysis stage

|                                                      |                   |
|------------------------------------------------------|-------------------|
| Analysis stage                                       | Final             |
| Date of interim/final analysis                       | 01 September 2016 |
| Is this the analysis of the primary completion data? | No                |
| Global end of trial reached?                         | Yes               |
| Global end of trial date                             | 01 September 2016 |
| Was the trial ended prematurely?                     | No                |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective was to assess the incidence of major bleeding and clinically relevant non-major bleeding.

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and the International Conference on Harmonization guideline E6: Good Clinical Practice. Before entering the study, the informed consent explained to all subjects and/or their legally authorized representative. Participating subjects and/or their legally authorized representative signed informed consent form and could withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. Only investigators qualified by training and experience were selected as appropriate experts to investigate the study drug.

Background therapy: -

Evidence for comparator: -

|                                                           |                  |
|-----------------------------------------------------------|------------------|
| Actual start date of recruitment                          | 19 February 2013 |
| Long term follow-up planned                               | No               |
| Independent data monitoring committee (IDMC) involvement? | Yes              |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                   |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | Austria: 6        |
| Country: Number of subjects enrolled | France: 5         |
| Country: Number of subjects enrolled | Germany: 8        |
| Country: Number of subjects enrolled | Italy: 12         |
| Country: Number of subjects enrolled | Australia: 6      |
| Country: Number of subjects enrolled | Canada: 3         |
| Country: Number of subjects enrolled | Switzerland: 4    |
| Country: Number of subjects enrolled | Israel: 2         |
| Country: Number of subjects enrolled | United States: 15 |
| Country: Number of subjects enrolled | Netherlands: 3    |
| Worldwide total number of subjects   | 64                |
| EEA total number of subjects         | 34                |

Notes:

| <b>Subjects enrolled per age group</b>    |    |
|-------------------------------------------|----|
| In utero                                  | 0  |
| Preterm newborn - gestational age < 37 wk | 0  |
| Newborns (0-27 days)                      | 0  |
| Infants and toddlers (28 days-23 months)  | 0  |
| Children (2-11 years)                     | 40 |
| Adolescents (12-17 years)                 | 24 |
| Adults (18-64 years)                      | 0  |
| From 65 to 84 years                       | 0  |
| 85 years and over                         | 0  |

## Subject disposition

### Recruitment

Recruitment details:

The study was conducted at multiple centers in 10 countries worldwide between 19 February 2013 (first subject first visit) and 01 September 2016 (last subject last visit).

### Pre-assignment

Screening details:

A total of 68 subjects were screened, of these 4 subjects failed screening. The remaining 64 subjects were randomized, of whom 63 subjects were treated.

### Period 1

|                              |                                |
|------------------------------|--------------------------------|
| Period 1 title               | Overall Trial (overall period) |
| Is this the baseline period? | Yes                            |
| Allocation method            | Not applicable                 |
| Blinding used                | Not blinded                    |

### Arms

|                              |                                                          |
|------------------------------|----------------------------------------------------------|
| Are arms mutually exclusive? | Yes                                                      |
| <b>Arm title</b>             | Rivaroxaban (BAY59-7939) tablet, OD, Age: 12 - <18 years |

Arm description:

Subjects aged from 12 - <18 years were administered with age- and body weight-adjusted oral dose of rivaroxaban (BAY59-7939) immediate-release (IR) tablet once daily under fed conditions for 30 days.

|                                        |                    |
|----------------------------------------|--------------------|
| Arm type                               | Experimental       |
| Investigational medicinal product name | Rivaroxaban        |
| Investigational medicinal product code | BAY59-7939         |
| Other name                             |                    |
| Pharmaceutical forms                   | Film-coated tablet |
| Routes of administration               | Oral use           |

Dosage and administration details:

Subjects aged from 12 - <18 years were administered with age and body weight-adjusted oral dose of rivaroxaban (BAY59-7939) IR tablet once daily under fed conditions for 30 days. Subjects with a body weight of 14 to less than 50 kilogram (kg) received a dose (equivalent to 20 milligram [mg] in adults) ranging from 5 to 15 mg, and subjects with a body weight (comparable to adults) of greater than or equal to 50 kg received a dose of 20 mg.

|                  |                                 |
|------------------|---------------------------------|
| <b>Arm title</b> | Comparator, Age: 12 - <18 years |
|------------------|---------------------------------|

Arm description:

Subjects aged from 12 - <18 years received comparator as per standard of care.

|                                        |                          |
|----------------------------------------|--------------------------|
| Arm type                               | Active comparator        |
| Investigational medicinal product name | Comparator               |
| Investigational medicinal product code |                          |
| Other name                             |                          |
| Pharmaceutical forms                   | Injection, Tablet        |
| Routes of administration               | Oral use, Parenteral use |

Dosage and administration details:

Subjects aged from 12 - <18 years received comparator as per standard of care. The dosage given was to be adjusted based on the individual body weight (low molecular weight heparin, fondaparinux) or international normalized ratio (INR) adjusted (vitamin K antagonist).

|                  |                                                         |
|------------------|---------------------------------------------------------|
| <b>Arm title</b> | Rivaroxaban (BAY59-7939) tablet, OD, Age: 6 - <12 years |
|------------------|---------------------------------------------------------|

Arm description:

Subjects aged from 6 - <12 years were administered with age- and body weight-adjusted oral dose of rivaroxaban (BAY59-7939) IR tablet once daily under fed conditions for 30 days.

|          |              |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

|                                        |                    |
|----------------------------------------|--------------------|
| Investigational medicinal product name | Rivaroxaban        |
| Investigational medicinal product code | BAY59-7939         |
| Other name                             |                    |
| Pharmaceutical forms                   | Film-coated tablet |
| Routes of administration               | Oral use           |

**Dosage and administration details:**

Subjects aged from 6 - <12 years were administered with age- and body weight-adjusted oral dose of rivaroxaban (BAY59-7939) IR tablet once daily under fed conditions for 30 days. Subjects with a body weight of 14 to less than 50 kg received a dose (equivalent to 20 mg in adults) ranging from 5 to 15 mg, and subjects with a body weight (comparable to adults) of greater than or equal to 50 kg received a dose of 20 mg.

|                  |                                                              |
|------------------|--------------------------------------------------------------|
| <b>Arm title</b> | Rivaroxaban (BAY59-7939) suspension, BID, Age: 6 - <12 years |
|------------------|--------------------------------------------------------------|

**Arm description:**

Subjects aged from 6 - <12 years were administered with age- and body weight-adjusted oral dose of rivaroxaban (BAY59-7939) suspension under fed conditions twice daily.

|                                        |                 |
|----------------------------------------|-----------------|
| Arm type                               | Experimental    |
| Investigational medicinal product name | Rivaroxaban     |
| Investigational medicinal product code | BAY59-7939      |
| Other name                             |                 |
| Pharmaceutical forms                   | Oral suspension |
| Routes of administration               | Oral use        |

**Dosage and administration details:**

Subjects aged from 6 - <12 years were administered with age- and body weight-adjusted oral dose of rivaroxaban (BAY59-7939) suspension under fed conditions twice daily. Subjects with a body weight of 9 to less than 50 kg received a total daily dose (equivalent to 20 mg in adults) ranging from 6.4 to 15 mg and subjects with a body weight of greater than or equal to 50 kg received a total daily dose of 20 mg.

|                  |                                |
|------------------|--------------------------------|
| <b>Arm title</b> | Comparator, Age: 6 - <12 years |
|------------------|--------------------------------|

**Arm description:**

Subjects aged from 6 - <12 years received comparator as per standard of care.

|                                        |                          |
|----------------------------------------|--------------------------|
| Arm type                               | Active comparator        |
| Investigational medicinal product name | Comparator               |
| Investigational medicinal product code |                          |
| Other name                             |                          |
| Pharmaceutical forms                   | Injection, Tablet        |
| Routes of administration               | Oral use, Parenteral use |

**Dosage and administration details:**

Subjects aged from 6 - <12 years received comparator as per standard of care. The dosage given was to be adjusted based on the individual body weight (low molecular weight heparin, fondaparinux) or INR-adjusted (vitamin K antagonist).

| <b>Number of subjects in period 1<sup>[1]</sup></b> | Rivaroxaban (BAY59-7939) tablet, OD, Age: 12 - <18 years | Comparator, Age: 12 - <18 years | Rivaroxaban (BAY59-7939) tablet, OD, Age: 6 - <12 years |
|-----------------------------------------------------|----------------------------------------------------------|---------------------------------|---------------------------------------------------------|
|                                                     |                                                          |                                 |                                                         |
| Started                                             | 11                                                       | 13                              | 13                                                      |
| Completed                                           | 11                                                       | 13                              | 12                                                      |
| Not completed                                       | 0                                                        | 0                               | 1                                                       |
| Withdrawal by subject                               | -                                                        | -                               | 1                                                       |

|                                                     |                                           |                                |
|-----------------------------------------------------|-------------------------------------------|--------------------------------|
| <b>Number of subjects in period 1<sup>[1]</sup></b> | Rivaroxaban (BAY59-7939) suspension, BID, | Comparator, Age: 6 - <12 years |
|-----------------------------------------------------|-------------------------------------------|--------------------------------|

|                       |                    |   |
|-----------------------|--------------------|---|
|                       | Age: 6 - <12 years |   |
| Started               | 19                 | 7 |
| Completed             | 19                 | 7 |
| Not completed         | 0                  | 0 |
| Withdrawal by subject | -                  | - |

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Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Not all enrolled subjects received treatment. Only treated subjects were included in the baseline period.

## Baseline characteristics

### Reporting groups

|                       |                                                          |
|-----------------------|----------------------------------------------------------|
| Reporting group title | Rivaroxaban (BAY59-7939) tablet, OD, Age: 12 - <18 years |
|-----------------------|----------------------------------------------------------|

Reporting group description:

Subjects aged from 12 - <18 years were administered with age- and body weight-adjusted oral dose of rivaroxaban (BAY59-7939) immediate-release (IR) tablet once daily under fed conditions for 30 days.

|                       |                                 |
|-----------------------|---------------------------------|
| Reporting group title | Comparator, Age: 12 - <18 years |
|-----------------------|---------------------------------|

Reporting group description:

Subjects aged from 12 - <18 years received comparator as per standard of care.

|                       |                                                         |
|-----------------------|---------------------------------------------------------|
| Reporting group title | Rivaroxaban (BAY59-7939) tablet, OD, Age: 6 - <12 years |
|-----------------------|---------------------------------------------------------|

Reporting group description:

Subjects aged from 6 - <12 years were administered with age- and body weight-adjusted oral dose of rivaroxaban (BAY59-7939) IR tablet once daily under fed conditions for 30 days.

|                       |                                                              |
|-----------------------|--------------------------------------------------------------|
| Reporting group title | Rivaroxaban (BAY59-7939) suspension, BID, Age: 6 - <12 years |
|-----------------------|--------------------------------------------------------------|

Reporting group description:

Subjects aged from 6 - <12 years were administered with age- and body weight-adjusted oral dose of rivaroxaban (BAY59-7939) suspension under fed conditions twice daily.

|                       |                                |
|-----------------------|--------------------------------|
| Reporting group title | Comparator, Age: 6 - <12 years |
|-----------------------|--------------------------------|

Reporting group description:

Subjects aged from 6 - <12 years received comparator as per standard of care.

| Reporting group values             | Rivaroxaban (BAY59-7939) tablet, OD, Age: 12 - <18 years | Comparator, Age: 12 - <18 years | Rivaroxaban (BAY59-7939) tablet, OD, Age: 6 - <12 years |
|------------------------------------|----------------------------------------------------------|---------------------------------|---------------------------------------------------------|
| Number of subjects                 | 11                                                       | 13                              | 13                                                      |
| Age categorical<br>Units: Subjects |                                                          |                                 |                                                         |

|                                       |       |      |       |
|---------------------------------------|-------|------|-------|
| Age continuous<br>Units: years        |       |      |       |
| arithmetic mean                       | 15.5  | 14.8 | 8.5   |
| standard deviation                    | ± 1.2 | ± 1  | ± 2.1 |
| Gender categorical<br>Units: Subjects |       |      |       |
| Female                                | 8     | 7    | 5     |
| Male                                  | 3     | 6    | 8     |

| Reporting group values             | Rivaroxaban (BAY59-7939) suspension, BID, Age: 6 - <12 years | Comparator, Age: 6 - <12 years | Total |
|------------------------------------|--------------------------------------------------------------|--------------------------------|-------|
| Number of subjects                 | 19                                                           | 7                              | 63    |
| Age categorical<br>Units: Subjects |                                                              |                                |       |

|                                |       |     |   |
|--------------------------------|-------|-----|---|
| Age continuous<br>Units: years |       |     |   |
| arithmetic mean                | 8.3   | 9   |   |
| standard deviation             | ± 1.9 | ± 2 | - |

|                    |    |   |    |
|--------------------|----|---|----|
| Gender categorical |    |   |    |
| Units: Subjects    |    |   |    |
| Female             | 6  | 3 | 29 |
| Male               | 13 | 4 | 34 |



## End points

### End points reporting groups

|                                                                                                                                                                                                                                         |                                                              |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------|
| Reporting group title                                                                                                                                                                                                                   | Rivaroxaban (BAY59-7939) tablet, OD, Age: 12 - <18 years     |
| Reporting group description:<br>Subjects aged from 12 - <18 years were administered with age- and body weight-adjusted oral dose of rivaroxaban (BAY59-7939) immediate-release (IR) tablet once daily under fed conditions for 30 days. |                                                              |
| Reporting group title                                                                                                                                                                                                                   | Comparator, Age: 12 - <18 years                              |
| Reporting group description:<br>Subjects aged from 12 - <18 years received comparator as per standard of care.                                                                                                                          |                                                              |
| Reporting group title                                                                                                                                                                                                                   | Rivaroxaban (BAY59-7939) tablet, OD, Age: 6 - <12 years      |
| Reporting group description:<br>Subjects aged from 6 - <12 years were administered with age- and body weight-adjusted oral dose of rivaroxaban (BAY59-7939) IR tablet once daily under fed conditions for 30 days.                      |                                                              |
| Reporting group title                                                                                                                                                                                                                   | Rivaroxaban (BAY59-7939) suspension, BID, Age: 6 - <12 years |
| Reporting group description:<br>Subjects aged from 6 - <12 years were administered with age- and body weight-adjusted oral dose of rivaroxaban (BAY59-7939) suspension under fed conditions twice daily.                                |                                                              |
| Reporting group title                                                                                                                                                                                                                   | Comparator, Age: 6 - <12 years                               |
| Reporting group description:<br>Subjects aged from 6 - <12 years received comparator as per standard of care.                                                                                                                           |                                                              |
| Subject analysis set title                                                                                                                                                                                                              | Safety analysis set (SAS)                                    |
| Subject analysis set type                                                                                                                                                                                                               | Safety analysis                                              |
| Subject analysis set description:<br>SAS (N= 63) included all subjects who received at least one dose of study medication.                                                                                                              |                                                              |
| Subject analysis set title                                                                                                                                                                                                              | Full analysis set (FAS)                                      |
| Subject analysis set type                                                                                                                                                                                                               | Full analysis                                                |
| Subject analysis set description:<br>FAS (N= 64) included all subjects who completed screening.                                                                                                                                         |                                                              |
| Subject analysis set title                                                                                                                                                                                                              | Pharmacokinetic analysis set (PKS)                           |
| Subject analysis set type                                                                                                                                                                                                               | Sub-group analysis                                           |
| Subject analysis set description:<br>PKS (N= 42) included all subjects with at least one pharmacokinetic sample in accordance with the pharmacokinetic sampling strategy.                                                               |                                                              |
| Subject analysis set title                                                                                                                                                                                                              | Pharmacodynamic analysis set (PDS)                           |
| Subject analysis set type                                                                                                                                                                                                               | Sub-group analysis                                           |
| Subject analysis set description:<br>PDS (N= 42) included all subjects with at least one blood sample for clotting parameters in accordance with the pharmacodynamic sampling strategy.                                                 |                                                              |

### Primary: Number of Subjects With Major and Clinically Relevant Non-Major Bleeding Events

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                                                                                |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Number of Subjects With Major and Clinically Relevant Non-Major Bleeding Events <sup>[1]</sup> |
| End point description:<br>Central independent adjudication committee (CIAC) classified bleeding as follows:<br>Major bleeding is defined as overt bleeding and: <ul style="list-style-type: none"><li>• associated with a fall in hemoglobin of 2 gram/decilitre (g/dL) or more, or</li><li>• leading to a transfusion of the equivalent of 2 or more units of packed red blood cells or whole blood in adults, or</li><li>• occurring in a critical site, e.g. intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal, or</li><li>• contributing to death.</li></ul> |                                                                                                |

Clinically relevant non-major bleeding is defined as overt bleeding not meeting the criteria for major bleeding, but associated with:

- medical intervention, or
- unscheduled contact (visit or telephone call) with a physician, or
- cessation (temporary) of study treatment, or
- discomfort for the child such as pain or
- impairment of activities of daily life (such as loss of school days or hospitalization).

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

From start of study drug administration until end of the 30-day treatment period

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Descriptive statistics were done, no inferential statistical analyses were performed.

| End point values                              | Rivaroxaban (BAY59-7939) tablet, OD, Age: 12 - <18 years | Comparator, Age: 12 - <18 years | Rivaroxaban (BAY59-7939) tablet, OD, Age: 6 - <12 years | Rivaroxaban (BAY59-7939) suspension, BID, Age: 6 - <12 years |
|-----------------------------------------------|----------------------------------------------------------|---------------------------------|---------------------------------------------------------|--------------------------------------------------------------|
| Subject group type                            | Reporting group                                          | Reporting group                 | Reporting group                                         | Reporting group                                              |
| Number of subjects analysed                   | 11 <sup>[2]</sup>                                        | 13 <sup>[3]</sup>               | 13 <sup>[4]</sup>                                       | 19 <sup>[5]</sup>                                            |
| Units: subjects                               |                                                          |                                 |                                                         |                                                              |
| Major bleeding events                         | 0                                                        | 0                               | 0                                                       | 0                                                            |
| Clinically relevant non-major bleeding events | 3                                                        | 0                               | 0                                                       | 1                                                            |

Notes:

[2] - FAS

[3] - FAS

[4] - FAS

[5] - FAS

| End point values                              | Comparator, Age: 6 - <12 years |  |  |  |
|-----------------------------------------------|--------------------------------|--|--|--|
| Subject group type                            | Reporting group                |  |  |  |
| Number of subjects analysed                   | 7 <sup>[6]</sup>               |  |  |  |
| Units: subjects                               |                                |  |  |  |
| Major bleeding events                         | 0                              |  |  |  |
| Clinically relevant non-major bleeding events | 0                              |  |  |  |

Notes:

[6] - FAS

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Subjects With Symptomatic Recurrent Venous Thromboembolism

|                 |                                                                      |
|-----------------|----------------------------------------------------------------------|
| End point title | Number of Subjects With Symptomatic Recurrent Venous Thromboembolism |
|-----------------|----------------------------------------------------------------------|

End point description:

The occurrence of recurrent venous thromboembolism was summarized by age group. Symptomatic recurrence of venous thrombosis was documented by the appropriate imaging test.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From start of study drug administration until end of the 30-day treatment period

| End point values            | Rivaroxaban (BAY59-7939) tablet, OD, Age: 12 - <18 years | Comparator, Age: 12 - <18 years | Rivaroxaban (BAY59-7939) tablet, OD, Age: 6 - <12 years | Rivaroxaban (BAY59-7939) suspension, BID, Age: 6 - <12 years |
|-----------------------------|----------------------------------------------------------|---------------------------------|---------------------------------------------------------|--------------------------------------------------------------|
| Subject group type          | Reporting group                                          | Reporting group                 | Reporting group                                         | Reporting group                                              |
| Number of subjects analysed | 11 <sup>[7]</sup>                                        | 13 <sup>[8]</sup>               | 13 <sup>[9]</sup>                                       | 19 <sup>[10]</sup>                                           |
| Units: subjects             | 0                                                        | 0                               | 0                                                       | 0                                                            |

Notes:

[7] - FAS

[8] - FAS

[9] - FAS

[10] - FAS

| End point values            | Comparator, Age: 6 - <12 years |  |  |  |
|-----------------------------|--------------------------------|--|--|--|
| Subject group type          | Reporting group                |  |  |  |
| Number of subjects analysed | 7 <sup>[11]</sup>              |  |  |  |
| Units: subjects             | 0                              |  |  |  |

Notes:

[11] - FAS

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Subjects With Asymptomatic Deterioration in Thrombotic Burden

|                 |                                                                         |
|-----------------|-------------------------------------------------------------------------|
| End point title | Number of Subjects With Asymptomatic Deterioration in Thrombotic Burden |
|-----------------|-------------------------------------------------------------------------|

End point description:

The occurrence of asymptomatic deterioration in thrombotic burden was summarized by age group. Asymptomatic deterioration in thrombotic burden was documented by the appropriate imaging test and the results were classified as normalized, improved, no relevant change, deteriorated, not evaluable or not available.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Repeat imaging at the end of the 30 day treatment period

| End point values            | Rivaroxaban (BAY59-7939) tablet, OD, Age: 12 - <18 years | Comparator, Age: 12 - <18 years | Rivaroxaban (BAY59-7939) tablet, OD, Age: 6 - <12 years | Rivaroxaban (BAY59-7939) suspension, BID, Age: 6 - <12 years |
|-----------------------------|----------------------------------------------------------|---------------------------------|---------------------------------------------------------|--------------------------------------------------------------|
| Subject group type          | Reporting group                                          | Reporting group                 | Reporting group                                         | Reporting group                                              |
| Number of subjects analysed | 11 <sup>[12]</sup>                                       | 13 <sup>[13]</sup>              | 13 <sup>[14]</sup>                                      | 19 <sup>[15]</sup>                                           |
| Units: subjects             |                                                          |                                 |                                                         |                                                              |
| Normalized                  | 3                                                        | 2                               | 2                                                       | 4                                                            |
| Improved                    | 4                                                        | 0                               | 8                                                       | 9                                                            |
| No relevant change          | 0                                                        | 0                               | 1                                                       | 2                                                            |
| Deteriorated                | 0                                                        | 0                               | 0                                                       | 0                                                            |
| Not evaluable               | 0                                                        | 2                               | 0                                                       | 0                                                            |
| Not available               | 4                                                        | 9                               | 2                                                       | 4                                                            |

Notes:

[12] - FAS

[13] - FAS

[14] - FAS

[15] - FAS

| End point values            | Comparator, Age: 6 - <12 years |  |  |  |
|-----------------------------|--------------------------------|--|--|--|
| Subject group type          | Reporting group                |  |  |  |
| Number of subjects analysed | 7 <sup>[16]</sup>              |  |  |  |
| Units: subjects             |                                |  |  |  |
| Normalized                  | 1                              |  |  |  |
| Improved                    | 4                              |  |  |  |
| No relevant change          | 0                              |  |  |  |
| Deteriorated                | 0                              |  |  |  |
| Not evaluable               | 1                              |  |  |  |
| Not available               | 1                              |  |  |  |

Notes:

[16] - FAS

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in Prothrombin Time at Specified Time Points

|                 |                                                                                   |
|-----------------|-----------------------------------------------------------------------------------|
| End point title | Change From Baseline in Prothrombin Time at Specified Time Points <sup>[17]</sup> |
|-----------------|-----------------------------------------------------------------------------------|

End point description:

Prothrombin time is a global clotting test used for the assessment of the extrinsic pathway of the blood coagulation cascade. In the below table, 'n' signifies those subjects who were evaluable for this measure at given time points for each group and '99999' signifies no subjects were evaluated for the given time points for respective reporting groups.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

0 hours (pre-dose) to 8 hours post-dose on Day 15 and 24 hours post-dose on Day 31

Notes:

[17] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Pharmacodynamic and pharmacokinetic parameters were evaluated only for subjects who

received active study medication.

| End point values                                | Rivaroxaban (BAY59-7939) tablet, OD, Age: 12 - <18 years | Rivaroxaban (BAY59-7939) tablet, OD, Age: 6 - <12 years | Rivaroxaban (BAY59-7939) suspension, BID, Age: 6 - <12 years |  |
|-------------------------------------------------|----------------------------------------------------------|---------------------------------------------------------|--------------------------------------------------------------|--|
| Subject group type                              | Reporting group                                          | Reporting group                                         | Reporting group                                              |  |
| Number of subjects analysed                     | 11 <sup>[18]</sup>                                       | 12 <sup>[19]</sup>                                      | 19 <sup>[20]</sup>                                           |  |
| Units: seconds                                  |                                                          |                                                         |                                                              |  |
| arithmetic mean (standard deviation)            |                                                          |                                                         |                                                              |  |
| Day 15: 2 to 4 hours post-dose (n= 11, 12, 19)  | 8.964 (± 3.822)                                          | 9.083 (± 2.513)                                         | 3.147 (± 2.099)                                              |  |
| Day 15: 6 to 8 hours post-dose (n= 11, 12, 19)  | 4.218 (± 2.977)                                          | 2.817 (± 1.628)                                         | 1.984 (± 1.341)                                              |  |
| Day 31: 10 to 16 hours post-dose (n= 0, 0, 18)  | 99999 (± 99999)                                          | 99999 (± 99999)                                         | 0.156 (± 1.155)                                              |  |
| Day 31: 20 to 24 hours post-dose (n= 11, 11, 0) | -0.082 (± 1.02)                                          | -0.327 (± 1.332)                                        | 99999 (± 99999)                                              |  |

Notes:

[18] - PDS with number of subjects evaluable for this specific end point

[19] - PDS with number of subjects evaluable for this specific end point

[20] - PDS with number of subjects evaluable for this specific end point

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in Activated Partial Thromboplastin Time at Specified Time Points

|                 |                                                                                                        |
|-----------------|--------------------------------------------------------------------------------------------------------|
| End point title | Change From Baseline in Activated Partial Thromboplastin Time at Specified Time Points <sup>[21]</sup> |
|-----------------|--------------------------------------------------------------------------------------------------------|

End point description:

The Activated partial thromboplastin time (aPTT) is a screening test for the intrinsic pathway. In the below table, 'n' signifies those subjects who were evaluable for this measure at given time points for each group and '99999' signifies no subjects were evaluated for the given time points for respective reporting groups.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

0 hours (pre-dose) to 8 hours post-dose on Day 15 and 24 hours post-dose on Day 31

Notes:

[21] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Pharmacodynamic and pharmacokinetic parameters were evaluated only for subjects who received active study medication.

| End point values                     | Rivaroxaban (BAY59-7939) tablet, OD, Age: 12 - <18 years | Rivaroxaban (BAY59-7939) tablet, OD, Age: 6 - <12 years | Rivaroxaban (BAY59-7939) suspension, BID, Age: 6 - <12 years |  |
|--------------------------------------|----------------------------------------------------------|---------------------------------------------------------|--------------------------------------------------------------|--|
| Subject group type                   | Reporting group                                          | Reporting group                                         | Reporting group                                              |  |
| Number of subjects analysed          | 11 <sup>[22]</sup>                                       | 12 <sup>[23]</sup>                                      | 19 <sup>[24]</sup>                                           |  |
| Units: seconds                       |                                                          |                                                         |                                                              |  |
| arithmetic mean (standard deviation) |                                                          |                                                         |                                                              |  |

|                                                 |                 |                 |                  |  |
|-------------------------------------------------|-----------------|-----------------|------------------|--|
| Day 15: 2 to 4 hours post-dose (n= 11, 12, 19)  | 10.982 (± 4.47) | 12.818 (± 5.21) | 2.995 (± 5.616)  |  |
| Day 15: 6 to 8 hours post-dose (n= 11, 12,19)   | 6.136 (± 2.641) | 5.9 (± 4.942)   | 1.858 (± 4.774)  |  |
| Day 31: 10 to 16 hours post-dose (n= 0, 0, 18)  | 99999 (± 99999) | 99999 (± 99999) | -0.483 (± 6.488) |  |
| Day 31: 20 to 24 hours post-dose (n= 11, 11, 0) | 1.345 (± 3.19)  | 1.24 (± 4.992)  | 99999 (± 99999)  |  |

Notes:

[22] - PDS with number of subjects evaluable for this specific end point

[23] - PDS with number of subjects evaluable for this specific end point

[24] - PDS with number of subjects evaluable for this specific end point

## Statistical analyses

No statistical analyses for this end point

## Secondary: Anti-factor Xa Values at Specified Time Points

|                 |                                                                |
|-----------------|----------------------------------------------------------------|
| End point title | Anti-factor Xa Values at Specified Time Points <sup>[25]</sup> |
|-----------------|----------------------------------------------------------------|

End point description:

The individual anti-Factor Xa activity was determined ex-vivo using a photometric method. In the below table, 'n' signifies those subjects who were evaluable for this measure at given time points for each group and '99999' signifies no subjects were evaluated for the given time points for respective reporting groups.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

0 hours (pre-dose) to 8 hours post-dose on Day 15 and 24 hours post-dose on Day 31

Notes:

[25] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Pharmacodynamic and pharmacokinetic parameters were evaluated only for subjects who received active study medication.

| End point values                               | Rivaroxaban (BAY59-7939) tablet, OD, Age: 12 - <18 years | Rivaroxaban (BAY59-7939) tablet, OD, Age: 6 - <12 years | Rivaroxaban (BAY59-7939) suspension, BID, Age: 6 - <12 years |  |
|------------------------------------------------|----------------------------------------------------------|---------------------------------------------------------|--------------------------------------------------------------|--|
| Subject group type                             | Reporting group                                          | Reporting group                                         | Reporting group                                              |  |
| Number of subjects analysed                    | 11 <sup>[26]</sup>                                       | 12 <sup>[27]</sup>                                      | 19 <sup>[28]</sup>                                           |  |
| Units: microgram per liter (mcg/L)             |                                                          |                                                         |                                                              |  |
| arithmetic mean (standard deviation)           |                                                          |                                                         |                                                              |  |
| Day 15: pre-dose                               | 16.081 (± 6.136)                                         | 8.136 (± 3.069)                                         | 31.553 (± 25.416)                                            |  |
| Day 15: 2 to 4 hours post-dose (n= 11, 12, 19) | 185.481 (± 53.326)                                       | 252.853 (± 71.072)                                      | 99.415 (± 54.415)                                            |  |
| Day 15: 6 to 8 hours post-dose (n= 11, 12,19)  | 105.223 (± 54.339)                                       | 68.67 (± 32.845)                                        | 77.929 (± 50.074)                                            |  |
| Day 31: 10 to 16 hours post-dose (n= 0, 0, 18) | 99999 (± 99999)                                          | 99999 (± 99999)                                         | 30.927 (± 18.037)                                            |  |
| Day 31: 20 to 24 hours post-dose (n= 9, 10, 0) | 16.038 (± 7.653)                                         | 8.409 (± 3.664)                                         | 99999 (± 99999)                                              |  |

Notes:

[26] - PDS with number of subjects evaluable for this specific end point

[27] - PDS with number of subjects evaluable for this specific end point

[28] - PDS with number of subjects evaluable for this specific end point

## Statistical analyses

No statistical analyses for this end point

### Secondary: Concentration of Rivaroxaban in Plasma as a Measure of Pharmacokinetics at Specified Time Points

|                 |                                                                                                                  |
|-----------------|------------------------------------------------------------------------------------------------------------------|
| End point title | Concentration of Rivaroxaban in Plasma as a Measure of Pharmacokinetics at Specified Time Points <sup>[29]</sup> |
|-----------------|------------------------------------------------------------------------------------------------------------------|

End point description:

Geometric and percentage geometric coefficient of variation (%CV) were reported. In the below table, 'n' signifies those subjects who were evaluable for this measure at given time points for each group.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

0 hours (pre-dose) to 8 hours post-dose on Day 15 and 20-24 hours (OD dosing) and 10-16 hours (BID dosing), respectively, post-dose on Day 31

Notes:

[29] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Pharmacodynamic and pharmacokinetic parameters were evaluated only for subjects who received active study medication.

| End point values                                    | Rivaroxaban (BAY59-7939) tablet, OD, Age: 12 - <18 years | Rivaroxaban (BAY59-7939) tablet, OD, Age: 6 - <12 years | Rivaroxaban (BAY59-7939) suspension, BID, Age: 6 - <12 years |  |
|-----------------------------------------------------|----------------------------------------------------------|---------------------------------------------------------|--------------------------------------------------------------|--|
| Subject group type                                  | Reporting group                                          | Reporting group                                         | Reporting group                                              |  |
| Number of subjects analysed                         | 11 <sup>[30]</sup>                                       | 12 <sup>[31]</sup>                                      | 19 <sup>[32]</sup>                                           |  |
| Units: microgram per liter (mcg/L)                  |                                                          |                                                         |                                                              |  |
| geometric mean (geometric coefficient of variation) |                                                          |                                                         |                                                              |  |
| Day 15: pre-dose                                    | 20.4822 (± 40.6726)                                      | 7.4367 (± 152.9768)                                     | 41.6025 (± 183.6873)                                         |  |
| Day 15: 2 to 4 hours post-dose (n= 11, 12, 19)      | 219.6933 (± 35.7518)                                     | 240.6319 (± 18.3387)                                    | 119.2201 (± 52.9889)                                         |  |
| Day 15: 6 to 8 hours post-dose (n= 11, 12, 19)      | 124.6723 (± 49.1882)                                     | 96.8051 (± 41.8155)                                     | 100.5992 (± 52.6497)                                         |  |
| Day 31: 10 to 16 hours post-dose (n= 0, 0, 19)      | 99999 (± 99999)                                          | 99999 (± 99999)                                         | 43.5223 (± 81.7283)                                          |  |
| Day 31: 20 to 24 hours post-dose (n= 11, 11, 0)     | 21.3252 (± 43.1274)                                      | 9.4654 (± 167.7545)                                     | 99999 (± 99999)                                              |  |

Notes:

[30] - PKS with number of subjects evaluable for this specific end point

[31] - PKS with number of subjects evaluable for this specific end point

[32] - PKS with number of subjects evaluable for this specific end point

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From start of study drug administration until 30 day post study treatment (approximately 60 days).

|                 |                |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |      |
|--------------------|------|
| Dictionary version | 19.0 |
|--------------------|------|

### Reporting groups

|                       |                                                          |
|-----------------------|----------------------------------------------------------|
| Reporting group title | Rivaroxaban (BAY59-7939) tablet, OD, Age: 12 - <18 years |
|-----------------------|----------------------------------------------------------|

Reporting group description:

Subjects aged from 12 - <18 years were administered with age- and body weight-adjusted oral dose of rivaroxaban (BAY59-7939) immediate-release (IR) tablet once daily under fed conditions for 30 days. Subjects with a body weight of 14 to 50 kilogram (kg) received a dose (equivalent to 20 milligram [mg] in adults) ranging from 5 to 15 mg, and subjects with a body weight (comparable to adults) of 50 to 100 kg received a dose of 20 mg.

|                       |                                               |
|-----------------------|-----------------------------------------------|
| Reporting group title | Anticoagulant Comparator, Age: 12 - <18 years |
|-----------------------|-----------------------------------------------|

Reporting group description:

Subjects aged from 12 - <18 years received anticoagulant comparator as per standard regimen. The dosage given was adjusted based on the individual age and body weight.

|                       |                                                         |
|-----------------------|---------------------------------------------------------|
| Reporting group title | Rivaroxaban (BAY59-7939) tablet, OD, Age: 6 - <12 years |
|-----------------------|---------------------------------------------------------|

Reporting group description:

Subjects aged from 6 - <12 years were administered with age- and body weight-adjusted oral dose of rivaroxaban (BAY59-7939) IR tablet once daily under fed conditions for 30 days. Subjects with a body weight of 14 to 50 kg received a dose (equivalent to 20 mg in adults) ranging from 5 to 15 mg, and subjects with a body weight (comparable to adults) of 50 to 100 kg received a dose of 20 mg.

|                       |                                                              |
|-----------------------|--------------------------------------------------------------|
| Reporting group title | Rivaroxaban (BAY59-7939) suspension, BID, Age: 6 - <12 years |
|-----------------------|--------------------------------------------------------------|

Reporting group description:

Subjects aged from 6 - <12 years were administered with age- and body weight-adjusted oral dose of rivaroxaban (BAY59-7939) suspension under fed conditions twice daily. Subjects with a body weight of 9 to 50 kg received a total daily dose (equivalent to 20 mg in adults) ranging from 6.4 to 15 mg and subjects with a body weight of 50 to 100 kg received a total daily dose of 20 mg.

|                       |                                              |
|-----------------------|----------------------------------------------|
| Reporting group title | Anticoagulant Comparator, Age: 6 - <12 years |
|-----------------------|----------------------------------------------|

Reporting group description:

Subjects aged from 6 - <12 years received anticoagulant comparator as per standard regimen. The dosage given was adjusted based on the individual age and body weight.

| Serious adverse events                            | Rivaroxaban (BAY59-7939) tablet, OD, Age: 12 - <18 years | Anticoagulant Comparator, Age: 12 - <18 years | Rivaroxaban (BAY59-7939) tablet, OD, Age: 6 - <12 years |
|---------------------------------------------------|----------------------------------------------------------|-----------------------------------------------|---------------------------------------------------------|
| Total subjects affected by serious adverse events |                                                          |                                               |                                                         |
| subjects affected / exposed                       | 0 / 11 (0.00%)                                           | 1 / 13 (7.69%)                                | 0 / 13 (0.00%)                                          |
| number of deaths (all causes)                     | 0                                                        | 0                                             | 0                                                       |
| number of deaths resulting from adverse events    | 0                                                        | 0                                             | 0                                                       |
| Investigations                                    |                                                          |                                               |                                                         |
| Influenza B virus test positive                   |                                                          |                                               |                                                         |



|                                                 |                |                |                |
|-------------------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 11 (0.00%) | 0 / 13 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Nervous system disorders                        |                |                |                |
| Multiple sclerosis relapse                      |                |                |                |
| subjects affected / exposed                     | 0 / 11 (0.00%) | 1 / 13 (7.69%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Endocrine disorders                             |                |                |                |
| Hypothalamo-pituitary disorder                  |                |                |                |
| subjects affected / exposed                     | 0 / 11 (0.00%) | 0 / 13 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |

| <b>Serious adverse events</b>                     | Rivaroxaban<br>(BAY59-7939)<br>suspension, BID,<br>Age: 6 - <12 years | Anticoagulant<br>Comparator, Age: 6<br>- <12 years |  |
|---------------------------------------------------|-----------------------------------------------------------------------|----------------------------------------------------|--|
| Total subjects affected by serious adverse events |                                                                       |                                                    |  |
| subjects affected / exposed                       | 2 / 19 (10.53%)                                                       | 0 / 7 (0.00%)                                      |  |
| number of deaths (all causes)                     | 0                                                                     | 0                                                  |  |
| number of deaths resulting from adverse events    | 0                                                                     | 0                                                  |  |
| Investigations                                    |                                                                       |                                                    |  |
| Influenza B virus test positive                   |                                                                       |                                                    |  |
| subjects affected / exposed                       | 1 / 19 (5.26%)                                                        | 0 / 7 (0.00%)                                      |  |
| occurrences causally related to treatment / all   | 0 / 1                                                                 | 0 / 0                                              |  |
| deaths causally related to treatment / all        | 0 / 0                                                                 | 0 / 0                                              |  |
| Nervous system disorders                          |                                                                       |                                                    |  |
| Multiple sclerosis relapse                        |                                                                       |                                                    |  |
| subjects affected / exposed                       | 0 / 19 (0.00%)                                                        | 0 / 7 (0.00%)                                      |  |
| occurrences causally related to treatment / all   | 0 / 0                                                                 | 0 / 0                                              |  |
| deaths causally related to treatment / all        | 0 / 0                                                                 | 0 / 0                                              |  |
| Endocrine disorders                               |                                                                       |                                                    |  |
| Hypothalamo-pituitary disorder                    |                                                                       |                                                    |  |
| subjects affected / exposed                       | 1 / 19 (5.26%)                                                        | 0 / 7 (0.00%)                                      |  |
| occurrences causally related to treatment / all   | 0 / 2                                                                 | 0 / 0                                              |  |
| deaths causally related to treatment / all        | 0 / 0                                                                 | 0 / 0                                              |  |

Frequency threshold for reporting non-serious adverse events: 2 %

| <b>Non-serious adverse events</b>                           | <b>Rivaroxaban<br/>(BAY59-7939)<br/>tablet, OD, Age: 12<br/>- &lt;18 years</b> | <b>Anticoagulant<br/>Comparator, Age: 12<br/>- &lt;18 years</b> | <b>Rivaroxaban<br/>(BAY59-7939)<br/>tablet, OD, Age: 6 -<br/>&lt;12 years</b> |
|-------------------------------------------------------------|--------------------------------------------------------------------------------|-----------------------------------------------------------------|-------------------------------------------------------------------------------|
| Total subjects affected by non-serious adverse events       |                                                                                |                                                                 |                                                                               |
| subjects affected / exposed                                 | 9 / 11 (81.82%)                                                                | 8 / 13 (61.54%)                                                 | 6 / 13 (46.15%)                                                               |
| <b>Vascular disorders</b>                                   |                                                                                |                                                                 |                                                                               |
| Post thrombotic syndrome                                    |                                                                                |                                                                 |                                                                               |
| subjects affected / exposed                                 | 0 / 11 (0.00%)                                                                 | 0 / 13 (0.00%)                                                  | 0 / 13 (0.00%)                                                                |
| occurrences (all)                                           | 0                                                                              | 0                                                               | 0                                                                             |
| Hot flush                                                   |                                                                                |                                                                 |                                                                               |
| subjects affected / exposed                                 | 0 / 11 (0.00%)                                                                 | 0 / 13 (0.00%)                                                  | 0 / 13 (0.00%)                                                                |
| occurrences (all)                                           | 0                                                                              | 0                                                               | 0                                                                             |
| <b>General disorders and administration site conditions</b> |                                                                                |                                                                 |                                                                               |
| Chest discomfort                                            |                                                                                |                                                                 |                                                                               |
| subjects affected / exposed                                 | 0 / 11 (0.00%)                                                                 | 1 / 13 (7.69%)                                                  | 0 / 13 (0.00%)                                                                |
| occurrences (all)                                           | 0                                                                              | 1                                                               | 0                                                                             |
| Chest pain                                                  |                                                                                |                                                                 |                                                                               |
| subjects affected / exposed                                 | 1 / 11 (9.09%)                                                                 | 0 / 13 (0.00%)                                                  | 0 / 13 (0.00%)                                                                |
| occurrences (all)                                           | 1                                                                              | 0                                                               | 0                                                                             |
| Fatigue                                                     |                                                                                |                                                                 |                                                                               |
| subjects affected / exposed                                 | 1 / 11 (9.09%)                                                                 | 0 / 13 (0.00%)                                                  | 0 / 13 (0.00%)                                                                |
| occurrences (all)                                           | 1                                                                              | 0                                                               | 0                                                                             |
| Pyrexia                                                     |                                                                                |                                                                 |                                                                               |
| subjects affected / exposed                                 | 0 / 11 (0.00%)                                                                 | 1 / 13 (7.69%)                                                  | 0 / 13 (0.00%)                                                                |
| occurrences (all)                                           | 0                                                                              | 1                                                               | 0                                                                             |
| Peripheral swelling                                         |                                                                                |                                                                 |                                                                               |
| subjects affected / exposed                                 | 1 / 11 (9.09%)                                                                 | 0 / 13 (0.00%)                                                  | 0 / 13 (0.00%)                                                                |
| occurrences (all)                                           | 1                                                                              | 0                                                               | 0                                                                             |
| Localised oedema                                            |                                                                                |                                                                 |                                                                               |
| subjects affected / exposed                                 | 0 / 11 (0.00%)                                                                 | 0 / 13 (0.00%)                                                  | 0 / 13 (0.00%)                                                                |
| occurrences (all)                                           | 0                                                                              | 0                                                               | 0                                                                             |
| Vessel puncture site haematoma                              |                                                                                |                                                                 |                                                                               |
| subjects affected / exposed                                 | 0 / 11 (0.00%)                                                                 | 1 / 13 (7.69%)                                                  | 0 / 13 (0.00%)                                                                |
| occurrences (all)                                           | 0                                                                              | 2                                                               | 0                                                                             |
| Vessel puncture site swelling                               |                                                                                |                                                                 |                                                                               |

|                                                                                                              |                      |                     |                     |
|--------------------------------------------------------------------------------------------------------------|----------------------|---------------------|---------------------|
| subjects affected / exposed<br>occurrences (all)                                                             | 0 / 11 (0.00%)<br>0  | 1 / 13 (7.69%)<br>1 | 0 / 13 (0.00%)<br>0 |
| Reproductive system and breast disorders<br>Menorrhagia<br>subjects affected / exposed<br>occurrences (all)  | 4 / 11 (36.36%)<br>8 | 0 / 13 (0.00%)<br>0 | 0 / 13 (0.00%)<br>0 |
| Respiratory, thoracic and mediastinal disorders<br>Cough<br>subjects affected / exposed<br>occurrences (all) | 0 / 11 (0.00%)<br>0  | 0 / 13 (0.00%)<br>0 | 1 / 13 (7.69%)<br>1 |
| Dyspnoea<br>subjects affected / exposed<br>occurrences (all)                                                 | 1 / 11 (9.09%)<br>1  | 0 / 13 (0.00%)<br>0 | 0 / 13 (0.00%)<br>0 |
| Epistaxis<br>subjects affected / exposed<br>occurrences (all)                                                | 1 / 11 (9.09%)<br>2  | 0 / 13 (0.00%)<br>0 | 1 / 13 (7.69%)<br>2 |
| Nasal congestion<br>subjects affected / exposed<br>occurrences (all)                                         | 1 / 11 (9.09%)<br>1  | 0 / 13 (0.00%)<br>0 | 1 / 13 (7.69%)<br>1 |
| Oropharyngeal pain<br>subjects affected / exposed<br>occurrences (all)                                       | 1 / 11 (9.09%)<br>1  | 0 / 13 (0.00%)<br>0 | 0 / 13 (0.00%)<br>0 |
| Psychiatric disorders<br>Suicidal ideation<br>subjects affected / exposed<br>occurrences (all)               | 1 / 11 (9.09%)<br>1  | 0 / 13 (0.00%)<br>0 | 0 / 13 (0.00%)<br>0 |
| Investigations<br>Haemoglobin decreased<br>subjects affected / exposed<br>occurrences (all)                  | 0 / 11 (0.00%)<br>0  | 0 / 13 (0.00%)<br>0 | 0 / 13 (0.00%)<br>0 |
| Platelet count decreased<br>subjects affected / exposed<br>occurrences (all)                                 | 0 / 11 (0.00%)<br>0  | 0 / 13 (0.00%)<br>0 | 0 / 13 (0.00%)<br>0 |
| Injury, poisoning and procedural complications                                                               |                      |                     |                     |

|                                      |                 |                |                 |
|--------------------------------------|-----------------|----------------|-----------------|
| Fall                                 |                 |                |                 |
| subjects affected / exposed          | 0 / 11 (0.00%)  | 0 / 13 (0.00%) | 0 / 13 (0.00%)  |
| occurrences (all)                    | 0               | 0              | 0               |
| Contusion                            |                 |                |                 |
| subjects affected / exposed          | 1 / 11 (9.09%)  | 1 / 13 (7.69%) | 0 / 13 (0.00%)  |
| occurrences (all)                    | 2               | 2              | 0               |
| Skin abrasion                        |                 |                |                 |
| subjects affected / exposed          | 0 / 11 (0.00%)  | 0 / 13 (0.00%) | 0 / 13 (0.00%)  |
| occurrences (all)                    | 0               | 0              | 0               |
| Nervous system disorders             |                 |                |                 |
| Headache                             |                 |                |                 |
| subjects affected / exposed          | 2 / 11 (18.18%) | 0 / 13 (0.00%) | 2 / 13 (15.38%) |
| occurrences (all)                    | 2               | 0              | 2               |
| Vocal cord paralysis                 |                 |                |                 |
| subjects affected / exposed          | 0 / 11 (0.00%)  | 0 / 13 (0.00%) | 0 / 13 (0.00%)  |
| occurrences (all)                    | 0               | 0              | 0               |
| Multiple sclerosis relapse           |                 |                |                 |
| subjects affected / exposed          | 0 / 11 (0.00%)  | 1 / 13 (7.69%) | 0 / 13 (0.00%)  |
| occurrences (all)                    | 0               | 2              | 0               |
| Blood and lymphatic system disorders |                 |                |                 |
| Anaemia                              |                 |                |                 |
| subjects affected / exposed          | 0 / 11 (0.00%)  | 0 / 13 (0.00%) | 0 / 13 (0.00%)  |
| occurrences (all)                    | 0               | 0              | 0               |
| Increased tendency to bruise         |                 |                |                 |
| subjects affected / exposed          | 0 / 11 (0.00%)  | 0 / 13 (0.00%) | 1 / 13 (7.69%)  |
| occurrences (all)                    | 0               | 0              | 2               |
| Neutropenia                          |                 |                |                 |
| subjects affected / exposed          | 0 / 11 (0.00%)  | 0 / 13 (0.00%) | 0 / 13 (0.00%)  |
| occurrences (all)                    | 0               | 0              | 0               |
| Ear and labyrinth disorders          |                 |                |                 |
| Vertigo                              |                 |                |                 |
| subjects affected / exposed          | 1 / 11 (9.09%)  | 0 / 13 (0.00%) | 0 / 13 (0.00%)  |
| occurrences (all)                    | 1               | 0              | 0               |
| Eye disorders                        |                 |                |                 |
| Eye pain                             |                 |                |                 |
| subjects affected / exposed          | 0 / 11 (0.00%)  | 0 / 13 (0.00%) | 1 / 13 (7.69%)  |
| occurrences (all)                    | 0               | 0              | 1               |

|                                        |                |                |                 |
|----------------------------------------|----------------|----------------|-----------------|
| Gastrointestinal disorders             |                |                |                 |
| Abdominal pain                         |                |                |                 |
| subjects affected / exposed            | 0 / 11 (0.00%) | 0 / 13 (0.00%) | 2 / 13 (15.38%) |
| occurrences (all)                      | 0              | 0              | 3               |
| Abdominal pain upper                   |                |                |                 |
| subjects affected / exposed            | 0 / 11 (0.00%) | 0 / 13 (0.00%) | 0 / 13 (0.00%)  |
| occurrences (all)                      | 0              | 0              | 0               |
| Diarrhoea                              |                |                |                 |
| subjects affected / exposed            | 1 / 11 (9.09%) | 1 / 13 (7.69%) | 1 / 13 (7.69%)  |
| occurrences (all)                      | 1              | 1              | 1               |
| Dyspepsia                              |                |                |                 |
| subjects affected / exposed            | 1 / 11 (9.09%) | 0 / 13 (0.00%) | 0 / 13 (0.00%)  |
| occurrences (all)                      | 1              | 0              | 0               |
| Gastrooesophageal reflux disease       |                |                |                 |
| subjects affected / exposed            | 0 / 11 (0.00%) | 0 / 13 (0.00%) | 1 / 13 (7.69%)  |
| occurrences (all)                      | 0              | 0              | 1               |
| Gingival bleeding                      |                |                |                 |
| subjects affected / exposed            | 0 / 11 (0.00%) | 1 / 13 (7.69%) | 0 / 13 (0.00%)  |
| occurrences (all)                      | 0              | 2              | 0               |
| Nausea                                 |                |                |                 |
| subjects affected / exposed            | 0 / 11 (0.00%) | 0 / 13 (0.00%) | 0 / 13 (0.00%)  |
| occurrences (all)                      | 0              | 0              | 0               |
| Tooth loss                             |                |                |                 |
| subjects affected / exposed            | 0 / 11 (0.00%) | 0 / 13 (0.00%) | 0 / 13 (0.00%)  |
| occurrences (all)                      | 0              | 0              | 0               |
| Vomiting                               |                |                |                 |
| subjects affected / exposed            | 1 / 11 (9.09%) | 1 / 13 (7.69%) | 0 / 13 (0.00%)  |
| occurrences (all)                      | 1              | 1              | 0               |
| Lower gastrointestinal haemorrhage     |                |                |                 |
| subjects affected / exposed            | 1 / 11 (9.09%) | 0 / 13 (0.00%) | 0 / 13 (0.00%)  |
| occurrences (all)                      | 2              | 0              | 0               |
| Skin and subcutaneous tissue disorders |                |                |                 |
| Alopecia                               |                |                |                 |
| subjects affected / exposed            | 0 / 11 (0.00%) | 0 / 13 (0.00%) | 0 / 13 (0.00%)  |
| occurrences (all)                      | 0              | 0              | 0               |
| Dermatitis allergic                    |                |                |                 |

|                                                 |                |                |                |
|-------------------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 11 (0.00%) | 1 / 13 (7.69%) | 0 / 13 (0.00%) |
| occurrences (all)                               | 0              | 1              | 0              |
| Erythema                                        |                |                |                |
| subjects affected / exposed                     | 0 / 11 (0.00%) | 0 / 13 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all)                               | 0              | 0              | 0              |
| Hyperhidrosis                                   |                |                |                |
| subjects affected / exposed                     | 0 / 11 (0.00%) | 1 / 13 (7.69%) | 0 / 13 (0.00%) |
| occurrences (all)                               | 0              | 1              | 0              |
| Pruritus                                        |                |                |                |
| subjects affected / exposed                     | 0 / 11 (0.00%) | 0 / 13 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all)                               | 0              | 0              | 0              |
| Rash                                            |                |                |                |
| subjects affected / exposed                     | 0 / 11 (0.00%) | 0 / 13 (0.00%) | 1 / 13 (7.69%) |
| occurrences (all)                               | 0              | 0              | 1              |
| Swelling face                                   |                |                |                |
| subjects affected / exposed                     | 0 / 11 (0.00%) | 1 / 13 (7.69%) | 0 / 13 (0.00%) |
| occurrences (all)                               | 0              | 1              | 0              |
| Musculoskeletal and connective tissue disorders |                |                |                |
| Arthralgia                                      |                |                |                |
| subjects affected / exposed                     | 0 / 11 (0.00%) | 0 / 13 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all)                               | 0              | 0              | 0              |
| Back pain                                       |                |                |                |
| subjects affected / exposed                     | 1 / 11 (9.09%) | 0 / 13 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all)                               | 1              | 0              | 0              |
| Flank pain                                      |                |                |                |
| subjects affected / exposed                     | 1 / 11 (9.09%) | 0 / 13 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all)                               | 1              | 0              | 0              |
| Musculoskeletal pain                            |                |                |                |
| subjects affected / exposed                     | 1 / 11 (9.09%) | 0 / 13 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all)                               | 1              | 0              | 0              |
| Pain in extremity                               |                |                |                |
| subjects affected / exposed                     | 1 / 11 (9.09%) | 1 / 13 (7.69%) | 1 / 13 (7.69%) |
| occurrences (all)                               | 1              | 1              | 1              |
| Pain in jaw                                     |                |                |                |

|                                                  |                     |                     |                     |
|--------------------------------------------------|---------------------|---------------------|---------------------|
| subjects affected / exposed<br>occurrences (all) | 0 / 11 (0.00%)<br>0 | 1 / 13 (7.69%)<br>1 | 0 / 13 (0.00%)<br>0 |
| Infections and infestations                      |                     |                     |                     |
| Nasopharyngitis                                  |                     |                     |                     |
| subjects affected / exposed                      | 1 / 11 (9.09%)      | 0 / 13 (0.00%)      | 1 / 13 (7.69%)      |
| occurrences (all)                                | 1                   | 0                   | 1                   |
| Rhinitis                                         |                     |                     |                     |
| subjects affected / exposed                      | 0 / 11 (0.00%)      | 0 / 13 (0.00%)      | 0 / 13 (0.00%)      |
| occurrences (all)                                | 0                   | 0                   | 0                   |
| Tooth abscess                                    |                     |                     |                     |
| subjects affected / exposed                      | 0 / 11 (0.00%)      | 0 / 13 (0.00%)      | 0 / 13 (0.00%)      |
| occurrences (all)                                | 0                   | 0                   | 0                   |
| Upper respiratory tract infection                |                     |                     |                     |
| subjects affected / exposed                      | 1 / 11 (9.09%)      | 0 / 13 (0.00%)      | 0 / 13 (0.00%)      |
| occurrences (all)                                | 1                   | 0                   | 0                   |
| Urinary tract infection                          |                     |                     |                     |
| subjects affected / exposed                      | 0 / 11 (0.00%)      | 0 / 13 (0.00%)      | 0 / 13 (0.00%)      |
| occurrences (all)                                | 0                   | 0                   | 0                   |
| Metabolism and nutrition disorders               |                     |                     |                     |
| Iron deficiency                                  |                     |                     |                     |
| subjects affected / exposed                      | 0 / 11 (0.00%)      | 1 / 13 (7.69%)      | 0 / 13 (0.00%)      |
| occurrences (all)                                | 0                   | 1                   | 0                   |

| <b>Non-serious adverse events</b>                        | Rivaroxaban<br>(BAY59-7939)<br>suspension, BID,<br>Age: 6 - <12 years | Anticoagulant<br>Comparator, Age: 6<br>- <12 years |  |
|----------------------------------------------------------|-----------------------------------------------------------------------|----------------------------------------------------|--|
| Total subjects affected by non-serious<br>adverse events |                                                                       |                                                    |  |
| subjects affected / exposed                              | 12 / 19 (63.16%)                                                      | 2 / 7 (28.57%)                                     |  |
| Vascular disorders                                       |                                                                       |                                                    |  |
| Post thrombotic syndrome                                 |                                                                       |                                                    |  |
| subjects affected / exposed                              | 0 / 19 (0.00%)                                                        | 1 / 7 (14.29%)                                     |  |
| occurrences (all)                                        | 0                                                                     | 1                                                  |  |
| Hot flush                                                |                                                                       |                                                    |  |
| subjects affected / exposed                              | 1 / 19 (5.26%)                                                        | 0 / 7 (0.00%)                                      |  |
| occurrences (all)                                        | 1                                                                     | 0                                                  |  |
| General disorders and administration<br>site conditions  |                                                                       |                                                    |  |

|                                                                                                              |                      |                     |  |
|--------------------------------------------------------------------------------------------------------------|----------------------|---------------------|--|
| Chest discomfort<br>subjects affected / exposed<br>occurrences (all)                                         | 0 / 19 (0.00%)<br>0  | 0 / 7 (0.00%)<br>0  |  |
| Chest pain<br>subjects affected / exposed<br>occurrences (all)                                               | 0 / 19 (0.00%)<br>0  | 1 / 7 (14.29%)<br>1 |  |
| Fatigue<br>subjects affected / exposed<br>occurrences (all)                                                  | 2 / 19 (10.53%)<br>2 | 0 / 7 (0.00%)<br>0  |  |
| Pyrexia<br>subjects affected / exposed<br>occurrences (all)                                                  | 2 / 19 (10.53%)<br>3 | 0 / 7 (0.00%)<br>0  |  |
| Peripheral swelling<br>subjects affected / exposed<br>occurrences (all)                                      | 0 / 19 (0.00%)<br>0  | 0 / 7 (0.00%)<br>0  |  |
| Localised oedema<br>subjects affected / exposed<br>occurrences (all)                                         | 1 / 19 (5.26%)<br>1  | 0 / 7 (0.00%)<br>0  |  |
| Vessel puncture site haematoma<br>subjects affected / exposed<br>occurrences (all)                           | 0 / 19 (0.00%)<br>0  | 0 / 7 (0.00%)<br>0  |  |
| Vessel puncture site swelling<br>subjects affected / exposed<br>occurrences (all)                            | 0 / 19 (0.00%)<br>0  | 0 / 7 (0.00%)<br>0  |  |
| Reproductive system and breast disorders<br>Menorrhagia<br>subjects affected / exposed<br>occurrences (all)  | 0 / 19 (0.00%)<br>0  | 0 / 7 (0.00%)<br>0  |  |
| Respiratory, thoracic and mediastinal disorders<br>Cough<br>subjects affected / exposed<br>occurrences (all) | 1 / 19 (5.26%)<br>1  | 0 / 7 (0.00%)<br>0  |  |
| Dyspnoea<br>subjects affected / exposed<br>occurrences (all)                                                 | 0 / 19 (0.00%)<br>0  | 0 / 7 (0.00%)<br>0  |  |
| Epistaxis                                                                                                    |                      |                     |  |



|                                                                                                            |                      |                     |  |
|------------------------------------------------------------------------------------------------------------|----------------------|---------------------|--|
| subjects affected / exposed<br>occurrences (all)                                                           | 0 / 19 (0.00%)<br>0  | 0 / 7 (0.00%)<br>0  |  |
| Nasal congestion<br>subjects affected / exposed<br>occurrences (all)                                       | 0 / 19 (0.00%)<br>0  | 0 / 7 (0.00%)<br>0  |  |
| Oropharyngeal pain<br>subjects affected / exposed<br>occurrences (all)                                     | 0 / 19 (0.00%)<br>0  | 0 / 7 (0.00%)<br>0  |  |
| Psychiatric disorders<br>Suicidal ideation<br>subjects affected / exposed<br>occurrences (all)             | 0 / 19 (0.00%)<br>0  | 0 / 7 (0.00%)<br>0  |  |
| Investigations<br>Haemoglobin decreased<br>subjects affected / exposed<br>occurrences (all)                | 1 / 19 (5.26%)<br>1  | 0 / 7 (0.00%)<br>0  |  |
| Platelet count decreased<br>subjects affected / exposed<br>occurrences (all)                               | 1 / 19 (5.26%)<br>1  | 0 / 7 (0.00%)<br>0  |  |
| Injury, poisoning and procedural complications<br>Fall<br>subjects affected / exposed<br>occurrences (all) | 0 / 19 (0.00%)<br>0  | 1 / 7 (14.29%)<br>1 |  |
| Contusion<br>subjects affected / exposed<br>occurrences (all)                                              | 0 / 19 (0.00%)<br>0  | 0 / 7 (0.00%)<br>0  |  |
| Skin abrasion<br>subjects affected / exposed<br>occurrences (all)                                          | 1 / 19 (5.26%)<br>1  | 0 / 7 (0.00%)<br>0  |  |
| Nervous system disorders<br>Headache<br>subjects affected / exposed<br>occurrences (all)                   | 3 / 19 (15.79%)<br>3 | 0 / 7 (0.00%)<br>0  |  |
| Vocal cord paralysis<br>subjects affected / exposed<br>occurrences (all)                                   | 0 / 19 (0.00%)<br>0  | 1 / 7 (14.29%)<br>1 |  |

|                                                                                      |                     |                     |  |
|--------------------------------------------------------------------------------------|---------------------|---------------------|--|
| Multiple sclerosis relapse<br>subjects affected / exposed<br>occurrences (all)       | 0 / 19 (0.00%)<br>0 | 0 / 7 (0.00%)<br>0  |  |
| Blood and lymphatic system disorders                                                 |                     |                     |  |
| Anaemia<br>subjects affected / exposed<br>occurrences (all)                          | 1 / 19 (5.26%)<br>1 | 0 / 7 (0.00%)<br>0  |  |
| Increased tendency to bruise<br>subjects affected / exposed<br>occurrences (all)     | 0 / 19 (0.00%)<br>0 | 0 / 7 (0.00%)<br>0  |  |
| Neutropenia<br>subjects affected / exposed<br>occurrences (all)                      | 1 / 19 (5.26%)<br>1 | 0 / 7 (0.00%)<br>0  |  |
| Ear and labyrinth disorders                                                          |                     |                     |  |
| Vertigo<br>subjects affected / exposed<br>occurrences (all)                          | 0 / 19 (0.00%)<br>0 | 0 / 7 (0.00%)<br>0  |  |
| Eye disorders                                                                        |                     |                     |  |
| Eye pain<br>subjects affected / exposed<br>occurrences (all)                         | 0 / 19 (0.00%)<br>0 | 0 / 7 (0.00%)<br>0  |  |
| Gastrointestinal disorders                                                           |                     |                     |  |
| Abdominal pain<br>subjects affected / exposed<br>occurrences (all)                   | 1 / 19 (5.26%)<br>1 | 0 / 7 (0.00%)<br>0  |  |
| Abdominal pain upper<br>subjects affected / exposed<br>occurrences (all)             | 1 / 19 (5.26%)<br>1 | 1 / 7 (14.29%)<br>1 |  |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)                        | 0 / 19 (0.00%)<br>0 | 1 / 7 (14.29%)<br>1 |  |
| Dyspepsia<br>subjects affected / exposed<br>occurrences (all)                        | 0 / 19 (0.00%)<br>0 | 0 / 7 (0.00%)<br>0  |  |
| Gastrooesophageal reflux disease<br>subjects affected / exposed<br>occurrences (all) | 0 / 19 (0.00%)<br>0 | 0 / 7 (0.00%)<br>0  |  |

|                                        |                 |                |  |
|----------------------------------------|-----------------|----------------|--|
| Gingival bleeding                      |                 |                |  |
| subjects affected / exposed            | 1 / 19 (5.26%)  | 0 / 7 (0.00%)  |  |
| occurrences (all)                      | 2               | 0              |  |
| Nausea                                 |                 |                |  |
| subjects affected / exposed            | 1 / 19 (5.26%)  | 0 / 7 (0.00%)  |  |
| occurrences (all)                      | 1               | 0              |  |
| Tooth loss                             |                 |                |  |
| subjects affected / exposed            | 1 / 19 (5.26%)  | 0 / 7 (0.00%)  |  |
| occurrences (all)                      | 1               | 0              |  |
| Vomiting                               |                 |                |  |
| subjects affected / exposed            | 2 / 19 (10.53%) | 1 / 7 (14.29%) |  |
| occurrences (all)                      | 2               | 1              |  |
| Lower gastrointestinal haemorrhage     |                 |                |  |
| subjects affected / exposed            | 0 / 19 (0.00%)  | 0 / 7 (0.00%)  |  |
| occurrences (all)                      | 0               | 0              |  |
| Skin and subcutaneous tissue disorders |                 |                |  |
| Alopecia                               |                 |                |  |
| subjects affected / exposed            | 1 / 19 (5.26%)  | 0 / 7 (0.00%)  |  |
| occurrences (all)                      | 1               | 0              |  |
| Dermatitis allergic                    |                 |                |  |
| subjects affected / exposed            | 0 / 19 (0.00%)  | 0 / 7 (0.00%)  |  |
| occurrences (all)                      | 0               | 0              |  |
| Erythema                               |                 |                |  |
| subjects affected / exposed            | 1 / 19 (5.26%)  | 0 / 7 (0.00%)  |  |
| occurrences (all)                      | 1               | 0              |  |
| Hyperhidrosis                          |                 |                |  |
| subjects affected / exposed            | 0 / 19 (0.00%)  | 0 / 7 (0.00%)  |  |
| occurrences (all)                      | 0               | 0              |  |
| Pruritus                               |                 |                |  |
| subjects affected / exposed            | 1 / 19 (5.26%)  | 0 / 7 (0.00%)  |  |
| occurrences (all)                      | 1               | 0              |  |
| Rash                                   |                 |                |  |
| subjects affected / exposed            | 1 / 19 (5.26%)  | 0 / 7 (0.00%)  |  |
| occurrences (all)                      | 3               | 0              |  |
| Swelling face                          |                 |                |  |

|                                                  |                     |                    |  |
|--------------------------------------------------|---------------------|--------------------|--|
| subjects affected / exposed<br>occurrences (all) | 0 / 19 (0.00%)<br>0 | 0 / 7 (0.00%)<br>0 |  |
| Musculoskeletal and connective tissue disorders  |                     |                    |  |
| Arthralgia                                       |                     |                    |  |
| subjects affected / exposed                      | 1 / 19 (5.26%)      | 0 / 7 (0.00%)      |  |
| occurrences (all)                                | 1                   | 0                  |  |
| Back pain                                        |                     |                    |  |
| subjects affected / exposed                      | 0 / 19 (0.00%)      | 0 / 7 (0.00%)      |  |
| occurrences (all)                                | 0                   | 0                  |  |
| Flank pain                                       |                     |                    |  |
| subjects affected / exposed                      | 0 / 19 (0.00%)      | 0 / 7 (0.00%)      |  |
| occurrences (all)                                | 0                   | 0                  |  |
| Musculoskeletal pain                             |                     |                    |  |
| subjects affected / exposed                      | 0 / 19 (0.00%)      | 0 / 7 (0.00%)      |  |
| occurrences (all)                                | 0                   | 0                  |  |
| Pain in extremity                                |                     |                    |  |
| subjects affected / exposed                      | 1 / 19 (5.26%)      | 0 / 7 (0.00%)      |  |
| occurrences (all)                                | 1                   | 0                  |  |
| Pain in jaw                                      |                     |                    |  |
| subjects affected / exposed                      | 0 / 19 (0.00%)      | 0 / 7 (0.00%)      |  |
| occurrences (all)                                | 0                   | 0                  |  |
| Infections and infestations                      |                     |                    |  |
| Nasopharyngitis                                  |                     |                    |  |
| subjects affected / exposed                      | 1 / 19 (5.26%)      | 0 / 7 (0.00%)      |  |
| occurrences (all)                                | 1                   | 0                  |  |
| Rhinitis                                         |                     |                    |  |
| subjects affected / exposed                      | 1 / 19 (5.26%)      | 0 / 7 (0.00%)      |  |
| occurrences (all)                                | 1                   | 0                  |  |
| Tooth abscess                                    |                     |                    |  |
| subjects affected / exposed                      | 1 / 19 (5.26%)      | 0 / 7 (0.00%)      |  |
| occurrences (all)                                | 1                   | 0                  |  |
| Upper respiratory tract infection                |                     |                    |  |
| subjects affected / exposed                      | 0 / 19 (0.00%)      | 0 / 7 (0.00%)      |  |
| occurrences (all)                                | 0                   | 0                  |  |
| Urinary tract infection                          |                     |                    |  |

|                                                                                                           |                     |                    |  |
|-----------------------------------------------------------------------------------------------------------|---------------------|--------------------|--|
| subjects affected / exposed<br>occurrences (all)                                                          | 1 / 19 (5.26%)<br>1 | 0 / 7 (0.00%)<br>0 |  |
| Metabolism and nutrition disorders<br>Iron deficiency<br>subjects affected / exposed<br>occurrences (all) | 0 / 19 (0.00%)<br>0 | 0 / 7 (0.00%)<br>0 |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date              | Amendment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|-------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 25 June 2013      | <p>The following modifications were done in this amendment:</p> <ul style="list-style-type: none"><li>•Addition of thrombotic burden assessment as a secondary objective. The secondary outcomes text was modified to reflect the addition of the asymptomatic deterioration in the thrombotic burden.</li><li>•Study indication was broadened to include right atrial thrombosis and catheter-related thrombosis. Also the inclusion criterion was broadened to include children with catheter-related thrombosis who had been treated with standard of care anticoagulant for at least 6 weeks.</li><li>•Lab tests for bilirubin and alanine aminotransferase (ALT) were added in the inclusion and exclusion criteria.</li><li>•Visit window at Day 15 was extended from +/-3 days to +/- 5 days. The text explaining when the repeat imaging needs to be done was also included.</li><li>•Addition of height collection and lab tests during the days Day -60 to Day -10 and at Day 1 (10 days prior to randomization)</li><li>•Clarification that the blood test as well as repeat imaging (when clinically feasible) was to be collected also at Day 31.</li><li>•Deletion of description of the type of thrombosis to be considered as outcomes</li><li>•Addition of the pharmacokinetic/pharmacodynamic sampling instructions for the case rivaroxaban dose was temporarily interrupted</li><li>•Adverse events of special interest were clarified to reflect the newly added exclusion criterion</li><li>•Added that subjects with concomitant therapy with other anticoagulants or fibrinolytic during the study treatment were to be prematurely discontinued from study treatment</li><li>•Clarifications for the: dose confirmation, catheter related thrombosis, results of the EINSTEIN adult studies, definition of vascular events, and for the content of the study booklet were done</li></ul> |
| 16 September 2014 | <p>In this amendment a more detailed description for the rivaroxaban oral suspension was added with clear separation from the tablet group.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| 14 April 2015     | <p>The following modifications were done in this amendment:</p> <ul style="list-style-type: none"><li>•The comparator arm was removed. The sample size was considered too small to support meaningful comparison of rivaroxaban versus standard of care with regard to safety and efficacy. Also, due to the comparator arm removal the total subject number was reduced.</li><li>•There was a change in the Inclusion criterion 1 to enable enrollment of children who are on long-term anticoagulant treatment. In addition to this, instructions on how to safely handle the switch from heparin, fondaparinux, and vitamin K antagonist to rivaroxaban and vice versa were made available in the protocol.</li><li>•The platelet count threshold for exclusion of children was adjusted from <math>&lt; 100 \times 10^9/\text{liter}</math> to <math>&lt; 50 \times 10^9/\text{liter}</math></li></ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Occurrence of "±" in relation with geometric CV is auto-generated. Decimal places were automatically truncated if last decimal equals zero.

Notes: