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	

Results information

Result version number	v2
This version publication date	19 August 2016
First version publication date	17 July 2016
Version creation reason	• New data added to full data set AE threshold changed

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 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	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
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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			
Units: Subjects			
Children (2-11 years)	32	29	61
Age continuous			
Units: years			
arithmetic mean	3.5	8.6	
standard deviation	± 1	± 1.5	-
Gender categorical			
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 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 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.

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

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

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

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

Non-serious adverse events	Age group 6 to <12 years	Age group Less than [<] 6 years	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	18 / 29 (62.07%)	24 / 32 (75.00%)	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	2 / 29 (6.90%)	6 / 32 (18.75%)	
occurrences (all)	2	6	
Arthropod bite			
subjects affected / exposed	0 / 29 (0.00%)	2 / 32 (6.25%)	
occurrences (all)	0	2	
Fall			
subjects affected / exposed	0 / 29 (0.00%)	3 / 32 (9.38%)	
occurrences (all)	0	3	
Post-traumatic pain			
subjects affected / exposed	0 / 29 (0.00%)	2 / 32 (6.25%)	
occurrences (all)	0	2	
Ligament sprain			
subjects affected / exposed	0 / 29 (0.00%)	2 / 32 (6.25%)	
occurrences (all)	0	2	
Head injury			
subjects affected / exposed	0 / 29 (0.00%)	2 / 32 (6.25%)	
occurrences (all)	0	4	
Subcutaneous haematoma			
subjects affected / exposed	0 / 29 (0.00%)	2 / 32 (6.25%)	
occurrences (all)	0	12	
Wound			
subjects affected / exposed	0 / 29 (0.00%)	2 / 32 (6.25%)	
occurrences (all)	0	2	
Vascular disorders			
Haematoma			
subjects affected / exposed	0 / 29 (0.00%)	2 / 32 (6.25%)	
occurrences (all)	0	16	
Nervous system disorders			
Headache			
subjects affected / exposed	6 / 29 (20.69%)	2 / 32 (6.25%)	
occurrences (all)	8	2	

General disorders and administration site conditions			
Mass			
subjects affected / exposed	0 / 29 (0.00%)	2 / 32 (6.25%)	
occurrences (all)	0	2	
Pyrexia			
subjects affected / exposed	2 / 29 (6.90%)	7 / 32 (21.88%)	
occurrences (all)	4	9	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	3 / 29 (10.34%)	2 / 32 (6.25%)	
occurrences (all)	3	2	
Diarrhoea			
subjects affected / exposed	2 / 29 (6.90%)	4 / 32 (12.50%)	
occurrences (all)	2	4	
Abdominal pain upper			
subjects affected / exposed	3 / 29 (10.34%)	0 / 32 (0.00%)	
occurrences (all)	3	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 29 (3.45%)	5 / 32 (15.63%)	
occurrences (all)	1	5	
Epistaxis			
subjects affected / exposed	4 / 29 (13.79%)	3 / 32 (9.38%)	
occurrences (all)	9	5	
Oropharyngeal pain			
subjects affected / exposed	5 / 29 (17.24%)	1 / 32 (3.13%)	
occurrences (all)	5	1	
Skin and subcutaneous tissue disorders			
Ecchymosis			
subjects affected / exposed	1 / 29 (3.45%)	2 / 32 (6.25%)	
occurrences (all)	1	2	
Rash			
subjects affected / exposed	1 / 29 (3.45%)	3 / 32 (9.38%)	
occurrences (all)	2	4	
Skin irritation			

subjects affected / exposed	0 / 29 (0.00%)	2 / 32 (6.25%)	
occurrences (all)	0	2	
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	3 / 29 (10.34%)	3 / 32 (9.38%)	
occurrences (all)	4	3	
Arthralgia			
subjects affected / exposed	3 / 29 (10.34%)	1 / 32 (3.13%)	
occurrences (all)	3	1	
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	3 / 29 (10.34%)	2 / 32 (6.25%)	
occurrences (all)	3	2	
Nasopharyngitis			
subjects affected / exposed	1 / 29 (3.45%)	5 / 32 (15.63%)	
occurrences (all)	1	8	
Rhinitis			
subjects affected / exposed	0 / 29 (0.00%)	3 / 32 (9.38%)	
occurrences (all)	0	3	
Tonsillitis			
subjects affected / exposed	2 / 29 (6.90%)	0 / 32 (0.00%)	
occurrences (all)	2	0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 29 (3.45%)	6 / 32 (18.75%)	
occurrences (all)	1	6	
Varicella			
subjects affected / exposed	1 / 29 (3.45%)	2 / 32 (6.25%)	
occurrences (all)	1	2	
Viral infection			
subjects affected / exposed	3 / 29 (10.34%)	1 / 32 (3.13%)	
occurrences (all)	3	1	

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: