



Clinical trial results:

A Phase 3 prospective, uncontrolled, multicenter study evaluating pharmacokinetics, efficacy, safety, and immunogenicity of BAX 855 (pegylated full-length recombinant FVIII) in previously treated pediatric patients with severe hemophilia A

Summary

EudraCT number	2014-000742-30
Trial protocol	LT ES BG RO NL GB
Global end of trial date	23 October 2015

Results information

Result version number	v1 (current)
This version publication date	22 April 2016
First version publication date	22 April 2016

Trial information

Trial identification

Sponsor protocol code	261202
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02210091
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, 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

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMA-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
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Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	23 October 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 October 2015
Global end of trial reached?	Yes
Global end of trial date	23 October 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the incidence of FVIII inhibitory antibodies (≥ 0.6 Bethesda units [BU] using the Nijmegen modification of the Bethesda assay).

Protection of trial subjects:

This study was conducted in accordance with the protocol, the ICH Guideline for Good Clinical Practice E6 (ICH GCP, April 1996), Title 21 of the United States Code of Federal Regulations, the European Clinical Trial Directive (2001/20/EC and 2005/28/EC) and applicable national and local regulatory requirements. Justification for enrollment of pediatric subjects is based on the requirements outlined in the ICH M3 and E11 guidelines. The clinical development program for BAX 855 followed the EMA guidance outlined in EMA/CHMP/BPWP/144533/2009. In line with this guidance the pediatric study did not start before the data of 20 previously treated patients (PTPs) ≥ 12 years of age that had been treated for at least 50 exposure days (EDs) and the pharmacokinetic (PK) data of at least 12 PTPs ≥ 12 years of age were available (study 261201), were reviewed by an independent data monitoring committee (DMC) and a decision to start the study was obtained. For the PK evaluation, a population PK approach was used to reduce the number of blood draws: the 3 post-infusion blood draws over 96 hours were randomly selected from 3 choices for each blood draw.

Background therapy: -

Evidence for comparator:

Prior to receiving prophylactic treatment with BAX 855, a subgroup of subjects within each age cohort underwent PK assessments with ADVATE followed by BAX 855 to compare the PK parameters of BAX 855 with ADVATE.

Actual start date of recruitment	31 October 2014
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: 22
Country: Number of subjects enrolled	Malaysia: 9
Country: Number of subjects enrolled	Hong Kong: 1
Country: Number of subjects enrolled	Taiwan: 1
Country: Number of subjects enrolled	Korea, Republic of: 3
Country: Number of subjects enrolled	Bulgaria: 3
Country: Number of subjects enrolled	Netherlands: 3

Country: Number of subjects enrolled	Spain: 5
Country: Number of subjects enrolled	Ukraine: 5
Country: Number of subjects enrolled	United Kingdom: 8
Country: Number of subjects enrolled	Turkey: 6
Worldwide total number of subjects	66
EEA total number of subjects	19

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)	2
Children (2-11 years)	64
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

52 sites participated in this study. 39 study sites enrolled subjects and 13 sites were initiated but were inactive.

Pre-assignment

Screening details:

A total of 73 subjects provided informed consent and were screened for study participation. There were 9 screen failures. Among these, 2 subjects were screen failures at first screening but entered the study later. 66 subjects were dosed in the prophylactic part of the study, of which 31 subjects were also dosed in the PK part prior to prophylaxis.

Pre-assignment period milestones

Number of subjects started	73 ^[1]
Number of subjects completed	66

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Screen failures: 7
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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 73 subjects provided informed consent and were screened for study participation. There were 9 screen failures. Among these, 2 subjects were Screen failures at first screening but entered the study later. 66 subjects were dosed in the prophylactic part of the study, of which 31 subjects were also dosed in the PK part prior to prophylaxis.

Period 1

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

Arms

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

Arm description:

Subjects were to be treated with prophylactic infusions of BAX 855 at a dose of 50 ±10 IU/kg administered twice weekly (at 3- and 4-day intervals or 3.5-day intervals) for a minimum of 50 exposure days to BAX855 or approximately 6 months, whichever occurred last.

Arm type	Experimental
Investigational medicinal product name	BAX 855
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Dose of 50 ±10 IU/kg twice weekly for prophylaxis

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

Subjects were to be treated with prophylactic infusions of BAX 855 at a dose of 50 ±10 IU/kg administered twice weekly (at 3- and 4-day intervals or 3.5-day intervals) for a minimum of 50 exposure days to BAX855 or approximately 6 months, whichever occurred last.

Arm type	Experimental
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Investigational medicinal product name	BAX 855
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Dose of 50 ±10 IU/kg twice weekly for prophylaxis

Number of subjects in period 1	Pediatric subjects <6 years of age	Pediatric subjects 6 to <12 years of age
Started	32	34
Completed	32	32
Not completed	0	2
Physician decision	-	1
Withdrawn by sponsor	-	1

Baseline characteristics

Reporting groups

Reporting group title	Overall trial
Reporting group description:	
Prophylactic Part (main study part)	

Reporting group values	Overall trial	Total	
Number of subjects	66	66	
Age categorical			
Units: Subjects			
85 years and over	0	0	
From 65-84 years	0	0	
Adults (18-64 years)	0	0	
Adolescents (12-17 years)	0	0	
Children (2-11 years)	64	64	
Infants and toddlers (28 days-23 months)	2	2	
Newborns (0-27 days)	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
In utero	0	0	
Age continuous			
Units: years			
arithmetic mean	6		
standard deviation	± 2.7	-	
Gender categorical			
Units:			
Female	1	1	
Male	65	65	

Subject analysis sets

Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis
Subject analysis set description:	
The full analysis set contains all subjects who received at least one dose of BAX 855 in either the PK part of the study or the prophylaxis part of the study. All efficacy analyses were performed on the full analysis set (FAS). The FAS is the primary analysis set.	
Subject analysis set title	ADVATE Safety Analysis Set
Subject analysis set type	Safety analysis
Subject analysis set description:	
The ADVATE safety analysis set contains all subjects who received at least one dose of ADVATE in the PK part of the study.	
Subject analysis set title	BAX 855 Safety Analysis Set
Subject analysis set type	Safety analysis
Subject analysis set description:	
The BAX 855 safety analysis set contains all subjects who received at least one dose of BAX 855.	
Subject analysis set title	Pharmacokinetic (PK) Full Analysis Set
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The pharmacokinetic full analysis set (PKFAS) contains all subjects who had been treated with at least 1 dose of ADVATE (60 ±5 IU/kg) and 1 dose of BAX 855 (60 ±5 IU/kg) in the PK part of the study (prior to prophylactic treatment) and had at least 1 PK concentration available for population PK and non-compartmental analysis.

Subject analysis set title	Pharmacokinetic (PK) Analysis Set - ADVATE
Subject analysis set type	Sub-group analysis

Subject analysis set description:

This analysis set contains all subjects who had been treated with at least 1 dose of ADVATE (60 ±5 IU/kg) and 1 dose of BAX 855 (60 ±5 IU/kg) in the PK part of the study (prior to prophylactic treatment) and had at least 1 PK concentration available for population PK and non-compartmental analysis.

Subject analysis set title	Pharmacokinetic (PK) Analysis Set - BAX 855
Subject analysis set type	Sub-group analysis

Subject analysis set description:

This analysis set contains all subjects who had been treated with at least 1 dose of ADVATE (60 ±5 IU/kg) and 1 dose of BAX 855 (60 ±5 IU/kg) in the PK part of the study (prior to prophylactic treatment) and had at least 1 PK concentration available for population PK and non-compartmental analysis.

Subject analysis set title	PK Analysis Set - BAX 855 - subjects <6 years of age
Subject analysis set type	Sub-group analysis

Subject analysis set description:

This analysis set contains all subjects <6 years of age who had been treated with at least 1 dose of ADVATE (60 ±5 IU/kg) and 1 dose of BAX 855 (60 ±5 IU/kg) in the PK part of the study (prior to prophylactic treatment) and had at least 1 PK concentration available for population PK and non-compartmental analysis.

Subject analysis set title	PK Analysis Set - BAX 855 - subjects 6 to <12 years of age
Subject analysis set type	Sub-group analysis

Subject analysis set description:

This analysis set contains all subjects 6 to <12 years of age who had been treated with at least 1 dose of ADVATE (60 ±5 IU/kg) and 1 dose of BAX 855 (60 ±5 IU/kg) in the PK part of the study (prior to prophylactic treatment) and had at least 1 PK concentration available for population PK and non-compartmental analysis.

Subject analysis set title	PK Analysis Set - ADVATE - subjects <6 years of age
Subject analysis set type	Sub-group analysis

Subject analysis set description:

This analysis set contains all subjects <6 years of age who had been treated with at least 1 dose of ADVATE (60 ±5 IU/kg) and 1 dose of BAX 855 (60 ±5 IU/kg) in the PK part of the study (prior to prophylactic treatment) and had at least 1 PK concentration available for population PK and non-compartmental analysis.

Subject analysis set title	PK Analysis Set- ADVATE - subjects 6 to <12 years of age
Subject analysis set type	Sub-group analysis

Subject analysis set description:

This analysis set contains all subjects 6 to <12 years of age who had been treated with at least 1 dose of ADVATE (60 ±5 IU/kg) and 1 dose of BAX 855 (60 ±5 IU/kg) in the PK part of the study (prior to prophylactic treatment) and had at least 1 PK concentration available for population PK and non-compartmental analysis.

Subject analysis set title	Per Protocol Analysis Set
Subject analysis set type	Per protocol

Subject analysis set description:

This analysis set contains all subjects in the Full Analysis Set (FAS) who fulfilled the following compliance criteria for prophylactic treatment: -) Infusion interval of 5 or more days did not occur more than five times in the observation period, -) the dose per infusion was below 40 IU/kg in no more than 10% of the infusions in the observation period, -) the dose per infusion was above 80 IU/kg in no more than 10% of the infusions in the observation period. The Per Protocol Analysis Set was a supportive analysis set.

Reporting group values	Full Analysis Set	ADVATE Safety Analysis Set	BAX 855 Safety Analysis Set
Number of subjects	66	31	66
Age categorical Units: Subjects			
85 years and over	0	0	0
From 65-84 years	0	0	0
Adults (18-64 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Children (2-11 years)	64	30	64
Infants and toddlers (28 days-23 months)	2	1	2
Newborns (0-27 days)	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
In utero	0	0	0
Age continuous Units: years			
arithmetic mean	6	5.8	6
standard deviation	± 2.7	± 2.61	± 2.7
Gender categorical Units:			
Female	1	1	1
Male	65	30	65

Reporting group values	Pharmacokinetic (PK) Full Analysis Set	Pharmacokinetic (PK) Analysis Set - ADVATE	Pharmacokinetic (PK) Analysis Set - BAX 855
Number of subjects	31	31	31
Age categorical Units: Subjects			
85 years and over	0	0	0
From 65-84 years	0	0	0
Adults (18-64 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Children (2-11 years)	30	30	30
Infants and toddlers (28 days-23 months)	1	1	1
Newborns (0-27 days)	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
In utero	0	0	0
Age continuous Units: years			
arithmetic mean	5.8	5.8	5.8
standard deviation	± 2.61	± 2.61	± 2.61
Gender categorical Units:			
Female	1	1	1
Male	30	30	30

Reporting group values	PK Analysis Set - BAX 855 - subjects <6 years of age	PK Analysis Set - BAX 855 - subjects 6 to <12 years of age	PK Analysis Set - ADVATE - subjects <6 years of age
Number of subjects	14	17	14

Age categorical			
Units: Subjects			
85 years and over	0	0	0
From 65-84 years	0	0	0
Adults (18-64 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Children (2-11 years)	13	17	13
Infants and toddlers (28 days-23 months)	1	0	1
Newborns (0-27 days)	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
In utero	0	0	0
Age continuous			
Units: years			
arithmetic mean	3.7	7.6	3.7
standard deviation	± 1.27	± 2.06	± 1.27
Gender categorical			
Units:			
Female	0	1	0
Male	14	16	14

Reporting group values	PK Analysis Set-ADVATE - subjects 6 to <12 years of age	Per Protocol Analysis Set	
Number of subjects	17	65	
Age categorical			
Units: Subjects			
85 years and over	0	0	
From 65-84 years	0	0	
Adults (18-64 years)	0	0	
Adolescents (12-17 years)	0	0	
Children (2-11 years)	17	63	
Infants and toddlers (28 days-23 months)	0	2	
Newborns (0-27 days)	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
In utero	0	0	
Age continuous			
Units: years			
arithmetic mean	7.6	6	
standard deviation	± 2.06	± 2.72	
Gender categorical			
Units:			
Female	1	1	
Male	16	64	

End points

End points reporting groups

Reporting group title	Pediatric subjects <6 years of age
Reporting group description: Subjects were to be treated with prophylactic infusions of BAX 855 at a dose of 50 ±10 IU/kg administered twice weekly (at 3- and 4-day intervals or 3.5-day intervals) for a minimum of 50 exposure days to BAX855 or approximately 6 months, whichever occurred last.	
Reporting group title	Pediatric subjects 6 to <12 years of age
Reporting group description: Subjects were to be treated with prophylactic infusions of BAX 855 at a dose of 50 ±10 IU/kg administered twice weekly (at 3- and 4-day intervals or 3.5-day intervals) for a minimum of 50 exposure days to BAX855 or approximately 6 months, whichever occurred last.	
Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis
Subject analysis set description: The full analysis set contains all subjects who received at least one dose of BAX 855 in either the PK part of the study or the prophylaxis part of the study. All efficacy analyses were performed on the full analysis set (FAS). The FAS is the primary analysis set.	
Subject analysis set title	ADVATE Safety Analysis Set
Subject analysis set type	Safety analysis
Subject analysis set description: The ADVATE safety analysis set contains all subjects who received at least one dose of ADVATE in the PK part of the study.	
Subject analysis set title	BAX 855 Safety Analysis Set
Subject analysis set type	Safety analysis
Subject analysis set description: The BAX 855 safety analysis set contains all subjects who received at least one dose of BAX 855.	
Subject analysis set title	Pharmacokinetic (PK) Full Analysis Set
Subject analysis set type	Sub-group analysis
Subject analysis set description: The pharmacokinetic full analysis set (PKFAS) contains all subjects who had been treated with at least 1 dose of ADVATE (60 ±5 IU/kg) and 1 dose of BAX 855 (60 ±5 IU/kg) in the PK part of the study (prior to prophylactic treatment) and had at least 1 PK concentration available for population PK and non-compartmental analysis.	
Subject analysis set title	Pharmacokinetic (PK) Analysis Set - ADVATE
Subject analysis set type	Sub-group analysis
Subject analysis set description: This analysis set contains all subjects who had been treated with at least 1 dose of ADVATE (60 ±5 IU/kg) and 1 dose of BAX 855 (60 ±5 IU/kg) in the PK part of the study (prior to prophylactic treatment) and had at least 1 PK concentration available for population PK and non-compartmental analysis.	
Subject analysis set title	Pharmacokinetic (PK) Analysis Set - BAX 855
Subject analysis set type	Sub-group analysis
Subject analysis set description: This analysis set contains all subjects who had been treated with at least 1 dose of ADVATE (60 ±5 IU/kg) and 1 dose of BAX 855 (60 ±5 IU/kg) in the PK part of the study (prior to prophylactic treatment) and had at least 1 PK concentration available for population PK and non-compartmental analysis.	
Subject analysis set title	PK Analysis Set - BAX 855 - subjects <6 years of age
Subject analysis set type	Sub-group analysis
Subject analysis set description: This analysis set contains all subjects <6 years of age who had been treated with at least 1 dose of ADVATE (60 ±5 IU/kg) and 1 dose of BAX 855 (60 ±5 IU/kg) in the PK part of the study (prior to prophylactic treatment) and had at least 1 PK concentration available for population PK and non-compartmental analysis.	

Subject analysis set title	PK Analysis Set - BAX 855 - subjects 6 to <12 years of age
Subject analysis set type	Sub-group analysis

Subject analysis set description:

This analysis set contains all subjects 6 to <12 years of age who had been treated with at least 1 dose of ADVATE (60 ±5 IU/kg) and 1 dose of BAX 855 (60 ±5 IU/kg) in the PK part of the study (prior to prophylactic treatment) and had at least 1 PK concentration available for population PK and non-compartmental analysis.

Subject analysis set title	PK Analysis Set - ADVATE - subjects <6 years of age
Subject analysis set type	Sub-group analysis

Subject analysis set description:

This analysis set contains all subjects <6 years of age who had been treated with at least 1 dose of ADVATE (60 ±5 IU/kg) and 1 dose of BAX 855 (60 ±5 IU/kg) in the PK part of the study (prior to prophylactic treatment) and had at least 1 PK concentration available for population PK and non-compartmental analysis.

Subject analysis set title	PK Analysis Set- ADVATE - subjects 6 to <12 years of age
Subject analysis set type	Sub-group analysis

Subject analysis set description:

This analysis set contains all subjects 6 to <12 years of age who had been treated with at least 1 dose of ADVATE (60 ±5 IU/kg) and 1 dose of BAX 855 (60 ±5 IU/kg) in the PK part of the study (prior to prophylactic treatment) and had at least 1 PK concentration available for population PK and non-compartmental analysis.

Subject analysis set title	Per Protocol Analysis Set
Subject analysis set type	Per protocol

Subject analysis set description:

This analysis set contains all subjects in the Full Analysis Set (FAS) who fulfilled the following compliance criteria for prophylactic treatment: -) Infusion interval of 5 or more days did not occur more than five times in the observation period, -) the dose per infusion was below 40 IU/kg in no more than 10% of the infusions in the observation period, -) the dose per infusion was above 80 IU/kg in no more than 10% of the infusions in the observation period. The Per Protocol Analysis Set was a supportive analysis set.

Primary: Incidence of FVIII inhibitory antibodies (≥0.6 Bethesda units [BU] using the Nijmegen modification of the Bethesda assay)

End point title	Incidence of FVIII inhibitory antibodies (≥0.6 Bethesda units [BU] using the Nijmegen modification of the Bethesda assay) ^[1]
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End point description:

Inhibitory antibodies were measured by the Nijmegen modification of the Bethesda assay at each study visit. The number of subjects included in the analysis was the sum of subjects that developed inhibitory antibodies to FVIII and the number of subjects that did not develop inhibitory antibodies to FVIII, had 50 or more exposure days and had a FVIII inhibitory test result after 50 exposure days. Per protocol, descriptive statistics were collected for this endpoint.

End point type	Primary
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End point timeframe:

Throughout the study period (1 year), approximately 6 months per subject

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

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

End point values	Pediatric subjects <6 years of age	Pediatric subjects 6 to <12 years of age	Full Analysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	29 ^[2]	28 ^[3]	57 ^[4]	
Units: subjects	0	0	0	

Notes:

[2] - 29 subjects <6 years of age included in this analysis

[3] - 28 subjects 6 to <12 years of age included in this analysis

[4] - 57 subjects included in this analysis

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized bleeding rate

End point title	Annualized bleeding rate
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End point description:

The annualized bleeding rate (ABR) was assessed based upon each individual bleeding episode, spontaneous or traumatic, recorded in the subject's diary and/or recorded in the physician/nurse/study site notes.

In the Full Analysis Set (n=66), the point estimate for the overall mean ABR was 3.04 (95% confidence interval [CI] 2.208 – 4.186). Point estimates for the mean ABR were 2.37 (95% CI 1.486 – 3.778) in subjects <6 years of age (n=32) and 3.75 (95% CI 2.429 – 5.781) in subjects 6 to <12 years of age (n=34).

Point estimates for the mean annualized spontaneous bleeding rate were 1.164 (95% CI 0.740 - 1.832) in the FAS (n=66), 1.018 (95% CI 0.523 - 1.978) in the younger (n=32) and 1.316 (95% CI 0.710 - 2.438) in the older (n=34) age cohort.

Point estimates for the mean annualized rate of joint bleeds were 1.103 (95% CI 0.637 - 1.910) in the FAS (n=66), 0.862 (95% CI 0.381 - 1.946) in the younger (n=32) and 1.355 (95% CI 0.648 - 2.833) in the older age cohort (n=34).

End point type	Secondary
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End point timeframe:

During prophylactic treatment: approx. 6 months per subject

End point values	Pediatric subjects <6 years of age	Pediatric subjects 6 to <12 years of age	Full Analysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	32	34	66	
Units: Annualized bleeding rate				
arithmetic mean (standard deviation)				
Overall annualized bleeding rate	2.4 (± 3.508)	4.76 (± 9.046)	3.61 (± 6.988)	
Annualized rate of joint bleeds	0.87 (± 2.622)	1.36 (± 2.59)	1.12 (± 2.597)	
Annualized rate of target joint bleeds	0.06 (± 0.354)	0.36 (± 1.146)	0.21 (± 0.865)	
Annualized rate of non-target joint bleeds	0.81 (± 2.618)	1 (± 2.253)	0.91 (± 2.42)	
Annualized spontaneous bleeding rate	1.05 (± 2.048)	1.31 (± 2.467)	1.18 (± 2.26)	
Annualized rate of injury-related bleeds	1.63 (± 2.308)	3.71 (± 8.678)	2.71 (± 6.471)	

Statistical analyses

No statistical analyses for this end point

Secondary: Consumption of BAX 855: number of prophylactic infusions per month and per year (annualized) per subject

End point title	Consumption of BAX 855: number of prophylactic infusions per month and per year (annualized) per subject
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End point description:

End point type	Secondary
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End point timeframe:

During prophylactic treatment: approx. 6 months per subject

End point values	Pediatric subjects <6 years of age	Pediatric subjects 6 to <12 years of age	BAX 855 Safety Analysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	32	34	66	
Units: Prophylactic infusions				
arithmetic mean (standard deviation)				
Per month	8.07 (± 0.245)	7.72 (± 0.974)	7.89 (± 0.736)	
Per year	96.82 (± 2.942)	92.61 (± 11.693)	94.65 (± 8.834)	

Statistical analyses

No statistical analyses for this end point

Secondary: Consumption of BAX 855: weight-adjusted dose of prophylactic infusions per month and per year (annualized) per subject

End point title	Consumption of BAX 855: weight-adjusted dose of prophylactic infusions per month and per year (annualized) per subject
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End point description:

End point type	Secondary
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End point timeframe:

During prophylactic treatment: approx. 6 months per subject

End point values	Pediatric subjects <6 years of age	Pediatric subjects 6 to <12 years of age	BAX 855 Safety Analysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	32	34	66	
Units: IU/kg				
arithmetic mean (standard deviation)				
Per month	458.93 (± 46.161)	455.86 (± 76.101)	457.35 (± 62.919)	

Per year	5507.2 (\pm 553.931)	5470.32 (\pm 913.21)	5488.2 (\pm 755.033)	
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Statistical analyses

No statistical analyses for this end point

Secondary: Consumption of BAX 855: number of infusions per bleeding episode

End point title	Consumption of BAX 855: number of infusions per bleeding episode
End point description: Of 66 subjects in the BAX855 Safety Analysis Set, 34 experienced bleeding episodes which were treated, 15 in the <6 year age group, 19 in the 6 to <12 year age group.	
End point type	Secondary
End point timeframe: During prophylactic treatment: approx. 6 months per subject	

End point values	Pediatric subjects <6 years of age	Pediatric subjects 6 to <12 years of age	BAX 855 Safety Analysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	15	19	34	
Units: infusions				
arithmetic mean (standard deviation)	1.17 (\pm 0.362)	1.4 (\pm 0.655)	1.3 (\pm 0.551)	

Statistical analyses

No statistical analyses for this end point

Secondary: Consumption of BAX 855: weight-adjusted dose per bleeding episode

End point title	Consumption of BAX 855: weight-adjusted dose per bleeding episode
End point description: Of 66 subjects in the BAX855 Safety Analysis Set, 34 experienced bleeding episodes which were treated, 15 in the <6 year age group, 19 in the 6 to <12 year age group.	
End point type	Secondary
End point timeframe: During prophylactic treatment: approx. 6 months per subject	

End point values	Pediatric subjects <6 years of age	Pediatric subjects 6 to <12 years of age	BAX 855 Safety Analysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	15	19	34	
Units: IU/kg				
arithmetic mean (standard deviation)	52.21 (± 16.681)	62.31 (± 38.764)	57.85 (± 31.041)	

Statistical analyses

No statistical analyses for this end point

Secondary: Hemostatic efficacy at resolution of bleed

End point title	Hemostatic efficacy at resolution of bleed
End point description:	
<p>A total of 70 treated bleeding episodes occurred in 34 subjects: 25 treated bleeding episodes in 15 subjects <6 years of age and 45 treated bleeding episodes in 19 subjects 6 to <12 years of age.</p> <p>Rating Scale for Treatment of Bleeding Episodes (BEs) (4-point ordinal scale):</p> <p>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.</p> <p>GOOD: Definite pain relief and/or improvement in signs of bleeding after a single infusion. Possibly requires more than 1 infusion for complete resolution.</p> <p>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.</p> <p>NONE: No improvement or condition worsens.</p>	
End point type	Secondary
End point timeframe:	
During prophylactic treatment: approx. 6 months per subject	

End point values	Pediatric subjects <6 years of age	Pediatric subjects 6 to <12 years of age	Full Analysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	15 ^[5]	19 ^[6]	34 ^[7]	
Units: bleeding episodes				
Excellent	15	19	34	
Good	9	20	29	
Fair	1	3	4	
Not reported	0	3	3	

Notes:

[5] - 15 subjects <6 years of age had 25 bleeding episodes which were treated.

[6] - 19 subjects 6 to <12 years of age had 45 bleeding episodes which were treated.

[7] - A total of 70 treated bleeding episodes occurred in 34 of 66 subjects in the FAS.

Statistical analyses

No statistical analyses for this end point

Secondary: Serious adverse events (SAEs) possibly or probably related to BAX 855

End point title	Serious adverse events (SAEs) possibly or probably related to BAX 855
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End point description:

End point type	Secondary
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End point timeframe:

Throughout the study period (1 year), approximately 6 months per subject

End point values	Pediatric subjects <6 years of age	Pediatric subjects 6 to <12 years of age	BAX 855 Safety Analysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	32	34	66	
Units: subjects				
Investigator assessment	0	0	0	
Sponsor assessment	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Non-serious AEs possibly or probably related to BAX 855

End point title	Non-serious AEs possibly or probably related to BAX 855
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End point description:

End point type	Secondary
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End point timeframe:

Throughout the study period (1 year), approximately 6 months per subject

End point values	Pediatric subjects <6 years of age	Pediatric subjects 6 to <12 years of age	BAX 855 Safety Analysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	32	34	66	
Units: subjects				
Investigator assessment	1	0	1	
Sponsor assessment	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Clinically significant changes in vital signs

End point title	Clinically significant changes in vital signs
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End point description:

Vital signs: body temperature, respiratory rate (breaths/min), pulse rate (beats/min), and systolic and diastolic blood pressure (mmHg). For each abnormal vital sign value, the investigator had to decide if he/she deemed this to be an AE.

End point type	Secondary
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End point timeframe:

Throughout the study period (1 year), approximately 6 months per subject

End point values	Pediatric subjects <6 years of age	Pediatric subjects 6 to <12 years of age	BAX 855 Safety Analysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	32	34	66	
Units: subjects	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Clinically significant changes in clinical laboratory parameters (hematology, clinical chemistry, lipids)

End point title	Clinically significant changes in clinical laboratory parameters (hematology, clinical chemistry, lipids)
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End point description:

The HEMATOLOGY PANEL consisted of complete blood count: hemoglobin, hematocrit, erythrocytes (ie, red blood cell count), leukocytes (ie, white blood cell count) with differential (ie, basophils, eosinophils, lymphocytes, monocytes, and neutrophils), mean corpuscular volume, mean corpuscular hemoglobin concentration, and platelet count.

The CLINICAL CHEMISTRY PANEL consisted of sodium, potassium, chloride, bicarbonate, total protein, albumin, ALT, aspartate aminotransferase (AST), total bilirubin, alkaline phosphatase, blood urea nitrogen, creatinine, and glucose.

The LIPID PANEL consisted of cholesterol, very low density lipoprotein, low density lipoprotein, high density lipoprotein, and triglycerides.

End point type	Secondary
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End point timeframe:

Throughout the study period (1 year), approximately 6 months per subject

End point values	Pediatric subjects <6 years of age	Pediatric subjects 6 to <12 years of age	BAX 855 Safety Analysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	32	34	66	
Units: subjects				
Hematology panel	1	0	1	
Clinical chemistry panel	1	0	1	
Lipid panel	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Positive post-baseline binding antibodies to FVIII, PEG-FVIII, polyethylene glycol (PEG), and Chinese hamster ovary (CHO) proteins

End point title	Positive post-baseline binding antibodies to FVIII, PEG-FVIII, polyethylene glycol (PEG), and Chinese hamster ovary (CHO) proteins
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End point description:

Binding antibodies to FVIII and PEG-FVIII, as well as to PEG, were measured using enzyme-linked immunosorbent assay (ELISA). Both immunoglobulin G (IgG) and immunoglobulin M (IgM) binding antibodies for FVIII, BAX 855, and PEG were routinely tested. Based on the variability of these tests, only samples with titers $\geq 1:80$ could be confirmed and were evaluated as positive. Furthermore, only increases of more than 2 titer steps between pre- and post-treatment samples were considered positive for treatment-related antibody development.

End point type	Secondary
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End point timeframe:

Throughout the study period (1 year), approximately 6 months per subject

End point values	Pediatric subjects <6 years of age	Pediatric subjects 6 to <12 years of age	BAX 855 Safety Analysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	32	33 ^[8]	65 ^[9]	
Units: subjects				
Positive binding IgG antibodies to FVIII	0	0	0	
Positive binding IgM antibodies to FVIII	0	0	0	
Positive binding IgG antibodies to PEG-FVIII	3	4	7	
Positive binding IgM antibodies to PEG-FVIII	0	0	0	
Positive binding IgG antibodies to PEG	0	0	0	
Positive binding IgM antibodies to PEG	0	0	0	

Positive binding Ig antibodies to CHO	0	0	0	
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Notes:

[8] - For 1 of 34 subjects in the 6 to <12 year age group of the SAS, no data are available.

[9] - For 1 of 66 subjects in the SAS (6 to <12 year age group), no data are available.

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics (PK): Area under the plasma concentration versus time curve from 0 to ∞ hours post-infusion (AUC_{0- ∞})

End point title	Pharmacokinetics (PK): Area under the plasma concentration versus time curve from 0 to ∞ hours post-infusion (AUC _{0-∞})
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End point description:

The first infusion given for PK assessment was ADVATE and the second infusion was BAX 855. All subjects undergoing PK assessment were to have a 72-hour washout period prior to administration of ADVATE or BAX 855. The timing of the infusion (morning or afternoon) and the timing of the second and third post-infusion blood draws were to be determined at randomization. All subjects had samples drawn at 15-30 minutes post-infusion. The second post-infusion sample was either 7 hours (if am PK dose) or 4 hours post infusion (if pm PK dose), or on Day 1 in the morning or Day 1 in the afternoon. The third post-infusion sample was either on Day 2, Day 3 or Day 4. A nonlinear mixed effects model approach (population PK) was implemented to analyze PK data.

End point type	Secondary
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End point timeframe:

(1) up to 30 minutes pre-infusion; (2) up to 30 min post-infusion, (3) Day 0 either 4 or 7 hours post infusion or Day 1; (4) Either Day 2, Day 3, or Day 4

End point values	Pharmacokinetic (PK) Analysis Set - ADVATE	Pharmacokinetic (PK) Analysis Set - BAX 855	PK Analysis Set - BAX 855 - subjects <6 years of age	PK Analysis Set - BAX 855 - subjects 6 to <12 years of age
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	31	31	14	17
Units: IU•hr/L				
arithmetic mean (standard deviation)				
One stage clotting assay	14200 (± 2420)	19800 (± 6160)	19500 (± 7580)	20100 (± 4930)
Chromogenic assay	14400 (± 4040)	22300 (± 11200)	21900 (± 15900)	22600 (± 5140)

End point values	PK Analysis Set - ADVATE - subjects <6 years of age	PK Analysis Set - ADVATE - subjects 6 to <12 years of age		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	14	17		
Units: IU•hr/L				
arithmetic mean (standard deviation)				

One stage clotting assay	14000 (\pm 3070)	14400 (\pm 1800)		
Chromogenic assay	11600 (\pm 3070)	16600 (\pm 3290)		

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics (PK): Mean residence time (MRT)

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

The first infusion given for PK assessment was ADVATE and the second infusion was BAX 855. All subjects undergoing PK assessment were to have a 72-hour washout period prior to administration of ADVATE or BAX 855. The timing of the infusion (morning or afternoon) and the timing of the second and third post-infusion blood draws were to be determined at randomization. All subjects had samples drawn at 15-30 minutes post-infusion. The second post-infusion sample was either 7 hours (if am PK dose) or 4 hours post infusion (if pm PK dose), or on Day 1 in the morning or Day 1 in the afternoon. The third post-infusion sample was either on Day 2, Day 3 or Day 4. A nonlinear mixed effects model approach (population PK) was implemented to analyze PK data.

End point type	Secondary
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End point timeframe:

(1) up to 30 minutes pre-infusion; (2) up to 30 min post-infusion, (3) Day 0 either 4 or 7 hours post infusion or Day 1; (4) Either Day 2, Day 3, or Day 4

End point values	Pharmacokinetic (PK) Analysis Set - ADVATE	Pharmacokinetic (PK) Analysis Set - BAX 855	PK Analysis Set - BAX 855 - subjects <6 years of age	PK Analysis Set - BAX 855 - subjects 6 to <12 years of age
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	31	31	14	17
Units: hour (hr)				
arithmetic mean (standard deviation)				
One stage clotting assay	13.8 (\pm 3.27)	17.5 (\pm 2.93)	17 (\pm 3.51)	17.8 (\pm 2.4)
Chromogenic assay	12 (\pm 1.93)	17.9 (\pm 8.76)	18.7 (\pm 12.6)	17.2 (\pm 3.72)

End point values	PK Analysis Set - ADVATE - subjects <6 years of age	PK Analysis Set- ADVATE - subjects 6 to <12 years of age		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	14	17		
Units: hour (hr)				
arithmetic mean (standard deviation)				
One stage clotting assay	13.3 (\pm 3.95)	14.2 (\pm 2.64)		
Chromogenic assay	12.5 (\pm 2.52)	11.6 (\pm 1.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics (PK): Clearance (CL)

End point title	Pharmacokinetics (PK): Clearance (CL)
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End point description:

The first infusion given for PK assessment was ADVATE and the second infusion was BAX 855. All subjects undergoing PK assessment were to have a 72-hour washout period prior to administration of ADVATE or BAX 855. The timing of the infusion (morning or afternoon) and the timing of the second and third post-infusion blood draws were to be determined at randomization. All subjects had samples drawn at 15-30 minutes post-infusion. The second post-infusion sample was either 7 hours (if am PK dose) or 4 hours post infusion (if pm PK dose), or on Day 1 in the morning or Day 1 in the afternoon. The third post-infusion sample was either on Day 2, Day 3 or Day 4. A nonlinear mixed effects model approach (population PK) was implemented to analyze PK data.

End point type	Secondary
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End point timeframe:

(1) up to 30 minutes pre-infusion; (2) up to 30 min post-infusion, (3) Day 0 either 4 or 7 hours post infusion or Day 1; (4) Either Day 2, Day 3, or Day 4

End point values	Pharmacokinetic (PK) Analysis Set - ADVATE	Pharmacokinetic (PK) Analysis Set - BAX 855	PK Analysis Set - BAX 855 - subjects <6 years of age	PK Analysis Set - BAX 855 - subjects 6 to <12 years of age
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	31	31	14	17
Units: L/hr				
arithmetic mean (standard deviation)				
One stage clotting assay	0.103 (± 0.0398)	0.77 (± 0.0286)	0.0596 (± 0.019)	0.0913 (± 0.0276)
Chromogenic assay	0.0994 (± 0.011)	0.0704 (± 0.0246)	0.0574 (± 0.0174)	0.0812 (± 0.0248)

End point values	PK Analysis Set - ADVATE - subjects <6 years of age	PK Analysis Set - ADVATE - subjects 6 to <12 years of age		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	14	17		
Units: L/hr				
arithmetic mean (standard deviation)				
One stage clotting assay	0.0775 (± 0.0132)	0.125 (± 0.042)		

Chromogenic assay	0.0933 (\pm 0.0106)	0.104 (\pm 0.00875)		
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Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics (PK): Incremental recovery (IR)

End point title	Pharmacokinetics (PK): Incremental recovery (IR)
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End point description:

The first infusion given for PK assessment was ADVATE and the second infusion was BAX 855. All subjects undergoing PK assessment were to have a 72-hour washout period prior to administration of ADVATE or BAX 855. The timing of the infusion (morning or afternoon) and the timing of the second and third post-infusion blood draws were to be determined at randomization. All subjects had samples drawn at 15-30 minutes post-infusion. The second post-infusion sample was either 7 hours (if am PK dose) or 4 hours post infusion (if pm PK dose), or on Day 1 in the morning or Day 1 in the afternoon. The third post-infusion sample was either on Day 2, Day 3 or Day 4. A nonlinear mixed effects model approach (population PK) was implemented to analyze PK data.

End point type	Secondary
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End point timeframe:

(1) up to 30 minutes pre-infusion; (2) up to 30 min post-infusion, (3) Day 0 either 4 or 7 hours post infusion or Day 1; (4) Either Day 2, Day 3, or Day 4

End point values	Pharmacokinetic (PK) Analysis Set - ADVATE	Pharmacokinetic (PK) Analysis Set - BAX 855	PK Analysis Set - BAX 855 - subjects <6 years of age	PK Analysis Set - BAX 855 - subjects 6 to <12 years of age
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	31	31	14	17
Units: IU/dL : IU/kg				
arithmetic mean (standard deviation)				
One stage clotting assay	1.8636 (\pm 0.53481)	1.9101 (\pm 0.47371)	1.8809 (\pm 0.48894)	1.9342 (\pm 0.47451)
Chromogenic assay	1.9065 (\pm 0.33879)	2.0402 (\pm 0.36355)	1.8813 (\pm 0.27069)	2.171 (\pm 0.38472)

End point values	PK Analysis Set - ADVATE - subjects <6 years of age	PK Analysis Set - ADVATE - subjects 6 to <12 years of age		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	14	17		
Units: IU/dL : IU/kg				
arithmetic mean (standard deviation)				
One stage clotting assay	1.8563 (\pm 0.76004)	1.8696 (\pm 0.25856)		

Chromogenic assay	1.7374 (\pm 0.2911)	2.0458 (\pm 0.31739)		
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Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics (PK): Incremental recovery (IR) of BAX 855 over time - one stage clotting assay

End point title	Pharmacokinetics (PK): Incremental recovery (IR) of BAX 855 over time - one stage clotting assay
End point description: Pre- and post-infusion levels of Factor VIII (FVIII) following infusion of BAX 855 were used to determine IR.	
End point type	Secondary
End point timeframe: Baseline, Week 5 (or 10-15 EDs, whichever occurs last), Week 12, and Month 6 (Completion/Termination)	

End point values	Pediatric subjects <6 years of age	Pediatric subjects 6 to <12 years of age	Full Analysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	27 ^[10]	30 ^[11]	57 ^[12]	
Units: IU/dL : IU/kg				
arithmetic mean (standard deviation)				
Baseline	1.6889 (\pm 0.2761)	1.7843 (\pm 0.35942)	1.7381 (\pm 0.32017)	
Week 5 (or after 10-15 EDs)	1.8952 (\pm 0.55483)	1.8661 (\pm 0.49785)	1.8799 (\pm 0.52105)	
Week 12	1.6818 (\pm 0.23069)	1.9212 (\pm 0.42496)	1.812 (\pm 0.36738)	
Month 6 (Completion/Termination)	1.5801 (\pm 0.31568)	1.712 (\pm 0.36588)	1.6472 (\pm 0.34546)	

Notes:

[10] - Baseline: n=15, Week 5: n=27, Week 12: n=26, Month 6: n=27

[11] - Baseline: n=16, Week 5: n=30, Week 12: n=31, Month 6: n=28

[12] - Baseline: n=31, Week 5: n=57, Week 12: n=57, Month 6: n=55

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics (PK): Incremental recovery (IR) of BAX 855 over time - chromogenic assay

End point title	Pharmacokinetics (PK): Incremental recovery (IR) of BAX 855 over time - chromogenic assay
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End point description:

Pre- and post-infusion levels of Factor VIII (FVIII) following infusion of BAX 855 were used to determine IR.

End point type	Secondary
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End point timeframe:

Baseline, Week 5 (or 10-15 EDs, whichever occurs last), Week 12, and Month 6 (Completion/Termination)

End point values	Pediatric subjects <6 years of age	Pediatric subjects 6 to <12 years of age	Full Analysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	27 ^[13]	30 ^[14]	57 ^[15]	
Units: IU/dL : IU/kg				
arithmetic mean (standard deviation)				
Baseline	1.7675 (± 0.34998)	1.9334 (± 0.3)	1.8532 (± 0.33055)	
Week 5 (or after 10-15 EDs)	1.9273 (± 0.324)	1.996 (± 0.39258)	1.9635 (± 0.36021)	
Week 12	1.8794 (± 0.24281)	1.9869 (± 0.423)	1.9379 (± 0.35368)	
Month 6 (Completion/Termination)	1.8359 (± 0.29188)	2.0659 (± 0.45723)	1.953 (± 0.39876)	

Notes:

[13] - Baseline: n=15, Week 5: n=27, Week 12: n=26, Month 6: n=27

[14] - Baseline: n=16, Week 5: n=30, Week 12: n=31, Month 6: n=28

[15] - Baseline: n=31, Week 5: n=57, Week 12: n=57, Month 6: n=55

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics (PK): Plasma half-life (T_{1/2})

End point title	Pharmacokinetics (PK): Plasma half-life (T _{1/2})
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End point description:

The first infusion given for PK assessment was ADVATE and the second infusion was BAX 855. All subjects undergoing PK assessment were to have a 72-hour washout period prior to administration of ADVATE or BAX 855. The timing of the infusion (morning or afternoon) and the timing of the second and third post-infusion blood draws were to be determined at randomization. All subjects had samples drawn at 15-30 minutes post-infusion. The second post-infusion sample was either 7 hours (if am PK dose) or 4 hours post infusion (if pm PK dose), or on Day 1 in the morning or Day 1 in the afternoon. The third post-infusion sample was either on Day 2, Day 3 or Day 4. A nonlinear mixed effects model approach (population PK) was implemented to analyze PK data.

End point type	Secondary
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End point timeframe:

(1) up to 30 minutes pre-infusion; (2) up to 30 min post-infusion, (3) Day 0 either 4 or 7 hours post infusion or Day 1; (4) Either Day 2, Day 3, or Day 4

End point values	Pharmacokinetic (PK) Analysis Set - ADVATE	Pharmacokinetic (PK) Analysis Set - BAX 855	PK Analysis Set - BAX 855 - subjects <6 years of age	PK Analysis Set - BAX 855 - subjects 6 to <12 years of age
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	31	31	14	17
Units: hr				
arithmetic mean (standard deviation)				
One stage clotting assay	9.56 (± 2.26)	12.1 (± 2.03)	11.8 (± 2.43)	12.4 (± 1.67)
Chromogenic assay	8.33 (± 1.34)	12.4 (± 6.07)	13 (± 8.74)	11.9 (± 2.58)

End point values	PK Analysis Set - ADVATE - subjects <6 years of age	PK Analysis Set - ADVATE - subjects 6 to <12 years of age		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	14	17		
Units: hr				
arithmetic mean (standard deviation)				
One stage clotting assay	9.24 (± 2.74)	9.82 (± 1.83)		
Chromogenic assay	8.68 (± 1.75)	8.04 (± 0.83)		

Statistical analyses

No statistical analyses for this end point

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

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

The first infusion given for PK assessment was ADVATE and the second infusion was BAX 855. All subjects undergoing PK assessment were to have a 72-hour washout period prior to administration of ADVATE or BAX 855. The timing of the infusion (morning or afternoon) and the timing of the second and third post-infusion blood draws were to be determined at randomization. All subjects had samples drawn at 15-30 minutes post-infusion. The second post-infusion sample was either 7 hours (if am PK dose) or 4 hours post infusion (if pm PK dose), or on Day 1 in the morning or Day 1 in the afternoon. The third post-infusion sample was either on Day 2, Day 3 or Day 4. A nonlinear mixed effects model approach (population PK) was implemented to analyze PK data.

End point type	Secondary
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End point timeframe:

(1) up to 30 minutes pre-infusion; (2) up to 30 min post-infusion, (3) Day 0 either 4 or 7 hours post infusion or Day 1; (4) Either Day 2, Day 3, or Day 4

End point values	Pharmacokinetic (PK) Analysis Set - ADVATE	Pharmacokinetic (PK) Analysis Set - BAX 855	PK Analysis Set - BAX 855 - subjects <6 years of age	PK Analysis Set - BAX 855 - subjects 6 to <12 years of age
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	31	31	14	17
Units: litre (L)				
arithmetic mean (standard deviation)				
One stage clotting assay	1.39 (± 0.47)	1.31 (± 0.427)	0.97 (± 0.23)	1.59 (± 0.343)
Chromogenic assay	1.18 (± 0.0857)	1.14 (± 0.285)	0.907 (± 0.124)	1.33 (± 0.233)

End point values	PK Analysis Set - ADVATE - subjects <6 years of age	PK Analysis Set- ADVATE - subjects 6 to <12 years of age		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	14	17		
Units: litre (L)				
arithmetic mean (standard deviation)				
One stage clotting assay	1.02 (± 0.302)	1.69 (± 0.35)		
Chromogenic assay	1.14 (± 0.107)	1.2 (± 0.0548)		

Statistical analyses

No statistical analyses for this end point

Post-hoc: Pharmacokinetics (PK): Plasma half-life ratio of BAX 855 to ADVATE

End point title	Pharmacokinetics (PK): Plasma half-life ratio of BAX 855 to ADVATE
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End point description:

This is a descriptive summary of the ratio of plasma half-life in the same subject for BAX 855 compared to ADVATE based on the final covariate model (first observation tabulation). In the one-stage clotting assay, the mean half-life of BAX 855 was 1.30 times longer compared to ADVATE. In the chromogenic assay, the mean half-life of BAX 855 was 1.50 times longer compared to ADVATE.

End point type	Post-hoc
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End point timeframe:

(1) up to 30 minutes pre-infusion; (2) up to 30 min post-infusion, (3) Day 0 either 4 or 7 hours post infusion or Day 1; (4) Either Day 2, Day 3, or Day 4

End point values	Pharmacokinetic (PK) Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	31			
Units: hr				
arithmetic mean (full range (min-max))				
One stage clotting assay	1.3 (0.944 to 2)			
Chromogenic assay	1.5 (0.894 to 4.81)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Throughout the study period (1 year), approximately 6 months per subject

Adverse event reporting additional description:

AEs were continuously monitored but specifically discussed and reviewed at these time points: pre- and post-PK infusion, at the baseline visit, during prophylactic treatment at these visits: Week 5 (or 10-15 exposure days (EDs)), Week 12, Week 20 (by phone); at the study completion visit at Month 6 or after at least 50 EDs, whichever occurred last

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	18.1
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Reporting groups

Reporting group title	BAX 855 Safety Analysis Set (n=66)
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Reporting group description:

The BAX 855 safety analysis set contains all subjects who received at least one dose of BAX 855.

Serious adverse events	BAX 855 Safety Analysis Set (n=66)		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 66 (4.55%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	1 / 66 (1.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pancytopenia			
subjects affected / exposed	1 / 66 (1.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 66 (1.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastritis			

subjects affected / exposed	1 / 66 (1.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	BAX 855 Safety Analysis Set (n=66)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	43 / 66 (65.15%)		
Nervous system disorders			
Headache			
subjects affected / exposed	5 / 66 (7.58%)		
occurrences (all)	7		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	13 / 66 (19.70%)		
occurrences (all)	20		
Gastrointestinal disorders			
Diarrhea			
subjects affected / exposed	5 / 66 (7.58%)		
occurrences (all)	5		
Vomiting			
subjects affected / exposed	5 / 66 (7.58%)		
occurrences (all)	6		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	4 / 66 (6.06%)		
occurrences (all)	8		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	5 / 66 (7.58%)		
occurrences (all)	5		
Upper respiratory tract infection			
subjects affected / exposed	9 / 66 (13.64%)		
occurrences (all)	9		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 November 2014	<p>-) The inclusion criterion "The subject has severe hemophilia A (FVIII <1%) as determined by the central laboratory" was amended to: "The subject has severe hemophilia A (FVIII <1%) as determined by the central laboratory, or a historical FVIII level <1% as determined at any local laboratory and/or a FVIII gene mutation consistent with severe hemophilia A". Reason for change: To avoid potential risk of bleeding episodes in the washout period.</p> <p>-) Text regarding dose adjustment of BAX 855 for prophylactic treatment was amended as follows: Original text: "Based on the Investigator's clinical evaluation, the dose may be increased for subjects receiving prophylactic treatment at any time to ensure patient safety is adequately managed." Revised text: "Based on the Investigator's clinical evaluation, the dose may be increased up to a maximum of 80 IU/kg but not exceeding plasmatic FVIII peak levels of 200% for subjects receiving prophylactic treatment at any time to ensure patient safety is adequately managed." Reason for change: To provide a maximum dose for prophylactic treatment.</p> <p>-) Addition of the following serious adverse event (SAE) criterion: "Hospitalization for planned port placement or removal is not considered an SAE, however, any hospitalization required for an emergency port removal is considered an SAE".</p>

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported