



## Clinical trial results:

### A Randomised, Open-label Study to Evaluate the Pharmacokinetics and Safety of Recombinant Factor VIII Fc Fusion Protein (Recombinant Coagulation Factor VIII Fc Fusion Protein [rFVIII-Fc]; BII031) Manufactured at 15K Scale and at Different Vial Strengths in Previously Treated Subjects With Severe Hemophilia A

#### Summary

EudraCT number	2014-003895-21
Trial protocol	Outside EU/EEA
Global end of trial date	03 April 2017

#### Results information

Result version number	v1 (current)
This version publication date	20 May 2021
First version publication date	20 May 2021

#### Trial information

##### Trial identification

Sponsor protocol code	997HA309
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02502149
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	Biogen MA Inc.
Sponsor organisation address	250 Binney Street, Cambridge, MA, United States, 02142
Public contact	Trial Transparency Team, Sanofi aventis recherche & développement, Contact-US@sanofi.com
Scientific contact	Trial Transparency Team, Sanofi aventis recherche & développement, Contact-US@sanofi.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	17 May 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	03 April 2017
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 compare the pharmacokinetics (PK) of Recombinant Coagulation Factor VIII Fc Fusion Protein (rFVIIIFc) manufactured at the current scale of 2000 litres (L) (2K [2000 litres bioreactor scale]) to the PK of rFVIIIFc manufactured at the 15,000 L (15K [15000 litres bioreactor scale]) scale in previously treated subjects with severe hemophilia A.

Protection of trial subjects:

The study was conducted by investigators experienced in the treatment of adolescent and adult subjects. The parent(s) or guardian(s) as well as the subjects were fully informed of all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time. In addition to the consent form for the parent(s)/guardian(s), an assent form in age-appropriate language was provided and explained to the subject. Repeated invasive procedures were minimised. The number of blood samples as well as the amount of blood drawn were adjusted according to age and weight. All subjects were fully informed of all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time in language and terms appropriate for the subject and considering the local culture. During the course of the trial, subjects were provided with individual subject cards indicating the nature of the trial the subject is participating, contact details and any information needed in the event of a medical emergency. Collected personal data and human biological samples were processed in accordance with the trial subjects' written informed consent and applicable personal data protection laws.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	31 August 2015
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 States: 7
Country: Number of subjects enrolled	Australia: 5
Country: Number of subjects enrolled	New Zealand: 12
Worldwide total number of subjects	24
EEA total number of subjects	0

Notes:

### Subjects enrolled per age group

In utero	0
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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)	2
Adults (18-64 years)	22
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

The study was conducted at 11 active centres in 3 countries. 24 subjects were enrolled between 31 August 2015 and 4 August 2016. Washout period (between PK1 and PK2) started at the time of the PK1 dosing (PK1 assessment); at this stage 1 subject of 15K 6000 International Unit (IU)/vial cohort discontinued before entering PK2 assessment period.

### Pre-assignment

Screening details:

Subjects were randomised on Day 1 of PK 1 via the Interactive Voice/Web Response System in a 1:1 ratio to receive either 1000 IU/vial or 6000 IU/vial of 15K rFVIIIFc in the subsequent PK2 and PK3 assessments.

### Period 1

Period 1 title	Pharmacokinetic 1 (PK1) Assessment
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

### Arms

Arm title	2K rFVIIIFc (1000 IU/Vial Strength) (PK1)
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Arm description:

All subjects received rFVIIIFc (1000 IU/vial strength), 50 IU per kilogram (IU/kg), manufactured in 2K for PK1 assessment.

Arm type	Experimental
Investigational medicinal product name	Recombinant coagulation factor VIII Fc fusion protein
Investigational medicinal product code	
Other name	rFVIIIFc; BIIB031
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

On Day 1, a single intravenous (IV) injection of 2K rFVIIIFc, 50 IU/kg of 1000 IU/vial.

Number of subjects in period 1	2K rFVIIIFc (1000 IU/Vial Strength) (PK1)
Started	24
Completed	24

### Period 2

Period 2 title	Washout Period (between PK1 and PK2)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

## Arms

Arm title	2K rFVIIIFc (1000 IU/Vial Strength) (PK1)
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Arm description:

All subjects received rFVIIIFc (1000 IU/vial strength), 50 IU/kg, manufactured in 2K for PK1.

Arm type	Experimental
Investigational medicinal product name	Recombinant coagulation factor VIII Fc fusion protein
Investigational medicinal product code	
Other name	rFVIIIFc; BIIB031
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

On Day 1, a single IV injection of 2K rFVIIIFc, 50 IU/kg of 1000 IU/vial.

Number of subjects in period 2	2K rFVIIIFc (1000 IU/Vial Strength) (PK1)
Started	24
Completed	23
Not completed	1
Discontinued prematurely	1

## Period 3

Period 3 title	Treatment Period - PK2 Assessment
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

## Arms

Are arms mutually exclusive?	Yes
Arm title	15K rFVIIIFc (1000 IU/Vial Strength) (PK2)

Arm description:

During the PK1 assessment period, subjects randomised in a 1:1 ratio to receive either 1000 IU/vial or 6000 IU/vial of 15K rFVIIIFc (a single IV injection of 50 IU/kg) in the subsequent pharmacokinetic 2 (PK2) assessment and pharmacokinetic 3 (PK3) assessment. For this treatment arm, subjects that received rFVIIIFc (1000 IU/vial strength), 50 IU/kg, manufactured in 15K for PK2 after a minimum of 120 hours (hr) of washout prior to the PK2. Following PK2 assessment, subjects received prophylactic treatment with any of 5 available 15K vial strengths during the treatment phase of 13 weeks.

Arm type	Experimental
Investigational medicinal product name	Recombinant coagulation factor VIII Fc fusion protein
Investigational medicinal product code	
Other name	rFVIIIFc; BIIB031
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Within 2 to 6 weeks after PK1 assessment, a single IV injection of 15K rFVIIIFc (1000 IU/vial strength), 50 IU/kg.

<b>Arm title</b>	15K rFVIIIFc (6000 IU/Vial Strength) (PK2)
Arm description: During the PK1 assessment period, subjects randomised in a 1:1 ratio to receive either 1000 IU/vial or 6000 IU/vial of 15K rFVIIIFc (a single IV injection of 50 IU/kg) in the subsequent PK2 and PK3 assessments. For this treatment arm, subjects that received rFVIIIFc (6000 IU/vial strength), 50 IU/kg, manufactured in 15K for PK2 after a minimum of 120 hr of washout prior to the PK2. Following PK2 assessment, subjects received prophylactic treatment with any of 5 available 15K vial strengths during the treatment phase of 13 weeks.	
Arm type	Experimental
Investigational medicinal product name	Recombinant coagulation factor VIII Fc fusion protein
Investigational medicinal product code	
Other name	rFVIIIFc; BIIB031
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

**Dosage and administration details:**

Within 2 to 6 weeks after PK1 assessment, a single IV injection of 15K rFVIIIFc (6000 IU/vial strength), 50 IU/kg.

<b>Number of subjects in period 3</b>	15K rFVIIIFc (1000 IU/Vial Strength) (PK2)	15K rFVIIIFc (6000 IU/Vial Strength) (PK2)
Started	11	12
Completed	11	12

**Period 4**

Period 4 title	Treatment Period - PK3 Assessment
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

**Arms**

Are arms mutually exclusive?	Yes
<b>Arm title</b>	15K rFVIIIFc (1000 IU/Vial Strength) (PK3)

**Arm description:**

During the PK1 assessment period, subjects randomised in a 1:1 ratio to receive either 1000 IU/vial or 6000 IU/vial of 15K rFVIIIFc (a single IV injection of 50 IU/kg) in the subsequent PK2 and PK3 assessments. For this treatment arm, subjects that received rFVIIIFc (1000 IU/vial strength), 50 IU/kg, manufactured in 15K for PK2 assessment were re-evaluated after 13 weeks on treatment for PK3 assessment at same vial strength.

Arm type	Experimental
Investigational medicinal product name	Recombinant coagulation factor VIII Fc fusion protein
Investigational medicinal product code	
Other name	rFVIIIFc; BIIB031
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

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**Dosage and administration details:**

After 13 weeks of PK2 assessment, a single IV injection of 15K rFVIIIFc (1000 IU/vial strength), 50 IU/kg.

<b>Arm title</b>	15K rFVIIIFc (6000 IU/Vial Strength) (PK3)
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**Arm description:**

During the PK1 assessment period, subjects randomised in a 1:1 ratio to receive either 1000 IU/vial or 6000 IU/vial of 15K rFVIIIFc (a single IV injection of 50 IU/kg) in the subsequent PK2 and PK3 assessments. For this treatment arm, subjects that received rFVIIIFc (6000 IU/vial strength), 50 IU/kg, manufactured in 15K for PK2 assessment were re-evaluated after 13 weeks on treatment for PK3 assessment at same vial strength.

Arm type	Experimental
Investigational medicinal product name	Recombinant coagulation factor VIII Fc fusion protein
Investigational medicinal product code	
Other name	rFVIIIFc; BIIB031
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

**Dosage and administration details:**

After 13 weeks of PK2 assessment, a single IV injection of 15K rFVIIIFc (6000 IU/vial strength), 50 IU/kg.

<b>Number of subjects in period 4</b>	15K rFVIIIFc (1000 IU/Vial Strength) (PK3)	15K rFVIIIFc (6000 IU/Vial Strength) (PK3)
Started	11	12
Completed	11	12

## Baseline characteristics

### Reporting groups

Reporting group title	Pharmacokinetic 1 (PK1) Assessment
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Reporting group description:

All subjects received rFVIIIFc (1000 IU/vial strength), 50 IU/kg, manufactured in 2K for PK1.

Reporting group values	Pharmacokinetic 1 (PK1) Assessment	Total	
Number of subjects	24	24	
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	30.8 ± 12.78	-	
Gender categorical Units: Subjects			
Female	0	0	
Male	24	24	
Ethnicity Units: Subjects			
Hispanic or Latino	1	1	
Not Hispanic or Latino	6	6	
Not reported	17	17	



## End points

### End points reporting groups

Reporting group title	2K rFVIIIFc (1000 IU/Vial Strength) (PK1)
Reporting group description: All subjects received rFVIIIFc (1000 IU/vial strength), 50 IU per kilogram (IU/kg), manufactured in 2K for PK1 assessment.	
Reporting group title	2K rFVIIIFc (1000 IU/Vial Strength) (PK1)
Reporting group description: All subjects received rFVIIIFc (1000 IU/vial strength), 50 IU/kg, manufactured in 2K for PK1.	
Reporting group title	15K rFVIIIFc (1000 IU/Vial Strength) (PK2)
Reporting group description: During the PK1 assessment period, subjects randomised in a 1:1 ratio to receive either 1000 IU/vial or 6000 IU/vial of 15K rFVIIIFc (a single IV injection of 50 IU/kg) in the subsequent pharmacokinetic 2 (PK2) assessment and pharmacokinetic 3 (PK3) assessment. For this treatment arm, subjects that received rFVIIIFc (1000 IU/vial strength), 50 IU/kg, manufactured in 15K for PK2 after a minimum of 120 hours (hr) of washout prior to the PK2. Following PK2 assessment, subjects received prophylactic treatment with any of 5 available 15K vial strengths during the treatment phase of 13 weeks.	
Reporting group title	15K rFVIIIFc (6000 IU/Vial Strength) (PK2)
Reporting group description: During the PK1 assessment period, subjects randomised in a 1:1 ratio to receive either 1000 IU/vial or 6000 IU/vial of 15K rFVIIIFc (a single IV injection of 50 IU/kg) in the subsequent PK2 and PK3 assessments. For this treatment arm, subjects that received rFVIIIFc (6000 IU/vial strength), 50 IU/kg, manufactured in 15K for PK2 after a minimum of 120 hr of washout prior to the PK2. Following PK2 assessment, subjects received prophylactic treatment with any of 5 available 15K vial strengths during the treatment phase of 13 weeks.	
Reporting group title	15K rFVIIIFc (1000 IU/Vial Strength) (PK3)
Reporting group description: During the PK1 assessment period, subjects randomised in a 1:1 ratio to receive either 1000 IU/vial or 6000 IU/vial of 15K rFVIIIFc (a single IV injection of 50 IU/kg) in the subsequent PK2 and PK3 assessments. For this treatment arm, subjects that received rFVIIIFc (1000 IU/vial strength), 50 IU/kg, manufactured in 15K for PK2 assessment were re-evaluated after 13 weeks on treatment for PK3 assessment at same vial strength.	
Reporting group title	15K rFVIIIFc (6000 IU/Vial Strength) (PK3)
Reporting group description: During the PK1 assessment period, subjects randomised in a 1:1 ratio to receive either 1000 IU/vial or 6000 IU/vial of 15K rFVIIIFc (a single IV injection of 50 IU/kg) in the subsequent PK2 and PK3 assessments. For this treatment arm, subjects that received rFVIIIFc (6000 IU/vial strength), 50 IU/kg, manufactured in 15K for PK2 assessment were re-evaluated after 13 weeks on treatment for PK3 assessment at same vial strength.	
Subject analysis set title	15K rFVIIIFc (1000 and 6000 IU/Vial Strength Combined) (PK2)
Subject analysis set type	Safety analysis
Subject analysis set description: Subjects who received 2K rFVIIIFc 1000 IU/vial (50 IU/kg) for PK1 were randomised to receive rFVIIIFc (1000 or 6000 IU/vial strength), 50 IU/kg, manufactured in 15K for PK2. Following PK2, subjects received prophylactic treatment with any of 5 available 15K vial strengths during the treatment phase. After 13 weeks of treatment with 15K rFVIIIFc, subjects were re-evaluated at PK3 at the same vial strength as in PK2. A minimum of 120 hr of washout was observed prior to the PK2. Following the PK3, subjects resumed rFVIIIFc in the Treatment Period until they complete a total of at least 26 weeks of treatment.	
Subject analysis set title	15K rFVIIIFc (1000 and 6000 IU/Vial Strength Combined) (PK3)
Subject analysis set type	Safety analysis
Subject analysis set description: Subjects who were randomised to receive 15K rFVIIIFc 1000 or 6000 IU/vial for PK2 assessment were re-evaluated after 13 weeks on treatment for PK3 assessment at same vial strength.	
Subject analysis set title	2K/15K rFVIIIFc (1000/6000 IU/Vial Strength)- All Subjects

Subject analysis set type	Safety analysis
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Subject analysis set description:

All subjects received rFVIIIFc (1000 IU/vial strength), 50 IU/kg, manufactured in 2K for PK1. At PK1, subjects were randomised to receive rFVIIIFc (1000 or 6000 IU/vial strength), 50 IU/kg, manufactured in 15K for PK2. Following PK2 assessments, subjects received prophylactic treatment with any of 5 available 15K vial strengths during the treatment phase. After 13 weeks of treatment with 15K rFVIIIFc, subjects were re-evaluated at PK3 at the same vial strength as in PK2. A minimum of 120 hr of washout was observed prior to the PK2 assessment. Following the PK3 assessment, subjects were resumed to treatment in the treatment period until they complete a total of at least 26 weeks of treatment.

Subject analysis set title	15K rFVIIIFc (1000 and 6000 IU/Vial Strength) (PK2 and PK3)
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Subject analysis set type	Safety analysis
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Subject analysis set description:

Subjects who received 2K rFVIIIFc 1000 IU/vial (50 IU/kg) for PK1 were randomised to receive rFVIIIFc (1000 or 6000 IU/vial strength), 50 IU/kg, manufactured in 15K for PK2. Following PK2, subjects received prophylactic treatment with any of 5 available 15K vial strengths during the treatment phase. After 13 weeks of treatment with 15K rFVIIIFc, subjects were re-evaluated at PK3 at the same vial strength as in PK2. A minimum of 120 hr of washout was observed prior to the PK2 assessment. Following the PK3, subjects were resumed to treatment in the Treatment Period until they complete a total of at least 26 weeks of treatment.

### **Primary: Area Under the Concentration-time Curve From Time Zero to Infinity (AUC<sub>0-inf</sub>) as Measured by One-stage Activated Partial Thromboplastin Time (aPTT) Clotting Assay for PK1 Assessment and PK2 Assessment**

End point title	Area Under the Concentration-time Curve From Time Zero to Infinity (AUC <sub>0-inf</sub> ) as Measured by One-stage Activated Partial Thromboplastin Time (aPTT) Clotting Assay for PK1 Assessment and PK2 Assessment
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End point description:

AUC<sub>0-inf</sub> is area under the concentration-time curve from time zero to infinity. Results were summarised overall for 15K rFVIIIFc 1000 IU/vial and 6000 IU/vial (PK2). The PK Analysis Set (PKAS) included all subjects who have evaluable PK profiles.

End point type	Primary
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End point timeframe:

Pre-dose and post dose at: 0.5 hr, 1 hr, 6 hr, 24 hr, 48 hr, 72 hr and 96 hr

<b>End point values</b>	2K rFVIIIFc (1000 IU/Vial Strength) (PK1)	15K rFVIIIFc (1000 and 6000 IU/Vial Strength Combined) (PK2)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	24	23		
Units: IU*hour per decilitre (IU*hr/dL)				
geometric mean (confidence interval 90%)	2255.6 (1886.2 to 2697.4)	2425.8 (2084.2 to 2823.4)		

### **Statistical analyses**

<b>Statistical analysis title</b>	PK1 versus PK2
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Statistical analysis description:

The adjusted geometric mean ratio is calculated as 15K (PK2)/2K (PK1).

Comparison groups	2K rFVIIIFc (1000 IU/Vial Strength) (PK1) v 15K rFVIIIFc
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	(1000 and 6000 IU/Vial Strength Combined) (PK2)
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Adjusted Geometric Mean Ratio
Point estimate	1.08
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.93
upper limit	1.24

### Primary: Incremental Recovery (IR) as Measured by One-stage aPTT Clotting Assay for PK1 and PK2

End point title	Incremental Recovery (IR) as Measured by One-stage aPTT Clotting Assay for PK1 and PK2
End point description:	
IR is defined as the increase in the circulating FVIII activity in international unit per decilitre (IU/dL) per unit dose administered in international unit per kilogram (IU/kg) (IU/dL per IU/kg). Results were summarised overall for 15K rFVIIIFc 1000 IU/vial and 6000 IU/vial (PK2). The PKAS included all subjects who have evaluable PK profiles.	
End point type	Primary
End point timeframe:	
Pre-dose and post dose at: 0.5 hr, 1 hr, 6 hr, 24 hr, 48 hr, 72 hr and 96 hr	

End point values	2K rFVIIIFc (1000 IU/Vial Strength) (PK1)	15K rFVIIIFc (1000 and 6000 IU/Vial Strength Combined) (PK2)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	24	23		
Units: IU/dL per IU/kg				
geometric mean (confidence interval 90%)	2.684 (2.364 to 3.049)	2.700 (2.458 to 2.964)		

### Statistical analyses

Statistical analysis title	PK1 versus PK2
Statistical analysis description:	
The adjusted geometric mean ratio is calculated as 15K (PK2)/2K (PK1).	
Comparison groups	2K rFVIIIFc (1000 IU/Vial Strength) (PK1) v 15K rFVIIIFc (1000 and 6000 IU/Vial Strength Combined) (PK2)

Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Adjusted Geometric Mean Ratio
Point estimate	1.01
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.87
upper limit	1.16

### Secondary: Maximum Activity (Cmax) of rFVIIIFc as Measured by One-stage aPTT Clotting Assay for PK1 and PK2

End point title	Maximum Activity (Cmax) of rFVIIIFc as Measured by One-stage aPTT Clotting Assay for PK1 and PK2
End point description:	Cmax is defined as maximum activity of rFVIIIFc. Results were summarised overall for 15K rFVIIIFc 1000 IU/vial and 6000 IU/vial (PK2). The PKAS included all subjects who have evaluable PK profiles.
End point type	Secondary
End point timeframe:	Pre-dose and post dose at: 0.5 hr, 1 hr, 6 hr, 24 hr, 48 hr, 72 hr and 96 hr

End point values	2K rFVIIIFc (1000 IU/Vial Strength) (PK1)	15K rFVIIIFc (1000 and 6000 IU/Vial Strength Combined) (PK2)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	24	23		
Units: IU/dL				
geometric mean (confidence interval 95%)	133.20 (123.00 to 144.24)	134.67 (121.46 to 149.32)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Half-life (t1/2) of rFVIIIFc as Measured by One-stage aPTT Clotting Assay for PK1 and PK2

End point title	Half-life (t1/2) of rFVIIIFc as Measured by One-stage aPTT Clotting Assay for PK1 and PK2
End point description:	t1/2 is time required for the concentration of the drug to reach half of its original value. Results were summarised overall for 15K 1000 IU/vial and 6000 IU/vial (PK2). The PKAS included all subjects who have evaluable PK profiles.
End point type	Secondary

End point timeframe:

Pre-dose and post dose at: 0.5 hr, 1 hr, 6 hr, 24 hr, 48 hr, 72 hr and 96 hr

End point values	2K rFVIIIFc (1000 IU/Vial Strength) (PK1)	15K rFVIIIFc (1000 and 6000 IU/Vial Strength Combined) (PK2)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	24	23		
Units: hours				
geometric mean (confidence interval 95%)	14.229 (12.458 to 16.252)	14.771 (12.910 to 16.900)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Clearance (CL) of rFVIIIFc as Measured by One-stage aPTT Clotting Assay for PK1 and PK2

End point title	Clearance (CL) of rFVIIIFc as Measured by One-stage aPTT Clotting Assay for PK1 and PK2
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End point description:

CL is a quantitative measure of the rate at which a drug substance is removed from the body. The total systemic clearance after IV dose was estimated by dividing the total administered dose by AUC(0-infinity). Results were summarised overall for 15K rFVIIIFc 1000 IU/vial and 6000 IU/vial (PK2). The PKAS included all subjects who have evaluable PK profiles.

End point type	Secondary
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End point timeframe:

Pre-dose and post dose at: 0.5 hr, 1 hr, 6 hr, 24 hr, 48 hr, 72 hr and 96 hr

End point values	2K rFVIIIFc (1000 IU/Vial Strength) (PK1)	15K rFVIIIFc (1000 and 6000 IU/Vial Strength Combined) (PK2)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	24	23		
Units: millilitre per hour per kilogram (mL/hr/kg)				
geometric mean (confidence interval 95%)	2.1847 (1.8943 to 2.5198)	2.0420 (1.7421 to 2.3935)		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Volume of Distribution at Steady State (Vss) of rFVIIIFc as Measured by One-stage aPTT Clotting Assay for PK1 and PK2

End point title	Volume of Distribution at Steady State (Vss) of rFVIIIFc as Measured by One-stage aPTT Clotting Assay for PK1 and PK2
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End point description:

Vss is defined as theoretical volume in which total amount of drug would need to be uniformly distributed to produce desired blood concentration of a drug. Vss is first moment curve extrapolated to infinity and AUC(0-infinity) is area under the plasma concentration-time curve from time zero to infinite time. Results were summarised overall for 15K rFVIIIFc 1000 IU/vial and 6000 apparent Vss which is estimated by  $(D/AUC[0\text{-infinity}]) \times (AUMC[0\text{-infinity}]/AUC[0\text{-infinity}])$  where D is dose of study drug, AUMC(0-infinity) is area under first moment curve extrapolated to infinity and AUC(0-infinity) is area under plasma concentration-time curve from time zero to infinite time. Results were summarised overall for 15K rFVIIIFc 1000 IU/vial and 6000 IU/vial (PK2). The PKAS included all subjects who have evaluable PK profiles.

End point type	Secondary
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End point timeframe:

Pre-dose and post dose at: 0.5 hr, 1 hr, 6 hr, 24 hr, 48 hr, 72 hr and 96 hr

End point values	2K rFVIIIFc (1000 IU/Vial Strength) (PK1)	15K rFVIIIFc (1000 and 6000 IU/Vial Strength Combined) (PK2)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	24	23		
Units: millilitre per kilogram (mL/kg)				
geometric mean (confidence interval 95%)	43.80 (40.70 to 47.14)	43.01 (39.69 to 46.61)		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Mean Residence Time (MRT) of rFVIIIFc as Measured by One-stage aPTT Clotting Assay for PK1 and PK2

End point title	Mean Residence Time (MRT) of rFVIIIFc as Measured by One-stage aPTT Clotting Assay for PK1 and PK2
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End point description:

The MRT is the average time at which the number of absorbed molecules reside in the body, after single-dose administration, and calculated as area under the first moment curve AUMC (0-infinity)/ AUC (0-infinity), where AUMC (0-infinity) is area under the plasma concentration-time first moment curve from time zero to infinite time and AUC (0-infinity) is the area under the plasma concentration-time curve from time zero to infinite time. Results were summarised overall for 15K rFVIIIFc 1000 IU/vial and 6000 IU/vial (PK2). The PKAS included all subjects who have evaluable PK profiles.

End point type	Secondary
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End point timeframe:

Pre-dose and post dose at: 0.5 hr, 1 hr, 6 hr, 24 hr, 48 hr, 72 hr and 96 hr

End point values	2K rFVIIIFc (1000 IU/Vial Strength) (PK1)	15K rFVIIIFc (1000 and 6000 IU/Vial Strength Combined) (PK2)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	24	23		
Units: hours				
geometric mean (confidence interval 95%)	20.048 (17.561 to 22.887)	21.063 (18.501 to 23.980)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Area Under the Concentration-time Curve From Time Zero to Infinity as Measured by One-stage aPTT Clotting Assay for PK2 and PK3

End point title	Area Under the Concentration-time Curve From Time Zero to Infinity as Measured by One-stage aPTT Clotting Assay for PK2 and PK3
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End point description:

AUC0-inf is area under the concentration-time curve from time zero to infinity. Results were summarised overall for 15K rFVIIIFc 1000 IU/vial and 6000 IU/vial for PK2 and PK3. The PKAS included all subjects who have evaluable PK profiles. Here, 'number of subjects analysed' signifies those subjects who were evaluable for this endpoint.

End point type	Secondary
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End point timeframe:

Pre-dose and post dose at: 0.5 hr, 1 hr, 6 hr, 24 hr, 48 hr, 72 hr and 96 hr

End point values	15K rFVIIIFc (1000 and 6000 IU/Vial Strength Combined) (PK2)	15K rFVIIIFc (1000 and 6000 IU/Vial Strength Combined) (PK3)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	23	21		
Units: IU*hr/dL				
geometric mean (confidence interval 95%)	2448.6 (2089.0 to 2870.1)	2697.8 (2295.1 to 3171.0)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Incremental Recovery as Measured by One-stage aPTT Clotting Assay for PK2 and PK3

End point title	Incremental Recovery as Measured by One-stage aPTT Clotting Assay for PK2 and PK3
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End point description:

IR is defined as the increase in the circulating FVIII activity in IU/dL per unit dose administered in IU/kg (IU/dL per IU/kg). Results were summarised overall for 15K rFVIIIFc 1000 IU/vial and 6000 IU/vial for PK2 and PK3. The PKAS included all subjects who have evaluable PK profiles.

End point type	Secondary
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End point timeframe:

Pre-dose and post dose at: 0.5 hr, 1 hr, 6 hr, 24 hr, 48 hr, 72 hr and 96 hr

End point values	15K rFVIIIFc (1000 and 6000 IU/Vial Strength Combined) (PK2)	15K rFVIIIFc (1000 and 6000 IU/Vial Strength Combined) (PK3)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	23	23		
Units: IU/dL per IU/kg				
geometric mean (confidence interval 95%)	2.693 (2.429 to 2.986)	2.804 (2.588 to 3.038)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Maximum Activity of rFVIIIFc as Measured by One-stage aPTT Clotting Assay for PK2 and PK3

End point title	Maximum Activity of rFVIIIFc as Measured by One-stage aPTT Clotting Assay for PK2 and PK3
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End point description:

Cmax is defined as maximum activity of rFVIIIFc. Results were summarised overall for 15K rFVIIIFc 1000 IU/vial and 6000 IU/vial for PK2 and PK3. The PKAS included all subjects who have evaluable PK profiles.

End point type	Secondary
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End point timeframe:

Pre-dose and post dose at: 0.5 hr, 1 hr, 6 hr, 24 hr, 48 hr, 72 hr and 96 hr



End point values	15K rFVIIIFc (1000 and 6000 IU/Vial Strength Combined) (PK2)	15K rFVIIIFc (1000 and 6000 IU/Vial Strength Combined) (PK3)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	23	23		
Units: IU/dL				
geometric mean (confidence interval 95%)	134.67 (121.46 to 149.32)	140.38 (129.62 to 152.04)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Half-life of rFVIIIFc as Measured by One-stage aPTT Clotting Assay for PK2 and PK3

End point title	Half-life of rFVIIIFc as Measured by One-stage aPTT Clotting Assay for PK2 and PK3
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End point description:

t<sub>1/2</sub> is time required for the concentration of the drug to reach half of its original value. Results were summarised overall for 15K rFVIIIFc 1000 IU/vial and 6000 IU/vial for PK2 and PK3. The PKAS included all subjects who have evaluable PK profiles. Here, 'number of subjects analysed' signifies those subjects who were evaluable for this endpoint.

End point type	Secondary
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End point timeframe:

Pre-dose and post dose at: 0.5 hr, 1 hr, 6 hr, 24 hr, 48 hr, 72 hr and 96 hr

End point values	15K rFVIIIFc (1000 and 6000 IU/Vial Strength Combined) (PK2)	15K rFVIIIFc (1000 and 6000 IU/Vial Strength Combined) (PK3)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	23	21		
Units: hours				
geometric mean (confidence interval 95%)	14.771 (12.910 to 16.900)	15.493 (13.625 to 17.617)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Clearance of rFVIIIFc as Measured by One-stage aPTT Clotting Assay for PK2 and PK3

End point title	Clearance of rFVIIIFc as Measured by One-stage aPTT Clotting Assay for PK2 and PK3
End point description:	
CL is a quantitative measure of the rate at which a drug substance is removed from the body. The total systemic clearance after IV dose was estimated by dividing the total administered dose by AUC(0-infinity). Results were summarised overall for 15K rFVIIIFc 1000 IU/vial and 6000 IU/vial for PK2 and PK3. The PKAS included all subjects who have evaluable PK profiles. Here, 'number of subjects analysed' signifies those subjects who were evaluable for this endpoint.	
End point type	Secondary
End point timeframe:	
Pre-dose and post dose at: 0.5 hr, 1 hr, 6 hr, 24 hr, 48 hr, 72 hr and 96 hr	

End point values	15K rFVIIIFc (1000 and 6000 IU/Vial Strength Combined) (PK2)	15K rFVIIIFc (1000 and 6000 IU/Vial Strength Combined) (PK3)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	23	21		
Units: mL/hr/kg				
geometric mean (confidence interval 95%)	2.0420 (1.7421 to 2.3935)	1.8556 (1.5786 to 2.1813)		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Volume of Distribution at Steady State of rFVIIIFc as Measured by One-stage aPTT Clotting Assay for PK2 and PK3

End point title	Volume of Distribution at Steady State of rFVIIIFc as Measured by One-stage aPTT Clotting Assay for PK2 and PK3
End point description:	
Vss 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. Vss is the apparent volume of distribution at steady-state which is estimated by $(D/AUC[0\text{-infinity}]) \cdot (AUMC[0\text{-infinity}]/AUC[0\text{-infinity}])$ where D is the dose of study drug, AUMC(0-infinity) is the area under the first moment curve extrapolated to infinity and AUC(0-infinity) is the area under the plasma concentration-time curve from time zero to infinite time. Results were summarised overall for 15K rFVIIIFc 1000 IU/vial and 6000 IU/vial for PK2 and PK3. The PKAS included all subjects who have evaluable PK profiles. Here, 'number of subjects analysed' signifies those subjects who were evaluable for this endpoint.	
End point type	Secondary
End point timeframe:	
Pre-dose and post dose at: 0.5 hr, 1 hr, 6 hr, 24 hr, 48 hr, 72 hr and 96 hr	

End point values	15K rFVIIIFc (1000 and 6000 IU/Vial Strength Combined) (PK2)	15K rFVIIIFc (1000 and 6000 IU/Vial Strength Combined) (PK3)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	23	21		
Units: mL/kg				
geometric mean (confidence interval 95%)	43.01 (39.69 to 46.61)	40.19 (37.44 to 43.14)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Mean Residence Time of rFVIIIFc as Measured by One-stage aPTT Clotting Assay for PK2 and PK3

End point title	Mean Residence Time of rFVIIIFc as Measured by One-stage aPTT Clotting Assay for PK2 and PK3
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End point description:

MRT is the average time at which the number of absorbed molecules reside in the body, after single-dose administration, and calculated as AUMC (0-infinity)/ AUC (0-infinity), where AUMC (0-infinity) is area under the plasma concentration-time first moment curve from time zero to infinite time and AUC (0-infinity) is the area under the plasma concentration-time curve from time zero to infinite time. Results were summarised overall for 15K rFVIIIFc 1000 IU/Vial and 6000 IU/Vial for PK2 and PK3. The PKAS included all subjects who have evaluable PK profiles. Here, 'number of subjects analysed' signifies those subjects who were evaluable for this endpoint.

End point type	Secondary
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End point timeframe:

Pre-dose and post dose at: 0.5 hr, 1 hr, 6 hr, 24 hr, 48 hr, 72 hr and 96 hr

End point values	15K rFVIIIFc (1000 and 6000 IU/Vial Strength Combined) (PK2)	15K rFVIIIFc (1000 and 6000 IU/Vial Strength Combined) (PK3)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	23	21		
Units: hours				
geometric mean (confidence interval 95%)	21.063 (18.501 to 23.980)	21.657 (18.877 to 24.847)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Area Under the Concentration-time Curve From Time Zero to Infinity as

**Measured by One-stage aPTT Clotting Assay for PK2 at Different Vial Strengths (1000 and 6000 IU/Vial)**

End point title	Area Under the Concentration-time Curve From Time Zero to Infinity as Measured by One-stage aPTT Clotting Assay for PK2 at Different Vial Strengths (1000 and 6000 IU/Vial)
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End point description:

AUC<sub>0-inf</sub> is area under the concentration-time curve from time zero to infinity. The PKAS included all subjects who have evaluable PK profiles.

End point type	Secondary
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End point timeframe:

Pre-dose and post dose at: 0.5 hr, 1 hr, 6 hr, 24 hr, 48 hr, 72 hr and 96 hr

End point values	15K rFVIIIFc (1000 IU/Vial Strength) (PK2)	15K rFVIIIFc (6000 IU/Vial Strength) (PK2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	12		
Units: IU*hr/dL				
geometric mean (confidence interval 95%)	2356.8 (1950.4 to 2847.9)	2535.8 (1915.6 to 3356.8)		

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Incremental Recovery of rFVIIIFc as Measured by One-stage aPTT Clotting Assay for PK2 at Different Vial Strengths (1000 and 6000 IU/Vial)**

End point title	Incremental Recovery of rFVIIIFc as Measured by One-stage aPTT Clotting Assay for PK2 at Different Vial Strengths (1000 and 6000 IU/Vial)
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End point description:

IR is defined as the increase in the circulating FVIII activity in IU/dL per unit dose administered in IU/kg (IU/dL per IU/kg). The PKAS included all subjects who have evaluable PK profiles.

End point type	Secondary
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End point timeframe:

Pre-dose and post dose at: 0.5 hr, 1 hr, 6 hr, 24 hr, 48 hr, 72 hr and 96 hr

End point values	15K rFVIIIFc (1000 IU/Vial Strength) (PK2)	15K rFVIIIFc (6000 IU/Vial Strength) (PK2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	12		
Units: IU/dL per IU/kg				
geometric mean (confidence interval 95%)	2.614 (2.186 to 3.126)	2.768 (2.408 to 3.181)		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Maximum Activity of rFVIIIFc as Measured by One-stage aPTT Clotting Assay for PK2 at Different Vial Strengths (1000 and 6000 IU/Vial)

End point title	Maximum Activity of rFVIIIFc as Measured by One-stage aPTT Clotting Assay for PK2 at Different Vial Strengths (1000 and 6000 IU/Vial)
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End point description:

C<sub>max</sub> is defined as maximum activity of rFVIIIFc. The PKAS included all subjects who have evaluable PK profiles.

End point type	Secondary
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End point timeframe:

Pre-dose and post dose at: 0.5 hr, 1 hr, 6 hr, 24 hr, 48 hr, 72 hr and 96 hr

End point values	15K rFVIIIFc (1000 IU/Vial Strength) (PK2)	15K rFVIIIFc (6000 IU/Vial Strength) (PK2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	12		
Units: IU/dL				
geometric mean (confidence interval 95%)	130.73 (109.33 to 156.31)	138.40 (120.42 to 159.06)		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Half-life of rFVIIIFc as Measured by One-stage aPTT Clotting Assay for PK2 at Different Vial Strengths (1000 and 6000 IU/Vial)

End point title	Half-life of rFVIIIFc as Measured by One-stage aPTT Clotting Assay for PK2 at Different Vial Strengths (1000 and 6000 IU/Vial)
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End point description:

t<sub>1/2</sub> is time required for the concentration of the drug to reach half of its original value. The PKAS included all subjects who have evaluable PK profiles.

End point type	Secondary
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End point timeframe:

Pre-dose and post dose at: 0.5 hr, 1 hr, 6 hr, 24 hr, 48 hr, 72 hr and 96 hr

End point values	15K rFVIIIFc (1000 IU/Vial Strength) (PK2)	15K rFVIIIFc (6000 IU/Vial Strength) (PK2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	12		
Units: hours				
geometric mean (confidence interval 95%)	14.118 (11.469 to 17.379)	15.395 (12.555 to 18.879)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Clearance of rFVIIIFc as Measured by One-stage aPTT Clotting Assay for PK2 at Different Vial Strengths (1000 and 6000 IU/Vial)

End point title	Clearance of rFVIIIFc as Measured by One-stage aPTT Clotting Assay for PK2 at Different Vial Strengths (1000 and 6000 IU/Vial)
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End point description:

CL is a quantitative measure of the rate at which a drug substance is removed from the body. The total systemic CL after IV dose was estimated by dividing the total administered dose by AUC(0-infinity). The PKAS included all subjects who have evaluable PK profiles.

End point type	Secondary
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End point timeframe:

Pre-dose and post dose at: 0.5 hr, 1 hr, 6 hr, 24 hr, 48 hr, 72 hr and 96 hr

End point values	15K rFVIIIFc (1000 IU/Vial Strength) (PK2)	15K rFVIIIFc (6000 IU/Vial Strength) (PK2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	12		
Units: mL/hr/kg				
geometric mean (confidence interval 95%)	2.1215 (1.7557 to 2.5635)	1.9718 (1.4895 to 2.6101)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Volume of Distribution at Steady State of rFVIIIFc as Measured by One-

**stage aPTT Clotting Assay for PK2 at Different Vial Strengths (1000 and 6000 IU/Vial)**

End point title	Volume of Distribution at Steady State of rFVIIIFc as Measured by One-stage aPTT Clotting Assay for PK2 at Different Vial Strengths (1000 and 6000 IU/Vial)
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End point description:

V<sub>ss</sub> 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. V<sub>ss</sub> is the apparent volume of distribution at steady-state which is estimated by  $(D/AUC[0\text{-}infinity]) \cdot (AUMC[0\text{-}infinity])/AUC[0\text{-}infinity]$  where D is the dose of study drug, AUMC(0-infinity) is the area under the first moment curve extrapolated to infinity and AUC(0-infinity) is the area under the plasma concentration-time curve from time zero to infinite time. The PKAS included all subjects who have evaluable PK profiles.

End point type	Secondary
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End point timeframe:

Pre-dose and post dose at: 0.5 hr, 1 hr, 6 hr, 24 hr, 48 hr, 72 hr and 96 hr

End point values	15K rFVIIIFc (1000 IU/Vial Strength) (PK2)	15K rFVIIIFc (6000 IU/Vial Strength) (PK2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	12		
Units: mL/kg				
geometric mean (confidence interval 95%)	42.61 (37.28 to 48.71)	43.38 (38.66 to 48.67)		

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Mean Residence Time of rFVIIIFc as Measured by One-stage aPTT Clotting Assay for PK2 at Different Vial Strengths (1000 and 6000 IU/Vial)**

End point title	Mean Residence Time of rFVIIIFc as Measured by One-stage aPTT Clotting Assay for PK2 at Different Vial Strengths (1000 and 6000 IU/Vial)
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End point description:

The MRT is the average time at which the number of absorbed molecules reside in the body, after single-dose administration, and calculated as  $AUMC(0\text{-}infinity)/AUC(0\text{-}infinity)$ , where AUMC (0-infinity) is area under the plasma concentration-time first moment curve from time zero to infinite time and AUC (0-infinity) is the area under the plasma concentration-time curve from time zero to infinite time. The PKAS included all subjects who have evaluable PK profiles.

End point type	Secondary
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End point timeframe:

Pre-dose and post dose at: 0.5 hr, 1 hr, 6 hr, 24 hr, 48 hr, 72 hr and 96 hr

End point values	15K rFVIIIFc (1000 IU/Vial Strength) (PK2)	15K rFVIIIFc (6000 IU/Vial Strength) (PK2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	12		
Units: hours				
geometric mean (confidence interval 95%)	20.087 (16.333 to 24.704)	22.000 (18.193 to 26.603)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Area Under the Concentration-time Curve From Time Zero to Infinity as Measured by One-stage aPTT Clotting Assay for PK3 at Different Vial Strengths (1000 and 6000 IU/Vial)

End point title	Area Under the Concentration-time Curve From Time Zero to Infinity as Measured by One-stage aPTT Clotting Assay for PK3 at Different Vial Strengths (1000 and 6000 IU/Vial)
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End point description:

AUC0-inf is area under the concentration-time curve from time zero to infinity. The PKAS included all subjects who have evaluable PK profiles. Here, 'number of subjects analysed' signifies those subjects who were evaluable for this endpoint.

End point type	Secondary
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End point timeframe:

Pre-dose and post dose at: 0.5 hr, 1 hr, 6 hr, 24 hr, 48 hr, 72 hr and 96 hr

End point values	15K rFVIIIFc (1000 IU/Vial Strength) (PK3)	15K rFVIIIFc (6000 IU/Vial Strength) (PK3)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	12		
Units: IU*hr/dL				
geometric mean (confidence interval 95%)	2634.5 (2079.8 to 3337.1)	2746.3 (2130.5 to 3539.9)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Incremental Recovery of rFVIIIFc as Measured by One-stage aPTT Clotting Assay for PK3 at Different Vial Strengths (1000 and 6000 IU/Vial)

End point title	Incremental Recovery of rFVIIIFc as Measured by One-stage aPTT Clotting Assay for PK3 at Different Vial Strengths (1000 and 6000 IU/Vial)
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End point description:

IR is defined as the increase in the circulating FVIII activity in IU/dL per unit dose administered in IU/kg (IU/dL per IU/kg). The PKAS included all subjects who have evaluable PK profiles.

End point type	Secondary
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End point timeframe:

Pre-dose and post dose at: 0.5 hr, 1 hr, 6 hr, 24 hr, 48 hr, 72 hr and 96 hr

End point values	15K rFVIIIFc (1000 IU/Vial Strength) (PK3)	15K rFVIIIFc (6000 IU/Vial Strength) (PK3)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	12		
Units: IU/dL per IU/kg				
geometric mean (confidence interval 95%)	2.623 (2.343 to 2.936)	2.982 (2.650 to 3.355)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Maximum Activity of rFVIIIFc as Measured by One-stage aPTT Clotting Assay for PK3 at Different Vial Strengths (1000 and 6000 IU/Vial)

End point title	Maximum Activity of rFVIIIFc as Measured by One-stage aPTT Clotting Assay for PK3 at Different Vial Strengths (1000 and 6000 IU/Vial)
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End point description:

Cmax is defined as maximum activity of rFVIIIFc. The PKAS included all subjects who have evaluable PK profiles.

End point type	Secondary
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End point timeframe:

Pre-dose and post dose at: 0.5 hr, 1 hr, 6 hr, 24 hr, 48 hr, 72 hr and 96 hr

End point values	15K rFVIIIFc (1000 IU/Vial Strength) (PK3)	15K rFVIIIFc (6000 IU/Vial Strength) (PK3)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	12		
Units: IU/dL				
geometric mean (confidence interval 95%)	131.15 (117.18 to 146.80)	149.41 (132.99 to 167.86)		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Half-life of rFVIIIFc as Measured by One-stage aPTT Clotting Assay for PK3 at Different Vial Strengths (1000 and 6000 IU/Vial)

End point title	Half-life of rFVIIIFc as Measured by One-stage aPTT Clotting Assay for PK3 at Different Vial Strengths (1000 and 6000 IU/Vial)
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End point description:

t<sub>1/2</sub> is time required for the concentration of the drug to reach half of its original value. The PKAS included all subjects who have evaluable PK profiles. Here, 'number of subjects analysed' signifies those subjects who were evaluable for this endpoint.

End point type	Secondary
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End point timeframe:

Pre-dose and post dose at: 0.5 hr, 1 hr, 6 hr, 24 hr, 48 hr, 72 hr and 96 hr

End point values	15K rFVIIIFc (1000 IU/Vial Strength) (PK3)	15K rFVIIIFc (6000 IU/Vial Strength) (PK3)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	12		
Units: hours				
geometric mean (confidence interval 95%)	15.599 (12.925 to 18.826)	15.414 (12.593 to 18.868)		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Clearance of rFVIIIFc as Measured by One-stage aPTT Clotting Assay for PK3 at Different Vial Strengths (1000 and 6000 IU/Vial)

End point title	Clearance of rFVIIIFc as Measured by One-stage aPTT Clotting Assay for PK3 at Different Vial Strengths (1000 and 6000 IU/Vial)
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End point description:

CL is a quantitative measure of the rate at which a drug substance is removed from the body. The total systemic clearance after IV dose was estimated by dividing the total administered dose by the plasma Area Under the Plasma Concentration-Time Curve From Time Zero to Infinite Time (AUC[0-infinity]). The PKAS included all subjects who have evaluable PK profiles. Here, 'number of subjects analysed' signifies those subjects who were evaluable for this endpoint.

End point type	Secondary
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End point timeframe:

Pre-dose and post dose at: 0.5 hr, 1 hr, 6 hr, 24 hr, 48 hr, 72 hr and 96 hr

End point values	15K rFVIIIFc (1000 IU/Vial Strength) (PK3)	15K rFVIIIFc (6000 IU/Vial Strength) (PK3)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	12		
Units: mL/hr/kg				
geometric mean (confidence interval 95%)	1.8979 (1.4983 to 2.4041)	1.8246 (1.4151 to 2.3524)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Volume of Distribution at Steady State of rFVIIIFc as Measured by One-stage aPTT Clotting Assay for PK3 at Different Vial Strengths (1000 and 6000 IU/Vial)

End point title	Volume of Distribution at Steady State of rFVIIIFc as Measured by One-stage aPTT Clotting Assay for PK3 at Different Vial Strengths (1000 and 6000 IU/Vial)
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End point description:

Vss 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. Vss is the apparent volume of distribution at steady-state which is estimated by  $(D/AUC[0\text{-infinity}]) \cdot (AUMC[0\text{-infinity}]/AUC[0\text{-infinity}])$  where D is the dose of study drug, AUMC(0-infinity) is the area under the first moment curve extrapolated to infinity and AUC(0-infinity) is the area under the plasma concentration-time curve from time zero to infinite time. The PKAS included all subjects who have evaluable PK profiles. Here, 'number of subjects analysed' signifies those subjects who were evaluable for this endpoint.

End point type	Secondary
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End point timeframe:

Pre-dose and post dose at: 0.5 hr, 1 hr, 6 hr, 24 hr, 48 hr, 72 hr and 96 hr

End point values	15K rFVIIIFc (1000 IU/Vial Strength) (PK3)	15K rFVIIIFc (6000 IU/Vial Strength) (PK3)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	12		
Units: mL/kg				
geometric mean (confidence interval 95%)	42.12 (36.95 to 48.02)	38.80 (35.47 to 42.43)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Mean Residence Time of rFVIIIFc as Measured by One-stage aPTT Clotting Assay for PK3 at Different Vial Strengths (1000 and 6000 IU/Vial)

End point title	Mean Residence Time of rFVIIIFc as Measured by One-stage aPTT Clotting Assay for PK3 at Different Vial Strengths (1000 and 6000 IU/Vial)
End point description: The MRT is the average time at which the number of absorbed molecules reside in the body, after single-dose administration, and calculated as AUMC (0-infinity)/ AUC (0-infinity), where AUMC (0-infinity) is area under the plasma concentration-time first moment curve from time zero to infinite time and AUC (0-infinity) is the area under the plasma concentration-time curve from time zero to infinite time. The PKAS included all subjects who have evaluable PK profiles. Here, 'number of subjects analysed' signifies those subject who were evaluable for this endpoint.	
End point type	Secondary
End point timeframe: Pre-dose and post dose at: 0.5 hr, 1 hr, 6 hr, 24 hr, 48 hr, 72 hr and 96 hr	

End point values	15K rFVIIIFc (1000 IU/Vial Strength) (PK3)	15K rFVIIIFc (6000 IU/Vial Strength) (PK3)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	12		
Units: hours				
geometric mean (confidence interval 95%)	22.193 (17.923 to 27.480)	21.264 (17.247 to 26.216)		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Area Under the Concentration-time Curve From Time Zero to Infinity as Measured by the Two-stage Chromogenic Assay for PK1 and PK2

End point title	Area Under the Concentration-time Curve From Time Zero to Infinity as Measured by the Two-stage Chromogenic Assay for PK1 and PK2
End point description: AUC0-inf is area under the concentration-time curve from time zero to infinity. Results were summarised overall for 15K rFVIIIFc 1000 IU/vial and 6000 IU/vial (PK2). The PKAS included all subjects who have evaluable PK profiles.	
End point type	Secondary
End point timeframe: Pre-dose and post dose at: 0.5 hr, 1 hr, 6 hr, 24 hr, 48 hr, 72 hr and 96 hr	

End point values	2K rFVIIIFc (1000 IU/Vial Strength) (PK1)	15K rFVIIIFc (1000 and 6000 IU/Vial Strength Combined) (PK2)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	24	23		

Units: IU*hr/dL				
geometric mean (confidence interval 95%)	2386.4 (2124.1 to 2681.0)	2777.6 (2453.0 to 3145.2)		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Incremental Recovery as Measured by the Two-stage Chromogenic Assay for PK1 and PK2

End point title	Incremental Recovery as Measured by the Two-stage Chromogenic Assay for PK1 and PK2
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End point description:

IR is defined as the increase in the circulating FVIII activity in IU/dL per unit dose administered in IU/kg (IU/dL per IU/kg). Results were summarised overall for 15K rFVIIIFc 1000 IU/vial and 6000 IU/vial (PK2). The PKAS included all subjects who have evaluable PK profiles.

End point type	Secondary
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End point timeframe:

Pre-dose and post dose at: 0.5 hr, 1 hr, 6 hr, 24 hr, 48 hr, 72 hr and 96 hr

End point values	2K rFVIIIFc (1000 IU/Vial Strength) (PK1)	15K rFVIIIFc (1000 and 6000 IU/Vial Strength Combined) (PK2)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	24	23		
Units: IU/dL per IU/kg				
geometric mean (confidence interval 95%)	2.807 (2.412 to 3.267)	3.253 (2.910 to 3.636)		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Maximum Activity of rFVIIIFc as Measured by the Two-stage Chromogenic Assay for PK1 and PK2

End point title	Maximum Activity of rFVIIIFc as Measured by the Two-stage Chromogenic Assay for PK1 and PK2
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End point description:

Cmax is defined as maximum activity of rFVIIIFc. Results were summarised overall for 15K rFVIIIFc 1000 IU/vial and 6000 IU/vial (PK2). The PKAS included all subjects who have evaluable PK profiles.

End point type	Secondary
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End point timeframe:

Pre-dose and post dose at: 0.5 hr, 1 hr, 6 hr, 24 hr, 48 hr, 72 hr and 96 hr

End point values	2K rFVIIIFc (1000 IU/Vial Strength) (PK1)	15K rFVIIIFc (1000 and 6000 IU/Vial Strength Combined) (PK2)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	24	23		
Units: IU/dL				
geometric mean (confidence interval 95%)	140.36 (120.61 to 163.34)	162.73 (145.61 to 181.86)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Half-life of rFVIIIFc as Measured by the Two-stage Chromogenic Assay for PK1 and PK2

End point title	Half-life of rFVIIIFc as Measured by the Two-stage Chromogenic Assay for PK1 and PK2
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End point description:

t<sub>1/2</sub> is time required for the concentration of the drug to reach half of its original value. Results were summarised overall for 15K rFVIIIFc 1000 IU/vial and 6000 IU/vial (PK2). The PKAS included all subjects who have evaluable PK profiles.

End point type	Secondary
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End point timeframe:

Pre-dose and post dose at: 0.5 hr, 1 hr, 6 hr, 24 hr, 48 hr, 72 hr and 96 hr

End point values	2K rFVIIIFc (1000 IU/Vial Strength) (PK1)	15K rFVIIIFc (1000 and 6000 IU/Vial Strength Combined) (PK2)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	24	23		
Units: hours				
geometric mean (confidence interval 95%)	17.312 (15.840 to 18.921)	18.146 (15.980 to 20.605)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Clearance of rFVIIIFc as Measured by the Two-stage Chromogenic Assay for PK1 and PK2

End point title	Clearance of rFVIIIFc as Measured by the Two-stage Chromogenic Assay for PK1 and PK2
End point description: CL is a quantitative measure of the rate at which a drug substance is removed from the body. The total systemic clearance after IV dose was estimated by dividing the total administered dose by AUC(0-infinity). Results were summarised overall for 15K rFVIIIFc 1000 IU/vial and 6000 IU/vial (PK2). The PKAS included all subjects who have evaluable PK profiles.	
End point type	Secondary
End point timeframe: Pre-dose and post dose at: 0.5 hr, 1 hr, 6 hr, 24 hr, 48 hr, 72 hr and 96 hr	

End point values	2K rFVIIIFc (1000 IU/Vial Strength) (PK1)	15K rFVIIIFc (1000 and 6000 IU/Vial Strength Combined) (PK2)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	24	23		
Units: mL/hr/kg				
geometric mean (confidence interval 95%)	2.0952 (1.8649 to 2.3539)	1.8001 (1.5897 to 2.0383)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Volume of Distribution at Steady State of rFVIIIFc as Measured by the Two-stage Chromogenic Assay for PK1 and PK2

End point title	Volume of Distribution at Steady State of rFVIIIFc as Measured by the Two-stage Chromogenic Assay for PK1 and PK2
End point description: Vss 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. Vss is the apparent volume of distribution at steady-state which is estimated by $(D/AUC[0\text{-}infinity]) \times (AUMC[0\text{-}infinity])/AUC[0\text{-}infinity]$ where D is the dose of study drug, AUMC(0-infinity) is the area under the first moment curve extrapolated to infinity and AUC(0-infinity) is the area under the plasma concentration-time curve from time zero to infinite time. Results were summarised overall for 15K rFVIIIFc 1000 IU/vial and 6000 IU/vial (PK2). The PKAS included all subjects who have evaluable PK profiles.	
End point type	Secondary
End point timeframe: Pre-dose and post dose at: 0.5 hr, 1 hr, 6 hr, 24 hr, 48 hr, 72 hr and 96 hr	

End point values	2K rFVIIIFc (1000 IU/Vial Strength) (PK1)	15K rFVIIIFc (1000 and 6000 IU/Vial Strength Combined) (PK2)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	24	23		
Units: mL/kg				
geometric mean (confidence interval 95%)	46.87 (41.48 to 52.96)	42.02 (37.96 to 46.51)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Mean Residence Time of rFVIIIFc as Measured by the Two-stage Chromogenic Assay for PK1 and PK2

End point title	Mean Residence Time of rFVIIIFc as Measured by the Two-stage Chromogenic Assay for PK1 and PK2
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End point description:

The MRT is the average time at which the number of absorbed molecules reside in the body, after single-dose administration, and calculated as  $AUMC(0\text{-infinity})/AUC(0\text{-infinity})$ , where  $AUMC(0\text{-infinity})$  is area under the plasma concentration-time first moment curve from time zero to infinite time and  $AUC(0\text{-infinity})$  is the area under the plasma concentration-time curve from time zero to infinite time. Results were summarised overall for 15K rFVIIIFc 1000 IU/vial and 6000 IU/vial (PK2). The PKAS included all subjects who have evaluable PK profiles.

End point type	Secondary
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End point timeframe:

Pre-dose and post dose at: 0.5 hr, 1 hr, 6 hr, 24 hr, 48 hr, 72 hr and 96 hr

End point values	2K rFVIIIFc (1000 IU/Vial Strength) (PK1)	15K rFVIIIFc (1000 and 6000 IU/Vial Strength Combined) (PK2)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	24	23		
Units: hours				
geometric mean (confidence interval 95%)	22.370 (19.921 to 25.120)	23.342 (20.472 to 26.615)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Area Under the Concentration-time Curve From Time Zero to Infinity as Measured by the Two-stage Chromogenic Assay for PK2 and PK3



End point title	Area Under the Concentration-time Curve From Time Zero to Infinity as Measured by the Two-stage Chromogenic Assay for PK2 and PK3
End point description: AUC0-inf is area under the concentration-time curve from time zero to infinity. Results were summarised overall for 15K rFVIIIFc 1000 IU/vial and 6000 IU/vial for PK2 and PK3. The PKAS included all subjects who have evaluable PK profiles. Here, 'number of subjects analysed' signifies those subjects who were evaluable for this endpoint.	
End point type	Secondary
End point timeframe: Pre-dose and post dose at: 0.5 hr, 1 hr, 6 hr, 24 hr, 48 hr, 72 hr and 96 hr	

End point values	15K rFVIIIFc (1000 and 6000 IU/Vial Strength Combined) (PK2)	15K rFVIIIFc (1000 and 6000 IU/Vial Strength Combined) (PK3)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	23	20		
Units: IU*hr/dL				
geometric mean (confidence interval 95%)	2777.6 (2453.0 to 3145.2)	2754.9 (2312.2 to 3282.4)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Incremental Recovery as Measured by the Two-stage Chromogenic Assay for PK2 and PK3

End point title	Incremental Recovery as Measured by the Two-stage Chromogenic Assay for PK2 and PK3
End point description: IR is defined as the increase in the circulating FVIII activity in IU/dL per unit dose administered in IU/kg (IU/dL per IU/kg). Results were summarised overall for 15K rFVIIIFc 1000 IU/vial and 6000 IU/vial for PK2 and PK3. The PKAS included all subjects who have evaluable PK profiles.	
End point type	Secondary
End point timeframe: Pre-dose and post dose at: 0.5 hr, 1 hr, 6 hr, 24 hr, 48 hr, 72 hr and 96 hr	

End point values	15K rFVIIIFc (1000 and 6000 IU/Vial Strength Combined) (PK2)	15K rFVIIIFc (1000 and 6000 IU/Vial Strength Combined) (PK3)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	23	23		

Units: IU/dL per IU/kg				
geometric mean (confidence interval 95%)	3.253 (2.910 to 3.636)	2.956 (2.656 to 3.289)		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Maximum Activity of rFVIIIFc as Measured by the Two-stage Chromogenic Assay for PK2 and PK3

End point title	Maximum Activity of rFVIIIFc as Measured by the Two-stage Chromogenic Assay for PK2 and PK3
End point description: Cmax is defined as maximum activity of rFVIIIFc. Results were summarised overall for 15K rFVIIIFc 1000 IU/vial and 6000 IU/vial for PK2 and PK3. The PKAS included all subjects who have evaluable PK profiles.	
End point type	Secondary
End point timeframe: Pre-dose and post dose at: 0.5 hr, 1 hr, 6 hr, 24 hr, 48 hr, 72 hr and 96 hr	

End point values	15K rFVIIIFc (1000 and 6000 IU/Vial Strength Combined) (PK2)	15K rFVIIIFc (1000 and 6000 IU/Vial Strength Combined) (PK3)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	23	23		
Units: IU/dL				
geometric mean (confidence interval 95%)	162.73 (145.61 to 181.86)	147.97 (133.02 to 164.60)		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Half-life of rFVIIIFc as Measured by the Two-stage Chromogenic Assay for PK2 and PK3

End point title	Half-life of rFVIIIFc as Measured by the Two-stage Chromogenic Assay for PK2 and PK3
End point description: t1/2 is the time required for the concentration of the drug to reach half of its original value. Results were summarised overall for 15K rFVIIIFc 1000 IU/vial and 6000 IU/vial for PK2 and PK3. The PKAS included all subjects who have evaluable PK profiles. Here, 'number of subjects analysed' signifies those subjects who were evaluable for this endpoint.	
End point type	Secondary

End point timeframe:

Pre-dose and post dose at: 0.5 hr, 1 hr, 6 hr, 24 hr, 48 hr, 72 hr and 96 hr

End point values	15K rFVIIIFc (1000 and 6000 IU/Vial Strength Combined) (PK2)	15K rFVIIIFc (1000 and 6000 IU/Vial Strength Combined) (PK3)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	23	20		
Units: hours				
geometric mean (confidence interval 95%)	18.146 (15.980 to 20.605)	17.289 (15.078 to 19.823)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Clearance of rFVIIIFc as Measured by the Two-stage Chromogenic Assay for PK2 and PK3

End point title	Clearance of rFVIIIFc as Measured by the Two-stage Chromogenic Assay for PK2 and PK3
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End point description:

CL is a quantitative measure of the rate at which a drug substance is removed from the body. The total systemic clearance after IV dose was estimated by dividing the total administered dose by AUC(0-infinity). Results were summarised overall for 15K rFVIIIFc 1000 IU/vial and 6000 IU/vial for PK2 and PK3. The PKAS included all subjects who have evaluable PK profiles. Here, 'number of subjects analysed' signifies those subjects who were evaluable for this endpoint.

End point type	Secondary
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End point timeframe:

Pre-dose and post dose at: 0.5 hr, 1 hr, 6 hr, 24 hr, 48 hr, 72 hr and 96 hr

End point values	15K rFVIIIFc (1000 and 6000 IU/Vial Strength Combined) (PK2)	15K rFVIIIFc (1000 and 6000 IU/Vial Strength Combined) (PK3)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	23	20		
Units: mL/hr/kg				
geometric mean (confidence interval 95%)	1.8001 (1.5897 to 2.0383)	1.8173 (1.5251 to 2.1654)		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Volume of Distribution at Steady State of rFVIIIFc as Measured the Two-stage Chromogenic Assay for PK2 and PK3

End point title	Volume of Distribution at Steady State of rFVIIIFc as Measured the Two-stage Chromogenic Assay for PK2 and PK3
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End point description:

V<sub>ss</sub> 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. V<sub>ss</sub> is the apparent volume of distribution at steady-state which is estimated by  $(D/AUC[0-\infty]) \times (AUMC[0-\infty]/AUC[0-\infty])$  where D is the dose of study drug, AUMC(0-infinity) is the area under the first moment curve extrapolated to infinity and AUC(0-infinity) is the area under the plasma concentration-time curve from time zero to infinite time. Results were summarised overall for 15K rFVIIIFc 1000 IU/vial and 6000 IU/vial for PK2 and PK3. The PKAS included all subjects who have evaluable PK profiles. Here, 'number of subjects analysed' signifies those subjects who were evaluable for this endpoint.

End point type	Secondary
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End point timeframe:

Pre-dose and post dose at: 0.5 hr, 1 hr, 6 hr, 24 hr, 48 hr, 72 hr and 96 hr

End point values	15K rFVIIIFc (1000 and 6000 IU/Vial Strength Combined) (PK2)	15K rFVIIIFc (1000 and 6000 IU/Vial Strength Combined) (PK3)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	23	20		
Units: mL/kg				
geometric mean (confidence interval 95%)	42.02 (37.96 to 46.51)	40.59 (36.01 to 45.75)		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Mean Residence Time of rFVIIIFc as Measured by the Two-stage Chromogenic Assay for PK2 and PK3

End point title	Mean Residence Time of rFVIIIFc as Measured by the Two-stage Chromogenic Assay for PK2 and PK3
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End point description:

The MRT is the average time at which the number of absorbed molecules reside in the body, after single-dose administration, and calculated as  $AUMC(0-\infty)/AUC(0-\infty)$ , where AUMC (0-infinity) is area under the plasma concentration-time first moment curve from time zero to infinite time and AUC (0-infinity) is the area under the plasma concentration-time curve from time zero to infinite time. Results were summarised overall for 15K rFVIIIFc 1000 IU/vial and 6000 IU/vial for PK2 and PK3. The PKAS included all subjects who have evaluable PK profiles. Here, 'number of subjects analysed' signifies those subjects who were evaluable for this endpoint.

End point type	Secondary
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End point timeframe:

Pre-dose and post dose at: 0.5 hr, 1 hr, 6 hr, 24 hr, 48 hr, 72 hr and 96 hr

End point values	15K rFVIIIFc (1000 and 6000 IU/Vial Strength Combined) (PK2)	15K rFVIIIFc (1000 and 6000 IU/Vial Strength Combined) (PK3)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	23	20		
Units: hours				
geometric mean (confidence interval 95%)	23.342 (20.472 to 26.615)	22.337 (19.574 to 25.490)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Area Under the Concentration-time Curve From Time Zero to Infinity as Measured by the Two-stage Chromogenic Assay for PK2 at Different Vial Strengths (1000 and 6000 IU/Vial)

End point title	Area Under the Concentration-time Curve From Time Zero to Infinity as Measured by the Two-stage Chromogenic Assay for PK2 at Different Vial Strengths (1000 and 6000 IU/Vial)
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End point description:

AUC0-inf is area under the concentration-time curve from time zero to infinity. The PKAS included all subjects who have evaluable PK profiles.

End point type	Secondary
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End point timeframe:

Pre-dose and post dose at: 0.5 hr, 1 hr, 6 hr, 24 hr, 48 hr, 72 hr and 96 hr

End point values	15K rFVIIIFc (1000 IU/Vial Strength) (PK2)	15K rFVIIIFc (6000 IU/Vial Strength) (PK2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	12		
Units: IU*hr/dL				
geometric mean (confidence interval 95%)	2599.2 (2257.2 to 2993.1)	2951.9 (2376.1 to 3667.2)		

### Statistical analyses

No statistical analyses for this end point

**Secondary: Incremental Recovery of rFVIIIFc as Measured by the Two-stage Chromogenic Assay for PK2 at Different Vial Strengths (1000 and 6000 IU/Vial)**

End point title	Incremental Recovery of rFVIIIFc as Measured by the Two-stage Chromogenic Assay for PK2 at Different Vial Strengths (1000 and 6000 IU/Vial)
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End point description:

IR is defined as the increase in the circulating FVIII activity in IU/dL per unit dose administered in IU/kg (IU/dL per IU/kg). The PKAS included all subjects who have evaluable PK profiles.

End point type	Secondary
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End point timeframe:

Pre-dose and post dose at: 0.5 hr, 1 hr, 6 hr, 24 hr, 48 hr, 72 hr and 96 hr

End point values	15K rFVIIIFc (1000 IU/Vial Strength) (PK2)	15K rFVIIIFc (6000 IU/Vial Strength) (PK2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	12		
Units: IU/dL per IU/kg				
geometric mean (confidence interval 95%)	3.225 (2.643 to 3.936)	3.278 (2.835 to 3.792)		

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Maximum Activity of rFVIIIFc as Measured by the Two-stage Chromogenic Assay for PK2 at Different Vial Strengths (1000 and 6000 IU/Vial)**

End point title	Maximum Activity of rFVIIIFc as Measured by the Two-stage Chromogenic Assay for PK2 at Different Vial Strengths (1000 and 6000 IU/Vial)
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End point description:

C<sub>max</sub> is defined as maximum activity of rFVIIIFc. The PKAS included all subjects who have evaluable PK profiles.

End point type	Secondary
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End point timeframe:

Pre-dose and post dose at: 0.5 hr, 1 hr, 6 hr, 24 hr, 48 hr, 72 hr and 96 hr

End point values	15K rFVIIIFc (1000 IU/Vial Strength) (PK2)	15K rFVIIIFc (6000 IU/Vial Strength) (PK2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	12		
Units: IU/dL				
geometric mean (confidence interval 95%)	161.38 (132.29 to 196.88)	163.97 (141.78 to 189.64)		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Half-life of rFVIIIFc as Measured by the Two-stage Chromogenic Assay for PK2 at Different Vial Strengths (1000 and 6000 IU/Vial)

End point title	Half-life of rFVIIIFc as Measured by the Two-stage Chromogenic Assay for PK2 at Different Vial Strengths (1000 and 6000 IU/Vial)
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End point description:

t<sub>1/2</sub> is time required for the concentration of the drug to reach half of its original value. The PKAS included all subjects who have evaluable PK profiles.

End point type	Secondary
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End point timeframe:

Pre-dose and post dose at: 0.5 hr, 1 hr, 6 hr, 24 hr, 48 hr, 72 hr and 96 hr

End point values	15K rFVIIIFc (1000 IU/Vial Strength) (PK2)	15K rFVIIIFc (6000 IU/Vial Strength) (PK2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	12		
Units: hours				
geometric mean (confidence interval 95%)	16.687 (14.593 to 19.080)	19.595 (15.680 to 24.488)		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Clearance of rFVIIIFc as Measured by the Two-stage Chromogenic Assay for PK2 at Different Vial Strengths (1000 and 6000 IU/vial)

End point title	Clearance of rFVIIIFc as Measured by the Two-stage Chromogenic Assay for PK2 at Different Vial Strengths (1000 and 6000 IU/vial)
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End point description:

CL is a quantitative measure of the rate at which a drug substance is removed from the body. The total systemic CL after IV dose was estimated by dividing the total administered dose by AUC(0-infinity). The PKAS included all subjects who have evaluable PK profiles.

End point type	Secondary
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End point timeframe:

Pre-dose and post dose at: 0.5 hr, 1 hr, 6 hr, 24 hr, 48 hr, 72 hr and 96 hr

End point values	15K rFVIIIFc (1000 IU/Vial Strength) (PK2)	15K rFVIIIFc (6000 IU/Vial Strength) (PK2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	12		
Units: mL/hr/kg				
geometric mean (confidence interval 95%)	1.9236 (1.6705 to 2.2152)	1.6938 (1.3634 to 2.1043)		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Volume of Distribution at Steady State of rFVIIIFc as Measured by the Two-stage Chromogenic Assay for PK2 at Different Vial Strengths (1000 and 6000 IU/Vial)

End point title	Volume of Distribution at Steady State of rFVIIIFc as Measured by the Two-stage Chromogenic Assay for PK2 at Different Vial Strengths (1000 and 6000 IU/Vial)
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End point description:

V<sub>ss</sub> 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. V<sub>ss</sub> is the apparent volume of distribution at steady-state which is estimated by  $(D/AUC[0\text{-}infinity]) \times (AUMC[0\text{-}infinity])/AUC[0\text{-}infinity]$  where D is the dose of study drug, AUMC(0-infinity) is the area under the first moment curve extrapolated to infinity and AUC(0-infinity) is the area under the plasma concentration-time curve from time zero to infinite time. The PKAS included all subjects who have evaluable PK profiles.

End point type	Secondary
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End point timeframe:

Pre-dose and post dose at: 0.5 hr, 1 hr, 6 hr, 24 hr, 48 hr, 72 hr and 96 hr

End point values	15K rFVIIIFc (1000 IU/Vial Strength) (PK2)	15K rFVIIIFc (6000 IU/Vial Strength) (PK2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	12		
Units: mL/kg				
geometric mean (confidence interval 95%)	41.15 (34.50 to 49.07)	42.83 (37.33 to 49.15)		

## Statistical analyses



No statistical analyses for this end point

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**Secondary: Mean Residence Time of rFVIIIFc as Measured by the Two-stage Chromogenic Assay for PK2 at Different Vial Strengths (1000 and 6000 IU/Vial)**

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End point title	Mean Residence Time of rFVIIIFc as Measured by the Two-stage Chromogenic Assay for PK2 at Different Vial Strengths (1000 and 6000 IU/Vial)
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End point description:

The MRT is the average time at which the number of absorbed molecules reside in the body, after single-dose administration, and calculated as  $AUMC(0-\infty)/AUC(0-\infty)$ , where  $AUMC(0-\infty)$  is area under the plasma concentration-time first moment curve from time zero to infinite time and  $AUC(0-\infty)$  is the area under the plasma concentration-time curve from time zero to infinite time. The PKAS included all subjects who have evaluable PK profiles.

End point type	Secondary
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End point timeframe:

Pre-dose and post dose at: 0.5 hr, 1 hr, 6 hr, 24 hr, 48 hr, 72 hr and 96 hr

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End point values	15K rFVIIIFc (1000 IU/Vial Strength) (PK2)	15K rFVIIIFc (6000 IU/Vial Strength) (PK2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	12		
Units: hours				
geometric mean (confidence interval 95%)	21.391 (17.713 to 25.833)	25.287 (20.729 to 30.847)		

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**Statistical analyses**

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No statistical analyses for this end point

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**Secondary: Area Under the Concentration-time Curve From Time Zero to Infinity as Measured by the Two-stage Chromogenic Assay for PK3 at Different Vial Strengths (1000 and 6000 IU/Vial)**

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End point title	Area Under the Concentration-time Curve From Time Zero to Infinity as Measured by the Two-stage Chromogenic Assay for PK3 at Different Vial Strengths (1000 and 6000 IU/Vial)
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End point description:

AUC<sub>0-inf</sub> is area under the concentration-time curve from time zero to infinity. The PKAS included all subjects who have evaluable PK profiles. Here, 'number of subjects analysed' signifies those subjects who were evaluable for this endpoint.

End point type	Secondary
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End point timeframe:

Pre-dose and post dose at: 0.5 hr, 1 hr, 6 hr, 24 hr, 48 hr, 72 hr and 96 hr

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End point values	15K rFVIIIFc (1000 IU/Vial Strength) (PK3)	15K rFVIIIFc (6000 IU/Vial Strength) (PK3)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	12		
Units: IU*hr/dL				
geometric mean (confidence interval 95%)	2646.8 (1891.8 to 3703.0)	2829.4 (2235.7 to 3580.8)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Incremental Recovery of rFVIIIFc as Measured by the Two-stage Chromogenic Assay for PK3 at Different Vial Strengths (1000 and 6000 IU/Vial)

End point title	Incremental Recovery of rFVIIIFc as Measured by the Two-stage Chromogenic Assay for PK3 at Different Vial Strengths (1000 and 6000 IU/Vial)
End point description:	IR is defined as the increase in the circulating FVIII activity in IU/dL per unit dose administered in IU/kg (IU/dL per IU/kg). The PKAS included all subjects who have evaluable PK profiles.
End point type	Secondary
End point timeframe:	Pre-dose and post dose at: 0.5 hr, 1 hr, 6 hr, 24 hr, 48 hr, 72 hr and 96 hr

End point values	15K rFVIIIFc (1000 IU/Vial Strength) (PK3)	15K rFVIIIFc (6000 IU/Vial Strength) (PK3)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	12		
Units: IU/dL per IU/kg				
geometric mean (confidence interval 95%)	2.891 (2.413 to 3.464)	3.016 (2.597 to 3.504)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Maximum Activity of rFVIIIFc as Measured by the Two-stage Chromogenic Assay for PK3 at Different Vial Strengths (1000 and 6000 IU/Vial)

End point title	Maximum Activity of rFVIIIFc as Measured by the Two-stage Chromogenic Assay for PK3 at Different Vial Strengths (1000 and 6000 IU/Vial)
End point description:	Cmax is defined as maximum activity of rFVIIIFc. The PKAS included all subjects who have evaluable PK profiles.

End point type	Secondary
End point timeframe:	
Pre-dose and post dose at: 0.5 hr, 1 hr, 6 hr, 24 hr, 48 hr, 72 hr and 96 hr	

End point values	15K rFVIIIFc (1000 IU/Vial Strength) (PK3)	15K rFVIIIFc (6000 IU/Vial Strength) (PK3)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	12		
Units: IU/dL				
geometric mean (confidence interval 95%)	144.58 (120.66 to 173.25)	151.15 (130.34 to 175.28)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Half-life of rFVIIIFc as Measured by the Two-stage Chromogenic Assay for PK3 at Different Vial Strengths (1000 and 6000 IU/Vial)

End point title	Half-life of rFVIIIFc as Measured by the Two-stage Chromogenic Assay for PK3 at Different Vial Strengths (1000 and 6000 IU/Vial)
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End point description:

t<sub>1/2</sub> is time required for the concentration of the drug to reach half of its original value. The PKAS included all subjects who have evaluable PK profiles. Here, 'number of subjects analysed' signifies those subjects who were evaluable for this endpoint.

End point type	Secondary
End point timeframe:	
Pre-dose and post dose at: 0.5 hr, 1 hr, 6 hr, 24 hr, 48 hr, 72 hr and 96 hr	

End point values	15K rFVIIIFc (1000 IU/Vial Strength) (PK3)	15K rFVIIIFc (6000 IU/Vial Strength) (PK3)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	12		
Units: hours				
geometric mean (confidence interval 95%)	16.945 (13.793 to 20.818)	17.522 (14.213 to 21.601)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Clearance of rFVIIIFc as Measured by the Two-stage Chromogenic Assay for PK3 at Different Vial Strengths (1000 and 6000 IU/Vial)

End point title	Clearance of rFVIIIFc as Measured by the Two-stage Chromogenic Assay for PK3 at Different Vial Strengths (1000 and 6000 IU/Vial)
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#### End point description:

CL is a quantitative measure of the rate at which a drug substance is removed from the body. The total systemic CL after IV dose was estimated by dividing the total administered dose by AUC(0-infinity). The PKAS included all subjects who have evaluable PK profiles. Here, 'number of subjects analysed' signifies those subjects who were evaluable for this endpoint.

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

Pre-dose and post dose at: 0.5 hr, 1 hr, 6 hr, 24 hr, 48 hr, 72 hr and 96 hr

End point values	15K rFVIIIFc (1000 IU/Vial Strength) (PK3)	15K rFVIIIFc (6000 IU/Vial Strength) (PK3)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	12		
Units: mL/hr/kg				
geometric mean (confidence interval 95%)	1.8891 (1.3502 to 2.6429)	1.7709 (1.3989 to 2.2419)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Volume of Distribution at Steady State of rFVIIIFc as Measured by the Two-stage Chromogenic Assay for PK3 at Different Vial Strengths (1000 and 6000 IU/Vial)

End point title	Volume of Distribution at Steady State of rFVIIIFc as Measured by the Two-stage Chromogenic Assay for PK3 at Different Vial Strengths (1000 and 6000 IU/Vial)
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#### End point description:

Vss 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. Vss is the apparent volume of distribution at steady-state which is estimated by  $(D/AUC[0\text{-}infinity]) \times (AUMC[0\text{-}infinity])/AUC[0\text{-}infinity]$  where D is the dose of study drug, AUMC(0-infinity) is the area under the first moment curve extrapolated to infinity and AUC(0-infinity) is the area under the plasma concentration-time curve from time zero to infinite time. The PKAS included all subjects who have evaluable PK profiles. Here, 'number of subjects analysed' signifies those subjects who were evaluable for this endpoints.

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

Pre-dose and post dose at: 0.5 hr, 1 hr, 6 hr, 24 hr, 48 hr, 72 hr and 96 hr

End point values	15K rFVIIIFc (1000 IU/Vial Strength) (PK3)	15K rFVIIIFc (6000 IU/Vial Strength) (PK3)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	12		
Units: mL/kg				
geometric mean (confidence interval 95%)	41.78 (30.70 to 56.87)	39.82 (35.98 to 44.06)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Mean Residence Time of rFVIIIFc as Measured by the Two-stage Chromogenic Assay for PK3 at Different Vial Strengths (1000 and 6000 IU/Vial)

End point title	Mean Residence Time of rFVIIIFc as Measured by the Two-stage Chromogenic Assay for PK3 at Different Vial Strengths (1000 and 6000 IU/Vial)
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End point description:

The MRT is the average time at which the number of absorbed molecules reside in the body, after single-dose administration, and calculated as  $AUMC(0-\infty)/AUC(0-\infty)$ , where  $AUMC(0-\infty)$  is area under the plasma concentration-time first moment curve from time zero to infinite time and  $AUC(0-\infty)$  is the area under the plasma concentration-time curve from time zero to infinite time. The PKAS included all subjects who have evaluable PK profiles. Here, 'number of subjects analysed' signifies those subjects who were evaluable for this endpoint.

End point type	Secondary
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End point timeframe:

Pre-dose and post dose at: 0.5 hr, 1 hr, 6 hr, 24 hr, 48 hr, 72 hr and 96 hr

End point values	15K rFVIIIFc (1000 IU/Vial Strength) (PK3)	15K rFVIIIFc (6000 IU/Vial Strength) (PK3)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	12		
Units: hours				
geometric mean (confidence interval 95%)	22.119 (17.717 to 27.614)	22.483 (18.532 to 27.277)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Development of Inhibitors as Measured by the Nijmegen-modified Bethesda Assay

End point title	Development of Inhibitors as Measured by the Nijmegen-modified Bethesda Assay
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**End point description:**

Defined as an inhibitor test result greater than or equal to ( $\geq$ ) 0.6 Bethesda units [BU]/mL, confirmed on 2 separate samples drawn approximately 2 to 4 weeks apart, was considered positive. The test was performed by the central laboratory using the Nijmegen-modified Bethesda Assay. An exact 95% confidence interval (CI) for the percentage of subjects with a confirmed inhibitor was calculated using the Clopper-Pearson method for a binomial proportion. Percentage of subjects with confirmed inhibitor development was summarised overall. The population analysed included all subjects who received at least 1 dose of rFVIIIFc.

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End point type	Secondary
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**End point timeframe:**

At screening, predose on Day 1, and 13 and 26 weeks after PK2 injection or at Early Termination (Approximately 43 weeks)

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<b>End point values</b>	2K/15K rFVIIIFc (1000/6000 IU/Vial Strength)- All Subjects			
Subject group type	Subject analysis set			
Number of subjects analysed	24			
Units: percentage of subjects				
number (confidence interval 95%)	0 (0 to 14.25)			

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**Statistical analyses**

No statistical analyses for this end point

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**Secondary: Number of Subjects With Treatment Emergent Adverse Events (TEAEs) at 15K Manufacturing Scale**

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End point title	Number of Subjects With Treatment Emergent Adverse Events (TEAEs) at 15K Manufacturing Scale
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**End point description:**

An AE was any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. Number of subjects with TEAEs were summarised overall. The population analysed included all subjects who received at least 1 dose of rFVIIIFc at 15k manufacturing scale.

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End point type	Secondary
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**End point timeframe:**

Approximately 43 weeks

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<b>End point values</b>	15K rFVIIIFc (1000 and 6000 IU/Vial Strength) (PK2 and PK3)			
Subject group type	Subject analysis set			
Number of subjects analysed	23			
Units: subjects				
number (not applicable)	10			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Subjects With Treatment Emergent Serious Adverse Events (TESAEs) at 15K Manufacturing Scale

End point title	Number of Subjects With Treatment Emergent Serious Adverse Events (TESAEs) at 15K Manufacturing Scale
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End point description:

An SAE was any untoward medical occurrence that at any dose: resulted in death or in the view of the Investigator, places the subject at immediate risk of death (a life-threatening event); required inpatient hospitalisation or prolongation of existing hospitalisation; resulted in persistent or significant disability/incapacity; or resulted in a congenital anomaly/birth defect. All major surgeries will be reported as SAEs. An SAE may also be any other medically important event that, in the opinion of the Investigator, may jeopardise the subject or may required intervention to prevent one of the other outcomes listed in the SAE definition. Number of subjects with TESAEs were summarised overall. The population analysed included all subjects who received at least 1 dose of rFVIIIFc at 15k manufacturing scale.

End point type	Secondary
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End point timeframe:

Approximately 43 weeks

<b>End point values</b>	15K rFVIIIFc (1000 and 6000 IU/Vial Strength) (PK2 and PK3)			
Subject group type	Subject analysis set			
Number of subjects analysed	23			
Units: subjects				
number (not applicable)	0			

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Approximately 43 weeks

Adverse event reporting additional description:

Safety Population included all subjects who received at least 1 dose of rFVIIIFc. AEs are reported based on overall number of subjects treated with 2K rFVIIIFc at 1000 IU/vial strength (PK1 assessment & Intermediate period) and 15K rFVIIIFc at 1000 & 6000 IU/vial strength (PK2 assessment period & Treatment Period [including PK3 assessment period]).

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	20.0
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### Reporting groups

Reporting group title	2K rFVIIIFc (1000 IU/Vial Strength) (PK1)
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Reporting group description:

All subjects received rFVIIIFc (1000 IU/vial strength), 50 IU/kg, manufactured in 2K for PK1.

Reporting group title	15K rFVIIIFc (1000 and 6000 IU/Vial Strength)
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Reporting group description:

During the PK1 assessment period, subjects randomised in a 1:1 ratio to receive either 1000 IU/vial or 6000 IU/vial of 15K rFVIIIFc (a single IV injection of 50 IU/kg) in the subsequent PK2 and PK3 assessments. Subjects received rFVIIIFc (1000/6000 IU/vial strength), 50 IU/kg, manufactured in 15K for PK2/PK3 after a minimum of 120 hr of washout prior to the PK2. Following PK2 assessment, subjects received prophylactic treatment with any of 5 available 15K vial strengths during the treatment phase of 13 weeks.

Serious adverse events	2K rFVIIIFc (1000 IU/Vial Strength) (PK1)	15K rFVIIIFc (1000 and 6000 IU/Vial Strength)	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 24 (0.00%)	0 / 23 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			

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

Non-serious adverse events	2K rFVIIIFc (1000 IU/Vial Strength) (PK1)	15K rFVIIIFc (1000 and 6000 IU/Vial Strength)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 24 (0.00%)	3 / 23 (13.04%)	
Nervous system disorders			
Headache			



subjects affected / exposed	0 / 24 (0.00%)	3 / 23 (13.04%)	
occurrences (all)	0	3	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported