



## Clinical trial results:

**FEIBA NF: a prospective, open-label, randomized, parallel study to evaluate efficacy and safety of prophylactic versus on-demand treatment in subjects with hemophilia A or B and a high titer inhibitor**

### Summary

EudraCT number	2008-003855-65
Trial protocol	FR BG IT PL
Global end of trial date	17 October 2012

### Results information

Result version number	v2 (current)
This version publication date	05 June 2016
First version publication date	06 August 2015
Version creation reason	<ul style="list-style-type: none"><li>• New data added to full data set</li></ul> Statistics added in description for endpoints on differences in mean transformed annualized bleeding rate as unable to add statistics to these endpoints in EudraCT due to EudraCT limitations of not currently accepting statistics for one analysis group. Pharmacoeconomics endpoints added.

### Trial information

#### Trial identification

Sponsor protocol code	090701
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#### Additional study identifiers

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

Notes:

### Sponsors

Sponsor organisation name	Baxalta US Inc.
Sponsor organisation address	One Baxter Way, Westlake Village CA, United States, 91362-3811
Public contact	Clinical Trial Registries and Results Disclosure, Baxalta US Inc., ClinicalTrialsDisclosure@baxalta.com
Scientific contact	Clinical Trial Registries and Results Disclosure, Baxalta US Inc., ClinicalTrialsDisclosure@baxalta.com
Sponsor organisation name	Baxalta Innovations GmbH
Sponsor organisation address	Industriestrasse 67, Vienna, Austria, 1221
Public contact	Clinical Trial Registries and Results Disclosure, Baxalta Innovations GmbH, ClinicalTrialsDisclosure@baxalta.com
Scientific contact	Clinical Trial Registries and Results Disclosure, Baxalta Innovations GmbH, ClinicalTrialsDisclosure@baxalta.com

Notes:

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**Paediatric regulatory details**

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Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

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**Results analysis stage**

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Analysis stage	Final
Date of interim/final analysis	17 October 2012
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 October 2012
Global end of trial reached?	Yes
Global end of trial date	17 October 2012
Was the trial ended prematurely?	No

Notes:

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**General information about the trial**

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Main objective of the trial:

To demonstrate that the annualized rate of all types of bleeds in subjects on the prophylaxis arm is less than that of the subjects in the on-demand arm

Protection of trial subjects:

This study was conducted in accordance with the protocol, the International Conference on Harmonisation Guideline for Good Clinical Practice (ICH GCP), Title 21 of the US Code of Federal Regulations (US CFR), the European Clinical Trial Directive (2001/20/EC and 2005/28/EC), and national and local requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	31 March 2009
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

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Country: Number of subjects enrolled	United States: 2
Country: Number of subjects enrolled	Poland: 2
Country: Number of subjects enrolled	Brazil: 5
Country: Number of subjects enrolled	Ukraine: 8
Country: Number of subjects enrolled	Romania: 1
Country: Number of subjects enrolled	Croatia: 1
Country: Number of subjects enrolled	Russian Federation: 11
Country: Number of subjects enrolled	Bulgaria: 2
Country: Number of subjects enrolled	Japan: 2
Country: Number of subjects enrolled	New Zealand: 2

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Worldwide total number of subjects	36
EEA total number of subjects	6

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)	7
Adults (18-64 years)	24
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

Enrollment was conducted in Europe, North America, Asia-Pacific, and South America at 17 clinical sites beginning in March 2009.

### Pre-assignment

Screening details:

52 participants were enrolled. Sixteen participants discontinued, (ten were screen failures and six were withdrawn before randomization (2 sponsor's decision- inhibitors, 3 withdrew consent, and 1 due to investigator decision to have participant on prophylaxis). Therefore 36 participants were randomized.

### Period 1

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

### Arms

Are arms mutually exclusive?	No
<b>Arm title</b>	On-demand arm
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	FEIBA NF
Investigational medicinal product code	
Other name	Anti-Inhibitor Coagulant Complex (AICC), Nanofiltered
Pharmaceutical forms	Infusion
Routes of administration	Intravenous bolus use

Dosage and administration details:

On demand: Subjects will be treated with the standard FEIBA NF dose and dosing interval prescribed by the treating physician throughout the 12-month study period. The recommended target dose of FEIBA NF for on-demand therapy will be based on the type of bleeding episode and the product will be infused as needed at the discretion of the investigator.

<b>Arm title</b>	Prophylaxis arm
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	FEIBA NF
Investigational medicinal product code	
Other name	Anti-Inhibitor Coagulant Complex (AICC), Nanofiltered
Pharmaceutical forms	Infusion
Routes of administration	Intravenous bolus use

Dosage and administration details:

Prophylaxis: 85 ± 15 U/kg (70-100 U/kg) every other day

<b>Arm title</b>	On-demand arm versus Prophylaxis arm
Arm description:	
Please note that all uniquely titled arms defined in the results posted in ClinicalTrials.gov are imported into EU results as well. Period arm 'On-demand arm versus Prophylaxis arm' is used for some endpoints and in the statistical analysis section. Baseline characteristics for this period arm contain on-demand and prophylaxis subjects.	
Arm type	Experimental

Investigational medicinal product name	FEIBA NF
Investigational medicinal product code	
Other name	Anti-Inhibitor Coagulant Complex (AICC), Nanofiltered
Pharmaceutical forms	Infusion
Routes of administration	Intravenous bolus use

Dosage and administration details:

Prophylaxis: 85 ± 15 U/kg (70-100 U/kg) every other day

Investigational medicinal product name	FEIBA NF
Investigational medicinal product code	
Other name	Anti-Inhibitor Coagulant Complex (AICC), Nanofiltered
Pharmaceutical forms	Infusion
Routes of administration	Intravenous bolus use

Dosage and administration details:

On demand: Subjects will be treated with the standard FEIBA NF dose and dosing interval prescribed by the treating physician throughout the 12-month study period. The recommended target dose of FEIBA NF for on-demand therapy will be based on the type of bleeding episode and the product will be infused as needed at the discretion of the investigator.

<b>Arm title</b>	On-demand
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Arm description:

Please note that all uniquely titled arms defined in the results posted in ClinicalTrials.gov are imported into EU results as well. 'On-demand' is the same as 'On-demand arm'.

Arm type	Experimental
Investigational medicinal product name	FEIBA NF
Investigational medicinal product code	
Other name	Anti-Inhibitor Coagulant Complex (AICC), Nanofiltered
Pharmaceutical forms	Infusion
Routes of administration	Intravenous bolus use

Dosage and administration details:

On demand: Subjects will be treated with the standard FEIBA NF dose and dosing interval prescribed by the treating physician throughout the 12-month study period. The recommended target dose of FEIBA NF for on-demand therapy will be based on the type of bleeding episode and the product will be infused as needed at the discretion of the investigator.

<b>Arm title</b>	Prophylaxis
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Arm description:

Please note that all uniquely titled arms defined in the results posted in ClinicalTrials.gov are imported into EU results as well. 'Prophylaxis' is the same as 'Prophylaxis arm'.

Arm type	Experimental
Investigational medicinal product name	FEIBA NF
Investigational medicinal product code	
Other name	Anti-Inhibitor Coagulant Complex (AICC), Nanofiltered
Pharmaceutical forms	Infusion
Routes of administration	Intravenous bolus use

Dosage and administration details:

Prophylaxis: 85 ± 15 U/kg (70-100 U/kg) every other day

Number of subjects in period 1	On-demand arm	Prophylaxis arm	On-demand arm versus Prophylaxis arm
Started	19	17	36
Completed	17	16	33
Not completed	2	1	3
Adverse event, serious fatal	1	-	1
Adverse event, non-fatal	-	1	1
planned surgery	1	-	1

Number of subjects in period 1	On-demand	Prophylaxis
Started	19	17
Completed	17	16
Not completed	2	1
Adverse event, serious fatal	1	-
Adverse event, non-fatal	-	1
planned surgery	1	-

## Baseline characteristics

### Reporting groups

Reporting group title	On-demand arm
Reporting group description: -	
Reporting group title	Prophylaxis arm
Reporting group description: -	
Reporting group title	On-demand arm versus Prophylaxis arm
Reporting group description:	
Please note that all uniquely titled arms defined in the results posted in ClinicalTrials.gov are imported into EU results as well. Period arm 'On-demand arm versus Prophylaxis arm' is used for some endpoints and in the statistical analysis section. Baseline characteristics for this period arm contain on-demand and prophylaxis subjects.	
Reporting group title	On-demand
Reporting group description:	
Please note that all uniquely titled arms defined in the results posted in ClinicalTrials.gov are imported into EU results as well. 'On-demand' is the same as 'On-demand arm'.	
Reporting group title	Prophylaxis
Reporting group description:	
Please note that all uniquely titled arms defined in the results posted in ClinicalTrials.gov are imported into EU results as well. 'Prophylaxis' is the same as 'Prophylaxis arm'.	

Reporting group values	On-demand arm	Prophylaxis arm	On-demand arm versus Prophylaxis arm
Number of subjects	19	17	36
Age categorical			
Units: Subjects			

Age continuous			
Age continuous description			
Units: years			
arithmetic mean	29.1	25.6	27.4
standard deviation	± 15.2	± 15.4	± 15.2
Gender categorical			
Gender categorical description			
Units: Subjects			
Female	0	0	0
Male	19	17	36
Region of Enrollment			
Units: Subjects			
United States	1	1	2
Poland	1	1	2
Brazil	3	2	5
Ukraine	4	4	8
Romania	0	1	1
Croatia	0	1	1
Russian Federation	8	3	11
Bulgaria	0	2	2
Japan	1	1	2

New Zealand	1	1	2
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Reporting group values	On-demand	Prophylaxis	Total
Number of subjects	19	17	108
Age categorical Units: Subjects			

Age continuous			
Age continuous description			
Units: years			
arithmetic mean	29.1	25.6	
standard deviation	± 15.2	± 15.4	-
Gender categorical			
Gender categorical description			
Units: Subjects			
Female	0	0	0
Male	19	17	108
Region of Enrollment Units: Subjects			
United States	1	1	6
Poland	1	1	6
Brazil	3	2	15
Ukraine	4	4	24
Romania	0	1	3
Croatia	0	1	3
Russian Federation	8	3	33
Bulgaria	0	2	6
Japan	1	1	6
New Zealand	1	1	6



## End points

### End points reporting groups

Reporting group title	On-demand arm
Reporting group description: -	
Reporting group title	Prophylaxis arm
Reporting group description: -	
Reporting group title	On-demand arm versus Prophylaxis arm
Reporting group description: Please note that all uniquely titled arms defined in the results posted in ClinicalTrials.gov are imported into EU results as well. Period arm 'On-demand arm versus Prophylaxis arm' is used for some endpoints and in the statistical analysis section. Baseline characteristics for this period arm contain on-demand and prophylaxis subjects.	
Reporting group title	On-demand
Reporting group description: Please note that all uniquely titled arms defined in the results posted in ClinicalTrials.gov are imported into EU results as well. 'On-demand' is the same as 'On-demand arm'.	
Reporting group title	Prophylaxis
Reporting group description: Please note that all uniquely titled arms defined in the results posted in ClinicalTrials.gov are imported into EU results as well. 'Prophylaxis' is the same as 'Prophylaxis arm'.	

### Primary: Reduction in annualized bleeding episode rate (ABR) among participants receiving prophylactic treatment as compared to those treated on-demand

End point title	Reduction in annualized bleeding episode rate (ABR) among participants receiving prophylactic treatment as compared to those treated on-demand <sup>[1]</sup>
End point description: Participants were Randomized to Receive 1 of the 2 Following Treatment Regimens: 1.On-Demand: FEIBA NF dose & dosing interval as prescribed by treating physician 2.Prophylaxis: 85 ± 15 U/kg of FEIBA NF every other day during 12-month prophylactic period Annualized rate of bleeding episodes was calculated as: (Number of bleeding episodes/observed treatment period in days) * 365.25	
End point type	Primary
End point timeframe: 12 months ± 14 days	

#### 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: Baseline period arms are not mutually exclusive. Details see under description of period arms.

End point values	On-demand arm	Prophylaxis arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	17		
Units: bleeds/year				
median (inter-quartile range (Q1-Q3))	28.7 (17.7 to 50)	7.9 (2.9 to 11)		

## Statistical analyses

<b>Statistical analysis title</b>	Statistical analysis 1
Statistical analysis description:	
H0: $\mu(\text{on-demand}) = \mu(\text{prophylaxis})$ Versus H1: $\mu(\text{on-demand}) \neq \mu(\text{prophylaxis})$ (Where H0 implies no difference in mean bleeding episode rate between prophylaxis and on-demand treatment arms and H1 implies otherwise. This test was performed at a significance level of 5%, two-sided, two sample)	
Comparison groups	On-demand arm v Prophylaxis arm
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0003
Method	Two-sample, two-sided t-test
Confidence interval	
level	95 %

## Secondary: Annualized Bleeding Rate by Treatment Regimen, Bleeding Etiology, and Bleed Type

End point title	Annualized Bleeding Rate by Treatment Regimen, Bleeding Etiology, and Bleed Type <sup>[2]</sup>
End point description:	
Spontaneous includes unknown/undermined etiology	
End point type	Secondary
End point timeframe:	
12 months $\pm$ 14 days	

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: Baseline period arms are not mutually exclusive. Details see under description of period arms.

End point values	On-demand arm	Prophylaxis arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	17		
Units: Bleeds per year				
median (inter-quartile range (Q1-Q3))				
Spontaneous	18.9 (10.9 to 43.5)	5.6 (2.9 to 8)		
Traumatic	4.7 (1.9 to 10.7)	2.5 (0 to 3.1)		
Joint	22.9 (14.1 to 46.9)	6 (2.9 to 10)		
Non-Joint	2.9 (1 to 4.9)	0.5 (0 to 2)		
Spontaneous Joint	16.6 (9.9 to 40.8)	4.5 (2.9 to 8)		
Spontaneous Non-Joint	1 (1 to 2.9)	0 (0 to 1)		
Traumatic Joint	4 (1 to 7.1)	1 (0 to 3.1)		
Traumatic Non-Joint	0 (0 to 1.9)	0 (0 to 1)		
All Bleeding Etiologies, and Bleed Types	28.7 (17.7 to 50)	7.9 (2.9 to 11)		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Differences in Mean Transformed Annualized Bleeding Rate Between On-Demand and Prophylaxis Treatment Regimens by Bleeding Etiology, and Bleeding Type

End point title	Differences in Mean Transformed Annualized Bleeding Rate Between On-Demand and Prophylaxis Treatment Regimens by Bleeding Etiology, and Bleeding Type <sup>[3]</sup>
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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 variance and align sample distribution with assumption of normality inherent in using t-test. Difference in mean transformed ABRs was used to perform statistical tests and generate p-values at a significance level of 5%. Participants were Randomized to Receive 1 of the 2 Following Treatment Regimens: 1.On-Demand: FEIBA NF dose & dosing interval as prescribed by treating physician 2.Prophylaxis: 85 ± 15 U/kg of FEIBA NF every other day during 12-month prophylactic period. Statistical Analysis (on-demand vs prophylaxis arm, 2-sample, 2-sided t-test): Spontaneous bleeds:  $p=0.0008$ ; traumatic bleeds:  $p=0.0199$ ; joint bleeds:  $p=0.0006$ ; non-joint bleeds:  $p=0.0227$ ; spontaneous joint bleeds:  $p=0.0013$ ; spontaneous non-joint bleeds:  $p=0.003$ ; traumatic joint bleeds:  $p=0.0254$ ; traumatic non-joint bleeds:  $p=0.9322$ .

End point type	Secondary
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End point timeframe:

12 months ± 14 days

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: Baseline period arms are not mutually exclusive. Details see under description of period arms.

End point values	On-demand arm versus Prophylaxis arm			
Subject group type	Reporting group			
Number of subjects analysed	36			
Units: (bleeds/year) <sup>(1/2)</sup>				
arithmetic mean (standard deviation)				
Spontaneous Bleeds	2.2 (± 1.8)			
Traumatic Bleeds	1 (± 1.2)			
Joint Bleeds	2.4 (± 1.9)			
Non-Joint Bleeds	0.8 (± 0.9)			
Spontaneous Joint Bleeds	2.1 (± 1.8)			
Spontaneous Non-Joint Bleeds	0.8 (± 0.8)			
Traumatic Joint Bleeds	0.9 (± 1.2)			
Traumatic Non-Joint Bleeds	0 (± 0.9)			

## Statistical analyses

No statistical analyses for this end point

### Secondary: Annualized Bleeding Rate for New Target Joints

End point title	Annualized Bleeding Rate for New Target Joints <sup>[4]</sup>
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End point description:

Target joints are  $\geq 4$  bleeds/6 months in any one of the following joints: ankles, knees, elbows, and hips; a target joint bleeding episode refers to an individual anatomical location.

End point type	Secondary
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End point timeframe:

12 months  $\pm$  14 days

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: Baseline period arms are not mutually exclusive. Details see under description of period arms.

End point values	On-demand arm	Prophylaxis arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	17		
Units: Bleeds per year				
median (inter-quartile range (Q1-Q3))	5.9 (0 to 12.9)	0 (0 to 4.1)		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Differences in Mean Transformed Annualized Bleeding Rate Between On-Demand and Prophylaxis Treatment Regimens: New Target Joints

End point title	Differences in Mean Transformed Annualized Bleeding Rate Between On-Demand and Prophylaxis Treatment Regimens: New Target Joints <sup>[5]</sup>
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End point description:

Annualized bleed rates (ABRs) 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 a two-sample, two-sided t-test. The difference in mean transformed ABRs was used to perform statistical tests and generate p-values at a significance level of 5%. Statistical Analysis (on-demand arm versus prophylaxis arm; two-sample, two-sided t-test):  $p=0.0271$ .

End point type	Secondary
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End point timeframe:

12 months  $\pm$  14 days

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: Baseline period arms are not mutually exclusive. Details see under description of period arms.

End point values	On-demand arm versus Prophylaxis arm			
Subject group type	Reporting group			
Number of subjects analysed	36			
Units: (bleeds/year) <sup>(1/2)</sup>				
arithmetic mean (standard deviation)	1.6 ( $\pm$ 2.2)			

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of New Target Joints

End point title	Number of New Target Joints <sup>[6]</sup>
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End point description:

Target Joints are defined as  $\geq 4$  bleeds/6 months in any one of the following joints: ankles, knees, elbows and hips

End point type	Secondary
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End point timeframe:

12 months  $\pm$  14 days

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: Baseline period arms are not mutually exclusive. Details see under description of period arms.

End point values	On-demand arm	Prophylaxis arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	17		
Units: new target joints	23	7		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Assessment of Objective Clinical Symptoms- Visual Analog Scale (VAS): Pain in Adolescents and Adults ( $\geq 12$ years old)

End point title	Assessment of Objective Clinical Symptoms- Visual Analog Scale (VAS): Pain in Adolescents and Adults ( $\geq 12$ years old) <sup>[7]</sup>
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End point description:

Pain caused by a bleeding episode in adolescents and adults ( $\geq 12$  years old) was measured at pre-infusion (pre-inf) and at  $6 \pm 0.5$  hours (h) and  $24 \pm 1$  h post-infusion (post-inf) (after the last infusion given to treat a bleeding episode) on the VAS pain scale in millimeters from 0 (no pain) to 100 (worst possible pain). For analysis purposes, if short acting analgesics (duration of activity approximately  $6 \pm 0.5$  h) were used, pain was assigned the highest possible score (100). Pain assessment occurred after each infusion related to single bleeding episodes. In case participants required an additional infusion within 24h, pain was assessed  $6 \pm 0.5$  h and  $24 \pm 1$  h following the subsequent infusion. Change in VAS scores at  $6 \pm 0.5$  h and  $24 \pm 1$  h post-infusion were also compared relative to pre-infusion VAS scores (ie, (pre-infusion VAS score) - (post-infusion VAS score)).

End point type	Secondary
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End point timeframe:

Throughout the study period, 12 months  $\pm$  14 days

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: Baseline period arms are not mutually exclusive. Details see under description of period arms.

End point values	On-demand arm	Prophylaxis arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	12		
Units: Scores on a scale				
median (inter-quartile range (Q1-Q3))				
Pre-Infusion (N= 513, 130)	29 (12 to 55)	49.5 (34.7 to 81.6)		
6 ± 0.5 hours post-infusion (N= 522, 158)	10 (4 to 37)	33.8 (8 to 52.6)		
24 ± 1 hours post-infusion (N= 512,131)	3 (1 to 14)	6.2 (1 to 20)		
Change (Pre-Inf to 6h post-inf) (N= 509, 129)	10 (4 to 21.8)	19.4 (5 to 41.6)		
Change (Pre-Inf to 24h post-inf) (N= 489, 102)	18 (8 to 39.6)	37.8 (17 to 75.5)		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Assessment of Clinical Symptoms - Visual Analog Scale (VAS): Pain in Pediatrics (<12 years old)

End point title	Assessment of Clinical Symptoms - Visual Analog Scale (VAS): Pain in Pediatrics (<12 years old) <sup>[8]</sup>
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End point description:

Pain caused by a bleeding episode (BE) in pediatric participants (<12 years old) was measured at pre-infusion (pre-inf) and at 6 ± 0.5 h and 24 ± 1 h post-infusion (post-inf) (after the last infusion given to treat a bleeding episode) using the children's VAS pain scale (a facial expression scale with one end marked as no pain and the opposite end marked as the worst possible pain). For analysis purposes, if short acting analgesics (duration of activity approximately 6 ± 0.5 h) were used, pain was assigned the highest possible score (worst possible pain). Scores on the children's VAS scale are presented as: -No Pain -Mild Pain -Moderate pain -Severe pain -Very severe pain

End point type	Secondary
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End point timeframe:

12 months ± 14 days

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: Baseline period arms are not mutually exclusive. Details see under description of period arms.

End point values	On-demand arm	Prophylaxis arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2	2		
Units: Bleeding episodes				
Pre-Infusion (N= 54, 8) - No Pain	27	3		
Pre-Infusion (N= 54, 8) - Mild Pain	3	1		

Pre-Infusion (N= 54, 8) - Moderate Pain	12	3		
Pre-Infusion (N= 54, 8) - Severe Pain	10	1		
Pre-Infusion (N= 54, 8) - Very Severe Pain	2	0		
6 ± 0.5 h post-infusion (N= 74, 8) - No Pain	47	3		
± 0.5 h post-infusion (N= 74, 8) - Mild Pain	9	3		
± 0.5 h post-infusion (N= 74, 8) - Moderate Pain	15	2		
± 0.5 h post-infusion (N= 74, 8) - Severe Pain	3	0		
± 0.5 h post-infusion (N= 74, 8)- Very Severe Pain	0	0		
24 ± 1 h post-infusion (N= 77, 9) - No Pain	60	7		
24 ± 1 h post-infusion (N= 77, 9) - Mild Pain	11	1		
24 ± 1 h post-infusion (N= 77, 9) - Moderate Pain	6	1		
24 ± 1 h post-infusion (N= 77, 9) - Severe Pain	0	0		
24± 1h post-infusion (N = 77, 9) -Very Severe Pain	0	0		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Assessment of Clinical Symptoms - Range of Motion (ROM)

End point title	Assessment of Clinical Symptoms - Range of Motion (ROM) <sup>[9]</sup>
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End point description:

ROM was measured using a goniometer for 3 key joints (ie, ankles, knees, and elbows) at screening, month 6, and termination (end of study visit)

End point type	Secondary
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End point timeframe:

12 months ± 14 days

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: Baseline period arms are not mutually exclusive. Details see under description of period arms.

End point values	On-demand arm	Prophylaxis arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	17		
Units: degrees				
median (inter-quartile range (Q1-Q3))				
Left Elbow - Extension: Screening	15 (0 to 45)	10 (0 to 25)		
Left Elbow - Extension: Month 6 (n = 18,16)	10 (0 to 41)	8 (0 to 42.5)		
Left Elbow - Extension: Termination (n = 17,16)	20 (0 to 41)	15.5 (0 to 40)		

Left Elbow - Flexion: Screening (n = 19,17)	125 (90 to 140)	115 (80 to 140)		
Left Elbow - Flexion: Month 6 (n = 18,16)	130 (90 to 140)	125 (72.5 to 143)		
Left Elbow - Flexion: Termination (n = 17,16)	110 (90 to 140)	125 (75 to 145)		
Left Elbow - Pronation: Screening (n = 18,16)	64 (55 to 90)	55 (22.5 to 77.5)		
Left Elbow - Pronation: Month 6 (n = 17,14)	80 (60 to 90)	67.5 (35 to 80)		
Left Elbow - Pronation: Termination (n = 17,15)	68 (60 to 90)	65 (30 to 80)		
Left Elbow - Supination: Screening (n = 18,16)	75 (50 to 90)	42.5 (17.5 to 77.5)		
Left Elbow - Supination: Month 6 (n = 17,14)	80 (50 to 90)	60 (35 to 80)		
Left Elbow - Supination: Termination (n = 17,15)	70 (50 to 90)	70 (35 to 80)		
Right Elbow - Extension: Screening (n = 19,17)	20 (0 to 50)	10 (0 to 50)		
Right Elbow - Extension: Month 6 (n = 18,16)	17.5 (0 to 50)	10 (0 to 42.5)		
Right Elbow - Extension: Termination (n = 18,16)	22.5 (0 to 45)	20 (0 to 62.5)		
Right Elbow - Flexion: Screening (n = 19,17)	120 (105 to 140)	100 (80 to 130)		
Right Elbow - Flexion: Month 6 (n = 18,16)	122.5 (110 to 140)	100 (85 to 136)		
Right Elbow - Flexion: Termination (n = 18,16)	121 (110 to 140)	99 (70 to 127.5)		
Right Elbow - Pronation: Screening (n = 18,16)	75 (55 to 90)	57.5 (27.5 to 80)		
Right Elbow - Pronation: Month 6 (n = 17,14)	80 (55 to 90)	72.5 (40 to 80)		
Right Elbow - Pronation: Termination (n = 18,15)	67.5 (55 to 90)	70 (40 to 80)		
Right Elbow - Supination: Screening (n = 18,16)	75 (45 to 90)	52.5 (20 to 80)		
Right Elbow - Supination: Month 6 (n = 17,14)	70 (45 to 90)	72.5 (30 to 80)		
Right Elbow - Supination: Termination (n = 18,15)	75 (45 to 90)	70 (30 to 80)		
Left Knee - Extension: Screening (n = 18,16)	15 (5 to 90)	1.5 (0 to 55.5)		
Left Knee - Extension: Month 6 (n = 17,14)	15 (5 to 70)	0 (0 to 20)		
Left Knee - Extension: Termination (n = 18,15)	15 (5 to 90)	0 (0 to 70)		
Left Knee - Flexion: Screening (n = 19,17)	100 (80 to 130)	90 (65 to 115)		
Left Knee - Flexion: Month 6 (n = 18,16)	112.5 (80 to 130)	97.5 (65 to 125)		
Left Knee - Flexion: Termination (n = 18,16)	105 (60 to 130)	92.5 (70 to 125)		
Right Knee - Extension: Screening (n = 18,16)	35 (10 to 90)	5 (0 to 30)		
Right Knee - Extension: Month 6 (n = 17,14)	20 (10 to 90)	10 (2 to 30)		
Right Knee - Extension: Termination (n = 18,15)	17.5 (10 to 90)	5 (0 to 30)		
Right Knee - Flexion: Screening (n = 19,17)	90 (20 to 122)	80 (60 to 125)		



Right Knee - Flexion: Month 6 (n = 18,16)	90 (20 to 130)	82.5 (56 to 127.5)		
Right Knee - Flexion: Termination (n = 18,16)	85 (20 to 120)	87.5 (56 to 127.5)		
Left Ankle - Dorsiflexion: Screening (n = 18,16)	20 (15 to 30)	17.5 (9 to 37.5)		
Left Ankle - Dorsiflexion: Month 6 (n = 17,14)	20 (11 to 35)	17.5 (8 to 50)		
Left Ankle - Dorsiflexion: Termination (n = 17,15)	15 (11 to 25)	20 (5 to 50)		
Left Ankle - Plantarflexion: Screening (n = 18,16)	34.5 (30 to 40)	30 (10 to 35)		
Left Ankle - Plantarflexion: Month 6 (n = 17,14)	34 (25 to 35)	30 (15 to 40)		
Left Ankle - Plantarflexion: Termination (n=17,15)	35 (30 to 40)	30 (15 to 35)		
Left Ankle - Pronation: Screening (n = 19,17)	14 (10 to 20)	15 (10 to 15)		
Left Ankle - Pronation: Month 6 (n = 18,15)	15 (10 to 20)	15 (10 to 16)		
Left Ankle - Pronation: Termination (n = 18,16)	15 (10 to 20)	12.5 (10 to 15.5)		
Left Ankle - Supination: Screening (n = 19,17)	25 (10 to 30)	15 (10 to 27)		
Left Ankle - Supination: Month 6 (n = 18,15)	25 (20 to 30)	25 (10 to 30)		
Left Ankle - Supination: Termination (n = 18,16)	25 (16 to 30)	20 (10 to 27.5)		
Right Ankle - Dorsiflexion: Screening (n = 18,16)	15 (10 to 20)	20 (7.5 to 35)		
Right Ankle - Dorsiflexion: Month 6 (n = 17,14)	15 (15 to 20)	25 (6 to 40)		
Right Ankle - Dorsiflexion: Termination (n= 17,15)	15 (14 to 20)	20 (10 to 40)		
Right Ankle - Plantarflexion: Screening (n= 18,16)	35 (30 to 40)	20 (9 to 39)		
Right Ankle - Plantarflexion: Month 6 (n= 17,14)	30 (25 to 40)	23 (10 to 40)		
Right Ankle - Plantarflexion: Termination(n=17,15)	30 (25 to 40)	21 (10 to 40)		
Right Ankle - Pronation: Screening (n = 19,17)	10 (10 to 15)	10 (10 to 20)		
Right Ankle - Pronation: Month 6 (n= 18,15)	10 (10 to 20)	10 (10 to 20)		
Right Ankle - Pronation: Termination (n= 18,16)	10 (10 to 17)	11 (10 to 17.5)		
Right Ankle - Supination: Screening (n = 19,17)	17 (10 to 30)	20 (10 to 30)		
Right Ankle - Supination: Month 6 (n= 18,15)	20 (10 to 30)	20 (10 to 30)		
Right Ankle - Supination: Termination (n= 18,16)	20 (10 to 30)	20 (10 to 30)		

## Statistical analyses

No statistical analyses for this end point

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

## Efficacy Rating at 6 hours

End point title	Assessment of Hemostasis for Treatment of Bleeding Episodes- Overall Efficacy Rating at 6 hours <sup>[10]</sup>
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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 ~6 hours of 1 infusion. Additional infusions may have been given to maintain hemostasis; Good: Definite pain relief and/or improvement in bleeding within ~6 hours after infusion. Possibly requires >1 infusion for complete resolution; Fair: Probable or slight relief of pain & slight improvement in bleeding within ~6 hours after infusion. Requires >1 infusion for complete resolution; None: No improvement or condition worsens

End point type	Secondary
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End point timeframe:

6 h ± 30 min post-infusion

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: Baseline period arms are not mutually exclusive. Details see under description of period arms.

End point values	On-demand arm	Prophylaxis arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	14		
Units: bleeding episodes				
Excellent (n = 16, 5)	109	16		
Good (n = 19, 14)	355	106		
Fair (n = 15, 6)	142	42		
None (n = 6, 2)	14	5		
Rating Not Done (n = 3, 2)	3	2		
Not Available (n = 0, 1)	0	2		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Assessment of Hemostasis for Treatment of Bleeding Episodes- Overall Efficacy Rating at 24 hours

End point title	Assessment of Hemostasis for Treatment of Bleeding Episodes- Overall Efficacy Rating at 24 hours <sup>[11]</sup>
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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 ~24 hours of 1 infusion. Additional infusions may have been given to maintain hemostasis; Good: Definite pain relief and/or improvement in bleeding within ~24 hours after infusion. Possibly requires >1 infusion for complete resolution; Fair: Probable or slight relief of pain & slight improvement in bleeding within ~24 hours after infusion. Requires >1 infusion for complete resolution; None: No improvement or condition worsens

End point type	Secondary
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End point timeframe:

24 ± 1 h post-infusion

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: Baseline period arms are not mutually exclusive. Details see under description of period

arms.

End point values	On-demand arm	Prophylaxis arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	14		
Units: bleeding episodes				
Excellent (n = 16, 6)	282	42		
Good (n = 19, 14)	280	89		
Fair (n = 9, 3)	36	12		
None (n = 1,0)	1	0		
Rating Not Done (n = 8, 3)	24	28		
Not Available (n = 0, 1)	0	2		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Total Weight Adjusted Dose to Control a Bleeding Episode

End point title	Total Weight Adjusted Dose to Control a Bleeding Episode <sup>[12]</sup>
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End point description:

End point type	Secondary
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End point timeframe:

12 months ± 14 days

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: Baseline period arms are not mutually exclusive. Details see under description of period arms.

End point values	On-demand arm	Prophylaxis arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	14		
Units: Units/kg				
median (inter-quartile range (Q1-Q3))	4049.7 (2324.5 to 7408.4)	1524.9 (293.2 to 2883.5)		

### Statistical analyses

Statistical analysis title	Statistical analysis 1
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Comparison groups	Prophylaxis arm v On-demand arm
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Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0067
Method	Mann-Whitney tests (Wilcoxon-Rank Sum)
Confidence interval	
level	95 %

### Secondary: The Number of Bleeding Episode (BE) Which Required 1, 2, 3, or ≥4 Infusions to Control Bleeding

End point title	The Number of Bleeding Episode (BE) Which Required 1, 2, 3, or ≥4 Infusions to Control Bleeding <sup>[13]</sup>
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End point description:

End point type	Secondary
End point timeframe:	
12 months ± 14 days	

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: Baseline period arms are not mutually exclusive. Details see under description of period arms.

End point values	On-demand arm	Prophylaxis arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	14		
Units: Bleeding Episodes (BEs)				
1 infusion	352	98		
2 infusions	134	41		
3 infusions	62	13		
≥4 infusions	75	21		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Abnormal Activated Partial Thromboplastin Time (aPTT) Assay Results

End point title	Abnormal Activated Partial Thromboplastin Time (aPTT) Assay Results <sup>[14]</sup>
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End point description:

The normal reference range of values for aPTT is 22.8 – 31 seconds.

End point type	Secondary
End point timeframe:	
Screening visit, Month 3, Month 6, Month 9, and Termination visit	

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: Baseline period arms are not mutually exclusive. Details see under description of period arms.

End point values	On-demand arm	Prophylaxis arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	16		
Units: seconds				
median (inter-quartile range (Q1-Q3))				
Screening visit (n= 19, 16)	67.3 (63.1 to 75.1)	68.5 (61 to 73.1)		
Month 3 (n= 14, 15)	68 (62.7 to 76.2)	62.7 (57.5 to 67.2)		
Month 6 (n= 17, 15)	68.2 (64.6 to 72.1)	65.6 (62.6 to 69.5)		
Month 9 (n= 17, 15)	70 (64.6 to 77.9)	68.1 (58.1 to 73.9)		
Termination visit (n= 18, 16)	69.8 (63.4 to 75.6)	69.4 (60.5 to 77.1)		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Abnormal D-Dimer Assay Results

End point title	Abnormal D-Dimer Assay Results <sup>[15]</sup>
End point description:	The normal reference range of values for D-dimers is <500 ng/mL.
End point type	Secondary
End point timeframe:	Screening visit, Month 3, Month 6, Month 9, and Termination visit

Notes:

[15] - 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: Baseline period arms are not mutually exclusive. Details see under description of period arms.

End point values	On-demand arm	Prophylaxis arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	9		
Units: ng/mL				
median (inter-quartile range (Q1-Q3))				
Screening visit (n= 7, 6)	862 (647 to 1035)	833.5 (644 to 1164)		
Month 3 (n= 7, 8)	690 (561 to 830)	1021.5 (730 to 1633.5)		
Month 6 (n= 9, 8)	969 (753 to 1103)	1032 (652 to 1442.5)		

Month 9 (n= 6, 8)	731.5 (592 to 1398)	1121 (942.5 to 1448.5)		
Termination visit (n= 5, 9)	813 (695 to 1386)	1031 (872 to 1258)		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Abnormal Fibrinogen Assay Results

End point title	Abnormal Fibrinogen Assay Results <sup>[16]</sup>
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End point description:

The normal reference range of values for fibrinogen is 200-400 mg/dL.

Note: 99999 entered where there were no abnormal fibrinogen assay results for this arm/group at this time point.

End point type	Secondary
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End point timeframe:

Screening visit, Month 3, Month 6, Month 9, and Termination visit

Notes:

[16] - 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: Baseline period arms are not mutually exclusive. Details see under description of period arms.

End point values	On-demand arm	Prophylaxis arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	6		
Units: mg/dL				
median (inter-quartile range (Q1-Q3))				
Screening visit (n= 4, 6)	428 (414 to 478.5)	422 (411 to 428)		
Month 3 (n= 0, 2)	99999 (99999 to 99999)	402 (199 to 605)		
Month 6 (n= 3, 1)	415 (412 to 418)	759 (759 to 759)		
Month 9 (n= 1, 4)	508 (508 to 508)	326.5 (183.5 to 635.5)		
Termination visit (n= 2, 2)	456.5 (425 to 488)	522.5 (414 to 631)		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Abnormal Fibrin Degradation Products (FDP) Assay Results

End point title	Abnormal Fibrin Degradation Products (FDP) Assay Results <sup>[17]</sup>
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End point description:

The normal reference range of values for FDP is 0-5 ug/mL.

Note: 99999 entered where there were no abnormal fibrin degradation products assay results for this

arm/group at this time point

End point type	Secondary
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End point timeframe:

Screening visit, Month 3, Month 6, Month 9, and Termination visit

Notes:

[17] - 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: Baseline period arms are not mutually exclusive. Details see under description of period arms.

End point values	On-demand arm	Prophylaxis arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	2		
Units: ug/mL				
median (inter-quartile range (Q1-Q3))				
Screening visit (n= 1, 2)	16 (16 to 16)	12 (8 to 16)		
Month 3 (n= 0, 2)	99999 (99999 to 99999)	8 (8 to 8)		
Month 6 (n= 1, 1)	8 (8 to 8)	8 (8 to 8)		
Month 9 (n= 1, 2)	8 (8 to 8)	8 (8 to 8)		
Termination visit (n= 3, 1)	8 (8 to 8)	8 (8 to 8)		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Abnormal Prothrombin Fragment F 1.2 Assay Results

End point title	Abnormal Prothrombin Fragment F 1.2 Assay Results <sup>[18]</sup>
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End point description:

The normal reference range of values for prothrombin fragment F 1.2 is 69-229 pmol/L.

End point type	Secondary
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End point timeframe:

Screening visit, Month 3, Month 6, Month 9, and Termination visit

Notes:

[18] - 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: Baseline period arms are not mutually exclusive. Details see under description of period arms.

End point values	On-demand arm	Prophylaxis arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	9		
Units: pmol/L				
median (inter-quartile range (Q1-Q3))				
Screening visit (n= 2, 1)	284 (278 to 290)	308 (308 to 308)		
Month 3 (n= 6, 7)	336.5 (267 to 414)	579 (354 to 972)		

Month 6 (n= 3, 9)	448 (272 to 714)	430 (366 to 504)		
Month 9 (n= 4, 9)	382 (313 to 405.5)	415 (272 to 472)		
Termination visit (n= 4, 7)	252.5 (250 to 265)	643 (376 to 1679)		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Abnormal Prothrombin Time Assay Results

End point title	Abnormal Prothrombin Time Assay Results <sup>[19]</sup>
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End point description:

The normal reference range of values for PT is 9.7-12.3 sec.

Note: 99999 entered where there were no abnormal prothrombin time assay results for this arm/group at this time point

End point type	Secondary
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End point timeframe:

Screening visit, Month 3, Month 6, Month 9, and Termination visit

Notes:

[19] - 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: Baseline period arms are not mutually exclusive. Details see under description of period arms.

End point values	On-demand arm	Prophylaxis arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1	1		
Units: seconds				
median (inter-quartile range (Q1-Q3))				
Screening visit (n= 1, 1)	9.4 (9.4 to 9.4)	9.6 (9.6 to 9.6)		
Month 3 (n= 1, 0)	9.5 (9.5 to 9.5)	99999 (99999 to 99999)		
Month 6 (n= 0, 1)	99999 (99999 to 99999)	12.5 (12.5 to 12.5)		
Month 9 (n= 1, 1)	12.7 (12.7 to 12.7)	13.6 (13.6 to 13.6)		
Termination visit (n= 0, 1)	99999 (99999 to 99999)	13.4 (13.4 to 13.4)		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Abnormal Thrombin-Antithrombin III (TAT) Assay Results

End point title	Abnormal Thrombin-Antithrombin III (TAT) Assay Results <sup>[20]</sup>
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End point description:

The normal reference range of values for TAT is 1-4.1 ug/L.



Note: 99999 entered where there were no abnormal Abnormal Thrombin-Antithrombin II assay results for this arm/group at this time point

End point type	Secondary
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End point timeframe:

Screening visit, Month 3, Month 6, Month 9, and Termination visit

Notes:

[20] - 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: Baseline period arms are not mutually exclusive. Details see under description of period arms.

End point values	On-demand arm	Prophylaxis arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	7		
Units: ug/L				
median (inter-quartile range (Q1-Q3))				
Screening visit (n= 4, 1)	5.1 (4.4 to 5.9)	5.6 (5.6 to 5.6)		
Month 3 (n= 3, 7)	4.7 (4.5 to 5.9)	12.3 (4.4 to 40.8)		
Month 6 (n= 3, 6)	7.9 (6.3 to 10.5)	5.6 (4.4 to 6.1)		
Month 9 (n= 0, 3)	99999 (99999 to 99999)	6 (5.6 to 52.9)		
Termination visit (n= 2, 5)	10.3 (8 to 12.5)	5.6 (5.1 to 7.3)		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Viral Serology from Screening Visit and Study Termination Visit: Hepatitis A, Hepatitis B, and Hepatitis C

End point title	Viral Serology from Screening Visit and Study Termination Visit: Hepatitis A, Hepatitis B, and Hepatitis C <sup>[21]</sup>
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End point description:

-Hepatitis A Virus Antibody (HAV Ab) -Hepatitis B Virus Core Antibody (HBcAb) -Hepatitis B Virus Surface Antibody (HBsAb) -Hepatitis B Virus Surface Antigen (HBsAg) -Hepatitis C Virus (HCV)

End point type	Secondary
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End point timeframe:

12 months ± 14 days

Notes:

[21] - 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: Baseline period arms are not mutually exclusive. Details see under description of period arms.

End point values	On-demand arm	Prophylaxis arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	17		
Units: participants				
HAV Ab: Screening Negative; Termination Positive	1	0		
HAV Ab: Screening Negative; Termination Negative	8	11		
HAV Ab: Screening Positive; Termination Positive	8	4		
HAV Ab: Screening Positive; Termination Negative	1	1		
HAV Ab: Serology not available	1	1		
HBcAb: Screening Negative; Termination Positive	0	1		
HBcAb: Screening Negative; Termination Negative	8	11		
HBcAb: Screening Positive; Termination Positive	9	4		
HBcAb: Screening Positive; Termination Negative	1	0		
HBcAb: Serology not available	1	1		
HBsAb: Screening Negative; Termination Positive	2	5		
HBsAb: Screening Negative; Termination Negative	2	2		
HBsAb: Screening Positive; Termination Positive	13	9		
HBsAb: Screening Positive; Termination Negative	1	0		
HBsAb: Serology not available	1	1		
HBsAg: Screening Negative; Termination Positive	0	0		
HBsAg: Screening Negative; Termination Negative	18	16		
HBsAg: Serology not available	1	1		
HCV: Screening Negative; Termination Positive	0	0		
HCV: Screening Negative; Termination Negative	6	10		
HCV: Screening Positive; Termination Positive	12	6		
HCV: Screening Positive; Termination Negative	0	0		
HCV: Serology not available	1	1		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Viral Serology From Screening Visit and Study Termination Visit: HIV-1/2 Antibody (Ab)

End point title	Viral Serology From Screening Visit and Study Termination Visit: HIV-1/2 Antibody (Ab) <sup>[22]</sup>
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End point description:

End point type	Secondary
End point timeframe:	
12 months $\pm$ 14 days	

Notes:

[22] - 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: Baseline period arms are not mutually exclusive. Details see under description of period arms.

End point values	On-demand	Prophylaxis		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	17		
Units: participants				
HIV 1/2 Ab: Screen Negative; Termination Positive	0	0		
HIV 1/2 Ab: Screen Negative; Termination Negative	18	16		
HIV 1/2 Ab: : Serology not available	1	1		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Viral Serology From Screening Visit and Study Termination Visit: Parvovirus B19 IgG Antibody [IV]

End point title	Viral Serology From Screening Visit and Study Termination Visit: Parvovirus B19 IgG Antibody [IV] <sup>[23]</sup>
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End point description:

Normal range (0 - 0.89 IV); High (> 0.89 IV) - Parvovirus B19 IgG Antibody [IV] (Parvo IgG Ab)

End point type	Secondary
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End point timeframe:

12 months  $\pm$  14 days

Notes:

[23] - 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: Baseline period arms are not mutually exclusive. Details see under description of period arms.

End point values	On-demand	Prophylaxis		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	17		
Units: participants				
Parvo IgG Ab: Screening High ; Termination Normal	3	1		
Parvo IgG Ab: Screening High ; Termination High	14	13		
Parvo IgG Ab: Screening Normal; Termination Normal	0	2		

Parvo IgG Ab: Screening Normal ; Termination High	1	0		
Parvo IgG Ab: Serology not available	1	1		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Viral Serology From Screening Visit and Study Termination Visit: Parvovirus B19 IgM Antibody [IV]

End point title	Viral Serology From Screening Visit and Study Termination Visit: Parvovirus B19 IgM Antibody [IV] <sup>[24]</sup>
End point description:	
Normal range (0 - 0.89 IV); High (> 0.89 IV) - Parvovirus B19 IgM Antibody [IV] (Parvo IgM Ab)	
End point type	Secondary
End point timeframe:	
12 months ± 14 days	

Notes:

[24] - 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: Baseline period arms are not mutually exclusive. Details see under description of period arms.

End point values	On-demand	Prophylaxis		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	17		
Units: participants				
Parvo IgM Ab: Screening High ; Termination Normal	0	0		
Parvo IgM Ab: Screening High ; Termination High	1	0		
Parvo IgM Ab: Screening Normal; Termination Normal	17	16		
Parvo IgM Ab: Screening Normal ; Termination High	0	0		
Parvo IgM Ab: Serology not available	1	1		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Rate of Related Adverse Events (AEs) per Year

End point title	Rate of Related Adverse Events (AEs) per Year <sup>[25]</sup>
End point description:	
End point type	Secondary
End point timeframe:	
12 months ± 14 days	

Notes:

[25] - 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: Baseline period arms are not mutually exclusive. Details see under description of period arms.

End point values	On-demand arm	Prophylaxis arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	17		
Units: Related AEs per year				
median (inter-quartile range (Q1-Q3))	0 (0 to 0)	0 (0 to 0.979)		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Rate of Related Adverse Events (AEs) during or within 1 Hour of Infusion per Year

End point title	Rate of Related Adverse Events (AEs) during or within 1 Hour of Infusion per Year <sup>[26]</sup>
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End point description:

End point type	Secondary
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End point timeframe:

12 months ± 14 days

Notes:

[26] - 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: Baseline period arms are not mutually exclusive. Details see under description of period arms.

End point values	On-demand arm	Prophylaxis arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	17		
Units: Related AEs within/during 1hr per year				
median (inter-quartile range (Q1-Q3))	0 (0 to 0)	0 (0 to 0)		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Related Thromboembolic Adverse Events (AEs)

End point title	Number of Related Thromboembolic Adverse Events (AEs) <sup>[27]</sup>
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End point description:

End point type	Secondary
End point timeframe:	
12 months ± 14 days	
Notes:	
[27] - 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: Baseline period arms are not mutually exclusive. Details see under description of period arms.	

End point values	On-demand arm	Prophylaxis arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	17		
Units: Related thromboembolic AEs	0	0		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Absolute Changes in Inhibitor Titer of Hemophilia A Participants with Shifts in Factor VIII (FVIII) Inhibitor Titer Levels

End point title	Absolute Changes in Inhibitor Titer of Hemophilia A Participants with Shifts in Factor VIII (FVIII) Inhibitor Titer Levels <sup>[28]</sup>
End point description:	
Absolute Changes in Inhibitor Titer (or no change in low or high titer status): -Inhibitor Titer went from Low (≤5 BU) to Low (≤5 BU) -Inhibitor Titer went from Low (≤5 BU) to High (>5 BU) -Inhibitor Titer went from High (>5 BU) to Low (≤5 BU) -Inhibitor Titer went from High (>5 BU) to High (>5 BU) Note: 99999 entered where there were no inhibitor titer shifts for this arm/group at this time point	
End point type	Secondary
End point timeframe:	
12 months ± 14 days	
Notes:	
[28] - 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: Baseline period arms are not mutually exclusive. Details see under description of period arms.	

End point values	On-demand arm	Prophylaxis arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	16		
Units: Bethesda Units (BU)				
median (inter-quartile range (Q1-Q3))				
Screening to 3 Month- Low to High (N=2, 3)	12.1 (12.1 to 12.1)	4 (0.7 to 16.8)		
Screening to 3 Month- High to Low (N=1, 0)	2 (2 to 2)	99999 (99999 to 99999)		
Screening to 6 Month- Low to High (N=2, 1)	12.9 (4.9 to 20.8)	5.3 (5.3 to 5.3)		
Screening to 6 Month- High to Low (N=1, 0)	3.4 (3.4 to 3.4)	99999 (99999 to 99999)		
Screening to 9 Month- Low to High (N=2, 1)	5 (4.3 to 5.6)	3.7 (3.7 to 3.7)		

Screening to 9 Month- High to Low (N=0, 2)	99999 (99999 to 99999)	2.1 (0.9 to 3.2)		
Screening to Termination- Low to High (N=2, 1)	39.2 (3.8 to 74.7)	5.8 (5.8 to 5.8)		
Screening to Termination- High to Low (N=1, 2)	14.6 (14.6 to 14.6)	3.3 (3.3 to 3.3)		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Absolute Changes in Inhibitor Titer of Hemophilia B Participants with Shifts in Factor IX (FIX) Inhibitor Titer Levels

End point title	Absolute Changes in Inhibitor Titer of Hemophilia B Participants with Shifts in Factor IX (FIX) Inhibitor Titer Levels <sup>[29]</sup>
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End point description:

Absolute Changes in Inhibitor Titer (or no change in low or high titer status): -Inhibitor Titer went from Low ( $\leq 5$  BU) to Low ( $\leq 5$  BU) -Inhibitor Titer went from Low ( $\leq 5$  BU) to High ( $> 5$  BU) -Inhibitor Titer went from High ( $> 5$  BU) to Low ( $\leq 5$  BU) -Inhibitor Titer went from High ( $> 5$  BU) to High ( $> 5$  BU)

Note: 99999 entered where there were no inhibitor titer shifts for this arm/group at this time point

End point type	Secondary
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End point timeframe:

12 months  $\pm$  14 days

Notes:

[29] - 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: Baseline period arms are not mutually exclusive. Details see under description of period arms.

End point values	On-demand arm	Prophylaxis arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1	1		
Units: Bethesda Units (BU)				
median (inter-quartile range (Q1-Q3))				
Screening to 3 Month- Low to Low (N=1, 0)	3.2 (3.2 to 3.2)	99999 (99999 to 99999)		
Screening to 3 Month- Low to High (N=0, 0)	99999 (99999 to 99999)	99999 (99999 to 99999)		
Screening to 3 Month- High to Low (N=0, 0)	99999 (99999 to 99999)	99999 (99999 to 99999)		
Screening to 3 Month- High to High (N=1, 1)	0.3 (0.3 to 0.3)	10.7 (10.7 to 10.7)		
Screening to 6 Month- Low to Low (N=1, 0)	1.5 (1.5 to 1.5)	99999 (99999 to 99999)		
Screening to 6 Month- Low to High (N=0, 0)	99999 (99999 to 99999)	99999 (99999 to 99999)		
Screening to 6 Month- High to Low (N=0, 0)	99999 (99999 to 99999)	99999 (99999 to 99999)		
Screening to 6 Month- High to High (N=1, 1)	1.7 (1.7 to 1.7)	23.2 (23.2 to 23.2)		
Screening to 9 Month- Low to Low (N=1, 0)	3.2 (3.2 to 3.2)	99999 (99999 to 99999)		
Screening to 9 Month- Low to High (N=0, 0)	99999 (99999 to 99999)	99999 (99999 to 99999)		

Screening to 9 Month- High to Low (N=0, 0)	99999 (99999 to 99999)	99999 (99999 to 99999)		
Screening to 9 Month- High to High (N=0, 1)	99999 (99999 to 99999)	37 (37 to 37)		
Screening to Termination - Low to Low (N=0, 0)	99999 (99999 to 99999)	99999 (99999 to 99999)		
Screening to Termination- Low to High (N=0, 0)	99999 (99999 to 99999)	99999 (99999 to 99999)		
Screening to Termination- High to Low (N=0, 0)	99999 (99999 to 99999)	99999 (99999 to 99999)		
Screening to Termination - High to High (N=1, 1)	11.3 (11.3 to 11.3)	21.4 (21.4 to 21.4)		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Pharmacoeconomics: Annual days lost due to bleeding (work or school)

End point title	Pharmacoeconomics: Annual days lost due to bleeding (work or school) <sup>[30]</sup>
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End point description:

End point type	Secondary
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End point timeframe:

12 months  $\pm$  14 days

Notes:

[30] - 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: Baseline period arms are not mutually exclusive. Details see under description of period arms.

End point values	On-demand arm	Prophylaxis arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	16		
Units: days				
arithmetic mean (standard deviation)	16.4 ( $\pm$ 25.76)	8.8 ( $\pm$ 14.42)		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Pharmacoeconomics: Annual number of hospitalizations for bleeding

End point title	Pharmacoeconomics: Annual number of hospitalizations for bleeding <sup>[31]</sup>
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End point description:

End point type	Secondary
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End point timeframe:

12 months  $\pm$  14 days



Notes:

[31] - 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: Baseline period arms are not mutually exclusive. Details see under description of period arms.

End point values	On-demand arm	Prophylaxis arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	16		
Units: hospitalizations				
arithmetic mean (standard deviation)	0.6 (± 1.15)	0.6 (± 2.03)		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Pharmacoeconomics: Annual number of hospitalizations for indwelling line

End point title	Pharmacoeconomics: Annual number of hospitalizations for indwelling line <sup>[32]</sup>
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End point description:

End point type	Secondary
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End point timeframe:

12 months ± 14 days

Notes:

[32] - 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: Baseline period arms are not mutually exclusive. Details see under description of period arms.

End point values	On-demand arm	Prophylaxis arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	16		
Units: hospitalizations				
arithmetic mean (standard deviation)	0.1 (± 0.32)	0.1 (± 0.25)		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Pharmacoeconomics: Annual number of emergency room visits

End point title	Pharmacoeconomics: Annual number of emergency room
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End point description:

End point type	Secondary
End point timeframe:	
12 months $\pm$ 14 days	
Notes:	
[33] - 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: Baseline period arms are not mutually exclusive. Details see under description of period arms.	

End point values	On-demand arm	Prophylaxis arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	16		
Units: Emergency room visits				
arithmetic mean (standard deviation)	0.4 ( $\pm$ 0.98)	0.4 ( $\pm$ 1.09)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Pharmacoeconomics: Annual number of physician's office visits

End point title	Pharmacoeconomics: Annual number of physician's office
End point description:	
End point type	Secondary
End point timeframe:	
12 months $\pm$ 14 days	
Notes:	
[34] - 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: Baseline period arms are not mutually exclusive. Details see under description of period arms.	

End point values	On-demand arm	Prophylaxis arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	16		
Units: Physician's office visits				
arithmetic mean (standard deviation)	2.2 ( $\pm$ 4.15)	2.6 ( $\pm$ 4.6)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Pharmacoeconomics: Annual total length of hospitalization for bleeding

End point title	Pharmacoeconomics: Annual total length of hospitalization for bleeding <sup>[35]</sup>
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End point description:

End point type	Secondary
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End point timeframe:

12 months  $\pm$  14 days

Notes:

[35] - 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: Baseline period arms are not mutually exclusive. Details see under description of period arms.

End point values	On-demand arm	Prophylaxis arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	16		
Units: Days				
arithmetic mean (standard deviation)	5 ( $\pm$ 9.48)	5.3 ( $\pm$ 17)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Pharmacoeconomics: Annual total length of hospitalization for indwelling line

End point title	Pharmacoeconomics: Annual total length of hospitalization for indwelling line <sup>[36]</sup>
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End point description:

End point type	Secondary
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End point timeframe:

12 months  $\pm$  14 days

Notes:

[36] - 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: Baseline period arms are not mutually exclusive. Details see under description of period arms.

End point values	On-demand arm	Prophylaxis arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	16		
Units: Days				
arithmetic mean (standard deviation)	0.7 ( $\pm$ 2.61)	0.7 ( $\pm$ 2.75)		

### Statistical analyses

No statistical analyses for this end point

**Secondary: Pharmacoeconomics: Annual total number of days lost (work or school)**

End point title	Pharmacoeconomics: Annual total number of days lost (work or school) <sup>[37]</sup>
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End point description:

End point type	Secondary
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End point timeframe:

12 months  $\pm$  14 days

Notes:

[37] - 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: Baseline period arms are not mutually exclusive. Details see under description of period arms.

End point values	On-demand arm	Prophylaxis arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	16		
Units: Days				
arithmetic mean (standard deviation)	17.4 ( $\pm$ 25.42)	15.4 ( $\pm$ 24.28)		

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Health-Related Quality of Life (HRQoL): EuroQoL (Quality of Life)-5 Dimensions (EQ-5D) Index Scores**

End point title	Health-Related Quality of Life (HRQoL): EuroQoL (Quality of Life)-5 Dimensions (EQ-5D) Index Scores <sup>[38]</sup>
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End point description:

EQ-5D is a participant answered questionnaire scoring 5 dimensions - mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The EQ-5D total score ranges from 0 (worst health state) to 1 (perfect health state) and 1 reflects the best outcome. EQ-5D Index scores based on EQ-5D questionnaire were calculated for participants  $\geq$ 14 years of age, at screening, 6 months, and at termination visit. Changes in scores at 6 months and termination were also calculated. A relatively higher score represents better quality of life.

End point type	Secondary
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End point timeframe:

12 months  $\pm$  14 days

Notes:

[38] - 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: Baseline period arms are not mutually exclusive. Details see under description of period arms.

End point values	On-demand arm	Prophylaxis arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	12		
Units: Scores on a scale				
arithmetic mean (standard deviation)				

Screening (N= 16, 12)	0.627 (± 0.2067)	0.62 (± 0.1841)		
6 Months (N= 15, 11)	0.621 (± 0.188)	0.729 (± 0.1392)		
Termination (N= 15, 10)	0.605 (± 0.2146)	0.7 (± 0.1233)		
Change (Screening - Month 6) (N= 15, 11)	-0.006 (± 0.2088)	-0.096 (± 0.2403)		
Change (Screening - Termination) (N= 15, 10)	0.01 (± 0.247)	-0.075 (± 0.2594)		
Change (Month 6 - Termination) (N= 15, 10)	0.016 (± 0.1765)	0.001 (± 0.1493)		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Hemophilia-specific Quality of Life questionnaire for adults (Haem-A-QoL) ≥ 16 Years Old

End point title	Hemophilia-specific Quality of Life questionnaire for adults (Haem-A-QoL) ≥ 16 Years Old <sup>[39]</sup>
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End point description:

The Haem-A-QoL instrument has been developed and used in Hemophilia A patients. As a hemophilia-specific instrument, this measure assesses very specific aspects of dealing with hemophilia. The areas covered by this instrument are: Physical Health (PH), Sports & Leisure (S&L), School & Work (W&S), Dealing with Hemophilia (Dealing), Family Planning (FP), Feeling, Relationships (R'ships), Treatment, View, and Outlook for the Future (Future). A Haem-A-QoL Total Score (Total) was also calculated. For the Haem-A-QoL, higher scores indicate a worse quality of life. Scores on a scale range between 0 and 100. Haem-A-QoL scores at screening, 6 months, and at termination visit were collected. Changes in scores at 6 months and termination were also calculated.

End point type	Secondary
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End point timeframe:

12 months ± 14 days

Notes:

[39] - 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: Baseline period arms are not mutually exclusive. Details see under description of period arms.

End point values	On-demand arm	Prophylaxis arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	12		
Units: Scores on a scale				
arithmetic mean (standard deviation)				
Dealing- Screening (N=15, 12)	35 (± 19.72)	26 (± 15.84)		
Dealing- Month 6 (N=14, 11)	25 (± 16.67)	18.9 (± 21.11)		
Dealing- Termination (N=14, 11)	25.6 (± 25.21)	23.7 (± 22.15)		
Dealing- Change (Screening - Month 6) (N=14, 11)	10.7 (± 18.61)	3.4 (± 22.62)		
Dealing- Change (Screening - Termination) (N=14, 11)	10.1 (± 27.19)	-1.4 (± 21.37)		
Dealing- Change (Month 6 - Termination) (N=14, 11)	-0.6 (± 16.81)	-4.8 (± 21.26)		
FP- Screening (N=9, 8)	16.7 (± 20.49)	34.9 (± 31.31)		

FP- Month 6 (N=12, 7)	20.5 (± 26.71)	14.3 (± 11.25)		
FP- Termination (N=13, 8)	19.1 (± 16.25)	21.1 (± 22.14)		
FP- Change (Screening - Month 6) (N=9, 7)	-3.7 (± 26.94)	14.9 (± 28.73)		
FP- Change(Screening - Termination)(N=9, 7)	-2.5 (± 25.57)	13.1 (± 20.26)		
FP- Change (Month 6 - Termination)(N=11, 6)	-0.8 (± 32.68)	-8.3 (± 28.41)		
Feeling- Screening (N=15, 12)	39.6 (± 28.22)	48.2 (± 29.02)		
Feeling- Month 6 (N=14, 11)	33.9 (± 28.77)	29 (± 17.29)		
Feeling- Termination (N=14, 11)	30.8 (± 28.53)	26.1 (± 20.69)		
Feeling- Change (Screening - Month 6) (N=14, 11)	4.9 (± 27.75)	17.3 (± 34.72)		
Feeling- Change(Screening - Termination)(N=14, 11)	8 (± 31.91)	20.2 (± 24.58)		
Feeling- Change (Month 6 - Termination)(N=14, 11)	3.1 (± 16.4)	2.8 (± 23.94)		
Future- Screening (N=14, 12)	46.8 (± 28.46)	48.6 (± 23.32)		
Future- Month 6 (N=14, 11)	40.2 (± 26.14)	46 (± 18.03)		
Future- Termination (N=14, 11)	47.9 (± 25.47)	46.8 (± 18.74)		
Future- Change (Screening - Month 6) (N=13, 11)	4 (± 26.84)	1.1 (± 24.34)		
Future- Change(Screening - Termination)(N=13, 11)	-3.8 (± 20.53)	0.3 (± 16.58)		
Future- Change (Month 6 - Termination)(N=14, 11)	-7.7 (± 20.25)	-0.8 (± 16.3)		
PH- Screening (N=15, 12)	64 (± 22.46)	66.4 (± 24.21)		
PH- Month 6 (N=14, 11)	50.8 (± 27.55)	43.1 (± 25.24)		
PH- Termination (N=14, 11)	56.1 (± 24.98)	42.3 (± 18.86)		
PH- Change (Screening - Month 6) (N=14, 11)	14.6 (± 21.7)	21.1 (± 28.77)		
PH- Change(Screening - Termination)(N=14, 11)	9.3 (± 23.93)	21.9 (± 24.79)		
PH- Change (Month 6 - Termination)(N=14, 11)	-5.3 (± 10.65)	0.8 (± 20.2)		
R'ships- Screening (N=15, 11)	28.3 (± 36.57)	26.9 (± 28.83)		
R'ships- Month 6 (N=14, 11)	19 (± 28.2)	15.2 (± 13.85)		
R'ships- Termination (N=14, 10)	17.9 (± 22.13)	15 (± 17.48)		
R'ships- Change (Screening - Month 6) (N=14, 10)	7.7 (± 34.04)	10.4 (± 27.45)		
R'ships- Change(Screening - Termination)(N=14, 10)	8.9 (± 30.57)	12.1 (± 25.49)		
R'ships- Change (Month 6 - Termination)(N=14, 10)	1.2 (± 21.4)	1.7 (± 16.57)		
S&L- Screening (N=12, 8)	69.3 (± 17.11)	83.1 (± 14.13)		
S&L- Month 6 (N=12, 8)	63.1 (± 23.09)	69.7 (± 19.75)		
S&L- Termination (N=12, 8)	72.3 (± 17.3)	78.1 (± 12.52)		
S&L- Change (Screening - Month 6) (N=9, 5)	9.9 (± 19.75)	20.5 (± 27.97)		
S&L- Change(Screening - Termination)(N=9, 5)	1.2 (± 15.91)	7 (± 21.68)		
S&L- Change (Month 6 - Termination)(N=11, 7)	-10.2 (± 13.44)	-2.5 (± 15.61)		
Treatment- Screening (N=15, 12)	36.9 (± 13.32)	39.6 (± 20.7)		
Treatment- Month 6 (N=14, 11)	30.4 (± 19.82)	40.9 (± 16.96)		
Treatment- Termination (N=14, 11)	34.8 (± 14.87)	42.6 (± 17.8)		
Treatment- Change (Screening - Month 6) (N=14, 11)	6.5 (± 23.72)	0 (± 16.74)		

Treatment-Change(Screening - Termination)(N=14, 11)	2.1 (± 17.81)	-1.7 (± 23.86)		
Treatment- Change (Month 6- Termination)(N=14, 11)	-4.4 (± 15.07)	-1.7 (± 18.7)		
View- Screening (N=15, 12)	52.3 (± 24.49)	55.6 (± 11.97)		
View- Month 6 (N=14, 11)	44.3 (± 27.66)	40 (± 13.23)		
View- Termination (N=14, 11)	47.9 (± 22.59)	37.7 (± 21.26)		
View- Change (Screening - Month 6) (N=14, 11)	7.5 (± 23.68)	14.3 (± 17.25)		
View- Change (Screening - Termination)(N=14, 11)	3.9 (± 23.79)	16.6 (± 15.01)		
View- Change (Month 6- Termination)(N=14, 11)	-3.6 (± 17.03)	2.3 (± 20.78)		
W&S-Screening (N=13, 10)	43.8 (± 25.9)	57.7 (± 17.87)		
W&S- Month 6 (N=13, 9)	31.7 (± 26.82)	37.5 (± 20.73)		
W&S- Termination (N=12, 9)	28.6 (± 22.53)	36.8 (± 19.63)		
W&S- Change (Screening - Month 6) (N=12, 8)	10.9 (± 30.98)	25.3 (± 25.6)		
W&S- Change (Screening - Termination)(N=12, 8)	16.1 (± 33.86)	25.3 (± 19.01)		
W&S- Change (Month 6- Termination)(N=12, 9)	5.2 (± 15.95)	0.7 (± 21.75)		
Total- Screening (N=14, 12)	44 (± 15.5)	49.2 (± 15.43)		
Total- Month 6 (N=14, 11)	37.4 (± 19.37)	38.1 (± 11.34)		
Total- Termination (N=14, 11)	40.2 (± 17.55)	38.7 (± 14.21)		
Total- Change (Screening - Month 6) (N=13, 11)	9.2 (± 18.44)	10.2 (± 17.84)		
Total- Change (Screening - Termination)(N=13, 11)	6.1 (± 15.41)	9.5 (± 12.77)		
Total- Change (Month 6- Termination)(N=14, 11)	-2.7 (± 9.21)	-0.7 (± 14.4)		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Hemophilia-specific Quality of Life questionnaire for Children and Adolescents < 16 Years Old (Haemo-QoL) - Parent's Evaluation

End point title	Hemophilia-specific Quality of Life questionnaire for Children and Adolescents < 16 Years Old (Haemo-QoL) - Parent's Evaluation <sup>[40]</sup>
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End point description:

The Haemo-QoL is a quality of life (QoL) assessment instrument for children and adolescents with haemophilia. As a hemophilia-specific instrument, this measure assesses very specific aspects of dealing with hemophilia. The areas covered by this instrument are: Physical Health (PH), Sports & School (S&S), Dealing with Hemophilia (Dealing), Family, Feeling, Relationships (R'ships), Treatment, View, Outlook for the Future (Future), Friends, Others, and Support. A Haemo-QoL Total Score (Total) was also calculated. For the Haemo-QoL, higher scores indicate a worse quality of life. Scores on a scale range between 0 and 100. Haemo-QoL scores at screening, 6 months, and at termination visit were collected. Changes in scores at 6 months and termination were also calculated.

End point type	Secondary
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End point timeframe:

12 months ± 14 days

Notes:

[40] - 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: Baseline period arms are not mutually exclusive. Details see under description of period arms.

End point values	On-demand arm	Prophylaxis arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	5		
Units: Scores on a scale				
arithmetic mean (standard deviation)				
Dealing- Screening (N=4, 4)	25.9 (± 11.8)	39.3 (± 17)		
Dealing- Month 6 (N=4, 4)	25.6 (± 19.31)	36.6 (± 16.07)		
Dealing- Termination (N=4, 5)	21.4 (± 16.24)	28.6 (± 13.36)		
Dealing- Change (Screening - Month 6) (N=4, 4)	0.3 (± 8.61)	2.7 (± 7.92)		
Dealing- Change(Screening - Termination)(N=4, 4)	4.5 (± 7.92)	13.4 (± 5.36)		
Dealing- Change (Month 6 - Termination)(N=4, 4)	4.2 (± 11.85)	10.7 (± 7.72)		
Family- Screening (N=4, 5)	55.3 (± 19.05)	50.9 (± 8.72)		
Family- Month 6 (N=4, 5)	50.3 (± 27.65)	49.1 (± 10.27)		
Family- Termination (N=4, 5)	45.8 (± 31.03)	39.8 (± 13.77)		
Family- Change (Screening - Month 6) (N=4, 5)	5 (± 9.26)	1.7 (± 15.65)		
Family- Change(Screening - Termination)(N=4, 5)	9.5 (± 15.52)	11.1 (± 19.22)		
Family- Change (Month 6 - Termination)(N=4, 5)	4.5 (± 12.16)	9.3 (± 5.24)		
Feeling- Screening (N=4, 5)	44.1 (± 14.25)	38.2 (± 2.77)		
Feeling- Month 6 (N=4, 5)	50.3 (± 27.02)	37.5 (± 22.21)		
Feeling- Termination (N=4, 5)	33.6 (± 36.07)	27.8 (± 16.97)		
Feeling- Change (Screening - Month 6) (N=4, 5)	-6.3 (± 24.27)	0.7 (± 24.02)		
Feeling- Change(Screening - Termination)(N=4, 5)	10.5 (± 27.92)	10.5 (± 19.45)		
Feeling- Change (Month 6 - Termination)(N=4, 5)	16.7 (± 13.85)	9.7 (± 20.64)		
Friends- Screening (N=4, 5)	35.9 (± 20.65)	52.1 (± 17.18)		
Friends- Month 6 (N=4, 5)	26.6 (± 17.95)	36.3 (± 29.78)		
Friends- Termination (N=4, 5)	34.4 (± 14.88)	66.3 (± 20.06)		
Friends- Change (Screening - Month 6) (N=4, 5)	9.4 (± 27.72)	15.8 (± 21.88)		
Friends- Change(Screening - Termination)(N=4, 5)	1.6 (± 17.95)	-14.2 (± 28.31)		
Friends- Change (Month 6 - Termination)(N=4, 5)	-7.8 (± 22.46)	-30 (± 31.68)		
Future- Screening (N=2, 2)	53.1 (± 13.26)	43.8 (± 17.68)		
Future- Month 6 (N=2, 2)	40.6 (± 13.26)	37.5 (± 8.84)		
Future- Termination (N=2, 2)	31.3 (± 0)	43.8 (± 8.84)		
Future- Change (Screening - Month 6) (N=2, 2)	12.5 (± 0)	6.3 (± 8.84)		
Future- Change(Screening - Termination)(N=2, 2)	21.9 (± 13.26)	0 (± 8.84)		
Future- Change (Month 6 - Termination)(N=2, 2)	9.4 (± 13.26)	-6.3 (± 0)		



Others- Screening (N=4, 5)	27.1 (± 34.44)	29.2 (± 16.67)		
Others- Month 6 (N=4, 5)	42.7 (± 39.14)	24.2 (± 15.7)		
Others- Termination (N=4, 5)	28.1 (± 32.87)	25.8 (± 13.63)		
Others- Change (Screening - Month 6) (N=4, 5)	-15.6 (± 16.8)	5 (± 20.28)		
Others- Change(Screening - Termination)(N=4, 5)	-1 (± 15.36)	3.3 (± 15.98)		
Others- Change (Month 6 - Termination)(N=4, 5)	14.6 (± 19.98)	-1.7 (± 10.87)		
PH- Screening (N=4, 5)	58 (± 11.06)	52.1 (± 23.23)		
PH- Month 6 (N=4, 5)	53.6 (± 13.98)	48 (± 17.23)		
PH- Termination (N=4, 5)	41.1 (± 11.85)	40.4 (± 17.02)		
PH- Change (Screening - Month 6) (N=4, 5)	4.5 (± 12.16)	4.1 (± 32.71)		
PH- Change(Screening - Termination)(N=4, 5)	17 (± 17.1)	11.8 (± 29.6)		
PH- Change (Month 6 - Termination)(N=4, 5)	12.5 (± 22.87)	7.7 (± 22.25)		
R'ships- Screening (N=2, 2)	12.5 (± 17.68)	43.8 (± 8.84)		
R'ships- Month 6 (N=2, 2)	25 (± 35.36)	43.8 (± 8.84)		
R'ships- Termination (N=2, 2)	0 (± 0)	37.5 (± 17.68)		
R'ships- Change (Screening - Month 6) (N=2, 2)	-12.5 (± 17.68)	0 (± 0)		
R'ships-Change(Screening - Termination)(N=2, 2)	12.5 (± 17.68)	6.3 (± 8.84)		
R'ships- Change (Month 6- Termination)(N=2, 2)	25 (± 35.36)	6.3 (± 8.84)		
S&S- Screening (N=4, 5)	67.1 (± 10.68)	59.1 (± 23.73)		
S&S- Month 6 (N=4, 5)	62.5 (± 7.74)	56.5 (± 9.07)		
S&S- Termination (N=4, 5)	55.6 (± 17.16)	57.2 (± 17.29)		
S&S- Change (Screening - Month 6) (N=4, 5)	4.6 (± 6.89)	2.6 (± 16.32)		
S&S- Change (Screening - Termination)(N=4, 5)	11.5 (± 12.02)	1.9 (± 10.22)		
S&S- Change (Month 6- Termination)(N=4, 5)	6.9 (± 18.07)	-0.8 (± 8.94)		
Support-Screening (N=4, 4)	28.1 (± 25.77)	51.6 (± 9.38)		
Support-Month 6 (N=4, 4)	18.8 (± 29.32)	42.2 (± 17.95)		
Support- Termination (N=4, 5)	32.8 (± 32.02)	48.8 (± 20.44)		
Support- Change (Screening - Month 6) (N=4, 4)	9.4 (± 24.21)	9.4 (± 10.83)		
Support- Change (Screening - Termination)(N=4, 4)	-4.7 (± 13.86)	3.1 (± 15.73)		
Support- Change (Month 6- Termination)(N=4, 4)	-14.1 (± 21.27)	-6.3 (± 8.84)		
Treatment- Screening (N=4, 5)	29 (± 13.23)	64.2 (± 22.6)		
Treatment- Month 6 (N=4, 5)	21.9 (± 6.9)	54.8 (± 14.53)		
Treatment- Termination (N=4, 5)	17.1 (± 22.12)	41 (± 13.34)		
Treatment- Change (Screening - Month 6) (N=4, 5)	7.1 (± 10.1)	9.4 (± 13.06)		
Treatment- Change(Screening - Termination)(N=4, 5)	11.9 (± 17.16)	23.2 (± 16.94)		
Treatment- Change (Month 6- Termination)(N=4, 5)	4.8 (± 22.47)	13.8 (± 11.14)		
View-Screening (N=4, 5)	47.4 (± 18.25)	36.7 (± 16.94)		
View-Month 6 (N=4, 5)	46.3 (± 24.45)	36.4 (± 22.04)		
View- Termination (N=4, 5)	32.8 (± 35.68)	30.8 (± 12.85)		

View- Change (Screening - Month 6) (N=4, 5)	1.1 (± 6.38)	0.3 (± 7.63)		
View- Change (Screening - Termination)(N=4, 5)	14.7 (± 18.62)	5.9 (± 10.08)		
View- Change (Month 6- Termination)(N=4, 5)	13.5 (± 13.02)	5.6 (± 16.7)		
Total-Screening (N=4, 5)	43.7 (± 13.67)	48.1 (± 8.84)		
Total-Month 6 (N=4, 5)	42 (± 13.84)	42.3 (± 11.08)		
Total- Termination (N=4, 5)	34.5 (± 21.83)	39.5 (± 8.52)		
Total- Change (Screening - Month 6) (N=4, 5)	1.7 (± 1.19)	5.7 (± 14.97)		
Total- Change (Screening - Termination)(N=4, 5)	9.1 (± 8.57)	8.6 (± 8.72)		
Total- Change (Month 6- Termination)(N=4, 5)	7.4 (± 8.91)	2.8 (± 7.06)		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Hemophilia-specific Quality of Life questionnaire for Children and Adolescents < 16 Years Old (Haemo-QoL) - Child's Evaluation

End point title	Hemophilia-specific Quality of Life questionnaire for Children and Adolescents < 16 Years Old (Haemo-QoL) - Child's Evaluation <sup>[41]</sup>
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End point description:

The Haemo-QoL is a quality of life (QoL) assessment instrument for children and adolescents with haemophilia. As a hemophilia-specific instrument, this measure assesses very specific aspects of dealing with hemophilia. The areas covered by this instrument are: Physical Health (PH), Sports & School (S&S), Dealing with Hemophilia (Dealing), Family, Feeling, Relationships (R'ships), Treatment, View, Outlook for the Future (Future), Friends, Others, and Support. A Haemo-QoL Total Score (Total) was also calculated. For the Haemo-QoL, higher scores indicate a worse quality of life. Scores on a scale range between 0 and 100. Haemo-QoL scores at screening, 6 months, and at termination visit were collected. Changes in scores at 6 months and termination were also calculated.

End point type	Secondary
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End point timeframe:

12 months ± 14 days

Notes:

[41] - 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: Baseline period arms are not mutually exclusive. Details see under description of period arms.

End point values	On-demand arm	Prophylaxis arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	5		
Units: Scores on a scale				
arithmetic mean (standard deviation)				
Dealing- Screening (N=4, 4)	33 (± 17.1)	44.6 (± 20.72)		
Dealing- Month 6 (N=4, 4)	21.4 (± 2.92)	37.5 (± 13.2)		
Dealing- Termination (N=4, 5)	25 (± 9.22)	32.9 (± 12.73)		
Dealing- Change (Screening - Month 6) (N=4, 4)	11.6 (± 15.26)	7.1 (± 8.75)		

Dealing- Change(Screening - Termination)(N=4, 4)	8 (± 15.26)	14.3 (± 12.37)		
Dealing- Change (Month 6 - Termination)(N=4, 4)	-3.6 (± 6.52)	7.1 (± 6.52)		
Family- Screening (N=4, 5)	50.5 (± 23.94)	35.6 (± 22.05)		
Family- Month 6 (N=4, 5)	43.4 (± 28.78)	36.4 (± 23.06)		
Family- Termination (N=4, 5)	38.3 (± 21.25)	32.5 (± 21.09)		
Family- Change (Screening - Month 6) (N=4, 5)	7 (± 20.31)	-0.7 (± 16.38)		
Family- Change(Screening - Termination)(N=4, 5)	12.2 (± 25.72)	3.1 (± 15.51)		
Family- Change (Month 6 - Termination)(N=4, 5)	5.2 (± 13.66)	3.9 (± 12.2)		
Feeling- Screening (N=4, 5)	54.8 (± 31.91)	34.9 (± 12.89)		
Feeling- Month 6 (N=4, 5)	41.4 (± 43.03)	22 (± 18.68)		
Feeling- Termination (N=4, 5)	34.4 (± 39.48)	19.2 (± 15.39)		
Feeling- Change (Screening - Month 6) (N=4, 5)	13.4 (± 16.91)	12.9 (± 27.77)		
Feeling- Change(Screening - Termination)(N=4, 5)	20.4 (± 11.77)	15.7 (± 23.2)		
Feeling- Change (Month 6 - Termination)(N=4, 5)	7 (± 7.79)	2.8 (± 15.26)		
Friends- Screening (N=4, 5)	34.4 (± 25.26)	58.8 (± 20.54)		
Friends- Month 6 (N=4, 5)	28.1 (± 15.73)	42.5 (± 29.78)		
Friends- Termination (N=4, 5)	32.8 (± 12.88)	56.3 (± 27.24)		
Friends- Change (Screening - Month 6) (N=4, 5)	6.3 (± 25.52)	16.3 (± 24.84)		
Friends- Change(Screening - Termination)(N=4, 5)	1.6 (± 28.58)	2.5 (± 22.79)		
Friends- Change (Month 6 - Termination)(N=4, 5)	-4.7 (± 17.95)	-13.8 (± 20.44)		
Future- Screening (N=2, 2)	40.6 (± 13.26)	43.8 (± 17.68)		
Future- Month 6 (N=2, 2)	43.8 (± 17.68)	43.8 (± 17.68)		
Future- Termination (N=2, 2)	46.9 (± 22.1)	28.1 (± 22.1)		
Future- Change (Screening - Month 6) (N=2, 2)	-3.1 (± 4.42)	0 (± 0)		
Future- Change(Screening - Termination)(N=2, 2)	-6.3 (± 8.84)	15.6 (± 4.42)		
Future- Change (Month 6 - Termination)(N=2, 2)	-3.1 (± 4.42)	15.6 (± 4.42)		
Others- Screening (N=4, 5)	42.7 (± 33.74)	26.7 (± 20.11)		
Others- Month 6 (N=4, 5)	33.3 (± 40.11)	16.7 (± 15.02)		
Others- Termination (N=4, 5)	18.8 (± 21.11)	13.3 (± 12.64)		
Others- Change (Screening - Month 6) (N=4, 5)	9.4 (± 8.59)	10 (± 25.79)		
Others- Change(Screening - Termination)(N=4, 5)	24 (± 14.18)	13.3 (± 23.09)		
Others- Change (Month 6 - Termination)(N=4, 5)	14.6 (± 19.39)	3.3 (± 16.24)		
PH- Screening (N=4, 5)	67 (± 24.98)	42.1 (± 32.28)		
PH- Month 6 (N=4, 5)	49.1 (± 14.69)	33.9 (± 16.66)		
PH- Termination (N=4, 5)	41.1 (± 23.05)	25.7 (± 10.83)		
PH- Change (Screening - Month 6) (N=4, 5)	17.9 (± 19.56)	8.2 (± 34.43)		
PH- Change(Screening - Termination)(N=4, 5)	25.9 (± 14.4)	16.4 (± 29.73)		
PH- Change (Month 6 - Termination)(N=4, 5)	8 (± 12.16)	8.2 (± 20.66)		

R'ships- Screening (N=2, 2)	6.3 (± 8.84)	43.8 (± 8.84)		
R'ships- Month 6 (N=2, 2)	18.8 (± 26.52)	43.8 (± 8.84)		
R'ships- Termination (N=2, 2)	6.3 (± 8.84)	18.8 (± 26.52)		
R'ships- Change (Screening - Month 6) (N=2, 2)	-12.5 (± 17.68)	0 (± 0)		
R'ships-Change(Screening - Termination)(N=2, 2)	0 (± 0)	25 (± 17.68)		
R'ships- Change (Month 6- Termination)(N=2, 2)	12.5 (± 17.68)	25 (± 17.68)		
S&S- Screening (N=4, 5)	53.3 (± 14.74)	51.3 (± 19.82)		
S&S- Month 6 (N=4, 5)	46.8 (± 13.42)	54.2 (± 5.53)		
S&S- Termination (N=4, 5)	33.2 (± 5.64)	49.8 (± 18.49)		
S&S- Change (Screening - Month 6) (N=4, 5)	6.5 (± 11.42)	-2.8 (± 18.53)		
S&S- Change (Screening - Termination)(N=4, 5)	20.1 (± 14.74)	1.5 (± 18.74)		
S&S- Change (Month 6- Termination)(N=4, 5)	13.5 (± 9.1)	4.4 (± 15.19)		
Support-Screening (N=4, 4)	32.8 (± 3.13)	62.5 (± 31.04)		
Support-Month 6 (N=4, 4)	28.1 (± 10.83)	56.3 (± 31.87)		
Support- Termination (N=4, 5)	17.2 (± 17.21)	65 (± 15.69)		
Support- Change (Screening - Month 6) (N=4, 4)	4.7 (± 12.88)	6.3 (± 31.46)		
Support- Change (Screening - Termination)(N=4, 4)	15.6 (± 18.75)	-3.1 (± 18.75)		
Support- Change (Month 6- Termination)(N=4, 4)	10.9 (± 10.67)	-9.4 (± 25.77)		
Treatment- Screening (N=4, 5)	27.3 (± 15.38)	69.6 (± 25.63)		
Treatment- Month 6 (N=4, 5)	30.6 (± 16.5)	56.8 (± 15.89)		
Treatment- Termination (N=4, 5)	35.9 (± 26.1)	44.2 (± 27.1)		
Treatment- Change (Screening - Month 6) (N=4, 5)	-3.2 (± 4.43)	12.9 (± 21.22)		
Treatment- Change(Screening - Termination)(N=4, 5)	-8.6 (± 13.86)	25.4 (± 28)		
Treatment- Change (Month 6- Termination)(N=4, 5)	-5.3 (± 11.25)	12.6 (± 15.53)		
View-Screening (N=4, 5)	46 (± 19.33)	31.9 (± 14.36)		
View-Month 6 (N=4, 5)	39.3 (± 33.02)	32.4 (± 19.41)		
View- Termination (N=4, 5)	32.5 (± 32.75)	32.2 (± 8.6)		
View- Change (Screening - Month 6) (N=4, 5)	6.7 (± 14.96)	-0.5 (± 18.94)		
View- Change (Screening - Termination)(N=4, 5)	13.5 (± 16.56)	-0.3 (± 10.77)		
View- Change (Month 6- Termination)(N=4, 5)	6.8 (± 8.67)	0.2 (± 13.48)		
Total-Screening (N=4, 5)	44.9 (± 12.28)	45.1 (± 9.16)		
Total-Month 6 (N=4, 5)	37.4 (± 17.91)	37.7 (± 9.87)		
Total- Termination (N=4, 5)	32.2 (± 17.96)	35.3 (± 9.06)		
Total- Change (Screening - Month 6) (N=4, 5)	7.5 (± 7.21)	7.4 (± 16.57)		
Total- Change (Screening - Termination)(N=4, 5)	12.7 (± 8.69)	9.8 (± 12.35)		
Total- Change (Month 6- Termination)(N=4, 5)	5.2 (± 3.55)	2.5 (± 9.46)		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Health-Related Quality of Life (HRQoL) - General Pain Assessment Using a Visual Analogue Scale (VAS) in Adults and Adolescents ≥12 Years Old

End point title	Health-Related Quality of Life (HRQoL) - General Pain Assessment Using a Visual Analogue Scale (VAS) in Adults and Adolescents ≥12 Years Old <sup>[42]</sup>
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End point description:

General pain was assessed using a VAS pain scale at screening, 6 months, and at termination. Unlike the VAS pain assessment for pain of bleeding episodes (Outcome above), this general pain assessment did not take use of analgesics into account. For the pain scale, a higher number indicates worse pain. The visual analog scale ranges from 0 to 100 where the endpoints are labeled 'Worst imaginable health state' (=0) and 'Best imaginable health state' (=100). A positive change from baseline indicates improvement. Change in VAS scores at 6 months and study termination were also compared relative to Baseline/Screening scores (ie, (Baseline/Screening VAS score) - (VAS score at 6 months and study termination)).

End point type	Secondary
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End point timeframe:

Baseline, 6 months and 12 months ± 14 days

Notes:

[42] - 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: Baseline period arms are not mutually exclusive. Details see under description of period arms.

End point values	On-demand arm	Prophylaxis arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	15		
Units: Scores on a scale				
arithmetic mean (standard deviation)				
Screening (N= 17, 15)	35.2 (± 30.15)	55.5 (± 23.68)		
Month 6 (N= 16, 14)	36.6 (± 25.81)	32.7 (± 26.24)		
Termination (N= 16, 14)	32.4 (± 21.97)	29.8 (± 30.48)		
Change (Screening - Month 6) (N= 16, 14)	0.8 (± 31.77)	20.3 (± 38.91)		
Change (Screening - Termination) (N= 16, 14)	5 (± 28.7)	23.2 (± 46.61)		
Change (Month 6 - Termination) (N= 16, 14)	4.2 (± 21.82)	2.9 (± 19.62)		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Health-Related Quality of Life (HRQoL) - General Pain Assessment Using a Visual Analogue Scale (VAS) in Pediatrics <12 Years Old

End point title	Health-Related Quality of Life (HRQoL) - General Pain Assessment Using a Visual Analogue Scale (VAS) in Pediatrics <12 Years Old <sup>[43]</sup>
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End point description:

General pain was assessed using the children's VAS pain scale (a facial expression scale with one end

marked as no pain and the opposite end marked as the worst possible pain). Assessments were done at the screening, 6 months, and termination visits. Scores on the children's VAS scale are presented as: - No Pain -Mild Pain -Moderate pain -Severe pain -Very severe pain Unlike the VAS pain assessment for pain of bleeding episodes (Outcome above), this general pain assessment did not take use of analgesics into account. Change in VAS scores at 6 months and study termination were also compared relative to Baseline/Screening scores (ie, (Baseline/Screening VAS score) - (VAS score at 6 months and study termination)).

End point type	Secondary
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End point timeframe:

Baseline, 6 months and 12 months  $\pm$  14 days

Notes:

[43] - 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: Baseline period arms are not mutually exclusive. Details see under description of period arms.

End point values	On-demand arm	Prophylaxis arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2	2		
Units: participants				
Screening - No Pain	1	0		
Screening - Mild Pain	0	1		
Screening - Moderate Pain	1	0		
Screening - Severe Pain	0	1		
Screening - Very Severe Pain	0	0		
Month 6 - No Pain	0	0		
Month 6 - Mild Pain	1	2		
Month 6 - Moderate Pain	1	0		
Month 6 - Severe Pain	0	0		
Month 6 - Very Severe Pain	0	0		
Termination visit - No Pain	0	1		
Termination visit - Mild Pain	0	0		
Termination visit - Moderate Pain	1	1		
Termination visit - Severe Pain	0	0		
Termination visit - Very Severe Pain	1	0		

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Throughout the study period of 3 years and 7 months

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	15.0
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### Reporting groups

Reporting group title	On-demand arm
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Reporting group description:

Factor VIII Inhibitor Bypassing Activity (nanofiltered, vapor heat-treated) : Standard FEIBA NF dose and dosing interval as prescribed by the treating physician

Reporting group title	Prophylaxis arm
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Reporting group description:

Factor VIII Inhibitor Bypassing Activity (nanofiltered, vapor heat-treated) : 85 ± 15 U/kg of FEIBA NF every other day during the 12-month ± 14 days prophylactic period

Serious adverse events	On-demand arm	Prophylaxis arm	
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 19 (36.84%)	6 / 17 (35.29%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events			
Investigations			
Hepatitis B Surface Antibody Positive			
subjects affected / exposed	1 / 19 (5.26%)	2 / 17 (11.76%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Femoral Neck Fracture			
subjects affected / exposed	1 / 19 (5.26%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Arteriosclerosis			
subjects affected / exposed	1 / 19 (5.26%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

Haematoma			
subjects affected / exposed	0 / 19 (0.00%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage			
subjects affected / exposed	1 / 19 (5.26%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive Crisis			
subjects affected / exposed	1 / 19 (5.26%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Catheter Removal			
subjects affected / exposed	1 / 19 (5.26%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal Wall Haematoma			
subjects affected / exposed	0 / 19 (0.00%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis Acute			
subjects affected / exposed	1 / 19 (5.26%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	1 / 19 (5.26%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Haematuria			



subjects affected / exposed	1 / 19 (5.26%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Musculoskeletal and connective tissue disorders</b>			
Arthropathy			
subjects affected / exposed	1 / 19 (5.26%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemarthrosis			
subjects affected / exposed	1 / 19 (5.26%)	2 / 17 (11.76%)	
occurrences causally related to treatment / all	0 / 3	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle Haemorrhage			
subjects affected / exposed	0 / 19 (0.00%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Infections and infestations</b>			
Haematoma Infection			
subjects affected / exposed	1 / 19 (5.26%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

<b>Non-serious adverse events</b>	On-demand arm	Prophylaxis arm	
<b>Total subjects affected by non-serious adverse events</b>			
subjects affected / exposed	4 / 19 (21.05%)	3 / 17 (17.65%)	
<b>Blood and lymphatic system disorders</b>			
Anaemia			
subjects affected / exposed	2 / 19 (10.53%)	0 / 17 (0.00%)	
occurrences (all)	2	0	
<b>General disorders and administration site conditions</b>			
Pyrexia			

subjects affected / exposed occurrences (all)	2 / 19 (10.53%) 4	0 / 17 (0.00%) 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 19 (5.26%)	1 / 17 (5.88%)	
occurrences (all)	2	1	
Nausea			
subjects affected / exposed	2 / 19 (10.53%)	0 / 17 (0.00%)	
occurrences (all)	2	0	
Vomiting			
subjects affected / exposed	2 / 19 (10.53%)	0 / 17 (0.00%)	
occurrences (all)	2	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 19 (5.26%)	1 / 17 (5.88%)	
occurrences (all)	1	1	
Oropharyngeal Pain			
subjects affected / exposed	1 / 19 (5.26%)	1 / 17 (5.88%)	
occurrences (all)	1	1	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	1 / 19 (5.26%)	1 / 17 (5.88%)	
occurrences (all)	1	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 19 (10.53%)	1 / 17 (5.88%)	
occurrences (all)	3	1	
Arthropathy			
subjects affected / exposed	1 / 19 (5.26%)	0 / 17 (0.00%)	
occurrences (all)	1	0	

## **More information**

### **Substantial protocol amendments (globally)**

Were there any global substantial amendments to the protocol? No

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### **Interruptions (globally)**

Were there any global interruptions to the trial? No

### **Limitations and caveats**

None reported