Clinical trial results:
An Open-Label, Multicenter Evaluation of Safety, Pharmacokinetics, and Efficacy of Recombinant Coagulation Factor VIII Fc Fusion Protein, BIIB031, in the Prevention and Treatment of Bleeding Episodes in Pediatric Subjects With Hemophilia A

Summary

EudraCT number	2011-003073-28
Trial protocol	GB IE NL PL
Global end of trial date	05 December 2013

Results information

Result version number	v2 (current)
This version publication date	05 February 2016
First version publication date	24 January 2015
Version creation reason	• Correction of full data set Correction to "n" required for a reported endpoint.

Trial information

Trial identification

Sponsor protocol code	8HA02PED

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01458106
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Biogen
Sponsor organisation address	225 Binney Street , Cambridge, United States, 02142
Public contact	Biogen Study Medical Director, Biogen, clinicaltrials@biogen.com
Scientific contact	Biogen Study Medical Director, Biogen, clinicaltrials@biogen.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-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	05 December 2013
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	05 December 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study is to evaluate the safety of recombinant coagulation factor VIII FC fusion protein (rFVIIIFc) in previously treated pediatric subjects with hemophilia A. Secondary objectives of this study in this study population are as follows: to evaluate the efficacy of rFVIIIFc for prevention and treatment of bleeding episodes; to evaluate and assess the pharmacokinetics (PK) of rFVIIIFc; and to evaluate rFVIIIFc consumption for prevention and treatment of bleeding episodes.

Protection of trial subjects:

Only subjects who met the eligibility criteria were randomized into the trial.

The first dose of rFVIIIFc was administered under medical supervision in the clinic and subjects were tested for inhibitor formation at screening and at each clinic visit prior to dosing. Medications and resuscitation equipment for the emergency management of anaphylactic reactions were available in the room where the subject's first injection was performed. In addition, the subject was provided with specific instructions by the Investigator on what to do if such an event occurred while at home, including how to seek emergency medical treatment.

In addition to scheduled clinic visits, at least one telephone call was planned midway between visits for study site staff to check on each subject’s status.

Background therapy: -	
Evidence for comparator: -	
Actual start date of recruitment	01 November 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 1
Country: Number of subjects enrolled	Poland: 3
Country: Number of subjects enrolled	United Kingdom: 20
Country: Number of subjects enrolled	Ireland: 8
Country: Number of subjects enrolled	Australia: 6
Country: Number of subjects enrolled	Hong Kong: 2
Country: Number of subjects enrolled	South Africa: 11
Country: Number of subjects enrolled	United States: 20
Worldwide total number of subjects	71
EEA total number of subjects	32

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)	1
Children (2-11 years)	70
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Subject eligibility for the study was determined up to 8 weeks prior to the Baseline Visit. This period could be extended if the subject had a bleeding episode requiring coagulation factor VIII (FVIII) treatment within 5 days prior to the first dose of prestudy FVIII or rFVIIIFc in cases where prestudy FVIII PK assessment was exempted.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Subjects < 6 Years Old

Arm description:

PK subgroup: After a Washout Period of ≥ 72 hours, at the Baseline Visit (28 ± 7 days prior to Day 1), subjects receive a single IV injection of prestudy FVIII over 5 (± 2) minutes at a dose of 50 IU/kg, rounded up to the nearest 250 IU increment, for a PK assessment. Following a second Washout Period of ≥ 72 hours, subjects receive a single IV injection of rFVIIIFc over 5 (± 2) minutes at a dose of 50 IU/kg for PK assessment. The first prophylactic dose of rFVIIIFc is administered at a starting dose of 25 IU/kg IV injection on Day 1 and 50 IU/kg on Day 4. Dose increases to a maximum of 80 IU/kg, and frequency of administration to a minimum interval of once every 2 days, are allowed as indicated.

Non-PK subgroup: On Day 1, a first prophylactic dose of rFVIIIFc of 25 IU/kg IV injection is given, followed by a dose of 50 IU/kg on Day 4. Dose increases to a maximum of 80 IU/kg, and frequency of administration to a minimum interval of once every 2 days, are allowed as indicated.

Arm type	Experimental
Investigational medicinal product name	Recombinant FVIIIFc
Investigational medicinal product code	
Other name	BIIB031, ELOCTATE, rFVIIIFc, antihemophilic factor (recombinant) Fc fusion protein, recombinant coagulation factor VIII Fc fusion protein, efmoroctocog alfa
Pharmaceutical forms	Powder and solvent for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Study site staff members were instructed to refer to the Directions for Handling and Administration Manual located in the Pharmacy Manual for specific instructions on the handling, preparation, administration, and disposal of the study treatment. Subjects were instructed to refer to the Information for Patients for instruction on the preparation and administration of rFVIIIFc. Vials of rFVIIIFc were combined as needed, based on the actual labeled potency to achieve the subject's calculated dose. Partial vial use was allowed, in order to achieve the calculated dose.

Investigational medicinal product name	Factor VIII
Investigational medicinal product code	
Other name	FVIII
Pharmaceutical forms	Powder and solvent for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Prestudy treatment was any current FVIII treatment prescribed by the Investigator. Prestudy drug for the PK assessment was prepared and administered according to the manufacturer’s prescribing information. Vials of prestudy FVIII were combined as needed, based on the nominal labeled potency (e.

g., 250 IU, 500 IU, and 1000 IU), to achieve the participant's calculated dose.

Arm title	Subjects 6 to < 12 Years Old

Arm description:

PK subgroup: After a Washout Period of ≥ 72 hours, at the Baseline Visit (28 ± 7 days prior to Day 1), subjects receive a single IV injection of prestudy FVIII over 5 (± 2) minutes at a dose of 50 IU/kg, rounded up to the nearest 250 IU increment, for a PK assessment. Following a second Washout Period of ≥ 72 hours, subjects receive a single IV injection of rFVIIIFc over 5 (± 2) minutes at a dose of 50 IU/kg for PK assessment. The first prophylactic dose of rFVIIIFc is administered at a starting dose of 25 IU/kg IV injection on Day 1 and 50 IU/kg on Day 4. Dose increases to a maximum of 80 IU/kg, and frequency of administration to a minimum interval of once every 2 days, are allowed as indicated.

Non-PK subgroup: On Day 1, a first prophylactic dose of rFVIIIFc of 25 IU/kg IV injection is given, followed by a dose of 50 IU/kg on Day 4. Dose increases to a maximum of 80 IU/kg, and frequency of administration to a minimum interval of once every 2 days, are allowed as indicated.

Arm type	Experimental
Investigational medicinal product name	Recombinant FVIIIFc
Investigational medicinal product code	
Other name	BIIB031, ELOCTATE, rFVIIIFc, antihemophilic factor (recombinant) Fc fusion protein, recombinant coagulation factor VIII Fc fusion protein, efmoroctocog alfa
Pharmaceutical forms	Powder and solvent for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Study site staff members were instructed to refer to the Directions for Handling and Administration Manual located in the Pharmacy Manual for specific instructions on the handling, preparation, administration, and disposal of the study treatment. Subjects were instructed to refer to the Information for Patients for instruction on the preparation and administration of rFVIIIFc. Vials of rFVIIIFc were combined as needed, based on the actual labeled potency to achieve the subject's calculated dose. Partial vial use was allowed, in order to achieve the calculated dose.

Investigational medicinal product name	Factor VIII
Investigational medicinal product code	
Other name	FVIII
Pharmaceutical forms	Powder and solvent for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Prestudy treatment was any current FVIII treatment prescribed by the Investigator. Prestudy drug for the PK assessment was prepared and administered according to the manufacturer’s prescribing information. Vials of prestudy FVIII were combined as needed, based on the nominal labeled potency (e.g., 250 IU, 500 IU, and 1000 IU), to achieve the participant's calculated dose.

Number of subjects in period 1	Subjects < 6 Years Old	Subjects 6 to < 12 Years Old
Started	36	35
PK Subgroup	25 [1]	35
Non-PK Subgroup	11 [2]	0 [3]
Completed	33	34
Not completed	3	1
Consent withdrawn by subject	2	-

Withdrawn Per Protocol	-	1
Pre-rFVIIIFc Adverse Event	1	-

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Number of subjects participating in the Subgroup.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Number of subjects participating in the Subgroup.

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Number of subjects participating in the Subgroup.

Baseline characteristics

Reporting groups	
Reporting group title	Subjects < 6 Years Old

Reporting group description:

PK subgroup: After a Washout Period of ≥ 72 hours, at the Baseline Visit (28 ± 7 days prior to Day 1), subjects receive a single IV injection of prestudy FVIII over 5 (± 2) minutes at a dose of 50 IU/kg, rounded up to the nearest 250 IU increment, for a PK assessment. Following a second Washout Period of ≥ 72 hours, subjects receive a single IV injection of rFVIIIFc over 5 (± 2) minutes at a dose of 50 IU/kg for PK assessment. The first prophylactic dose of rFVIIIFc is administered at a starting dose of 25 IU/kg IV injection on Day 1 and 50 IU/kg on Day 4. Dose increases to a maximum of 80 IU/kg, and frequency of administration to a minimum interval of once every 2 days, are allowed as indicated.

Non-PK subgroup: On Day 1, a first prophylactic dose of rFVIIIFc of 25 IU/kg IV injection is given, followed by a dose of 50 IU/kg on Day 4. Dose increases to a maximum of 80 IU/kg, and frequency of administration to a minimum interval of once every 2 days, are allowed as indicated.

Reporting group title	Subjects 6 to < 12 Years Old

Reporting group description:

PK subgroup: After a Washout Period of ≥ 72 hours, at the Baseline Visit (28 ± 7 days prior to Day 1), subjects receive a single IV injection of prestudy FVIII over 5 (± 2) minutes at a dose of 50 IU/kg, rounded up to the nearest 250 IU increment, for a PK assessment. Following a second Washout Period of ≥ 72 hours, subjects receive a single IV injection of rFVIIIFc over 5 (± 2) minutes at a dose of 50 IU/kg for PK assessment. The first prophylactic dose of rFVIIIFc is administered at a starting dose of 25 IU/kg IV injection on Day 1 and 50 IU/kg on Day 4. Dose increases to a maximum of 80 IU/kg, and frequency of administration to a minimum interval of once every 2 days, are allowed as indicated.

Non-PK subgroup: On Day 1, a first prophylactic dose of rFVIIIFc of 25 IU/kg IV injection is given, followed by a dose of 50 IU/kg on Day 4. Dose increases to a maximum of 80 IU/kg, and frequency of administration to a minimum interval of once every 2 days, are allowed as indicated.

Reporting group values	Subjects < 6 Years Old	Subjects 6 to < 12 Years Old	Total
Number of subjects	36	35	71
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)	1	0	1
Children (2-11 years)	35	35	70
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
median	4	8	
full range (min-max)	1 to 5	6 to 11	-
Gender categorical Units: Subjects			
Female	0	0	0
Male	36	35	71

End points

End points reporting groups

Reporting group title	Subjects < 6 Years Old

Reporting group description:

PK subgroup: After a Washout Period of ≥ 72 hours, at the Baseline Visit (28 ± 7 days prior to Day 1), subjects receive a single IV injection of prestudy FVIII over 5 (± 2) minutes at a dose of 50 IU/kg, rounded up to the nearest 250 IU increment, for a PK assessment. Following a second Washout Period of ≥ 72 hours, subjects receive a single IV injection of rFVIIIFc over 5 (± 2) minutes at a dose of 50 IU/kg for PK assessment. The first prophylactic dose of rFVIIIFc is administered at a starting dose of 25 IU/kg IV injection on Day 1 and 50 IU/kg on Day 4. Dose increases to a maximum of 80 IU/kg, and frequency of administration to a minimum interval of once every 2 days, are allowed as indicated.

Non-PK subgroup: On Day 1, a first prophylactic dose of rFVIIIFc of 25 IU/kg IV injection is given, followed by a dose of 50 IU/kg on Day 4. Dose increases to a maximum of 80 IU/kg, and frequency of administration to a minimum interval of once every 2 days, are allowed as indicated.

Reporting group title	Subjects 6 to < 12 Years Old

Reporting group description:

PK subgroup: After a Washout Period of ≥ 72 hours, at the Baseline Visit (28 ± 7 days prior to Day 1), subjects receive a single IV injection of prestudy FVIII over 5 (± 2) minutes at a dose of 50 IU/kg, rounded up to the nearest 250 IU increment, for a PK assessment. Following a second Washout Period of ≥ 72 hours, subjects receive a single IV injection of rFVIIIFc over 5 (± 2) minutes at a dose of 50 IU/kg for PK assessment. The first prophylactic dose of rFVIIIFc is administered at a starting dose of 25 IU/kg IV injection on Day 1 and 50 IU/kg on Day 4. Dose increases to a maximum of 80 IU/kg, and frequency of administration to a minimum interval of once every 2 days, are allowed as indicated.

Non-PK subgroup: On Day 1, a first prophylactic dose of rFVIIIFc of 25 IU/kg IV injection is given, followed by a dose of 50 IU/kg on Day 4. Dose increases to a maximum of 80 IU/kg, and frequency of administration to a minimum interval of once every 2 days, are allowed as indicated.

Primary: Occurrence of FVIII Inhibitor Development

End point title	Occurrence of FVIII Inhibitor Development[1]

End point description:

An inhibitor test result ≥0.6 Bethesda units (BU)/mL, confirmed on 2 separate samples drawn 2 to 4 weeks apart, was considered positive. Both tests were to be performed by the central laboratory using the Nijmegen-modified Bethesda Assay. Incidences were summarized for any positive inhibitor for subjects with ≥50 exposure days (EDs) to rFVIIIFc. In addition, the incidence for all subjects, regardless of their EDs to rFVIIIFc, was also summarized. An exact 95% CI for the proportion of subjects with a confirmed inhibitor was calculated using the Clopper-Pearson method for a binomial proportion. Safety Analysis Set: subjects who received at least 1 dose of prestudy FVIII, or at least 1 dose of rFVIIIFc.

End point type	Primary

End point timeframe:

Up to Week 26 +/- 7 days, or up to 50 exposure days (EDs) if reached prior to Week 26

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: The incidence of confirmed inhibitor formation from the central laboratory was summarized for each age cohort and a 95% CI was calculated for each incidence for this endpoint, as presented in this data table. No further statistical analyses were planned.

End point values	Subjects < 6 Years Old	Subjects 6 to < 12 Years Old		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36[2]	35[3]		
Units: Percentage of Subjects				
number (confidence interval 95%)				
Subjects with ≥50 EDs; n=27, 34	0 (0 to 12.77)	0 (0 to 10.28)		
All subjects; n=36, 35	0 (0 to 9.74)	0 (0 to 10)		

Notes:

[2] - Safety Analysis Set; n=subjects with given number of exposure days who had a valid inhibitor test.

[3] - Safety Analysis Set; n=subjects with given number of exposure days who had a valid inhibitor test.

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized Bleeding Rate

End point title	Annualized Bleeding Rate

End point description:

Annualized bleeding rate=(number of bleeding episodes during the efficacy period/total number of days during the efficacy period)*365.25. The efficacy period begins with the first prophylactic dose of rFVIIIFc and ends with the last dose (for prophylaxis or a bleed); surgery/rehabilitation periods and PK evaluation periods are not included. A bleeding episode started from the first sign of a bleed and ended ≤72 hours after the last treatment for the bleed, within which any symptoms of bleeding at the same location or injections ≤72 hours apart were considered the same bleeding episode. Any injection to treat the bleeding episode taken >72 hours after the preceding one was considered the first injection to treat a new bleeding episode at the same location. Any bleeding at a different location was considered a separate bleeding episode, regardless of time from last injection. Full Analysis Set: subjects who received ≥1 dose of rFVIIIFc.

End point type	Secondary

End point timeframe:

Up to Week 26 +/- 7 days (efficacy period as defined in description)

End point values	Subjects < 6 Years Old	Subjects 6 to < 12 Years Old		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35[4]	34[5]		
Units: bleeding episodes per subject per year				
median (inter-quartile range (Q1-Q3))	0 (0 to 3.96)	2.01 (0 to 4.04)		

Notes:

[4] - Full Analysis Set; based on the number of subjects whose efficacy period was ≥1 day in duration.

[5] - Full Analysis Set; based on the number of subjects whose efficacy period was ≥1 day in duration.

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized Joint Bleeding Rate (Spontaneous)

End point title	Annualized Joint Bleeding Rate (Spontaneous)

End point description:

Annualized bleeding rate for spontaneous joint bleed=(number of bleeding episodes meeting those

criteria during the efficacy period/total number of days during the efficacy period)*365.25. The efficacy period begins with the first prophylactic dose of rFVIIIFc and ends with the last dose (for prophylaxis or a bleed); surgery/rehabilitation periods and PK evaluation periods are not included. A bleeding episode started from the first sign of a bleed and ended ≤72 hours after the last treatment for the bleed, within which any symptoms of bleeding at the same location or injections ≤72 hours apart were considered the same bleeding episode. Any injection to treat the bleeding episode taken >72 hours after the preceding one was considered the first injection to treat a new bleeding episode at the same location. Any bleeding at a different location was considered a separate bleeding episode, regardless of time from last injection. Full Analysis Set: subjects who received ≥1 dose of rFVIIIFc.

End point type	Secondary

End point timeframe:

Up to Week 26 +/- 7 days (efficacy period as defined in description)

End point values	Subjects < 6 Years Old	Subjects 6 to < 12 Years Old		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35[6]	34[7]		
Units: bleeding episodes per subject per year				
median (inter-quartile range (Q1-Q3))	0 (0 to 0)	0 (0 to 0)		

Notes:

[6] - Full Analysis Set; based on the number of participants whose efficacy period was ≥1 day in duration.
[7] - Full Analysis Set; based on the number of participants whose efficacy period was ≥1 day in duration.

Statistical analyses

No statistical analyses for this end point

Secondary: Subject Assessment of Response to Injections to Treat a Bleeding Episode

End point title	Subject Assessment of Response to Injections to Treat a Bleeding Episode

End point description:

Subject's assessment (provided by the caregiver) of the response to the first rFVIIIFc injection for each bleeding episode. Percentages were based on the number of first injections for which a response was provided, using the following 4-point scale: excellent=abrupt pain relief and/or improvement in signs of bleeding within approximately 8 hours after the initial injection; good=definite pain relief and/or improvement in signs of bleeding within approximately 8 hours after a single injection, but possibly requiring more than one injection after 24 to 48 hours for complete resolution; moderate=probable or slight beneficial effect within approximately 8 hours after the initial injection and requiring more than one injection; no response=no improvement, or condition worsened, within approximately 8 hours after the initial injection. Full Analysis Set: subjects who received at least 1 dose of rFVIIIFc and had a bleeding episode.

End point type	Secondary

End point timeframe:

Up to Week 26 +/- 7 days

End point values	Subjects < 6 Years Old	Subjects 6 to < 12 Years Old		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17[8]	20[9]		
Units: percent of 1st injections w/ a response				
number (not applicable)				
Excellent or Good	91.4	93.5		
Excellent	65.7	47.8		
Good	25.7	45.7		
Moderate	8.6	2.2		
No Response	0	4.3		

Notes:

[8] - subjects with a non-evaluable bleed are counted in n's but not percentages; total # of injections=35

[9] - subjects with a non-evaluable bleed are counted in n's but not percentages; total # of injections=46

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized rFVIIIFc Consumption Per Subject

End point title	Annualized rFVIIIFc Consumption Per Subject

End point description:

Consumption is calculated for the efficacy period. The efficacy period begins with the first prophylactic dose of rFVIIIFc and ends with the last dose (for prophylaxis or a bleed). Surgery/rehabilitation periods and PK evaluation periods are not included in the efficacy period. Annualized consumption = (total IU/kg of study treatment received during the efficacy period/total number of days during the efficacy period)*365.25. Consumption was calculated overall for all subjects and for the last 3 months (91 days) on study, counted backwards from the end of the efficacy period, for subjects with at least 24 weeks on study. Full Analysis Set: subjects who received at least 1 dose of rFVIIIFc. 'Overall' = number of subjects with evaluable data in the efficacy period overall; 'Last 3 months on Study' = number of subjects with ≥24 weeks on study.

End point type	Secondary

End point timeframe:

Up to Week 26 +/- 7 days (efficacy period as defined in description)

End point values	Subjects < 6 Years Old	Subjects 6 to < 12 Years Old		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35[10]	34[11]		
Units: IU/kg rFVIIIFc per subject per year				
arithmetic mean (standard deviation)				
Overall (n=35, 34)	5331.8 (± 1106.68)	4973.5 (± 976.06)		
Last 3 months on study (n=26, 33)	5562.1 (± 1474.42)	5092.6 (± 1013.01)		

Notes:

[10] - Full Analysis Set;n=subjects with evaluable data in the efficacy period overall or ≥24 wks on study.

[11] - Full Analysis Set;n=subjects with evaluable data in the efficacy period overall or ≥24 wks on study.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Days From Last Treatment Injection to a Spontaneous Bleeding Episode

End point title	Number of Days From Last Treatment Injection to a Spontaneous Bleeding Episode

End point description:

The number of days from the last prophylaxis injection to the onset of a new spontaneous bleeding episode, analyzed across all evaluable bleeding episodes per subject and per episode, based on the efficacy period. Evaluable bleeding episodes are those for which both a date and time are available for both the onset of the bleeding episode and the previous prophylactic injection. The efficacy period begins with the first prophylactic dose of rFVIIIFc and ends with the last dose (for prophylaxis or a bleed). Surgery/rehabilitation periods and PK evaluation periods are not included in the efficacy period. For 'Per subject' values, the number of days from the last prophylactic injection to a spontaneous bleeding episode is averaged across all evaluable spontaneous bleeding episodes per subject. Full Analysis Set: subjects who received at least 1 dose of rFVIIIFc; number of subjects and number of episodes were determined for subjects with at least 1 evaluable spontaneous bleeding episode.

End point type	Secondary

End point timeframe:

Up to Week 26 +/- 7 days (efficacy period as defined in description)

End point values	Subjects < 6 Years Old	Subjects 6 to < 12 Years Old		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8[12]	7[13]		
Units: days				
median (inter-quartile range (Q1-Q3))				
Per Subject	2.17 (1.51 to 2.84)	2.55 (1.58 to 3.04)		
Per Spontaneous Bleeding Episode	2.16 (1.35 to 2.87)	2.77 (1.58 to 3.29)		

Notes:

[12] - Full Analysis Set; the number of evaluable spontaneous bleeding episodes analyzed was 17.

[13] - Full Analysis Set; the number of evaluable spontaneous bleeding episodes analyzed was 19.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Injections Required for Resolution of a Bleeding Episode

End point title	Number of Injections Required for Resolution of a Bleeding Episode

End point description:

The number of injections required to resolve a bleeding episode per subject and per episode, based on the efficacy period. The efficacy period begins with the first prophylactic dose of rFVIIIFc and ends with the last dose (for prophylaxis or a bleed). Surgery/rehabilitation periods and PK evaluation periods are not included in the efficacy period. All injections given from the initial sign of a bleed, until the last date/time within the bleed window are counted. The resolution of a bleed is defined as no sign of bleeding following injection for the bleed. For 'Per subject' values, the number of injections required to resolve each bleed is averaged across all bleeding episodes per subject. Full Analysis Set: subjects who received at least 1 dose of rFVIIIFc; number of subjects and number of episodes were determined for subjects with at least 1 evaluable bleeding episode.

End point type	Secondary

End point timeframe:

Up to Week 26 +/- 7 days (efficacy period as defined in description)

End point values	Subjects < 6 Years Old	Subjects 6 to < 12 Years Old		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17[14]	20[15]		
Units: injections				
median (inter-quartile range (Q1-Q3))				
Per Subject	1 (1 to 1.2)	1 (1 to 1.2)		
Per Bleeding Episode	1 (1 to 1)	1 (1 to 1)		

Notes:

[14] - Full Analysis Set; the number of bleeding episodes analyzed was 38.

[15] - Full Analysis Set; the number of bleeding episodes analyzed was 48.

Statistical analyses

No statistical analyses for this end point

Secondary: Total Dose Required for Resolution of a Bleeding Episode

End point title	Total Dose Required for Resolution of a Bleeding Episode

End point description:

The total dose required to resolved a bleeding episode per participant and per episode, based on the efficacy period. The efficacy period begins with the first prophylactic dose of rFVIIIFc and ends with the last dose (for prophylaxis or a bleed). Surgery/rehabilitation periods and PK evaluation periods are not included in the efficacy period. For 'Per bleeding episode' values, for each bleeding episode, the total dose is the sum of the doses (IU/kg) administered across all injections given to treat that bleeding episode. For 'Per participant' values, the total dose (IU/kg) used to resolve each bleed is averaged across all bleeding episodes per participant. Full Analysis Set: subjects who received at least 1 dose of rFVIIIFc; number of subjects and number of episodes were determined for subjects who had complete information on the dose administered to treat a bleeding episode.

End point type	Secondary

End point timeframe:

Up to Week 26 +/- 7 days (efficacy period as defined in description)

End point values	Subjects < 6 Years Old	Subjects 6 to < 12 Years Old		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17[16]	20[17]		
Units: IU/kg				
median (full range (min-max))				
Per Subject	55.56 (22.6 to 150.7)	51.35 (20.1 to 152.3)		
Per Bleeding Epidose	56.4 (13.9 to 200)	53.49 (14 to 196.6)		

Notes:

[16] - Full Analysis Set; the number of bleeding episodes analyzed was 38.

[17] - Full Analysis Set; the number of bleeding episodes analyzed was 48.

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Plasma Activity (Cmax; One-stage Activated Partial Thromboplastin Time [aPTT] Clotting Assay)

End point title	Maximum Plasma Activity (Cmax; One-stage Activated Partial Thromboplastin Time [aPTT] Clotting Assay)

End point description:

Maximum plasma activity during a dosing interval for participants in the PK subgroup. The values for Cmax were adjusted to the nominal dose of 50 IU/kg. The 95% confidence interval on the geometric mean is based on the t-statistic back-transformed from the log scale. PK Analysis Set: All subjects in the PK subgroup with adequate PK data, defined as complete and evaluable PK samples through 72 hours after rFVIIIFc dosing. Complete means the availability of the 72-hour sample and at least enough other samples to allow for all the PK parameters to be estimated.

End point type	Secondary

End point timeframe:

Baseline (28 ±7 days prior to Day 1) Prestudy FVIII Dosing: predose; 30 ±5 min, 3 hours ±30 min, 24 ±3 hours, 48 ±4 hours post-dose. Day 1 (rFVIIIFc Dosing): predose; 30 ±5 min, 3 hours ±30 min, 24 ±3 hours, 48 ±4 hours, 72 ±7 hours post-dose

End point values	Subjects < 6 Years Old	Subjects 6 to < 12 Years Old		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23[18]	31[19]		
Units: IU/dL				
geometric mean (confidence interval 95%)	95.03 (89.23 to 101.21)	114.94 (102.13 to 129.35)		

Notes:

[18] - All subjects in the PK subgroup with adequate PK data

[19] - All subjects in the PK subgroup with adequate PK data

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Plasma Activity (Cmax; Two-stage Chromogenic Assay)

End point title	Maximum Plasma Activity (Cmax; Two-stage Chromogenic Assay)

End point description:

Maximum plasma activity during a dosing interval for participants in the PK subgroup. The values for Cmax were adjusted to the nominal dose of 50 IU/kg. The 95% confidence interval on the geometric mean is based on the t-statistic back-transformed from the log scale. PK Analysis Set: All subjects in the PK subgroup with adequate PK data, defined as complete and evaluable PK samples through 72 hours after rFVIIIFc dosing. Complete means the availability of the 72-hour sample and at least enough other samples to allow for all the PK parameters to be estimated.

End point type	Secondary

End point timeframe:

Baseline (28 ±7 days prior to Day 1) Prestudy FVIII Dosing: predose; 30 ±5 min, 3 hours ±30 min, 24 ±3 hours, 48 ±4 hours post-dose. Day 1 (rFVIIIFc Dosing): predose; 30 ±5 min, 3 hours ±30 min, 24 ±3 hours, 48 ±4 hours, 72 ±7 hours post-dose

End point values	Subjects < 6 Years Old	Subjects 6 to < 12 Years Old		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24[20]	27[21]		
Units: IU/dL				
geometric mean (confidence interval 95%)	94.11 (86.4 to 102.51)	103.8 (95.68 to 112.6)		

Notes:

[20] - All subjects in the PK subgroup with adequate PK data

[21] - All subjects in the PK subgroup with adequate PK data

Statistical analyses

No statistical analyses for this end point

Secondary: Elimination Half Life (t1/2; One-stage aPTT Clotting Assay)

End point title	Elimination Half Life (t1/2; One-stage aPTT Clotting Assay)

End point description:

Time required for the activity of the drug to reach half of its original value for participants in the PK subgroup. The 95% confidence interval on the geometric mean is based on the t-statistic back-transformed from the log scale. PK Analysis Set: All subjects in the PK subgroup with adequate PK data, defined as complete and evaluable PK samples through 72 hours after rFVIIIFc dosing. Complete means the availability of the 72-hour sample and at least enough other samples to allow for all the PK parameters to be estimated.

End point type	Secondary

End point timeframe:

Baseline (28 ±7 days prior to Day 1) Prestudy FVIII Dosing: predose; 30 ±5 min, 3 hours ±30 min, 24 ±3 hours, 48 ±4 hours post-dose. Day 1 (rFVIIIFc Dosing): predose; 30 ±5 min, 3 hours ±30 min, 24 ±3 hours, 48 ±4 hours, 72 ±7 hours post-dose

End point values	Subjects < 6 Years Old	Subjects 6 to < 12 Years Old		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23[22]	31[23]		
Units: hours				
geometric mean (confidence interval 95%)	12.277 (10.988 to 13.718)	13.451 (11.445 to 15.808)		

Notes:

[22] - All subjects in the PK subgroup with adequate PK data

[23] - All subjects in the PK subgroup with adequate PK data

Statistical analyses

No statistical analyses for this end point

Secondary: Elimination Half Life (t1/2; Two-stage Chromogenic Assay)

End point title	Elimination Half Life (t1/2; Two-stage Chromogenic Assay)

End point description:

Time required for the activity of the drug to reach half of its original value for participants in the PK subgroup. The 95% confidence interval on the geometric mean is based on the t-statistic back-transformed from the log scale. PK Analysis Set: All subjects in the PK subgroup with adequate PK data, defined as complete and evaluable PK samples through 72 hours after rFVIIIFc dosing. Complete means the availability of the 72-hour sample and at least enough other samples to allow for all the PK parameters to be estimated.

End point type	Secondary

End point timeframe:

Baseline (28 ±7 days prior to Day 1) Prestudy FVIII Dosing: predose; 30 ±5 min, 3 hours ±30 min, 24 ±3 hours, 48 ±4 hours post-dose. Day 1 (rFVIIIFc Dosing): predose; 30 ±5 min, 3 hours ±30 min, 24 ±3 hours, 48 ±4 hours, 72 ±7 hours post-dose

End point values	Subjects < 6 Years Old	Subjects 6 to < 12 Years Old		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24[24]	27[25]		
Units: hours				
geometric mean (confidence interval 95%)	14.268 (12.559 to 16.21)	15.861 (13.814 to 18.21)		

Notes:

[24] - All subjects in the PK subgroup with adequate PK data

[25] - All subjects in the PK subgroup with adequate PK data

Statistical analyses

No statistical analyses for this end point

Secondary: Clearance (CL; One-stage aPTT Clotting Assay)

End point title	Clearance (CL; One-stage aPTT Clotting Assay)

End point description:

Rate at which the body removes the drug, measured as the volume of the plasma cleared of drug per unit time per unit weight for participants in the PK subgroup. The 95% confidence interval on the geometric mean is based on the t-statistic back-transformed from the log scale. PK Analysis Set: All subjects in the PK subgroup with adequate PK data, defined as complete and evaluable PK samples through 72 hours after rFVIIIFc dosing. Complete means the availability of the 72-hour sample and at least enough other samples to allow for all the PK parameters to be estimated.

End point type	Secondary

End point timeframe:

Baseline (28 ±7 days prior to Day 1) Prestudy FVIII Dosing: predose; 30 ±5 min, 3 hours ±30 min, 24 ±3 hours, 48 ±4 hours post-dose. Day 1 (rFVIIIFc Dosing): predose; 30 ±5 min, 3 hours ±30 min, 24 ±3 hours, 48 ±4 hours, 72 ±7 hours post-dose

End point values	Subjects < 6 Years Old	Subjects 6 to < 12 Years Old		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23[26]	31[27]		
Units: mL/h/kg				
geometric mean (confidence interval 95%)	3.4561 (3.0564 to 3.908)	2.6067 (2.2559 to 3.0119)		

Notes:

[26] - All subjects in the PK subgroup with adequate PK data

[27] - All subjects in the PK subgroup with adequate PK data

Statistical analyses

No statistical analyses for this end point

Secondary: Clearance (CL; Two-stage Chromogenic Assay)

End point title	Clearance (CL; Two-stage Chromogenic Assay)

End point description:

Rate at which the body removes the drug, measured as the volume of the plasma cleared of drug per unit time per unit weight for participants in the PK subgroup. The 95% confidence interval on the geometric mean is based on the t-statistic back-transformed from the log scale. PK Analysis Set: All subjects in the PK subgroup with adequate PK data, defined as complete and evaluable PK samples through 72 hours after rFVIIIFc dosing. Complete means the availability of the 72-hour sample and at least enough other samples to allow for all the PK parameters to be estimated.

End point type	Secondary

End point timeframe:

Baseline (28 ±7 days prior to Day 1) Prestudy FVIII Dosing: predose; 30 ±5 min, 3 hours ±30 min, 24 ±3 hours, 48 ±4 hours post-dose. Day 1 (rFVIIIFc Dosing): predose; 30 ±5 min, 3 hours ±30 min, 24 ±3 hours, 48 ±4 hours, 72 ±7 hours post-dose

End point values	Subjects < 6 Years Old	Subjects 6 to < 12 Years Old		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24[28]	27[29]		
Units: mL/h/kg				
geometric mean (confidence interval 95%)	3.86 (3.4839 to 4.2767)	3.0486 (2.6187 to 3.5491)		

Notes:

[28] - All subjects in the PK subgroup with adequate PK data

[29] - All subjects in the PK subgroup with adequate PK data

Statistical analyses

No statistical analyses for this end point

Secondary: Volume at Steady State (Vss; One-stage aPTT Clotting Assay)

End point title	Volume at Steady State (Vss; One-stage aPTT Clotting Assay)

End point description:

Volume of distribution at steady state for participants in the PK subgroup. The 95% confidence interval on the geometric mean is based on the t-statistic back-transformed from the log scale. PK Analysis Set: All subjects in the PK subgroup with adequate PK data, defined as complete and evaluable PK samples through 72 hours after rFVIIIFc dosing. Complete means the availability of the 72-hour sample and at least enough other samples to allow for all the PK parameters to be estimated.

End point type	Secondary

End point timeframe:

Baseline (28 ±7 days prior to Day 1) Prestudy FVIII Dosing: predose; 30 ±5 min, 3 hours ±30 min, 24 ±3 hours, 48 ±4 hours post-dose. Day 1 (rFVIIIFc Dosing): predose; 30 ±5 min, 3 hours ±30 min, 24

End point values	Subjects < 6 Years Old	Subjects 6 to < 12 Years Old		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23[30]	31[31]		
Units: mL/kg				
geometric mean (confidence interval 95%)	57.94 (54.13 to 62.01)	49.51 (44.08 to 55.6)		

Notes:

[30] - All subjects in the PK subgroup with adequate PK data

[31] - All subjects in the PK subgroup with adequate PK data

Statistical analyses

No statistical analyses for this end point

Secondary: Volume at Steady State (Vss; Two-stage Chromogenic Assay)

End point title	Volume at Steady State (Vss; Two-stage Chromogenic Assay)

End point description:

Volume of distribution at steady state for participants in the PK subgroup. The 95% confidence interval on the geometric mean is based on the t-statistic back-transformed from the log scale. PK Analysis Set: All subjects in the PK subgroup with adequate PK data, defined as complete and evaluable PK samples through 72 hours after rFVIIIFc dosing. Complete means the availability of the 72-hour sample and at least enough other samples to allow for all the PK parameters to be estimated.

End point type	Secondary

End point timeframe:

Baseline (28 ±7 days prior to Day 1) Prestudy FVIII Dosing: predose; 30 ±5 min, 3 hours ±30 min, 24 ±3 hours, 48 ±4 hours post-dose. Day 1 (rFVIIIFc Dosing): predose; 30 ±5 min, 3 hours ±30 min, 24 ±3 hours, 48 ±4 hours, 72 ±7 hours post-dose

End point values	Subjects < 6 Years Old	Subjects 6 to < 12 Years Old		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24[32]	27[33]		
Units: mL/kg				
geometric mean (confidence interval 95%)	66.48 (59.77 to 73.93)	63.15 (56.26 to 70.87)		

Notes:

[32] - All subjects in the PK subgroup with adequate PK data

[33] - All subjects in the PK subgroup with adequate PK data

Statistical analyses

No statistical analyses for this end point

Secondary: Dose Normalized Area Under the Curve (DNAUC; One-stage aPTT Clotting Assay)

End point title	Dose Normalized Area Under the Curve (DNAUC; One-stage aPTT Clotting Assay)

End point description:

Dose normalized area under the FVIII activity-time curve for participants in the PK subgroup. The 95% confidence interval on the geometric mean is based on the t-statistic back-transformed from the log scale. PK Analysis Set: All subjects in the PK subgroup with adequate PK data, defined as complete and evaluable PK samples through 72 hours after rFVIIIFc dosing. Complete means the availability of the 72-hour sample and at least enough other samples to allow for all the PK parameters to be estimated.

End point type	Secondary

End point timeframe:

Baseline (28 ±7 days prior to Day 1) Prestudy FVIII Dosing: predose; 30 ±5 min, 3 hours ±30 min, 24 ±3 hours, 48 ±4 hours post-dose. Day 1 (rFVIIIFc Dosing): predose; 30 ±5 min, 3 hours ±30 min, 24 ±3 hours, 48 ±4 hours, 72 ±7 hours post-dose

End point values	Subjects < 6 Years Old	Subjects 6 to < 12 Years Old		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23[34]	31[35]		
Units: IU*h/dL per IU/kg				
geometric mean (confidence interval 95%)	28.93 (25.59 to 32.72)	38.37 (33.2 to 44.35)		

Notes:

[34] - All subjects in the PK subgroup with adequate PK data

[35] - All subjects in the PK subgroup with adequate PK data

Statistical analyses

No statistical analyses for this end point

Secondary: Dose Normalized Area Under the Curve (DNAUC; Two-stage Chromogenic Assay)

End point title	Dose Normalized Area Under the Curve (DNAUC; Two-stage Chromogenic Assay)

End point description:

Dose normalized area under the FVIII activity-time curve for participants in the PK subgroup. The 95% confidence interval on the geometric mean is based on the t-statistic back-transformed from the log scale. PK Analysis Set: All subjects in the PK subgroup with adequate PK data, defined as complete and evaluable PK samples through 72 hours after rFVIIIFc dosing. Complete means the availability of the 72-hour sample and at least enough other samples to allow for all the PK parameters to be estimated.

End point type	Secondary

End point timeframe:

Baseline (28 ±7 days prior to Day 1) Prestudy FVIII Dosing: predose; 30 ±5 min, 3 hours ±30 min, 24 ±3 hours, 48 ±4 hours post-dose. Day 1 (rFVIIIFc Dosing): predose; 30 ±5 min, 3 hours ±30 min, 24 ±3 hours, 48 ±4 hours, 72 ±7 hours post-dose

End point values	Subjects < 6 Years Old	Subjects 6 to < 12 Years Old		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24[36]	27[37]		
Units: IU*h/dL per IU/kg				
geometric mean (confidence interval 95%)	25.9 (23.38 to 28.69)	32.8 (28.18 to 38.19)		

Notes:

[36] - All subjects in the PK subgroup with adequate PK data

[37] - All subjects in the PK subgroup with adequate PK data

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Residence Time (MRT; One-stage aPTT Clotting Assay)

End point title	Mean Residence Time (MRT; One-stage aPTT Clotting Assay)

End point description:

The average time that a drug molecule is present in the systemic circulation for participants in the PK subgroup. The 95% confidence interval on the geometric mean is based on the t-statistic back-transformed from the log scale. PK Analysis Set: All subjects in the PK subgroup with adequate PK data, defined as complete and evaluable PK samples through 72 hours after rFVIIIFc dosing. Complete means the availability of the 72-hour sample and at least enough other samples to allow for all the PK parameters to be estimated.

End point type	Secondary

End point timeframe:

Baseline (28 ±7 days prior to Day 1) Prestudy FVIII Dosing: predose; 30 ±5 min, 3 hours ±30 min, 24 ±3 hours, 48 ±4 hours post-dose. Day 1 (rFVIIIFc Dosing): predose; 30 ±5 min, 3 hours ±30 min, 24 ±3 hours, 48 ±4 hours, 72 ±7 hours post-dose

End point values	Subjects < 6 Years Old	Subjects 6 to < 12 Years Old		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23[38]	31[39]		
Units: hours				
geometric mean (confidence interval 95%)	16.762 (15.106 to 18.599)	18.999 (16.213 to 22.263)		

Notes:

[38] - All subjects in the PK subgroup with adequate PK data

[39] - All subjects in the PK subgroup with adequate PK data

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Residence Time (MRT; Two-stage Chromogenic Assay)

End point title	Mean Residence Time (MRT; Two-stage Chromogenic Assay)

End point description:

The average time that a drug molecule is present in the systemic circulation for participants in the PK subgroup. The 95% confidence interval on the geometric mean is based on the t-statistic back-transformed from the log scale. PK Analysis Set: All subjects in the PK subgroup with adequate PK data, defined as complete and evaluable PK samples through 72 hours after rFVIIIFc dosing. Complete means the availability of the 72-hour sample and at least enough other samples to allow for all the PK parameters to be estimated.

End point type	Secondary

End point timeframe:

Baseline (28 ±7 days prior to Day 1) Prestudy FVIII Dosing: predose; 30 ±5 min, 3 hours ±30 min, 24

±3 hours, 48 ±4 hours post-dose. Day 1 (rFVIIIFc Dosing): predose; 30 ±5 min, 3 hours ±30 min, 24 ±3 hours, 48 ±4 hours, 72 ±7 hours post-dose

End point values	Subjects < 6 Years Old	Subjects 6 to < 12 Years Old		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24[40]	27[41]		
Units: hours				
geometric mean (confidence interval 95%)	17.22 (15.407 to 19.246)	20.708 (18.036 to 23.776)		

Notes:

[40] - All subjects in the PK subgroup with adequate PK data

[41] - All subjects in the PK subgroup with adequate PK data

Statistical analyses

No statistical analyses for this end point

Secondary: Incremental Recovery (IR; One-stage aPTT Clotting Assay)

End point title	Incremental Recovery (IR; One-stage aPTT Clotting Assay)

End point description:

The rise in FVIII activity in IU/dL per unit dose administered in IU/kg for participants in the PK subgroup. The 95% confidence interval on the geometric mean is based on the t-statistic back-transformed from the log scale. PK Analysis Set: All subjects in the PK subgroup with adequate PK data, defined as complete and evaluable PK samples through 72 hours after rFVIIIFc dosing. Complete means the availability of the 72-hour sample and at least enough other samples to allow for all the PK parameters to be estimated.

End point type	Secondary

End point timeframe:

Baseline (28 ±7 days prior to Day 1) Prestudy FVIII Dosing: predose; 30 ±5 min, 3 hours ±30 min, 24 ±3 hours, 48 ±4 hours post-dose. Day 1 (rFVIIIFc Dosing): predose; 30 ±5 min, 3 hours ±30 min, 24 ±3 hours, 48 ±4 hours, 72 ±7 hours post-dose

End point values	Subjects < 6 Years Old	Subjects 6 to < 12 Years Old		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23[42]	31[43]		
Units: IU/dL per IU/kg				
geometric mean (confidence interval 95%)	1.901 (1.785 to 2.024)	2.299 (2.042 to 2.587)		

Notes:

[42] - All subjects in the PK subgroup with adequate PK data

[43] - All subjects in the PK subgroup with adequate PK data

Statistical analyses

No statistical analyses for this end point

Secondary: Incremental Recovery (IR; Two-stage Chromogenic Assay)

End point title	Incremental Recovery (IR; Two-stage Chromogenic Assay)

End point description:

The rise in FVIII activity in IU/dL per unit dose administered in IU/kg for participants in the PK subgroup. The 95% confidence interval on the geometric mean is based on the t-statistic back-transformed from the log scale. PK Analysis Set: All subjects in the PK subgroup with adequate PK data, defined as complete and evaluable PK samples through 72 hours after rFVIIIFc dosing. Complete means the availability of the 72-hour sample and at least enough other samples to allow for all the PK parameters to be estimated.

End point type	Secondary

End point timeframe:

Baseline (28 ±7 days prior to Day 1) Prestudy FVIII Dosing: predose; 30 ±5 min, 3 hours ±30 min, 24 ±3 hours, 48 ±4 hours post-dose. Day 1 (rFVIIIFc Dosing): predose; 30 ±5 min, 3 hours ±30 min, 24 ±3 hours, 48 ±4 hours, 72 ±7 hours post-dose

End point values	Subjects < 6 Years Old	Subjects 6 to < 12 Years Old		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24[44]	27[45]		
Units: IU/dL per IU/kg				
geometric mean (confidence interval 95%)	1.882 (1.728 to 2.05)	2.076 (1.914 to 2.252)		

Notes:

[44] - All subjects in the PK subgroup with adequate PK data

[45] - All subjects in the PK subgroup with adequate PK data

Statistical analyses

No statistical analyses for this end point

Secondary: Time at Maximum Activity (Tmax; One-stage aPTT Clotting Assay)

End point title	Time at Maximum Activity (Tmax; One-stage aPTT Clotting Assay)

End point description:

Time at which maximum activity (Cmax) is observed for participants in the PK subgroup. The 95% confidence interval on the geometric mean is based on the t-statistic back-transformed from the log scale. PK Analysis Set: All subjects in the PK subgroup with adequate PK data, defined as complete and evaluable PK samples through 72 hours after rFVIIIFc dosing. Complete means the availability of the 72-hour sample and at least enough other samples to allow for all the PK parameters to be estimated.

End point type	Secondary

End point timeframe:

Baseline (28 ±7 days prior to Day 1) Prestudy FVIII Dosing: predose; 30 ±5 min, 3 hours ±30 min, 24 ±3 hours, 48 ±4 hours post-dose. Day 1 (rFVIIIFc Dosing): predose; 30 ±5 min, 3 hours ±30 min, 24 ±3 hours, 48 ±4 hours, 72 ±7 hours post-dose

End point values	Subjects < 6 Years Old	Subjects 6 to < 12 Years Old		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23[46]	31[47]		
Units: hours				
geometric mean (confidence interval 95%)	0.6987 (0.5256 to 0.9287)	0.7257 (0.5685 to 0.9264)		

Notes:

[46] - All subjects in the PK subgroup with adequate PK data

[47] - All subjects in the PK subgroup with adequate PK data

Statistical analyses

No statistical analyses for this end point

Secondary: Time at Maximum Activity (Tmax; Two-stage Chromogenic Assay)

End point title	Time at Maximum Activity (Tmax; Two-stage Chromogenic Assay)

End point description:

Time at which maximum activity (Cmax) is observed for participants in the PK subgroup. The 95% confidence interval on the geometric mean is based on the t-statistic back-transformed from the log scale. PK Analysis Set: All subjects in the PK subgroup with adequate PK data, defined as complete and evaluable PK samples through 72 hours after rFVIIIFc dosing. Complete means the availability of the 72-hour sample and at least enough other samples to allow for all the PK parameters to be estimated.

End point type	Secondary

End point timeframe:

Baseline (28 ±7 days prior to Day 1) Prestudy FVIII Dosing: predose; 30 ±5 min, 3 hours ±30 min, 24 ±3 hours, 48 ±4 hours post-dose. Day 1 (rFVIIIFc Dosing): predose; 30 ±5 min, 3 hours ±30 min, 24 ±3 hours, 48 ±4 hours, 72 ±7 hours post-dose

End point values	Subjects < 6 Years Old	Subjects 6 to < 12 Years Old		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24[48]	27[49]		
Units: hours				
geometric mean (confidence interval 95%)	0.7313 (0.5408 to 0.9889)	0.6334 (0.5184 to 0.7741)		

Notes:

[48] - All subjects in the PK subgroup with adequate PK data

[49] - All subjects in the PK subgroup with adequate PK data

Statistical analyses

No statistical analyses for this end point

Secondary: Lambda Z (One-stage aPTT Clotting Assay)

End point title	Lambda Z (One-stage aPTT Clotting Assay)

End point description:

First order rate constant associated with the terminal portion of the curve (lambda z) for participants in the PK subgroup. The 95% confidence interval on the geometric mean is based on the t-statistic back-transformed from the log scale. PK Analysis Set: All subjects in the PK subgroup with adequate PK data, defined as complete and evaluable PK samples through 72 hours after rFVIIIFc dosing. Complete means the availability of the 72-hour sample and at least enough other samples to allow for all the PK parameters to be estimated.

End point type	Secondary

End point timeframe:

Baseline (28 ±7 days prior to Day 1) Prestudy FVIII Dosing: predose; 30 ±5 min, 3 hours ±30 min, 24

±3 hours, 48 ±4 hours post-dose. Day 1 (rFVIIIFc Dosing): predose; 30 ±5 min, 3 hours ±30 min, 24 ±3 hours, 48 ±4 hours, 72 ±7 hours post-dose

End point values	Subjects < 6 Years Old	Subjects 6 to < 12 Years Old		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23[50]	31[51]		
Units: 1/hours				
geometric mean (confidence interval 95%)	0.05644 (0.05053 to 0.06304)	0.05158 (0.0439 to 0.06061)		

Notes:

[50] - All subjects in the PK subgroup with adequate PK data

[51] - All subjects in the PK subgroup with adequate PK data

Statistical analyses

No statistical analyses for this end point

Secondary: Lambda Z (Two-stage Chromogenic Assay)

End point title	Lambda Z (Two-stage Chromogenic Assay)

End point description:

First order rate constant associated with the terminal portion of the curve (lambda z) for participants in the PK subgroup. The 95% confidence interval on the geometric mean is based on the t-statistic back-transformed from the log scale. PK Analysis Set: All subjects in the PK subgroup with adequate PK data, defined as complete and evaluable PK samples through 72 hours after rFVIIIFc dosing. Complete means the availability of the 72-hour sample and at least enough other samples to allow for all the PK parameters to be estimated.

End point type	Secondary

End point timeframe:

Baseline (28 ±7 days prior to Day 1) Prestudy FVIII Dosing: predose; 30 ±5 min, 3 hours ±30 min, 24 ±3 hours, 48 ±4 hours post-dose. Day 1 (rFVIIIFc Dosing): predose; 30 ±5 min, 3 hours ±30 min, 24 ±3 hours, 48 ±4 hours, 72 ±7 hours post-dose

End point values	Subjects < 6 Years Old	Subjects 6 to < 12 Years Old		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24[52]	27[53]		
Units: 1/hours				
geometric mean (confidence interval 95%)	0.04848 (0.04264 to 0.05511)	0.04367 (0.03801 to 0.05018)		

Notes:

[52] - All subjects in the PK subgroup with adequate PK data

[53] - All subjects in the PK subgroup with adequate PK data

Statistical analyses

No statistical analyses for this end point

Secondary: Volume at Terminal Phase (Vz; One-stage aPTT Clotting Assay)

End point title	Volume at Terminal Phase (Vz; One-stage aPTT Clotting Assay)

End point description:

Volume of distribution estimated from the terminal phase for participants in the PK subgroup. The 95% confidence interval on the geometric mean is based on the t-statistic back-transformed from the log scale. PK Analysis Set: All subjects in the PK subgroup with adequate PK data, defined as complete and evaluable PK samples through 72 hours after rFVIIIFc dosing. Complete means the availability of the 72-hour sample and at least enough other samples to allow for all the PK parameters to be estimated.

End point type	Secondary

End point timeframe:

Baseline (28 ±7 days prior to Day 1) Prestudy FVIII Dosing: predose; 30 ±5 min, 3 hours ±30 min, 24 ±3 hours, 48 ±4 hours post-dose. Day 1 (rFVIIIFc Dosing): predose; 30 ±5 min, 3 hours ±30 min, 24 ±3 hours, 48 ±4 hours, 72 ±7 hours post-dose

End point values	Subjects < 6 Years Old	Subjects 6 to < 12 Years Old		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23[54]	31[55]		
Units: mL/kg				
geometric mean (confidence interval 95%)	61.22 (56.54 to 66.29)	50.58 (44.54 to 57.43)		

Notes:

[54] - All subjects in the PK subgroup

[55] - All subjects in the PK subgroup

Statistical analyses

No statistical analyses for this end point

Secondary: Volume at Terminal Phase (Vz; Two-stage Chromogenic Assay)

End point title	Volume at Terminal Phase (Vz; Two-stage Chromogenic Assay)

End point description:

Volume of distribution estimated from the terminal phase for participants in the PK subgroup. The 95% confidence interval on the geometric mean is based on the t-statistic back-transformed from the log scale. PK Analysis Set: All subjects in the PK subgroup with adequate PK data, defined as complete and evaluable PK samples through 72 hours after rFVIIIFc dosing. Complete means the availability of the 72-hour sample and at least enough other samples to allow for all the PK parameters to be estimated.

End point type	Secondary

End point timeframe:

Baseline (28 ±7 days prior to Day 1) Prestudy FVIII Dosing: predose; 30 ±5 min, 3 hours ±30 min, 24 ±3 hours, 48 ±4 hours post-dose. Day 1 (rFVIIIFc Dosing): predose; 30 ±5 min, 3 hours ±30 min, 24 ±3 hours, 48 ±4 hours, 72 ±7 hours post-dose

End point values	Subjects < 6 Years Old	Subjects 6 to < 12 Years Old		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24[56]	27[57]		
Units: mL/kg				
geometric mean (confidence interval 95%)	79.48 (69.2 to 91.3)	69.75 (62.98 to 77.25)		

Notes:

[56] - All subjects in the PK subgroup with adequate PK data

[57] - All subjects in the PK subgroup with adequate PK data

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Curve to the Last Measurable Timepoint (AUClast; One-stage aPTT Clotting Assay)

End point title	Area Under the Curve to the Last Measurable Timepoint (AUClast; One-stage aPTT Clotting Assay)

End point description:

Dose-normalized area under the FVIII activity-time curve to the last measurable timepoint for participants in the PK subgroup. The 95% confidence interval on the geometric mean is based on the t-statistic back-transformed from the log scale. PK Analysis Set: All subjects in the PK subgroup with adequate PK data, defined as complete and evaluable PK samples through 72 hours after rFVIIIFc dosing. Complete means the availability of the 72-hour sample and at least enough other samples to allow for all the PK parameters to be estimated.

End point type	Secondary

End point timeframe:

Baseline (28 ±7 days prior to Day 1) Prestudy FVIII Dosing: predose; 30 ±5 min, 3 hours ±30 min, 24 ±3 hours, 48 ±4 hours post-dose. Day 1 (rFVIIIFc Dosing): predose; 30 ±5 min, 3 hours ±30 min, 24 ±3 hours, 48 ±4 hours, 72 ±7 hours post-dose

End point values	Subjects < 6 Years Old	Subjects 6 to < 12 Years Old		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23[58]	31[59]		
Units: IU*h/dL				
geometric mean (confidence interval 95%)	1410.4 (1254.8 to 1585.2)	1823.4 (1602.2 to 2075)		

Notes:

[58] - All subjects in the PK subgroup with adequate PK data

[59] - All subjects in the PK subgroup with adequate PK data

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Curve to the Last Measurable Timepoint (AUClast; Two-stage Chromogenic Assay)

End point title	Area Under the Curve to the Last Measurable Timepoint (AUClast; Two-stage Chromogenic Assay)

End point description:

Dose-normalized area under the FVIII activity-time curve to the last measurable timepoint for participants in the PK subgroup. The 95% confidence interval on the geometric mean is based on the t-statistic back-transformed from the log scale. PK Analysis Set: All subjects in the PK subgroup with adequate PK data, defined as complete and evaluable PK samples through 72 hours after rFVIIIFc dosing. Complete means the availability of the 72-hour sample and at least enough other samples to allow for all the PK parameters to be estimated.

End point type	Secondary

End point timeframe:

Baseline (28 ±7 days prior to Day 1) Prestudy FVIII Dosing: predose; 30 ±5 min, 3 hours ±30 min, 24 ±3 hours, 48 ±4 hours post-dose. Day 1 (rFVIIIFc Dosing): predose; 30 ±5 min, 3 hours ±30 min, 24 ±3 hours, 48 ±4 hours, 72 ±7 hours post-dose

End point values	Subjects < 6 Years Old	Subjects 6 to < 12 Years Old		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24[60]	27[61]		
Units: IU*h/dL				
geometric mean (confidence interval 95%)	1250.1 (1133.2 to 1379)	1540.4 (1346.5 to 1762.3)		

Notes:

[60] - All subjects in the PK subgroup with adequate PK data

[61] - All subjects in the PK subgroup with adequate PK data

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Curve to Infinity (AUCinf; One-stage aPTT Clotting Assay)

End point title	Area Under the Curve to Infinity (AUCinf; One-stage aPTT Clotting Assay)

End point description:

Dose normalized area under the FVIII activity-time curve to infinity for participants in the PK subgroup. The 95% confidence interval on the geometric mean is based on the t-statistic back-transformed from the log scale. PK Analysis Set: All subjects in the PK subgroup with adequate PK data, defined as complete and evaluable PK samples through 72 hours after rFVIIIFc dosing. Complete means the availability of the 72-hour sample and at least enough other samples to allow for all the PK parameters to be estimated.

End point type	Secondary

End point timeframe:

Baseline (28 ±7 days prior to Day 1) Prestudy FVIII Dosing: predose; 30 ±5 min, 3 hours ±30 min, 24 ±3 hours, 48 ±4 hours post-dose. Day 1 (rFVIIIFc Dosing): predose; 30 ±5 min, 3 hours ±30 min, 24 ±3 hours, 48 ±4 hours, 72 ±7 hours post-dose

End point values	Subjects < 6 Years Old	Subjects 6 to < 12 Years Old		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23[62]	31[63]		
Units: IU*h/dL				
geometric mean (confidence interval 95%)	1446.5 (1279.2 to 1635.7)	1918.5 (1660 to 2217.3)		

Notes:

[62] - All subjects in the PK subgroup with adequate PK data

[63] - All subjects in the PK subgroup with adequate PK data

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Curve to Infinity (AUCinf; Two-stage Chromogenic Assay)

End point title	Area Under the Curve to Infinity (AUCinf; Two-stage Chromogenic Assay)

End point description:

Dose normalized area under the FVIII activity-time curve to infinity for participants in the PK subgroup. The 95% confidence interval on the geometric mean is based on the t-statistic back-transformed from the log scale. PK Analysis Set: All subjects in the PK subgroup with adequate PK data, defined as complete and evaluable PK samples through 72 hours after rFVIIIFc dosing. Complete means the availability of the 72-hour sample and at least enough other samples to allow for all the PK parameters to be estimated.

End point type	Secondary

End point timeframe:

Baseline (28 ±7 days prior to Day 1) Prestudy FVIII Dosing: predose; 30 ±5 min, 3 hours ±30 min, 24 ±3 hours, 48 ±4 hours post-dose. Day 1 (rFVIIIFc Dosing): predose; 30 ±5 min, 3 hours ±30 min, 24 ±3 hours, 48 ±4 hours, 72 ±7 hours post-dose

End point values	Subjects < 6 Years Old	Subjects 6 to < 12 Years Old		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24[64]	27[65]		
Units: IU*h/dL				
geometric mean (confidence interval 95%)	1294.7 (1168.7 to 1434.3)	1640 (1408.7 to 1909.4)		

Notes:

[64] - All subjects in the PK subgroup with adequate PK data

[65] - All subjects in the PK subgroup with adequate PK data

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of AUCinf Extrapolated From the Last Data Point to Infinity (%AUCext; One-stage aPTT Clotting Assay)

End point title	Percentage of AUCinf Extrapolated From the Last Data Point to Infinity (%AUCext; One-stage aPTT Clotting Assay)

End point description:

Percentage of AUCinf extrapolated from the last data point to infinity for participants in the PK subgroup. The 95% confidence interval on the geometric mean is based on the t-statistic back-transformed from the log scale. PK Analysis Set: All subjects in the PK subgroup with adequate PK data, defined as complete and evaluable PK samples through 72 hours after rFVIIIFc dosing. Complete means the availability of the 72-hour sample and at least enough other samples to allow for all the PK parameters to be estimated.

End point type	Secondary

End point timeframe:

Baseline (28 ±7 days prior to Day 1) Prestudy FVIII Dosing: predose; 30 ±5 min, 3 hours ±30 min, 24 ±3 hours, 48 ±4 hours post-dose. Day 1 (rFVIIIFc Dosing): predose; 30 ±5 min, 3 hours ±30 min, 24 ±3 hours, 48 ±4 hours, 72 ±7 hours post-dose

End point values	Subjects < 6 Years Old	Subjects 6 to < 12 Years Old		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23[66]	31[67]		
Units: percentage of AUCinf				
geometric mean (confidence interval 95%)	1.8421 (1.3218 to 2.5673)	2.7777 (1.9611 to 3.9344)		

Notes:

[66] - All subjects in the PK subgroup with adequate PK data

[67] - All subjects in the PK subgroup with adequate PK data

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of AUCinf Extrapolated From the Last Data Point to Infinity (%AUCext; Two-stage Chromogenic Assay)

End point title	Percentage of AUCinf Extrapolated From the Last Data Point to Infinity (%AUCext; Two-stage Chromogenic Assay)

End point description:

Percentage of AUCinf extrapolated from the last data point to infinity for participants in the PK subgroup. The 95% confidence interval on the geometric mean is based on the t-statistic back-transformed from the log scale. PK Analysis Set: All subjects in the PK subgroup with adequate PK data, defined as complete and evaluable PK samples through 72 hours after rFVIIIFc dosing. Complete means the availability of the 72-hour sample and at least enough other samples to allow for all the PK parameters to be estimated.

End point type	Secondary

End point timeframe:

Baseline (28 ±7 days prior to Day 1) Prestudy FVIII Dosing: predose; 30 ±5 min, 3 hours ±30 min, 24 ±3 hours, 48 ±4 hours post-dose. Day 1 (rFVIIIFc Dosing): predose; 30 ±5 min, 3 hours ±30 min, 24 ±3 hours, 48 ±4 hours, 72 ±7 hours post-dose

End point values	Subjects < 6 Years Old	Subjects 6 to < 12 Years Old		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24[68]	27[69]		
Units: percentage of AUCinf				
geometric mean (confidence interval 95%)	2.753 (2.1052 to 3.6001)	3.9476 (2.8296 to 5.5074)		

Notes:

[68] - All subjects in the PK subgroup with adequate PK data

[69] - All subjects in the PK subgroup with adequate PK data

Statistical analyses

No statistical analyses for this end point

Secondary: Physician’s Global Assessment of the Subject’s Response to His rFVIIIFc

Regimen

End point title	Physician’s Global Assessment of the Subject’s Response to His rFVIIIFc Regimen

End point description:

Investigators assessed each subject’s response to his rFVIIIFc regimen using a 4-point scale: excellent=bleeding episodes responded to ≤ the usual number of injections or ≤ the usual dose of rFVIIIFc or the rate of breakthrough bleeding during prophylaxis was ≤ 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 bleeding; 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; ineffective=routine failure to control hemostasis, or hemostatic control required additional agents. Percentages are based on the total number of responses; multiple responses per subject are counted. Full Analysis Set: subjects who received at least 1 dose of rFVIIIFc.

End point type	Secondary

End point timeframe:

Up to Week 26 +/- 7 days

End point values	Subjects < 6 Years Old	Subjects 6 to < 12 Years Old		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35[70]	34[71]		
Units: percentage of responses				
number (not applicable)				
Excellent	96.5	89.7		
Effective	3.5	9.1		
Partially Effective	0	1.2		
Ineffective	0	0		

Notes:

[70] - Full Analysis Set; percentages are based on the number of responses (total number of responses=141).
[71] - Full Analysis Set; percentages are based on the number of responses (total number of responses=165).

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Serious adverse events (AEs): from informed consent up to 21 days after last treatment visit (LTV); AEs: from Baseline (28 ± 7 days prior to Day 1) for PK Subgroup or from Day 1 (first dose of rFVIIIFc) for non-PK subgroup, up to 14 (+7) days after LTV.

Adverse event reporting additional description:

Length of rFVIIIFc dosing was up to 26 weeks ± 7 days. Serious and non-serious AEs that were treatment-emergent with respect to rFVIIIFc are presented for those participants who were treated with rFVIIIFc. Data are presented for the Full Analysis Set (subjects who received at least 1 dose of rFVIIIFc).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.0

Reporting groups

Reporting group title	Subjects < 6 Years Old

Reporting group description:

PK subgroup: After a Washout Period of ≥ 72 hours, at the Baseline Visit (28 ± 7 days prior to Day 1), subjects receive a single IV injection of prestudy FVIII over 5 (± 2) minutes at a dose of 50 IU/kg, rounded up to the nearest 250 IU increment, for a PK assessment. Following a second Washout Period of ≥ 72 hours, subjects receive a single IV injection of rFVIIIFc over 5 (± 2) minutes at a dose of 50 IU/kg for PK assessment. The first prophylactic dose of rFVIIIFc is administered at a starting dose of 25 IU/kg IV injection on Day 1 and 50 IU/kg on Day 4. Dose increases to a maximum of 80 IU/kg, and frequency of administration to a minimum interval of once every 2 days, are allowed as indicated.

Non-PK subgroup: On Day 1, a first prophylactic dose of rFVIIIFc of 25 IU/kg IV injection is given, followed by a dose of 50 IU/kg on Day 4. Dose increases to a maximum of 80 IU/kg, and frequency of administration to a minimum interval of once every 2 days, are allowed as indicated.

Reporting group title	Subjects 6 to < 12 Years Old

Reporting group description:

PK subgroup: After a Washout Period of ≥ 72 hours, at the Baseline Visit (28 ± 7 days prior to Day 1), subjects receive a single IV injection of prestudy FVIII over 5 (± 2) minutes at a dose of 50 IU/kg, rounded up to the nearest 250 IU increment, for a PK assessment. Following a second Washout Period of ≥ 72 hours, subjects receive a single IV injection of rFVIIIFc over 5 (± 2) minutes at a dose of 50 IU/kg for PK assessment. The first prophylactic dose of rFVIIIFc is administered at a starting dose of 25 IU/kg IV injection on Day 1 and 50 IU/kg on Day 4. Dose increases to a maximum of 80 IU/kg, and frequency of administration to a minimum interval of once every 2 days, are allowed as indicated.

Non-PK subgroup: On Day 1, a first prophylactic dose of rFVIIIFc of 25 IU/kg IV injection is given, followed by a dose of 50 IU/kg on Day 4. Dose increases to a maximum of 80 IU/kg, and frequency of administration to a minimum interval of once every 2 days, are allowed as indicated.

Serious adverse events	Subjects < 6 Years Old	Subjects 6 to < 12 Years Old	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 35 (11.43%)	1 / 34 (2.94%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Fall			

subjects affected / exposed	1 / 35 (2.86%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head Injury			
subjects affected / exposed	2 / 35 (5.71%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bacillus Infection			
subjects affected / exposed	0 / 35 (0.00%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Croup Infectious			
subjects affected / exposed	1 / 35 (2.86%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia Infection			
subjects affected / exposed	0 / 35 (0.00%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metapneumovirus Infection			
subjects affected / exposed	1 / 35 (2.86%)	0 / 34 (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 %

Non-serious adverse events	Subjects < 6 Years Old	Subjects 6 to < 12 Years Old	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	31 / 35 (88.57%)	28 / 34 (82.35%)	
Injury, poisoning and procedural complications			
Face Injury			
subjects affected / exposed	0 / 35 (0.00%)	2 / 34 (5.88%)	
occurrences (all)	0	2	

Fall			
subjects affected / exposed	3 / 35 (8.57%)	2 / 34 (5.88%)	
occurrences (all)	3	2	
Head Injury			
subjects affected / exposed	1 / 35 (2.86%)	2 / 34 (5.88%)	
occurrences (all)	1	2	
Limb Injury			
subjects affected / exposed	0 / 35 (0.00%)	2 / 34 (5.88%)	
occurrences (all)	0	3	
Lip Injury			
subjects affected / exposed	2 / 35 (5.71%)	0 / 34 (0.00%)	
occurrences (all)	2	0	
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 35 (2.86%)	4 / 34 (11.76%)	
occurrences (all)	1	8	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 35 (2.86%)	3 / 34 (8.82%)	
occurrences (all)	1	4	
Pyrexia			
subjects affected / exposed	1 / 35 (2.86%)	2 / 34 (5.88%)	
occurrences (all)	1	2	
Ear and labyrinth disorders			
Ear Pain			
subjects affected / exposed	2 / 35 (5.71%)	0 / 34 (0.00%)	
occurrences (all)	3	0	
Immune system disorders			
Seasonal Allergy			
subjects affected / exposed	2 / 35 (5.71%)	2 / 34 (5.88%)	
occurrences (all)	2	2	
Gastrointestinal disorders			
Abdominal Pain Upper			
subjects affected / exposed	1 / 35 (2.86%)	4 / 34 (11.76%)	
occurrences (all)	1	4	
Diarrhoea			

subjects affected / exposed	3 / 35 (8.57%)	1 / 34 (2.94%)	
occurrences (all)	4	1	
Vomiting			
subjects affected / exposed	3 / 35 (8.57%)	2 / 34 (5.88%)	
occurrences (all)	5	2	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	7 / 35 (20.00%)	6 / 34 (17.65%)	
occurrences (all)	7	6	
Oropharyngeal Pain			
subjects affected / exposed	0 / 35 (0.00%)	2 / 34 (5.88%)	
occurrences (all)	0	2	
Rhinorrhoea			
subjects affected / exposed	2 / 35 (5.71%)	1 / 34 (2.94%)	
occurrences (all)	2	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 35 (5.71%)	1 / 34 (2.94%)	
occurrences (all)	2	2	
Joint Swelling			
subjects affected / exposed	2 / 35 (5.71%)	1 / 34 (2.94%)	
occurrences (all)	2	1	
Myalgia			
subjects affected / exposed	0 / 35 (0.00%)	2 / 34 (5.88%)	
occurrences (all)	0	2	
Pain In Extremity			
subjects affected / exposed	2 / 35 (5.71%)	2 / 34 (5.88%)	
occurrences (all)	2	2	
Infections and infestations			
Bronchitis			
subjects affected / exposed	2 / 35 (5.71%)	0 / 34 (0.00%)	
occurrences (all)	2	0	
Conjunctivitis Infective			
subjects affected / exposed	0 / 35 (0.00%)	2 / 34 (5.88%)	
occurrences (all)	0	2	
Ear Infection			

subjects affected / exposed	2 / 35 (5.71%)	2 / 34 (5.88%)	
occurrences (all)	2	2	
Gastroenteritis			
subjects affected / exposed	2 / 35 (5.71%)	0 / 34 (0.00%)	
occurrences (all)	2	0	
Nasopharyngitis			
subjects affected / exposed	2 / 35 (5.71%)	4 / 34 (11.76%)	
occurrences (all)	4	6	
Otitis Media			
subjects affected / exposed	2 / 35 (5.71%)	0 / 34 (0.00%)	
occurrences (all)	2	0	
Pharyngitis			
subjects affected / exposed	2 / 35 (5.71%)	2 / 34 (5.88%)	
occurrences (all)	2	2	
Tonsillitis			
subjects affected / exposed	2 / 35 (5.71%)	2 / 34 (5.88%)	
occurrences (all)	2	4	
Upper Respiratory Tract Infection			
subjects affected / exposed	7 / 35 (20.00%)	2 / 34 (5.88%)	
occurrences (all)	11	2	
Varicella			
subjects affected / exposed	2 / 35 (5.71%)	0 / 34 (0.00%)	
occurrences (all)	2	0	
Viral Upper Respiratory Tract Infection			
subjects affected / exposed	3 / 35 (8.57%)	0 / 34 (0.00%)	
occurrences (all)	5	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 April 2012	The primary reason for this amendment was to revise the PK sampling schedule based on recommendations from the US Food and Drug Administration. The 96-hour sample was removed and a 48-hour sample was added.
09 April 2013	The primary reasons for this amendment were as follows: - Added an interim PK analyses. Data from the interim PK analyses were used to support marketing authorization in specific countries (e.g., US) for individuals under the age of 12. In addition, these PK data were used to inform the design of a clinical study in previously untreated patients that was required by the EU. - Increased the sample size from approximately 60 subjects dosed to approximately 68 subjects to be dosed to ensure that 25 subjects per cohort complete the PK assessments and had valid inhibitor test results following at least 50 EDs to rFVIIIFc. - Modified the statistical analysis: o Clarified the demography and baseline disease characteristics, efficacy, PK, and safety methods of analysis; o Removed sensitivity analysis of annualized bleeding episodes and annualized consumption for the prophylactic period, excluding PK profiling, surgical, nonmedical, and any irregular treatment due to increase in activity level (e.g., during summer camp); o Added analysis for the following efficacy assessments: total dose, Investigator's assessment of subject's overall response to rFVIIIFc regimen. - Clarified dose and interval titration. The clarification allowed for adequate prophylactic dosing based on both PK results and bleeding patterns by adjusting dose and/or interval and accounted for known pediatric PK differences for rFVIII products, accommodating subtle differences in standards of care at the different participating sites. - Modified text to note that major surgeries were to be classified as SAEs. - Recategorized endpoints for patient-reported and health outcomes from secondary endpoints to exploratory endpoints, and notified that these will be analyzed in a separate report.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported