

**Clinical trial results:**

BAX326 (recombinant factor IX): a phase 2/3, prospective, uncontrolled, multicenter study evaluating pharmacokinetics, efficacy, safety, and immunogenicity in previously treated pediatric patients with severe (FIX level <1%) or moderately severe (FIX level 1-2%) hemophilia B

Summary

EudraCT number	2011-002437-19
Trial protocol	GB BG
Global end of trial date	14 May 2013

Results information

Result version number	v1 (current)
This version publication date	18 February 2016
First version publication date	06 August 2015

Trial information**Trial identification**

Sponsor protocol code	251101
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01488994
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Baxalta US Inc.
Sponsor organisation address	One Baxter Way, Westlake Village, United States, CA 91362
Public contact	Clinical Trial Registries and Results Disclosure, Baxalta US Inc., ClinicalTrialsDisclosure@baxalta.com
Scientific contact	Clinical Trial Registries and Results Disclosure, Baxalta US Inc., ClinicalTrialsDisclosure@baxalta.com
Sponsor organisation name	Baxalta Innovations GmbH
Sponsor organisation address	Industriestrasse 67, Vienna, Austria, 1221
Public contact	Clinical Trial Registries and Results Disclosure, Baxalta Innovations GmbH, ClinicalTrialsDisclosure@baxalta.com
Scientific contact	Clinical Trial Registries and Results Disclosure, Baxalta Innovations GmbH, ClinicalTrialsDisclosure@baxalta.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
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Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	26 August 2013
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	14 May 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate all adverse events possibly or probably related to BAX326

Protection of trial subjects:

This study was conducted in accordance with the clinical protocol, the International Conference on Harmonization 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.

There were 2 age cohorts: <6 years and 6 to <12 years. To reduce the burden of frequent blood sampling on the individual subject for the pharmacokinetic assessment (total of 7 post-infusion sampling time points over 72 hours), subjects within each age cohort were randomized to one of 2 blood sampling sequences of 4 post-infusion blood sampling time points each.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 December 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	Poland: 5
Country: Number of subjects enrolled	Romania: 5
Country: Number of subjects enrolled	Ukraine: 3
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	Russian Federation: 7
Country: Number of subjects enrolled	India: 1
Worldwide total number of subjects	23
EEA total number of subjects	12

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)	23
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:

Enrollment was conducted at 11 clinical sites in 6 countries (United Kingdom, Poland, Romania, Russian Federation, Ukraine, India). A total of 23 subjects were enrolled in the study. Of these, 11 were <6 years of age and 12 were 6 to <12 years of age.

Pre-assignment

Screening details: -

Pre-assignment period milestones

Number of subjects started	23
Number of subjects completed	23

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Paediatric subjects <6 years of age

Arm description:

Subjects in this cohort had their pharmacokinetic infusion with BAX326 in the morning and were assigned to the following 4 post-infusion blood sampling time points: 15-30 min, 7±1 hour(s), anytime during the 2nd day, anytime during the 3rd day

Arm type	Experimental
Investigational medicinal product name	BAX326 (recombinant factor IX)
Investigational medicinal product code	
Other name	Rixubis
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Subjects underwent a pharmacokinetic evaluation with BAX326 (1 infusion) which was followed by a twice weekly prophylactic treatment with BAX326. Bleeding episodes were also treated with BAX326.

Arm title	Paediatric subjects 6 to <12 years of age
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Arm description:

Subjects in this cohort had their pharmacokinetic infusion with BAX326 in the afternoon and were assigned to the following 4 post-infusion blood sampling time points: 15-30 min, 4±1 hour(s), anytime during the 2nd day, morning of the 4th day

Arm type	Experimental
Investigational medicinal product name	BAX326 (recombinant factor IX)
Investigational medicinal product code	
Other name	Rixubis
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Subjects underwent a pharmacokinetic evaluation with BAX326 (1 infusion) which was followed by a twice weekly prophylactic treatment with BAX326. Bleeding episodes were also treated with BAX326.

Number of subjects in period 1	Paediatric subjects <6 years of age	Paediatric subjects 6 to <12 years of age
Started	11	12
Completed	11	11
Not completed	0	1
Consent withdrawn by subject	-	1

Baseline characteristics

Reporting groups

Reporting group title	Paediatric subjects <6 years of age
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Reporting group description:

Subjects in this cohort had their pharmacokinetic infusion with BAX326 in the morning and were assigned to the following 4 post-infusion blood sampling time points: 15-30 min, 7±1 hour(s), anytime during the 2nd day, anytime during the 3rd day

Reporting group title	Paediatric subjects 6 to <12 years of age
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Reporting group description:

Subjects in this cohort had their pharmacokinetic infusion with BAX326 in the afternoon and were assigned to the following 4 post-infusion blood sampling time points: 15-30 min, 4±1 hour(s), anytime during the 2nd day, morning of the 4th day

Reporting group values	Paediatric subjects <6 years of age	Paediatric subjects 6 to <12 years of age	Total
Number of subjects	11	12	23
Age categorical			
Units: Subjects			
<6 years of age	11	0	11
6 to <12 years of age	0	12	12
Age continuous			
Units: years			
arithmetic mean	3.83	9.8	
full range (min-max)	1.8 to 6	7.1 to 11.8	-
Gender categorical			
Units:			
Male	11	12	23
Female	0	0	0

Subject analysis sets

Subject analysis set title	Full Analysis Set
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Subject analysis set type	Full analysis
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Subject analysis set description:

Comprised all subjects who received at least one infusion of investigational product

Subject analysis set title	Pharmacokinetic Full Analysis Set
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Subject analysis set type	Sub-group analysis
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Subject analysis set description:

Comprised all subjects who had at least one plasma factor IX activity level available during post-infusion time points

Reporting group values	Full Analysis Set	Pharmacokinetic Full Analysis Set	
Number of subjects	23	23	
Age categorical			
Units: Subjects			
<6 years of age	11	11	
6 to <12 years of age	12	12	

Age continuous			
Units: years			
arithmetic mean	6.94	6.94	
full range (min-max)	1.8 to 11.8	1.8 to 11.8	
Gender categorical			
Units:			
Male	23	23	
Female	0	0	

End points

End points reporting groups

Reporting group title	Paediatric subjects <6 years of age
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Reporting group description:

Subjects in this cohort had their pharmacokinetic infusion with BAX326 in the morning and were assigned to the following 4 post-infusion blood sampling time points: 15-30 min, 7±1 hour(s), anytime during the 2nd day, anytime during the 3rd day

Reporting group title	Paediatric subjects 6 to <12 years of age
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Reporting group description:

Subjects in this cohort had their pharmacokinetic infusion with BAX326 in the afternoon and were assigned to the following 4 post-infusion blood sampling time points: 15-30 min, 4±1 hour(s), anytime during the 2nd day, morning of the 4th day

Subject analysis set title	Full Analysis Set
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Subject analysis set type	Full analysis
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Subject analysis set description:

Comprised all subjects who received at least one infusion of investigational product

Subject analysis set title	Pharmacokinetic Full Analysis Set
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Subject analysis set type	Sub-group analysis
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Subject analysis set description:

Comprised all subjects who had at least one plasma factor IX activity level available during post-infusion time points

Primary: Adverse events (AEs) possibly or probably related to BAX326

End point title	Adverse events (AEs) possibly or probably related to BAX326 ^[1]
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End point description:

Probable, possible, or unknown causality assessment of an AE were to be counted as "related". AEs that occurred during or after treatment application were presented in summary tables. An overview summary table presented the number (%) of AEs, the number (%) of subjects with AEs by seriousness, severity, and relationship to the study product. Descriptive statistics were presented by age stratum.

End point type	Primary
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End point timeframe:

Approximately 7 months per subject

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, descriptive statistics were collected for this endpoint.

End point values	Paediatric subjects <6 years of age	Paediatric subjects 6 to <12 years of age	Full Analysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	11	12	23	
Units: possibly or probably related AEs	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics (PK): Total Area under the plasma concentration

versus time curve per dose (Total AUC/dose)

End point title	Pharmacokinetics (PK): Total Area under the plasma concentration versus time curve per dose (Total AUC/dose)
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End point description:

End point type	Secondary
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End point timeframe:

72 hours

End point values	Paediatric subjects <6 years of age	Paediatric subjects 6 to <12 years of age	Pharmacokinetic Full Analysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	11	12	23	
Units: IU•hour (hr)/dL				
arithmetic mean (standard deviation)	723.7 (± 119)	886 (± 133.66)	808.4 (± 149.14)	

Statistical analyses

No statistical analyses for this end point

Secondary: PK: Mean residence time (MRT)

End point title	PK: Mean residence time (MRT)
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End point description:

Computed as total area under the first moment curve (total AUMC) divided by the total area under the concentration versus time curve (total AUC)

End point type	Secondary
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End point timeframe:

72 hours

End point values	Paediatric subjects <6 years of age	Paediatric subjects 6 to <12 years of age	Pharmacokinetic Full Analysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	11	12	23	
Units: hours (hr)				
arithmetic mean (standard deviation)	30.62 (± 3.266)	25.31 (± 1.83)	27.85 (± 3.726)	

Statistical analyses

No statistical analyses for this end point

Secondary: PK: Factor IX (FIX) clearance (CL)

End point title PK: Factor IX (FIX) clearance (CL)

End point description:

Computed as the dose divided by total AUC

End point type Secondary

End point timeframe:

72 hours

End point values	Paediatric subjects <6 years of age	Paediatric subjects 6 to <12 years of age	Pharmacokinetic Full Analysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	11	12	23	
Units: dL/(kg•hr)				
arithmetic mean (standard deviation)	0.1058 (± 0.0165)	0.0874 (± 0.01213)	0.0962 (± 0.01689)	

Statistical analyses

No statistical analyses for this end point

Secondary: PK: Incremental recovery (IR)

End point title PK: Incremental recovery (IR)

End point description:

Calculated as follows: (FIX activity at post-infusion minus FIX activity at pre-infusion) divided by weight-adjusted dose

End point type Secondary

End point timeframe:

30 minutes

End point values	Paediatric subjects <6 years of age	Paediatric subjects 6 to <12 years of age	Pharmacokinetic Full Analysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	10 ^[2]	12	22	
Units: IU/dL : IU/kg				
arithmetic mean (standard deviation)	0.586 (± 0.132)	0.731 (± 0.1615)	0.665 (± 0.1632)	

Notes:

[2] - 1 subject <6 yrs had a biologically implausible FIX level at 15-30 min post-infusion -> was excluded

Statistical analyses

No statistical analyses for this end point

Secondary: PK: Elimination phase half-life (T 1/2)

End point title PK: Elimination phase half-life (T 1/2)

End point description:

Calculated as $\log_e 2/\lambda$, where λ is the regression slope in the terminal phase of the least absolute deviations regression model

End point type Secondary

End point timeframe:

72 hours

End point values	Paediatric subjects <6 years of age	Paediatric subjects 6 to <12 years of age	Pharmacokinetic Full Analysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	11	12	23	
Units: hr				
arithmetic mean (standard deviation)	27.67 (\pm 2.658)	23.15 (\pm 1.582)	25.31 (\pm 3.13)	

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

Computed as Clearance (CL) * Mean residence time (MRT)

End point type Secondary

End point timeframe:

72 hours

End point values	Paediatric subjects <6 years of age	Paediatric subjects 6 to <12 years of age	Pharmacokinetic Full Analysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	11	12	23	
Units: dL/kg				
arithmetic mean (standard deviation)	3.225 (\pm 0.5233)	2.209 (\pm 0.3165)	2.695 (\pm 0.6662)	

Statistical analyses

No statistical analyses for this end point

Secondary: PK: Incremental recovery (IR) over time

End point title PK: Incremental recovery (IR) over time

End point description:

Calculated as follows: (FIX activity at post-infusion minus FIX activity at pre-infusion) divided by weight-adjusted dose

End point type Secondary

End point timeframe:

Week 5, Week 13, Week 26 and study completion/termination visit (for participants receiving BAX326 beyond Week 26)

End point values	Paediatric subjects <6 years of age	Paediatric subjects 6 to <12 years of age	Pharmacokinetic Full Analysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	11 ^[3]	12 ^[4]	23 ^[5]	
Units: IU/dL : IU/kg				
arithmetic mean (standard deviation)				
Week 5	0.63 (± 0.1028)	0.726 (± 0.1291)	0.68 (± 0.1245)	
Week 13	0.676 (± 0.1211)	0.733 (± 0.14)	0.706 (± 0.1313)	
Week 26	0.647 (± 0.1274)	0.795 (± 0.1445)	0.724 (± 0.1533)	

Notes:

[3] - Only 10 subjects in the <6-year age group were analyzed for Week 13 and Week 26.

[4] - Only 11 subjects in the 6-to-<12-year age group were analyzed for Week 13 and Week 26.

[5] - Only 21 subjects were analyzed for Week 13 and Week 26.

Statistical analyses

No statistical analyses for this end point

Secondary: Haemostatic efficacy: Treatment of bleeding episodes: number of infusions per bleeding episode

End point title Haemostatic efficacy: Treatment of bleeding episodes: number of infusions per bleeding episode

End point description:

End point type Secondary

End point timeframe:
Approximately 7 months per subject

End point values	Paediatric subjects <6 years of age	Paediatric subjects 6 to <12 years of age	Full Analysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	7 ^[6]	7 ^[7]	14 ^[8]	
Units: Bleeding episodes				
Controlled with 1 infusion	9	6	15	
Controlled with 2 infusions	1	7	8	
Controlled with 3 or more infusions	1	2	3	

Notes:

[6] - 7 subjects <6 yrs had total of 11 bleeding episodes after first BAX326 exposure which were treated

[7] - 7 subjects 6 - <12 yrs had 15 bleeding episodes after first BAX326 exposure which were treated

[8] - 14 subjects in FAS had total of 26 bleeding episodes after first BAX326 exposure which were treated

Statistical analyses

No statistical analyses for this end point

Secondary: Haemostatic efficacy: Treatment of bleeding episodes: overall haemostatic efficacy rating at resolution of bleed

End point title	Haemostatic efficacy: Treatment of bleeding episodes: overall haemostatic efficacy rating at resolution of bleed
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End point description:

Rating Scale for Treatment of BEs (4-point ordinal scale):

- Excellent: Full relief of pain and cessation of objective signs of bleeding (eg, swelling, tenderness, and decreased range of motion in the case of musculoskeletal hemorrhage) after a single infusion. No additional infusion required for the control of bleeding. Administration of further infusions to maintain hemostasis did not affect this 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 single infusion. Required more than 1 infusion for complete resolution.
- None: No improvement or condition worsens.

End point type	Secondary
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End point timeframe:

Approximately 7 months per subject

End point values	Paediatric subjects <6 years of age	Paediatric subjects 6 to <12 years of age	Full Analysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	7 ^[9]	7 ^[10]	14 ^[11]	
Units: rating				
Excellent	9	4	13	
Good	2	10	12	

Fair	0	1	1	
None	0	0	0	

Notes:

[9] - 7 subjects <6 yrs had total of 11 bleeding episodes after first BAX326 exposure which were treated

[10] - 7 subjects 6 - <12 yrs had 15 bleeding episodes after first BAX326 exposure which were treated

[11] - 14 subjects in FAS had total of 26 bleeding episodes after first BAX326 exposure which were treated

Statistical analyses

No statistical analyses for this end point

Secondary: Haemostatic efficacy: Prophylaxis: annualized bleeding rate (ABR)

End point title	Haemostatic efficacy: Prophylaxis: annualized bleeding rate (ABR)
End point description:	
End point type	Secondary
End point timeframe:	
Approximately 7 months per subject	

End point values	Paediatric subjects <6 years of age	Paediatric subjects 6 to <12 years of age	Full Analysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	11 ^[12]	12 ^[13]	23 ^[14]	
Units: Annualized bleeding rate (ABR)				
arithmetic mean (standard deviation)	1.9 (± 1.89)	3.4 (± 3.93)	2.7 (± 3.14)	

Notes:

[12] - All 11 subjects <6 yrs had at least 3 months of prophylactic treatment with BAX326

[13] - All 12 subjects 6 - <12 yrs had at least 3 months of prophylactic treatment with BAX326

[14] - All 23 subjects in the FAS had at least 3 months of prophylactic treatment with BAX326

Statistical analyses

No statistical analyses for this end point

Secondary: Consumption of BAX326: number of infusions per month and per year (annualized)

End point title	Consumption of BAX326: number of infusions per month and per year (annualized)
End point description:	
End point type	Secondary
End point timeframe:	
Approximately 7 months per subject	

End point values	Paediatric subjects <6 years of age	Paediatric subjects 6 to <12 years of age	Full Analysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	11	12	23	
Units: infusions				
arithmetic mean (standard deviation)				
Per month	6.8 (± 0.44)	7.2 (± 0.4)	7 (± 0.44)	
Per year	82.1 (± 5.27)	85.9 (± 4.79)	84.1 (± 5.27)	

Statistical analyses

No statistical analyses for this end point

Secondary: Consumption of BAX326: weight-adjusted consumption per month and per year (annualized)

End point title	Consumption of BAX326: weight-adjusted consumption per month and per year (annualized)
End point description:	
End point type	Secondary
End point timeframe:	
Approximately 7 months per subject	

End point values	Paediatric subjects <6 years of age	Paediatric subjects 6 to <12 years of age	Full Analysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	11	12	23	
Units: IU/kg				
arithmetic mean (standard deviation)				
Per month	393.4 (± 50.53)	414.8 (± 58.44)	404.6 (± 54.66)	
Per year	4720.9 (± 606.31)	4978.2 (± 701.26)	4855.1 (± 655.93)	

Statistical analyses

No statistical analyses for this end point

Secondary: Consumption of BAX326: weight-adjusted consumption per event

End point title	Consumption of BAX326: weight-adjusted consumption per event
End point description:	

End point type	Secondary
End point timeframe:	
Approximately 7 months per subject	

End point values	Paediatric subjects <6 years of age	Paediatric subjects 6 to <12 years of age	Full Analysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	11 ^[15]	12 ^[16]	23 ^[17]	
Units: IU/kg				
arithmetic mean (standard deviation)				
Prophylactic Infusions	56.3 (± 10.29)	56.2 (± 6.55)	56.2 (± 8.34)	
Infusions for treatment of bleeding episodes	57.6 (± 11.87)	62.1 (± 16)	59.9 (± 13.74)	

Notes:

[15] - All 11 subjects received prophylactic infusions but only 7 received treatment for bleeding episodes

[16] - All 12 subjects received prophylactic infusions but only 7 received treatment for bleeding episodes

[17] - All 23 subjects received prophylactic infusions but only 14 received treatment for bleeding episodes

Statistical analyses

No statistical analyses for this end point

Secondary: Safety and Immunogenicity: Development of inhibitory antibodies to factor IX (FIX)

End point title	Safety and Immunogenicity: Development of inhibitory antibodies to factor IX (FIX)
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End point description:

End point type	Secondary
End point timeframe:	
Approximately 7 months per subject	

End point values	Paediatric subjects <6 years of age	Paediatric subjects 6 to <12 years of age	Full Analysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	11	12	23	
Units: subjects	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Safety and Immunogenicity: Development of total binding antibodies to FIX

End point title	Safety and Immunogenicity: Development of total binding antibodies to FIX
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End point description:

If more than 2-dilution increase as compared to pre-study level at screening and titers verified for specificity in the confirmatory assay

End point type	Secondary
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End point timeframe:

Approximately 7 months per subject

End point values	Paediatric subjects <6 years of age	Paediatric subjects 6 to <12 years of age	Full Analysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	11	12	23	
Units: subjects	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Safety: Occurrence of severe allergic reactions (eg, anaphylaxis)

End point title	Safety: Occurrence of severe allergic reactions (eg, anaphylaxis)
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End point description:

End point type	Secondary
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End point timeframe:

Approximately 7 months per subject

End point values	Paediatric subjects <6 years of age	Paediatric subjects 6 to <12 years of age	Full Analysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	11	12	23	
Units: severe allergic reactions	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Safety: Occurrence of thrombotic events

End point title	Safety: Occurrence of thrombotic events
End point description:	
End point type	Secondary
End point timeframe:	
Approximately 7 months per subject	

End point values	Paediatric subjects <6 years of age	Paediatric subjects 6 to <12 years of age	Full Analysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	11	12	23	
Units: thrombotic events	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Safety: Clinically significant (CS) changes in routine laboratory parameters (haematology and clinical chemistry), and vital signs

End point title	Safety: Clinically significant (CS) changes in routine laboratory parameters (haematology and clinical chemistry), and vital signs			
End point description:				
End point type	Secondary			
End point timeframe:				
Approximately 7 months per subject				

End point values	Paediatric subjects <6 years of age	Paediatric subjects 6 to <12 years of age	Full Analysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	11	12	23	
Units: subjects				
CS changes in haematology parameters	0	2	2	
CS changes in clinical chemistry parameters	0	0	0	
CS changes in vital signs	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Safety and Immunogenicity: Development of antibodies to Chinese hamster ovary (CHO) proteins and recombinant furin (rFurin)

End point title	Safety and Immunogenicity: Development of antibodies to Chinese hamster ovary (CHO) proteins and recombinant furin (rFurin)
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End point description:

End point type	Secondary
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End point timeframe:

Approximately 7 months per subject

End point values	Paediatric subjects <6 years of age	Paediatric subjects 6 to <12 years of age	Full Analysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	11	12	23	
Units: subjects				
Treatment-related Antibodies to CHO proteins	0	0	0	
Treatment-related Antibodies to rFurin	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Health-related Quality of Life (HRQoL): Peds-QL: Change from baseline in total score

End point title	Health-related Quality of Life (HRQoL): Peds-QL: Change from baseline in total score
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End point description:

The Peds-QL is a generic HR QoL instrument designed specifically for a paediatric population. It captures the following domains: general health/activities, feelings/emotional, social functioning, school functioning. For this study, the Peds-QL questionnaires for subjects 2 to 7 years of age (parent-proxy versions for age groups 2-4 years and 5-7 years) and for subjects 8 to 12 years of age were used. Higher scores indicate better quality of life for all domains of the Peds-QL.

End point type	Secondary
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End point timeframe:

Approximately 6 months per subject

End point values	Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	23 ^[18]			
Units: score				
arithmetic mean (standard deviation)				
Peds-QL 2-4	3.27 (± 10.119)			
Peds-QL 5-7	-7.07 (± 6.917)			
PedsQL 8-12	4.02 (± 11.038)			

Notes:

[18] - Results for 4 subjects 2-4 years, 2 subjects 5-7 years and 10 subjects 8-12 years

Statistical analyses

No statistical analyses for this end point

Secondary: HRQoL: Haemo-QoL (short version): Change from baseline in total score

End point title	HRQoL: Haemo-QoL (short version): Change from baseline in total score
End point description:	The Haemo-QoL instrument assesses specific aspects of dealing with haemophilia. The areas covered by this instrument are: physical health, sports/leisure, school, dealing with haemophilia, and outlook for the future. For this study, the Haemo-QoL for subjects 8-16 years of age was used. Higher scores indicate worse quality of life.
End point type	Secondary
End point timeframe:	Approximately 6 months per subject

End point values	Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	23 ^[19]			
Units: score				
arithmetic mean (standard deviation)	-0.18 (± 0.456)			

Notes:

[19] - Results are only available for 10 subjects >8 years of age.

Statistical analyses

No statistical analyses for this end point

Secondary: HRQoL: Number of hospitalizations

End point title	HRQoL: Number of hospitalizations
End point description:	
End point type	Secondary

End point timeframe:
Approximately 6 months per subject

End point values	Paediatric subjects <6 years of age	Paediatric subjects 6 to <12 years of age	Full Analysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	11	12	23	
Units: subjects who were hospitalized	1	2	3	

Statistical analyses

No statistical analyses for this end point

Secondary: HRQoL: Length of hospitalization

End point title | HRQoL: Length of hospitalization

End point description:

End point type | Secondary

End point timeframe:

Approximately 6 months per subject

End point values	Paediatric subjects <6 years of age	Paediatric subjects 6 to <12 years of age	Full Analysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	11 ^[20]	12 ^[21]	23	
Units: days in hospital				
median (full range (min-max))				
Week 13	2 (2 to 2)	4 (4 to 4)	3 (2 to 4)	
Week 26	0 (0 to 0)	13 (13 to 13)	13 (13 to 13)	

Notes:

[20] - One subject in the <6-year age group underwent hospitalization by Week 13.

[21] - Of 2 subjects 6 - <12 yrs who were hospitalized, 1 had data for Week 13 and the other for Week 26

Statistical analyses

No statistical analyses for this end point

Secondary: HRQoL: Unscheduled visits to a doctor's office

End point title | HRQoL: Unscheduled visits to a doctor's office

End point description:

End point type	Secondary
End point timeframe:	
Approximately 6 months per subject	

End point values	Paediatric subjects <6 years of age	Paediatric subjects 6 to <12 years of age	Full Analysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	11	12	23	
Units: Visits to a doctor's office	9	5	14	

Statistical analyses

No statistical analyses for this end point

Secondary: HRQoL: Emergency Room (ER) visits

End point title	HRQoL: Emergency Room (ER) visits
End point description:	

End point type	Secondary
End point timeframe:	
Approximately 6 months per subject	

End point values	Paediatric subjects <6 years of age	Paediatric subjects 6 to <12 years of age	Full Analysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	11 ^[22]	12 ^[23]	23 ^[24]	
Units: ER visits	8	3	11	

Notes:

[22] - ER visits were recorded for 3 subjects in the <6-year age cohort.

[23] - ER visits were recorded for 3 subjects in the 6-to-<12-year age cohort.

[24] - ER visits were recorded for a total of 6 subjects.

Statistical analyses

No statistical analyses for this end point

Secondary: HRQoL: Days lost from school

End point title	HRQoL: Days lost from school
End point description:	

End point type	Secondary
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End point timeframe:
Approximately 6 months per subject

End point values	Paediatric subjects <6 years of age	Paediatric subjects 6 to <12 years of age	Full Analysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	11 ^[25]	12 ^[26]	23 ^[27]	
Units: days	29	53	82	

Notes:

[25] - 2 subjects in the <6-year age group missed days from school.

[26] - 8 subjects in the 6-to-<12-year age group missed days from school.

[27] - A total of 10 subjects missed days from school.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Approximately 7 months per subject

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	N/A
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Reporting groups

Reporting group title	Paediatric subjects less than 6 years of age
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Reporting group description:

Subjects in this cohort had their pharmacokinetic infusion with BAX326 in the morning and were assigned to the following 4 post-infusion blood sampling time points: 15-30 min, 7±1 hour(s), anytime during the 2nd day, anytime during the 3rd day

Reporting group title	Paediatric subjects between 6 and less than 12 years of age
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Reporting group description:

Subjects in this cohort had their pharmacokinetic infusion with BAX326 in the afternoon and were assigned to the following 4 post-infusion blood sampling time points: 15-30 min, 4±1 hour(s), anytime during the 2nd day, anytime during the 3rd day

Serious adverse events	Paediatric subjects less than 6 years of age	Paediatric subjects between 6 and less than 12 years of age	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 11 (0.00%)	3 / 12 (25.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Humerus fracture			
subjects affected / exposed	0 / 11 (0.00%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Haemorrhage subcutaneous			
subjects affected / exposed	0 / 11 (0.00%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Haemarthrosis			

subjects affected / exposed	0 / 11 (0.00%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Device related infection			
subjects affected / exposed	0 / 11 (0.00%)	1 / 12 (8.33%)	
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	Paediatric subjects less than 6 years of age	Paediatric subjects between 6 and less than 12 years of age	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 11 (63.64%)	9 / 12 (75.00%)	
Investigations			
Immunology test abnormal	Additional description: The abnormal test results refer to total binding antibodies to FIX and/or rFurin of indeterminate specificity (titers of 1:20 or 1:40, ie, <2-dilution steps) which could not be verified in the confirmatory assay.		
subjects affected / exposed	1 / 11 (9.09%)	5 / 12 (41.67%)	
occurrences (all)	1	7	
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 11 (9.09%)	1 / 12 (8.33%)	
occurrences (all)	1	1	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 11 (9.09%)	1 / 12 (8.33%)	
occurrences (all)	1	1	
Toothache			
subjects affected / exposed	0 / 11 (0.00%)	2 / 12 (16.67%)	
occurrences (all)	0	2	
Infections and infestations			
Respiratory tract infection viral			
subjects affected / exposed	0 / 11 (0.00%)	2 / 12 (16.67%)	
occurrences (all)	0	2	
Rhinitis			

subjects affected / exposed occurrences (all)	2 / 11 (18.18%) 4	0 / 12 (0.00%) 0	
Bronchitis subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1	1 / 12 (8.33%) 1	
Nasopharyngitis subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1	1 / 12 (8.33%) 2	
Upper respiratory tract infection subjects affected / exposed occurrences (all)	2 / 11 (18.18%) 2	1 / 12 (8.33%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported