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)	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	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:

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)	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
Arm title	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.

Arm title	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.

Arm title	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.

Number of subjects in period 1	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

Arm title	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[1]	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 Units: Subjects			
Children (2-11 years)	32	29	12
Age continuous Units: years			
arithmetic mean	3.5	8.6	3.5
standard deviation	± 1.0	± 1.5	± 1.24
Gender categorical Units: Subjects			
Female	0	0	0
Male	32	29	12

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

End points

End points 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.	
Subject analysis set title	Safety Analysis Set (SAF) - Main study
Subject analysis set type	Safety analysis
Subject analysis set description:	
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:	
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:	
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:	
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:	
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[1][2]
End point description:	
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[3]	28[4]		
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[5][6]

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[7]	15[8]		
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 (t1/2) in plasma of BAY94-9027

End point title	Half-life associated with the terminal slope (t1/2) in plasma of BAY94-9027[9][10]

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[11]	16[12]		
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[13][14]

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[15]	13[16]		
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[17][18]

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[19]	14[20]		
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[21][22]

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:

[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[23]	14[24]		
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[25][26]

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[27]	14[28]		
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[29][30]

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[31]	28[32]		
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: Expansion group <6 years			
Subject group type	Reporting group			
Number of subjects analysed	12[35]			
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[36][37]

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.

End point values	Part 2: Expansion group <6 years			
Subject group type	Reporting group			
Number of subjects analysed	6[38]			
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[39][40]

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.

End point values	Part 2: Expansion group <6 years			
Subject group type	Reporting group			
Number of subjects analysed	4[41]			
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[42][43]

End point description:

Subject in Part 2 were evaluated for positive FVIII inhibitor level (>=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.

End point values	Part 2: Expansion group <6 years			
Subject group type	Reporting group			
Number of subjects analysed	12[44]			
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[45]

End point description:

Subject in Part 2 were evaluated for positive FVIII inhibitor level (>=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.

End point values	Extension: Age group <12 years			
Subject group type	Reporting group			
Number of subjects analysed	59[46]			
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 (>=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[48]	29[49]		
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[50]

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[51]	28[52]		
Units: Kilogram/deciliter (kg/dL)				
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:
[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 %

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

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

Seasonal allergy subjects affected / exposed occurrences (all)	4 / 59 (6.78%) 4		
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all)	8 / 59 (13.56%) 13		
Abdominal pain upper subjects affected / exposed occurrences (all)	3 / 59 (5.08%) 4		
Dental caries subjects affected / exposed occurrences (all)	3 / 59 (5.08%) 4		
Diarrhoea subjects affected / exposed occurrences (all)	7 / 59 (11.86%) 14		
Gingival bleeding subjects affected / exposed occurrences (all)	5 / 59 (8.47%) 7		
Loose tooth subjects affected / exposed occurrences (all)	3 / 59 (5.08%) 4		
Nausea subjects affected / exposed occurrences (all)	7 / 59 (11.86%) 9		
Vomiting subjects affected / exposed occurrences (all)	12 / 59 (20.34%) 21		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	16 / 59 (27.12%) 30		
Epistaxis subjects affected / exposed occurrences (all)	16 / 59 (27.12%) 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			
subjects affected / exposed	5 / 59 (8.47%)		
occurrences (all)	7		
Pneumonia			
subjects affected / exposed	4 / 59 (6.78%)		
occurrences (all)	4		
Rhinitis			
subjects affected / exposed	9 / 59 (15.25%)		
occurrences (all)	11		
Sinusitis			
subjects affected / exposed	5 / 59 (8.47%)		
occurrences (all)	13		
Tonsillitis			
subjects affected / exposed	7 / 59 (11.86%)		
occurrences (all)	9		
Upper respiratory tract infection			
subjects affected / exposed	9 / 59 (15.25%)		
occurrences (all)	16		
Varicella			
subjects affected / exposed	4 / 59 (6.78%)		
occurrences (all)	4		
Viral infection			
subjects affected / exposed	4 / 59 (6.78%)		
occurrences (all)	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 had been suspected to be associated with the development of antibodies to BAY 94-9027. These events were now to be identified in this studydefined 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