Clinical trial results:
BAX326 (recombinant Factor IX): A Phase 1/3 Prospective, Controlled, Multicenter Study Evaluating Pharmacokinetics, Efficacy, Safety, and Immunogenicity in Previously Treated Patients With Severe (FIX level <1%) or Moderately Severe (FIX level 2%) Hemophilia B

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

Summary

EudraCT number	2009-016720-31
Trial protocol	GB DE CZ ES BG SE
Global end of trial date	03 May 2012

Results information

Result version number	v1 (current)
This version publication date	13 February 2016
First version publication date	13 February 2016

Trial information

Trial identification

Sponsor protocol code	250901

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01174446
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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	11 September 2012
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 May 2012
Global end of trial reached?	Yes
Global end of trial date	03 May 2012
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objective of Part 1 of the study was to compare the PK parameters of BAX326 with those of BeneFIX and to determine pharmacokinetic (PK) equivalence.

Part 2 of the study was to assess the hemostatic efficacy, safety, and immunogenicity of BAX326 and health-related quality of life in those subjects receiving BAX326 for prevention and treatment of bleeding episodes.

The objective of Part 3 was to re-evaluate the PK parameters for BAX326 after a period of 6 months of treatment, in 27 subjects who had accumulated at least 30 exposure days to BAX326, and to compare them with those determined in the same subjects who participated in Part 1.

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.

Background therapy: -

Evidence for comparator:

BeneFIX was the comparator product used in Part 1 of this study.The objective was to compare the pharmacokinetic (PK) parameters of BAX326 with BeneFIX and to determine PK equivalence. BeneFIX, manufactured by Wyeth (recently acquired by Pfizer), was the only recombinant FIX product available on the hemophilia B market at the time of the study.

Actual start date of recruitment	29 July 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: 12
Country: Number of subjects enrolled	Russian Federation: 12
Country: Number of subjects enrolled	Bulgaria: 10
Country: Number of subjects enrolled	Ukraine: 8

Country: Number of subjects enrolled	Romania: 8
Country: Number of subjects enrolled	Colombia: 5
Country: Number of subjects enrolled	Japan: 5
Country: Number of subjects enrolled	Chile: 4
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	Czech Republic: 2
Country: Number of subjects enrolled	Argentina: 2
Country: Number of subjects enrolled	Spain: 1
Country: Number of subjects enrolled	Sweden: 1
Country: Number of subjects enrolled	Brazil: 1
Worldwide total number of subjects	73
EEA total number of subjects	36

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)	0
Adolescents (12-17 years)	3
Adults (18-64 years)	70
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Enrollment was conducted at 32 clinical sites in Europe, the United States, South America, and Japan.

Pre-assignment

Screening details:

86 subjects were enrolled. 13 subjects discontinued before treatment: 7 withdrew consent, 1 was withdrawn due to an adverse event (suicide attempt), 2 were screen failures, and 3 withdrew due to site closure.

Pre-assignment period milestones

Number of subjects started	73
Number of subjects completed	73[1]

Notes:

[1] - The number of subjects reported to be in the pre-assignment period is not consistent with the number starting period 1. It is expected that the number completing the pre-assignment period are also present in the arms in period 1.
Justification: 86 subjects were enrolled. 13 subjects discontinued before treatment.

Period 1

Period 1 title	Part 1 -Pharmacokinetic Crossover
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

Subjects and investigators in study Part 1 were blinded. To maintain the blind, the investigational products were reconstituted by the hospital pharmacist in the hospital pharmacy who was unblinded.

Arms

Arm title	Pharmacokinetic Crossover with BAX326 and BeneFIX

Arm description:

In Part 1, randomized subjects received 2 infusions each, 1 infusion with BAX326 and 1 infusion with BeneFIX, at a dose of 75 ± 5 IU/kg, each in a randomized order.

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

Dosage and administration details:

Study Part 1: PK Crossover with BAX326 and BeneFIX, at a dose of 75 ± 5 IU/kg - Study Part 2: Open-label evaluation of prophylaxis and on-demand - Study Part 3: Open-label repeat of PK evaluation (repeat Study Part 1) with BAX326 only in the same study subjects as in Study Part 1

Investigational medicinal product name	BeneFIX
Investigational medicinal product code	Recombinant factor IX (rFIX)
Other name	
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Study Part 1: PK Crossover with BAX326 and BeneFIX, at a dose of 75 ± 5 IU/kg

Number of subjects in period 1	Pharmacokinetic Crossover with BAX326 and BeneFIX
Started	28
Completed	28

Period 2	
Period 2 title	Part 2 -BAX326 Prophylaxis and On-demand
Is this the baseline period?	Yes[2]
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Part 2 Only: BAX326 Prophylaxis

Arm description:

Participants were only in Study Part 2 (i.e., did not participate in Study Parts 1 and 3)

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

Dosage and administration details:

Study Part 1: PK Crossover with BAX326 and BeneFIX, at a dose of 75 ± 5 IU/kg - Study Part 2: Open-label evaluation of prophylaxis and on-demand - Study Part 3: Open-label repeat of PK evaluation (repeat Study Part 1) with BAX326 only in the same study subjects as in Study Part 1

Arm title	Part 2 Only: BAX326 On-Demand

Arm description:

Participants were only in Study Part 2 (i.e., did not participate in Study Parts 1 and 3)

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

Dosage and administration details:

Study Part 1: PK Crossover with BAX326 and BeneFIX, at a dose of 75 ± 5 IU/kg - Study Part 2: Open-label evaluation of prophylaxis and on-demand - Study Part 3: Open-label repeat of PK evaluation (repeat Study Part 1) with BAX326 only in the same study subjects as in Study Part 1

Arm title	Part 1: PK crossover - Part 2: Prophylaxis - Part 3: PK BAX326

Arm description:

-Study Part 1: Pharmacokinetic (PK) Crossover with BeneFIX (75 ± 5 IU/kg) and BAX326 (75 ± 5

IU/kg). -Study Part 2: Open-label evaluation of prophylaxis -Study Part 3: Open-label repeat of PK evaluation (repeat Study Part 1) with BAX326 (75 ± 5 IU/kg) only and same study participants as Study Part 1

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

Dosage and administration details:

Study Part 1: PK Crossover with BAX326 and BeneFIX, at a dose of 75 ± 5 IU/kg - Study Part 2: Open-label evaluation of prophylaxis and on-demand - Study Part 3: Open-label repeat of PK evaluation (repeat Study Part 1) with BAX326 only in the same study subjects as in Study Part 1

Notes:

[2] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: Period 1 corresponds to Part 1 - Pharmacokinetic Crossover. Randomized subjects received 2 infusions each, 1 infusion with BAX326 and 1 infusion with
BeneFIX, at a dose of 75 ± 5 IU/kg, each in a randomized order. All subjects from Part 1 transitioned to Part 2, which is the main part of the study and is defined as the baseline period.

Number of subjects in period 2	Part 2 Only: BAX326 Prophylaxis	Part 2 Only: BAX326 On-Demand	Part 1: PK crossover - Part 2: Prophylaxis - Part 3: PK BAX326
Started	31	14	28
Completed	29	14	28
Not completed	2	0	0
Consent withdrawn by subject	1	-	-
Physician decision	1	-	-

Period 3

Period 3 title	Part 3 -Pharmacokinetic BAX326 Only
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Arm title	PK BAX326 Only

Arm description:

Open-label repeat of PK evaluation (repeat Study Part 1) with BAX326 (75 ± 5 IU/kg) only and same study participants as Study Part 1

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

Dosage and administration details:

Study Part 1: PK Crossover with BAX326 and BeneFIX, at a dose of 75 ± 5 IU/kg - Study Part 2: Open-label evaluation of prophylaxis and on-demand - Study Part 3: Open-label repeat of PK evaluation (repeat Study Part 1) with BAX326 only in the same study subjects as in Study Part 1

Number of subjects in period 3	PK BAX326 Only
Started	28
Completed	25
Not completed	3
Emergency surgery	1
Protocol deviation	2

Baseline characteristics

Reporting groups	
Reporting group title	Part 2 -BAX326 Prophylaxis and On-demand
Reporting group description:	
Part 2 -BAX326 Prophylaxis and On-demand	

Reporting group values	Part 2 -BAX326 Prophylaxis and On-demand	Total	
Number of subjects	73	73	
Age categorical Units: Subjects			
Age continuous			
Age continuous description			
Units: years			
arithmetic mean	34.5		
standard deviation	± 12.2	-	
Gender categorical			
Gender categorical description			
Units: Subjects			
Female	0	0	
Male	73	73	
Region of Enrollment Units: Subjects			
Spain	1	1	
Ukraine	8	8	
Chile	4	4	
Russian Federation	12	12	
Colombia	5	5	
United Kingdom	2	2	
Czech Republic	2	2	
Argentina	2	2	
Brazil	1	1	
Poland	12	12	
Romania	8	8	
Bulgaria	10	10	
Japan	5	5	
Sweden	1	1	

Subject analysis sets	
Subject analysis set title	Study Part 1: PK with BAX326
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
In Part 1, randomized subjects received 2 infusions each, 1 infusion with BAX326 and 1 infusion with BeneFIX, at a dose of 75 ± 5 IU/kg, each in a randomized order.	

Subject analysis set title	Study Part 1: PK with BeneFIX
Subject analysis set type	Sub-group analysis

Subject analysis set description:

In Part 1, randomized subjects received 2 infusions each, 1 infusion with BAX326 and 1 infusion with BeneFIX, at a dose of 75 ± 5 IU/kg, each in a randomized order.

Subject analysis set title	Study Part 2: Prophylactic cohort
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects in the prophylactic cohort were to be treated with a prophylactic regimen of 50 IU/kg BAX326 twice weekly for a period of 6 months or for at least 50 EDs, whichever occurred last. 56 subjects received a minimum of 3 months of prophylactic treatment with BAX326. A further 3 subjects received less than 3 months of prophylactic treatment with BAX326.

Subject analysis set title	Study Part 2: On-demand cohort
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects in the on-demand cohort were to receive BAX326 for on-demand treatment.

Subject analysis set title	Study Part 3: Repeat PK with BAX326 only
Subject analysis set type	Sub-group analysis

Subject analysis set description:

In Part 3, subjects who had participated in Part 1 and had a minimum of 30 exposure days to BAX326 in Part 2 underwent a repeat PK with BAX326 only, at a dose of 75 ± 5 IU/kg.

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

Subject analysis set description:

Comprises 73 subjects who were exposed to investigational product.

Reporting group values	Study Part 1: PK with BAX326	Study Part 1: PK with BeneFIX	Study Part 2: Prophylactic cohort
Number of subjects	28	28	59
Age categorical Units: Subjects			
Age continuous			
Age continuous description			
Units: years			
arithmetic mean	33.9	33.9	34.7
standard deviation	± 11.2	± 11.2	± 12
Gender categorical			
Gender categorical description			
Units: Subjects			
Female	0	0	0
Male	28	28	59
Region of Enrollment Units: Subjects			
Spain	0	0	1
Ukraine	1	1	5
Chile	0	0	4
Russian Federation	4	4	7
Colombia	4	4	5
United Kingdom	2	2	2
Czech Republic	0	0	1
Argentina	1	1	2

Brazil	0	0	1
Poland	7	7	12
Romania	1	1	7
Bulgaria	6	6	6
Japan	2	2	5
Sweden	0	0	1

Reporting group values	Study Part 2: On-demand cohort	Study Part 3: Repeat PK with BAX326 only	Full Analysis Set
Number of subjects	14	25	73
Age categorical Units: Subjects			
Age continuous			
Age continuous description			
Units: years			
arithmetic mean	33.1	33.9	34.5
standard deviation	± 12.4	± 11.3	± 12.2
Gender categorical			
Gender categorical description			
Units: Subjects			
Female	0	0	0
Male	14	25	73
Region of Enrollment Units: Subjects			
Spain	0	0	1
Ukraine	3	1	8
Chile	0	0	4
Russian Federation	5	4	12
Colombia	0	3	5
United Kingdom	0	1	2
Czech Republic	1	0	2
Argentina	0	1	2
Brazil	0	0	1
Poland	0	6	12
Romania	1	1	8
Bulgaria	4	6	10
Japan	0	2	5
Sweden	0	0	1

End points

End points reporting groups

Reporting group title	Pharmacokinetic Crossover with BAX326 and BeneFIX
Reporting group description:	
In Part 1, randomized subjects received 2 infusions each, 1 infusion with BAX326 and 1 infusion with BeneFIX, at a dose of 75 ± 5 IU/kg, each in a randomized order.	
Reporting group title	Part 2 Only: BAX326 Prophylaxis
Reporting group description:	
Participants were only in Study Part 2 (i.e., did not participate in Study Parts 1 and 3)	
Reporting group title	Part 2 Only: BAX326 On-Demand
Reporting group description:	
Participants were only in Study Part 2 (i.e., did not participate in Study Parts 1 and 3)	
Reporting group title	Part 1: PK crossover - Part 2: Prophylaxis - Part 3: PK BAX326
Reporting group description:	
-Study Part 1: Pharmacokinetic (PK) Crossover with BeneFIX (75 ± 5 IU/kg) and BAX326 (75 ± 5 IU/kg). -Study Part 2: Open-label evaluation of prophylaxis -Study Part 3: Open-label repeat of PK evaluation (repeat Study Part 1) with BAX326 (75 ± 5 IU/kg) only and same study participants as Study Part 1	
Reporting group title	PK BAX326 Only
Reporting group description:	
Open-label repeat of PK evaluation (repeat Study Part 1) with BAX326 (75 ± 5 IU/kg) only and same study participants as Study Part 1	
Subject analysis set title	Study Part 1: PK with BAX326
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
In Part 1, randomized subjects received 2 infusions each, 1 infusion with BAX326 and 1 infusion with BeneFIX, at a dose of 75 ± 5 IU/kg, each in a randomized order.	
Subject analysis set title	Study Part 1: PK with BeneFIX
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
In Part 1, randomized subjects received 2 infusions each, 1 infusion with BAX326 and 1 infusion with BeneFIX, at a dose of 75 ± 5 IU/kg, each in a randomized order.	
Subject analysis set title	Study Part 2: Prophylactic cohort
Subject analysis set type	Full analysis
Subject analysis set description:	
Subjects in the prophylactic cohort were to be treated with a prophylactic regimen of 50 IU/kg BAX326 twice weekly for a period of 6 months or for at least 50 EDs, whichever occurred last. 56 subjects received a minimum of 3 months of prophylactic treatment with BAX326. A further 3 subjects received less than 3 months of prophylactic treatment with BAX326.	
Subject analysis set title	Study Part 2: On-demand cohort
Subject analysis set type	Full analysis
Subject analysis set description:	
Subjects in the on-demand cohort were to receive BAX326 for on-demand treatment.	
Subject analysis set title	Study Part 3: Repeat PK with BAX326 only
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
In Part 3, subjects who had participated in Part 1 and had a minimum of 30 exposure days to BAX326 in Part 2 underwent a repeat PK with BAX326 only, at a dose of 75 ± 5 IU/kg.	
Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis
Subject analysis set description:	
Comprises 73 subjects who were exposed to investigational product.	

Primary: Study Part 1- Area under the plasma concentration versus time curve from 0 to 72 hours per dose

End point title	Study Part 1- Area under the plasma concentration versus time curve from 0 to 72 hours per dose

End point description:

Computed using the linear trapezoidal method. The concentration at 72 hours was interpolated from the two nearest sampling time points or extrapolated using the last quantifiable concentration and the terminal rate constant λz. λz was estimated from the slope of natural log-linear fitting to latter quantifiable concentrations, with largest adjusted R^2. The pharmacokinetic per-protocol analysis set comprises 25 subjects who participated in Parts 1 and 3 and completed Part 1 without any major protocol deviation.

End point type	Primary

End point timeframe:

72 hours

End point values	Study Part 1: PK with BAX326	Study Part 1: PK with BeneFIX		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	25	25		
Units: (IU·hr/dL) / (IU/kg)				
median (inter-quartile range (Q1-Q3))	14.3 (11.2 to 15.95)	13.42 (11.08 to 15.1)		

Statistical analyses

Statistical analysis title	PK equivalence of BAX326 with BeneFIX

Statistical analysis description:

To assess PK equivalence of BAX326 and BeneFIX, the 90% confidence interval for the difference of the mean natural logarithms of the area under the plasma concentration versus time curve from 0 to 72 hours per dose (AUC0-72h/dose) between the 2 groups was calculated. To establish the equivalence in AUC0-72h /dose with a type I error of 5%, the calculated two-sided 90% confidence interval for the ratio had to be contained completely within the margins of equivalence defined as 80% to 125%.

Comparison groups	Study Part 1: PK with BAX326 v Study Part 1: PK with BeneFIX
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	Ratio of Geometric Means
Point estimate	1.063
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.03
upper limit	1.09

Secondary: Study Parts 1 and 3: Area under the plasma concentration/time curve from time 0 to infinity per dose (AUC0-∞/ dose)

End point title	Study Parts 1 and 3: Area under the plasma concentration/time

	curve from time 0 to infinity per dose (AUC0-∞/ dose)

End point description:

Defined as (AUC0-t + Ct)/ λz/ dose, where t is the time of last quantifiable concentration, Ct is the last quantifiable concentration. λz will be estimated from the slope of natural log-linear fitting to latter quantifiable concentrations, with largest adjusted R^2. The objective of Study Part 3 was to re-evaluate the Pharmacokinetic (PK) parameters for BAX 326 after a period of 6 months of treatment, in participants who accumulated at least 30 EDs to BAX 326, and to compare them with those determined in the same participants participating in Study Part 1. The PK per-protocol analysis set comprises 25 subjects for Part 1 and 23 subjects for Part 3.

End point type	Secondary

End point timeframe:

0-30 minutes before infusion up to 72 hours post-infusion

End point values	Study Part 1: PK with BAX326	Study Part 1: PK with BeneFIX	Study Part 3: Repeat PK with BAX326 only	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	25	25	23	
Units: (IU·hr)/ dL/ (IU/kg)				
median (inter-quartile range (Q1-Q3))	16.07 (13.43 to 17.48)	15.26 (13.71 to 17.05)	17.38 (14.17 to 20.7)	

Statistical analyses

No statistical analyses for this end point

Secondary: Study Parts 1 and 3: Mean residence time (MRT)

End point title	Study Parts 1 and 3: Mean residence time (MRT)

End point description:

Computed as Area under the moment curve 0-∞ (AUMC0-∞) / AUC0-∞- TI/2, where AUMC0-∞ will be determined in a similar manner as AUC0-∞ and TI represents infusion duration [hr] The objective of Study Part 3 was to re-evaluate the Pharmacokinetic (PK) parameters for BAX 326 after a period of 6 months of treatment, in participants who accumulated at least 30 EDs to BAX 326, and to compare them with those determined in the same participants participating in Study Part 1. The PK per-protocol analysis set comprises 25 subjects for Part 1 and 23 subjects for Part 3.

End point type	Secondary

End point timeframe:

0-30 minutes before infusion up to 72 hours post-infusion

End point values	Study Part 1: PK with BAX326	Study Part 1: PK with BeneFIX	Study Part 3: Repeat PK with BAX326 only	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	25	25	23	
Units: Hour				
median (inter-quartile range (Q1-Q3))	28.93 (26.45 to 31.5)	30.59 (28.13 to 34.84)	29.04 (28 to 32.31)	

Statistical analyses

No statistical analyses for this end point

Secondary: Study Parts 1 and 3: Clearance (CL)

End point title	Study Parts 1 and 3: Clearance (CL)

End point description:

Computed as Dose/ AUC0-∞. The objective of Study Part 3 was to re-evaluate the Pharmacokinetic (PK) parameters for BAX 326 after a period of 6 months of treatment, in participants who accumulated at least 30 EDs to BAX 326, and to compare them with those determined in the same participants participating in Study Part 1. The pharmacokinetic per-protocol analysis set comprises 25 subjects for Part 1 and 23 subjects for Part 3.

End point type	Secondary

End point timeframe:

0-30 minutes before infusion up to 72 hours post-infusion

End point values	Study Part 1: PK with BAX326	Study Part 1: PK with BeneFIX	Study Part 3: Repeat PK with BAX326 only	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	25	25	23	
Units: dL/(kg·hr)				
median (inter-quartile range (Q1-Q3))	0.0622 (0.0572 to 0.0745)	0.0655 (0.0587 to 0.073)	0.0576 (0.0483 to 0.0706)	

Statistical analyses

No statistical analyses for this end point

Secondary: Study Parts 1 and 3: Incremental Recovery at Cmax (IR at Cmax)

End point title	Study Parts 1 and 3: Incremental Recovery at Cmax (IR at Cmax)

End point description:

Defined as (Cmax - Cpre-infusion)/Dose, where maximum concentration (Cmax) will be determined as the highest concentration achieved within one hour after infusion. The objective of Study Part 3 was to re-evaluate the Pharmacokinetic (PK) parameters for BAX 326 after a period of 6 months of treatment, in participants who accumulated at least 30 EDs to BAX 326, and to compare them with those determined in the same participants participating in Study Part 1. The pharmacokinetic per-protocol analysis set comprises 25 subjects for Part 1 and 23 subjects for Part 3.

End point type	Secondary

End point timeframe:

0-30 minutes before infusion up to 1 hour post-infusion

End point values	Study Part 1: PK with BAX326	Study Part 1: PK with BeneFIX	Study Part 3: Repeat PK with BAX326 only	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	25	25	23	
Units: (IU/dL) / (IU/kg)				
median (inter-quartile range (Q1-Q3))	0.88 (0.79 to 0.98)	0.73 (0.66 to 0.87)	0.93 (0.76 to 1.18)	

Statistical analyses

No statistical analyses for this end point

Secondary: Incremental Recovery (IR) at 30 Minutes Over Time

End point title	Incremental Recovery (IR) at 30 Minutes Over Time

End point description:

IR at 30 Minutes was measured at the following time points during the study: - Part 1 or Part 2, Exposure Day (ED) 1. (If participant was present for Study Part 1, then ED 1 from Part 1 was used. If Participant entered study in Study Part 2, then ED 1 from Part 2 was used.) - Part 2: Week 5 - Part 2: Week 13 - Part 2 or Part 3: Week 26 (Week 26 of study participation) - Study Completion or Termination Visit

End point type	Secondary

End point timeframe:

0-30 minutes before infusion and 30 minutes post-infusion

End point values	Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	73			
Units: (IU/dL) / (IU/kg)				
median (inter-quartile range (Q1-Q3))				
Part 1 or Part 2, Exposure Day 1 (n=73)	0.78 (0.7 to 0.91)			
Part 2: Week 5 (n=71)	0.79 (0.68 to 0.96)			
Part 2: Week 13 (n=68)	0.83 (0.655 to 1.015)			
Part 2 or 3: Week 26 (n=55)	0.88 (0.75 to 1.04)			
Study Completion or Termination Visit (n=23)	0.89 (0.73 to 0.96)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Incremental Recovery (IR) at 30 Minutes Over Time

End point title	Change in Incremental Recovery (IR) at 30 Minutes Over Time

End point description:

The median changes in IR at 30 Minutes, calculated as the change in IR value from exposure day 1 (ED1).

End point type	Secondary

End point timeframe:

0-30 minutes before infusion and 30 minutes post-infusion

End point values	Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	71			
Units: (IU/dL) / (IU/kg)				
median (inter-quartile range (Q1-Q3))				
Part 2: Week 5 (n=71)	0.03 (-0.09 to 0.11)			
Part 2: Week 13 (n=68)	0.075 (-0.07 to 0.17)			
Part 2 or Part 3: Week 26 (n=55)	0.06 (0.02 to 0.17)			
Study Completion or Termination Visit (n=23)	0.12 (0 to 0.21)			

Statistical analyses

No statistical analyses for this end point

Secondary: Study Parts 1 and 3: Half Life (T 1/2)

End point title	Study Parts 1 and 3: Half Life (T 1/2)

End point description:

Elimination phase half-life will be determined as ln2/ λz. The objective of Study Part 3 was to re-evaluate the Pharmacokinetic (PK) parameters for BAX 326 after a period of 6 months of treatment, in participants who accumulated at least 30 EDs to BAX 326, and to compare them with those determined in the same participants participating in Study Part 1. The pharmacokinetic per-protocol analysis set comprises 25 subjects for Part 1 and 23 subjects for Part 3.

End point type	Secondary

End point timeframe:

0-30 minutes before infusion up to 72 hours post-infusion

End point values	Study Part 1: PK with BAX326	Study Part 1: PK with BeneFIX	Study Part 3: Repeat PK with BAX326 only	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	25	25	23	
Units: Hour				
median (inter-quartile range (Q1-Q3))	24.58 (20.98 to 29.68)	26.28 (22.51 to 29.46)	24.59 (19.68 to 29.14)	

Statistical analyses

No statistical analyses for this end point

Secondary: Study Parts 1 and 3: Volume of distribution at steady state (Vss)

End point title	Study Parts 1 and 3: Volume of distribution at steady state (Vss)

End point description:

Vss computed as CL·MRT. The objective of Study Part 3 was to re-evaluate the Pharmacokinetic (PK) parameters for BAX 326 after a period of 6 months of treatment, in participants who accumulated at least 30 EDs to BAX 326, and to compare them with those determined in the same participants participating in Study Part 1. The pharmacokinetic per-protocol analysis set comprises 25 subjects for Part 1 and 23 subjects for Part 3.

End point type	Secondary

End point timeframe:

0-30 minutes before infusion up to 72 hours post-infusion

End point values	Study Part 1: PK with BAX326	Study Part 1: PK with BeneFIX	Study Part 3: Repeat PK with BAX326 only	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	25	25	23	
Units: dL/kg				
median (inter-quartile range (Q1-Q3))	1.72 (1.56 to 2.3)	1.98 (1.76 to 2.51)	1.74 (1.49 to 2.05)	

Statistical analyses

No statistical analyses for this end point

Secondary: Study Part 2: Annualized Bleed Rate (ABR) during prophylactic treatment with BAX326

End point title	Study Part 2: Annualized Bleed Rate (ABR) during prophylactic treatment with BAX326

End point description:

ABR during prophylaxis (twice-weekly) in Part 2 was calculated as (Number of bleeding episodes/observed treatment period in days) * 365.25. The treatment period on prophylaxis was defined as time between the first and the last prophylactic infusions and ABR on prophylaxis was calculated for participants who received a minimum of 3 months of prophylactic treatment with BAX326.

End point type	Secondary

End point timeframe:

Study Part 2 = 26 weeks ± 1 week (Note: Study Part 1 = 2-4 weeks)

End point values	Study Part 2: Prophylactic cohort			
Subject group type	Subject analysis set			
Number of subjects analysed	56			
Units: Bleeds per year				
median (inter-quartile range (Q1-Q3))				
Joint bleeding episode	0 (0 to 4.5)			
Non-Joint bleeding episode	0 (0 to 2)			
Spontaneous bleeding episode	0 (0 to 2)			
Bleeding episode caused by injury	0 (0 to 2.1)			
Unknown cause of bleeding episode	0 (0 to 0)			
All bleeding episodes	1.99 (0 to 6.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Bleeding Episodes Treated With 1, 2 or ≥3 Infusions of BAX326

End point title	Bleeding Episodes Treated With 1, 2 or ≥3 Infusions of BAX326

End point description:

The number of bleeding episodes treated with 1, 2, or ≥3 infusions of BAX326 to achieve adequate hemostasis. Only infusions required until resolution of bleed were considered. There were a total of 249 bleeding episodes in 47 subjects in the Full Analysis Set (ie, in all 14 on-demand subjects and in 33 of 59 subjects who received prophylaxis).

End point type	Secondary

End point timeframe:

Study Part 2 = 26 weeks ± 1 week (Study Part 2 began at week 3-5)

End point values	Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	47			
Units: Bleeding episodes				
1 infusion	153			
2 infusions	58			
3 or more infusions	38			

Statistical analyses

No statistical analyses for this end point

Secondary: Hemostatic Efficacy at Resolution of All Bleeding Episodes (BEs) Treated with BAX326

End point title	Hemostatic Efficacy at Resolution of All Bleeding Episodes (BEs) Treated with BAX326

End point description:

There were a total of 249 bleeding episodes in 47 subjects in the Full Analysis Set (ie, in all 14 on-demand subjects and in 33 of 59 subjects who received prophylaxis). 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

End point timeframe:

At bleed resolution throughout the study period of 22 months (Study Parts 1, 2, and 3)

End point values	Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	47			
Units: Bleeding episodes				
Excellent	102			
Good	137			
Fair	5			
None	0			
Not Reported	5			

Statistical analyses

No statistical analyses for this end point

Secondary: Total Weight-adjusted Dose per Bleeding Episode (BEs) of All BEs Treated with BAX326 by Bleeding Site and Cause

End point title	Total Weight-adjusted Dose per Bleeding Episode (BEs) of All BEs Treated with BAX326 by Bleeding Site and Cause

End point description:

There were a total of 249 bleeding episodes in 47 subjects in the Full Analysis Set (ie, in all 14 on-demand subjects and in 33 of 59 subjects who received prophylaxis).

End point type	Secondary

End point timeframe:

Study Part 2 = 26 weeks ± 1 week (Note: Study Part 1 = 2-4 weeks)

End point values	Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	47			
Units: IU/kg				
median (inter-quartile range (Q1-Q3))				
Bleeding Site: Target Joint (107 BEs)	56.5 (48 to 97)			
Bleeding Site: Non-Target Joint (90 BEs)	59 (46 to 97)			
Bleeding Site: All Joint (197 BEs)	56.5 (47 to 97)			
Bleeding Site: Non-Joint (52 BEs)	68.7 (50 to 130)			
Bleeding Cause: Spontaneous (130 BEs)	52.3 (45 to 92)			
Bleeding Cause: Inury (90 BEs)	70 (48 to 116)			
Bleeding Cause: Unknown (29 BEs)	56.5 (51 to 108)			

Statistical analyses

No statistical analyses for this end point

Secondary: Consumption of BAX326 per Event per Subject

End point title	Consumption of BAX326 per Event per Subject

End point description:

Weight-adjusted consumption of BAX326 by event per participant, i.e., for prophylactic treatment and for treatment of bleeds until resolution of bleed. Includes all participants who received any infusions for bleeding treatment in the Full Analysis Set (ie, includes all on-demand arm (n=14) and 33 subjects from the prophylaxis arm who experienced a bleeding episode).

End point type	Secondary

End point timeframe:

Study Part 2 = 26 weeks ± 1 week (Note: Study Part 1 = 2-4 weeks)

End point values	Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	73[1]			
Units: IU/kg				
median (inter-quartile range (Q1-Q3))				
Prophylactic Treatment (n=59)	50.5 (46 to 52)			
Bleeding Treatment (n=47)	87.1 (56 to 125)			

Notes:

[1] - Of 73 subjects in the FAS, 59 had prophylactic treatment and 47 had bleed treatment.

Statistical analyses

No statistical analyses for this end point

Secondary: Consumption of BAX326 per Subject: Median Number of Infusions per Month

End point title	Consumption of BAX326 per Subject: Median Number of Infusions per Month

End point description:

End point type	Secondary

End point timeframe:

Study Part 1 = 2-4 weeks, Study Part 2 = 26 weeks ± 1 week (Prophylaxis and On-Demand period), Study Part 3 = 1 week (Total = 29-31 weeks)

End point values	Study Part 2: Prophylactic cohort	Study Part 2: On-demand cohort		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	59	14		
Units: Infusions				
median (inter-quartile range (Q1-Q3))	6.7 (6 to 7)	2.7 (2 to 4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Consumption of BAX326 per Subject: Median Weight-adjusted Consumption per Month

End point title	Consumption of BAX326 per Subject: Median Weight-adjusted Consumption per Month

End point description:

End point type	Secondary

End point timeframe:

Study Part 1 = 2-4 weeks, Study Part 2 = 26 weeks ± 1 week (Prophylaxis and On-Demand period), Study Part 3 = 1 week (Total = 29-31 weeks)

End point values	Study Part 2: Prophylactic cohort	Study Part 2: On-demand cohort		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	59	14		
Units: IU/kg				
median (inter-quartile range (Q1-Q3))	347.8 (320 to 396)	167.3 (102 to 234)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Who Developed Inhibitory Antibodies to Factor IX (FIX)

End point title	Number of Participants Who Developed Inhibitory Antibodies to Factor IX (FIX)

End point description:

End point type	Secondary

End point timeframe:

Study Part 1 = 2-4 weeks, Study Part 2 = 26 weeks ± 1 week, Study Part 3 = 1 week (Total = 29-31 weeks)

End point values	Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	73			
Units: participants	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Occurrence of total binding antibodies of indeterminate specificity (within assay variability)

End point title	Occurrence of total binding antibodies of indeterminate specificity (within assay variability)

End point description:

Occurrence of total binding antibodies of indeterminate specificity (within assay variability) to FIX, antibodies to CHO proteins and rFurin is defined by a dilution of 2 or less increase as compared to levels at screening visit (e.g. negative to 1:20 or 1:40).

End point type	Secondary

End point timeframe:

Study Part 1 = 2-4 weeks, Study Part 2 = 26 weeks ± 1 week, Study Part 3 = 1 week (Total = 29-31 weeks)

End point values	Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	73			
Units: participants				
Binding Antibody to Factor IX (FIX)	6			
Antibody to Chinese hamster ovary (CHO) Protein	0			
Antibody to recombinant Furin (rFurin)	9			

Statistical analyses

No statistical analyses for this end point

Secondary: Occurrence of treatment related total binding antibodies

End point title	Occurrence of treatment related total binding antibodies

End point description:

Occurrence of treatment related total binding antibodies to Factor IX (FIX), antibodies to Chinese hamster ovary (CHO) proteins, and recombinant furin (rFurin) is defined by more than 2-dilution increase as compared to levels at screening visit and confirmed specificity (e.g. negative to 1:80)

End point type	Secondary

End point timeframe:

Study Part 1 = 2-4 weeks, Study Part 2 = 26 weeks ± 1 week, Study Part 3 = 1 week (Total = 29-31 weeks)

End point values	Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	73			
Units: participants				
Treatment Related Binding Antibody to Factor IX	0			
Treatment Related Antibody to CHO Protein	0			
Treatment Related Antibody to rFurin	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Who Experienced Severe Allergic Reactions (e.g. Anaphylaxis)

End point title	Number of Subjects Who Experienced Severe Allergic Reactions (e.g. Anaphylaxis)

End point description:

End point type	Secondary

End point timeframe:

Study Part 1 = 2-4 weeks, Study Part 2 = 26 weeks ± 1 week, Study Part 3 = 1 week (Total = 29-31 weeks)

End point values	Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	73			
Units: subjects	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Who Experienced Thrombotic Events

End point title	Number of Subjects Who Experienced Thrombotic Events

End point description:

End point type	Secondary

End point timeframe:

Study Part 1 = 2-4 weeks, Study Part 2 = 26 weeks ± 1 week, Study Part 3 = 1 week (Total = 29-31 weeks)

End point values	Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	73			
Units: subjects	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with clinically significant changes in laboratory parameters: clinical chemistry

End point title	Number of subjects with clinically significant changes in laboratory parameters: clinical chemistry

End point description:

Clinically significant changes in chemistry assessments for Alanine Aminotransferase, Albumin, Alkaline Phosphatase, Aspartate Aminotransferase, Bicarbonate, Bilirubin, Blood Urea Nitrogen, Chloride, Glucose, Potassium, Protein (Serum), Sodium. Clinically Significant (CS) defined as: -1. The abnormal value constitutes an adverse event (AE) and, -2. The abnormal value is a symptom of or related to a disease that is already recorded as an AE in Case Report Form (CRF).

End point type	Secondary

End point timeframe:

Study Part 1 = 2-4 weeks, Study Part 2 = 26 weeks ± 1 week, Study Part 3 = 1 week (Total = 29-31 weeks)

End point values	Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	73			
Units: subjects	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with clinically significant changes in laboratory parameters: hematology

End point title	Number of subjects with clinically significant changes in laboratory parameters: hematology

End point description:

Clinically significant changes in hematology assessments for Basophils, Basophils/Leukocytes, Eosinophils, Eosinophils/Leukocytes, Erythrocyte Mean Corpuscular Hemoglobin Concentration, Erythrocyte Mean Corpuscular Volume, Erythrocytes, Hematocrit, Hemoglobin, Leukocytes, Lymphocytes, Lymphocytes/Leukocytes, Monocytes, Monocytes/Leukocytes, Neutrophils, Neutrophils/Leukocytes, Platelets,

End point type	Secondary

End point timeframe:

Study Part 1 = 2-4 weeks, Study Part 2 = 26 weeks ± 1 week, Study Part 3 = 1 week (Total = 29-31 weeks)

End point values	Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	73			
Units: subjects	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Clinically significant changes in laboratory parameters: vital signs

End point title	Number of Subjects With Clinically significant changes in laboratory parameters: vital signs

End point description:

Clinically significant changes in vital signs assessments for pulse rate, systolic/diastolic blood pressure, respiratory rate, body temperature

End point type	Secondary

End point timeframe:

Study Part 1 = 2-4 weeks, Study Part 2 = 26 weeks ± 1 week, Study Part 3 = 1 week (Total = 29-31 weeks)

End point values	Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	73			
Units: subjects	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Clinically significant changes in laboratory parameters: thrombogenic markers

End point title	Number of Subjects With Clinically significant changes in laboratory parameters: thrombogenic markers

End point description:

Clinically significant changes in thrombogenic markers assessments for thrombin-antithrombin (TAT), prothrombin fragment 1.2, and D-dimer as evaluated by an independent Data Monitoring Committee (DMC)

End point type	Secondary

End point timeframe:

Study Part 1 = 2-4 weeks, Study Part 2 = 26 weeks ± 1 week, Study Part 3 = 1 week (Total = 29-31 weeks)

End point values	Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	73			
Units: subjects	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Adverse Events (AEs) Considered Related to BAX326 Treatment

End point title	Number of Adverse Events (AEs) Considered Related to

	BAX326 Treatment

End point description:

Probable, possible, or unknown causality assessment of an AE was to be counted as "related".

End point type	Secondary

End point timeframe:

Study Part 1 = 2-4 weeks, Study Part 2 = 26 weeks ± 1 week, and Study Part 3 = 1 week (Total = 29-31 weeks)

End point values	Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	73			
Units: related adverse events				
Serious- Mild	0			
Serious- Moderate	0			
Serious- Severe	0			
Serious- Unknown	0			
Non-Serious- Mild	2			
Non-Serious- Moderate	0			
Non-Serious- Severe	0			
Non-Serious- Unknown	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Adverse Events (AEs) Considered Related to BAX326 Treatment

End point title	Number of Subjects with Adverse Events (AEs) Considered Related to BAX326 Treatment

End point description:

End point type	Secondary

End point timeframe:

Study Part 1 = 2-4 weeks, Study Part 2 = 26 weeks ± 1 week, and Study Part 3 = 1 week (Total = 29-31 weeks)

End point values	Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	73			
Units: subjects				
Serious- Mild	0			
Serious- Moderate	0			
Serious- Severe	0			

Serious- Unknown	0			
Non-Serious- Mild	1			
Non-Serious- Moderate	0			
Non-Serious- Severe	0			
Non-Serious- Unknown	1			

Statistical analyses

No statistical analyses for this end point

Secondary: EuroQoL (Quality of Life)-5 Dimensions (EQ-5D) Total Index Scores

End point title	EuroQoL (Quality of Life)-5 Dimensions (EQ-5D) Total Index Scores

End point description:

EQ-5D is a subject answered questionnaire scoring 5 dimensions - mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The EQ-5D total score ranges from 0 (worst health state) to 1 (perfect health state) and 1 reflects the best outcome.

End point type	Secondary

End point timeframe:

Baseline at either Study Part 1, or Study Part 2, and End of Study (study weeks 29-31)

End point values	Study Part 2: Prophylactic cohort	Study Part 2: On-demand cohort		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	55[2]	14		
Units: Score on a scale				
arithmetic mean (standard deviation)				
Part 1 or Part 2, Exposure Day 1 (Baseline)	0.75 (± 0.16)	0.72 (± 0.14)		
End of Study	0.75 (± 0.16)	0.73 (± 0.09)		
Change from Baseline	0.01 (± 0.18)	0 (± 0.13)		

Notes:

[2] - N=56 at baseline, N=55 at end of study

Statistical analyses

No statistical analyses for this end point

Secondary: EuroQoL (Quality of Life)-5 Dimensions Visual Analogue Scale (EQ-5D VAS) Scores

End point title	EuroQoL (Quality of Life)-5 Dimensions Visual Analogue Scale (EQ-5D VAS) Scores

End point description:

Subject rated questionnaire to assess health-related quality of life in terms of a single index value. The VAS component rates current health state on a scale from 0 (worst imaginable health state) to 100 (best imaginable health state); higher scores indicate a better quality of life.

End point type	Secondary

End point timeframe:

Baseline at either Study Part 1, or Study Part 2, and End of Study (study weeks 29-31)

End point values	Study Part 2: Prophylactic cohort	Study Part 2: On-demand cohort		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	54[3]	14		
Units: Score on a scale				
arithmetic mean (standard deviation)				
Part 1 or Part 2, Exposure Day 1 (Baseline)	58.75 (± 24.89)	56.64 (± 25.97)		
End of Study	68.22 (± 22.78)	62.07 (± 19)		
Change from Baseline	9.98 (± 25.41)	5.43 (± 24.02)		

Notes:

[3] - N=56 at baseline, N=54 at end of study

Statistical analyses

No statistical analyses for this end point

Secondary: General pain assessment through a visual analog scale (VAS)

End point title	General pain assessment through a visual analog scale (VAS)

End point description:

Participant rated assessment of health-related quality of life. The VAS Pain Scale rates current health state on a scale from 0 (no pain) to 100 (worst imaginable pain). For the pain scale, a higher score indicates worse pain.

End point type	Secondary

End point timeframe:

Baseline at either Study Part 1, or Study Part 2, and End of Study (study weeks 29-31)

End point values	Study Part 2: Prophylactic cohort	Study Part 2: On-demand cohort		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	54[4]	14		
Units: Score on a scale				
arithmetic mean (standard deviation)				
Part 1 or Part 2, Exposure Day 1 (Baseline)	32.67 (± 26.62)	47.57 (± 30.82)		
End of Study	33.09 (± 25.9)	39.93 (± 22.57)		
Change from Baseline	0.35 (± 21.77)	-7.64 (± 33.58)		

Notes:

[4] - N=55 at baseline, N=54 at end of study

Statistical analyses

No statistical analyses for this end point

Secondary: Short Form (36) Health Survey (SF-36): HRQoL 'Physical Component Score' (PCS)

End point title	Short Form (36) Health Survey (SF-36): HRQoL 'Physical Component Score' (PCS)

End point description:

The PCS is a summary scale of the dimensions physical functioning, role physical, bodily pain, and general health. The component score is normalized to a standard population. Scores range from 0 to 100 with higher scores representing better health. There is no total overall score; scoring is done for both subscores and summary scores.

End point type	Secondary

End point timeframe:

Baseline at either Study Part 1, or Study Part 2, and End of Study (study weeks 29-31)

End point values	Study Part 2: Prophylactic cohort	Study Part 2: On-demand cohort		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	52[5]	13		
Units: Score on a scale				
arithmetic mean (standard deviation)				
Part 1 or Part 2, Exposure Day 1 (Baseline)	39.08 (± 9.39)	37.38 (± 7.2)		
End of Study	41.35 (± 8.73)	38.92 (± 8.53)		
Change from Baseline	2.6 (± 7.72)	1.54 (± 5.11)		

Notes:

[5] - N=54 at baseline, N=52 at end of study

Statistical analyses

No statistical analyses for this end point

Secondary: SF-36: HRQoL 'Mental Health' (MH)

End point title	SF-36: HRQoL 'Mental Health' (MH)

End point description:

Quality of life survey response as measured using the SF-36 questionnaire. Scores range from 0 to 100 with higher scores representing better health. There is no total overall score; scoring is done for both subscores and summary scores. The raw data from the SF-36 items were transformed to norm based scores for each of the 8 HRQoL/SF-36 health domain scores.

End point type	Secondary

End point timeframe:

Baseline at either Study Part 1, or Study Part 2, and End of Study (study weeks 29-31)

End point values	Study Part 2: Prophylactic cohort	Study Part 2: On-demand cohort		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	52[6]	13		
Units: Score on a scale				
arithmetic mean (standard deviation)				
Part 1 or Part 2, Exposure Day 1 (Baseline)	47.53 (± 9.46)	47.24 (± 8.8)		
End of Study	49.67 (± 9.3)	45.03 (± 9.96)		
Change from Baseline	2.01 (± 11.17)	-2.21 (± 8.28)		

Notes:

[6] - N=54 at baseline, N=52 at end of study

Statistical analyses

No statistical analyses for this end point

Secondary: SF-36: HRQoL Physical Functioning' (PF)

End point title	SF-36: HRQoL Physical Functioning' (PF)

End point description:

Quality of life survey response as measured using the SF-36 questionnaire. Scores range from 0 to 100 with higher scores representing better health. There is no total overall score; scoring is done for both subscores and summary scores. The raw data from the SF-36 items were transformed to norm based scores for each of the 8 HRQoL/SF-36 health domain scores.

End point type	Secondary

End point timeframe:

Baseline at either Study Part 1, or Study Part 2, and End of Study (study weeks 29-31)

End point values	Study Part 2: Prophylactic cohort	Study Part 2: On-demand cohort		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	53[7]	13		
Units: Score on a scale				
arithmetic mean (standard deviation)				
Part 1 or Part 2, Exposure Day 1 (Baseline) vs. En	40.2 (± 10.57)	40.04 (± 10.57)		
End of Study	40.75 (± 10.14)	39.87 (± 10.55)		
Change from Baseline	0.68 (± 7.48)	-0.16 (± 5.86)		

Notes:

[7] - N=54 at baseline, N=53 at end of study

Statistical analyses

No statistical analyses for this end point

Secondary: SF-36: HRQoL Role-Physical (RP)

End point title	SF-36: HRQoL Role-Physical (RP)

End point description:

Quality of life survey response as measured using the SF-36 questionnaire. Scores range from 0 to 100 with higher scores representing better health. There is no total overall score; scoring is done for both subscores and summary scores. The raw data from the SF-36 items were transformed to norm based scores for each of the 8 HRQoL/SF-36 health domain scores.

End point type	Secondary

End point timeframe:

Baseline at either Study Part 1, or Study Part 2, and End of Study (study weeks 29-31)

End point values	Study Part 2: Prophylactic cohort	Study Part 2: On-demand cohort		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	53[8]	13		
Units: Score on a scale				
arithmetic mean (standard deviation)				
Part 1 or Part 2, Exposure Day 1 (Baseline)	40.39 (± 10.7)	39.15 (± 8.13)		
End of Study	43.82 (± 8.67)	37.45 (± 10.12)		
Change from Baseline	3.47 (± 10.15)	-1.7 (± 5.86)		

Notes:

[8] - N=54 at baseline, N=53 at end of study

Statistical analyses

No statistical analyses for this end point

Secondary: SF-36: HRQoL Role-Emotional

End point title	SF-36: HRQoL Role-Emotional

End point description:

Quality of life survey response as measured using the SF-36 questionnaire. Scores range from 0 to 100 with higher scores representing better health. There is no total overall score; scoring is done for both subscores and summary scores. The raw data from the SF-36 items were transformed to norm based scores for each of the 8 HRQoL/SF-36 health domain scores.

End point type	Secondary

End point timeframe:

Baseline at either Study Part 1, or Study Part 2, and End of Study (study weeks 29-31)

End point values	Study Part 2: Prophylactic cohort	Study Part 2: On-demand cohort		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	53[9]	13		
Units: Score on a scale				
arithmetic mean (standard deviation)				
Part 1 or Part 2, Exposure Day 1 (Baseline)	44.22 (± 11.45)	40.93 (± 9.1)		
End of Study	44.8 (± 10.15)	39.43 (± 11.57)		

Change from Baseline	0.37 (± 11.74)	-1.5 (± 8.91)		

Notes:

[9] - N=54 at baseline, N=53 at end of study

Statistical analyses

No statistical analyses for this end point

Secondary: SF-36: HRQoL Bodily Pain

End point title	SF-36: HRQoL Bodily Pain

End point description:

Quality of life survey response as measured using the SF-36 questionnaire. Scores range from 0 to 100 with higher scores representing better health. There is no total overall score; scoring is done for both subscores and summary scores. The raw data from the SF-36 items were transformed to norm based scores for each of the 8 HRQoL/SF-36 health domain scores.

End point type	Secondary

End point timeframe:

Baseline at either Study Part 1, or Study Part 2, and End of Study (study weeks 29-31)

End point values	Study Part 2: Prophylactic cohort	Study Part 2: On-demand cohort		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	53[10]	13		
Units: Score on a scale				
arithmetic mean (standard deviation)				
Part 1 or Part 2, Exposure Day 1 (Baseline)	42.09 (± 10.21)	36.89 (± 7.84)		
End of Study	45.72 (± 8.68)	39.33 (± 8.91)		
Change from Baseline	3.45 (± 9.95)	2.44 (± 10.18)		

Notes:

[10] - N=54 at baseline, N=53 at end of study

Statistical analyses

No statistical analyses for this end point

Secondary: SF-36: HRQoL Mental Health

End point title	SF-36: HRQoL Mental Health

End point description:

Quality of life survey response as measured using the SF-36 questionnaire. Scores range from 0 to 100 with higher scores representing better health. There is no total overall score; scoring is done for both subscores and summary scores. The raw data from the SF-36 items were transformed to norm based scores for each of the 8 HRQoL/SF-36 health domain scores.

End point type	Secondary

End point timeframe:

Baseline at either Study Part 1, or Study Part 2, and End of Study (study weeks 29-31)

End point values	Study Part 2: Prophylactic cohort	Study Part 2: On-demand cohort		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	52[11]	13		
Units: Score on a scale				
arithmetic mean (standard deviation)				
Part 1 or Part 2, Exposure Day 1 (Baseline)	45.52 (± 8.78)	45.46 (± 10.57)		
End of Study	47.95 (± 8.84)	42.64 (± 10.63)		
Change from Baseline	2.44 (± 11.29)	-2.82 (± 8.53)		

Notes:

[11] - N=54 at baseline, N=52 at end of study

Statistical analyses

No statistical analyses for this end point

Secondary: SF-36: HRQoL Vitality

End point title	SF-36: HRQoL Vitality

End point description:

Quality of life survey response as measured using the SF-36 questionnaire. Scores range from 0 to 100 with higher scores representing better health. There is no total overall score; scoring is done for both subscores and summary scores. The raw data from the SF-36 items were transformed to norm based scores for each of the 8 HRQoL/SF-36 health domain scores.

End point type	Secondary

End point timeframe:

Baseline at either Study Part 1, or Study Part 2, and End of Study (study weeks 29-31)

End point values	Study Part 2: Prophylactic cohort	Study Part 2: On-demand cohort		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	52[12]	13		
Units: Score on a scale				
arithmetic mean (standard deviation)				
Part 1 or Part 2, Exposure Day 1 (Baseline)	50.07 (± 8.47)	50.17 (± 5.63)		
End of Study	52.75 (± 8.88)	50.89 (± 6.81)		
Change from Baseline	2.46 (± 10.75)	0.72 (± 5.43)		

Notes:

[12] - N=54 at baseline, N=52 at end of study

Statistical analyses

No statistical analyses for this end point

Secondary: SF-36: HRQoL Social Functioning

End point title	SF-36: HRQoL Social Functioning

End point description:

Quality of life survey response as measured using the SF-36 questionnaire. Scores range from 0 to 100 with higher scores representing better health. There is no total overall score; scoring is done for both subscores and summary scores. The raw data from the SF-36 items were transformed to norm based scores for each of the 8 HRQoL/SF-36 health domain scores.

End point type	Secondary

End point timeframe:

Baseline at either Study Part 1, or Study Part 2, and End of Study (study weeks 29-31)

End point values	Study Part 2: Prophylactic cohort	Study Part 2: On-demand cohort		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	53[13]	13		
Units: Score on a scale				
arithmetic mean (standard deviation)				
Part 1 or Part 2, Exposure Day 1 (Baseline)	41.8 (± 10.54)	43.42 (± 9.61)		
End of Study	44.6 (± 8.94)	42.17 (± 9.8)		
Change from Baseline	2.78 (± 10.78)	-1.26 (± 6.36)		

Notes:

[13] - N=54 at baseline, N=53 at end of study

Statistical analyses

No statistical analyses for this end point

Secondary: SF-36: HRQoL General Health

End point title	SF-36: HRQoL General Health

End point description:

Quality of life survey response as measured using the SF-36 questionnaire. Scores range from 0 to 100 with higher scores representing better health. There is no total overall score; scoring is done for both subscores and summary scores. The raw data from the SF-36 items were transformed to norm based scores for each of the 8 HRQoL/SF-36 health domain scores.

End point type	Secondary

End point timeframe:

Baseline at either Study Part 1, or Study Part 2, and End of Study (study weeks 29-31)

End point values	Study Part 2: Prophylactic cohort	Study Part 2: On-demand cohort		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	53[14]	13		
Units: Score on a scale				
arithmetic mean (standard deviation)				
Part 1 or Part 2, Exposure Day 1 (Baseline)	37.84 (± 8.38)	37.09 (± 10.47)		
End of Study	39.98 (± 9.03)	39.07 (± 8.88)		
Change from Baseline	2.2 (± 8.22)	1.98 (± 7.94)		

Notes:

[14] - N=54 at baseline, N=53 at end of study

Statistical analyses

No statistical analyses for this end point

Secondary: Pediatric Quality of Life Questionnaire (PedsQL) Physical Health Summary Score (Ages 12-16)

End point title	Pediatric Quality of Life Questionnaire (PedsQL) Physical Health Summary Score (Ages 12-16)

End point description:

The Peds-QL is a generic Health-Related Quality of Life (HR QoL) instrument designed specifically for a pediatric population. It captures the following domains: general health/activities, feelings/emotional, social functioning, school functioning. For this study, the Peds-QL for 12 to 16-year-old subjects was used. Higher scores indicate better quality of life (QOL) for all domains of the Peds-QL. This modular instrument uses a 5-point scale: from 0 (never) to 4 (almost always). Items are reversed scored and linearly transformed to a 0-100 scale as follows: 0=100, 1=75, 2=50, 3=25, 4=0. 4 dimensions (physical, emotional, social, & school functioning) are scored.

End point type	Secondary

End point timeframe:

Baseline at either Study Part 1, or Study Part 2, and End of Study (study weeks 29-31)

End point values	Study Part 2: Prophylactic cohort	Study Part 2: On-demand cohort		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	2	1		
Units: Score on a scale				
arithmetic mean (standard deviation)				
Part 1 or Part 2, Exposure Day 1 (Baseline)	65.63 (± 13.26)	65.63 (± 0)		
End of Study	54.69 (± 6.63)	65.63 (± 0)		
Change from Baseline	-10.94 (± 19.89)	0 (± 0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Pediatric Quality of Life Questionnaire (PedsQL) Psychosocial Health Summary Score (Ages 12-16)

End point title	Pediatric Quality of Life Questionnaire (PedsQL) Psychosocial Health Summary Score (Ages 12-16)

End point description:

The Peds-QL is a generic Health-Related Quality of Life (HR QoL) instrument designed specifically for a pediatric population. It captures the following domains: general health/activities, feelings/emotional, social functioning, school functioning. For this study, the Peds-QL for 12 to 16-year-old subjects was used. Higher scores indicate better quality of life (QOL) for all domains of the Peds-QL. This modular instrument uses a 5-point scale: from 0 (never) to 4 (almost always). Items are reversed scored and linearly transformed to a 0-100 scale as follows: 0=100, 1=75, 2=50, 3=25, 4=0. 4 dimensions (physical, emotional, social, & school functioning) are scored.

End point type	Secondary

End point timeframe:

Baseline at either Study Part 1, or Study Part 2, and End of Study (study weeks 29-31)

End point values	Study Part 2: Prophylactic cohort	Study Part 2: On-demand cohort		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	2	1		
Units: Score on a scale				
arithmetic mean (standard deviation)				
Part 1 or Part 2, Exposure Day 1 (Baseline)	63.33 (± 11.79)	88.33 (± 0)		
End of Study	55.83 (± 3.54)	86.67 (± 0)		
Change from Baseline	-7.5 (± 8.25)	-1.67 (± 0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Pediatric Quality of Life Questionnaire (PedsQL) Total Score (Ages 12-16)

End point title	Pediatric Quality of Life Questionnaire (PedsQL) Total Score (Ages 12-16)

End point description:

The Peds-QL is a generic Health-Related Quality of Life (HR QoL) instrument designed specifically for a pediatric population. It captures the following domains: general health/activities, feelings/emotional, social functioning, school functioning. For this study, the Peds-QL for 12 to 16-year-old subjects was used. Higher scores indicate better quality of life (QOL) for all domains of the Peds-QL. This modular instrument uses a 5-point scale: from 0 (never) to 4 (almost always). Items are reversed scored and linearly transformed to a 0-100 scale as follows: 0=100, 1=75, 2=50, 3=25, 4=0. 4 dimensions (physical, emotional, social, & school functioning) are scored.

End point type	Secondary

End point timeframe:

Baseline at either Study Part 1, or Study Part 2, and End of Study (study weeks 29-31)

End point values	Study Part 2: Prophylactic cohort	Study Part 2: On-demand cohort		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	2	1		
Units: Score on a scale				
arithmetic mean (standard deviation)				
Part 1 or Part 2, Exposure Day 1 (Baseline)	64.13 (± 12.3)	80.43 (± 0)		
End of Study	55.43 (± 0)	79.35 (± 0)		
Change from Baseline	-8.7 (± 12.3)	-1.09 (± 0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Health-Related Quality of Life (HRQoL) Disease-specific: Haem-A-QoL

End point title	Health-Related Quality of Life (HRQoL) Disease-specific: Haem-A-QoL

End point description:

The Haem-A-QOL instrument has 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 the Haem-A-QOL, higher scores indicate a worse quality of life. Scores on a scale range between 0 and 100.

End point type	Secondary

End point timeframe:

Baseline at either Study Part 1, or Study Part 2, and End of Study (study weeks 29-31)

End point values	Study Part 2: Prophylactic cohort	Study Part 2: On-demand cohort		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	48[15]	13		
Units: Score on a scale				
arithmetic mean (standard deviation)				
Part 1 or Part 2, Exposure Day 1 (Baseline)	40.68 (± 15.33)	41.65 (± 15.19)		
End of Study	37.85 (± 16.57)	41.37 (± 16.64)		
Change from Baseline	-3.52 (± 12.81)	-0.28 (± 12.18)		

Notes:

[15] - N=51 at baseline, N=50 at end of study, N=48 for change from baseline

Statistical analyses

No statistical analyses for this end point

Secondary: Health-Related Quality of Life (HRQoL) Disease-specific: Haemo-QoL - Participants On-Demand (Ages 12-16)

End point title	Health-Related Quality of Life (HRQoL) Disease-specific: Haemo-QoL - Participants On-Demand (Ages 12-16)

End point description:

The Haemo-QoL is a quality of life (QoL) assessment instrument for children and adolescents with haemophilia. As a hemophilia-specific instrument, this measure assesses very specific aspects of dealing with hemophilia. For the Haemo-QoL, higher scores indicate a worse quality of life. Scores on a scale range between 0 and 100.

End point type	Secondary

End point timeframe:

Baseline at either Study Part 1, or Study Part 2, and End of Study (study weeks 29-31)

End point values	Study Part 2: On-demand cohort			
Subject group type	Subject analysis set			
Number of subjects analysed	1			
Units: Score on a scale				
arithmetic mean (standard deviation)				
Part 1 or Part 2, Exposure Day 1 (Baseline)	40 (± 0)			
End of Study	40 (± 0)			
Change from Baseline	0 (± 0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Health Resource Use - Number of Hospitalizations

End point title	Health Resource Use - Number of Hospitalizations

End point description:

End point type	Secondary

End point timeframe:

Study Part 1 = 2-4 weeks, Study Part 2 = 26 weeks ± 1 week, Study Part 3 = 1 week (Total = 29-31 weeks)

End point values	Study Part 2: Prophylactic cohort	Study Part 2: On-demand cohort		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	57	14[16]		
Units: Hospitalizations				
median (full range (min-max))				
Part 1 - PK (N= 28/prophy; NA/on-demand)	0 (0 to 0)	0 (0 to 0)		
Part 2: Exp Day 1 (N= 31/prophy, 14/on-demand)	0 (0 to 0)	0 (0 to 0)		
Part 2: Week 5 (N= 57/prophy, 14/on-demand)	0 (0 to 1)	0 (0 to 0)		
Part 2: Week 13 (N= 56/prophy, 12/on-demand)	0 (0 to 0)	0 (0 to 0)		
Part 2: Week 26 (N= 30/prophy, NA/on-demand)	0 (0 to 0)	0 (0 to 0)		
Part 3 (N= 25/prophy, NA/on-demand)	0 (0 to 3)	0 (0 to 0)		
Completion/Termination (N= 20 /prophy, 9/on-dem)	0 (0 to 1)	0 (0 to 0)		
Unscheduled Study Visit (N= 1/prophy, NA/on-dem)	0 (0 to 0)	0 (0 to 0)		

Notes:

[16] - No on-demand subjects in Part 1, in Part 2 at Week 26, in Part 3, and with an unscheduled visit.

Statistical analyses

No statistical analyses for this end point

Secondary: Health Resource Use - Total Days of Hospital Stay

End point title	Health Resource Use - Total Days of Hospital Stay

End point description:

This endpoint is only applicable to 4 subjects in the propyhlactic cohort who were hospitalized.

End point type	Secondary

End point timeframe:

Study Part 1 = 2-4 weeks, Study Part 2 = 26 weeks ± 1 week, Study Part 3 = 1 week (Total = 29-31 weeks)

End point values	Study Part 2: Prophylactic cohort			
Subject group type	Subject analysis set			
Number of subjects analysed	4			
Units: Days				
median (full range (min-max))				
Part 2: Week 5 (N= 1)	46 (46 to 46)			
Part 2: Week 13 (N= 1)	23 (23 to 23)			
Part 3 (N= 3)	2 (1 to 16)			
Completion/Termination (N= 2)	5.5 (2 to 9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Health Resource Use - Emergency Room Visits

End point title	Health Resource Use - Emergency Room Visits

End point description:

End point type	Secondary

End point timeframe:

Study Part 1 = 2-4 weeks, Study Part 2 = 26 weeks ± 1 week, Study Part 3 = 1 week (Total = 29-31 weeks)

End point values	Study Part 2: Prophylactic cohort	Study Part 2: On-demand cohort		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	57	14[17]		
Units: Visits				
median (full range (min-max))				
Part 1 - PK (N= 28/prophy, NA/on-demand)	0 (0 to 0)	0 (0 to 0)		
Part 2: Exp Day 1 (N= 31/prophy, 14/on-demand)	0 (0 to 10)	0 (0 to 0)		
Part 2: Week 5 (N= 57/prophy, 14/on-demand)	0 (0 to 1)	0 (0 to 0)		
Part 2: Week 13 (N= 56/prophy, 12/on-demand)	0 (0 to 1)	0 (0 to 0)		
Part 2: Week 26 (N= 30/prophy, NA/on-demand)	0 (0 to 0)	0 (0 to 0)		
Part 3 (N= 25/prophy, NA/on-demand)	0 (0 to 0)	0 (0 to 0)		
Completion/Termination (N= 20/prophy, 9/on-demand)	0 (0 to 1)	0 (0 to 0)		
Unscheduled Study Visit (N= 1/prophy, NA/on-dem)	0 (0 to 0)	0 (0 to 0)		

Notes:

[17] - No on-demand subjects in Part 1, in Part 2 at Week 26, in Part 3, and with an unscheduled visit.

Statistical analyses

No statistical analyses for this end point

Secondary: Health Resource Use - Unscheduled Doctor's Office Visits

End point title	Health Resource Use - Unscheduled Doctor's Office Visits

End point description:

End point type	Secondary

End point timeframe:

Study Part 1 = 2-4 weeks, Study Part 2 = 26 weeks ± 1 week, Study Part 3 = 1 week (Total = 29-31 weeks)

End point values	Study Part 2: Prophylactic cohort	Study Part 2: On-demand cohort		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	57	14[18]		
Units: Visits				
median (full range (min-max))				
Part 1 - PK (N= 28/prophy, NA/on-demand)	0 (0 to 1)	0 (0 to 0)		
Part 2: Exp Day 1 (N= 31/prophy, 14/on-demand)	0 (0 to 0)	0 (0 to 0)		
Part 2: Week 5 (N= 57/prophy, 14/on-demand)	0 (0 to 3)	0 (0 to 0)		
Part 2: Week 13 (N= 56/prophy, 12/on-demand)	0 (0 to 2)	0 (0 to 0)		
Part 2: Week 26 (N= 30/prophy, NA/on-demand)	0 (0 to 1)	0 (0 to 0)		
Part 3 (N= 25/prophy, NA/on-demand)	0 (0 to 1)	0 (0 to 0)		
Completion/Termination (N= 20/prophy, 9/on-demand)	0 (0 to 2)	0 (0 to 1)		
Unscheduled Study Visit (N= 1/prophy, NA/on-dem)	1 (1 to 1)	0 (0 to 0)		

Notes:

[18] - No on-demand subjects in Part 1, in Part 2 at Week 26, in Part 3, and with an unscheduled visit.

Statistical analyses

No statistical analyses for this end point

Secondary: Health Resource Use - Days Lost from Work or School

End point title	Health Resource Use - Days Lost from Work or School

End point description:

End point type	Secondary

End point timeframe:

Study Part 1 = 2-4 weeks, Study Part 2 = 26 weeks ± 1 week, Study Part 3 = 1 week (Total = 29-31 weeks)

End point values	Study Part 2: Prophylactic cohort	Study Part 2: On-demand cohort		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	57	14[19]		
Units: Days				
median (full range (min-max))				
Part 1 - PK (N= 28/prophy, NA/on-demand)	0 (0 to 10)	0 (0 to 0)		
Part 2: Exp Day 1 (N= 31/prophy, 14/on-demand)	0 (0 to 2)	0 (0 to 0)		

Part 2: Week 5 (N= 57/prophy, 14/on-demand)	0 (0 to 8)	0 (0 to 4)		
Part 2: Week 13 (N= 56/prophy, 12/on-demand)	0 (0 to 7)	0 (0 to 0)		
Part 2: Week 26 (N= 30/prophy, NA/on-demand)	0 (0 to 5)	0 (0 to 0)		
Part 3 (N= 25/prophy, NA/on-demand)	0 (0 to 1)	0 (0 to 0)		
Completion/Termination (N= 20/prophy, 9/on-demand)	0 (0 to 24)	0 (0 to 0)		
Unscheduled Study Visit (N= 1/prophy, NA/on-dem)	0 (0 to 0)	0 (0 to 0)		

Notes:

[19] - No on-demand subjects in Part 1, in Part 2 at Week 26, in Part 3, and with an unscheduled visit.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Study Part 1 = 2-4 weeks, Study Part 2 = 26 weeks ± 1 week, Study Part 3 = 1 week (Total = 29-31 weeks)

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	N/A

Reporting groups

Reporting group title	BAX326

Reporting group description:

BAX326: -Study Part 1: Pharmacokinetic (PK) Crossover with BAX326 and BeneFIX
•Study Part 2: Open-label evaluation of prophylaxis and on-demand BAX326 only
•Study Part 3: Open-label repeat of PK evaluation (repeat Study Part 1) with BAX326 only and same study participants as Study Part 1

Serious adverse events	BAX326		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 73 (5.48%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Investigations			
Hepatitis B Core Antibody Positive	Additional description: The subject´s medical history included chronic hepatitis B.		
subjects affected / exposed	1 / 73 (1.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Cervical Vertebral Fracture			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Traumatic Haematoma			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Convulsion			

subjects affected / exposed	1 / 73 (1.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Intestinal Obstruction			
subjects affected / exposed	1 / 73 (1.37%)		
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	BAX326		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 73 (20.55%)		
Investigations			
Immunology Test Abnormal			
subjects affected / exposed	12 / 73 (16.44%)		
occurrences (all)	12		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	6 / 73 (8.22%)		
occurrences (all)	8		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 July 2010	- In the eligibility criteria, the acceptable upper limit of normal for ALT and AST was increased from ≥2 times to >5 times. - To ensure that subject weight is within a reasonable range, the following exclusion criterion was added: The subject´s weight is < 35 kg or > 120 kg. - It was clarified that hospitalization for elective surgery would not be considered a serious adverse event (SAE). - It was clarified that in Part 1 thrombotic markers would not only be assessed prior to and following the BAX326 infusion but also prior to and following the BeneFIX infusion. - The number of bleeding episodes (BEs) beginning within 24 and 48 hours of an infusion was added as an exploratory endpoint (per request of FDA). - The assessment time point for the main overall hemostatic efficacy rating for the treatment of BEs was set at "resolution of bleed" to be consistent with previous hemophilia studies. Overall hemostatic efficacy ratings performed at 12 ± 1 and 24 ± 1 h time points were added as exploratory endpoints. - It was emphasized that in case of inadequate response to BAX326, the subject should be managed according to the clinical judgment of the Investigator. - A third interim safety review was added which was to be performed after 24 subjects (20 evaluable) had completed Part 2 of whom 16 subjects had also completed Parts 1 and 3, and had been evaluated for hemostatic efficacy, safety, and immunogenicity for a period 50 EDs or 6 months, whichever occurred last.
03 May 2011	- An additional on-demand cohort of 15 to 20 subjects was added to Part 2 of the study. The total sample size was therefore increased from 60 up to 75-80 PTPs. The 2 cohorts are described as 'prophylactic cohort' and 'on-demand cohort'. The reason for adding an on-demand cohort was to ensure sufficient data on the hemostatic efficacy of BAX326 in the treatment of BEs. It was specified that the decision regarding the type of treatment regimen was at the discretion of the Investigator and subject. However, once enrollment in the prophylactic cohort was completed (n = 60), only subjects willing to receive on-demand treatment would be recruited. The on-demand cohort would basically follow the same study schedule as the prophylactic cohort, except that they would only receive BAX326 to treat BEs and to determine IR at the scheduled study visits. - The following subject participation periods for the respective cohorts (prophylactic and on-demand) were added: a) Prophylactic cohort: 8-12 months for subjects taking part in Parts 1, 2 and 3; approximately 7-10 months for subject taking part in Part 2 only (unless prematurely discontinued) b) On-demand cohort: approximately 2-10 months, depending on when the subject is enrolled. - The upper acceptable limit of the International Normalized Ratio (INR) in the eligibility criteria was increased from 1.2 (upper limit of normal as defined by the central laboratory) to 1.4 to account for the fluctuating INR values between 1.1 and 1.4, in particular in subjects with hepatitis. - It was clarified that only vials with a nominal potency of 500 IU could be used for the PK parts and the determination of IR. - Although the required minimum wash-out period prior to the PK infusions in Parts 1 and 3 and prior to all study visits in Part 2 was 5 days, it was added that a wash-out period of 7 days would be preferable to ensure that the baseline FIX activity level was reached.
02 March 2012	The sample size for the third interim safety review was increased from 24 to 50 subjects (as suggested by FDA).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/24832133

http://www.ncbi.nlm.nih.gov/pubmed/23834666

http://www.ncbi.nlm.nih.gov/pubmed/24251442