



Clinical trial results:

A Randomized, Open-Label, Crossover Study to Evaluate the Pharmacokinetics of 2 Vial Strengths of Recombinant Factor VIII Fc Fusion Protein (rFVIII-Fc; BIIIB031) in Previously Treated Subjects With Severe Hemophilia A

Summary

EudraCT number	2013-003013-18
Trial protocol	GB
Global end of trial date	20 May 2015

Results information

Result version number	v1 (current)
This version publication date	28 July 2016
First version publication date	28 July 2016

Trial information

Trial identification

Sponsor protocol code	997HA307
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02083965
WHO universal trial number (UTN)	-

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	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	20 May 2015
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	20 May 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to characterize the pharmacokinetics (PK) of rFVIIIFc administered at vial strengths of 1000 and 3000 IU in subjects with severe hemophilia A. The secondary objective of the study was to evaluate the safety of rFVIIIFc beyond the PK assessment for up to 6 months for a continued treatment period.

Protection of trial subjects:

Written informed consent was obtained from each subject prior to evaluations being performed for eligibility. Subjects were given adequate time to review the information in the informed consent and were allowed to ask, and have answered, questions concerning all portions of the conduct of the study. Through the informed consent process each subject was made aware of the purpose of the study, the procedures, the benefits and risks of the study, the discomforts and the precautions taken. Any side effects or other health issues occurring during the study were followed up by the study doctor. Subjects were able to stop taking part in the study at any time without giving any reason.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	24 March 2014
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	United Kingdom: 9
Country: Number of subjects enrolled	Australia: 5
Country: Number of subjects enrolled	United States: 5
Worldwide total number of subjects	19
EEA total number of subjects	9

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)	0
Adolescents (12-17 years)	10
Adults (18-64 years)	9
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

During screening, subjects continued on their prior FVIII treatment/regimen and treated any bleeding episodes accordingly. After eligibility was confirmed at a screening visit, subjects underwent a 4-day washout period before receiving rFVIIIFc. Subjects may have repeated the washout period only once if bleeding occurred during the washout period.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	rFVIIIFc 1000/3000

Arm description:

Following the minimum 4-day washout, subjects received a single injection 50 IU/kg at a strength of 1000 IU/vial of rFVIIIFc (on Injection 1 Day 1) with 96 hours of PK assessments followed by a minimum of a 5-day washout prior to a second single injection of rFVIIIFc 50 IU/kg at a strength of 3000 IU/vial (on Injection 2 Day 1) with 96 hours of PK assessments.

After completing the PK assessment, all subjects began 1 of 3 continued treatment regimens for up to 6 months:

1. A prophylaxis regimen at a starting dose of 50 IU/kg of rFVIIIFc given every 3 to 5 days; further dose and interval adjustments were based on the Investigator's discretion as needed to prevent or treat bleeding
2. A prophylaxis regimen of 65 IU/kg administered every 7 days was considered for appropriate subjects who were selected based on the opinion of the Investigator
3. An episodic (on-demand) treatment with rFVIIIFc at 20 to 50 IU/kg, depending on the severity of the bleeding episode.

Arm type	Experimental
Investigational medicinal product name	recombinant Factor VIII-Fc
Investigational medicinal product code	rFVIIIFc
Other name	BIIB031, Eloctate, Elocta, antihemophilic factor (recombinant) Fc fusion protein, recombinant coagulation factor VIII Fc fusion protein, efmoctocog alfa
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

During the PK assessment, rFVIIIFc injections were prepared and administered in the clinic by study personnel. During continued treatment, rFVIIIFc injections were prepared and administered at home. At home and in the clinic, rFVIIIFc was to be delivered by IV injection over 5 minutes.

Arm title	rFVIIIFc 3000/1000
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Arm description:

Following the minimum 4-day washout, subjects received a single injection 50 IU/kg at a strength of 3000 IU/vial of rFVIIIFc (on Injection 1 Day 1) with 96 hours of PK assessments followed by a minimum of a 5-day washout prior to a second single injection of rFVIIIFc 50 IU/kg at a strength of 1000 IU/vial (on Injection 2 Day 1) with 96 hours of PK assessments.

After completing the PK assessment, all subjects began 1 of 3 continued treatment regimens for up to 6 months:

1. A prophylaxis regimen at a starting dose of 50 IU/kg of rFVIIIFc given every 3 to 5 days; further dose and interval adjustments were based on the Investigator's discretion as needed to prevent or treat

bleeding

2. A prophylaxis regimen of 65 IU/kg administered every 7 days was considered for appropriate subjects who were selected based on the opinion of the Investigator

3. An episodic (on-demand) treatment with rFVIIIFc at 20 to 50 IU/kg, depending on the severity of the bleeding episode.

Arm type	Experimental
Investigational medicinal product name	recombinant Factor VIII-Fc
Investigational medicinal product code	rFVIIIFc
Other name	BIIB031, Eloctate, Elocta, antihemophilic factor (recombinant) Fc fusion protein, recombinant coagulation factor VIII Fc fusion protein, efmoctocog alfa
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

During the PK assessment, rFVIIIFc injections were prepared and administered in the clinic by study personnel. During continued treatment, rFVIIIFc injections were prepared and administered at home. At home and in the clinic, rFVIIIFc was to be delivered by IV injection over 5 minutes.

Number of subjects in period 1	rFVIIIFc 1000/3000	rFVIIIFc 3000/1000
Started	10	9
Completed	9	8
Not completed	1	1
Not specified	1	-
Withdrawal by subject	-	1

Baseline characteristics

Reporting groups

Reporting group title	rFVIIIFc 1000/3000
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Reporting group description:

Following the minimum 4-day washout, subjects received a single injection 50 IU/kg at a strength of 1000 IU/vial of rFVIIIFc (on Injection 1 Day 1) with 96 hours of PK assessments followed by a minimum of a 5-day washout prior to a second single injection of rFVIIIFc 50 IU/kg at a strength of 3000 IU/vial (on Injection 2 Day 1) with 96 hours of PK assessments.

After completing the PK assessment, all subjects began 1 of 3 continued treatment regimens for up to 6 months:

1. A prophylaxis regimen at a starting dose of 50 IU/kg of rFVIIIFc given every 3 to 5 days; further dose and interval adjustments were based on the Investigator's discretion as needed to prevent or treat bleeding
2. A prophylaxis regimen of 65 IU/kg administered every 7 days was considered for appropriate subjects who were selected based on the opinion of the Investigator
3. An episodic (on-demand) treatment with rFVIIIFc at 20 to 50 IU/kg, depending on the severity of the bleeding episode.

Reporting group title	rFVIIIFc 3000/1000
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Reporting group description:

Following the minimum 4-day washout, subjects received a single injection 50 IU/kg at a strength of 3000 IU/vial of rFVIIIFc (on Injection 1 Day 1) with 96 hours of PK assessments followed by a minimum of a 5-day washout prior to a second single injection of rFVIIIFc 50 IU/kg at a strength of 1000 IU/vial (on Injection 2 Day 1) with 96 hours of PK assessments.

After completing the PK assessment, all subjects began 1 of 3 continued treatment regimens for up to 6 months:

1. A prophylaxis regimen at a starting dose of 50 IU/kg of rFVIIIFc given every 3 to 5 days; further dose and interval adjustments were based on the Investigator's discretion as needed to prevent or treat bleeding
2. A prophylaxis regimen of 65 IU/kg administered every 7 days was considered for appropriate subjects who were selected based on the opinion of the Investigator
3. An episodic (on-demand) treatment with rFVIIIFc at 20 to 50 IU/kg, depending on the severity of the bleeding episode.

Reporting group values	rFVIIIFc 1000/3000	rFVIIIFc 3000/1000	Total
Number of subjects	10	9	19
Age categorical			
Units: Subjects			

Age Continuous			
Units: years			
arithmetic mean	23	30.9	
standard deviation	± 12.45	± 19.76	-
Gender, Male/Female			
Units: participants			
Female	0	0	0
Male	10	9	19

End points

End points reporting groups

Reporting group title	rFVIIIFc 1000/3000
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Reporting group description:

Following the minimum 4-day washout, subjects received a single injection 50 IU/kg at a strength of 1000 IU/vial of rFVIIIFc (on Injection 1 Day 1) with 96 hours of PK assessments followed by a minimum of a 5-day washout prior to a second single injection of rFVIIIFc 50 IU/kg at a strength of 3000 IU/vial (on Injection 2 Day 1) with 96 hours of PK assessments.

After completing the PK assessment, all subjects began 1 of 3 continued treatment regimens for up to 6 months:

1. A prophylaxis regimen at a starting dose of 50 IU/kg of rFVIIIFc given every 3 to 5 days; further dose and interval adjustments were based on the Investigator's discretion as needed to prevent or treat bleeding
2. A prophylaxis regimen of 65 IU/kg administered every 7 days was considered for appropriate subjects who were selected based on the opinion of the Investigator
3. An episodic (on-demand) treatment with rFVIIIFc at 20 to 50 IU/kg, depending on the severity of the bleeding episode.

Reporting group title	rFVIIIFc 3000/1000
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Reporting group description:

Following the minimum 4-day washout, subjects received a single injection 50 IU/kg at a strength of 3000 IU/vial of rFVIIIFc (on Injection 1 Day 1) with 96 hours of PK assessments followed by a minimum of a 5-day washout prior to a second single injection of rFVIIIFc 50 IU/kg at a strength of 1000 IU/vial (on Injection 2 Day 1) with 96 hours of PK assessments.

After completing the PK assessment, all subjects began 1 of 3 continued treatment regimens for up to 6 months:

1. A prophylaxis regimen at a starting dose of 50 IU/kg of rFVIIIFc given every 3 to 5 days; further dose and interval adjustments were based on the Investigator's discretion as needed to prevent or treat bleeding
2. A prophylaxis regimen of 65 IU/kg administered every 7 days was considered for appropriate subjects who were selected based on the opinion of the Investigator
3. An episodic (on-demand) treatment with rFVIIIFc at 20 to 50 IU/kg, depending on the severity of the bleeding episode.

Subject analysis set title	Pharmacokinetic Analysis Set: rFVIIIFc 1000 IU
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Subject analysis set type	Per protocol
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Subject analysis set description:

The Pharmacokinetic Analysis Set is defined as all eligible subjects who received at least one dose of rFVIIIFc and had sufficient PK data points to calculate at least one of the PK parameters of interest from either the aPTT clotting assay or the two-stage chromogenic clotting assay.

Subject analysis set title	Pharmacokinetic Analysis Set: rFVIIIFc 3000 IU
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Subject analysis set type	Per protocol
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Subject analysis set description:

The Pharmacokinetic Analysis Set is defined as all eligible subjects who received at least one dose of rFVIIIFc and had sufficient PK data points to calculate at least one of the PK parameters of interest from either the aPTT clotting assay or the two-stage chromogenic clotting assay.

Subject analysis set title	Safety Analysis Set
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Subject analysis set type	Safety analysis
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Subject analysis set description:

The Safety Analysis Set included subjects who received at least 1 dose of rFVIIIFc.

Primary: Area Under the Concentration-time Curve From Time Zero to Infinity (AUCinf) as Measured by Activated Partial Thromboplastin Time (aPTT) Clotting Assay

End point title	Area Under the Concentration-time Curve From Time Zero to Infinity (AUCinf) as Measured by Activated Partial Thromboplastin Time (aPTT) Clotting Assay ^[1]
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End point description:

Area under the plasma concentration versus time curve (AUC) from time zero (pre-dose) to extrapolated infinite time (0 - ∞).

End point type	Primary
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End point timeframe:

Up to 96 hours (± 60 minutes) after each of 2 injections

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 are presented, per protocol.

End point values	Pharmacokinetic Analysis Set: rFVIIIFc 1000 IU	Pharmacokinetic Analysis Set: rFVIIIFc 3000 IU		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	17 ^[2]	18		
Units: IU*h/dL				
geometric mean (confidence interval 95%)	2888.9 (2440 to 3420.5)	2646.3 (2149.8 to 3257.5)		

Notes:

[2] - subjects with sufficient PK data

Statistical analyses

No statistical analyses for this end point

Primary: Incremental Recovery (IR, K value) as Estimated From the FVIII Activity Data Measured by aPTT Clotting Assay

End point title	Incremental Recovery (IR, K value) as Estimated From the FVIII Activity Data Measured by aPTT Clotting Assay ^[3]
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End point description:

The rise in FVIII activity in IU/dL per unit dose administered in IU/kg (IR, K value), as estimated from the FVIII activity data.

End point type	Primary
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End point timeframe:

Up to 96 hours (± 60 minutes) after each of 2 injections

Notes:

[3] - 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 are presented, per protocol.

End point values	Pharmacokinetic Analysis Set: rFVIIIFc 1000 IU	Pharmacokinetic Analysis Set: rFVIIIFc 3000 IU		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	18	18		
Units: IU/dL				
geometric mean (confidence interval 95%)	2.33 (2.182 to 2.487)	2.412 (2.169 to 2.682)		

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Activity (Cmax) as Measured by the aPTT Clotting Assay

End point title	Maximum Activity (Cmax) as Measured by the aPTT Clotting Assay
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End point description:

Maximum measured concentration of rFVIIIFc.

End point type	Secondary
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End point timeframe:

Up to 96 hours (±60 minutes) after each of 2 injections

End point values	Pharmacokinetic Analysis Set: rFVIIIFc 1000 IU	Pharmacokinetic Analysis Set: rFVIIIFc 3000 IU		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	18	18		
Units: IU/dL				
geometric mean (confidence interval 95%)	122.2 (113.77 to 131.25)	129.08 (114.62 to 145.37)		

Statistical analyses

No statistical analyses for this end point

Secondary: Half-life (t_{1/2}) as Measured by aPTT Clotting Assay

End point title	Half-life (t _{1/2}) as Measured by aPTT Clotting Assay
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End point description:

Time required for the concentration of the drug to reach half of its original value.

End point type	Secondary
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End point timeframe:

Up to 96 hours (±60 minutes) after each of 2 injections

End point values	Pharmacokinetic Analysis Set: rFVIIIFc 1000 IU	Pharmacokinetic Analysis Set: rFVIIIFc 3000 IU		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	17 ^[4]	18		
Units: hours				
geometric mean (confidence interval 95%)	18.28 (16.1 to 20.75)	17.49 (15.22 to 20.1)		

Notes:

[4] - subjects with sufficient PK data

Statistical analyses

No statistical analyses for this end point

Secondary: Clearance (CL) as Measured by the aPTT Clotting Assay

End point title	Clearance (CL) as Measured by the aPTT Clotting Assay
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End point description:

The measure of the efficiency of the body to remove the drug and the unit is the volume of the plasma or blood cleared of drug per unit time.

End point type	Secondary
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End point timeframe:

Up to 96 hours (± 60 minutes) after each of 2 injections

End point values	Pharmacokinetic Analysis Set: rFVIIIFc 1000 IU	Pharmacokinetic Analysis Set: rFVIIIFc 3000 IU		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	17 ^[5]	18		
Units: mL/h/kg				
geometric mean (confidence interval 95%)	1.807 (1.534 to 2.128)	2.016 (1.642 to 2.476)		

Notes:

[5] - subjects with sufficient PK data

Statistical analyses

No statistical analyses for this end point

Secondary: Volume of Distribution at Steady State (Vss) as Measured by the aPTT Clotting Assay

End point title	Volume of Distribution at Steady State (Vss) as Measured by the aPTT Clotting Assay
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End point description:

The apparent volume of distribution at steady state. (Volume of distribution is defined as the theoretical volume in which the total amount of drug would need to be uniformly distributed to produce the desired blood concentration of a drug.)

End point type	Secondary
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End point timeframe:

Up to 96 hours (± 60 minutes) after each of 2 injections

End point values	Pharmacokinetic Analysis Set: rFVIIIFc 1000 IU	Pharmacokinetic Analysis Set: rFVIIIFc 3000 IU		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	17 ^[6]	18		
Units: mL/kg				
geometric mean (confidence interval 95%)	47 (43.87 to 50.35)	48.65 (44.83 to 52.79)		

Notes:

[6] - subjects with sufficient PK data

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Residence Time (MRT) as Measured by the aPTT Clotting Assay

End point title	Mean Residence Time (MRT) as Measured by the aPTT Clotting Assay
End point description: The average time at which the number of absorbed molecules reside in the body, after single-dose administration.	
End point type	Secondary
End point timeframe: Up to 96 hours (±60 minutes) after each of 2 injections	

End point values	Pharmacokinetic Analysis Set: rFVIIIFc 1000 IU	Pharmacokinetic Analysis Set: rFVIIIFc 3000 IU		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	17 ^[7]	18		
Units: hours				
geometric mean (confidence interval 95%)	26.01 (22.49 to 30.08)	24.13 (20.46 to 28.46)		

Notes:

[7] - subjects with sufficient PK data

Statistical analyses

No statistical analyses for this end point

Secondary: Time of Cmax (Tmax) as Measured by aPTT Clotting Assay

End point title	Time of Cmax (Tmax) as Measured by aPTT Clotting Assay
End point description: Time at which maximum activity (Cmax) is observed.	
End point type	Secondary
End point timeframe: Up to 96 hours (±60 minutes) after each of 2 injections	

End point values	Pharmacokinetic Analysis Set: rFVIIIFc 1000 IU	Pharmacokinetic Analysis Set: rFVIIIFc 3000 IU		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	18	18		
Units: hours				
geometric mean (confidence interval 95%)	0.66 (0.55 to 0.79)	0.58 (0.51 to 0.67)		

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Curve to the Last Measurable Time Point (AUClast) as Measured by aPTT Clotting Assay

End point title	Area Under the Curve to the Last Measurable Time Point (AUClast) as Measured by aPTT Clotting Assay
End point description:	Area under the plasma concentration time-curve from zero to the last measured concentration.
End point type	Secondary
End point timeframe:	Up to 96 hours (±60 minutes) after each of 2 injections

End point values	Pharmacokinetic Analysis Set: rFVIIIFc 1000 IU	Pharmacokinetic Analysis Set: rFVIIIFc 3000 IU		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	17 ^[8]	18		
Units: IU*h/dL				
geometric mean (confidence interval 95%)	2792.5 (2378.5 to 3278.6)	2562.2 (2100.8 to 3125)		

Notes:

[8] - subjects with sufficient PK data

Statistical analyses

No statistical analyses for this end point

Secondary: Terminal Exponential Rate Constant (Lambda Z) as Measured by aPTT Clotting Assay

End point title	Terminal Exponential Rate Constant (Lambda Z) as Measured by aPTT Clotting Assay
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End point description:

First order rate constant associated with the terminal portion of the curve (λ_z).

End point type	Secondary
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End point timeframe:

Up to 96 hours (± 60 minutes) after each of 2 injections

End point values	Pharmacokinetic Analysis Set: rFVIIIFc 1000 IU	Pharmacokinetic Analysis Set: rFVIIIFc 3000 IU		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	17 ^[9]	18		
Units: 1/h				
geometric mean (confidence interval 95%)	0.03792 (0.0334 to 0.04304)	0.03963 (0.03449 to 0.04554)		

Notes:

[9] - subjects with sufficient PK data

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of AUCinf From the Last Data Point to Infinity (AUCext) as Measured by aPTT Clotting Assay

End point title	Percentage of AUCinf From the Last Data Point to Infinity (AUCext) as Measured by aPTT Clotting Assay
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End point description:

Percentage of AUCinf extrapolated from the last data point to infinity.

End point type	Secondary
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End point timeframe:

Up to 96 hours (± 60 minutes) after each of 2 injections

End point values	Pharmacokinetic Analysis Set: rFVIIIFc 1000 IU	Pharmacokinetic Analysis Set: rFVIIIFc 3000 IU		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	17 ^[10]	18		
Units: percentage of AUCinf				
geometric mean (confidence interval 95%)	2.561 (1.703 to 3.852)	2.279 (1.505 to 3.45)		

Notes:

[10] - subjects with sufficient PK data

Statistical analyses

No statistical analyses for this end point

Secondary: Dose Normalized Area Under the Curve (DNAUC) as Measured by aPTT Clotting Assay

End point title	Dose Normalized Area Under the Curve (DNAUC) as Measured by aPTT Clotting Assay
End point description: Dose normalized area under the FVIII activity-time curve.	
End point type	Secondary
End point timeframe: Up to 96 hours (± 60 minutes) after each of 2 injections	

End point values	Pharmacokinetic Analysis Set: rFVIIIIFc 1000 IU	Pharmacokinetic Analysis Set: rFVIIIIFc 3000 IU		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	17 ^[11]	18		
Units: IU*h/dL per IU/kg				
geometric mean (confidence interval 95%)	55.35 (47 to 65.18)	49.6 (40.4 to 60.9)		

Notes:

[11] - subjects with sufficient PK data

Statistical analyses

No statistical analyses for this end point

Secondary: Terminal Exponential Volume of Distribution (V_z) as Measured by aPTT Clotting Assay

End point title	Terminal Exponential Volume of Distribution (V _z) as Measured by aPTT Clotting Assay
End point description: The theoretical volume in which the total amount of drug would need to be uniformly distributed to produce the desired plasma concentration of a drug.	
End point type	Secondary
End point timeframe: Up to 96 hours (± 60 minutes) after each of 2 injections	

End point values	Pharmacokinetic Analysis Set: rFVIIIIFc 1000 IU	Pharmacokinetic Analysis Set: rFVIIIIFc 3000 IU		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	17 ^[12]	18		
Units: mL/kg				
geometric mean (confidence interval 95%)	47.65 (43.73 to 51.93)	50.87 (45.56 to 56.8)		

Notes:

[12] - subjects with sufficient PK data

Statistical analyses

No statistical analyses for this end point

Secondary: AUCinf as Estimated From the FVIII Activity Data as Measured by Two-Stage Chromogenic Clotting Assay

End point title	AUCinf as Estimated From the FVIII Activity Data as Measured by Two-Stage Chromogenic Clotting Assay
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End point description:

Area under the plasma concentration versus time curve (AUC) from time zero (pre-dose) to extrapolated infinite time (0 - ∞).

End point type	Secondary
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End point timeframe:

Up to 96 hours (± 60 minutes) after each of 2 injections

End point values	Pharmacokinetic Analysis Set: rFVIIIFc 1000 IU	Pharmacokinetic Analysis Set: rFVIIIFc 3000 IU		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15 ^[13]	16 ^[14]		
Units: IU*h/dL				
geometric mean (confidence interval 95%)	2649 (2230.2 to 3146.5)	2628 (2206.2 to 3130.5)		

Notes:

[13] - subjects with sufficient PK data

[14] - subjects with sufficient PK data

Statistical analyses

No statistical analyses for this end point

Secondary: IR, K Value as Measured by Two-Stage Chromogenic Clotting Assay

End point title	IR, K Value as Measured by Two-Stage Chromogenic Clotting Assay
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End point description:

The rise in FVIII activity in IU/dL per unit dose administered in IU/kg (IR, K value), as estimated from the FVIII activity data.

End point type	Secondary
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End point timeframe:

Up to 96 hours (± 60 minutes) after each of 2 injections

End point values	Pharmacokinetic Analysis Set: rFVIIIFc 1000 IU	Pharmacokinetic Analysis Set: rFVIIIFc 3000 IU		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	17 ^[15]	18		
Units: IU/dL per IU/kg				
geometric mean (confidence interval 95%)	2.535 (2.245 to 2.862)	2.287 (2.01 to 2.601)		

Notes:

[15] - subjects with sufficient PK data

Statistical analyses

No statistical analyses for this end point

Secondary: Cmax as Measured by Two-Stage Chromogenic Clotting Assay

End point title	Cmax as Measured by Two-Stage Chromogenic Clotting Assay
End point description:	Maximum measured concentration of rFVIIIFc.
End point type	Secondary
End point timeframe:	Up to 96 hours (±60 minutes) after each of 2 injections

End point values	Pharmacokinetic Analysis Set: rFVIIIFc 1000 IU	Pharmacokinetic Analysis Set: rFVIIIFc 3000 IU		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	17 ^[16]	18		
Units: IU/dL				
geometric mean (confidence interval 95%)	132.61 (116.85 to 150.5)	122.29 (106.8 to 140.03)		

Notes:

[16] - subjects with sufficient PK data

Statistical analyses

No statistical analyses for this end point

Secondary: t_{1/2} as Measured by Two-Stage Chromogenic Clotting Assay

End point title	t _{1/2} as Measured by Two-Stage Chromogenic Clotting Assay
End point description:	Time required for the concentration of the drug to reach half of its original value.
End point type	Secondary
End point timeframe:	Up to 96 hours (±60 minutes) after each of 2 injections

End point values	Pharmacokinetic Analysis Set: rFVIIIFc 1000 IU	Pharmacokinetic Analysis Set: rFVIIIFc 3000 IU		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15 ^[17]	16 ^[18]		
Units: hours				
geometric mean (confidence interval 95%)	18.58 (16.35 to 21.12)	19.1 (16.44 to 22.19)		

Notes:

[17] - subjects with sufficient PK data

[18] - subjects with sufficient PK data

Statistical analyses

No statistical analyses for this end point

Secondary: CL as Measured by Two-Stage Chromogenic Clotting Assay

End point title	CL as Measured by Two-Stage Chromogenic Clotting Assay
End point description:	
The measure of the efficiency of the body to remove the drug and the unit is the volume of the plasma or blood cleared of drug per unit time.	
End point type	Secondary
End point timeframe:	
Up to 96 hours (±60 minutes) after each of 2 injections	

End point values	Pharmacokinetic Analysis Set: rFVIIIFc 1000 IU	Pharmacokinetic Analysis Set: rFVIIIFc 3000 IU		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15 ^[19]	16 ^[20]		
Units: mL/h/kg				
geometric mean (confidence interval 95%)	1.962 (1.665 to 2.311)	2.006 (1.72 to 2.339)		

Notes:

[19] - subjects with sufficient PK data

[20] - subjects with sufficient PK data

Statistical analyses

No statistical analyses for this end point

Secondary: Vss as Measured by Two-Stage Chromogenic Clotting Assay

End point title	Vss as Measured by Two-Stage Chromogenic Clotting Assay
End point description:	
The apparent volume of distribution at steady state. (Volume of distribution is defined as the theoretical volume in which the total amount of drug would need to be uniformly distributed to produce the desired blood concentration of a drug.)	

End point type	Secondary
End point timeframe:	
Up to 96 hours (±60 minutes) after each of 2 injections	

End point values	Pharmacokinetic Analysis Set: rFVIIIFc 1000 IU	Pharmacokinetic Analysis Set: rFVIIIFc 3000 IU		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15 ^[21]	16 ^[22]		
Units: mL/kg				
geometric mean (confidence interval 95%)	47.41 (43.01 to 52.26)	51.27 (44.65 to 58.88)		

Notes:

[21] - subjects with sufficient PK data

[22] - subjects with sufficient PK data

Statistical analyses

No statistical analyses for this end point

Secondary: MRT as Measured by Two-Stage Chromogenic Clotting Assay

End point title	MRT as Measured by Two-Stage Chromogenic Clotting Assay
End point description:	
The average time at which the number of absorbed molecules reside in the body, after single-dose administration.	
End point type	Secondary
End point timeframe:	
Up to 96 hours (±60 minutes) after each of 2 injections	

End point values	Pharmacokinetic Analysis Set: rFVIIIFc 1000 IU	Pharmacokinetic Analysis Set: rFVIIIFc 3000 IU		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15 ^[23]	16 ^[24]		
Units: hours				
geometric mean (confidence interval 95%)	24.17 (21.16 to 27.6)	25.56 (22.15 to 29.5)		

Notes:

[23] - subjects with sufficient PK data

[24] - subjects with sufficient PK data

Statistical analyses

No statistical analyses for this end point

Secondary: Tmax as Measured by Two-Stage Chromogenic Clotting Assay

End point title	Tmax as Measured by Two-Stage Chromogenic Clotting Assay
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End point description:	
Time at which maximum activity (Cmax) is observed.	
End point type	Secondary
End point timeframe:	
Up to 96 hours (±60 minutes) after each of 2 injections	

End point values	Pharmacokinetic Analysis Set: rFVIIIFc 1000 IU	Pharmacokinetic Analysis Set: rFVIIIFc 3000 IU		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	17 ^[25]	18		
Units: hours				
geometric mean (confidence interval 95%)	0.61 (0.51 to 0.71)	0.61 (0.52 to 0.72)		

Notes:

[25] - subjects with sufficient PK data

Statistical analyses

No statistical analyses for this end point

Secondary: AUClast as Measured by Two-Stage Chromogenic Clotting Assay

End point title	AUClast as Measured by Two-Stage Chromogenic Clotting Assay
End point description:	
Area under the plasma concentration time-curve from zero to the last measured concentration.	
End point type	Secondary
End point timeframe:	
Up to 96 hours (±60 minutes) after each of 2 injections	

End point values	Pharmacokinetic Analysis Set: rFVIIIFc 1000 IU	Pharmacokinetic Analysis Set: rFVIIIFc 3000 IU		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15 ^[26]	16 ^[27]		
Units: IU*h/dL				
geometric mean (confidence interval 95%)	2555.4 (2166.7 to 3013.9)	2520.5 (2124.4 to 2990.5)		

Notes:

[26] - subjects with sufficient PK data

[27] - subjects with sufficient PK data

Statistical analyses

No statistical analyses for this end point

Secondary: Lambda Z as Measured by Two-Stage Chromogenic Clotting Assay

End point title	Lambda Z as Measured by Two-Stage Chromogenic Clotting Assay
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End point description:

First order rate constant associated with the terminal portion of the curve (lambda z).

End point type	Secondary
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End point timeframe:

Up to 96 hours (± 60 minutes) after each of 2 injections

End point values	Pharmacokinetic Analysis Set: rFVIIIFc 1000 IU	Pharmacokinetic Analysis Set: rFVIIIFc 3000 IU		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15 ^[28]	16 ^[29]		
Units: 1/h				
geometric mean (confidence interval 95%)	0.0373 (0.03282 to 0.04239)	0.03629 (0.03124 to 0.04216)		

Notes:

[28] - subjects with sufficient PK data

[29] - subjects with sufficient PK data

Statistical analyses

No statistical analyses for this end point

Secondary: AUCext as Measured by Two-Stage Chromogenic Clotting Assay

End point title	AUCext as Measured by Two-Stage Chromogenic Clotting Assay
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End point description:

Percentage of AUCinf extrapolated from the last data point to infinity.

End point type	Secondary
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End point timeframe:

Up to 96 hours (± 60 minutes) after each of 2 injections

End point values	Pharmacokinetic Analysis Set: rFVIIIFc 1000 IU	Pharmacokinetic Analysis Set: rFVIIIFc 3000 IU		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15 ^[30]	16 ^[31]		
Units: percentage of AUCinf				
geometric mean (confidence interval 95%)	2.923 (2.106 to 4.057)	2.965 (1.89 to 4.65)		

Notes:

[30] - subjects with sufficient PK data

[31] - subjects with sufficient PK data

Statistical analyses

No statistical analyses for this end point

Secondary: DNAUC as Measured by Two-Stage Chromogenic Clotting Assay

End point title	DNAUC as Measured by Two-Stage Chromogenic Clotting Assay
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End point description:

Dose normalized area under the FVIII activity-time curve.

End point type	Secondary
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End point timeframe:

Up to 96 hours (± 60 minutes) after each of 2 injections

End point values	Pharmacokinetic Analysis Set: rFVIIIFc 1000 IU	Pharmacokinetic Analysis Set: rFVIIIFc 3000 IU		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15 ^[32]	16 ^[33]		
Units: IU*h/dL per IU/kg				
geometric mean (confidence interval 95%)	50.97 (43.27 to 60.05)	49.85 (42.75 to 58.13)		

Notes:

[32] - subjects with sufficient PK data

[33] - subjects with sufficient PK data

Statistical analyses

No statistical analyses for this end point

Secondary: Vz as Measured by Two-Stage Chromogenic Clotting Assay

End point title	Vz as Measured by Two-Stage Chromogenic Clotting Assay
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End point description:

The theoretical volume in which the total amount of drug would need to be uniformly distributed to produce the desired plasma concentration of a drug.

End point type	Secondary
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End point timeframe:

Up to 96 hours (± 60 minutes) after each of 2 injections

End point values	Pharmacokinetic Analysis Set: rFVIIIFc 1000 IU	Pharmacokinetic Analysis Set: rFVIIIFc 3000 IU		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15 ^[34]	16 ^[35]		
Units: mL/kg				
geometric mean (confidence interval 95%)	52.59 (47.31 to 58.47)	55.28 (47.12 to 64.84)		

Notes:

[34] - subjects with sufficient PK data

[35] - subjects with sufficient PK data

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Developing Confirmed Inhibitors as Measured by the Nijmegen-modified Bethesda Assay

End point title	Percentage of Subjects Developing Confirmed Inhibitors as Measured by the Nijmegen-modified Bethesda Assay
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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. An exact 95% CI for the percentage of subjects with a confirmed inhibitor was calculated using the Clopper-Pearson exact method.

End point type	Secondary
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End point timeframe:

up to Month 6 (26 \pm 2 weeks) or Early Withdrawal

End point values	Safety Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	19			
Units: percentage of subjects				
number (confidence interval 95%)	0 (0 to 17.65)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From screening (for serious adverse events) or first dose of study drug (for adverse events) until end of study (up to approximately 6 months).

Adverse event reporting additional description:

Adverse events presented are treatment-emergent (ie, those that occurred or worsened following the first injection of rFVIIIFc).

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	Total active
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Reporting group description:

Following the minimum 4-day washout, subjects received their first injection of rFVIIIFc (on Injection 1 Day 1) rFVIIIFc 50 IU/kg at a strength of either 1000 IU/vial or 3000 IU/vial. The second injection of rFVIIIFc 50 IU/kg at a strength of either 1000 IU/vial or 3000 IU/vial was administered, in a crossover fashion, after a minimum of a 5-day washout (on Injection 2 Day 1).

After completing the PK assessment, all subjects began 1 of 3 continued treatment regimens for up to 6 months:

1. A prophylaxis regimen at a starting dose of 50 IU/kg of rFVIIIFc given every 3 to 5 days; further dose and interval adjustments were based on the Investigator's discretion as needed to prevent or treat bleeding
2. A prophylaxis regimen of 65 IU/kg administered every 7 days was considered for appropriate subjects who were selected based on the opinion of the Investigator
3. An episodic (on-demand) treatment with rFVIIIFc at 20 to 50 IU/kg, depending on the severity of the bleeding episode

Serious adverse events	Total active		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 19 (10.53%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Congenital, familial and genetic disorders			
Hydrocele			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Arthropathy			

subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Total active		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 19 (63.16%)		
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Fall			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Joint injury			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Limb injury			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	2		
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Ear and labyrinth disorders			
Tympanic membrane perforation			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			

Acne subjects affected / exposed occurrences (all)	2 / 19 (10.53%) 2		
Musculoskeletal and connective tissue disorders Musculoskeletal chest pain subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1		
Infections and infestations Influenza subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all) Oral herpes subjects affected / exposed occurrences (all) Post procedural cellulitis subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1 2 / 19 (10.53%) 2 1 / 19 (5.26%) 1 1 / 19 (5.26%) 1 1 / 19 (5.26%) 1		
Metabolism and nutrition disorders Vitamin d deficiency subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported