Clinical trial results:
BAX326 (recombinant Factor IX): Evaluation of Safety, Immunogenicity, and Hemostatic Efficacy in Previously Treated Patients with Severe (FIX level < 1%) or Moderately Severe (FIX level 1-2 %) Hemophilia B - A Continuation Study

Summary

EudraCT number	2010-022726-33
Trial protocol	BG CZ GB DE SE PL ES IT IE
Global end of trial date	29 June 2017

Results information

Result version number	v1 (current)
This version publication date	05 January 2018
First version publication date	05 January 2018

Trial information

Trial identification

Sponsor protocol code	251001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01286779
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Baxalta, now part of Shire
Sponsor organisation address	Industriestrasse 67, Vienna, Austria, 1221
Public contact	Study Physician, Baxalta, now part of Shire, ClinicalTransparency@shire.com
Scientific contact	Study Physician, Baxalta, now part of Shire, ClinicalTransparency@shire.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001139-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	29 June 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 June 2017
Global end of trial reached?	Yes
Global end of trial date	29 June 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Further evaluate safety of BAX326 in terms of IP-related AEs as well as clinically significant changes in routine laboratory parameters and vital signs. Further evaluate the hemostatic efficacy of BAX326 in the prevention and routine prophylaxis of acute bleeding episodes using various dose regimens. Further evaluate the hemostatic efficacy of BAX326 in the management of acute bleeding episodes. Further evaluate the immunogenicity of BAX326 for up to 100 exposure days to BAX326. Monitor IR of BAX326 over time. Evaluate changes in health related quality of life (HR QoL), patient activity level and health resource use.

Protection of trial subjects:

This study was conducted in accordance with the study protocol, the International Conference on Harmonisation Guideline for Good Clinical Practice E6 (ICH GCP, April 1996), Title 21 of the US Code of Federal Regulations (US CFR), the European Clinical Trial Directive (2001/20/EC and 2005/28/EC), and applicable national and local regulatory requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	12 April 2011
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	Bulgaria: 10
Country: Number of subjects enrolled	Czech Republic: 2
Country: Number of subjects enrolled	Ireland: 2
Country: Number of subjects enrolled	Italy: 4
Country: Number of subjects enrolled	Poland: 22
Country: Number of subjects enrolled	Romania: 12
Country: Number of subjects enrolled	Sweden: 1
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	India: 1
Country: Number of subjects enrolled	Japan: 3
Country: Number of subjects enrolled	Korea, Republic of: 1
Country: Number of subjects enrolled	Taiwan: 6
Country: Number of subjects enrolled	Argentina: 2
Country: Number of subjects enrolled	Brazil: 1
Country: Number of subjects enrolled	Chile: 5
Country: Number of subjects enrolled	Colombia: 4

Country: Number of subjects enrolled	Russian Federation: 18
Country: Number of subjects enrolled	Ukraine: 21
Worldwide total number of subjects	117
EEA total number of subjects	55

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)	21
Adolescents (12-17 years)	5
Adults (18-64 years)	89
From 65 to 84 years	2
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Enrollment was conducted at 40 clinical sites in 18 countries. A total of 117 participants were enrolled. Of these, 65 participants transitioned from BAX326 pivotal study, 20 participants transitioned from BAX326 pediatric study and 32 participant were newly recruited.

Pre-assignment

Screening details:

Of 117 enrolled participants, 115 received treatment with IP. All 85 participants who transitioned from the pivotal/pediatric studies continued to receive IP in this study. Of the 32 newly recruited participants, 30 received treatment with IP. 1 participant did not meet the entry criteria and 1 participant discontinued the study prior treatment.

Pre-assignment period milestones

Number of subjects started	117
Number of subjects completed	115

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Subject discontinued the study prior treatment: 1
Reason: Number of subjects	Screen failure: 1

Period 1

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

Arms

Arm title	Overall study

Arm description:

Participants treated with BAX 326

Arm type	Experimental
Investigational medicinal product name	Rixubis
Investigational medicinal product code	BAX 326
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Treatment with BAX326 is at the discretion of the investigator and consists of either prophylaxis or on-demand. Newly recruited subjects receive prophylactic treatment only. Standard Prophylaxis with twice weekly infusions of 50 IU/kg (range 40-60 IU/kg) which may be increased to 75 IU/kg in subjects ≥12 years of age; range 40-80 IU/kg in subjects <12 years of age. Modified Prophylaxis is determined by the investigator and dose can be increased up to 100 IU/kg, if applicable. PK-tailored Prophylaxis is based on subject's individual PK. The maximum dose is 120 IU/kg.

Number of subjects in period 1[1]	Overall study
Started	115
Completed	96
Not completed	19
Consent withdrawn by subject	9
Physician decision	2
Participant moved to another country	1
Discontinued by sponsor	1
Participant had scheduled surgery	1
Protocol deviation	5

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Of 117 enrolled participants (who signed informed consent), 115 received treatment with investigational product. 1 participant did not meet the entry criteria and 1 participant discontinued the study prior treatment.

Baseline characteristics

Reporting groups	
Reporting group title	Overall study
Reporting group description:	
Participants treated with BAX 326	

Reporting group values	Overall study	Total	
Number of subjects	115	115	
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	29.6		
standard deviation	± 16.39	-	
Gender categorical Units: Subjects			
Female	0	0	
Male	115	115	
Race/Ethnicity, Customized Units: Subjects			
Race White	99	99	
Race Black or African American	1	1	
Race Asian	10	10	
Race Other	5	5	

Subject analysis sets	
Subject analysis set title	Full analysis set
Subject analysis set type	Full analysis
Subject analysis set description:	
Comprises all participants who are exposed to any amount of investigational product.	
Subject analysis set title	Standard prophylaxis
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants treated with BAX 326 with twice weekly prophylactic infusions of 50 IU/kg	
Subject analysis set title	Modified prophylaxis
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants treated with BAX 326 with prophylactic treatment determined by the investigator. The dose could be increased up to 100 IU/kg if indicated.	
Subject analysis set title	PK-tailored prophylaxis
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants treated with BAX 326 with PK tailored prophylaxis based on participant's individual PK with maximum dose of 120 IU/kg.	
Subject analysis set title	Overall prophylaxis

Subject analysis set type	Sub-group analysis

Subject analysis set description:

All participants who received BAX 326 as prophylactic regimen (standard prophylaxis, modified prophylaxis and PK-tailored prophylaxis)

Subject analysis set title	On-demand
Subject analysis set type	Sub-group analysis

Subject analysis set description:

All participants who received BAX 326 as on-demand regimen.

Subject analysis set title	Pharmacokinetic full analysis set
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Comprises all participants from the full analysis set who underwent an abbreviated PK study.

Reporting group values	Full analysis set	Standard prophylaxis	Modified prophylaxis
Number of subjects	115	108	26
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	29.6	28.9	32.3
standard deviation	± 16.39	± 16.19	± 17.76
Gender categorical Units: Subjects			
Female	0	0	0
Male	115	108	26
Race/Ethnicity, Customized Units: Subjects			
Race White	99	95	23
Race Black or African American	1	1	0
Race Asian	10	7	1
Race Other	5	5	2

Reporting group values	PK-tailored prophylaxis	Overall prophylaxis	On-demand
Number of subjects	3	110	13
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	43.0	29.1	36.6
standard deviation	± 18.52	± 16.28	± 11.64
Gender categorical Units: Subjects			
Female	0	0	0
Male	3	110	13
Race/Ethnicity, Customized Units: Subjects			
Race White	0	95	12

Race Black or African American	0	1	0
Race Asian	3	9	1
Race Other	0	5	0

Reporting group values	Pharmacokinetic full analysis set		
Number of subjects	6		
Age categorical Units: Subjects			

Age continuous Units: years			
arithmetic mean	38.5		
standard deviation	± 12.77		
Gender categorical Units: Subjects			
Female	0		
Male	6		
Race/Ethnicity, Customized Units: Subjects			
Race White	2		
Race Black or African American	0		
Race Asian	4		
Race Other	0		

End points

End points reporting groups

Reporting group title	Overall study
Reporting group description: Participants treated with BAX 326	
Subject analysis set title	Full analysis set
Subject analysis set type	Full analysis
Subject analysis set description: Comprises all participants who are exposed to any amount of investigational product.	
Subject analysis set title	Standard prophylaxis
Subject analysis set type	Sub-group analysis
Subject analysis set description: Participants treated with BAX 326 with twice weekly prophylactic infusions of 50 IU/kg	
Subject analysis set title	Modified prophylaxis
Subject analysis set type	Sub-group analysis
Subject analysis set description: Participants treated with BAX 326 with prophylactic treatment determined by the investigator. The dose could be increased up to 100 IU/kg if indicated.	
Subject analysis set title	PK-tailored prophylaxis
Subject analysis set type	Sub-group analysis
Subject analysis set description: Participants treated with BAX 326 with PK tailored prophylaxis based on participant's individual PK with maximum dose of 120 IU/kg.	
Subject analysis set title	Overall prophylaxis
Subject analysis set type	Sub-group analysis
Subject analysis set description: All participants who received BAX 326 as prophylactic regimen (standard prophylaxis, modified prophylaxis and PK-tailored prophylaxis)	
Subject analysis set title	On-demand
Subject analysis set type	Sub-group analysis
Subject analysis set description: All participants who received BAX 326 as on-demand regimen.	
Subject analysis set title	Pharmacokinetic full analysis set
Subject analysis set type	Sub-group analysis
Subject analysis set description: Comprises all participants from the full analysis set who underwent an abbreviated PK study.	

Primary: Adverse events possibly or probably related to the investigational product

End point title	Adverse events possibly or probably related to the investigational product[1]
End point description: Possibly or probably related adverse events that occurred during or after first BAX326 infusion.	
End point type	Primary
End point timeframe: Assessed (based on patient diary) every 3 months until study completion.	

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: Per protocol, only descriptive statistics were collected for this endpoint.

End point values	Overall study			
Subject group type	Reporting group			
Number of subjects analysed	115			
Units: Adverse Events				
Related adverse events	2			

Statistical analyses

No statistical analyses for this end point

Secondary: Treatment of bleeding episodes: Number of infusions per bleeding episode

End point title	Treatment of bleeding episodes: Number of infusions per bleeding episode

End point description:

Infusions of BAX326 that were required until bleed resolution.

End point type	Secondary

End point timeframe:

Throughout the study from screening to study completion

End point values	Overall study	Standard prophylaxis	Modified prophylaxis	PK-tailored prophylaxis
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	115	108	26	3
Units: Number of infusions				
arithmetic mean (standard deviation)				
Number of infusions	1.8 (± 1.65)	2.1 (± 2.12)	1.9 (± 1.41)	1.3 (± 0.46)

End point values	Overall prophylaxis	On-demand		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	110	13		
Units: Number of infusions				
arithmetic mean (standard deviation)				
Number of infusions	2.0 (± 2.01)	1.5 (± 0.79)		

Statistical analyses

No statistical analyses for this end point

Secondary: Treatment of bleeding episodes: Overall hemostatic efficacy rating at resolution of bleed

End point title	Treatment of bleeding episodes: Overall hemostatic efficacy rating at resolution of bleed

End point description:

Excellent: Full relief of pain and cessation of objective signs of bleeding after a single infusion. No additional infusion is required for the control of bleeding. Administration of further infusion would not affect the scoring. Good: Definite pain relief and/or improvement in signs of bleeding after a single infusion. Possibly requires more than 1 infusion for complete resolution. Fair: Probable and/or slight relief of pain and slight improvement in signs of bleeding after a single infusion. Required more than 1 infusion for complete resolution. None: No improvement or condition worsens.

End point type	Secondary

End point timeframe:

Throughout the study from screening to study completion.

End point values	Overall study	Standard prophylaxis	Modified prophylaxis	PK-tailored prophylaxis
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	115	108	26	3
Units: Bleeding episodes				
Excellent	341	168	51	0
Good	650	281	40	0
Fair	115	90	17	6
None	6	3	0	2

End point values	Overall prophylaxis	On-demand		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	110	13		
Units: Bleeding episodes				
Excellent	219	122		
Good	321	329		
Fair	113	2		
None	5	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized bleed rate during prophylaxis treatment

End point title	Annualized bleed rate during prophylaxis treatment

End point description:

Annualized bleed rate (ABR) was calculated as (number of bleeding episodes / observed treatment period in days) * 365.25. The ABR was calculated for participants with an observation period of at least 3 months with BAX326 on the specified treatment regimen.

End point type	Secondary

End point timeframe:

For Prophylactic treatment the period from first to last prophylactic infusion is considered.

End point values	Standard prophylaxis	Modified prophylaxis	PK-tailored prophylaxis	Overall prophylaxis
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	106	22	2	108
Units: Annualized bleed rate				
median (full range (min-max))	1.3 (0.0 to 78.7)	1.4 (0.0 to 34.6)	1.9 (0.5 to 3.3)	1.3 (0.0 to 52.2)

Statistical analyses

No statistical analyses for this end point

Secondary: Consumption of BAX 326: Number of infusions per month and per year

End point title	Consumption of BAX 326: Number of infusions per month and per year

End point description:

The number of infusions consumed per month and per year for the prophylactic and on-demand treatment regimens.

End point type	Secondary

End point timeframe:

Throughout the study from screening to study completion.

End point values	Standard prophylaxis	Modified prophylaxis	PK-tailored prophylaxis	Overall prophylaxis
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	108	26	3	110
Units: Number of infusions				
arithmetic mean (standard deviation)				
Number of infusions per month	8.5 (± 1.25)	10.8 (± 4.34)	4.0 (± 0.60)	8.4 (± 1.38)
Number of infusions per year	101.8 (± 15.03)	130.2 (± 52.13)	48.3 (± 7.23)	101.1 (± 16.50)

End point values	On-demand			
Subject group type	Subject analysis set			
Number of subjects analysed	13			
Units: Number of infusions				
arithmetic mean (standard deviation)				
Number of infusions per month	3.6 (± 2.44)			
Number of infusions per year	43.1 (± 29.28)			

Statistical analyses

No statistical analyses for this end point

Secondary: Consumption of BAX 326: Weight adjusted consumption per month and per year

End point title	Consumption of BAX 326: Weight adjusted consumption per month and per year

End point description:

The weight adjusted consumption of BAX 326 per month and per year for the prophylactic and on-demand treatment regimens.

End point type	Secondary

End point timeframe:

Throughout the study from screening to study completion.

End point values	Standard prophylaxis	Modified prophylaxis	PK-tailored prophylaxis	Overall prophylaxis
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	108	26	3	110
Units: IU/kg				
arithmetic mean (standard deviation)				
Weight adjusted BAX 326 consumption per month	462.3 (± 102.05)	684.4 (± 337.70)	250.9 (± 41.37)	464.2 (± 111.46)
Weight adjusted BAX 326 consumption per year	5547.8 (± 1224.65)	8212.4 (± 4052.36)	3010.3 (± 496.44)	5570.7 (± 1337.53)

End point values	On-demand			
Subject group type	Subject analysis set			
Number of subjects analysed	13			
Units: IU/kg				
arithmetic mean (standard deviation)				
Weight adjusted BAX 326 consumption per month	199.8 (± 124.18)			
Weight adjusted BAX 326 consumption per year	2397.4 (± 1490.22)			

Statistical analyses

No statistical analyses for this end point

Secondary: Consumption of BAX326: Weight adjusted consumption per bleeding episode

End point title	Consumption of BAX326: Weight adjusted consumption per bleeding episode

End point description:

The weight adjusted consumption of BAX 326 per bleeding episode for the prophylactic and on-demand treatment regimens. Only infusions required until the resolution of bleed are considered.

End point type	Secondary

End point timeframe:

Throughout the study from screening to study completion.

End point values	Standard prophylaxis	Modified prophylaxis	PK-tailored prophylaxis	Overall prophylaxis
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	108	26	3	110
Units: IU/kg				
arithmetic mean (standard deviation)				
IU/kg	124.2 (± 140.70)	114.8 (± 99.41)	67.4 (± 34.39)	122.0 (± 134.02)

End point values	On-demand			
Subject group type	Subject analysis set			
Number of subjects analysed	13			
Units: IU/kg				
arithmetic mean (standard deviation)				
IU/kg	82.6 (± 48.21)			

Statistical analyses

No statistical analyses for this end point

Secondary: Development of inhibitory and total binding antibodies to FIX

End point title	Development of inhibitory and total binding antibodies to FIX

End point description:

Testing for inhibitory and total binding antibodies to FIX. Development during study means negative at screening and positive at any subsequent visit. Treatment emergent means more than 2-dilution increase as compared to the pre-study titer at screening.

End point type	Secondary

End point timeframe:

Laboratory assessment for immunology were done at screening, at exposure day 1, at week 4 (± 1 week), at month 3 (±1 week), thereafter, every 3 months (± 1 week) and at study completion/termination.

End point values	Overall study			
Subject group type	Reporting group			
Number of subjects analysed	115			
Units: Participants				
Inhibitory antibody to FIX	0			
Total binding antibody to FIX-develop.during study	0			
Total binding antibody to FIX-treatment emergent	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Development of antibodies to Chinese Hamster Ovary Proteins (CHO proteins) and rFurin

End point title	Development of antibodies to Chinese Hamster Ovary Proteins (CHO proteins) and rFurin

End point description:

Testing for antibodies to CHO proteins and rFurin. Development during study means negative at screening and positive at any subsequent visit. Treatment emergent means more than 2-dilution increase as compared to the pre-study titer at screening.

End point type	Secondary

End point timeframe:

Laboratory assessment for immunology were done at screening, at exposure day 1, at week 4 (± 1 week), at month 3 (±1 week), thereafter, every 3 months (± 1 week) and at study completion/termination.

End point values	Overall study			
Subject group type	Reporting group			
Number of subjects analysed	115			
Units: Participants				
Antibodies to CHO	0			
Antibodies to rFurin - development during study	4			
Antibodies to rFurin - treatment emergent	4			

Statistical analyses

No statistical analyses for this end point

Secondary: Occurrence of severe allergic reactions and thrombotic events

End point title	Occurrence of severe allergic reactions and thrombotic events

End point description:

The occurrence of severe allergic reactions and thrombotic events was assessed.

End point type	Secondary

End point timeframe:

Throughout the study from screening to study completion.

End point values	Overall study			
Subject group type	Reporting group			
Number of subjects analysed	115			
Units: Participants				
Severe allergic reactions	0			
Thrombotic events	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical significant changes in routine laboratory parameters and vital signs

End point title	Clinical significant changes in routine laboratory parameters and vital signs

End point description:

Hematology panel consists of complete blood count (hemoglobin, hematocrit, erythrocytes, leukocytes) with differential (ie, basophils, eosinophils, lymphocytes, monocytes, neutrophils), mean corpuscular volume, mean corpuscular hemoglobin concentration and platelet count. Clinical chemistry panel consists of sodium, potassium, chloride, bicarbonate, total protein, albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, alkaline phosphatase, blood urea nitrogen, creatinine and glucose. Vital signs include body temperature, respiratory rate, pulse rate, supine systolic and diastolic blood pressure.
CS = clinically significant, NCS = not clinically significant
Change from Screening to End of Study is reported.

End point type	Secondary

End point timeframe:

Measurements at screening and at study completion/termination are included in the analysis.

End point values	Overall study			
Subject group type	Reporting group			
Number of subjects analysed	115			
Units: Participants				
Hematology: Change from normal to abnormal CS	2			
Hematology:Change from abnormal NCS to abnormal CS	1			
Chemistry: Change from normal to abnormal, CS	1			
Chemistry: Change from abnormal NCS to abnormal CS	3			
Change in vital signs	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics: Incremental Recovery (IR) over time

End point title	Pharmacokinetics: Incremental Recovery (IR) over time

End point description:

PK infusion with investigational product was administered after a wash out period of at least 5 days. Incremental recovery is calculated as IR30min = (C30min [IU/dL] - Cpre-infusion [IU/dL]) / dose per kg body weight [IU/kg] where C30min and Cpre-infusion relate to the unadjusted concentration values. All subjects treated with investigational product were included in this analysis.

End point type	Secondary

End point timeframe:

IR over time was analysed at Baseline and at Completion/Termination visit within 30 minutes pre-infusion and at 30 (± 5) minutes post-infusion.

End point values	Overall study			
Subject group type	Reporting group			
Number of subjects analysed	110[2]			
Units: (IU/dL)/(IU/kg)				
arithmetic mean (standard deviation)				
Baseline	0.85 (± 0.207)			
End of study	0.85 (± 0.286)			
Change from baseline to end of study	-0.005 (± 0.259)			

Notes:

[2] - n=110 at baseline, n=108 at end of study, n=104 for change

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics: Area under the plasma concentration versus time curve from time 0 to infinity (AUC 0-∞)

End point title	Pharmacokinetics: Area under the plasma concentration versus time curve from time 0 to infinity (AUC 0-∞)

End point description:

After a wash out period of at least 5 days PK infusion with investigational product was administered. AUC 0-∞ is defined as AUC 0-t + Ct/lambda z, where t is the time of last quantifiable concentration, Ct is the last quantifiable concentration.

End point type	Secondary

End point timeframe:

PK assessments were done within 30 minutes pre-infusion and post-infusion at 30 minutes, 9 hours, 24 hours, 48 hours and 72 hours

End point values	Pharmacokinetic full analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	6			
Units: IU*hr/dL				
arithmetic mean (standard deviation)				
IU*hr/dL	1335.56 (± 299.83)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics: Elimination phase half-life (T1/2)

End point title	Pharmacokinetics: Elimination phase half-life (T1/2)

End point description:

PK infusion with investigational product was administered after a wash out period of at least 5 days. Elimination phase half-life is calculated as T1/2=log e (2) / lambda z where the elimination rate constant (lambda z) will be obtained by log e - linear fitting using least squares deviation to at least the last 3 quantifiable concentrations above pre-infusion level.

End point type	Secondary

End point timeframe:

PK assessments were done within 30 minutes pre-infusion and post-infusion at 30 minutes, 9 hours, 24 hours, 48 hours and 72 hours

End point values	Pharmacokinetic full analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	6			
Units: hours				
arithmetic mean (standard deviation)				
hours	28.52 (± 4.12)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics: Mean residence time (MRT)

End point title	Pharmacokinetics: Mean residence time (MRT)

End point description:

PK infusion with investigational product was administered after a wash out period of at least 5 days.

Mean residence time is calculated as total area under the moment curve divided by the total area under the curve. MRT=(AUMC0-∞[h2*IU/dL])/(AUC0-∞[h*IU/dL]) - TI/2 where AUMC0-∞ is determined in a similar manner as AUC0-∞ and TI represents infusion duration in hours.

End point type	Secondary

End point timeframe:

PK assessments were done within 30 minutes pre-infusion and post-infusion at 30 minutes, 9 hours, 24 hours, 48 hours and 72 hours

End point values	Pharmacokinetic full analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	6			
Units: hours				
arithmetic mean (standard deviation)				
hours	29.97 (± 2.72)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics: Systemic Clearance (CL)

End point title	Pharmacokinetics: Systemic Clearance (CL)

End point description:

PK infusion with investigational product was administered after a wash out period of at least 5 days. Systemic clearance is calculated as the dose in IU/kg divided by the total AUC. CL= Dose[IU/kg] / AUC0-∞[h*IU/dL]

End point type	Secondary

End point timeframe:

PK assessments were done within 30 minutes pre-infusion and post-infusion at 30 minutes, 9 hours, 24 hours, 48 hours and 72 hours

End point values	Pharmacokinetic full analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	6			
Units: dL/kg/hours				
arithmetic mean (standard deviation)				
dL/kg/hours	0.06 (± 0.014)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics: Volume of distribution at steady state (Vss)

End point title	Pharmacokinetics: Volume of distribution at steady state (Vss)

End point description:

PK infusion with investigational product was administered after a wash out period of at least 5 days. Apparent steady state volume of distribution is calculated as Vss = CL * MRT CL=Systemic Clearance and MRT=Mean residence time

End point type	Secondary

End point timeframe:

PK assessments were done within 30 minutes pre-infusion and post-infusion at 30 minutes, 9 hours, 24 hours, 48 hours and 72 hours

End point values	Pharmacokinetic full analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	6			
Units: dL/kg				
arithmetic mean (standard deviation)				
dL/kg	1.78 (± 0.42)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics: Incremental recovery (IR)

End point title	Pharmacokinetics: Incremental recovery (IR)

End point description:

PK infusion with investigational product was administered after a wash out period of at least 5 days. Incremental recovery is calculated as IR30min = (C30min [IU/dL] - Cpre-infusion [IU/dL]) / dose per kg body weight [IU/kg] where C30min and Cpre-infusion relate to the unadjusted concentration values.

End point type	Secondary

End point timeframe:

IR assessments were done within 30 minutes pre-infusion and post-infusion at 30 (± 5) minutes.

End point values	Pharmacokinetic full analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	6			
Units: (IU/dL)/(IU/kg)				
arithmetic mean (standard deviation)				
(IU/dL)/(IU/kg)	0.85 (± 0.196)			

Statistical analyses

No statistical analyses for this end point

Secondary: Changes in health related quality of life (HR QoL) based on questionnaire SF-36

End point title	Changes in health related quality of life (HR QoL) based on questionnaire SF-36

End point description:

The SF-36 is a validated, generic HR QoL instrument, measuring physical, emotional, social functioning as well as overall general health, suitable for subjects of 17 years of age or older. Higher scores indicate better health status. The Change in health related quality of life is analyzed from baseline to study completion. Only newly recruited subjects are included in the analysis of change as baseline values were not reported for transitioning subjects. Only subjects who received prophylaxis treatment are included.

End point type	Secondary

End point timeframe:

Baseline at exposure day 1 and at study completion/termination.

End point values	Overall prophylaxis			
Subject group type	Subject analysis set			
Number of subjects analysed	24			
Units: Score				
arithmetic mean (standard deviation)				
SF-36 Bodily Pain	6.7 (± 12.66)			
SF-36 General Health	3.2 (± 9.32)			
SF-36 Mental Health	0.7 (± 14.72)			
SF-36 Mental Health Component Score	0.8 (± 12.08)			
SF-36 Physical Funcioning	4.2 (± 10.46)			
SF-36 Physical Health Component Score	5.7 (± 8.43)			
SF-36 Role-Emotional	2.3 (± 11.57)			
SF-36 Role-Physical	4.5 (± 10.28)			
SF-36 Social Functioning	4.5 (± 11.67)			
SF-36 Vitality	2.0 (± 8.87)			

Statistical analyses

No statistical analyses for this end point

Secondary: Changes in health related quality of life using the Peds QL

End point title	Changes in health related quality of life using the Peds QL

End point description:

The Peds QL is a generic HR QoL instrument designed specifically for a pediatric population. It captures following domains: general health/activities, feelings/emotional, social functioning, school functioning. Higher scores indicate better quality of life. The Change in health related quality of life is analyzed from baseline to study completion. Only newly recruited subjects are included in the analysis of change as baseline values were not reported for transitioning subjects. Only subjects who received prophylaxis treatment are included.

End point type	Secondary

End point timeframe:

Baseline at exposure day 1 and at study completion/termination.

End point values	Overall prophylaxis			
Subject group type	Subject analysis set			
Number of subjects analysed	4			
Units: Change from baseline to end of study				
arithmetic mean (standard deviation)				
Peds-QL Physical Health Summary Score	-2.3 (± 18.47)			
Peds-QL Psychosocial Health Summary Score	3.8 (± 5.99)			
Peds-QL Total Score	1.6 (± 10.14)			

Statistical analyses

No statistical analyses for this end point

Secondary: Changes in health related quality of life (HR QoL) based on questionnaire Haemo-QoL and Haem-A-QoL

End point title	Changes in health related quality of life (HR QoL) based on questionnaire Haemo-QoL and Haem-A-QoL

End point description:

The Haemo-QoL and Haem-A-Qol instruments have been developed and used in hemophilia A patients. As a hemophilia-specific instrument, this measure assesses very specific aspects of dealing with hemophilia. The areas covered by this instrument are: physical health, sports/leisure, school/work, dealing with hemophilia, and outlook for the future. For both instruments higher scores indicate worse quality of life.
The Change in health related quality of life is analyzed from baseline to study completion. Only newly recruited subjects are included in the analysis of change as baseline values were not reported for transitioning subjects. Only subjects who received prophylaxis treatment are included.

End point type	Secondary

End point timeframe:

Baseline at exposure day 1 and at study completion/termination.

End point values	Overall prophylaxis			
Subject group type	Subject analysis set			
Number of subjects analysed	16[3]			
Units: Change from baseline to end of study				
arithmetic mean (standard deviation)				
Haem-A-QoL Total Score	-3.0 (± 9.45)			
Haemo-QoL Total Score	-0.7 (± 99.999)			

Notes:

[3] - n=16 for Haem-A-QoL and n=1 for Haemo-Qol - Dispersion not applicable as n=1, entered as 99.999

Statistical analyses

No statistical analyses for this end point

Secondary: Changes in health related quality of life (HR QoL) based on questionnaire EQ-5D and pain score.

End point title	Changes in health related quality of life (HR QoL) based on questionnaire EQ-5D and pain score.

End point description:

The EQ-5D captures overall HR QoL (phyiscal, mental and social functioning). A health utility score can be calculated from this measure, adult and proxy versions available. General pain assessment are done through a visual analog scale (VAS). For the EQ-5D Index score and EQ-5D VAS score, a higher score represents better quality of life. For the pain scale, a higher score indicates worse pain.
The Change in health related quality of life is analyzed from baseline to study completion. Only newly recruited subjects are included in the analysis of change as baseline values were not reported for transitioning subjects. Only subjects who received prophylaxis treatment are included.

End point type	Secondary

End point timeframe:

Baseline at exposure day 1 and at study completion/termination.

End point values	Overall prophylaxis			
Subject group type	Subject analysis set			
Number of subjects analysed	26[4]			
Units: Change from baseline to end of study				
arithmetic mean (standard deviation)				
EQ-5D Total Index	0.0 (± 0.13)			
EQ-5D VAS	5.1 (± 21.75)			
Pain Score	-8.0 (± 36.62)			

Notes:

[4] - n=26 for EQ-5D Total Index, n=25 for EQ-5D VAS, n=24 for Pain Score

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Throughout the entire study period from screening to completion/termination. Overall 6 years and 2 months.	
Assessment type	Non-systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	N/A
Reporting groups	
Reporting group title	BAX 326
Reporting group description:	
Participants treated with BAX 326	

Serious adverse events	BAX 326		
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 115 (7.83%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Brain contusion			
subjects affected / exposed	1 / 115 (0.87%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Extradural hematoma			
subjects affected / exposed	1 / 115 (0.87%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Head injury			
subjects affected / exposed	1 / 115 (0.87%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Scroctal haematoma			
subjects affected / exposed	1 / 115 (0.87%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Nervous system disorders			
Seizure			
subjects affected / exposed	1 / 115 (0.87%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Transient ischaemic attack			
subjects affected / exposed	1 / 115 (0.87%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 115 (0.87%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Duodenal ulcer hemorrhage			
subjects affected / exposed	1 / 115 (0.87%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Testicular appendage torsion			
subjects affected / exposed	1 / 115 (0.87%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 115 (0.87%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Renal colic			
subjects affected / exposed	2 / 115 (1.74%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Corneal abscess			

subjects affected / exposed	1 / 115 (0.87%)		
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	BAX 326		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	63 / 115 (54.78%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	6 / 115 (5.22%)		
occurrences (all)	6		
Nervous system disorders			
Headache			
subjects affected / exposed	8 / 115 (6.96%)		
occurrences (all)	20		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	14 / 115 (12.17%)		
occurrences (all)	23		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	11 / 115 (9.57%)		
occurrences (all)	15		
Oropharyngeal pain			
subjects affected / exposed	6 / 115 (5.22%)		
occurrences (all)	6		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	15 / 115 (13.04%)		
occurrences (all)	48		
Infections and infestations			
Bronchhitis			
subjects affected / exposed	6 / 115 (5.22%)		
occurrences (all)	8		

Influenza subjects affected / exposed occurrences (all)	8 / 115 (6.96%) 8		
Nasopharyngitis subjects affected / exposed occurrences (all)	25 / 115 (21.74%) 55		
Pharyngitis subjects affected / exposed occurrences (all)	6 / 115 (5.22%) 8		
Rhinitis subjects affected / exposed occurrences (all)	8 / 115 (6.96%) 15		
Upper respiratory tract infection subjects affected / exposed occurrences (all)	11 / 115 (9.57%) 17		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 December 2011	Enrollment opened to pediatric subjects who participated in BAX326 pediatric study 251101 (to enable pediatric subjects to continue to receive BAX326 after completion of the pediatric study); other changes made due to the inclusion of pediatric subjects: - 80 IU/kg stated as upper end of dose range for pediatric subjects - Anticipated IR of 0.7 [IU/dL]/[IU/kg] stated for pediatric subjects for calculation of the required number of units to treat a bleeding episode - Separate analyses between adult and pediatric subjects, if applicable
31 July 2013	- Enrollment opened to at least 25 subjects naïve to BAX326 (per regulatory authority request). - Addition of PK-tailored prophylactic administration of BAX326 as an additional prophylactic treatment option. - Clarification provided that newly recruited subjects had to receive prophylactic treatment. - IR for calculating dose for subjects ≥ 12 years of age updated from 0.8 to 0.9 (based on PK data of BAX326 pivotal protocol 250901) -> Formula changed to: 'body weight (kg) x desired FIX rise (% or (IU/dL)) x 1.1 IU/kg' (previously 1.3 IU/kg) - Addition of TGA testing for the following new exploratory objective: "To correlate pre-infusion TGA parameters with pre-infusion FIX levels and spontaneous breakthrough bleeds in a subset of subjects receiving twice weekly standard or modified prophylactic treatment, including PK-tailored prophylaxis" (to evaluate whether and which TGA parameters, in particular endogenous thrombin potential (ETP) and/or peak thrombin generation may be a better parameter to monitor the adequacy of prophylactic treatment instead of FIX activity trough levels and/or clinical outcome); TGA testing was only to be performed in subjects ≥ 12 years of age
19 October 2015	- Term "Cohort 1" introduced for subjects who were previously treated in BAX326 Studies 250901 or 251101; term "Cohort 2" introduced for newly recruited, BAX326 naïve subjects - Maximum dose of 120 IU/kg introduced for PK-tailored prophylaxis

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported