



Clinical trial results:

An Open-Label, Multicenter Evaluation of the Long-Term Safety and Efficacy of Recombinant Human Coagulation Factor VIII Fusion Protein (rFVIII-Fc) in the Prevention and Treatment of Bleeding Episodes in Previously Treated Subjects With Hemophilia A

Summary

EudraCT number	2011-003072-37
Trial protocol	SE BE GB DE AT ES IT IE PL NL
Global end of trial date	18 October 2017

Results information

Result version number	v1 (current)
This version publication date	03 May 2018
First version publication date	03 May 2018

Trial information

Trial identification

Sponsor protocol code	8HA01EXT
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01454739
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bioverativ Therapeutics Inc.
Sponsor organisation address	225 Second Avenue, Waltham, Massachusetts (MA), United States, 02451
Public contact	Not available, Bioverativ Therapeutics Inc., clinicaltrials@bioverativ.com
Scientific contact	Not available, Bioverativ Therapeutics Inc., clinicaltrials@bioverativ.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMA-001114-PIP01-10
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	18 October 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 October 2017
Global end of trial reached?	Yes
Global end of trial date	18 October 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this study was to evaluate the long-term safety of Recombinant human Factor VIII (rFVIIIFc) in subjects with hemophilia A.

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and the International Conference on Harmonization guideline E6: Good Clinical Practice. Safety evaluations included monitoring of adverse events (AEs) and serious adverse events (SAEs), physical examination, medical and surgical history (from previous study and updated), height, weight and Concomitant therapy and procedure recording and Laboratory Safety Assessments (hematology, blood chemistry and Nijmegen-modified Bethesda assay).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 December 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 1
Country: Number of subjects enrolled	Poland: 3
Country: Number of subjects enrolled	Spain: 2
Country: Number of subjects enrolled	Sweden: 1
Country: Number of subjects enrolled	United Kingdom: 46
Country: Number of subjects enrolled	Austria: 3
Country: Number of subjects enrolled	Germany: 3
Country: Number of subjects enrolled	Ireland: 8
Country: Number of subjects enrolled	Italy: 5
Country: Number of subjects enrolled	Belgium: 1
Country: Number of subjects enrolled	France: 2
Country: Number of subjects enrolled	Australia: 21
Country: Number of subjects enrolled	Brazil: 3
Country: Number of subjects enrolled	Canada: 2
Country: Number of subjects enrolled	Hong Kong: 6
Country: Number of subjects enrolled	India: 14
Country: Number of subjects enrolled	Israel: 3

Country: Number of subjects enrolled	Japan: 13
Country: Number of subjects enrolled	New Zealand: 15
Country: Number of subjects enrolled	South Africa: 27
Country: Number of subjects enrolled	Switzerland: 1
Country: Number of subjects enrolled	United States: 60
Worldwide total number of subjects	240
EEA total number of subjects	75

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	59
Adolescents (12-17 years)	24
Adults (18-64 years)	155
From 65 to 84 years	2
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Subjects provided their written informed consent to participate in this study after the Investigator has verified that they are eligible per protocol defined criteria. For subjects, unable to provide written informed consent, parents or legal guardian(s) obtained the informed consent form.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	rFVIIIFc [Subjects from Study 8HA02PED]

Arm description:

Tailored Prophylaxis(TP): 25 IU/kg-65 IU/kg rFVIIIFc every 3-5 days or 2 times/week at approximately 20 IU/kg to 65 IU/kg rFVIIIFc on Day 1 & 40 IU/kg-65 IU/kg rFVIIIFc on Day 4 as intravenous (IV) injection. Weekly: rFVIIIFc IV injection once weekly at approximately 65 IU/kg. Personalized P: If optimal prophylaxis dosing not achieved using TP/WP, Investigator personalized dosing to meet individual subjects's needs (options: adding "prevention" dose prior to strenuous activity; targeting FVIII trough level of >3%, if bleeding history &/or activity level requires/dosing less frequently. Episodic (On demand): individual dose of rFVIIIFc IV based on clinical condition, type & severity of bleeding event & if indicated, FVIII levels (per investigator & Sponsor decision). The rate of administration determined by subject's comfort level. For subjects <12 years of age, weekly and episodic treatment regimens were only available once subjects were at least 12 years old.

Arm type	Experimental
Investigational medicinal product name	Recombinant Factor VIII-Fc
Investigational medicinal product code	rFVIIIFc
Other name	BIIB031
Pharmaceutical forms	Powder for injection
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received rFVIIIFc as tailored, weekly, personalized prophylaxis or episodic (on-demand regimen). Subjects were allowed to change treatment regimens (for example, from prophylaxis to on-demand, or from on-demand to prophylaxis) per investigator decision.

Arm title	rFVIIIFc [Subjects from Studies 997HA301/997HA307/997HA309]
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Arm description:

Tailored Prophylaxis (TP): 25 IU/kg-65 IU/kg rFVIIIFc every 3-5 days or 2 times/week at approximately 20 IU/kg to 65 IU/kg rFVIIIFc on Day 1 & 40 IU/kg-65 IU/kg rFVIIIFc on Day 4 as intravenous (IV) injection. Weekly: rFVIIIFc IV injection once weekly at approximately 65 IU/kg. Personalized P: If optimal prophylaxis dosing not achieved using TP/WP, Investigator personalized dosing to meet individual subjects's needs (options: adding "prevention" dose prior to strenuous activity; targeting FVIII trough level of >3%, if bleeding history &/or activity level requires/dosing less frequently. Episodic (On demand): individual dose of rFVIIIFc IV based on clinical condition, type & severity of bleeding event & if indicated, FVIII levels (per investigator & Sponsor decision). The rate of administration determined by subject's comfort level.

Arm type	Experimental
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Investigational medicinal product name	Recombinant Factor VIII-Fc
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Dosage and administration details:

Subjects received rFVIIIFc as tailored, weekly, personalized prophylaxis or episodic (on-demand regimen). Subjects were allowed to change treatment regimens (for example, from prophylaxis to on-demand, or from on-demand to prophylaxis) per investigator decision.

Number of subjects in period 1	rFVIIIFc [Subjects from Study 8HA02PED]	rFVIIIFc [Subjects from Studies 997HA301/997HA307/997HA309]
Started	61	179
Completed	54	158
Not completed	7	21
Consent withdrawn by subject	2	6
Physician decision	-	5
Adverse Event	-	1
Protocol violation	2	3
Other	3	5
Lost to follow-up	-	1

Baseline characteristics

Reporting groups

Reporting group title	rFVIIIFc [Subjects from Study 8HA02PED]
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Reporting group description:

Tailored Prophylaxis(TP): 25 IU/kg-65 IU/kg rFVIIIFc every 3-5 days or 2 times/week at approximately 20 IU/kg to 65 IU/kg rFVIIIFc on Day 1 & 40 IU/kg-65 IU/kg rFVIIIFc on Day 4 as intravenous (IV) injection. Weekly: rFVIIIFc IV injection once weekly at approximately 65 IU/kg. Personalized P: If optimal prophylaxis dosing not achieved using TP/WP, Investigator personalized dosing to meet individual subjects's needs (options: adding "prevention" dose prior to strenuous activity; targeting FVIII trough level of >3%, if bleeding history &/or activity level requires/dosing less frequently. Episodic (On demand): individual dose of rFVIIIFc IV based on clinical condition, type & severity of bleeding event & if indicated, FVIII levels (per investigator & Sponsor decision). The rate of administration determined by subject's comfort level. For subjects <12 years of age, weekly and episodic treatment regimens were only available once subjects were at least 12 years old.

Reporting group title	rFVIIIFc [Subjects from Studies 997HA301/997HA307/997HA309]
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Reporting group description:

Tailored Prophylaxis (TP): 25 IU/kg-65 IU/kg rFVIIIFc every 3-5 days or 2 times/week at approximately 20 IU/kg to 65 IU/kg rFVIIIFc on Day 1 & 40 IU/kg-65 IU/kg rFVIIIFc on Day 4 as intravenous (IV) injection. Weekly: rFVIIIFc IV injection once weekly at approximately 65 IU/kg. Personalized P: If optimal prophylaxis dosing not achieved using TP/WP, Investigator personalized dosing to meet individual subjects's needs (options: adding "prevention" dose prior to strenuous activity; targeting FVIII trough level of >3%, if bleeding history &/or activity level requires/dosing less frequently. Episodic (On demand): individual dose of rFVIIIFc IV based on clinical condition, type & severity of bleeding event & if indicated, FVIII levels (per investigator & Sponsor decision). The rate of administration determined by subject's comfort level.

Reporting group values	rFVIIIFc [Subjects from Study 8HA02PED]	rFVIIIFc [Subjects from Studies 997HA301/997HA307/997HA309]	Total
Number of subjects	61	179	240
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	59	0	59
Adolescents (12-17 years)	2	22	24
Adults (18-64 years)	0	155	155
From 65-84 years	0	2	2
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	6.7	33.5	
standard deviation	± 2.74	± 13.48	-
Gender categorical Units: Subjects			
Female	0	0	0
Male	61	179	240

End points

End points reporting groups

Reporting group title	rFVIIIFc [Subjects from Study 8HA02PED]
Reporting group description: Tailored Prophylaxis(TP): 25 IU/kg-65 IU/kg rFVIIIFc every 3-5 days or 2 times/week at approximately 20 IU/kg to 65 IU/kg rFVIIIFc on Day 1 & 40 IU/kg-65 IU/kg rFVIIIFc on Day 4 as intravenous (IV) injection. Weekly: rFVIIIFc IV injection once weekly at approximately 65 IU/kg. Personalized P: If optimal prophylaxis dosing not achieved using TP/WP, Investigator personalized dosing to meet individual subjects's needs (options: adding "prevention" dose prior to strenuous activity; targeting FVIII trough level of >3%, if bleeding history &/or activity level requires/dosing less frequently. Episodic (On demand): individual dose of rFVIIIFc IV based on clinical condition, type & severity of bleeding event & if indicated, FVIII levels (per investigator & Sponsor decision). The rate of administration determined by subject's comfort level. For subjects <12 years of age, weekly and episodic treatment regimens were only available once subjects were at least 12 years old.	
Reporting group title	rFVIIIFc [Subjects from Studies 997HA301/997HA307/997HA309]
Reporting group description: Tailored Prophylaxis (TP): 25 IU/kg-65 IU/kg rFVIIIFc every 3-5 days or 2 times/week at approximately 20 IU/kg to 65 IU/kg rFVIIIFc on Day 1 & 40 IU/kg-65 IU/kg rFVIIIFc on Day 4 as intravenous (IV) injection. Weekly: rFVIIIFc IV injection once weekly at approximately 65 IU/kg. Personalized P: If optimal prophylaxis dosing not achieved using TP/WP, Investigator personalized dosing to meet individual subjects's needs (options: adding "prevention" dose prior to strenuous activity; targeting FVIII trough level of >3%, if bleeding history &/or activity level requires/dosing less frequently. Episodic (On demand): individual dose of rFVIIIFc IV based on clinical condition, type & severity of bleeding event & if indicated, FVIII levels (per investigator & Sponsor decision). The rate of administration determined by subject's comfort level.	
Subject analysis set title	rFVIIIFc [8HA02PED (<6 years old age cohort)]
Subject analysis set type	Full analysis
Subject analysis set description: Subjects enrolled from the study 8HA02PED with <6 years old age.	
Subject analysis set title	rFVIIIFc [8HA02PED (6 - <12 years old age cohort)]
Subject analysis set type	Full analysis
Subject analysis set description: Subjects enrolled from the study 8HA02PED with 6 - <12 years old age.	
Subject analysis set title	rFVIIIFc [Subjects from Study 997HA301/997HA307/997HA309]
Subject analysis set type	Full analysis
Subject analysis set description: Subjects were included from studies 997HA301/997HA307/997HA309.	

Primary: Number of Subjects with any Positive Inhibitor Development

End point title	Number of Subjects with any Positive Inhibitor Development ^[1]
End point description: An inhibitor test result ≥ 0.6 Bethesda units (BU)/mL, identified and confirmed by re-testing of a second sample obtained within 2 to 4 weeks, was considered positive. Both tests were to be performed using the Nijmegen-modified Bethesda Assay by the central laboratory. Safety Analysis Set included subjects who received at least 1 dose of rFVIIIFc in study 8HA01EXT.	
End point type	Primary
End point timeframe: Approximately 5 years	
Notes:	

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

Justification: Descriptive statistics were done, no inferential statistical analyses were performed.

End point values	rFVIIIFc [Subjects from Study 8HA02PED]	rFVIIIFc [Subjects from Studies 997HA301/997 HA307/997HA3 09]		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	179		
Units: subjects with any positive inhibitor	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized Bleeding Rate

End point title	Annualized Bleeding Rate
End point description:	
Bleeding episodes should be classified as spontaneous if a subject records a bleeding event when there is no known contributing factor such as definite trauma or antecedent strenuous activity. Bleeding episodes should be classified as traumatic if a subject records a bleeding event when there is a known or believed reason for the bleed. Full Analysis Set (FAS) included all subjects who received at least 1 dose of rFVIIIFc. Here, "n" indicates number of subject analyzed in specified treatment regimen. "99999" indicates that the data was not analyzed for the arm in the specified category. Annualized bleeding episodes=(Number of bleeding episodes during the efficacy period/number of days during efficacy period)*365.25. The efficacy period reflects the sum of all intervals of time during which subjects were treated with rFVIIIFc according to the treatment regimens of the study excluding major and minor surgical/rehabilitation periods and large injection intervals.	
End point type	Secondary
End point timeframe:	
Approximately 5 years	

End point values	rFVIIIFc [8HA02PED (<6 years old age cohort)]	rFVIIIFc [8HA02PED (6 - <12 years old age cohort)]	rFVIIIFc [Subjects from Study 997HA301/997 HA307/997HA3 09]	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	30	31	179	
Units: episodes per subject per year				
median (inter-quartile range (Q1-Q3))				
Tailored Prophylaxis (n= 29, 30, 131)	1.18 (0.60 to 2.37)	1.59 (0.55 to 3.55)	0.64 (0.00 to 2.84)	
Weekly Prophylaxis (n= 0, 0, 34)	99999 (99999 to 99999)	99999 (99999 to 99999)	1.90 (0.27 to 4.85)	
Personalized Prophylaxis (n= 2, 1, 23)	3.72 (3.35 to 4.09)	1.01 (1.01 to 1.01)	4.11 (0.64 to 8.78)	
Episodic (n= 0, 0, 13)	99999 (99999 to 99999)	99999 (99999 to 99999)	19.10 (15.12 to 30.46)	

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized Spontaneous Joint Bleeding Episodes

End point title	Annualized Spontaneous Joint Bleeding Episodes
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End point description:

Bleeding episodes should be classified as spontaneous if a subject records a bleeding event when there is no known contributing factor such as definite trauma or antecedent strenuous activity. In addition of type of bleeding episode (e.g., spontaneous, traumatic), the location of the bleed (joint, internal, skin/mucosa, or muscle) were also collected. FAS included all subjects who received at least 1 dose of rFVIIIFc. Annualized spontaneous joint bleeding episodes = (Number of spontaneous joint bleeding episodes during the efficacy period / number of days during efficacy period) *365.25. Here, "n" indicates number of subject analyzed in specified treatment regimen. "99999" indicates that the data was not analyzed for the arm in the specified category.

End point type	Secondary
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End point timeframe:

Approximately 5 years

End point values	rFVIIIFc [8HA02PED (<6 years old age cohort)]	rFVIIIFc [8HA02PED (6 - <12 years old age cohort)]	rFVIIIFc [Subjects from Study 997HA301/997 HA307/997HA3 09]	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	30	31	179	
Units: episodes per subject per year				
median (inter-quartile range (Q1-Q3))				
Tailored Prophylaxis (n= 29, 30, 131)	0.00 (0.00 to 0.55)	0.00 (0.00 to 0.55)	0.00 (0.00 to 0.63)	
Weekly Prophylaxis (n= 0, 0, 34)	99999 (99999 to 99999)	99999 (99999 to 99999)	0.58 (0.00 to 1.90)	
Personalized Prophylaxis (n= 2, 1, 23)	2.20 (1.34 to 3.07)	0.00 (0.00 to 0.00)	0.91 (0.00 to 2.84)	
Episodic (n= 0, 0, 13)	99999 (99999 to 99999)	99999 (99999 to 99999)	9.22 (4.35 to 15.70)	

Statistical analyses

No statistical analyses for this end point

Secondary: Total Number of Days of Exposure

End point title	Total Number of Days of Exposure
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End point description:

An exposure day is a 24-hour period in which one or more rFVIIIFc injections are given. The total number of days of exposure to rFVIIIFc were summarized. Safety Analysis Set included subjects who received at least 1 dose of rFVIIIFc in study 8HA01EXT. Here, "n" indicates number of subject analyzed in specified treatment regimen. "99999" indicates that the data was not analyzed for the arm in the specified category.

End point type	Secondary
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End point timeframe:
Approximately 5 years

End point values	rFVIIIFc [Subjects from Study 8HA02PED]	rFVIIIFc [Subjects from Studies 997HA301/997 HA307/997HA3 09]		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	179		
Units: days				
median (full range (min-max))				
Tailored Prophylaxis (n= 59, 131)	332.00 (18.0 to 467.0)	257.00 (4.0 to 660.0)		
Weekly Prophylaxis (n= 0, 34)	99999 (99999 to 99999)	203.50 (5.0 to 318.0)		
Personalized Prophylaxis (n= 3, 23)	107.00 (102.0 to 152.0)	223.00 (14.0 to 535.0)		
Episodic (n= 0, 13)	99999 (99999 to 99999)	27.00 (0.0 to 88.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized rFVIIIFc Consumption as Total Dose per Kilogram (kg) per Subject per Year

End point title	Annualized rFVIIIFc Consumption as Total Dose per Kilogram (kg) per Subject per Year
End point description: Annualized consumption = (total IU/kg of study treatment received during the efficacy period / total number of days during the efficacy period) multiplied by 365.25. FAS included all subjects who received at least 1 dose of rFVIIIFc. Here, "n" indicates number of subject analyzed in specified treatment regimen. "99999" indicates that the data was not analyzed for the arm in the specified category.	
End point type	Secondary
End point timeframe: Approximately 5 years	

End point values	rFVIIIFc [8HA02PED (<6 years old age cohort)]	rFVIIIFc [8HA02PED (6 - <12 years old age cohort)]	rFVIIIFc [Subjects from Study 997HA301/997 HA307/997HA3 09]	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	30	31	179	
Units: dose per kilogram per subject per year				

median (inter-quartile range (Q1-Q3))				
Tailored Prophylaxis (n= 29, 30, 131)	5417.9 (4683.4 to 6303.9)	4989.7 (4293.8 to 5842.4)	4359.8 (3993.8 to 5630.3)	
Weekly Prophylaxis (n= 0, 0, 34)	99999 (99999 to 99999)	99999 (99999 to 99999)	3505.2 (3267.9 to 3639.0)	
Personalized Prophylaxis (n= 2, 1, 23)	5457.1 (4435.0 to 6479.1)	4572.3 (4572.3 to 4572.3)	3926.7 (3261.8 to 6194.8)	
Episodic (n= 0, 0, 13)	99999 (99999 to 99999)	99999 (99999 to 99999)	801.7 (286.2 to 1057.7)	

Statistical analyses

No statistical analyses for this end point

Secondary: Physician's Global Assessment of Response to Treatment Using a 4-point Scale

End point title	Physician's Global Assessment of Response to Treatment Using a 4-point Scale
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End point description:

Subjects were assessed for response to their rFVIIIFc regimen using the following 4-point scale: Excellent: bleeding episodes responded to less than or equal to ($\leq$) the usual number of injections or $\leq$ the usual dose of rFVIIIFc, or the rate of breakthrough bleeding during prophylaxis was $\leq$ that usually observed; Effective: most bleeding episodes responded to the same number of injections and dose, but some required more injections or higher doses, or there was a minor increase in the rate of breakthrough; Partially Effective: bleeding episodes most often required more injections and/or higher doses than expected, or adequate breakthrough bleeding prevention during prophylaxis required more frequent injections and/or higher doses and Ineffective: routine failure to control hemostasis or hemostatic control require additional agents. FAS included all subjects who received at least 1 dose of rFVIIIFc. The results were reported based on the efficacy period for overall treatment regimen.

End point type	Secondary
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End point timeframe:

Approximately 5 years

End point values	rFVIIIFc [Subjects from Study 8HA02PED]	rFVIIIFc [Subjects from Studies 997HA301/997 HA307/997HA3 09]		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	179		
Units: percentage of visits				
number (not applicable)				
Excellent	94.2	84.7		
Effective	5.6	14.9		
Partially Effective	0.2	0.4		
Ineffective	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Excellent or Good Response to Treatment Using a 4-Point Scale

End point title	Percentage of Subjects with Excellent or Good Response to Treatment Using a 4-Point Scale
End point description: Using eDiary, subject received rating for treatment response to any bleeding episode (BE) using 4-point scale-Excellent: Abrupt pain relief and/or improvement in signs of bleeding within approximately (approx.) 8 hours (h) after initial injection (inj.); Good: Definite pain relief and/or improvement in signs of bleeding within approx. 8h after an injection, but possibly requiring more than 1 injection after 24–48h for complete resolution; Moderate: Probable/slight beneficial effect within 8h after initial injection and requires more than 1 injection and None: No improvement, or condition worsens within approx. 8h after initial injection. This assessment was to be made approx. 8 to 12h from time the injection was given to treat BE and prior to any additional doses of rFVIIIFc given for same bleeding episode. FAS population included. "n"=number of subject analyzed in specified treatment regimen during efficacy period. "99999"=data was not analyzed for the arm in the specified category.	
End point type	Secondary
End point timeframe: Approximately 5 years	

End point values	rFVIIIFc [8HA02PED (<6 years old age cohort)]	rFVIIIFc [8HA02PED (6 - <12 years old age cohort)]	rFVIIIFc [Subjects from Study 997HA301/997 HA307/997HA3 09]	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	30	31	179	
Units: % of first inj. with evaluations for BE				
number (not applicable)				
Tailored Prophylaxis (n= 29, 30, 131)	88.0	90.6	74.5	
Weekly Prophylaxis (n= 0, 0, 34)	99999	99999	76.2	
Personalized Prophylaxis (n= 2, 1, 23)	100.0	100.0	82.2	
Episodic (n= 0, 0, 13)	99999	99999	91.8	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From signing of ICF through follow-up [7 (+7) days after the last dose of rFVIIIFc] or final visit/early termination visit (approximately 5 years)

Adverse event reporting additional description:

The Safety Analysis Set consisted of subjects who received at least 1 dose of rFVIIIFc in study. AEs emergent during major surgical/rehabilitation periods are excluded.

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	rFVIIIFc [Subjects from Study 8HA02PED]
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Reporting group description:

Tailored Prophylaxis (TP): 25 IU/kg-65 IU/kg rFVIIIFc every 3-5 days or 2 times/week at approximately 20 IU/kg to 65 IU/kg rFVIIIFc on Day 1 & 40 IU/kg-65 IU/kg rFVIIIFc on Day 4 as intravenous (IV) injection. Weekly: rFVIIIFc IV injection once weekly at approximately 65 IU/kg. Personalized P: If optimal prophylaxis dosing not achieved using TP/WP, Investigator personalized dosing to meet individual subjects's needs (options: adding "prevention" dose prior to strenuous activity; targeting FVIII trough level of >3%, if bleeding history &/or activity level requires/dosing less frequently. Episodic (On demand): individual dose of rFVIIIFc IV based on clinical condition, type & severity of bleeding event & if indicated, FVIII levels (per investigator & Sponsor decision). The rate of administration determined by subject's comfort level. For subjects <12 years of age, weekly and episodic treatment regimens were only available once subjects were at least 12 years old.

Reporting group title	rFVIIIFc [Subjects from studies 997HA301/997HA307/997HA309]
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Reporting group description:

Tailored Prophylaxis (TP): 25 IU/kg-65 IU/kg rFVIIIFc every 3-5 days or 2 times/week at approximately 20 IU/kg to 65 IU/kg rFVIIIFc on Day 1 & 40 IU/kg-65 IU/kg rFVIIIFc on Day 4 as intravenous (IV) injection. Weekly: rFVIIIFc IV injection once weekly at approximately 65 IU/kg. Personalized P: If optimal prophylaxis dosing not achieved using TP/WP, Investigator personalized dosing to meet individual subjects's needs (options: adding "prevention" dose prior to strenuous activity; targeting FVIII trough level of >3%, if bleeding history &/or activity level requires/dosing less frequently. Episodic (On demand): individual dose of rFVIIIFc IV based on clinical condition, type & severity of bleeding event & if indicated, FVIII levels (per investigator & Sponsor decision). The rate of administration determined by subject's comfort level.

Reporting group title	Overall rFVIIIFc
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Reporting group description: -

Serious adverse events	rFVIIIFc [Subjects from Study 8HA02PED]	rFVIIIFc [Subjects from studies 997HA301/997HA307/997HA309]	Overall rFVIIIFc
Total subjects affected by serious adverse events			
subjects affected / exposed	20 / 61 (32.79%)	43 / 179 (24.02%)	63 / 240 (26.25%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Hepatic Neoplasm Malignant			

subjects affected / exposed	0 / 61 (0.00%)	1 / 179 (0.56%)	1 / 240 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to peritoneum			
subjects affected / exposed	0 / 61 (0.00%)	1 / 179 (0.56%)	1 / 240 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Bleeding varicose vein			
subjects affected / exposed	0 / 61 (0.00%)	1 / 179 (0.56%)	1 / 240 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Superior vena cava syndrome			
subjects affected / exposed	1 / 61 (1.64%)	0 / 179 (0.00%)	1 / 240 (0.42%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Superior vena cava stenosis			
subjects affected / exposed	1 / 61 (1.64%)	0 / 179 (0.00%)	1 / 240 (0.42%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Bone graft			
subjects affected / exposed	0 / 61 (0.00%)	1 / 179 (0.56%)	1 / 240 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Carpal tunnel decompression			
subjects affected / exposed	0 / 61 (0.00%)	1 / 179 (0.56%)	1 / 240 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Central venous catheter removal			
subjects affected / exposed	4 / 61 (6.56%)	0 / 179 (0.00%)	4 / 240 (1.67%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Central venous catheterisation			

subjects affected / exposed	2 / 61 (3.28%)	1 / 179 (0.56%)	3 / 240 (1.25%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Circumcision			
subjects affected / exposed	1 / 61 (1.64%)	0 / 179 (0.00%)	1 / 240 (0.42%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint arthroplasty			
subjects affected / exposed	0 / 61 (0.00%)	1 / 179 (0.56%)	1 / 240 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Knee arthroplasty			
subjects affected / exposed	0 / 61 (0.00%)	2 / 179 (1.12%)	2 / 240 (0.83%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Device breakage			
subjects affected / exposed	1 / 61 (1.64%)	0 / 179 (0.00%)	1 / 240 (0.42%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device dislocation			
subjects affected / exposed	0 / 61 (0.00%)	1 / 179 (0.56%)	1 / 240 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infusion site mass			
subjects affected / exposed	0 / 61 (0.00%)	1 / 179 (0.56%)	1 / 240 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	1 / 61 (1.64%)	0 / 179 (0.00%)	1 / 240 (0.42%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			

Epistaxis			
subjects affected / exposed	1 / 61 (1.64%)	1 / 179 (0.56%)	2 / 240 (0.83%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nasal polyps			
subjects affected / exposed	0 / 61 (0.00%)	1 / 179 (0.56%)	1 / 240 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 61 (0.00%)	1 / 179 (0.56%)	1 / 240 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Body temperature increased			
subjects affected / exposed	1 / 61 (1.64%)	0 / 179 (0.00%)	1 / 240 (0.42%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nuclear magnetic resonance imaging abnormal			
subjects affected / exposed	1 / 61 (1.64%)	0 / 179 (0.00%)	1 / 240 (0.42%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Accident			
subjects affected / exposed	0 / 61 (0.00%)	1 / 179 (0.56%)	1 / 240 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	6 / 61 (9.84%)	0 / 179 (0.00%)	6 / 240 (2.50%)
occurrences causally related to treatment / all	0 / 7	0 / 0	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Forearm fracture			

subjects affected / exposed	2 / 61 (3.28%)	0 / 179 (0.00%)	2 / 240 (0.83%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Head injury			
subjects affected / exposed	6 / 61 (9.84%)	1 / 179 (0.56%)	7 / 240 (2.92%)
occurrences causally related to treatment / all	0 / 6	0 / 1	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury			
subjects affected / exposed	0 / 61 (0.00%)	1 / 179 (0.56%)	1 / 240 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint dislocation			
subjects affected / exposed	0 / 61 (0.00%)	1 / 179 (0.56%)	1 / 240 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Periprosthetic fracture			
subjects affected / exposed	0 / 61 (0.00%)	1 / 179 (0.56%)	1 / 240 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skull fracture			
subjects affected / exposed	1 / 61 (1.64%)	0 / 179 (0.00%)	1 / 240 (0.42%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Toxicity to various agents			
subjects affected / exposed	0 / 61 (0.00%)	1 / 179 (0.56%)	1 / 240 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transplant failure			
subjects affected / exposed	0 / 61 (0.00%)	1 / 179 (0.56%)	1 / 240 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Traumatic haematoma			

subjects affected / exposed	0 / 61 (0.00%)	2 / 179 (1.12%)	2 / 240 (0.83%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Traumatic haemorrhage			
subjects affected / exposed	1 / 61 (1.64%)	0 / 179 (0.00%)	1 / 240 (0.42%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 61 (0.00%)	1 / 179 (0.56%)	1 / 240 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina pectoris			
subjects affected / exposed	0 / 61 (0.00%)	1 / 179 (0.56%)	1 / 240 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	0 / 61 (0.00%)	1 / 179 (0.56%)	1 / 240 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cubital tunnel syndrome			
subjects affected / exposed	0 / 61 (0.00%)	1 / 179 (0.56%)	1 / 240 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	1 / 61 (1.64%)	0 / 179 (0.00%)	1 / 240 (0.42%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydrocephalus			
subjects affected / exposed	0 / 61 (0.00%)	1 / 179 (0.56%)	1 / 240 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nerve compression			

subjects affected / exposed	0 / 61 (0.00%)	1 / 179 (0.56%)	1 / 240 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 61 (0.00%)	1 / 179 (0.56%)	1 / 240 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	0 / 61 (0.00%)	1 / 179 (0.56%)	1 / 240 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Food poisoning			
subjects affected / exposed	0 / 61 (0.00%)	1 / 179 (0.56%)	1 / 240 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis haemorrhagic			
subjects affected / exposed	0 / 61 (0.00%)	1 / 179 (0.56%)	1 / 240 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal haemorrhage			
subjects affected / exposed	0 / 61 (0.00%)	1 / 179 (0.56%)	1 / 240 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tooth impacted			
subjects affected / exposed	0 / 61 (0.00%)	1 / 179 (0.56%)	1 / 240 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Varices oesophageal			
subjects affected / exposed	0 / 61 (0.00%)	1 / 179 (0.56%)	1 / 240 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			

subjects affected / exposed	0 / 61 (0.00%)	1 / 179 (0.56%)	1 / 240 (0.42%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Biliary colic			
subjects affected / exposed	0 / 61 (0.00%)	1 / 179 (0.56%)	1 / 240 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholangitis acute			
subjects affected / exposed	0 / 61 (0.00%)	1 / 179 (0.56%)	1 / 240 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Haemorrhage subcutaneous			
subjects affected / exposed	0 / 61 (0.00%)	1 / 179 (0.56%)	1 / 240 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urticaria			
subjects affected / exposed	1 / 61 (1.64%)	0 / 179 (0.00%)	1 / 240 (0.42%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Calculus ureteric			
subjects affected / exposed	0 / 61 (0.00%)	1 / 179 (0.56%)	1 / 240 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematuria			
subjects affected / exposed	1 / 61 (1.64%)	0 / 179 (0.00%)	1 / 240 (0.42%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrolithiasis			
subjects affected / exposed	0 / 61 (0.00%)	1 / 179 (0.56%)	1 / 240 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Renal impairment			
subjects affected / exposed	0 / 61 (0.00%)	1 / 179 (0.56%)	1 / 240 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthropathy			
subjects affected / exposed	0 / 61 (0.00%)	2 / 179 (1.12%)	2 / 240 (0.83%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemarthrosis			
subjects affected / exposed	2 / 61 (3.28%)	3 / 179 (1.68%)	5 / 240 (2.08%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemophilic arthropathy			
subjects affected / exposed	0 / 61 (0.00%)	11 / 179 (6.15%)	11 / 240 (4.58%)
occurrences causally related to treatment / all	0 / 0	0 / 12	0 / 12
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc disorder			
subjects affected / exposed	0 / 61 (0.00%)	1 / 179 (0.56%)	1 / 240 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			
subjects affected / exposed	0 / 61 (0.00%)	1 / 179 (0.56%)	1 / 240 (0.42%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal osteoarthritis			
subjects affected / exposed	0 / 61 (0.00%)	2 / 179 (1.12%)	2 / 240 (0.83%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Synovitis			
subjects affected / exposed	0 / 61 (0.00%)	1 / 179 (0.56%)	1 / 240 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Infections and infestations Appendicitis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 61 (0.00%) 0 / 0 0 / 0	1 / 179 (0.56%) 0 / 1 0 / 0	1 / 240 (0.42%) 0 / 1 0 / 0
Cellulitis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 61 (1.64%) 0 / 1 0 / 0	0 / 179 (0.00%) 0 / 0 0 / 0	1 / 240 (0.42%) 0 / 1 0 / 0
Chronic sinusitis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 61 (0.00%) 0 / 0 0 / 0	1 / 179 (0.56%) 0 / 1 0 / 0	1 / 240 (0.42%) 0 / 1 0 / 0
Device related infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 61 (0.00%) 0 / 0 0 / 0	1 / 179 (0.56%) 0 / 1 0 / 0	1 / 240 (0.42%) 0 / 1 0 / 0
Hepatitis C subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 61 (0.00%) 0 / 0 0 / 0	2 / 179 (1.12%) 0 / 2 0 / 0	2 / 240 (0.83%) 0 / 2 0 / 0
Infectious pleural effusion subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 61 (0.00%) 0 / 0 0 / 0	1 / 179 (0.56%) 0 / 1 0 / 0	1 / 240 (0.42%) 0 / 1 0 / 0
Influenza subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 61 (0.00%) 0 / 0 0 / 0	1 / 179 (0.56%) 0 / 1 0 / 0	1 / 240 (0.42%) 0 / 1 0 / 0
Pericoronitis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 61 (0.00%) 0 / 0 0 / 0	1 / 179 (0.56%) 0 / 1 0 / 0	1 / 240 (0.42%) 0 / 1 0 / 0
Pneumonia			

subjects affected / exposed	1 / 61 (1.64%)	1 / 179 (0.56%)	2 / 240 (0.83%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinusitis			
subjects affected / exposed	1 / 61 (1.64%)	0 / 179 (0.00%)	1 / 240 (0.42%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal bacteraemia			
subjects affected / exposed	0 / 61 (0.00%)	1 / 179 (0.56%)	1 / 240 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal infection			
subjects affected / exposed	1 / 61 (1.64%)	0 / 179 (0.00%)	1 / 240 (0.42%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Streptococcal sepsis			
subjects affected / exposed	0 / 61 (0.00%)	1 / 179 (0.56%)	1 / 240 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subcutaneous abscess			
subjects affected / exposed	0 / 61 (0.00%)	1 / 179 (0.56%)	1 / 240 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tooth abscess			
subjects affected / exposed	1 / 61 (1.64%)	0 / 179 (0.00%)	1 / 240 (0.42%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	1 / 61 (1.64%)	0 / 179 (0.00%)	1 / 240 (0.42%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral infection			

subjects affected / exposed	1 / 61 (1.64%)	0 / 179 (0.00%)	1 / 240 (0.42%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 61 (1.64%)	0 / 179 (0.00%)	1 / 240 (0.42%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 61 (0.00%)	1 / 179 (0.56%)	1 / 240 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	rFVIIIFc [Subjects from Study 8HA02PED]	rFVIIIFc [Subjects from studies 997HA301/997HA307/997HA309]	Overall rFVIIIFc
Total subjects affected by non-serious adverse events			
subjects affected / exposed	49 / 61 (80.33%)	110 / 179 (61.45%)	159 / 240 (66.25%)
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	11 / 61 (18.03%)	14 / 179 (7.82%)	25 / 240 (10.42%)
occurrences (all)	22	14	36
Laceration			
subjects affected / exposed	1 / 61 (1.64%)	15 / 179 (8.38%)	16 / 240 (6.67%)
occurrences (all)	1	19	20
Limb injury			
subjects affected / exposed	4 / 61 (6.56%)	10 / 179 (5.59%)	14 / 240 (5.83%)
occurrences (all)	4	10	14
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 61 (0.00%)	9 / 179 (5.03%)	9 / 240 (3.75%)
occurrences (all)	0	9	9
Nervous system disorders			

Headache subjects affected / exposed occurrences (all)	10 / 61 (16.39%) 19	15 / 179 (8.38%) 18	25 / 240 (10.42%) 37
General disorders and administration site conditions Pyrexia subjects affected / exposed occurrences (all)	6 / 61 (9.84%) 8	5 / 179 (2.79%) 6	11 / 240 (4.58%) 14
Immune system disorders Seasonal allergy subjects affected / exposed occurrences (all)	9 / 61 (14.75%) 12	5 / 179 (2.79%) 5	14 / 240 (5.83%) 17
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	5 / 61 (8.20%) 5 2 / 61 (3.28%) 2 8 / 61 (13.11%) 9	16 / 179 (8.94%) 17 8 / 179 (4.47%) 8 6 / 179 (3.35%) 6	21 / 240 (8.75%) 22 10 / 240 (4.17%) 10 14 / 240 (5.83%) 15
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	8 / 61 (13.11%) 9	9 / 179 (5.03%) 10	17 / 240 (7.08%) 19
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Pain in extremity subjects affected / exposed occurrences (all)	7 / 61 (11.48%) 11 5 / 61 (8.20%) 6	20 / 179 (11.17%) 26 11 / 179 (6.15%) 12	27 / 240 (11.25%) 37 16 / 240 (6.67%) 18
Infections and infestations Gastroenteritis viral subjects affected / exposed occurrences (all)	6 / 61 (9.84%) 8	2 / 179 (1.12%) 2	8 / 240 (3.33%) 10

Influenza			
subjects affected / exposed	3 / 61 (4.92%)	14 / 179 (7.82%)	17 / 240 (7.08%)
occurrences (all)	3	16	19
Nasopharyngitis			
subjects affected / exposed	6 / 61 (9.84%)	37 / 179 (20.67%)	43 / 240 (17.92%)
occurrences (all)	13	61	74
Pharyngitis			
subjects affected / exposed	4 / 61 (6.56%)	2 / 179 (1.12%)	6 / 240 (2.50%)
occurrences (all)	9	2	11
Tonsillitis			
subjects affected / exposed	12 / 61 (19.67%)	2 / 179 (1.12%)	14 / 240 (5.83%)
occurrences (all)	14	2	16
Upper respiratory tract infection			
subjects affected / exposed	13 / 61 (21.31%)	19 / 179 (10.61%)	32 / 240 (13.33%)
occurrences (all)	34	27	61
Viral infection			
subjects affected / exposed	4 / 61 (6.56%)	3 / 179 (1.68%)	7 / 240 (2.92%)
occurrences (all)	4	4	8
Viral upper respiratory tract infection			
subjects affected / exposed	7 / 61 (11.48%)	0 / 179 (0.00%)	7 / 240 (2.92%)
occurrences (all)	22	0	22

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 August 2013	This amendment was commenced to allow interim analyses of safety and/or efficacy data to support regulatory submissions and planning of future clinical studies, mandate tailored or personalized prophylaxis for pediatric subjects <12 years of age, update the maximum dose and minimum interval for prophylaxis dosing in pediatric subjects, mandate that subjects first dosed with rFVIIIFc when <12 years of age would be followed to at least 100 EDs and update the statistical section.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported