



## Clinical trial results:

**A multi-center, phase III, non-controlled, open-label trial to evaluate the pharmacokinetics, safety, and efficacy of BAY 94-9027 for prophylaxis and treatment of bleeding in previously treated children (age <12 years) with severe hemophilia A**

### Summary

|                          |   |
|--------------------------|---|
| EudraCT number           | 2012-004434-42                                  |
| Trial protocol           | GB BE IT NL LT BG Outside EU/EEA PL AT NO ES GR |
| Global end of trial date | 19 February 2020                                |

### Results information

|                                |                   |
|--------------------------------|-------------------|
| Result version number          | v3 (current)      |
| This version publication date  | 03 September 2020 |
| First version publication date | 17 July 2016      |
| Version creation reason        |                   |

### Trial information

#### Trial identification

|                       |       |
|-----------------------|-------|
| Sponsor protocol code | 15912 |
|-----------------------|-------|

#### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01775618 |
| 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-001229-PIP01-11 |
| 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                       | 26 March 2020    |
| Is this the analysis of the primary completion data? | No               |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 19 February 2020 |
| Was the trial ended prematurely?                     | No               |

Notes:

## General information about the trial

Main objective of the trial:

To evaluate pharmacokinetics (PK), safety, and efficacy of BAY94-9027 for prophylaxis and treatment of bleeding in previously treated patients (PTPs) with hemophilia A.

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 form was read by and explained to all subjects and/or their legally authorized representative. Participating subjects 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                          | 29 May 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 | Spain: 1          |
| Country: Number of subjects enrolled | Greece: 1         |
| Country: Number of subjects enrolled | Norway: 2         |
| Country: Number of subjects enrolled | New Zealand: 3    |
| Country: Number of subjects enrolled | Netherlands: 6    |
| Country: Number of subjects enrolled | Poland: 3         |
| Country: Number of subjects enrolled | Austria: 3        |
| Country: Number of subjects enrolled | Belgium: 3        |
| Country: Number of subjects enrolled | Bulgaria: 5       |
| Country: Number of subjects enrolled | Italy: 7          |
| Country: Number of subjects enrolled | Lithuania: 1      |
| Country: Number of subjects enrolled | Canada: 3         |
| Country: Number of subjects enrolled | Argentina: 1      |
| Country: Number of subjects enrolled | Israel: 9         |
| Country: Number of subjects enrolled | United States: 13 |
| Country: Number of subjects enrolled | Romania: 4        |
| Country: Number of subjects enrolled | United Kingdom: 8 |

|                                    |    |
|------------------------------------|----|
| Worldwide total number of subjects | 73 |
| EEA total number of subjects       | 44 |

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)                     | 73 |
| Adolescents (12-17 years)                 | 0  |
| Adults (18-64 years)                      | 0  |
| From 65 to 84 years                       | 0  |
| 85 years and over                         | 0  |

## Subject disposition

### Recruitment

Recruitment details:

The main study period was conducted at 31 centers; Part 2 of the study (expansion group) was conducted at 7 centers; and the extension study period was conducted at 32 centers. The entire study included subjects between 29 May 2013 (first subject first visit) and 19 February 2020 (last subject last visit).

### Pre-assignment

Screening details:

Overall 65 subjects were screened in the main study, of them 61 subjects were allocated to treatment. A total of 13 subjects were screened for enrollment in Part 2 and 12 subjects completed screening. 59 subjects were transitioned from the the main study or from Part 2 into the extension study period.

### Period 1

|                              |                       |
|------------------------------|-----------------------|
| Period 1 title               | Main study and Part 2 |
| Is this the baseline period? | Yes                   |
| Allocation method            | Not applicable        |
| Blinding used                | Not blinded           |

### Arms

|                              |                          |
|------------------------------|--------------------------|
| Are arms mutually exclusive? | Yes                      |
| <b>Arm title</b>             | Main: Age group <6 years |

Arm description:

Subjects with age less than (<) 6 years were treated and prophylaxis administered with BAY94-9027 at a dose of 25-60 international units/kilogram (IU/kg) twice per week or 45-60 IU/kg every 5 days or 60 IU/kg every 7 days as an intravenous (IV) infusion as per clinical needs of each subject up to at least 50 exposure days (EDs) and a minimum of at least 6 months.

|  |                         |
|--|-------------------------|
| Arm type                               | Experimental            |
| Investigational medicinal product name | Recombinant Factor VIII |
| Investigational medicinal product code | BAY94-9027              |
| Other name                             |                         |
| Pharmaceutical forms                   | Infusion                |
| Routes of administration               | Intravenous use         |

Dosage and administration details:

25-60 IU/kg twice per week or 45-60 IU/kg every 5 days or 60 IU/kg every 7 days as an IV infusion as per clinical needs of each subject up to at least 50 EDs and a minimum of at least 6 months.

|                  |                                |
|------------------|--------------------------------|
| <b>Arm title</b> | Main: Age group 6 to <12 years |
|------------------|--------------------------------|

Arm description:

Subjects with age 6 to <12 years were treated and prophylaxis administered with BAY94-9027 at a dose of 25-60 IU/kg twice per week or 45-60 IU/kg every 5 days or 60 IU/kg every 7 days as an IV infusion as per clinical needs of each subject up to at least 50 EDs and a minimum of at least 6 months.

|  |                         |
|--|-------------------------|
| Arm type                               | Experimental            |
| Investigational medicinal product name | Recombinant Factor VIII |
| Investigational medicinal product code | BAY94-9027              |
| Other name                             |                         |
| Pharmaceutical forms                   | Infusion                |
| Routes of administration               | Intravenous use         |

Dosage and administration details:

25-60 IU/kg/administration twice per week or 45-60 IU/kg every 5 days or 60 IU/kg every 7 days as an IV infusion as per clinical needs of each subject up to at least 50 EDs and a minimum of at least 6 months.

|                  |                                  |
|------------------|----------------------------------|
| <b>Arm title</b> | Part 2: Expansion group <6 years |
|------------------|----------------------------------|

**Arm description:**

Subjects with age <6 years were administered with BAY94-9027 at a dose of 25-60 IU/kg twice per week for prophylaxis for 12 weeks.

|  |                         |
|--|-------------------------|
| Arm type                               | Experimental            |
| Investigational medicinal product name | Recombinant Factor VIII |
| Investigational medicinal product code | BAY94-9027              |
| Other name                             |                         |
| Pharmaceutical forms                   | Infusion                |
| Routes of administration               | Intravenous use         |

**Dosage and administration details:**

25-60 IU/kg twice per week for prophylaxis for 12 weeks.

| <b>Number of subjects in period 1</b> | Main: Age group <6 years | Main: Age group 6 to <12 years | Part 2: Expansion group <6 years |
|---------------------------------------|--------------------------|--------------------------------|----------------------------------|
| Started                               | 32                       | 29                             | 12                               |
| Completed                             | 25                       | 28                             | 8                                |
| Not completed                         | 7                        | 1                              | 4                                |
| Adverse event, non-fatal              | 6                        | 1                              | 4                                |
| Withdrawal by parent/guardian         | 1                        | -                              | -                                |

**Period 2**

|                              |                 |
|------------------------------|-----------------|
| Period 2 title               | Extension study |
| Is this the baseline period? | No              |
| Allocation method            | Not applicable  |
| Blinding used                | Not blinded     |

**Arms**

|                  |                                |
|------------------|--------------------------------|
| <b>Arm title</b> | Extension: Age group <12 years |
|------------------|--------------------------------|

**Arm description:**

Subjects with age <12 years were treated and prophylaxis administered with BAY94-9027 at a dose of 25-60 IU/kg twice per week or 45-60 IU/kg every 5 days or 60 IU/kg every 7 days as an IV infusion as per clinical needs of each subject for at least 50 EDs or until marketing authorization of the drug.

|  |                         |
|--|-------------------------|
| Arm type                               | Experimental            |
| Investigational medicinal product name | Recombinant Factor VIII |
| Investigational medicinal product code | BAY94-9027              |
| Other name                             |                         |
| Pharmaceutical forms                   | Infusion                |
| Routes of administration               | Intravenous use         |

**Dosage and administration details:**

25-60 IU/kg twice per week or 45-60 IU/kg every 5 days or 60 IU/kg every 7 days as an IV infusion as per clinical needs of each subject for at least 50 EDs or until marketing authorization of the drug.

| Number of subjects in period 2 <sup>[1]</sup> | Extension: Age group <12 years |
|---|--------------------------------|
|   |                                |
| Started                                       | 59                             |
| Completed                                     | 57                             |
| Not completed                                 | 2                              |
| Adverse event, non-fatal                      | 1                              |
| Other   | 1                              |

---

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Optional participation of the extension study were offered to subjects completing the main study or Part 2.

## Baseline characteristics

### Reporting groups

|   |                                  |
|---|----------------------------------|
| Reporting group title   | Main: Age group <6 years         |
| Reporting group description:  |                                  |
| Subjects with age less than (<) 6 years were treated and prophylaxis administered with BAY94-9027 at a dose of 25-60 international units/kilogram (IU/kg) twice per week or 45-60 IU/kg every 5 days or 60 IU/kg every 7 days as an intravenous (IV) infusion as per clinical needs of each subject up to at least 50 exposure days (EDs) and a minimum of at least 6 months. |                                  |
| Reporting group title   | Main: Age group 6 to <12 years   |
| Reporting group description:  |                                  |
| Subjects with age 6 to <12 years were treated and prophylaxis administered with BAY94-9027 at a dose of 25-60 IU/kg twice per week or 45-60 IU/kg every 5 days or 60 IU/kg every 7 days as an IV infusion as per clinical needs of each subject up to at least 50 EDs and a minimum of at least 6 months.   |                                  |
| Reporting group title   | Part 2: Expansion group <6 years |
| Reporting group description:  |                                  |
| Subjects with age <6 years were administered with BAY94-9027 at a dose of 25-60 IU/kg twice per week for prophylaxis for 12 weeks.  |                                  |

| Reporting group values                | Main: Age group <6 years | Main: Age group 6 to <12 years | Part 2: Expansion group <6 years |
|---------------------------------------|--------------------------|--------------------------------|----------------------------------|
| Number of subjects                    | 32                       | 29                             | 12                               |
| Age categorical<br>Units: Subjects    |                          |                                |                                  |
| Children (2-11 years)                 | 32                       | 29                             | 12                               |
| Age continuous<br>Units: years        |                          |                                |                                  |
| arithmetic mean                       | 3.5                      | 8.6                            | 3.5                              |
| standard deviation                    | ± 1.0                    | ± 1.5                          | ± 1.24                           |
| Gender categorical<br>Units: Subjects |                          |                                |                                  |
| Female                                | 0                        | 0                              | 0                                |
| Male                                  | 32                       | 29                             | 12                               |

| Reporting group values                | Total |  |  |
|---------------------------------------|-------|--|--|
| Number of subjects                    | 73    |  |  |
| Age categorical<br>Units: Subjects    |       |  |  |
| Children (2-11 years)                 | 73    |  |  |
| Age continuous<br>Units: years        |       |  |  |
| arithmetic mean                       | -     |  |  |
| standard deviation                    | -     |  |  |
| Gender categorical<br>Units: Subjects |       |  |  |
| Female                                | 0     |  |  |
| Male                                  | 73    |  |  |

## End points

### End points reporting groups

|   |  |
|---|--|
| Reporting group title   | Main: Age group <6 years                             |
| Reporting group description:<br>Subjects with age less than (<) 6 years were treated and prophylaxis administered with BAY94-9027 at a dose of 25-60 international units/kilogram (IU/kg) twice per week or 45-60 IU/kg every 5 days or 60 IU/kg every 7 days as an intravenous (IV) infusion as per clinical needs of each subject up to at least 50 exposure days (EDs) and a minimum of at least 6 months. |  |
| Reporting group title   | Main: Age group 6 to <12 years                       |
| Reporting group description:<br>Subjects with age 6 to <12 years were treated and prophylaxis administered with BAY94-9027 at a dose of 25-60 IU/kg twice per week or 45-60 IU/kg every 5 days or 60 IU/kg every 7 days as an IV infusion as per clinical needs of each subject up to at least 50 EDs and a minimum of at least 6 months.   |  |
| Reporting group title   | Part 2: Expansion group <6 years                     |
| Reporting group description:<br>Subjects with age <6 years were administered with BAY94-9027 at a dose of 25-60 IU/kg twice per week for prophylaxis for 12 weeks.  |  |
| Reporting group title   | Extension: Age group <12 years                       |
| Reporting group description:<br>Subjects with age <12 years were treated and prophylaxis administered with BAY94-9027 at a dose of 25-60 IU/kg twice per week or 45-60 IU/kg every 5 days or 60 IU/kg every 7 days as an IV infusion as per clinical needs of each subject for at least 50 EDs or until marketing authorization of the drug.  |  |
| Subject analysis set title  | Safety Analysis Set (SAF) - Main study               |
| Subject analysis set type   | Safety analysis                                      |
| Subject analysis set description:<br>All subjects enrolled into the main study who received at least one dose of study medication.  |  |
| Subject analysis set title  | Intent-to-treat (ITT) Analysis set - Main study      |
| Subject analysis set type   | Intention-to-treat                                   |
| Subject analysis set description:<br>All safety subjects enrolled into the main study who had infusion/bleeding data from the Electronic Patient Diary (EPD).   |  |
| Subject analysis set title  | Pharmacokinetic (PK) Analysis Set (PKS) - Main study |
| Subject analysis set type   | Sub-group analysis                                   |
| Subject analysis set description:<br>All subjects enrolled into the main study with a valid profile of BAY94-9027 were included in the analysis of PK data.   |  |
| Subject analysis set title  | Safety Analysis Set (SAF) - Part 2                   |
| Subject analysis set type   | Safety analysis                                      |
| Subject analysis set description:<br>All subjects enrolled into the Part 2 of the study (expansion group) who received at least one dose of study medication.   |  |
| Subject analysis set title  | Safety Analysis Set (SAF) - Extension study          |
| Subject analysis set type   | Safety analysis                                      |
| Subject analysis set description:<br>All subjects enrolled into the extension study who received at least one dose of study medication in the extension study period.   |  |

### Primary: Annualized number of total bleeds in main study

|   |   |
|---|---|
| End point title   | Annualized number of total bleeds in main study <sup>[1][2]</sup> |
| End point description:<br>The annualized number of total bleeds included sum of all spontaneous bleeds and traumatic bleeds during prophylactic treatment. An exposure day defined as a calendar day during which at least one infusion was taken by the subject. |   |
| End point type  | Primary   |



End point timeframe:

Baseline up to 50 exposure days (ED) over 6 months

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: Only descriptive summary statistics were planned for this endpoint.

[2] - 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: The primary objective of Part 2 and extension study was to evaluate the safety of BAY94-9027.

| End point values                      | Main: Age group <6 years | Main: Age group 6 to <12 years |  |  |
|---------------------------------------|--------------------------|--------------------------------|--|--|
| Subject group type                    | Reporting group          | Reporting group                |  |  |
| Number of subjects analysed           | 32 <sup>[3]</sup>        | 28 <sup>[4]</sup>              |  |  |
| Units: Bleeds                         |                          |                                |  |  |
| median (inter-quartile range (Q1-Q3)) |                          |                                |  |  |
| Overall Bleeds                        | 2.68 (1.08 to 6.79)      | 2.92 (0 to 6.66)               |  |  |

Notes:

[3] - ITT - Main study

[4] - ITT - Main study

## Statistical analyses

No statistical analyses for this end point

## Primary: Maximum observed drug concentration (Cmax) in plasma of BAY94-9027

|                 |  |
|-----------------|--|
| End point title | Maximum observed drug concentration (Cmax) in plasma of BAY94-9027 <sup>[5]</sup> <sup>[6]</sup> |
|-----------------|--|

End point description:

Maximum observed drug concentration, directly taken from analytical data. Geometric mean and geometric standard deviation (Geom SD) were reported.

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

End point timeframe:

Pre-dose to 72 hours post-dose

Notes:

[5] - 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: Only descriptive summary statistics were planned for this endpoint.

[6] - 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: The primary objective of Part 2 and extension study was to evaluate the safety of BAY94-9027.

| End point values                             | Main: Age group <6 years | Main: Age group 6 to <12 years |  |  |
|--|--------------------------|--------------------------------|--|--|
| Subject group type                           | Reporting group          | Reporting group                |  |  |
| Number of subjects analysed                  | 15 <sup>[7]</sup>        | 15 <sup>[8]</sup>              |  |  |
| Units: International units/deciliter (IU/dL) |                          |                                |  |  |
| geometric mean (standard deviation)          | 110.9 (± 1.33)           | 127 (± 1.21)                   |  |  |

Notes:

[7] - PKS - Main study with evaluable subjects for this endpoint.

[8] - PKS - Main study with evaluable subjects for this endpoint.

## Statistical analyses

No statistical analyses for this end point

### Primary: Half-life associated with the terminal slope (t<sub>1/2</sub>) in plasma of BAY94-9027

|                 |   |
|-----------------|---|
| End point title | Half-life associated with the terminal slope (t <sub>1/2</sub> ) in plasma of BAY94-9027 <sup>[9][10]</sup> |
|-----------------|---|

End point description:

Half-life associated with the terminal slope. Geometric mean and geometric standard deviation (Geo SD) were reported.

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

End point timeframe:

Pre-dose to 72 hours post-dose

Notes:

[9] - 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: Only descriptive summary statistics were planned for this endpoint.

[10] - 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: The primary objective of Part 2 and extension study was to evaluate the safety of BAY94-9027.

| End point values                    | Main: Age group <6 years | Main: Age group 6 to <12 years |  |  |
|-------------------------------------|--------------------------|--------------------------------|--|--|
| Subject group type                  | Reporting group          | Reporting group                |  |  |
| Number of subjects analysed         | 16 <sup>[11]</sup>       | 16 <sup>[12]</sup>             |  |  |
| Units: Hours                        |                          |                                |  |  |
| geometric mean (standard deviation) | 14.1 (± 1.39)            | 15.8 (± 1.25)                  |  |  |

Notes:

[11] - PKS - Main study with evaluable subjects for this endpoint.

[12] - PKS - Main study with evaluable subjects for this endpoint.

## Statistical analyses

No statistical analyses for this end point

### Primary: Area under the concentration versus time curve from zero to infinity (AUC) in plasma of BAY94-9027

|                 |  |
|-----------------|--|
| End point title | Area under the concentration versus time curve from zero to infinity (AUC) in plasma of BAY94-9027 <sup>[13][14]</sup> |
|-----------------|--|

End point description:

Area under the concentration versus time curve from zero to infinity after single (first) dose. Geometric mean and geometric standard deviation (Geo SD) were reported.

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

End point timeframe:

Pre-dose to 72 hours post-dose

Notes:

[13] - 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: Only descriptive summary statistics were planned for this endpoint.

[14] - 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: The primary objective of Part 2 and extension study was to evaluate the safety of BAY94-9027.

| End point values                    | Main: Age group <6 years | Main: Age group 6 to <12 years |  |  |
|-------------------------------------|--------------------------|--------------------------------|--|--|
| Subject group type                  | Reporting group          | Reporting group                |  |  |
| Number of subjects analysed         | 15 <sup>[15]</sup>       | 13 <sup>[16]</sup>             |  |  |
| Units: IU*hours/deciliter (IU*h/dL) |                          |                                |  |  |
| geometric mean (standard deviation) | 1804.3 (± 1.94)          | 2837.03 (± 1.21)               |  |  |

Notes:

[15] - PKS - Main study with evaluable subjects for this endpoint.

[16] - PKS - Main study with evaluable subjects for this endpoint.

## Statistical analyses

No statistical analyses for this end point

## Primary: Mean residence time (MRT) of BAY94-9027

|  |   |
|--|---|
| End point title  | Mean residence time (MRT) of BAY94-9027 <sup>[17]</sup> <sup>[18]</sup> |
| End point description:   |   |
| Mean residence time after intravenous infusion was reported. Geometric mean and geometric standard deviation (Geo SD) were reported. |   |
| End point type   | Primary   |
| End point timeframe:   |   |
| Pre-dose to 72 hours post-dose   |   |

Notes:

[17] - 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: Only descriptive summary statistics were planned for this endpoint.

[18] - 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: The primary objective of Part 2 and extension study was to evaluate the safety of BAY94-9027.

| End point values                    | Main: Age group <6 years | Main: Age group 6 to <12 years |  |  |
|-------------------------------------|--------------------------|--------------------------------|--|--|
| Subject group type                  | Reporting group          | Reporting group                |  |  |
| Number of subjects analysed         | 16 <sup>[19]</sup>       | 14 <sup>[20]</sup>             |  |  |
| Units: Hours                        |                          |                                |  |  |
| geometric mean (standard deviation) | 19.1 (± 1.42)            | 23.7 (± 1.25)                  |  |  |

Notes:

[19] - PKS - Main study with evaluable subjects for this endpoint.

[20] - PKS - Main study with evaluable subjects for this endpoint

## Statistical analyses

No statistical analyses for this end point

### Primary: Apparent volume of distribution at steady state after intravascular administration (Vss) of BAY94-9027

|                 |  |
|-----------------|--|
| End point title | Apparent volume of distribution at steady state after intravascular administration (Vss) of BAY94-9027 <sup>[21][22]</sup> |
|-----------------|--|

End point description:

Apparent volume of distribution at steady state after intravascular administration (Vss) of BAY94-9027. Geometric mean and geometric standard deviation (Geo SD) were reported.

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

End point timeframe:

Pre-dose to 72 hours post-dose

Notes:

[21] - 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: Only descriptive summary statistics were planned for this endpoint.

[22] - 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: The primary objective of Part 2 and extension study was to evaluate the safety of BAY94-9027.

| End point values                      | Main: Age group <6 years | Main: Age group 6 to <12 years |  |  |
|---------------------------------------|--------------------------|--------------------------------|--|--|
| Subject group type                    | Reporting group          | Reporting group                |  |  |
| Number of subjects analysed           | 16 <sup>[23]</sup>       | 14 <sup>[24]</sup>             |  |  |
| Units: Deciliter per kilogram (dL/kg) |                          |                                |  |  |
| geometric mean (standard deviation)   | 0.62 (± 1.48)            | 0.49 (± 1.2)                   |  |  |

Notes:

[23] - PKS - Main study with evaluable subjects for this endpoint.

[24] - PKS - Main study with evaluable subjects for this endpoint.

### Statistical analyses

No statistical analyses for this end point

### Primary: Systemic clearance (CL) of BAY94-9027

|                 |   |
|-----------------|---|
| End point title | Systemic clearance (CL) of BAY94-9027 <sup>[25][26]</sup> |
|-----------------|---|

End point description:

Total body clearance of drug in the measured matrix (volume/time) or (volume/time/body weight) calculated after intravenous application (expression by qualifier or matrix). Geometric mean and geometric standard deviation (Geo SD) were reported.

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

End point timeframe:

Pre-dose to 72 hours post-dose

Notes:

[25] - 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: Only descriptive summary statistics were planned for this endpoint.

[26] - 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: The primary objective of Part 2 and extension study was to evaluate the safety of BAY94-9027.

| End point values                                | Main: Age group <6 years | Main: Age group 6 to <12 years |  |  |
|---|--------------------------|--------------------------------|--|--|
| Subject group type                              | Reporting group          | Reporting group                |  |  |
| Number of subjects analysed                     | 16 <sup>[27]</sup>       | 14 <sup>[28]</sup>             |  |  |
| Units: Deciliter per hour per kilogram[dL/h/kg) |                          |                                |  |  |
| geometric mean (standard deviation)             | 0.032 (± 1.94)           | 0.021 (± 1.22)                 |  |  |

Notes:

[27] - PKS - Main study with evaluable subjects for this endpoint.

[28] - PKS - Main study with evaluable subjects for this endpoint.

## Statistical analyses

No statistical analyses for this end point

## Primary: Number of subjects with assessment of adequacy of hemostasis for treatment of bleeds

|                 |  |
|-----------------|--|
| End point title | Number of subjects with assessment of adequacy of hemostasis for treatment of bleeds <sup>[29][30]</sup> |
|-----------------|--|

End point description:

Subjects/caregivers' assessment for adequacy of hemostasis (stopping bleeding) for each bleed was reported using 4 point scale as 'excellent', 'good', 'moderate', and 'poor'; where, Excellent: Abrupt pain relief and /or improvement in signs of bleeding with no additional infusion administered, Good: Definite pain relief and/or improvement in signs of bleeding, but possibly requiring more than one infusion for complete resolution, Moderate: Probable or slight improvement in signs of bleeding, with at least one additional infusion for complete resolution, Poor: No improvement or condition worsened.

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

End point timeframe:

Pre-dose to 72 hours post-dose

Notes:

[29] - 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: Only descriptive summary statistics were planned for this endpoint.

[30] - 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: The primary objective of Part 2 and extension study was to evaluate the safety of BAY94-9027.

| End point values            | Main: Age group <6 years | Main: Age group 6 to <12 years |  |  |
|-----------------------------|--------------------------|--------------------------------|--|--|
| Subject group type          | Reporting group          | Reporting group                |  |  |
| Number of subjects analysed | 32 <sup>[31]</sup>       | 28 <sup>[32]</sup>             |  |  |
| Units: Bleeds               |                          |                                |  |  |
| Excellent                   | 29                       | 26                             |  |  |
| Good                        | 34                       | 31                             |  |  |
| Moderate                    | 6                        | 9                              |  |  |
| Poor                        | 3                        | 2                              |  |  |

Notes:

[31] - ITT - Main study

[32] - ITT - Main study

## Statistical analyses

No statistical analyses for this end point

---

**Primary: Number of subjects with events of special interest in Part 2**

---

|                 |  |
|-----------------|--|
| End point title | Number of subjects with events of special interest in Part |
|-----------------|--|

End point description:

Hypersensitivity reactions to the study drug and loss of efficacy of the drug product were defined in the study as events of special interest.

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

End point timeframe:

12 weeks

Notes:

[33] - 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: Only descriptive summary statistics were planned for this endpoint.

[34] - 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: Characterization of the potential immune response was defined as primary endpoint only for Part 2.

| End point values            | Part 2:<br>Expansion<br>group <6 years |  |  |  |
|-----------------------------|--|--|--|--|
| Subject group type          | Reporting group                        |  |  |  |
| Number of subjects analysed | 12 <sup>[35]</sup>                     |  |  |  |
| Units: Subjects             | 4                                      |  |  |  |

Notes:

[35] - SAF - Part 2

---

**Statistical analyses**

---

No statistical analyses for this end point

---

**Primary: Number of subjects with any anti-drug antibody development in Part 2**

---

|                 |  |
|-----------------|--|
| End point title | Number of subjects with any anti-drug antibody development in Part 2 <sup>[36][37]</sup> |
|-----------------|--|

End point description:

Number of subjects in Part 2 with any antibody in plasma, not present before, but developed after first infusion of study drug was reported.

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

End point timeframe:

12 weeks

Notes:

[36] - 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: Only descriptive summary statistics were planned for this endpoint.

[37] - 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: Characterization of the potential immune response was defined as primary endpoint only for Part 2.

|                             |  |  |  |  |
|-----------------------------|--|--|--|--|
| <b>End point values</b>     | Part 2:<br>Expansion<br>group <6 years |  |  |  |
| Subject group type          | Reporting group                        |  |  |  |
| Number of subjects analysed | 6 <sup>[38]</sup>                      |  |  |  |
| Units: Subjects             | 2                                      |  |  |  |

Notes:

[38] - Subjects in SAF - Part 2 with no positive baseline assessments for any antibody

## Statistical analyses

No statistical analyses for this end point

## Primary: Number of subjects with events of special interest and any anti-drug antibody development in Part 2

|                 |   |
|-----------------|---|
| End point title | Number of subjects with events of special interest and any anti-drug antibody development in Part 2 <sup>[39][40]</sup> |
|-----------------|---|

End point description:

Number of subjects in Part 2 with with events of special interest and any antibody in plasma, not present before, but developed after first infusion of study drug was reported.

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

End point timeframe:

12 weeks

Notes:

[39] - 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: Only descriptive summary statistics were planned for this endpoint.

[40] - 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: Characterization of the potential immune response was defined as primary endpoint only for Part 2.

|                             |  |  |  |  |
|-----------------------------|--|--|--|--|
| <b>End point values</b>     | Part 2:<br>Expansion<br>group <6 years |  |  |  |
| Subject group type          | Reporting group                        |  |  |  |
| Number of subjects analysed | 4 <sup>[41]</sup>                      |  |  |  |
| Units: Subjects             | 3                                      |  |  |  |

Notes:

[41] - Subjects in SAF - Part 2 with events of special interest

## Statistical analyses

No statistical analyses for this end point

## Primary: Number of subjects with inhibitor development in Part 2

|                 |   |
|-----------------|---|
| End point title | Number of subjects with inhibitor development in Part 2 <sup>[42][43]</sup> |
|-----------------|---|

End point description:

Subject in Part 2 were evaluated for positive FVIII inhibitor level ( $\geq 0.6$  BU/mL, using Nijmegen modified Bethesda assay).

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

End point timeframe:

12 weeks

Notes:

[42] - 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: Only descriptive summary statistics were planned for this endpoint.

[43] - 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: Inhibitor development in main study and extension study was reported as separate endpoints.

|                             |  |  |  |  |
|-----------------------------|--|--|--|--|
| <b>End point values</b>     | Part 2:<br>Expansion<br>group <6 years |  |  |  |
| Subject group type          | Reporting group                        |  |  |  |
| Number of subjects analysed | 12 <sup>[44]</sup>                     |  |  |  |
| Units: Subjects             | 0                                      |  |  |  |

Notes:

[44] - SAF - Part 2

## Statistical analyses

No statistical analyses for this end point

### Primary: Number of subjects with inhibitor development in extension study

|                 |  |
|-----------------|--|
| End point title | Number of subjects with inhibitor development in extension study <sup>[45]</sup> |
|-----------------|--|

End point description:

Subject in Part 2 were evaluated for positive FVIII inhibitor level ( $\geq 0.6$  BU/mL, using Nijmegen modified Bethesda assay).

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

End point timeframe:

Up to the final visit of the extension study

Notes:

[45] - 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: Only descriptive summary statistics were planned for this endpoint. None of the inhibitors was confirmed in a second sample.

|                             |                                      |  |  |  |
|-----------------------------|--------------------------------------|--|--|--|
| <b>End point values</b>     | Extension: Age<br>group <12<br>years |  |  |  |
| Subject group type          | Reporting group                      |  |  |  |
| Number of subjects analysed | 59 <sup>[46]</sup>                   |  |  |  |
| Units: Subjects             | 3                                    |  |  |  |

Notes:

[46] - SAF - Extension study

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of subjects with inhibitor development in main study

|                 |   |
|-----------------|---|
| End point title | Number of subjects with inhibitor development in main |
|-----------------|---|



End point description:

Subject were evaluated for positive FVIII inhibitor level ( $\geq 0.6$  BU/mL, using Nijmegen modified Bethesda assay).

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

End point timeframe:

After 10 to 15 and 50 exposure days over 6 months.

Notes:

[47] - 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: Inhibitor development in Part 2 and extension study was reported as separate endpoints.

| End point values            | Main: Age group <6 years | Main: Age group 6 to <12 years |  |  |
|-----------------------------|--------------------------|--------------------------------|--|--|
| Subject group type          | Reporting group          | Reporting group                |  |  |
| Number of subjects analysed | 32 <sup>[48]</sup>       | 29 <sup>[49]</sup>             |  |  |
| Units: Subjects             | 0                        | 0                              |  |  |

Notes:

[48] - SAF - Main study

[49] - SAF - Main study

## Statistical analyses

No statistical analyses for this end point

## Secondary: Assessment of incremental recovery in main study

|                 |  |
|-----------------|--|
| End point title | Assessment of incremental recovery in main study <sup>[50]</sup> |
|-----------------|--|

End point description:

Incremental recovery was determined by collecting a sample for FVIII level before the scheduled infusion, and a second sample collected 20-30 minutes after end of the infusion. The exact sampling times before and after infusion were documented in the CRF.

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

End point timeframe:

Baseline to the final visit of the main study

Notes:

[50] - 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: Incremental recovery was defined as secondary endpoint only for main study.

| End point values                     | Main: Age group <6 years | Main: Age group 6 to <12 years |  |  |
|--------------------------------------|--------------------------|--------------------------------|--|--|
| Subject group type                   | Reporting group          | Reporting group                |  |  |
| Number of subjects analysed          | 32 <sup>[51]</sup>       | 28 <sup>[52]</sup>             |  |  |
| Units: Kilogram/deciliter (kg/dL)    |                          |                                |  |  |
| arithmetic mean (standard deviation) |                          |                                |  |  |
| Baseline (N= 32, 28)                 | 1.698 ( $\pm$ 0.58)      | 1.941 ( $\pm$ 0.53)            |  |  |
| Month 1 (N= 1, 3)                    | 2.326 ( $\pm$ 99999)     | 6.416 ( $\pm$ 7.85)            |  |  |
| Month 2 (N= 1, 1)                    | 1.991 ( $\pm$ 99999)     | 2.261 ( $\pm$ 99999)           |  |  |
| Month 3 (N= 22, 26)                  | 1.843 ( $\pm$ 0.53)      | 2.277 ( $\pm$ 0.7)             |  |  |
| Month 6 (N= 22, 27)                  | 2.227 ( $\pm$ 0.58)      | 2.33 ( $\pm$ 0.67)             |  |  |

---

Notes:

[51] - ITT - Main study

[52] - ITT - Main study

---

### **Statistical analyses**

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From the start of study treatment up to 7 days after the last dose.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 22.1 |
|--------------------|------|

### Reporting groups

|                       |                          |
|-----------------------|--------------------------|
| Reporting group title | Main: Age group <6 years |
|-----------------------|--------------------------|

Reporting group description:

Subjects with age less than (<) 6 years were treated and prophylaxis administered with BAY94-9027 at a dose of 25-60 international units/kilogram (IU/kg) twice per week or 45-60 IU/kg every 5 days or 60 IU/kg every 7 days as an intravenous (IV) infusion as per clinical needs of each subject up to at least 50 exposure days (EDs) and a minimum of at least 6 months

|                       |                                |
|-----------------------|--------------------------------|
| Reporting group title | Main: Age group 6 to <12 years |
|-----------------------|--------------------------------|

Reporting group description:

Subjects with age 6 to <12 years were treated and prophylaxis administered with BAY94-9027 at a dose of 25-60 IU/kg twice per week or 45-60 IU/kg every 5 days or 60 IU/kg every 7 days as an IV infusion as per clinical needs of each subject up to at least 50 EDs and a minimum of at least 6 months

|                       |                                  |
|-----------------------|----------------------------------|
| Reporting group title | Part 2: Expansion group <6 years |
|-----------------------|----------------------------------|

Reporting group description:

Subjects with age <6 years were administered with BAY94-9027 at a dose of 25-60 IU/kg twice per week for prophylaxis for 12 weeks

|                       |                                |
|-----------------------|--------------------------------|
| Reporting group title | Extension: Age group <12 years |
|-----------------------|--------------------------------|

Reporting group description:

Subjects with age <12 years were treated and prophylaxis administered with BAY94-9027 at a dose of 25-60 IU/kg twice per week or 45-60 IU/kg every 5 days or 60 IU/kg every 7 days as an IV infusion as per clinical needs of each subject for at least 50 EDs or until marketing authorization of the drug

| Serious adverse events                            | Main: Age group <6 years | Main: Age group 6 to <12 years | Part 2: Expansion group <6 years |
|---|--------------------------|--------------------------------|----------------------------------|
| Total subjects affected by serious adverse events |                          |                                |                                  |
| subjects affected / exposed                       | 8 / 32 (25.00%)          | 3 / 29 (10.34%)                | 2 / 12 (16.67%)                  |
| number of deaths (all causes)                     | 0                        | 0                              | 0                                |
| number of deaths resulting from adverse events    | 0                        | 0                              | 0                                |
| Surgical and medical procedures                   |                          |                                |                                  |
| Catheter management                               |                          |                                |                                  |
| subjects affected / exposed                       | 1 / 32 (3.13%)           | 0 / 29 (0.00%)                 | 0 / 12 (0.00%)                   |
| occurrences causally related to treatment / all   | 0 / 1                    | 0 / 0                          | 0 / 0                            |
| deaths causally related to treatment / all        | 0 / 0                    | 0 / 0                          | 0 / 0                            |
| Central venous catheter removal                   |                          |                                |                                  |

|  |                |                |                |
|--|----------------|----------------|----------------|
| subjects affected / exposed                          | 0 / 32 (0.00%) | 0 / 29 (0.00%) | 0 / 12 (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          |
| Central venous catheterisation                       |                |                |                |
| subjects affected / exposed                          | 1 / 32 (3.13%) | 0 / 29 (0.00%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| Synoviorthesis                                       |                |                |                |
| subjects affected / exposed                          | 0 / 32 (0.00%) | 0 / 29 (0.00%) | 0 / 12 (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          |
| General disorders and administration site conditions |                |                |                |
| Catheter site swelling                               |                |                |                |
| subjects affected / exposed                          | 1 / 32 (3.13%) | 0 / 29 (0.00%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| Drug ineffective                                     |                |                |                |
| subjects affected / exposed                          | 0 / 32 (0.00%) | 0 / 29 (0.00%) | 1 / 12 (8.33%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| Immune system disorders                              |                |                |                |
| Drug hypersensitivity                                |                |                |                |
| subjects affected / exposed                          | 1 / 32 (3.13%) | 0 / 29 (0.00%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all      | 1 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| Hypersensitivity                                     |                |                |                |
| subjects affected / exposed                          | 1 / 32 (3.13%) | 1 / 29 (3.45%) | 1 / 12 (8.33%) |
| occurrences causally related to treatment / all      | 1 / 1          | 1 / 1          | 1 / 1          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| Social circumstances                                 |                |                |                |
| Physical assault                                     |                |                |                |
| subjects affected / exposed                          | 0 / 32 (0.00%) | 0 / 29 (0.00%) | 0 / 12 (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          |

|   |                |                |                |
|---|----------------|----------------|----------------|
| Respiratory, thoracic and mediastinal disorders |                |                |                |
| Pharyngeal haemorrhage                          |                |                |                |
| subjects affected / exposed                     | 0 / 32 (0.00%) | 0 / 29 (0.00%) | 0 / 12 (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          |
| Tonsillar inflammation                          |                |                |                |
| subjects affected / exposed                     | 0 / 32 (0.00%) | 0 / 29 (0.00%) | 0 / 12 (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          |
| Product issues                                  |                |                |                |
| Device connection issue                         |                |                |                |
| subjects affected / exposed                     | 0 / 32 (0.00%) | 1 / 29 (3.45%) | 0 / 12 (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          |
| Device occlusion                                |                |                |                |
| subjects affected / exposed                     | 0 / 32 (0.00%) | 0 / 29 (0.00%) | 0 / 12 (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          |
| Investigations                                  |                |                |                |
| Anti factor VIII antibody positive              |                |                |                |
| subjects affected / exposed                     | 1 / 32 (3.13%) | 0 / 29 (0.00%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Drug specific antibody present                  |                |                |                |
| subjects affected / exposed                     | 3 / 32 (9.38%) | 0 / 29 (0.00%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 5 / 5          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Injury, poisoning and procedural complications  |                |                |                |
| Concussion                                      |                |                |                |
| subjects affected / exposed                     | 0 / 32 (0.00%) | 0 / 29 (0.00%) | 0 / 12 (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          |
| Fibula fracture                                 |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 32 (0.00%) | 0 / 29 (0.00%) | 0 / 12 (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          |
| Head injury                                     |                |                |                |
| subjects affected / exposed                     | 0 / 32 (0.00%) | 0 / 29 (0.00%) | 0 / 12 (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          |
| Skin laceration                                 |                |                |                |
| subjects affected / exposed                     | 0 / 32 (0.00%) | 0 / 29 (0.00%) | 0 / 12 (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          |
| Subcutaneous haematoma                          |                |                |                |
| subjects affected / exposed                     | 1 / 32 (3.13%) | 0 / 29 (0.00%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Congenital, familial and genetic disorders      |                |                |                |
| Cryptorchism                                    |                |                |                |
| subjects affected / exposed                     | 0 / 32 (0.00%) | 0 / 29 (0.00%) | 0 / 12 (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          |
| Cardiac disorders                               |                |                |                |
| Cardiomyopathy                                  |                |                |                |
| subjects affected / exposed                     | 0 / 32 (0.00%) | 0 / 29 (0.00%) | 0 / 12 (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                        |                |                |                |
| Haemorrhage intracranial                        |                |                |                |
| subjects affected / exposed                     | 0 / 32 (0.00%) | 1 / 29 (3.45%) | 0 / 12 (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          |
| Headache  |                |                |                |
| subjects affected / exposed                     | 0 / 32 (0.00%) | 1 / 29 (3.45%) | 0 / 12 (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          |

|   |                |                |                |
|---|----------------|----------------|----------------|
| Somnolence                                      |                |                |                |
| subjects affected / exposed                     | 0 / 32 (0.00%) | 0 / 29 (0.00%) | 0 / 12 (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          |
| Subarachnoid haemorrhage                        |                |                |                |
| subjects affected / exposed                     | 0 / 32 (0.00%) | 1 / 29 (3.45%) | 0 / 12 (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          |
| Syncope   |                |                |                |
| subjects affected / exposed                     | 0 / 32 (0.00%) | 0 / 29 (0.00%) | 0 / 12 (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          |
| Eye disorders                                   |                |                |                |
| Diplopia  |                |                |                |
| subjects affected / exposed                     | 0 / 32 (0.00%) | 0 / 29 (0.00%) | 0 / 12 (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          |
| Photophobia                                     |                |                |                |
| subjects affected / exposed                     | 0 / 32 (0.00%) | 1 / 29 (3.45%) | 0 / 12 (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          |
| Gastrointestinal disorders                      |                |                |                |
| Abdominal pain                                  |                |                |                |
| subjects affected / exposed                     | 0 / 32 (0.00%) | 0 / 29 (0.00%) | 0 / 12 (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          |
| Abdominal wall haematoma                        |                |                |                |
| subjects affected / exposed                     | 0 / 32 (0.00%) | 0 / 29 (0.00%) | 0 / 12 (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          |
| Crohn's disease                                 |                |                |                |
| subjects affected / exposed                     | 0 / 32 (0.00%) | 0 / 29 (0.00%) | 0 / 12 (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          |

|   |                |                |                |
|---|----------------|----------------|----------------|
| Gastritis                                       |                |                |                |
| subjects affected / exposed                     | 0 / 32 (0.00%) | 0 / 29 (0.00%) | 0 / 12 (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          |
| Inguinal hernia                                 |                |                |                |
| subjects affected / exposed                     | 0 / 32 (0.00%) | 0 / 29 (0.00%) | 0 / 12 (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          |
| Nausea  |                |                |                |
| subjects affected / exposed                     | 0 / 32 (0.00%) | 1 / 29 (3.45%) | 0 / 12 (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          |
| Musculoskeletal and connective tissue disorders |                |                |                |
| Haemarthrosis                                   |                |                |                |
| subjects affected / exposed                     | 0 / 32 (0.00%) | 0 / 29 (0.00%) | 0 / 12 (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          |
| Infections and infestations                     |                |                |                |
| Appendicitis                                    |                |                |                |
| subjects affected / exposed                     | 0 / 32 (0.00%) | 0 / 29 (0.00%) | 0 / 12 (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          |
| Device related sepsis                           |                |                |                |
| subjects affected / exposed                     | 0 / 32 (0.00%) | 0 / 29 (0.00%) | 0 / 12 (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          |
| Gastroenteritis                                 |                |                |                |
| subjects affected / exposed                     | 0 / 32 (0.00%) | 1 / 29 (3.45%) | 0 / 12 (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          |
| Otitis media                                    |                |                |                |
| subjects affected / exposed                     | 0 / 32 (0.00%) | 0 / 29 (0.00%) | 0 / 12 (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          |



|   |                |                |                |
|---|----------------|----------------|----------------|
| Pneumonia                                       |                |                |                |
| subjects affected / exposed                     | 0 / 32 (0.00%) | 0 / 29 (0.00%) | 0 / 12 (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          |
| Staphylococcal infection                        |                |                |                |
| subjects affected / exposed                     | 1 / 32 (3.13%) | 0 / 29 (0.00%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Viral infection                                 |                |                |                |
| subjects affected / exposed                     | 0 / 32 (0.00%) | 0 / 29 (0.00%) | 0 / 12 (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          |

| Serious adverse events                            | Extension: Age group <12 years |  |  |
|---|--------------------------------|--|--|
| Total subjects affected by serious adverse events |                                |  |  |
| subjects affected / exposed                       | 20 / 59 (33.90%)               |  |  |
| number of deaths (all causes)                     | 0                              |  |  |
| number of deaths resulting from adverse events    | 0                              |  |  |
| Surgical and medical procedures                   |                                |  |  |
| Catheter management                               |                                |  |  |
| subjects affected / exposed                       | 0 / 59 (0.00%)                 |  |  |
| occurrences causally related to treatment / all   | 0 / 0                          |  |  |
| deaths causally related to treatment / all        | 0 / 0                          |  |  |
| Central venous catheter removal                   |                                |  |  |
| subjects affected / exposed                       | 1 / 59 (1.69%)                 |  |  |
| occurrences causally related to treatment / all   | 0 / 1                          |  |  |
| deaths causally related to treatment / all        | 0 / 0                          |  |  |
| Central venous catheterisation                    |                                |  |  |
| subjects affected / exposed                       | 0 / 59 (0.00%)                 |  |  |
| occurrences causally related to treatment / all   | 0 / 0                          |  |  |
| deaths causally related to treatment / all        | 0 / 0                          |  |  |
| Synoviorthesis                                    |                                |  |  |
| subjects affected / exposed                       | 1 / 59 (1.69%)                 |  |  |
| occurrences causally related to treatment / all   | 0 / 1                          |  |  |
| deaths causally related to treatment / all        | 0 / 0                          |  |  |

|  |                |  |  |
|--|----------------|--|--|
| General disorders and administration site conditions |                |  |  |
| Catheter site swelling                               |                |  |  |
| subjects affected / exposed                          | 0 / 59 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Drug ineffective                                     |                |  |  |
| subjects affected / exposed                          | 0 / 59 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Immune system disorders                              |                |  |  |
| Drug hypersensitivity                                |                |  |  |
| subjects affected / exposed                          | 0 / 59 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Hypersensitivity                                     |                |  |  |
| subjects affected / exposed                          | 0 / 59 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Social circumstances                                 |                |  |  |
| Physical assault                                     |                |  |  |
| subjects affected / exposed                          | 1 / 59 (1.69%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Respiratory, thoracic and mediastinal disorders      |                |  |  |
| Pharyngeal haemorrhage                               |                |  |  |
| subjects affected / exposed                          | 1 / 59 (1.69%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Tonsillar inflammation                               |                |  |  |
| subjects affected / exposed                          | 1 / 59 (1.69%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Product issues                                       |                |  |  |
| Device connection issue                              |                |  |  |

|   |                |  |  |
|---|----------------|--|--|
| subjects affected / exposed                     | 0 / 59 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Device occlusion                                |                |  |  |
| subjects affected / exposed                     | 1 / 59 (1.69%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Investigations                                  |                |  |  |
| Anti factor VIII antibody positive              |                |  |  |
| subjects affected / exposed                     | 2 / 59 (3.39%) |  |  |
| occurrences causally related to treatment / all | 2 / 2          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Drug specific antibody present                  |                |  |  |
| subjects affected / exposed                     | 0 / 59 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Injury, poisoning and procedural complications  |                |  |  |
| Concussion                                      |                |  |  |
| subjects affected / exposed                     | 1 / 59 (1.69%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Fibula fracture                                 |                |  |  |
| subjects affected / exposed                     | 1 / 59 (1.69%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Head injury                                     |                |  |  |
| subjects affected / exposed                     | 3 / 59 (5.08%) |  |  |
| occurrences causally related to treatment / all | 0 / 3          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Skin laceration                                 |                |  |  |
| subjects affected / exposed                     | 1 / 59 (1.69%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |

|   |                |  |  |
|---|----------------|--|--|
| Subcutaneous haematoma                          |                |  |  |
| subjects affected / exposed                     | 0 / 59 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Congenital, familial and genetic disorders      |                |  |  |
| Cryptorchism                                    |                |  |  |
| subjects affected / exposed                     | 1 / 59 (1.69%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Cardiac disorders                               |                |  |  |
| Cardiomyopathy                                  |                |  |  |
| subjects affected / exposed                     | 1 / 59 (1.69%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Nervous system disorders                        |                |  |  |
| Haemorrhage intracranial                        |                |  |  |
| subjects affected / exposed                     | 0 / 59 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Headache  |                |  |  |
| subjects affected / exposed                     | 1 / 59 (1.69%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Somnolence                                      |                |  |  |
| subjects affected / exposed                     | 1 / 59 (1.69%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Subarachnoid haemorrhage                        |                |  |  |
| subjects affected / exposed                     | 0 / 59 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Syncope   |                |  |  |

|   |                |  |  |
|---|----------------|--|--|
| subjects affected / exposed                     | 1 / 59 (1.69%) |  |  |
| occurrences causally related to treatment / all | 0 / 2          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Eye disorders                                   |                |  |  |
| Diplopia  |                |  |  |
| subjects affected / exposed                     | 1 / 59 (1.69%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Photophobia                                     |                |  |  |
| subjects affected / exposed                     | 0 / 59 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Gastrointestinal disorders                      |                |  |  |
| Abdominal pain                                  |                |  |  |
| subjects affected / exposed                     | 2 / 59 (3.39%) |  |  |
| occurrences causally related to treatment / all | 0 / 2          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Abdominal wall haematoma                        |                |  |  |
| subjects affected / exposed                     | 1 / 59 (1.69%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Crohn's disease                                 |                |  |  |
| subjects affected / exposed                     | 1 / 59 (1.69%) |  |  |
| occurrences causally related to treatment / all | 0 / 2          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Gastritis                                       |                |  |  |
| subjects affected / exposed                     | 1 / 59 (1.69%) |  |  |
| occurrences causally related to treatment / all | 0 / 2          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Inguinal hernia                                 |                |  |  |
| subjects affected / exposed                     | 1 / 59 (1.69%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Nausea  |                |  |  |

|   |                |  |  |
|---|----------------|--|--|
| subjects affected / exposed                     | 0 / 59 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Musculoskeletal and connective tissue disorders |                |  |  |
| Haemarthrosis                                   |                |  |  |
| subjects affected / exposed                     | 5 / 59 (8.47%) |  |  |
| occurrences causally related to treatment / all | 0 / 5          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Infections and infestations                     |                |  |  |
| Appendicitis                                    |                |  |  |
| subjects affected / exposed                     | 1 / 59 (1.69%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Device related sepsis                           |                |  |  |
| subjects affected / exposed                     | 1 / 59 (1.69%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Gastroenteritis                                 |                |  |  |
| subjects affected / exposed                     | 1 / 59 (1.69%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Otitis media                                    |                |  |  |
| subjects affected / exposed                     | 1 / 59 (1.69%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Pneumonia                                       |                |  |  |
| subjects affected / exposed                     | 1 / 59 (1.69%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Staphylococcal infection                        |                |  |  |
| subjects affected / exposed                     | 0 / 59 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |

|   |                |  |  |
|---|----------------|--|--|
| Viral infection                                 |                |  |  |
| subjects affected / exposed                     | 1 / 59 (1.69%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |

Frequency threshold for reporting non-serious adverse events: 5 %

| <b>Non-serious adverse events</b>                     | Main: Age group <6 years | Main: Age group 6 to <12 years | Part 2: Expansion group <6 years |
|---|--------------------------|--------------------------------|----------------------------------|
| Total subjects affected by non-serious adverse events |                          |                                |                                  |
| subjects affected / exposed                           | 24 / 32 (75.00%)         | 19 / 29 (65.52%)               | 10 / 12 (83.33%)                 |
| Injury, poisoning and procedural complications        |                          |                                |                                  |
| Arthropod bite  |                          |                                |                                  |
| subjects affected / exposed                           | 2 / 32 (6.25%)           | 0 / 29 (0.00%)                 | 0 / 12 (0.00%)                   |
| occurrences (all)                                     | 2                        | 0                              | 0                                |
| Contusion   |                          |                                |                                  |
| subjects affected / exposed                           | 5 / 32 (15.63%)          | 2 / 29 (6.90%)                 | 3 / 12 (25.00%)                  |
| occurrences (all)                                     | 5                        | 2                              | 3                                |
| Fall  |                          |                                |                                  |
| subjects affected / exposed                           | 3 / 32 (9.38%)           | 0 / 29 (0.00%)                 | 2 / 12 (16.67%)                  |
| occurrences (all)                                     | 3                        | 0                              | 3                                |
| Hand fracture   |                          |                                |                                  |
| subjects affected / exposed                           | 0 / 32 (0.00%)           | 0 / 29 (0.00%)                 | 0 / 12 (0.00%)                   |
| occurrences (all)                                     | 0                        | 0                              | 0                                |
| Head injury   |                          |                                |                                  |
| subjects affected / exposed                           | 2 / 32 (6.25%)           | 0 / 29 (0.00%)                 | 0 / 12 (0.00%)                   |
| occurrences (all)                                     | 4                        | 0                              | 0                                |
| Joint injury  |                          |                                |                                  |
| subjects affected / exposed                           | 1 / 32 (3.13%)           | 0 / 29 (0.00%)                 | 1 / 12 (8.33%)                   |
| occurrences (all)                                     | 1                        | 0                              | 1                                |
| Ligament sprain                                       |                          |                                |                                  |
| subjects affected / exposed                           | 2 / 32 (6.25%)           | 0 / 29 (0.00%)                 | 0 / 12 (0.00%)                   |
| occurrences (all)                                     | 2                        | 0                              | 0                                |
| Limb injury   |                          |                                |                                  |
| subjects affected / exposed                           | 1 / 32 (3.13%)           | 0 / 29 (0.00%)                 | 0 / 12 (0.00%)                   |
| occurrences (all)                                     | 1                        | 0                              | 0                                |

|                                      |                |                 |                |
|--------------------------------------|----------------|-----------------|----------------|
| Lip injury                           |                |                 |                |
| subjects affected / exposed          | 2 / 32 (6.25%) | 0 / 29 (0.00%)  | 0 / 12 (0.00%) |
| occurrences (all)                    | 2              | 0               | 0              |
| Mouth injury                         |                |                 |                |
| subjects affected / exposed          | 2 / 32 (6.25%) | 0 / 29 (0.00%)  | 0 / 12 (0.00%) |
| occurrences (all)                    | 2              | 0               | 0              |
| Post-traumatic pain                  |                |                 |                |
| subjects affected / exposed          | 2 / 32 (6.25%) | 0 / 29 (0.00%)  | 0 / 12 (0.00%) |
| occurrences (all)                    | 2              | 0               | 0              |
| Skin abrasion                        |                |                 |                |
| subjects affected / exposed          | 0 / 32 (0.00%) | 0 / 29 (0.00%)  | 0 / 12 (0.00%) |
| occurrences (all)                    | 0              | 0               | 0              |
| Skin injury                          |                |                 |                |
| subjects affected / exposed          | 1 / 32 (3.13%) | 0 / 29 (0.00%)  | 1 / 12 (8.33%) |
| occurrences (all)                    | 1              | 0               | 1              |
| Skin laceration                      |                |                 |                |
| subjects affected / exposed          | 1 / 32 (3.13%) | 0 / 29 (0.00%)  | 0 / 12 (0.00%) |
| occurrences (all)                    | 1              | 0               | 0              |
| Subcutaneous haematoma               |                |                 |                |
| subjects affected / exposed          | 2 / 32 (6.25%) | 0 / 29 (0.00%)  | 1 / 12 (8.33%) |
| occurrences (all)                    | 12             | 0               | 1              |
| Vascular disorders                   |                |                 |                |
| Haematoma                            |                |                 |                |
| subjects affected / exposed          | 3 / 32 (9.38%) | 0 / 29 (0.00%)  | 1 / 12 (8.33%) |
| occurrences (all)                    | 18             | 0               | 1              |
| Nervous system disorders             |                |                 |                |
| Headache                             |                |                 |                |
| subjects affected / exposed          | 2 / 32 (6.25%) | 6 / 29 (20.69%) | 0 / 12 (0.00%) |
| occurrences (all)                    | 2              | 8               | 0              |
| Presyncope                           |                |                 |                |
| subjects affected / exposed          | 0 / 32 (0.00%) | 0 / 29 (0.00%)  | 1 / 12 (8.33%) |
| occurrences (all)                    | 0              | 0               | 2              |
| Blood and lymphatic system disorders |                |                 |                |
| Lymphadenopathy                      |                |                 |                |
| subjects affected / exposed          | 0 / 32 (0.00%) | 0 / 29 (0.00%)  | 0 / 12 (0.00%) |
| occurrences (all)                    | 0              | 0               | 0              |
| General disorders and administration |                |                 |                |



|                             |                 |                 |                 |
|-----------------------------|-----------------|-----------------|-----------------|
| site conditions             |                 |                 |                 |
| Drug ineffective            |                 |                 |                 |
| subjects affected / exposed | 0 / 32 (0.00%)  | 0 / 29 (0.00%)  | 2 / 12 (16.67%) |
| occurrences (all)           | 0               | 0               | 2               |
| Injection site pruritus     |                 |                 |                 |
| subjects affected / exposed | 0 / 32 (0.00%)  | 0 / 29 (0.00%)  | 1 / 12 (8.33%)  |
| occurrences (all)           | 0               | 0               | 1               |
| Malaise                     |                 |                 |                 |
| subjects affected / exposed | 0 / 32 (0.00%)  | 0 / 29 (0.00%)  | 0 / 12 (0.00%)  |
| occurrences (all)           | 0               | 0               | 0               |
| Mass                        |                 |                 |                 |
| subjects affected / exposed | 2 / 32 (6.25%)  | 0 / 29 (0.00%)  | 0 / 12 (0.00%)  |
| occurrences (all)           | 2               | 0               | 0               |
| Pain                        |                 |                 |                 |
| subjects affected / exposed | 0 / 32 (0.00%)  | 1 / 29 (3.45%)  | 0 / 12 (0.00%)  |
| occurrences (all)           | 0               | 1               | 0               |
| Peripheral swelling         |                 |                 |                 |
| subjects affected / exposed | 1 / 32 (3.13%)  | 0 / 29 (0.00%)  | 0 / 12 (0.00%)  |
| occurrences (all)           | 1               | 0               | 0               |
| Pyrexia                     |                 |                 |                 |
| subjects affected / exposed | 7 / 32 (21.88%) | 2 / 29 (6.90%)  | 3 / 12 (25.00%) |
| occurrences (all)           | 9               | 4               | 3               |
| Ear and labyrinth disorders |                 |                 |                 |
| Ear pain                    |                 |                 |                 |
| subjects affected / exposed | 1 / 32 (3.13%)  | 0 / 29 (0.00%)  | 0 / 12 (0.00%)  |
| occurrences (all)           | 3               | 0               | 0               |
| Immune system disorders     |                 |                 |                 |
| Seasonal allergy            |                 |                 |                 |
| subjects affected / exposed | 0 / 32 (0.00%)  | 1 / 29 (3.45%)  | 0 / 12 (0.00%)  |
| occurrences (all)           | 0               | 1               | 0               |
| Gastrointestinal disorders  |                 |                 |                 |
| Abdominal pain              |                 |                 |                 |
| subjects affected / exposed | 0 / 32 (0.00%)  | 1 / 29 (3.45%)  | 0 / 12 (0.00%)  |
| occurrences (all)           | 0               | 1               | 0               |
| Abdominal pain upper        |                 |                 |                 |
| subjects affected / exposed | 0 / 32 (0.00%)  | 3 / 29 (10.34%) | 0 / 12 (0.00%)  |
| occurrences (all)           | 0               | 3               | 0               |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Dental caries                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 32 (0.00%)  | 0 / 29 (0.00%)  | 0 / 12 (0.00%)  |
| occurrences (all)                               | 0               | 0               | 0               |
| Diarrhoea                                       |                 |                 |                 |
| subjects affected / exposed                     | 4 / 32 (12.50%) | 2 / 29 (6.90%)  | 0 / 12 (0.00%)  |
| occurrences (all)                               | 4               | 2               | 0               |
| Gingival bleeding                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 32 (0.00%)  | 0 / 29 (0.00%)  | 0 / 12 (0.00%)  |
| occurrences (all)                               | 0               | 0               | 0               |
| Loose tooth                                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 32 (0.00%)  | 0 / 29 (0.00%)  | 0 / 12 (0.00%)  |
| occurrences (all)                               | 0               | 0               | 0               |
| Nausea  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 32 (0.00%)  | 0 / 29 (0.00%)  | 0 / 12 (0.00%)  |
| occurrences (all)                               | 0               | 0               | 0               |
| Vomiting  |                 |                 |                 |
| subjects affected / exposed                     | 2 / 32 (6.25%)  | 3 / 29 (10.34%) | 0 / 12 (0.00%)  |
| occurrences (all)                               | 2               | 3               | 0               |
| Respiratory, thoracic and mediastinal disorders |                 |                 |                 |
| Cough   |                 |                 |                 |
| subjects affected / exposed                     | 5 / 32 (15.63%) | 1 / 29 (3.45%)  | 2 / 12 (16.67%) |
| occurrences (all)                               | 5               | 1               | 3               |
| Epistaxis                                       |                 |                 |                 |
| subjects affected / exposed                     | 3 / 32 (9.38%)  | 4 / 29 (13.79%) | 2 / 12 (16.67%) |
| occurrences (all)                               | 5               | 9               | 2               |
| Nasal congestion                                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 32 (0.00%)  | 0 / 29 (0.00%)  | 0 / 12 (0.00%)  |
| occurrences (all)                               | 0               | 0               | 0               |
| Oropharyngeal pain                              |                 |                 |                 |
| subjects affected / exposed                     | 1 / 32 (3.13%)  | 5 / 29 (17.24%) | 0 / 12 (0.00%)  |
| occurrences (all)                               | 1               | 5               | 0               |
| Rhinorrhoea                                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 32 (0.00%)  | 0 / 29 (0.00%)  | 0 / 12 (0.00%)  |
| occurrences (all)                               | 0               | 0               | 0               |
| Skin and subcutaneous tissue disorders          |                 |                 |                 |

|  |                     |                      |                      |
|--|---------------------|----------------------|----------------------|
| Dermatitis contact<br>subjects affected / exposed<br>occurrences (all) | 0 / 32 (0.00%)<br>0 | 0 / 29 (0.00%)<br>0  | 0 / 12 (0.00%)<br>0  |
| Rash<br>subjects affected / exposed<br>occurrences (all)               | 3 / 32 (9.38%)<br>4 | 1 / 29 (3.45%)<br>2  | 1 / 12 (8.33%)<br>1  |
| Urticaria<br>subjects affected / exposed<br>occurrences (all)          | 0 / 32 (0.00%)<br>0 | 0 / 29 (0.00%)<br>0  | 0 / 12 (0.00%)<br>0  |
| Musculoskeletal and connective tissue disorders                        |                     |                      |                      |
| Arthralgia<br>subjects affected / exposed<br>occurrences (all)         | 1 / 32 (3.13%)<br>1 | 3 / 29 (10.34%)<br>3 | 1 / 12 (8.33%)<br>1  |
| Back pain<br>subjects affected / exposed<br>occurrences (all)          | 0 / 32 (0.00%)<br>0 | 0 / 29 (0.00%)<br>0  | 0 / 12 (0.00%)<br>0  |
| Haemarthrosis<br>subjects affected / exposed<br>occurrences (all)      | 0 / 32 (0.00%)<br>0 | 1 / 29 (3.45%)<br>1  | 1 / 12 (8.33%)<br>1  |
| Joint swelling<br>subjects affected / exposed<br>occurrences (all)     | 1 / 32 (3.13%)<br>1 | 0 / 29 (0.00%)<br>0  | 0 / 12 (0.00%)<br>0  |
| Pain in extremity<br>subjects affected / exposed<br>occurrences (all)  | 3 / 32 (9.38%)<br>3 | 3 / 29 (10.34%)<br>4 | 2 / 12 (16.67%)<br>2 |
| Synovitis<br>subjects affected / exposed<br>occurrences (all)          | 0 / 32 (0.00%)<br>0 | 0 / 29 (0.00%)<br>0  | 0 / 12 (0.00%)<br>0  |
| Tendonitis<br>subjects affected / exposed<br>occurrences (all)         | 0 / 32 (0.00%)<br>0 | 0 / 29 (0.00%)<br>0  | 0 / 12 (0.00%)<br>0  |
| Infections and infestations  |                     |                      |                      |
| Bronchitis<br>subjects affected / exposed<br>occurrences (all)         | 1 / 32 (3.13%)<br>1 | 0 / 29 (0.00%)<br>0  | 0 / 12 (0.00%)<br>0  |
| Conjunctivitis   |                     |                      |                      |

|                             |                 |                 |                |
|-----------------------------|-----------------|-----------------|----------------|
| subjects affected / exposed | 1 / 32 (3.13%)  | 0 / 29 (0.00%)  | 0 / 12 (0.00%) |
| occurrences (all)           | 1               | 0               | 0              |
| Ear infection               |                 |                 |                |
| subjects affected / exposed | 1 / 32 (3.13%)  | 1 / 29 (3.45%)  | 1 / 12 (8.33%) |
| occurrences (all)           | 2               | 1               | 1              |
| Gastroenteritis             |                 |                 |                |
| subjects affected / exposed | 2 / 32 (6.25%)  | 3 / 29 (10.34%) | 0 / 12 (0.00%) |
| occurrences (all)           | 2               | 3               | 0              |
| Impetigo                    |                 |                 |                |
| subjects affected / exposed | 0 / 32 (0.00%)  | 0 / 29 (0.00%)  | 0 / 12 (0.00%) |
| occurrences (all)           | 0               | 0               | 0              |
| Influenza                   |                 |                 |                |
| subjects affected / exposed | 1 / 32 (3.13%)  | 0 / 29 (0.00%)  | 0 / 12 (0.00%) |
| occurrences (all)           | 1               | 0               | 0              |
| Nasopharyngitis             |                 |                 |                |
| subjects affected / exposed | 5 / 32 (15.63%) | 1 / 29 (3.45%)  | 0 / 12 (0.00%) |
| occurrences (all)           | 8               | 1               | 0              |
| Otitis externa              |                 |                 |                |
| subjects affected / exposed | 0 / 32 (0.00%)  | 0 / 29 (0.00%)  | 0 / 12 (0.00%) |
| occurrences (all)           | 0               | 0               | 0              |
| Otitis media                |                 |                 |                |
| subjects affected / exposed | 0 / 32 (0.00%)  | 0 / 29 (0.00%)  | 0 / 12 (0.00%) |
| occurrences (all)           | 0               | 0               | 0              |
| Pharyngitis                 |                 |                 |                |
| subjects affected / exposed | 0 / 32 (0.00%)  | 0 / 29 (0.00%)  | 0 / 12 (0.00%) |
| occurrences (all)           | 0               | 0               | 0              |
| Pharyngitis streptococcal   |                 |                 |                |
| subjects affected / exposed | 0 / 32 (0.00%)  | 1 / 29 (3.45%)  | 0 / 12 (0.00%) |
| occurrences (all)           | 0               | 1               | 0              |
| Pneumonia                   |                 |                 |                |
| subjects affected / exposed | 0 / 32 (0.00%)  | 0 / 29 (0.00%)  | 0 / 12 (0.00%) |
| occurrences (all)           | 0               | 0               | 0              |
| Rhinitis                    |                 |                 |                |
| subjects affected / exposed | 3 / 32 (9.38%)  | 0 / 29 (0.00%)  | 0 / 12 (0.00%) |
| occurrences (all)           | 3               | 0               | 0              |
| Sinusitis                   |                 |                 |                |

|                                   |                 |                 |                |
|-----------------------------------|-----------------|-----------------|----------------|
| subjects affected / exposed       | 1 / 32 (3.13%)  | 1 / 29 (3.45%)  | 0 / 12 (0.00%) |
| occurrences (all)                 | 2               | 1               | 0              |
| Tonsillitis                       |                 |                 |                |
| subjects affected / exposed       | 0 / 32 (0.00%)  | 2 / 29 (6.90%)  | 0 / 12 (0.00%) |
| occurrences (all)                 | 0               | 2               | 0              |
| Upper respiratory tract infection |                 |                 |                |
| subjects affected / exposed       | 6 / 32 (18.75%) | 1 / 29 (3.45%)  | 1 / 12 (8.33%) |
| occurrences (all)                 | 6               | 1               | 1              |
| Varicella                         |                 |                 |                |
| subjects affected / exposed       | 2 / 32 (6.25%)  | 1 / 29 (3.45%)  | 0 / 12 (0.00%) |
| occurrences (all)                 | 2               | 1               | 0              |
| Viral infection                   |                 |                 |                |
| subjects affected / exposed       | 1 / 32 (3.13%)  | 3 / 29 (10.34%) | 0 / 12 (0.00%) |
| occurrences (all)                 | 1               | 3               | 0              |

| <b>Non-serious adverse events</b>                     | Extension: Age group <12 years |  |  |
|---|--------------------------------|--|--|
| Total subjects affected by non-serious adverse events |                                |  |  |
| subjects affected / exposed                           | 53 / 59 (89.83%)               |  |  |
| Injury, poisoning and procedural complications        |                                |  |  |
| Arthropod bite  |                                |  |  |
| subjects affected / exposed                           | 1 / 59 (1.69%)                 |  |  |
| occurrences (all)                                     | 2                              |  |  |
| Contusion   |                                |  |  |
| subjects affected / exposed                           | 10 / 59 (16.95%)               |  |  |
| occurrences (all)                                     | 13                             |  |  |
| Fall  |                                |  |  |
| subjects affected / exposed                           | 7 / 59 (11.86%)                |  |  |
| occurrences (all)                                     | 9                              |  |  |
| Hand fracture   |                                |  |  |
| subjects affected / exposed                           | 3 / 59 (5.08%)                 |  |  |
| occurrences (all)                                     | 3                              |  |  |
| Head injury   |                                |  |  |
| subjects affected / exposed                           | 12 / 59 (20.34%)               |  |  |
| occurrences (all)                                     | 17                             |  |  |
| Joint injury  |                                |  |  |

|                             |                  |  |  |
|-----------------------------|------------------|--|--|
| subjects affected / exposed | 10 / 59 (16.95%) |  |  |
| occurrences (all)           | 12               |  |  |
| Ligament sprain             |                  |  |  |
| subjects affected / exposed | 7 / 59 (11.86%)  |  |  |
| occurrences (all)           | 10               |  |  |
| Limb injury                 |                  |  |  |
| subjects affected / exposed | 10 / 59 (16.95%) |  |  |
| occurrences (all)           | 16               |  |  |
| Lip injury                  |                  |  |  |
| subjects affected / exposed | 0 / 59 (0.00%)   |  |  |
| occurrences (all)           | 0                |  |  |
| Mouth injury                |                  |  |  |
| subjects affected / exposed | 0 / 59 (0.00%)   |  |  |
| occurrences (all)           | 0                |  |  |
| Post-traumatic pain         |                  |  |  |
| subjects affected / exposed | 7 / 59 (11.86%)  |  |  |
| occurrences (all)           | 11               |  |  |
| Skin abrasion               |                  |  |  |
| subjects affected / exposed | 3 / 59 (5.08%)   |  |  |
| occurrences (all)           | 7                |  |  |
| Skin injury                 |                  |  |  |
| subjects affected / exposed | 0 / 59 (0.00%)   |  |  |
| occurrences (all)           | 0                |  |  |
| Skin laceration             |                  |  |  |
| subjects affected / exposed | 3 / 59 (5.08%)   |  |  |
| occurrences (all)           | 4                |  |  |
| Subcutaneous haematoma      |                  |  |  |
| subjects affected / exposed | 5 / 59 (8.47%)   |  |  |
| occurrences (all)           | 6                |  |  |
| Vascular disorders          |                  |  |  |
| Haematoma                   |                  |  |  |
| subjects affected / exposed | 6 / 59 (10.17%)  |  |  |
| occurrences (all)           | 9                |  |  |
| Nervous system disorders    |                  |  |  |
| Headache                    |                  |  |  |

|   |                        |  |  |
|---|------------------------|--|--|
| subjects affected / exposed<br>occurrences (all)  | 16 / 59 (27.12%)<br>36 |  |  |
| Presyncope<br>subjects affected / exposed<br>occurrences (all)  | 0 / 59 (0.00%)<br>0    |  |  |
| Blood and lymphatic system disorders<br>Lymphadenopathy<br>subjects affected / exposed<br>occurrences (all)                     | 4 / 59 (6.78%)<br>4    |  |  |
| General disorders and administration<br>site conditions<br>Drug ineffective<br>subjects affected / exposed<br>occurrences (all) | 0 / 59 (0.00%)<br>0    |  |  |
| Injection site pruritus<br>subjects affected / exposed<br>occurrences (all)   | 0 / 59 (0.00%)<br>0    |  |  |
| Malaise<br>subjects affected / exposed<br>occurrences (all)   | 3 / 59 (5.08%)<br>7    |  |  |
| Mass<br>subjects affected / exposed<br>occurrences (all)  | 3 / 59 (5.08%)<br>3    |  |  |
| Pain<br>subjects affected / exposed<br>occurrences (all)  | 5 / 59 (8.47%)<br>7    |  |  |
| Peripheral swelling<br>subjects affected / exposed<br>occurrences (all)   | 3 / 59 (5.08%)<br>3    |  |  |
| Pyrexia<br>subjects affected / exposed<br>occurrences (all)   | 24 / 59 (40.68%)<br>63 |  |  |
| Ear and labyrinth disorders<br>Ear pain<br>subjects affected / exposed<br>occurrences (all)                                     | 4 / 59 (6.78%)<br>6    |  |  |
| Immune system disorders   |                        |  |  |

|  |                        |  |  |
|--|------------------------|--|--|
| Seasonal allergy<br>subjects affected / exposed<br>occurrences (all)     | 4 / 59 (6.78%)<br>4    |  |  |
| Gastrointestinal disorders   |                        |  |  |
| Abdominal pain<br>subjects affected / exposed<br>occurrences (all)       | 8 / 59 (13.56%)<br>13  |  |  |
| Abdominal pain upper<br>subjects affected / exposed<br>occurrences (all) | 3 / 59 (5.08%)<br>4    |  |  |
| Dental caries<br>subjects affected / exposed<br>occurrences (all)        | 3 / 59 (5.08%)<br>4    |  |  |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)            | 7 / 59 (11.86%)<br>14  |  |  |
| Gingival bleeding<br>subjects affected / exposed<br>occurrences (all)    | 5 / 59 (8.47%)<br>7    |  |  |
| Loose tooth<br>subjects affected / exposed<br>occurrences (all)          | 3 / 59 (5.08%)<br>4    |  |  |
| Nausea<br>subjects affected / exposed<br>occurrences (all)               | 7 / 59 (11.86%)<br>9   |  |  |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)             | 12 / 59 (20.34%)<br>21 |  |  |
| Respiratory, thoracic and mediastinal disorders                          |                        |  |  |
| Cough<br>subjects affected / exposed<br>occurrences (all)                | 16 / 59 (27.12%)<br>30 |  |  |
| Epistaxis<br>subjects affected / exposed<br>occurrences (all)            | 16 / 59 (27.12%)<br>41 |  |  |
| Nasal congestion   |                        |  |  |



|   |                  |  |  |
|---|------------------|--|--|
| subjects affected / exposed                     | 3 / 59 (5.08%)   |  |  |
| occurrences (all)                               | 3                |  |  |
| Oropharyngeal pain                              |                  |  |  |
| subjects affected / exposed                     | 14 / 59 (23.73%) |  |  |
| occurrences (all)                               | 20               |  |  |
| Rhinorrhoea                                     |                  |  |  |
| subjects affected / exposed                     | 3 / 59 (5.08%)   |  |  |
| occurrences (all)                               | 5                |  |  |
| Skin and subcutaneous tissue disorders          |                  |  |  |
| Dermatitis contact                              |                  |  |  |
| subjects affected / exposed                     | 3 / 59 (5.08%)   |  |  |
| occurrences (all)                               | 4                |  |  |
| Rash  |                  |  |  |
| subjects affected / exposed                     | 4 / 59 (6.78%)   |  |  |
| occurrences (all)                               | 4                |  |  |
| Urticaria                                       |                  |  |  |
| subjects affected / exposed                     | 3 / 59 (5.08%)   |  |  |
| occurrences (all)                               | 3                |  |  |
| Musculoskeletal and connective tissue disorders |                  |  |  |
| Arthralgia                                      |                  |  |  |
| subjects affected / exposed                     | 11 / 59 (18.64%) |  |  |
| occurrences (all)                               | 16               |  |  |
| Back pain                                       |                  |  |  |
| subjects affected / exposed                     | 4 / 59 (6.78%)   |  |  |
| occurrences (all)                               | 8                |  |  |
| Haemarthrosis                                   |                  |  |  |
| subjects affected / exposed                     | 2 / 59 (3.39%)   |  |  |
| occurrences (all)                               | 4                |  |  |
| Joint swelling                                  |                  |  |  |
| subjects affected / exposed                     | 3 / 59 (5.08%)   |  |  |
| occurrences (all)                               | 4                |  |  |
| Pain in extremity                               |                  |  |  |
| subjects affected / exposed                     | 14 / 59 (23.73%) |  |  |
| occurrences (all)                               | 20               |  |  |
| Synovitis                                       |                  |  |  |

|                             |                  |  |  |
|-----------------------------|------------------|--|--|
| subjects affected / exposed | 4 / 59 (6.78%)   |  |  |
| occurrences (all)           | 5                |  |  |
| Tendonitis                  |                  |  |  |
| subjects affected / exposed | 6 / 59 (10.17%)  |  |  |
| occurrences (all)           | 7                |  |  |
| Infections and infestations |                  |  |  |
| Bronchitis                  |                  |  |  |
| subjects affected / exposed | 4 / 59 (6.78%)   |  |  |
| occurrences (all)           | 12               |  |  |
| Conjunctivitis              |                  |  |  |
| subjects affected / exposed | 3 / 59 (5.08%)   |  |  |
| occurrences (all)           | 4                |  |  |
| Ear infection               |                  |  |  |
| subjects affected / exposed | 5 / 59 (8.47%)   |  |  |
| occurrences (all)           | 8                |  |  |
| Gastroenteritis             |                  |  |  |
| subjects affected / exposed | 7 / 59 (11.86%)  |  |  |
| occurrences (all)           | 7                |  |  |
| Impetigo                    |                  |  |  |
| subjects affected / exposed | 3 / 59 (5.08%)   |  |  |
| occurrences (all)           | 6                |  |  |
| Influenza                   |                  |  |  |
| subjects affected / exposed | 10 / 59 (16.95%) |  |  |
| occurrences (all)           | 12               |  |  |
| Nasopharyngitis             |                  |  |  |
| subjects affected / exposed | 19 / 59 (32.20%) |  |  |
| occurrences (all)           | 34               |  |  |
| Otitis externa              |                  |  |  |
| subjects affected / exposed | 3 / 59 (5.08%)   |  |  |
| occurrences (all)           | 6                |  |  |
| Otitis media                |                  |  |  |
| subjects affected / exposed | 4 / 59 (6.78%)   |  |  |
| occurrences (all)           | 5                |  |  |
| Pharyngitis                 |                  |  |  |
| subjects affected / exposed | 5 / 59 (8.47%)   |  |  |
| occurrences (all)           | 7                |  |  |

|   |                       |  |  |
|---|-----------------------|--|--|
| Pharyngitis streptococcal<br>subjects affected / exposed<br>occurrences (all)         | 5 / 59 (8.47%)<br>7   |  |  |
| Pneumonia<br>subjects affected / exposed<br>occurrences (all)                         | 4 / 59 (6.78%)<br>4   |  |  |
| Rhinitis<br>subjects affected / exposed<br>occurrences (all)                          | 9 / 59 (15.25%)<br>11 |  |  |
| Sinusitis<br>subjects affected / exposed<br>occurrences (all)                         | 5 / 59 (8.47%)<br>13  |  |  |
| Tonsillitis<br>subjects affected / exposed<br>occurrences (all)                       | 7 / 59 (11.86%)<br>9  |  |  |
| Upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all) | 9 / 59 (15.25%)<br>16 |  |  |
| Varicella<br>subjects affected / exposed<br>occurrences (all)                         | 4 / 59 (6.78%)<br>4   |  |  |
| Viral infection<br>subjects affected / exposed<br>occurrences (all)                   | 4 / 59 (6.78%)<br>5   |  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date           | Amendment   |
|----------------|---|
| 18 June 2013   | Amendment 1, primarily revised the protocol by adding a more structured approach to increasing the dose or dose frequency if breakthrough bleeds occur. Also, in order to make the extension consistent with the main study, a visit window of +/- 1 week was added to the extension visits.  |
| 12 August 2014 | Amendment 2, updated the protocol in response to adverse events that were observed in study performance. Both hypersensitivity reactions and potential loss of efficacy of the drug product had also been reported and may have been suspected to be associated with the development of antibodies to BAY 94-9027. These events were now to be identified in this study defined as adverse events of special interest and required study observations and the timeline required for obtaining these observations were defined listed in more detail. Additionally, the protocol was modified to allow doses up to 60 IU/kg in the 2x/week treatment group, if clinically indicated. Also, major surgeries were now to be allowed. |
| 18 June 2015   | Amendment 3, provided primarily the addition of an expansion group (Part 2) of the protocol to enroll a minimum of 8-10 subjects in the age group <6 years, for a period of 12 weeks of therapy with twice weekly dosing. The primary objective of the expansion arm was safety, with an aim to characterize the potential immune response to BAY 94-9027. The goal was to better characterize the adverse events of special interest (hypersensitivity to the infused study drug or loss of efficacy).   |
| 13 June 2017   | Amendment 4, included clarification of the objective for the extension study to assess the long term safety of BAY 94-9027 over at least 100 accumulated ED. The measurement of body height, documentation of body height at all past study visits, the renal safety assessment using serum biomarkers and urinary biomarkers, and standard assessment of neurological examination including vision and fundus examination were added to the extension study visits. The guidelines for neurological examination were provided in the Appendices.   |

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 SD is autogenerated and cannot be deleted. '99999' indicates that standard deviation was not estimable because only 1 subject was evaluable for this timepoint.

Notes:

### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/32212300>