Clinical trial results:
A Phase 2/3, Multi-Center, Open Label Study of Efficacy, Safety, and Pharmacokinetics of PEGylated Recombinant Factor VIII (BAX 855) Administered for Prophylaxis and Treatment of Bleeding in Previously Treated Patients with Severe Hemophilia A

Summary

EudraCT number	2012-003599-38
Trial protocol	DE GB AT LT CZ SE ES BE NL BG PL HU RO
Global end of trial date	17 July 2014

Results information

Result version number	v1 (current)
This version publication date	18 February 2016
First version publication date	05 August 2015

Trial information

Trial identification

Sponsor protocol code	261201

Additional study identifiers

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

Notes:

Sponsors

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
Sponsor organisation name	Baxalta US Inc
Sponsor organisation address	One Baxter Way, Westlake Village CA, United States, 91362-3811
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

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001296-PIP01-12
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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	17 July 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 July 2014
Global end of trial reached?	Yes
Global end of trial date	17 July 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Compare the annualized rates of bleeding episodes (ABR) between subjects who received a prophylactic dosing regimen of BAX 855 with those who received an on-demand treatment regimen

Protection of trial subjects:

This study was conducted in accordance with the standards of Good Clinical Practice (GCP) in effect at the time of the study.
Justification for enrollment of adolescent subjects was based on requirements outlined in the ICH M3 Guideline, Section 12 as well as the ICH E11 Guideline on clinical investigation of medicinal products in the pediatric population.Baxalta follows a stepwise approach and starts the clinical investigation of efficacy and safety in patients ≥12 years before starting studies in patients < 12 years.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	31 January 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 32
Country: Number of subjects enrolled	Australia: 6
Country: Number of subjects enrolled	Japan: 11
Country: Number of subjects enrolled	Malaysia: 9
Country: Number of subjects enrolled	Korea, Republic of: 10
Country: Number of subjects enrolled	Taiwan: 1
Country: Number of subjects enrolled	Austria: 7
Country: Number of subjects enrolled	Bulgaria: 1
Country: Number of subjects enrolled	Czech Republic: 7
Country: Number of subjects enrolled	Germany: 5
Country: Number of subjects enrolled	Israel: 4
Country: Number of subjects enrolled	Lithuania: 6
Country: Number of subjects enrolled	Netherlands: 1
Country: Number of subjects enrolled	Poland: 6

Country: Number of subjects enrolled	Romania: 2
Country: Number of subjects enrolled	Spain: 8
Country: Number of subjects enrolled	Sweden: 3
Country: Number of subjects enrolled	Switzerland: 2
Country: Number of subjects enrolled	Ukraine: 9
Country: Number of subjects enrolled	United Kingdom: 8
Worldwide total number of subjects	138
EEA total number of subjects	54

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)	25
Adults (18-64 years)	113
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were enrolled (signed informed consent) from 72 sites.

Pre-assignment

Screening details:

A total of 159 subjects provided informed consent and were screened for study participation, of which there were 21 screen failures. 138 subjects were assigned to the prophylactic arm or the on-demand treatment regimen.

Pre-assignment period milestones

Number of subjects started	159[1]
Number of subjects completed	138

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Screen failures: 21

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: A total of 159 subjects provided informed consent and were screened for study participation, of which there were 21 screen failures. 138 subjects were assigned to the prophylactic arm or the on-demand treatment regimen.

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A: Prophylactic treatment

Arm description:

Prophylactic treatment with BAX 855 at a dose of 45 ± 5 IU/kg twice weekly

Arm type	Experimental
Investigational medicinal product name	BAX 855
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous bolus use

Dosage and administration details:

45 ± 5 IU/kg twice weekly

Arm title	Arm B: On-demand treatment

Arm description:

On-demand therapy with BAX 855 at a dose of 10 to 60 IU/kg dose

Arm type	Experimental
Investigational medicinal product name	BAX 855
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous bolus use

Dosage and administration details:
10 to 60 IU/kg dose

Number of subjects in period 1	Arm A: Prophylactic treatment	Arm B: On-demand treatment
Started	121	17
Completed	109	17
Not completed	12	0
Consent withdrawn by subject	2	-
Adverse event, non-fatal	4	-
Screen failure -1; surgical procedure -1	2	-
Protocol deviation	4	-

Baseline characteristics

Reporting groups	
Reporting group title	Arm A: Prophylactic treatment
Reporting group description:	
Prophylactic treatment with BAX 855 at a dose of 45 ± 5 IU/kg twice weekly	
Reporting group title	Arm B: On-demand treatment
Reporting group description:	
On-demand therapy with BAX 855 at a dose of 10 to 60 IU/kg dose	

Reporting group values	Arm A: Prophylactic treatment	Arm B: On-demand treatment	Total
Number of subjects	121	17	138
Age categorical Units: Subjects			
Adults (18-64 years)	98	15	113
Adolescents (12-17 years)	23	2	25
Age continuous Units: years			
arithmetic mean	29.8	31.5	
standard deviation	± 12.53	± 11.05	-
Gender categorical Units:			
Female	0	0	0
Male	121	17	138

Subject analysis sets	
Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis
Subject analysis set description:	
Comprised all subjects who were assigned to the prophylactic arm or the on-demand treatment regimen	
Subject analysis set title	Pharmacokinetic Full Analysis Set
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Comprised all subjects in Arm A who consented to PK evaluation, who were treated with at least 1 ADVATE and 1 BAX 855 PK dose, and who were evaluable for PK for the ADVATE and initial BAX 855 PK infusions (PK-1 and PK-2). Subjects were PK evaluable if they had at least 3 post-infusion FVIII measurements above the limit of quantification (LoQ) before the first FVIII measurement below the LoQ.	
Subject analysis set title	Safety Analysis Set
Subject analysis set type	Safety analysis
Subject analysis set description:	
Comprised all subjects treated with at least 1 BAX 855 dose.	

Reporting group values	Full Analysis Set	Pharmacokinetic Full Analysis Set	Safety Analysis Set
Number of subjects	138	26	137

Age categorical Units: Subjects			
Adults (18-64 years)	113	18	112
Adolescents (12-17 years)	25	8	25
Age continuous Units: years			
arithmetic mean	30	25.6	30
standard deviation	± 12.34	± 12.03	± 12.38
Gender categorical Units:			
Female	0	0	0
Male	138	26	137

End points

End points reporting groups

Reporting group title	Arm A: Prophylactic treatment
Reporting group description:	
Prophylactic treatment with BAX 855 at a dose of 45 ± 5 IU/kg twice weekly	
Reporting group title	Arm B: On-demand treatment
Reporting group description:	
On-demand therapy with BAX 855 at a dose of 10 to 60 IU/kg dose	
Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis
Subject analysis set description:	
Comprised all subjects who were assigned to the prophylactic arm or the on-demand treatment regimen	
Subject analysis set title	Pharmacokinetic Full Analysis Set
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Comprised all subjects in Arm A who consented to PK evaluation, who were treated with at least 1 ADVATE and 1 BAX 855 PK dose, and who were evaluable for PK for the ADVATE and initial BAX 855 PK infusions (PK-1 and PK-2). Subjects were PK evaluable if they had at least 3 post-infusion FVIII measurements above the limit of quantification (LoQ) before the first FVIII measurement below the LoQ.	
Subject analysis set title	Safety Analysis Set
Subject analysis set type	Safety analysis
Subject analysis set description:	
Comprised all subjects treated with at least 1 BAX 855 dose.	

Primary: Annualized Bleeding Episode Rates (ABRs)

End point title	Annualized Bleeding Episode Rates (ABRs)
End point description:	
Comparisons between prophylactic and on-demand treatment were based on ABR estimates from a negative binomial regression model, taking into account the treatment regimen, target joints and age at screening, and duration of the observation period for efficacy.	
End point type	Primary
End point timeframe:	
At least 50 exposure days or 6 months (±2 weeks), whichever occurs last, for the prophylaxis arm and 6 months (± 2 weeks) for the on-demand arm.	

End point values	Arm A: Prophylactic treatment	Arm B: On-demand treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	120	17		
Units: ABR				
least squares mean (confidence interval 95%)	4.3 (3.4 to 5.5)	43.4 (25.2 to 74.8)		

Statistical analyses

Statistical analysis title	Ratio Annualized Bleeding Rate Prophyl./On-demand

Statistical analysis description:

Ratio Annualized Bleeding Rate (ABR) Prophylaxis/On-demand:
Prophylaxis treatment will be considered to be successful if the upper limit of the 95% CI for the ratio between treatment regimen does not exceed 0.5 (corresponding to a 50% reduction of the mean ABR compared to the on-demand treatment).
H01: μ1 ≥0.5*μ2 Ha1: μ1<0.5*μ2 where μ1 and μ2 are the mean ABRs in on prophylaxis and on-demand, respectively

Comparison groups	Arm A: Prophylactic treatment v Arm B: On-demand treatment
Number of subjects included in analysis	137
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Regression, Negative binomial
Parameter estimate	Ratio of means
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.06
upper limit	0.19

Secondary: Rate of success for BAX 855 treatment of bleeding episodes

End point title	Rate of success for BAX 855 treatment of bleeding episodes

End point description:

Success in the control of bleeding was defined as a rating of excellent or good using the Efficacy Rating Scale for Treatment of Bleeding Episodes measured 24 hours after initiation of treatment for the bleeding episode.
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 is required for the control of bleeding. Administration of further infusions to maintain hemostasis would 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 a single infusion. Required more than 1 infusion for complete resolution.
NONE: No improvement or condition worsens.

End point type	Secondary

End point timeframe:

All bleeding episodes treated with BAX 855 in subjects on on-demand and prophylaxis treatment regimens. At least 50 exposure days or 6 months (±2 weeks), whichever occurs last, for the prophylaxis arm and 6 months (± 2 weeks) for the on-demand arm.

End point values	Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	81			
Units: Proportion of excellent/good bleeds				
number (confidence interval 95%)	0.96 (0.91 to 0.98)			

Statistical analyses

No statistical analyses for this end point

Secondary: Total weight-adjusted consumption of BAX 855

End point title	Total weight-adjusted consumption of BAX 855

End point description:

End point type	Secondary

End point timeframe:

At least 50 exposure days or 6 months (±2 weeks), whichever occurs last, for the prophylaxis arm and 6 months (± 2 weeks) for the on-demand arm.

End point values	Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed				
Units: IU/kg				
arithmetic mean (standard deviation)				
Per Prophylactic Infusion	44.51 (± 4.556)			
Per PK Infusion	45.48 (± 2.592)			
Per Treatment of Bleeding Episode	37.44 (± 28.105)			
Per Bleeding Episode for Maintenance of Hemostasis	39.29 (± 34.206)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Positive Inhibitory Antibodies to FVIII, Binding Antibodies to FVIII, BAX 855, PEG and Anti-CHO Antibodies at Study Completion/Termination

End point title	Number of Subjects with Positive Inhibitory Antibodies to FVIII, Binding Antibodies to FVIII, BAX 855, PEG and Anti-CHO Antibodies at Study Completion/Termination

End point description:

Note for Inhibitory Antibodies to FVIII: Subjects = 112 for Arm A; 14 for Arm B; 126 for Safety Analysis Set.

End point type	Secondary

End point timeframe:

From first exposure to BAX 855 until the end of the study [at least 50 exposure days or 6 months (±2 weeks), whichever occurs last, for the prophylaxis arm and 6 months (± 2 weeks) for the on-demand arm].

End point values	Arm A: Prophylactic treatment	Arm B: On-demand treatment	Safety Analysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	117	15	132	
Units: Number of subjects				
number (not applicable)				
Inhibitory Antibodies to FVIII	0	0	0	
IgG: Binding Antibodies FVIII	0	0	0	
IgM: Binding Antibodies FVIII	0	0	0	
IgG: Binding Antibodies PEG	0	0	0	
IgM: Binding Antibodies PEG	0	0	0	
IgG: Binding Antibodies PEG-FVIII	0	1	1	
IgM: Binding Antibodies PEG-FVIII	0	0	0	
CHO-Protein Ab	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Safety - Occurrence of adverse events (AEs) following BAX 855 administration

End point title	Safety - Occurrence of adverse events (AEs) following BAX 855 administration

End point description:

Abbreviations: serious adverse event - SAE; non-serious adverse event - nSAE

End point type	Secondary

End point timeframe:

From first exposure to BAX 855 until the end of the study [at least 50 exposure days or 6 months (±2 weeks), whichever occurs last, for the prophylaxis arm and 6 months (± 2 weeks) for the on-demand arm].

End point values	Safety Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	137			
Units: Percentage of subjects with AEs				
number (not applicable)				
SAE-Moderate-Unrelated	0.7			
SAE-Severe-Unrelated	2.9			
nSAE-Mild-Unrelated	40.1			

nSAE-Mild-Related	3.6			
nSAE-Moderate-Unrelated	19			
nSAE-Moderate-Related	1.5			
nSAE-Unknown Severity-Unrelated	0.7			
nSAE-Severe-Unrelated	1.5			

Statistical analyses

No statistical analyses for this end point

Secondary: Terminal half-life (One-stage Clotting)

End point title	Terminal half-life (One-stage Clotting)

End point description:

Terminal half-life of BAX 855 following initial and repeat administration after at least 50 exposure days, and as compared to ADVATE. Terminal half-life calculated as log_e2/λ where λ is the terminal elimination rate constant calculate by WinNonlin NCA (Model 201, curve stripping as described in the User's Guide, page 263). Subjects: 26 subjects for PK1 and PK2; 22 subjects for PK3

End point type	Secondary

End point timeframe:

Pharmacokinetic (PK) evaluation: Within 30 minutes prior to start of infusion; and post-infusion at 10, 30 minutes, and 1, 3, 6, 9, 24, 32, 48, 56, 72 (PK2 and PK3 only), and 96 hours (PK2 and PK3 only).

End point values	Pharmacokinetic Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	26			
Units: hours				
arithmetic mean (standard deviation)				
PK 1 ADVATE	10.4 (± 2.244)			
PK2 BAX855	14.3 (± 3.838)			
PK3 BAX855	16.02 (± 4.922)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Residence Time (One-stage Clotting)

End point title	Mean Residence Time (One-stage Clotting)

End point description:

Mean Residence Time (One-stage Clotting) of BAX 855 following initial and repeat administration after at least 50 exposure days, and as compared to ADVATE.
The mean residence time (MRT) was calculated as total area under the moment curve divided by the total area under the curve starting from the begin of infusion (or the end of infusion if start time is not available).
Subjects: 26 subjects for PK1 and PK2; 22 subjects for PK3

End point type	Secondary

End point timeframe:

Pharmacokinetic (PK) evaluation: Within 30 minutes prior to start of infusion; and post-infusion at 10, 30 minutes, and 1, 3, 6, 9, 24, 32, 48, 56, 72 (PK2 and PK3 only), and 96 hours (PK2 and PK3 only).

End point values	Pharmacokinetic Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	26			
Units: hours				
arithmetic mean (standard deviation)				
PK1 ADVATE	12.86 (± 3.044)			
PK2 BAX 855	19.56 (± 5.315)			
PK3 BAX 855	20.65 (± 4.821)			

Statistical analyses

No statistical analyses for this end point

Secondary: Total body clearance (One-stage Clotting)

End point title	Total body clearance (One-stage Clotting)

End point description:

Total body clearance (One-stage Clotting) of BAX 855 following initial and repeat administration after at least 50 EDs, and as compared to ADVATE.
Clearance in dL/(kg*hours) was calculated as the dose in IU/kg divided by the total area under the curve starting from the begin of infusion (or the end of infusion if start time is not available).
Subjects: 26 subjects for PK1 and PK2; 22 subjects for PK3.

End point type	Secondary

End point timeframe:

Pharmacokinetic (PK) evaluation: Within 30 minutes prior to start of infusion; and post-infusion at 10, 30 minutes, and 1, 3, 6, 9, 24, 32, 48, 56, 72 (PK2 and PK3 only), and 96 hours (PK2 and PK3 only).

End point values	Pharmacokinetic Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	26			
Units: dL/(kg*hours)				
arithmetic mean (standard deviation)				
PK1 ADVATE	0.04551 (± 0.021725)			
PK2 BAX 855	0.0276 (± 0.020288)			

PK3 BAX 855	0.02474 (± 0.008225)			

Statistical analyses

No statistical analyses for this end point

Secondary: Incremental recovery (One-stage Clotting)

End point title	Incremental recovery (One-stage Clotting)

End point description:

Incremental recovery (One-stage Clotting) of BAX 855 following initial and repeat administration after at least 50 EDs, and as compared to ADVATE.
Subjects: 26 subjects for PK1 and PK2; 22 subjects for PK3

End point type	Secondary

End point timeframe:

Pharmacokinetic (PK) evaluation: Within 30 minutes prior to start of infusion; and post-infusion at 10, 30 minutes, and 1, 3, 6, 9, 24, 32, 48, 56, 72 (PK2 and PK3 only), and 96 hours (PK2 and PK3 only).

End point values	Pharmacokinetic Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	26			
Units: (IU/dL)/(IU/kg)				
arithmetic mean (standard deviation)				
PK1 ADVATE	2.372 (± 0.5357)			
PK2 BAX 855	2.493 (± 0.6944)			
PK3 BAX 855	2.297 (± 0.6377)			

Statistical analyses

No statistical analyses for this end point

Secondary: Patient Reporting Outcome Short Form (SF)-36

End point title	Patient Reporting Outcome Short Form (SF)-36

End point description:

Change from Baseline to Completion of Study for SF-36 Questionnaire is provided.
Scores for individual SF-36 categories range from 0 to 100 with higher scores representing better health.
Given that higher scores indicate better health-related quality of life (HRQoL) and that the change scores were calculated as the value at study completion minus the value at baseline, a negative change score indicates a worsening of HRQoL.
Subjects for Treatment Arm A (prophylactic treatment): 97 subjects for physical functioning, role-physical, bodily pain, social functioning, role emotional; 96 for general health, vitality, mental health,

physical component score, mental component score.

End point type	Secondary

End point timeframe:

From screening to end of study visit [at least 50 exposure days or 6 months (±2 weeks), whichever occurs last, for the prophylaxis arm and 6 months (± 2 weeks) for the on-demand arm].

End point values	Arm A: Prophylactic treatment	Arm B: On-demand treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	97	12		
Units: point change				
arithmetic mean (standard deviation)				
Physical Functioning	0.49 (± 5.27)	-2.46 (± 4.29)		
Role-physical	1.31 (± 7.36)	-3.67 (± 9.01)		
Bodily Pain	2.08 (± 8.19)	0.6 (± 4.44)		
General Health	0.4 (± 6.43)	-0.28 (± 9.04)		
Vitality	-0.38 (± 7.43)	0.26 (± 9.36)		
Social Functioning	0.9 (± 7.54)	-3.18 (± 6.35)		
Role Emotional	-0.2 (± 8.46)	0.65 (± 7.92)		
Mental Health	0.09 (± 7.26)	-3.29 (± 7.95)		
Physical Component Score	1.36 (± 5.76)	-1.58 (± 4.97)		
Mental Component Score	-0.37 (± 7.38)	-1.14 (± 5.03)		

Statistical analyses

No statistical analyses for this end point

Secondary: Patient Reporting Outcome Haemo-SYM Questionnaire

End point title	Patient Reporting Outcome Haemo-SYM Questionnaire

End point description:

Change from Baseline to Completion of Study for Haemo-SYM Questionnaire. The 17-item HAEMO-SYM has two subscales: pain and bleeds. Given that higher scores indicate more severe symptoms on the Haemo-SYM and that the change scores were calculated as the value at study completion minus the value at
baseline, a negative change score indicates an improvement (reduction in symptoms). Conversely, a positive change score indicates worsening symptoms.

End point type	Secondary

End point timeframe:

From screening to end of study visit [at least 50 exposure days or 6 months (±2 weeks), whichever occurs last, for the prophylaxis arm and 6 months (± 2 weeks) for the on-demand arm].

End point values	Arm A: Prophylactic treatment	Arm B: On-demand treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	11		
Units: Point change				
arithmetic mean (standard deviation)				
Bleed Severity Total Score	-4.17 (± 17.05)	-4.24 (± 15.71)		
Paint Severity Total Score	-1.22 (± 12.5)	-0.17 (± 11.88)		
Total Score	-2.7 (± 13.42)	-2.2 (± 10.92)		

Statistical analyses

No statistical analyses for this end point

Secondary: Average number of BAX855 infusions needed for the treatment of bleeding episodes

End point title	Average number of BAX855 infusions needed for the treatment of bleeding episodes

End point description:

End point type	Secondary

End point timeframe:

From first exposure to BAX 855 until the end of the study [at least 50 exposure days or 6 months (±2 weeks), whichever occurs last, for the prophylaxis arm and 6 months (± 2 weeks) for the on-demand arm].

End point values	Arm A: Prophylactic treatment	Arm B: On-demand treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65	17		
Units: Average number of infusions				
arithmetic mean (standard deviation)	1.37 (± 0.8)	1.21 (± 0.35)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time intervals between bleeding episodes

End point title	Time intervals between bleeding episodes

End point description:

Interval between Bleeds in months was calculated as:
Observation period for efficacy (in days)/(number of bleeds)*(12/365.2425)

End point type	Secondary

End point timeframe:

From first exposure to BAX 855 until the end of the study [at least 50 exposure days or 6 months (±2 weeks), whichever occurs last, for the prophylaxis arm and 6 months (± 2 weeks) for the on-demand arm].

End point values	Arm A: Prophylactic treatment	Arm B: On-demand treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	120	17		
Units: Number of subjects				
No bleed	45	0		
Interval: > 6 months	5	0		
Interval: 6 months	20	0		
Interval: 5 months	3	0		
Interval: 4 months	0	0		
Interval: 3 months	11	0		
Interval: 2 months	16	0		
Interval: <= 1 month	20	17		

Statistical analyses

No statistical analyses for this end point

Secondary: Area under the concentration versus time curve from 0 to infinity (One-stage Clotting)

End point title	Area under the concentration versus time curve from 0 to infinity (One-stage Clotting)

End point description:

Area under the concentration versus time curve from 0 to infinity of BAX 855 following initial and repeat administration after at least 50 EDs, and as compared to ADVATE. Calculated by WinNonlin NCA (Model 201, calculation method: Linear Trapezoidal Linear/Log Interpolation).
Subjects: 26 subjects for PK1 and PK2; 22 subjects for PK3

End point type	Secondary

End point timeframe:

Pharmacokinetic (PK) evaluation: Within 30 minutes prior to start of infusion; and post-infusion at 10, 30 minutes, and 1, 3, 6, 9, 24, 32, 48, 56, 72 (PK2 and PK3 only), and 96 hours (PK2 and PK3 only).

End point values	Pharmacokinetic Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	26			
Units: IU*hours/dL				
arithmetic mean (standard deviation)				
PK1 ADVATE	1168 (± 425.4)			

PK2 BAX855	2073.3 (± 778.41)			
PK3 BAX855	2008.7 (± 631.53)			

Statistical analyses

No statistical analyses for this end point

Secondary: Apparent Volume of Distribution at Steady State (One-stage Clotting)

End point title	Apparent Volume of Distribution at Steady State (One-stage Clotting)

End point description:

Apparent Volume of Distribution at Steady State of BAX 855 following initial and repeat administration after at least 50 EDs, and as compared to ADVATE. Calculated as Clearance * Mean Residence Time.
Subjects: 26 subjects for PK1 and PK2; 22 subjects for PK3

End point type	Secondary

End point timeframe:

Pharmacokinetic (PK) evaluation: Within 30 minutes prior to start of infusion; and post-infusion at 10, 30 minutes, and 1, 3, 6, 9, 24, 32, 48, 56, 72 (PK2 and PK3 only), and 96 hours (PK2 and PK3 only).

End point values	Pharmacokinetic Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	26			
Units: dL/kg				
arithmetic mean (standard deviation)				
PK1 ADVATE	0.5487 (± 0.20213)			
PK2 BAX855	0.4715 (± 0.14602)			
PK3 BAX855	0.497 (± 0.15756)			

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum plasma concentration (One-stage Clotting)

End point title	Maximum plasma concentration (One-stage Clotting)

End point description:

Maximum plasma concentration of BAX 855 following initial and repeat administration after at least 50 EDs, and as compared to ADVATE. Determined as the maximum concentration achieved post-infusion.
Subjects: 26 subjects for PK1 and PK2; 22 subjects for PK3

End point type	Secondary

End point timeframe:

Pharmacokinetic (PK) evaluation: Within 30 minutes prior to start of infusion; and post-infusion at 10,

30 minutes, and 1, 3, 6, 9, 24, 32, 48, 56, 72 (PK2 and PK3 only), and 96 hours (PK2 and PK3 only).

End point values	Pharmacokinetic Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	26			
Units: IU/dL				
arithmetic mean (standard deviation)				
PK1 ADVATE	108.45 (± 26.25)			
PK2 BAX855	113.68 (± 30.259)			
PK3 BAX855	103.34 (± 29.311)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to maximum concentration in plasma (One-stage Clotting)

End point title	Time to maximum concentration in plasma (One-stage Clotting)

End point description:

Time to maximum concentration in plasma of BAX 855 following initial and repeat administration after at least 50 EDs, and as compared to ADVATE. Defined as the time to reach maximum plasma concentration.
Subjects: 26 subjects for PK1 and PK2; 22 subjects for PK3

End point type	Secondary

End point timeframe:

Pharmacokinetic (PK) evaluation: Within 30 minutes prior to start of infusion; and post-infusion at 10, 30 minutes, and 1, 3, 6, 9, 24, 32, 48, 56, 72 (PK2 and PK3 only), and 96 hours (PK2 and PK3 only).

End point values	Pharmacokinetic Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	26			
Units: hours				
arithmetic mean (standard deviation)				
PK1 ADVATE	0.296 (± 0.1662)			
PK2 BAX855	0.397 (± 0.2632)			
PK3 BAX855	0.467 (± 0.6044)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first exposure to BAX 855 until the end of the study [at least 50 exposure days or 6 months (±2 weeks), whichever occurs last, for the prophylaxis arm and 6 months (± 2 weeks) for the on-demand arm].

Adverse event reporting additional description:

The population consisted of subjects who received at least one dose of BAX 855 during the study.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Safety Analysis Set

Reporting group description:

Comprised all subjects treated with at least 1 BAX 855 dose.

Serious adverse events	Safety Analysis Set		
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 137 (3.65%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neuroendocrine carcinoma			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Injury, poisoning and procedural complications			
Humerus fracture			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Muscle haemorrhage			
subjects affected / exposed	1 / 137 (0.73%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Herpes zoster infection neurological			
subjects affected / exposed	1 / 137 (0.73%)		
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	Safety Analysis Set		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	27 / 137 (19.71%)		
Nervous system disorders			
Headache			
subjects affected / exposed	7 / 137 (5.11%)		
occurrences (all)	13		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	14 / 137 (10.22%)		
occurrences (all)	16		
Upper respiratory tract infection			
subjects affected / exposed	9 / 137 (6.57%)		
occurrences (all)	10		

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