



## Clinical trial results:

### **ADVATE Antihemophilic Factor (Recombinant), Plasma/Albumin-Free Method (ADVATE rAHF-PFM): A Phase 4 Study Comparing Two Prophylactic Regimens In Subjects With Severe Or Moderately Severe Hemophilia A**

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

#### **Summary**

EudraCT number	2005-000347-29
Trial protocol	GB AT HU CZ SI IT
Global end of trial date	16 June 2010

#### **Results information**

Result version number	v1 (current)
This version publication date	05 March 2016
First version publication date	05 March 2016

#### **Trial information**

##### **Trial identification**

Sponsor protocol code	060201
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##### **Additional study identifiers**

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00243386
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)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

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	16 June 2010
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	16 June 2010
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of this study was to compare the rates of bleeding episodes between a standard prophylaxis regimen (20 to 40 IU/kg every  $48 \pm 6$  hours) and a pharmacokinetics (PK)-driven prophylaxis regimen (20 to 80 IU/kg every  $72 \pm 6$  hours).

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.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	04 January 2006
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	Austria: 1
Country: Number of subjects enrolled	Czech Republic: 6
Country: Number of subjects enrolled	Greece: 2
Country: Number of subjects enrolled	Hungary: 9
Country: Number of subjects enrolled	Italy: 4
Country: Number of subjects enrolled	Poland: 26
Country: Number of subjects enrolled	Russian Federation: 8
Country: Number of subjects enrolled	Slovenia: 1
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	United States: 23
Worldwide total number of subjects	82
EEA total number of subjects	51

Notes:

<b>Subjects enrolled per age group</b>	
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)	5
Adolescents (12-17 years)	8
Adults (18-64 years)	69
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

Subjects were enrolled (signed informed consent) at 21 European and 9 United States clinical sites beginning January 2006 and completing in June 2010

### Pre-assignment

Screening details:

82 subjects were enrolled and screened. 7 were screen failures, 1 was withdrawn for non-compliance, and 1 requested withdrawal. Therefore, 73 of the 82 enrolled were treated with investigational product (rAFH-PFM).

### Pre-assignment period milestones

Number of subjects started	82
Number of subjects completed	73

### Pre-assignment subject non-completion reasons

Reason: Number of subjects	Consent withdrawn by subject: 1
Reason: Number of subjects	Screen Failure: 7
Reason: Number of subjects	Withdrawn for non compliance: 1

### Period 1

Period 1 title	Overall study (Parts 1 and 2) (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

This open-label study had 2 parts

Part 1: Subjects underwent PK evaluation for 48 hours followed by on-demand treatment with rAFH-PFM for 6 months

Part 2: Subjects were randomized either to standard prophylaxis or PK-driven prophylaxis (both with rAFH-PFM) for 12 months.

Randomization in part 2 stratified based on presence of target joints [joint in which at least 4 bleeds occurred within 6 months or > 20 lifetime bleeds (0 target joints; 1-2 target joints;  $\geq$  target joints) to reduce bias

### Arms

Are arms mutually exclusive?	No
Arm title	All subjects

Arm description:

All subjects who were exposed to investigational product (rAHF-PFM).

Arm type	Experimental
Investigational medicinal product name	ADVATE
Investigational medicinal product code	rAHF-PFM
Other name	
Pharmaceutical forms	Powder and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Standard Prophylaxis - 20-40 IU/kg every 48 $\pm$ 6h; PK-driven Prophylaxis 20-80 IU/kg (determined by PK results) every 72 $\pm$ 6h; On-demand - 10-100 IU/kg - dose and frequency dependent on severity and location of bleed

<b>Arm title</b>	On-Demand
Arm description:	
On-demand regimen - rAHF-PFM was to be used for the treatment of bleeding episodes according to the severity and type of episode by the protocol-recommended dosing until the episode resolved: superficial (10-20 IU/kg every 12-14 hours), minor joint (20-40 IU/kg every 12-14 hours), deep muscle (30-60 IU/kg every 12-14 hours), major joint or life-threatening (60-100 IU/kg every 8-12 hours), genitourinary, GI, and intracranial (60-100 IU/kg every 8-12 hours).	
Arm type	Experimental
Investigational medicinal product name	ADVATE
Investigational medicinal product code	rAHF-PFM
Other name	
Pharmaceutical forms	Powder and solvent for solution for infusion
Routes of administration	Intravenous use
Dosage and administration details:	
Standard Prophylaxis - 20-40 IU/kg every 48±6h; PK-driven Prophylaxis 20-80 IU/kg (determined by PK results) every 72±6h; On-demand - 10-100 IU/kg - dose and frequency dependent on severity and location of bleed	
<b>Arm title</b>	Standard Prophylaxis
Arm description:	
Standard prophylaxis regimen - subjects dosed at 20-40 IU/kg of rAHF-PFM every 48 ± 6 hours, exact regimen to be determined by the investigator.	
Arm type	Experimental
Investigational medicinal product name	ADVATE
Investigational medicinal product code	rAHF-PFM
Other name	
Pharmaceutical forms	Powder and solvent for solution for infusion
Routes of administration	Intravenous use
Dosage and administration details:	
Standard Prophylaxis - 20-40 IU/kg every 48±6h; PK-driven Prophylaxis 20-80 IU/kg (determined by PK results) every 72±6h; On-demand - 10-100 IU/kg - dose and frequency dependent on severity and location of bleed	
<b>Arm title</b>	PK-Driven Prophylaxis
Arm description:	
Pharmacokinetic (PK)-Driven prophylaxis regimen - subjects dosed at 20-80 IU/kg of rAHF-PFM every 72 ± 6 hours, exact regimen to be determined by the sponsor.	
Arm type	Experimental
Investigational medicinal product name	ADVATE
Investigational medicinal product code	rAHF-PFM
Other name	
Pharmaceutical forms	Powder and solvent for solution for infusion
Routes of administration	Intravenous use
Dosage and administration details:	
Standard Prophylaxis - 20-40 IU/kg every 48±6h; PK-driven Prophylaxis 20-80 IU/kg (determined by PK results) every 72±6h; On-demand - 10-100 IU/kg - dose and frequency dependent on severity and location of bleed	
<b>Arm title</b>	Any Prophylaxis
Arm description:	
Standard Prophylaxis: 20-40 IU/kg of rAHF-PFM every 48 ± 6 hours, exact regimen to be determined by the investigator.	
PK-Driven Prophylaxis: 20-80 IU/kg of rAHF-PFM every 72 ± 6 hours, exact regimen to be determined by the sponsor	
Arm type	Experimental

Investigational medicinal product name	ADVATE
Investigational medicinal product code	rAHF-PFM
Other name	
Pharmaceutical forms	Powder and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Standard Prophylaxis - 20-40 IU/kg every 48±6h; PK-driven Prophylaxis 20-80 IU/kg (determined by PK results) every 72±6h; On-demand - 10-100 IU/kg - dose and frequency dependent on severity and location of bleed

<b>Number of subjects in period 1</b>	All subjects	On-Demand	Standard Prophylaxis
Started	73	73	32
Completed	63	66	32
Not completed	10	7	0
Consent withdrawn by subject	2	2	-
Lost to follow-up	2	2	-
Screen-failure	2	2	-
Withdrawn for non-compliance	3	1	-
Lack of efficacy	1	-	-

<b>Number of subjects in period 1</b>	PK-Driven Prophylaxis	Any Prophylaxis
Started	34	66
Completed	31	63
Not completed	3	3
Consent withdrawn by subject	-	-
Lost to follow-up	-	-
Screen-failure	-	-
Withdrawn for non-compliance	2	2
Lack of efficacy	1	1

## Baseline characteristics

### Reporting groups<sup>[1]</sup>

Reporting group title	Overall study (Parts 1 and 2)
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Reporting group description:

Overall study (Parts 1 and 2)

Notes:

[1] - The number of subjects reported to be in the baseline period is not equal to the worldwide number of subjects enrolled in the trial. It is expected that these numbers will be the same.

Justification: The worldwide number of subjects enrolled only included subjects treated with study product (N=73) as per definition of enrolled in EudraCT (Enrolled=Treated). The number of subjects reported in the baseline period includes all subjects enrolled in the study i.e. signed informed consent (N=82).

Reporting group values	Overall study (Parts 1 and 2)	Total	
Number of subjects	73	73	
Age categorical			
Units: Subjects			
Age continuous			
Age continuous description			
Units: years			
median	26		
full range (min-max)	7 to 59	-	
Gender categorical			
Gender categorical description			
Units: Subjects			
Female	0	0	
Male	73	73	

## End points

### End points reporting groups

Reporting group title	All subjects
Reporting group description: All subjects who were exposed to investigational product (rAHF-PFM).	
Reporting group title	On-Demand
Reporting group description: On-demand regimen - rAHF-PFM was to be used for the treatment of bleeding episodes according to the severity and type of episode by the protocol-recommended dosing until the episode resolved: superficial (10-20 IU/kg every 12-14 hours), minor joint (20-40 IU/kg every 12-14 hours), deep muscle (30-60 IU/kg every 12-14 hours), major joint or life-threatening (60-100 IU/kg every 8-12 hours), genitourinary, GI, and intracranial (60-100 IU/kg every 8-12 hours).	
Reporting group title	Standard Prophylaxis
Reporting group description: Standard prophylaxis regimen - subjects dosed at 20-40 IU/kg of rAHF-PFM every $48 \pm 6$ hours, exact regimen to be determined by the investigator.	
Reporting group title	PK-Driven Prophylaxis
Reporting group description: Pharmacokinetic (PK)-Driven prophylaxis regimen - subjects dosed at 20-80 IU/kg of rAHF-PFM every $72 \pm 6$ hours, exact regimen to be determined by the sponsor.	
Reporting group title	Any Prophylaxis
Reporting group description: Standard Prophylaxis: 20-40 IU/kg of rAHF-PFM every $48 \pm 6$ hours, exact regimen to be determined by the investigator.  PK-Driven Prophylaxis: 20-80 IU/kg of rAHF-PFM every $72 \pm 6$ hours, exact regimen to be determined by the sponsor	
Subject analysis set title	Subjects $\geq 14$ Years
Subject analysis set type	Sub-group analysis
Subject analysis set description: Comprised of subjects $\geq 14$ Years	
Subject analysis set title	Subjects $< 14$ Years
Subject analysis set type	Sub-group analysis
Subject analysis set description: Comprised of subjects $< 14$ Years	
Subject analysis set title	On-Demand Versus Standard Prophylaxis
Subject analysis set type	Sub-group analysis
Subject analysis set description: On-demand: rAHF-PFM was to be used for the treatment of bleeding episodes according to the severity and type of episode by the protocol-recommended dosing until the episode resolved: superficial (10-20 IU/kg every 12-14 hours), minor joint (20-40 IU/kg every 12-14 hours), deep muscle (30-60 IU/kg every 12-14 hours), major joint or life-threatening (60-100 IU/kg every 8-12 hours), genitourinary, Gastrointestinal (GI), and intracranial (60-100 IU/kg every 8-12 hours).  Standard Prophylaxis: 20-40 IU/kg of rAHF-PFM every $48 \pm 6$ hours, exact regimen to be determined by the investigator.	
Subject analysis set title	On-Demand Versus PK-Driven Prophylaxis
Subject analysis set type	Sub-group analysis
Subject analysis set description: On-demand: rAHF-PFM was to be used for the treatment of bleeding episodes according to the severity and type of episode by the protocol-recommended dosing until the episode resolved: superficial (10-20 IU/kg every 12-14 hours), minor joint (20-40 IU/kg every 12-14 hours), deep muscle (30-60 IU/kg every 12-14 hours), major joint or life-threatening (60-100 IU/kg every 8-12 hours), genitourinary, GI, and intracranial (60-100 IU/kg every 8-12 hours).  PK-driven prophylaxis: 20-80 IU/kg of rAHF-PFM every $72 \pm 6$ hours, exact regimen to be determined	



by the sponsor.

Subject analysis set title	On-Demand Versus Any Prophylaxis
Subject analysis set type	Sub-group analysis

Subject analysis set description:

On-demand: rAHF-PFM was to be used for the treatment of bleeding episodes according to the severity and type of episode by the protocol-recommended dosing until the episode resolved: superficial (10-20 IU/kg every 12-14 hours), minor joint (20-40 IU/kg every 12-14 hours), deep muscle (30-60 IU/kg every 12-14 hours), major joint or life-threatening (60-100 IU/kg every 8-12 hours), genitourinary, GI, and intracranial (60-100 IU/kg every 8-12 hours)

Prophylaxis:

- Standard prophylaxis: 20-40 IU/kg of rAHF-PFM every  $48 \pm 6$  hours, exact regimen to be determined by the investigator
- PK-driven prophylaxis: 20-80 IU/kg of rAHF-PFM every  $72 \pm 6$  hours, exact regimen to be determined by the sponsor

Subject analysis set title	Subjects with SAEs outside of 3 Treatment Arms
Subject analysis set type	Safety analysis

Subject analysis set description:

Subjects with SAEs that occurred after exposure to investigational product, but outside of the on-demand, standard prophylaxis and PK-driven prophylaxis treatment arms.

Subject analysis set title	On-Demand to Standard Prophylaxis
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Comprised of subjects who completed the on-demand and standard prophylaxis regimens.

Subject analysis set title	On-Demand to PK-Driven Prophylaxis
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Comprised of subjects who completed the on-demand and PK-driven prophylaxis regimens.

Subject analysis set title	On-Demand to Any Prophylaxis
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Comprised of subjects who completed the on-demand and any prophylaxis regimens.

Subject analysis set title	Subjects Assessed Before Treatment
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects assessed before treatment with investigational product (rAFH-PFM).

### **Primary: Mean Transformed Annualized Bleed Rate Estimates From Each of the 1-year Prophylaxis Regimens**

End point title	Mean Transformed Annualized Bleed Rate Estimates From Each of the 1-year Prophylaxis Regimens <sup>[1]</sup>
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End point description:

Subjects were randomized to receive 1 of the 2 following prophylaxis regimens (Study Part 2):

1. Standard prophylaxis (20-40 IU/kg (every  $48 \pm 6$  hours), exact regimen determined by investigator)
2. PK-driven prophylaxis (20-80 IU/kg (every  $72 \pm 6$  hours), exact regimen determined by sponsor)

Annualized bleed rates were transformed using the square root of the number of bleeding episodes observed ( $X$  = bleeds/year),  $X' = \sqrt{(X + 0.5)}$ . This transformation was performed to stabilize the variance and align the sample distribution with the assumption of normality inherent in using the t-test.

Population: Subjects in the efficacy per-protocol set comprising of all subjects who completed, according to the protocol, both the on-demand treatment regimen and the randomly assigned prophylactic regimen. Subjects did not have major protocol deviations that would impact the assessment of the primary efficacy endpoint.

End point type	Primary
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End point timeframe:

12 months  $\pm$  2 weeks

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Arms in the baseline period are not mutually exclusive. Refer to the description of arms in period 1 (baseline period).

Please also note that it is not currently possible to enter statistics for some endpoints in this study due to limitations of EudraCT.

All statistics are available for these study results in ClinicalTrials.gov (NCT00243386).

End point values	Standard Prophylaxis	PK-Driven Prophylaxis		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	23		
Units: (bleeds/year) <sup>(1/2)</sup>				
arithmetic mean (standard deviation)	1.46 (± 0.98)	1.61 (± 1.1)		

## Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
A t-test was used to compare the means of the transformed data. The null-hypothesis tested was H0: X'A(PK-driven prophylaxis) - X'B (standard prophylaxis) = 0 (i.e., no difference for treatment under the 2 prophylactic regimens. $X' = (ABR + 0.5)^{(1/2)}$	
Comparison groups	Standard Prophylaxis v PK-Driven Prophylaxis
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6016
Method	t-test, 2 sided

## Primary: Median Annualized Bleed Rate Estimates From Each of the 1 Year Prophylaxis Regimens

End point title	Median Annualized Bleed Rate Estimates From Each of the 1 Year Prophylaxis Regimens <sup>[2]</sup>
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End point description:

Subjects were randomized to receive 1 of the 2 following prophylaxis regimens (part 2 of the study):

1. Standard prophylaxis- infusions every 48 ±6 hours, dosed at 20 to 40 IU/kg.
2. PK-driven prophylaxis- infusions every 72 ±6 hours dosed at 20 to 80 IU/kg.

Population: Subjects in the efficacy intent-to-treat set comprising of all subjects in the prophylaxis treatment regimen who had at least 1 assessment (1 quarterly visit) or who had withdrawn after 3 bleeding episodes prior to reaching the first assessment period.

End point type	Primary
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End point timeframe:

12 months ±2 weeks

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Arms in the baseline period are not mutually exclusive. Refer to the description of arms in period 1 (baseline period).

End point values	Standard Prophylaxis	PK-Driven Prophylaxis		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	34		
Units: Bleeds per year				
median (full range (min-max))	1 (0 to 25.87)	2.01 (0 to 17.06)		

## Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Standard Prophylaxis v PK-Driven Prophylaxis
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1467
Method	Wilcoxon-Rank Sum (Mann-Whitney)
Confidence interval	
level	95 %

## Secondary: Mean Difference of Transformed Annualized Bleeding Rate Between On-Demand and Standard Prophylaxis Treatment Regimens

End point title	Mean Difference of Transformed Annualized Bleeding Rate Between On-Demand and Standard Prophylaxis Treatment Regimens
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### End point description:

Annualized bleed rates were transformed using the square root of the number of bleeding episodes observed ( $X$  bleeds/year),  $X' = \sqrt{X + 0.5}$ . This transformation was performed to stabilize the variance and align the sample distribution with the assumption of normality inherent in using the paired t-test. Mean Difference of Transformed Annualized Bleeding Rate (TABR) = (On-Demand Treatment TABR) - (Standard Prophylaxis Treatment TABR). Participants from the On-Demand portion of the study were subsequently randomized to either Standard Prophylaxis or PK-Driven Prophylaxis, (i.e the same participants were analyzed across the two measurement time periods).

Population: Subjects in the efficacy intent-to-treat set comprising of all subjects in the prophylaxis treatment regimen who had at least 1 assessment (1 quarterly visit) or who had withdrawn after 3 bleeding episodes prior to reaching the first assessment period.

End point type	Secondary
End point timeframe:	
On-demand 6 months ( $\pm$ 2 weeks); followed by Prophylaxis 12 months ( $\pm$ 2 weeks)	

End point values	On-Demand Versus Standard Prophylaxis			
Subject group type	Subject analysis set			
Number of subjects analysed	32			
Units: (bleeds/year) <sup>(1/2)</sup>				
arithmetic mean (standard deviation)	5.29 ( $\pm$ 1.46)			

## Statistical analyses

No statistical analyses for this end point

### Secondary: Mean Difference of Transformed Annualized Bleeding Rate Between On-Demand and PK-Driven Prophylaxis Treatment Regimens

End point title	Mean Difference of Transformed Annualized Bleeding Rate Between On-Demand and PK-Driven Prophylaxis Treatment Regimens
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#### End point description:

Annualized bleed rates were transformed using the square root of the number of bleeding episodes observed ( $X$  bleeds/year),  $X' = \sqrt{X + 0.5}$ . This transformation was performed to stabilize the variance and align the sample distribution with the assumption of normality inherent in using the paired t-test. Mean Difference of Transformed Annualized Bleeding Rate (TABR) = (On-Demand Treatment TABR) - (PK-Driven Prophylaxis Treatment TABR) Participants from the On-Demand portion of the study were subsequently randomized to either Standard Prophylaxis or PK-Driven Prophylaxis, (i.e the same participants were analyzed across the two measurement time periods).

Population: Subjects in the efficacy intent-to-treat set comprising of all subjects in the prophylaxis treatment regimen who had at least 1 assessment (1 quarterly visit) or who had withdrawn after 3 bleeding episodes prior to reaching the first assessment period.

End point type	Secondary
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#### End point timeframe:

On-demand 6 months ( $\pm 2$  weeks); followed by Prophylaxis 12 months ( $\pm 2$  weeks)

End point values	On-Demand Versus PK-Driven Prophylaxis			
Subject group type	Subject analysis set			
Number of subjects analysed	34			
Units: (bleeds/year) <sup>(1/2)</sup>				
arithmetic mean (standard deviation)	5 ( $\pm 1.85$ )			

## Statistical analyses

No statistical analyses for this end point

### Secondary: Mean Difference of Transformed Annualized Bleeding Rate Between On-Demand and Any Prophylaxis Treatment Regimens

End point title	Mean Difference of Transformed Annualized Bleeding Rate Between On-Demand and Any Prophylaxis Treatment Regimens
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#### End point description:

Annualized bleed rates were transformed using the square root of the number of bleeding episodes observed ( $X$  bleeds/year),  $X' = \sqrt{X + 0.5}$ . This transformation was performed to stabilize the variance

and align the sample distribution with the assumption of normality inherent in using the paired t-test. Mean Difference of Transformed Annualized Bleeding Rate (TABR) = (On-Demand Treatment TABR) - (Any Prophylaxis Treatment TABR). Any Prophylaxis = Standard or PK-Driven Prophylaxis Participants from the On-Demand portion of the study were subsequently randomized to either Standard Prophylaxis or PK-Driven Prophylaxis, (i.e the same participants were analyzed across the two measurement time periods).

Population: Subjects in the efficacy intent-to-treat set comprising of all subjects in the prophylaxis treatment regimen who had at least 1 assessment (1 quarterly visit) or who had withdrawn after 3 bleeding episodes prior to reaching the first assessment period.

End point type	Secondary
End point timeframe:	
On-demand 6 months ( $\pm$ 2 weeks); Prophylaxis 12 months ( $\pm$ 2 weeks)	

End point values	On-Demand Versus Any Prophylaxis			
Subject group type	Subject analysis set			
Number of subjects analysed	66			
Units: (bleeds/year) <sup>(1/2)</sup>				
arithmetic mean (standard deviation)	5.14 ( $\pm$ 1.66)			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Total Weight-Adjusted Dose of rAHF-PFM Used Per Year for Each Prophylaxis Arm

End point title	Total Weight-Adjusted Dose of rAHF-PFM Used Per Year for Each Prophylaxis Arm <sup>[3]</sup>
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End point description:

Subjects were randomized to receive 1 of the 2 following prophylaxis regimens (part 2 of the study):

1. Standard prophylaxis- infusions every 48  $\pm$ 6 hours, dosed at 20 to 40 IU/kg.
2. PK-driven prophylaxis- infusions every 72  $\pm$ 6 hours dosed at 20 to 80 IU/kg.

Population: Subjects in the efficacy intent-to-treat set comprising of all subjects in the prophylaxis treatment regimen who had at least 1 assessment (1 quarterly visit) or who had withdrawn after 3 bleeding episodes prior to reaching the first assessment period.

End point type	Secondary
End point timeframe:	
12 months $\pm$ 2 weeks	

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Arms in the baseline period are not mutually exclusive. Refer to the description of arms in period 1 (baseline period).

End point values	Standard Prophylaxis	PK-Driven Prophylaxis		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	34		
Units: IU/kg				
median (inter-quartile range (Q1-Q3))	5768.2 (4728 to 6425.4)	5197.8 (3268.4 to 8273.5)		

## Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	PK-Driven Prophylaxis v Standard Prophylaxis
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4924
Method	Wilcoxon-Rank Sum (Mann-Whitney)
Confidence interval	
level	95 %

## Secondary: Bleeding Episodes Treated With 1 to ≥4 Infusions

End point title	Bleeding Episodes Treated With 1 to ≥4 Infusions <sup>[4]</sup>
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End point description:

The number of bleeding episodes treated with 1, 2, 3, or ≥4 infusions of rAHF-PFM to achieve adequate hemostasis.

Population: Subjects in the efficacy intent-to-treat set comprising of all subjects in the prophylaxis treatment regimen who had at least 1 assessment (1 quarterly visit) or who had withdrawn after 3 bleeding episodes prior to reaching the first assessment period.

End point type	Secondary
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End point timeframe:

Throughout the study period (4 years and 5 months)

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Arms in the baseline period are not mutually exclusive. Refer to the description of arms in period 1 (baseline period) for this endpoint.

End point values	On-Demand	Standard Prophylaxis	PK-Driven Prophylaxis	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	62	13	22	
Units: Bleeding episodes				
1 infusion (n = 62, 13, 22)	1168	68	90	
2 infusions (n = 51, 6, 9)	277	12	37	
3 infusions (n = 27, 2, 4)	128	4	5	
4 or more infusions (n = 21, 5, 5)	50	9	7	

## Statistical analyses

No statistical analyses for this end point

### Secondary: Assessment of Hemostasis for Treatment of Bleeding Episodes

End point title	Assessment of Hemostasis for Treatment of Bleeding
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End point description:

Number of rAHF-PFM-treated bleeding episodes with an assessment of hemostasis (4-point ordinal scale):

Excellent: Full pain relief & bleeding cessation within ~8 hrs of 1 infusion. Additional infusions may have been given to maintain hemostasis;

Good: Definite pain relief and/or improvement in bleeding within ~8 hrs after infusion. Possibly requires >1 infusion for complete resolution;

Fair: Probable or slight relief of pain & slight improvement in bleeding within ~8 hrs after infusion.

Requires >1 infusion for complete resolution;

None: No improvement or condition worsens.

Population: Subjects in the hemostatic efficacy rating set comprising of subjects who reported a bleeding episode that was treated with rAFH-PFM.

End point type	Secondary
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End point timeframe:

On-demand 6 months ( $\pm$  2 weeks); Prophylaxis 12 months ( $\pm$  2 weeks)

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Arms in the baseline period are not mutually exclusive. Refer to the description of arms in period 1 (baseline period).

End point values	On-Demand	Standard Prophylaxis	PK-Driven Prophylaxis	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	70	18	25	
Units: Bleeding episodes				
Excellent	547	39	33	
Good	943	38	75	
Fair	167	16	11	
None	3	0	20	
Unknown	13	0	0	

## Statistical analyses

No statistical analyses for this end point

### Secondary: Total Area Under the Curve (AUC)

End point title	Total Area Under the Curve (AUC)
-----------------	----------------------------------

End point description:

Total AUC estimated by AUC 0-48h plus an area extrapolated from the log-linear regression model.

Population: Subjects in the pharmacokinetic (PK) intent-to-treat set comprising of subjects who provided at least 1 evaluable PK assessment.

End point type	Secondary
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End point timeframe:

Pharmacokinetic evaluations: 30 minutes pre-infusion up to 48 hours post-infusion

End point values	Subjects ≥14 Years	Subjects <14 Years		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	65	6		
Units: IU*h/dL				
geometric mean (standard deviation)	1334.45 (± 454.33)	1061.26 (± 452.87)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Area Under the Curve

End point title	Area Under the Curve
-----------------	----------------------

End point description:

Area under the factor VIII (FVIII) plasma concentration versus time curve (AUC) from 0 to 48 hours estimated using the linear trapezoidal method.

Population: Subjects in the pharmacokinetic (PK) intent-to-treat set comprising of subjects who provided at least 1 evaluable PK assessment.

End point type	Secondary
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End point timeframe:

Pharmacokinetic evaluations: 30 minutes pre-infusion up to 48 hours post-infusion

End point values	Subjects ≥14 Years	Subjects <14 Years		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	65	6		
Units: IU*h/dL				
geometric mean (standard deviation)	1213.98 (± 323.96)	966.68 (± 330.83)		

### Statistical analyses

No statistical analyses for this end point



## Secondary: Maximum Plasma Concentration (C-max)

End point title	Maximum Plasma Concentration (C-max)
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End point description:

Maximal Factor VIII Concentration After Infusion.

Population: Subjects in the pharmacokinetic (PK) intent-to-treat set comprising of subjects who provided at least 1 evaluable PK assessment.

End point type	Secondary
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End point timeframe:

Within 1 hour post-infusion

End point values	Subjects ≥14 Years	Subjects <14 Years		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	65	6		
Units: IU/dL				
geometric mean (standard deviation)	91.12 (± 20.15)	74.47 (± 11.3)		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Adjusted Incremental Recovery (IR)

End point title	Adjusted Incremental Recovery (IR)
-----------------	------------------------------------

End point description:

Change in factor VIII concentration from pre- to post-infusion at initial and termination study visits.  
Adjusted IR defined as:  $[C_{\max} \text{ (IU/dL)} - \text{pre-infusion FVIII (IU/dL)}] / \text{dose (IU/kg)}$ .

Population: Subjects in the pharmacokinetic (PK) intent-to-treat set comprising of subjects who provided at least 1 evaluable PK assessment.

End point type	Secondary
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End point timeframe:

30 minutes pre-infusion to 48 hours post-infusion

End point values	Subjects ≥14 Years	Subjects <14 Years		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	65	6		
Units: IU/dL per IU/kg				
geometric mean (standard deviation)	1.81 (± 0.41)	1.47 (± 0.27)		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Terminal Half-life

End point title	Terminal Half-life
-----------------	--------------------

End point description:

Computed from the regression slope in the terminal phase of the model. Terminal half life is the time it takes for the plasma concentration or the amount of drug in the body to be reduced by 50%.

Population: Subjects in the pharmacokinetic (PK) intent-to-treat set comprising of subjects who provided at least 1 evaluable PK assessment.

End point type	Secondary
----------------	-----------

End point timeframe:

Pharmacokinetic evaluations: 30 minutes pre-infusion up to 48 hours post-infusion

End point values	Subjects ≥14 Years	Subjects <14 Years		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	65	6		
Units: Hours				
arithmetic mean (standard deviation)	13.91 (± 5.07)	14.66 (± 5.21)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Weight-Adjusted Clearance

End point title	Weight-Adjusted Clearance
-----------------	---------------------------

End point description:

Computed as the weight-adjusted dose divided by total area under the curve (AUC).

Population: Subjects in the pharmacokinetic (PK) intent-to-treat set comprising of subjects who provided at least 1 evaluable PK assessment.

End point type	Secondary
----------------	-----------

End point timeframe:

Pharmacokinetic evaluations: 30 minutes pre-infusion up to 48 hours post-infusion

End point values	Subjects ≥14 Years	Subjects <14 Years		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	65	6		
Units: mL/(kg*h)				
arithmetic mean (standard deviation)	3.89 (± 1.21)	5.17 (± 1.94)		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Mean Residence Time

End point title	Mean Residence Time
-----------------	---------------------

End point description:

Computed as total Area Under the Moment Curve (AUMC) divided by the total area under the curve (AUC).

Population: Subjects in the pharmacokinetic (PK) intent-to-treat set comprising of subjects who provided at least 1 evaluable PK assessment. Population: Comprised of subjects who provided at least 1 evaluable pharmacokinetic (PK) assessment.

End point type	Secondary
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End point timeframe:

Pharmacokinetic evaluations: 30 minutes pre-infusion up to 48 hours post-infusion

End point values	Subjects ≥14 Years	Subjects <14 Years		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	65	6		
Units: Hours				
arithmetic mean (standard deviation)	17.71 (± 7.16)	17.88 (± 5.67)		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Volume of Distribution at Steady State

End point title	Volume of Distribution at Steady State
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End point description:

Computed as weight-adjusted clearance \* mean residence time.

Population: Subjects in the pharmacokinetic (PK) intent-to-treat set comprising of subjects who provided at least 1 evaluable PK assessment.

End point type	Secondary
----------------	-----------

End point timeframe:

Pharmacokinetic evaluations: 30 minutes pre-infusion up to 48 hours post-infusion

End point values	Subjects ≥14 Years	Subjects <14 Years		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	65	6		
Units: dL/kg				
arithmetic mean (standard deviation)	0.65 (± 0.19)	0.84 (± 0.19)		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Factor VIII Inhibitor Development

End point title	Factor VIII Inhibitor Development <sup>[6]</sup>
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End point description:

Number of treated subjects who developed factor VIII inhibitors.

Population: All subjects in the safety analysis set comprising of all subjects who were exposed to rAHF-PFM.

End point type	Secondary
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End point timeframe:

Throughout study period (4 years and 5 months)

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Arms in the baseline period are not mutually exclusive. Refer to the description of arms in period 1 (baseline period).

End point values	All subjects			
Subject group type	Reporting group			
Number of subjects analysed	73			
Units: Subjects	0			

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Subjects with AEs Related to Investigational Product (IP)

End point title	Number of Subjects with AEs Related to Investigational Product (IP) <sup>[7]</sup>
-----------------	--

End point description:

Number of treated subjects with AEs judged to be possibly or probably related to treatment with IP.

Population: All subjects in the safety analysis set comprising of all subjects who were exposed to rAHF-PFM.

End point type	Secondary
----------------	-----------

End point timeframe:

Throughout study period (4 years and 5 months)

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Arms in the baseline period are not mutually exclusive. Refer to the description of arms in period 1 (baseline period).

<b>End point values</b>	All subjects			
Subject group type	Reporting group			
Number of subjects analysed	73			
Units: Subjects	4			

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Subjects who reported $\geq 1$ AE Regardless of Relatedness to Investigational Product (IP)

End point title	Number of Subjects who reported $\geq 1$ AE Regardless of Relatedness to Investigational Product (IP) <sup>[8]</sup>
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End point description:

Number of treated subjects with 1 or more AE regardless of relatedness to IP.

Population: All subjects in the safety analysis set comprising of all subjects who were exposed to rAHF-PFM.

End point type	Secondary
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End point timeframe:

Throughout study period (4 years and 5 months)

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Arms in the baseline period are not mutually exclusive. Refer to the description of arms in period 1 (baseline period) .

<b>End point values</b>	All subjects			
Subject group type	Reporting group			
Number of subjects analysed	73			
Units: Subjects	44			

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Subjects who reported $\geq 1$ AE Regardless of Relatedness to Investigational Product (IP) by treatment regimen

End point title	Number of Subjects who reported $\geq 1$ AE Regardless of Relatedness to Investigational Product (IP) by treatment regimen <sup>[9]</sup>
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End point description:

Population: All subjects in the safety analysis set comprising of all subjects who were exposed to rAHF-PFM.

End point type	Secondary
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End point timeframe:

Throughout the study period (4 years and 5 months)

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Arms in the baseline period are not mutually exclusive. Refer to the description of arms in period 1 (baseline period).

End point values	On-Demand	Standard Prophylaxis	PK-Driven Prophylaxis	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	72	32	34	
Units: Subjects	33	15	19	

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Subjects with SAEs by Preferred MedDRA Term and Treatment Regimen

End point title	Number of Subjects with SAEs by Preferred MedDRA Term and Treatment Regimen <sup>[10]</sup>
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End point description:

Number of Subjects with serious adverse events (SAEs) by Preferred MedDRA Term and Treatment Regimen (On-demand; Standard Prophylaxis and pharmacokinetic (PK)-driven Prophylaxis)

Population: All subjects in the safety analysis set comprising of all subjects who were exposed to rAHF-PFM.

End point type	Secondary
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End point timeframe:

Throughout the study period (4 years and 5 months)

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Arms in the baseline period are not mutually exclusive. Refer to the description of arms in period 1 (baseline period).

End point values	On-Demand	Standard Prophylaxis	PK-Driven Prophylaxis	Subjects with SAEs outside of 3 Treatment Arms
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	72	32	34	1
Units: Subjects				
ABDOMINAL PAIN	1	0	0	0
NAUSEA	1	0	0	0
TOOTH ABSCESS	1	0	0	0
JOINT DISLOCATION	1	0	0	0
HAEMOPHILIC ARTHROPATHY	1	0	1	0
SYNOVITIS	1	0	0	0
CALCULUS URINARY	1	0	0	0
HOSPITALIZATION	1	0	0	0
PULPITIS DENTAL	0	1	0	0
SOMNAMBULISM	0	1	0	0

FACTOR VIII INHIBITION (UNCONFIRMED)	0	0	1	0
APPENDICITIS	0	0	1	0
PAIN IN EXTREMITY	0	0	0	1

## Statistical analyses

No statistical analyses for this end point

### Secondary: AEs with onset ≤1 hour following the end of an infusion, regardless of relatedness

End point title	AEs with onset ≤1 hour following the end of an infusion, regardless of relatedness <sup>[11]</sup>
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End point description:

Population: All subjects in the safety analysis set comprising of all subjects who were exposed to rAHF-PFM.

End point type	Secondary
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End point timeframe:

Throughout study period (4 years and 5 months)

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Arms in the baseline period are not mutually exclusive. Refer to the description of arms in period 1 (baseline period).

<b>End point values</b>	All subjects			
Subject group type	Reporting group			
Number of subjects analysed	73			
Units: Adverse events	39			

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Subjects with Severe SAEs and Severe non-SAEs by Preferred MedDRA Term and Treatment Regimen

End point title	Number of Subjects with Severe SAEs and Severe non-SAEs by Preferred MedDRA Term and Treatment Regimen <sup>[12]</sup>
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End point description:

This outcome is focused only on SEVERE serious adverse events (SAEs) and SEVERE non-SAEs.

Population: All subjects in the safety analysis set comprising of all subjects who were exposed to rAHF-PFM.

End point type	Secondary
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End point timeframe:

Throughout the study period (4 years and 5 months)

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Arms in the baseline period are not mutually exclusive. Refer to the description of arms in period 1 (baseline period).

End point values	On-Demand	Standard Prophylaxis	PK-Driven Prophylaxis	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	72	32	34	
Units: Subjects				
TOOTH ABSCESS (SAE)	1	0	0	
HAEMOPHILIC ARTHROPATHY (SAE)	0	0	1	
HAEMOPHILIC ARTHROPATHY (non-SAE)	1	0	1	
ABDOMINAL PAIN (non-SAE)	1	0	0	
ARTHRALGIA (non-SAE)	1	0	0	

## Statistical analyses

No statistical analyses for this end point

## Secondary: Baseline Health-related Quality of Life (HRQoL) Scores: PF, RP, BP, GH, VT, SF, RE, MH, PCS, and MCS

End point title	Baseline Health-related Quality of Life (HRQoL) Scores: PF, RP, BP, GH, VT, SF, RE, MH, PCS, and MCS
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End point description:

Physical Functioning (PF); Role Limitation Due to Physical Health (RP); Bodily Pain (BP); General Health (GH); Vitality (VT); Social Functioning (SF); Role Limitation Due to Emotional Problems (RE); Mental Health (MH), Physical Component Score (PCS); Mental Component Score (MCS). Baseline SF-36v1 Scores, where data available. Scores range 0-100, higher scores represent better health. There is no total overall score; scoring is done for subscores and summary scores. The raw data from the SF-36 items were transformed to norm based scores for each of the 8 HRQoL/SF-36 health domain scores.

Population: All subjects in pharmacoeconomic (PE) set comprising of subjects who completed a HRQoL assessment.

End point type	Secondary
----------------	-----------

End point timeframe:

Baseline

End point values	Subjects Assessed Before Treatment			
Subject group type	Subject analysis set			
Number of subjects analysed	71			
Units: Scores on a scale				
median (full range (min-max))				
Physical Functioning (PF)	44.56 (17.29 to 57.14)			



Role-Physical (RP)	42.1 (27.95 to 56.24)			
Bodily Pain (BP)	46.48 (25.07 to 62.75)			
General Health (GH)	43.87 (19.52 to 64)			
Vitality (VT)	51.42 (25.39 to 67.2)			
Social Functioning (SF)	46.28 (19.14 to 57.14)			
Role-Emotional (RE)	55.34 (23.74 to 55.34)			
Mental Health (MH)	50.44 (20.91 to 64.07)			
Physical Component Score (PCS)	42.32 (20.1 to 67.67)			
Mental Component Score (MCS)	52.65 (22.56 to 68.1)			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Health-related Quality of Life (HRQoL) Scores: PF, RP, BP, GH, VT, SF, RE, MH, PCS, and MCS at the End of Treatment Regimens

End point title	Health-related Quality of Life (HRQoL) Scores: PF, RP, BP, GH, VT, SF, RE, MH, PCS, and MCS at the End of Treatment Regimens <sup>[13]</sup>
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End point description:

Physical Functioning (PF); Role Limitation Due to Physical Health (RP); Bodily Pain (BP); General Health (GH); Vitality (VT); Social Functioning (SF); Role Limitation Due to Emotional Problems (RE); Mental Health (MH); Physical Component Score (PCS); Mental Component Score (MCS). Baseline SF-36v1 Scores, where data available. Scores range 0-100, higher scores represent better health. There is no total overall score; scoring is done for subscores and summary scores. The raw data from the SF-36 items were transformed to norm based scores for each of the 8 HRQoL/SF-36 health domain scores.

Population: All subjects in pharmacoeconomic (PE) set comprising of subjects who completed a HRQoL assessment.

End point type	Secondary
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End point timeframe:

End of on-demand treatment period (6 months) and at study termination (approximately 18 months)

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Arms in the baseline period are not mutually exclusive. Refer to the description of arms in period 1 (baseline period).

End point values	On-Demand	Standard Prophylaxis	PK-Driven Prophylaxis	Any Prophylaxis
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	63	31	34	65
Units: Scores on a scale				
median (full range (min-max))				
Bodily Pain (BP)	46.5 (29.4 to 62.8)	51.6 (19.9 to 62.8)	51.6 (29.4 to 62.8)	51.6 (19.9 to 62.8)

General Health (GH)	43.9 (19.5 to 64)	48.6 (19.5 to 64)	46.2 (29.8 to 60.3)	48.6 (19.5 to 64)
Mental Component Score (MCS), On-Demand n=62	54.9 (22.8 to 69.9)	56.1 (13.3 to 69.6)	54.5 (11.4 to 62.5)	55 (11.4 to 69.6)
Mental Health (MH), On-Demand n=62	51.6 (14.1 to 64.1)	50.4 (20.9 to 64.1)	52.7 (7.3 to 64.1)	50.4 (7.3 to 64.1)
Physical Component Score (PCS), On-Demand n=62	44 (16.1 to 61.2)	50.2 (17.6 to 68.8)	47.3 (25.3 to 62.3)	47.8 (17.6 to 68.8)
Physical Functioning (PF), On-Demand n=62	48.8 (17.3 to 57.1)	46.7 (21.5 to 57.1)	46.7 (17.3 to 57.1)	46.7 (17.3 to 57.1)
Role Emotional (RE)	55.3 (23.7 to 55.3)	55.3 (23.7 to 55.3)	55.3 (23.7 to 55.3)	55.3 (23.7 to 55.3)
Role Physical (RP)	49.2 (28 to 56.2)	56.2 (28 to 56.2)	56.2 (28 to 56.2)	56.2 (28 to 56.2)
Social Functioning (SF)	46.3 (30 to 57.1)	51.7 (24.6 to 57.1)	51.7 (13.7 to 57.1)	51.7 (13.7 to 57.1)
Vitality (VT)	53.8 (32.5 to 70.4)	56.2 (27.8 to 70.4)	56.2 (23 to 68)	56.2 (23 to 70.4)

## Statistical analyses

No statistical analyses for this end point

## Secondary: HRQoL Scores Change From On-Demand Treatment Regimen Period Through Prophylaxis Period

End point title	HRQoL Scores Change From On-Demand Treatment Regimen Period Through Prophylaxis Period
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End point description:

Differences in health domain scores = (End of on-demand treatment) – (End of prophylaxis regimen). A negative value for the median difference equates to a larger domain score for the prophylaxis regimen.

Physical Functioning (PF); Role Limitation Due to Physical Health (RP); Bodily Pain (BP); General Health (GH); Vitality (VT); Social Functioning (SF); Role Limitation Due to Emotional Problems (RE); Mental Health (MH), Physical Component Score (PCS); Mental Component Score (MCS).

Scores range 0-100, higher scores represent better health. There is no total overall score; scoring is done for subscores and summary scores. The raw data from the SF-36 items were transformed to norm based scores for each of the 8 HRQoL/SF-36 health domain scores.

Population: Subjects ≥14 years in pharmacoeconomic (PE) set comprising of subjects ≥14 years who completed a Health Related Quality of Life (HRQoL) assessment.

End point type	Secondary
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End point timeframe:

End of on-demand treatment period (6 months) and at study termination (approximately 18 months)

End point values	On-Demand to Standard Prophylaxis	On-Demand to PK-Driven Prophylaxis	On-Demand to Any Prophylaxis	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	27	30	57	
Units: Scores on a scale				
median (full range (min-max))				
Physical Functioning (PF)	0 (-10.48 to 14.68)	-2.1 (-18.88 to 20.97)	-2.1 (-18.88 to 20.97)	

Role Physical (RP)	0 (-28.29 to 21.21)	0 (-28.29 to 28.29)	0 (-28.29 to 28.29)	
Bodily Pain (BP)	0 (-29.55 to 17.55)	-4.29 (-25.27 to 13.28)	0 (-29.55 to 17.55)	
General Health (GH)	-3.74 (-21.07 to 18.73)	-2.34 (-20.13 to 17.79)	-2.34 (-21.07 to 18.73)	
Vitality (VT)	0 (-9.47 to 23.67)	0 (-16.57 to 30.77)	0 (-16.57 to 30.77)	
Social Functioning (SF)	0 (-21.72 to 16.29)	0 (-16.29 to 16.29)	0 (-21.72 to 16.29)	
Role Emotional (RE)	0 (-10.53 to 31.6)	0 (-31.6 to 21.07)	0 (-31.6 to 31.6)	
Mental Health (MH)	0 (-13.63 to 15.9)	-1.13 (-40.9 to 34.08)	0 (-40.9 to 34.08)	
Physical Component Score (PCS)	-2.55 (-20.22 to 8.69)	-3.14 (-16.78 to 19.7)	-2.76 (-20.22 to 19.7)	
Mental Component Score (MCS)	1.52 (-8.31 to 21.64)	0.79 (-35.25 to 24.56)	1.3 (-35.25 to 24.56)	

## Statistical analyses

No statistical analyses for this end point

## Secondary: Bodily Pain HRQoL Scores Change From On-Demand Period Through Prophylaxis Period

End point title	Bodily Pain HRQoL Scores Change From On-Demand Period Through Prophylaxis Period
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End point description:

After an on-demand treatment period, subjects were randomized to 1 of 2 prophylactic regimens for 12 months. The standard prophylactic regimen was dosed at 20 to 40 IU/kg every 48 ±6 hours, and the PK-driven prophylaxis regimen was dosed at 20 to 80 IU/kg every 72 ±6 hours.

Bodily Pain Health Related Quality of Life (HRQoL) Scores Change = (End of on-demand treatment) – (End of prophylaxis regimen). A negative value for the median difference equates to a larger domain score for the prophylaxis regimen.

Scores range 0-100, higher scores represent better health. There is no total overall score; scoring is done for subscores and summary scores. The raw data from the SF-36 items were transformed to norm based scores.

Population: Subjects ≥14 years in pharmacoeconomic (PE) set comprising of subjects ≥14 years who completed a HRQoL assessment.

End point type	Secondary
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End point timeframe:

End of on-demand treatment period (6 months) and at study termination (approximately 18 months)

<b>End point values</b>	On-Demand to Any Prophylaxis			
Subject group type	Subject analysis set			
Number of subjects analysed	57			
Units: Scores on a scale				
median (full range (min-max))	0 (-29.55 to 17.55)			

## Statistical analyses

No statistical analyses for this end point

### Secondary: Physical Component Scores (PCS) HRQoL Scores Change From On-Demand Period Through Prophylaxis Period

End point title	Physical Component Scores (PCS) HRQoL Scores Change From On-Demand Period Through Prophylaxis Period
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End point description:

After an on-demand treatment period, subjects were randomized to 1 of 2 prophylactic regimens for 12 months. The standard prophylactic regimen was dosed at 20 to 40 IU/kg every 48 ±6 hours, and the PK-driven prophylaxis regimen was dosed at 20 to 80 IU/kg every 72 ±6 hours.

PCS Health Related Quality of Life (HRQoL) Scores Change = (End of on-demand treatment) – (End of prophylaxis regimen) A negative value for the median difference equates to a larger domain score for the prophylaxis regimen. Scores range 0-100, higher scores represent better health. There is no total overall score; scoring is done for subscores and summary scores. The raw data from the SF-36 items were transformed to norm based scores.

Population: Subjects ≥14 years in pharmacoeconomic (PE) set comprising of subjects ≥14 years who completed a HRQoL assessment.

End point type	Secondary
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End point timeframe:

End of on-demand treatment period (6 months) and at study termination (approximately 18 months)

<b>End point values</b>	On-Demand to Any Prophylaxis			
Subject group type	Subject analysis set			
Number of subjects analysed	57			
Units: Scores on a scale				
median (full range (min-max))	-2.76 (-20.22 to 19.7)			

## Statistical analyses

No statistical analyses for this end point

### Post-hoc: Median (IQR) Annualized Bleed Rates

End point title	Median (IQR) Annualized Bleed Rates <sup>[14]</sup>
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End point description:

Bleed rates (number of bleeding episodes per subject) were annualized to account for the varying number of days a subject may have actually been on each regimen.

Population: Subjects in the efficacy intent-to-treat set comprising of all subjects in the prophylaxis

treatment segment who had at least 1 assessment (1 quarterly visit) or who had withdrawn after 3 bleeding episodes prior to reaching the first assessment period.

End point type	Post-hoc
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End point timeframe:

On-demand 6 months ( $\pm$  2 weeks); Prophylaxis 12 months ( $\pm$  2 weeks)

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Arms in the baseline period are not mutually exclusive. Refer to the description of arms in period 1 (baseline period).

End point values	On-Demand	Standard Prophylaxis	PK-Driven Prophylaxis	Any Prophylaxis
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	53	30	23	53
Units: Bleeding episodes				
median (inter-quartile range (Q1-Q3))	43.98 (35.73 to 56.53)	0.99 (0 to 2.14)	1 (0 to 4.08)	1 (0 to 4.07)

## Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	On-Demand v Any Prophylaxis
Number of subjects included in analysis	106
Analysis specification	Post-hoc
Analysis type	superiority
P-value	< 0.0001
Method	Wilcoxon Signed-Rank Test
Confidence interval	
level	95 %

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Throughout the study period (4 years and 5 months)

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	N/A
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### Reporting groups

Reporting group title	On-Demand
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Reporting group description:

On-demand: rAHF-PFM was to be used for the treatment of bleeding episodes according to the severity and type of episode by the protocol-recommended dosing until the episode resolved: superficial (10-20 IU/kg every 12-14 hours), minor joint (20-40 IU/kg every 12-14 hours), deep muscle (30-60 IU/kg every 12-14 hours), major joint or life-threatening (60-100 IU/kg every 8-12 hours), genitourinary, GI, and intracranial (60-100 IU/kg every 8-12 hours)

Reporting group title	PK-Driven Prophylaxis
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Reporting group description:

PK-driven prophylaxis regimen dosed at 20 to 80 IU/kg (every 72  $\pm$  6 hours) exact regimen to be determined by the sponsor

Reporting group title	SAEs Outside of the 3 Treatment Arms
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Reporting group description:

Participants with SAEs that occurred after exposure to investigational product, but outside of the three treatment arms

Reporting group title	Standard Prophylaxis
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Reporting group description:

Standard prophylaxis regimen dosed at 20 to 40 IU/kg (every 48  $\pm$  6 hours), exact regimen to be determined by the investigator

Serious adverse events	On-Demand	PK-Driven Prophylaxis	SAEs Outside of the 3 Treatment Arms
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 73 (9.59%)	3 / 34 (8.82%)	1 / 1 (100.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
JOINT DISLOCATION			
subjects affected / exposed	1 / 73 (1.37%)	0 / 34 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
HOSPITALIZATION			

subjects affected / exposed	1 / 73 (1.37%)	0 / 34 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders FACTOR VIII INHIBITION	Additional description: This event was unconfirmed and therefore did not meet protocol definition for a Factor VIII inhibitor.		
subjects affected / exposed	0 / 73 (0.00%)	1 / 34 (2.94%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders ABDOMINAL PAIN			
subjects affected / exposed	1 / 73 (1.37%)	0 / 34 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
NAUSEA			
subjects affected / exposed	1 / 73 (1.37%)	0 / 34 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders CALCULUS URINARY			
subjects affected / exposed	1 / 73 (1.37%)	0 / 34 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders SOMNAMBULISM			
subjects affected / exposed	0 / 73 (0.00%)	0 / 34 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders HAEMOPHILIC ARTHROPATHY			
subjects affected / exposed	1 / 73 (1.37%)	1 / 34 (2.94%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SYNOVITIS			

subjects affected / exposed	1 / 73 (1.37%)	0 / 34 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>PAIN IN EXTREMITY</b>			
subjects affected / exposed	0 / 73 (0.00%)	0 / 34 (0.00%)	1 / 1 (100.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Infections and infestations</b>			
<b>TOOTH ABSCESS</b>			
subjects affected / exposed	1 / 73 (1.37%)	0 / 34 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>PULPITIS DENTAL</b>			
subjects affected / exposed	0 / 73 (0.00%)	0 / 34 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>APPENDICITIS</b>			
subjects affected / exposed	0 / 73 (0.00%)	1 / 34 (2.94%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

<b>Serious adverse events</b>	Standard Prophylaxis		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 32 (6.25%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
<b>Injury, poisoning and procedural complications</b>			
<b>JOINT DISLOCATION</b>			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>Surgical and medical procedures</b>			
<b>HOSPITALIZATION</b>			



subjects affected / exposed	0 / 32 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
FACTOR VIII INHIBITION	Additional description: This event was unconfirmed and therefore did not meet protocol definition for a Factor VIII inhibitor.		
subjects affected / exposed	0 / 32 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
ABDOMINAL PAIN			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
NAUSEA			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
CALCULUS URINARY			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
SOMNAMBULISM			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
HAEMOPHILIC ARTHROPATHY			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
SYNOVITIS			

subjects affected / exposed	0 / 32 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>PAIN IN EXTREMITY</b>			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>Infections and infestations</b>			
<b>TOOTH ABSCESS</b>			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>PULPITIS DENTAL</b>			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>APPENDICITIS</b>			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

<b>Non-serious adverse events</b>	On-Demand	PK-Driven Prophylaxis	SAEs Outside of the 3 Treatment Arms
<b>Total subjects affected by non-serious adverse events</b>			
subjects affected / exposed	18 / 73 (24.66%)	7 / 34 (20.59%)	0 / 1 (0.00%)
<b>Nervous system disorders</b>			
<b>HEADACHE</b>			
subjects affected / exposed	4 / 73 (5.48%)	3 / 34 (8.82%)	0 / 1 (0.00%)
occurrences (all)	6	5	0
<b>Gastrointestinal disorders</b>			
<b>DIARRHOEA</b>			
subjects affected / exposed	4 / 73 (5.48%)	0 / 34 (0.00%)	0 / 1 (0.00%)
occurrences (all)	4	0	0
<b>IRRITABLE BOWEL SYNDROME</b>			

subjects affected / exposed occurrences (all)	0 / 73 (0.00%) 0	2 / 34 (5.88%) 4	0 / 1 (0.00%) 0
Respiratory, thoracic and mediastinal disorders COUGH subjects affected / exposed occurrences (all)	0 / 73 (0.00%) 0	0 / 34 (0.00%) 0	0 / 1 (0.00%) 0
Musculoskeletal and connective tissue disorders ARTHRALGIA subjects affected / exposed occurrences (all)	0 / 73 (0.00%) 0	0 / 34 (0.00%) 0	0 / 1 (0.00%) 0
Infections and infestations NASOPHARYNGITIS subjects affected / exposed occurrences (all)  UPPER RESPIRATORY TRACT INFECTION subjects affected / exposed occurrences (all)	6 / 73 (8.22%) 7  4 / 73 (5.48%) 4	0 / 34 (0.00%) 0  2 / 34 (5.88%) 2	0 / 1 (0.00%) 0  0 / 1 (0.00%) 0

<b>Non-serious adverse events</b>	Standard Prophylaxis		
Total subjects affected by non-serious adverse events subjects affected / exposed	4 / 32 (12.50%)		
Nervous system disorders HEADACHE subjects affected / exposed occurrences (all)	0 / 32 (0.00%) 0		
Gastrointestinal disorders DIARRHOEA subjects affected / exposed occurrences (all)  IRRITABLE BOWEL SYNDROME subjects affected / exposed occurrences (all)	0 / 32 (0.00%) 0  0 / 32 (0.00%) 0		
Respiratory, thoracic and mediastinal disorders COUGH subjects affected / exposed occurrences (all)	2 / 32 (6.25%) 2		

Musculoskeletal and connective tissue disorders ARTHRALGIA subjects affected / exposed occurrences (all)	2 / 32 (6.25%) 3		
Infections and infestations NASOPHARYNGITIS subjects affected / exposed occurrences (all)  UPPER RESPIRATORY TRACT INFECTION subjects affected / exposed occurrences (all)	0 / 32 (0.00%) 0  0 / 32 (0.00%) 0		

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 May 2006	Provision of criteria for assessing the severity and cause of bleeding episodes and recording the anatomical site(s) affected.
20 September 2007	Change in inclusion criteria.

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported

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### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/22212248>