# 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

Due to the EudraCT – Results system being out of service between 31 July 2015 and 12 January 2016, these results have been published in compliance with revised timelines.

## 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 | |

**Results information**

| | |
|---|---|
| Result version number | v1 |
| This version publication date | 17 July 2016 |
| First version publication date | 17 July 2016 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | BAY94-9027/15912 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01775618 |
| WHO universal trial number (UTN) | - |

Notes:

**Sponsors**

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

Notes:

**Paediatric regulatory details**

| | |
|---|---|
| Is trial part of an agreed paediatric investigation plan (PIP) | Yes |
| EMA paediatric investigation plan number(s) | EMEA-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 | Interim |
| Date of interim/final analysis | 19 March 2015 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 19 March 2015 |
| Global end of trial reached? | 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 | 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: 5 |
| Country: Number of subjects enrolled | United States: 12 |
| Country: Number of subjects enrolled | Romania: 4 |
| Country: Number of subjects enrolled | United Kingdom: 8 |
| Worldwide total number of subjects | 61 |
| EEA total number of subjects | 40 |

Notes:

| Subjects enrolled per age group | |
|---|---|
| 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) | 61 |
| 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 study was conducted at 31 centers that enrolled subjects across 13 countries, between 29 May 2013 (first subject first visit) and 19 March 2015 (last subject last visit).

### Pre-assignment

Screening details:

Overall 65 subjects were screened, of them 3 subjects initially failed screening but successfully re-screened and resulting in 68 subjects and 61 subjects were allocated to treatment.

### Period 1

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

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Age group less than (<) 6 years |

Arm description:

Subjects with age group <6 years were treated and prophylaxis administered with BAY94-9027 at a dose of 25-60 international units/kilogram (IU/kg)/administration 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 (ED) and a minimum of at least 6 months.

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

Dosage and administration details:

Subjects received a dose of 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 exposure days (ED) and a minimum of at least 6 months.

| | |
|---|---|
| **Arm title** | Age group 6 to <12 years |

Arm description:

Subjects with age group 6 to <12 years were treated and prophylaxis administered with BAY94-9027 at a dose of 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 ED and a minimum of at least 6 months.

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

Dosage and administration details:

Subjects received a dose of 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 exposure days (ED) and a minimum of at least 6 months.

| **Number of subjects in period 1** | Age group less than (<) 6 years | Age group 6 to <12 years |
|---|---|---|
| Started | 32 | 29 |
| Completed | 25 | 28 |
| Not completed | 7 | 1 |
| Adverse event, non-fatal | 6 | 1 |
| Withdrawal by parent/guardian | 1 | - |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Age group less than (<) 6 years |
| Reporting group description: | |
| Subjects with age group <6 years were treated and prophylaxis administered with BAY94-9027 at a dose of 25-60 international units/kilogram (IU/kg)/administration 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 (ED) and a minimum of at least 6 months. | |
| Reporting group title | Age group 6 to <12 years |
| Reporting group description: | |
| Subjects with age group 6 to <12 years were treated and prophylaxis administered with BAY94-9027 at a dose of 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 ED and a minimum of at least 6 months. | |

| Reporting group values | Age group less than (<) 6 years | Age group 6 to <12 years | Total |
|---|---|---|---|
| Number of subjects | 32 | 29 | 61 |
| Age categorical<br>Units: Subjects | | | |
| Children (2-11 years) | 32 | 29 | 61 |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 3.5 | 8.6 | |
| standard deviation | ± 1 | ± 1.5 | - |
| Gender categorical<br>Units: Subjects | | | |
| Female | 0 | 0 | 0 |
| Male | 32 | 29 | 61 |

## End points

### End points reporting groups

| Reporting group title | Age group less than (<) 6 years |
|---|---|

Reporting group description:

Subjects with age group <6 years were treated and prophylaxis administered with BAY94-9027 at a dose of 25-60 international units/kilogram (IU/kg)/administration 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 (ED) and a minimum of at least 6 months.

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

Reporting group description:

Subjects with age group 6 to <12 years were treated and prophylaxis administered with BAY94-9027 at a dose of 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 ED and a minimum of at least 6 months.

| Subject analysis set title | Safety Analysis Set (SAF)-Main part |
|---|---|
| Subject analysis set type | Safety analysis |

Subject analysis set description:

SAF included all subjects who enrolled into the main part of the study and who received at least one dose of study medication.

| Subject analysis set title | Intent-to-treat (ITT)-Analysis set Main part |
|---|---|
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

ITT included all safety subjects who had infusion/bleeding data from the Electronic Patient Diary (EPD).

| Subject analysis set title | Pharmacokinetic (PK) Analysis Set (PKS) |
|---|---|
| Subject analysis set type | Per protocol |

Subject analysis set description:

All subjects with a valid profile of BAY94-9027 were included in the analysis of PK data.

### Primary: Annualized Number of Total Bleeds

| End point title | Annualized Number of Total Bleeds[1] |
|---|---|

End point description:

The annualized number of total bleeds included sum of all spontaneous bleeds and traumatic bleeds during prophylactic treatment, assessment of PK, and assessment of response to treatment of bleeds. 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 outcome measure.

| End point values | Age group less than (<) 6 years | Age group 6 to <12 years | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 32[2] | 28[3] | | |
| Units: Bleeds | | | | |
| median (inter-quartile range (Q1-Q3)) | | | | |
| Overall Bleeds | 2.68 (1.08 to 6.79) | 2.92 (0 to 6.66) | | |

Notes:

[2] - ITT with evaluable subjects for this endpoint.

[3] - ITT with evaluable subjects for this endpoint.

## 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[4] |
|---|---|

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:

[4] - 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 outcome measure.

| **End point values** | Age group less than (<) 6 years | Age group 6 to <12 years | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 15[5] | 15[6] | | |
| Units: IU/dL | | | | |
| geometric mean (standard deviation) | 110.9 (± 1.33) | 127 (± 1.21) | | |

Notes:

[5] - PKS with evaluable subjects for this endpoint.

[6] - PKS with evaluable subjects for this endpoint.

## Statistical analyses

No statistical analyses for this end point

## Primary: Half Life Associated With the Terminal Slope (t1/2) in Plasma of BAY94-9027

| End point title | Half Life Associated With the Terminal Slope (t1/2) in Plasma of BAY94-9027[7] |
|---|---|

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:

[7] - 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 outcome measure.

| End point values | Age group less than (<) 6 years | Age group 6 to <12 years | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 16[8] | 16[9] | | |
| Units: hour | | | | |
| geometric mean (standard deviation) | 14.1 (± 1.39) | 15.8 (± 1.25) | | |

Notes:

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

[9] - PKS 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[10] |
|---|---|

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:

[10] - 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 outcome measure.

| End point values | Age group less than (<) 6 years | Age group 6 to <12 years | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 15[11] | 13[12] | | |
| Units: IU*h/dL | | | | |
| geometric mean (standard deviation) | 1804.3 (± 1.94) | 2837.03 (± 1.21) | | |

Notes:

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

[12] - PKS 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[13] |
|---|---|

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:

[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 outcome measure.

| **End point values** | Age group less than (<) 6 years | Age group 6 to <12 years | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 16[14] | 14[15] | | |
| Units: hour | | | | |
| geometric mean (standard deviation) | 19.1 (± 1.42) | 23.7 (± 1.25) | | |

Notes:

[14] - PKS with evaluable subjects for this endpoint.

[15] - PKS 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[16] |
|---|---|

End point description:

Apparent volume of distribution at steady state after intravascular administration (Vss) of BAY949027. 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:

[16] - 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 outcome measure.

| **End point values** | Age group less than (<) 6 years | Age group 6 to <12 years | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 16[17] | 14[18] | | |
| Units: Deciliter per kilogram (dL/kg) | | | | |
| geometric mean (standard deviation) | 0.62 (± 1.48) | 0.49 (± 1.2) | | |

Notes:

[17] - PKS with evaluable subjects for this endpoint.

[18] - PKS 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[19] |
|---|---|

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:

[19] - 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 outcome measure.

| **End point values** | Age group less than (<) 6 years | Age group 6 to <12 years | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 16[20] | 14[21] | | |
| Units: Deciliter per hour per kilogram[dL/h/kg) | | | | |
| geometric mean (standard deviation) | 0.032 (± 1.94) | 0.021 (± 1.22) | | |

Notes:

[20] - PKS with evaluable subjects for this endpoint.

[21] - PKS 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[22] |
|---|---|

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:

[22] - 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 outcome measure.

| **End point values** | Age group less than (<) 6 years | Age group 6 to <12 years | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 32[23] | 28[24] | | |
| Units: Number of bleed | | | | |
| Excellent | 29 | 26 | | |
| Good | 34 | 31 | | |
| Moderate | 6 | 9 | | |
| Poor | 3 | 2 | | |

Notes:

[23] - ITT

[24] - ITT

## Statistical analyses

No statistical analyses for this end point

## Primary: Number of Subjects With Development of Clinically Significant Levels of Inhibitory Antibodies to FVIII

| End point title | Number of Subjects With Development of Clinically Significant Levels of Inhibitory Antibodies to FVIII[25] |
|---|---|

End point description:

Subjects were monitored for the development of inhibitory antibodies to FVIII.

| 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 outcome measure.

| **End point values** | Age group less than (<) 6 years | Age group 6 to <12 years | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0[26] | 0[27] | | |
| Units: Subjects | | | | |

Notes:

[26] - Data was not available since the expansion phase of study is ongoing.

[27] - Data was not available since the expansion phase of study is ongoing.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Subjects With Inhibitor Development After 10 to 15 and 50 Exposure Days

| End point title | Number of Subjects With Inhibitor Development After 10 to 15 and 50 Exposure Days |
|---|---|

End point description:

Subject were evaluated for positive FVIII inhibitor level (>=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.

| End point values | Age group less than (<) 6 years | Age group 6 to <12 years | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 32 | 29 | | |
| Units: Subjects | 0 | 0 | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Assessment of Incremental Recovery

| End point title | Assessment of Incremental Recovery |
|---|---|

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 final visit of the extension study, (a minimum total of 100 ED)

| End point values | Age group less than (<) 6 years | Age group 6 to <12 years | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 32[28] | 28[29] | | |
| Units: Recovery values | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline (N= 32, 28) | 1.698 (± 0.58) | 1.941 (± 0.53) | | |
| Month 1 (N= 1, 3) | 2.326 (± 99999) | 6.416 (± 7.85) | | |
| Month 2 (N= 1, 1) | 1.991 (± 99999) | 2.261 (± 99999) | | |
| Month 3 (N= 22, 26) | 1.843 (± 0.53) | 2.277 (± 0.7) | | |
| Month 6 (N= 22, 27) | 2.227 (± 0.58) | 2.33 (± 0.67) | | |

Notes:

[28] - ITT

[29] - ITT

## 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.

Adverse event reporting additional description:

Actually the investigator suspected that the subject has anti FVIII inhibitor development, without any lab test support. The test came back to show that the antibody is negative.

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

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 17.1 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Age group Less than [<] 6 years |

Reporting group description:

Subjects with age group <6 years were treated and prophylaxis administered with BAY94-9027 at a dose of 25-60 international units/kilogram (IU/kg)/administration 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 (ED) and a minimum of at least 6 months.

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

Reporting group description:

Subjects with age group 6 to <12 years were treated and prophylaxis administered with BAY94-9027 at a dose of 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 ED and a minimum of at least 6 months.

| Serious adverse events | Age group Less than [<] 6 years | Age group 6 to <12 years | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 8 / 32 (25.00%) | 3 / 29 (10.34%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Investigations | | | |
| Anti factor VIII antibody positive | | | |
| subjects affected / exposed | 1 / 32 (3.13%) | 0 / 29 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Drug specific antibody present | | | |
| subjects affected / exposed | 3 / 32 (9.38%) | 0 / 29 (0.00%) | |
| occurrences causally related to treatment / all | 5 / 5 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Red blood cells CSF positive | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 32 (0.00%) | 1 / 29 (3.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Subcutaneous haematoma | | | |
| subjects affected / exposed | 1 / 32 (3.13%) | 0 / 29 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Surgical and medical procedures | | | |
| Catheter management | | | |
| subjects affected / exposed | 1 / 32 (3.13%) | 0 / 29 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Central venous catheterisation | | | |
| subjects affected / exposed | 1 / 32 (3.13%) | 0 / 29 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Haemorrhage intracranial | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 1 / 29 (3.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Headache | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 1 / 29 (3.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Catheter site swelling | | | |
| subjects affected / exposed | 1 / 32 (3.13%) | 0 / 29 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Device connection issue | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 32 (0.00%) | 1 / 29 (3.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Immune system disorders | | | |
| Hypersensitivity | | | |
| subjects affected / exposed | 1 / 32 (3.13%) | 1 / 29 (3.45%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Drug hypersensitivity | | | |
| subjects affected / exposed | 1 / 32 (3.13%) | 0 / 29 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eye disorders | | | |
| Photophobia | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 1 / 29 (3.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Nausea | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 1 / 29 (3.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 1 / 29 (3.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Staphylococcal infection | | | |
| subjects affected / exposed | 1 / 32 (3.13%) | 0 / 29 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

Frequency threshold for reporting non-serious adverse events: 0 %

| **Non-serious adverse events** | Age group Less than [<] 6 years | Age group 6 to <12 years | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 27 / 32 (84.38%) | 20 / 29 (68.97%) | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Haemangioma of skin | | | |
| subjects affected / exposed | 1 / 32 (3.13%) | 0 / 29 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Vascular disorders | | | |
| Haematoma | | | |
| subjects affected / exposed | 2 / 32 (6.25%) | 0 / 29 (0.00%) | |
| occurrences (all) | 16 | 0 | |
| Vascular rupture | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 1 / 29 (3.45%) | |
| occurrences (all) | 0 | 1 | |
| Pregnancy, puerperium and perinatal conditions | | | |
| Perineal haematoma | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 1 / 32 (3.13%) | 0 / 29 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| General disorders and administration site conditions | | | |
| Chills | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 1 / 29 (3.45%) | |
| occurrences (all) | 0 | 1 | |
| Chest pain | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 1 / 29 (3.45%) | |
| occurrences (all) | 0 | 1 | |
| Device malfunction | | | |
| subjects affected / exposed | 1 / 32 (3.13%) | 0 / 29 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Oedema | | | |
| subjects affected / exposed | 1 / 32 (3.13%) | 0 / 29 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Mass | | | |
| subjects affected / exposed | 2 / 32 (6.25%) | 0 / 29 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Pain | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 32 (0.00%) | 1 / 29 (3.45%) | |
| occurrences (all) | 0 | 1 | |
| Pyrexia | | | |
| subjects affected / exposed | 7 / 32 (21.88%) | 2 / 29 (6.90%) | |
| occurrences (all) | 9 | 4 | |
| Peripheral swelling | | | |
| subjects affected / exposed | 1 / 32 (3.13%) | 0 / 29 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Vessel puncture site pruritus | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 1 / 29 (3.45%) | |
| occurrences (all) | 0 | 1 | |
| Immune system disorders | | | |
| Allergy to arthropod bite | | | |
| subjects affected / exposed | 1 / 32 (3.13%) | 0 / 29 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Seasonal allergy | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 1 / 29 (3.45%) | |
| occurrences (all) | 0 | 1 | |
| Hypersensitivity | | | |
| subjects affected / exposed | 1 / 32 (3.13%) | 0 / 29 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 1 / 32 (3.13%) | 5 / 29 (17.24%) | |
| occurrences (all) | 1 | 5 | |
| Epistaxis | | | |
| subjects affected / exposed | 3 / 32 (9.38%) | 4 / 29 (13.79%) | |
| occurrences (all) | 5 | 9 | |
| Cough | | | |
| subjects affected / exposed | 5 / 32 (15.63%) | 1 / 29 (3.45%) | |
| occurrences (all) | 5 | 1 | |
| Productive cough | | | |
| subjects affected / exposed | 1 / 32 (3.13%) | 0 / 29 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Asthma | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 32 (3.13%) | 0 / 29 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Respiratory disorder | | | |
| subjects affected / exposed | 1 / 32 (3.13%) | 0 / 29 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Psychiatric disorders | | | |
| Insomnia | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 1 / 29 (3.45%) | |
| occurrences (all) | 0 | 1 | |
| Abnormal behaviour | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 1 / 29 (3.45%) | |
| occurrences (all) | 0 | 1 | |
| Injury, poisoning and procedural complications | | | |
| Arthropod bite | | | |
| subjects affected / exposed | 2 / 32 (6.25%) | 0 / 29 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Arthropod sting | | | |
| subjects affected / exposed | 1 / 32 (3.13%) | 0 / 29 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Bone contusion | | | |
| subjects affected / exposed | 1 / 32 (3.13%) | 0 / 29 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Back injury | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 1 / 29 (3.45%) | |
| occurrences (all) | 0 | 1 | |
| Chest injury | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 1 / 29 (3.45%) | |
| occurrences (all) | 0 | 1 | |
| Contusion | | | |
| subjects affected / exposed | 6 / 32 (18.75%) | 2 / 29 (6.90%) | |
| occurrences (all) | 6 | 2 | |
| Fall | | | |
| subjects affected / exposed | 3 / 32 (9.38%) | 0 / 29 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Gingival injury | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 32 (3.13%) | 0 / 29 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Injury | | | |
| subjects affected / exposed | 1 / 32 (3.13%) | 0 / 29 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Head injury | | | |
| subjects affected / exposed | 2 / 32 (6.25%) | 0 / 29 (0.00%) | |
| occurrences (all) | 4 | 0 | |
| Joint injury | | | |
| subjects affected / exposed | 1 / 32 (3.13%) | 0 / 29 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Laceration | | | |
| subjects affected / exposed | 1 / 32 (3.13%) | 0 / 29 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Ligament sprain | | | |
| subjects affected / exposed | 2 / 32 (6.25%) | 0 / 29 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Limb crushing injury | | | |
| subjects affected / exposed | 1 / 32 (3.13%) | 0 / 29 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Limb injury | | | |
| subjects affected / exposed | 1 / 32 (3.13%) | 0 / 29 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Lip injury | | | |
| subjects affected / exposed | 1 / 32 (3.13%) | 0 / 29 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Mouth injury | | | |
| subjects affected / exposed | 1 / 32 (3.13%) | 0 / 29 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Skin injury | | | |
| subjects affected / exposed | 1 / 32 (3.13%) | 0 / 29 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Post-traumatic pain | | | |
| subjects affected / exposed | 2 / 32 (6.25%) | 0 / 29 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Skin wound | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 32 (3.13%) | 0 / 29 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Traumatic haemorrhage | | | |
| subjects affected / exposed | 1 / 32 (3.13%) | 0 / 29 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Subcutaneous haematoma | | | |
| subjects affected / exposed | 2 / 32 (6.25%) | 0 / 29 (0.00%) | |
| occurrences (all) | 12 | 0 | |
| Wound secretion | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 1 / 29 (3.45%) | |
| occurrences (all) | 0 | 1 | |
| Wound | | | |
| subjects affected / exposed | 2 / 32 (6.25%) | 0 / 29 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Nervous system disorders | | | |
| Dysgeusia | | | |
| subjects affected / exposed | 1 / 32 (3.13%) | 0 / 29 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Psychomotor hyperactivity | | | |
| subjects affected / exposed | 1 / 32 (3.13%) | 0 / 29 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Headache | | | |
| subjects affected / exposed | 2 / 32 (6.25%) | 6 / 29 (20.69%) | |
| occurrences (all) | 2 | 8 | |
| Tongue biting | | | |
| subjects affected / exposed | 1 / 32 (3.13%) | 0 / 29 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Blood and lymphatic system disorders | | | |
| Spontaneous haemorrhage | | | |
| subjects affected / exposed | 1 / 32 (3.13%) | 0 / 29 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Spontaneous haematoma | | | |
| subjects affected / exposed | 1 / 32 (3.13%) | 0 / 29 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Ear and labyrinth disorders | | | |

| | | | |
|---|---|---|---|
| Cerumen impaction | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 1 / 29 (3.45%) | |
| occurrences (all) | 0 | 2 | |
| Ear discomfort | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 1 / 29 (3.45%) | |
| occurrences (all) | 0 | 1 | |
| Ear pain | | | |
| subjects affected / exposed | 1 / 32 (3.13%) | 0 / 29 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Tinnitus | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 1 / 29 (3.45%) | |
| occurrences (all) | 0 | 1 | |
| Eye disorders | | | |
| Eye swelling | | | |
| subjects affected / exposed | 1 / 32 (3.13%) | 0 / 29 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 1 / 29 (3.45%) | |
| occurrences (all) | 0 | 1 | |
| Haemorrhoids | | | |
| subjects affected / exposed | 1 / 32 (3.13%) | 0 / 29 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Diarrhoea | | | |
| subjects affected / exposed | 4 / 32 (12.50%) | 2 / 29 (6.90%) | |
| occurrences (all) | 4 | 2 | |
| Constipation | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 1 / 29 (3.45%) | |
| occurrences (all) | 0 | 2 | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 3 / 29 (10.34%) | |
| occurrences (all) | 0 | 3 | |
| Mouth haemorrhage | | | |
| subjects affected / exposed | 1 / 32 (3.13%) | 0 / 29 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Tooth loss | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 32 (3.13%) | 0 / 29 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Tongue haematoma | | | |
| subjects affected / exposed | 1 / 32 (3.13%) | 0 / 29 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Toothache | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 1 / 29 (3.45%) | |
| occurrences (all) | 0 | 1 | |
| Vomiting | | | |
| subjects affected / exposed | 2 / 32 (6.25%) | 3 / 29 (10.34%) | |
| occurrences (all) | 2 | 3 | |
| Skin and subcutaneous tissue disorders | | | |
| Dry skin | | | |
| subjects affected / exposed | 1 / 32 (3.13%) | 1 / 29 (3.45%) | |
| occurrences (all) | 1 | 1 | |
| Ecchymosis | | | |
| subjects affected / exposed | 2 / 32 (6.25%) | 1 / 29 (3.45%) | |
| occurrences (all) | 2 | 1 | |
| Erythema | | | |
| subjects affected / exposed | 1 / 32 (3.13%) | 0 / 29 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Eczema | | | |
| subjects affected / exposed | 1 / 32 (3.13%) | 0 / 29 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Scab | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 1 / 29 (3.45%) | |
| occurrences (all) | 0 | 2 | |
| Rash papular | | | |
| subjects affected / exposed | 1 / 32 (3.13%) | 0 / 29 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Rash | | | |
| subjects affected / exposed | 3 / 32 (9.38%) | 1 / 29 (3.45%) | |
| occurrences (all) | 4 | 2 | |
| Pruritus | | | |
| subjects affected / exposed | 1 / 32 (3.13%) | 0 / 29 (0.00%) | |
| occurrences (all) | 2 | 0 | |

| | | | |
|---|---|---|---|
| Skin swelling | | | |
| subjects affected / exposed | 1 / 32 (3.13%) | 0 / 29 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Skin irritation | | | |
| subjects affected / exposed | 2 / 32 (6.25%) | 0 / 29 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Skin haemorrhage | | | |
| subjects affected / exposed | 1 / 32 (3.13%) | 1 / 29 (3.45%) | |
| occurrences (all) | 1 | 1 | |
| Musculoskeletal and connective tissue disorders | | | |
| Haemarthrosis | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 1 / 29 (3.45%) | |
| occurrences (all) | 0 | 1 | |
| Arthralgia | | | |
| subjects affected / exposed | 1 / 32 (3.13%) | 3 / 29 (10.34%) | |
| occurrences (all) | 1 | 3 | |
| Musculoskeletal discomfort | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 1 / 29 (3.45%) | |
| occurrences (all) | 0 | 1 | |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 1 / 29 (3.45%) | |
| occurrences (all) | 0 | 1 | |
| Metatarsalgia | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 1 / 29 (3.45%) | |
| occurrences (all) | 0 | 1 | |
| Pain in extremity | | | |
| subjects affected / exposed | 3 / 32 (9.38%) | 3 / 29 (10.34%) | |
| occurrences (all) | 3 | 4 | |
| Joint swelling | | | |
| subjects affected / exposed | 1 / 32 (3.13%) | 0 / 29 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Infections and infestations | | | |
| Cellulitis | | | |
| subjects affected / exposed | 1 / 32 (3.13%) | 0 / 29 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Bronchitis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 32 (3.13%) | 0 / 29 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Ear infection | | | |
| subjects affected / exposed | 1 / 32 (3.13%) | 1 / 29 (3.45%) | |
| occurrences (all) | 2 | 1 | |
| Conjunctivitis | | | |
| subjects affected / exposed | 1 / 32 (3.13%) | 0 / 29 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Febrile infection | | | |
| subjects affected / exposed | 1 / 32 (3.13%) | 0 / 29 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Gastroenteritis | | | |
| subjects affected / exposed | 2 / 32 (6.25%) | 3 / 29 (10.34%) | |
| occurrences (all) | 2 | 3 | |
| Gastroenteritis viral | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 1 / 29 (3.45%) | |
| occurrences (all) | 0 | 1 | |
| Gingivitis | | | |
| subjects affected / exposed | 1 / 32 (3.13%) | 0 / 29 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Influenza | | | |
| subjects affected / exposed | 1 / 32 (3.13%) | 0 / 29 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Molluscum contagiosum | | | |
| subjects affected / exposed | 1 / 32 (3.13%) | 0 / 29 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 5 / 32 (15.63%) | 1 / 29 (3.45%) | |
| occurrences (all) | 8 | 1 | |
| Pharyngotonsillitis | | | |
| subjects affected / exposed | 1 / 32 (3.13%) | 0 / 29 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Pharyngitis streptococcal | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 1 / 29 (3.45%) | |
| occurrences (all) | 0 | 1 | |
| Rhinitis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 3 / 32 (9.38%) | 0 / 29 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Tinea infection | | | |
| subjects affected / exposed | 1 / 32 (3.13%) | 0 / 29 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Sinusitis | | | |
| subjects affected / exposed | 1 / 32 (3.13%) | 1 / 29 (3.45%) | |
| occurrences (all) | 2 | 1 | |
| Varicella | | | |
| subjects affected / exposed | 2 / 32 (6.25%) | 1 / 29 (3.45%) | |
| occurrences (all) | 2 | 1 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 6 / 32 (18.75%) | 1 / 29 (3.45%) | |
| occurrences (all) | 6 | 1 | |
| Tracheitis | | | |
| subjects affected / exposed | 1 / 32 (3.13%) | 0 / 29 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Tonsillitis | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 2 / 29 (6.90%) | |
| occurrences (all) | 0 | 2 | |
| Viral infection | | | |
| subjects affected / exposed | 1 / 32 (3.13%) | 3 / 29 (10.34%) | |
| occurrences (all) | 1 | 3 | |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 18 June 2013 | The main purpose of this amendment was the addition of a more structured approach to increasing the dose or dose frequency if breakthrough bleeds occurred and a visit window of plus or minus 1 week was added to the extension visits. In addition, the following clarifications were made: references to incremental recovery were removed when they were redundant; the amount of time after reconstitution that the drug product must be used was corrected; the timing of collection of one of the Work Productivity and Activity Impairment (WPAI) assessments was corrected; the protocol for inhibitor testing was clarified; a reference to an integrated subject/parent information sheet and informed consent form was corrected. Finally, editorial changes, correction of typographical errors, and minor revisions of language were made to ensure clarity and consistency throughout the document. |
| 12 August 2014 | The primary purpose of this Amendment was to update the protocol in response to adverse events that have been observed in study performance. |

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: