Clinical trial results:
A-LONG: An Open-label, Multicenter Evaluation of the Safety, Pharmacokinetics, and Efficacy of Recombinant Factor VIII Fc Fusion Protein (rFVIIIFc) in the Prevention and Treatment of Bleeding in Previously Treated Subjects With Severe Hemophilia A

Summary

EudraCT number	2010-020558-33
Trial protocol	SE GB FR DE BE ES AT IT PT
Global end of trial date	06 August 2012

Results information

Result version number	v1 (current)
This version publication date	04 February 2016
First version publication date	20 June 2015

Trial information

Trial identification

Sponsor protocol code	997HA301

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01181128
WHO universal trial number (UTN)	-

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	06 August 2012
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	06 August 2012
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objectives of this study are: to evaluate the safety and tolerability of rFVIIIFc administered as a prophylaxis (Arm 1), weekly (Arm 2), on-demand (Arm 3), and surgical treatment regimen; to evaluate the efficacy of the rFVIIIFc tailored prophylaxis regimen (Arm 1); to evaluate the efficacy of rFVIIIFc administered as an on-demand (Arm 3) and surgical treatment regimen. The secondary objectives of this study are: to characterize the pharmacokinetic (PK) profile of rFVIIIFc and compare the PK of rFVIIIFc with the currently marketed product, Advate®; to characterize the range of dose and schedules required to adequately prevent bleeding in a prophylaxis regimen, maintain hemostasis in a surgical setting, or to treat bleeding episodes in an on-demand, weekly treatment, or prophylaxis setting.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	29 November 2010
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 8
Country: Number of subjects enrolled	Brazil: 3
Country: Number of subjects enrolled	Canada: 2
Country: Number of subjects enrolled	Hong Kong: 4
Country: Number of subjects enrolled	India: 15
Country: Number of subjects enrolled	Israel: 4
Country: Number of subjects enrolled	Japan: 14
Country: Number of subjects enrolled	New Zealand: 3
Country: Number of subjects enrolled	South Africa: 17
Country: Number of subjects enrolled	Switzerland: 1
Country: Number of subjects enrolled	United States: 54
Country: Number of subjects enrolled	Spain: 2

Country: Number of subjects enrolled	Sweden: 1
Country: Number of subjects enrolled	United Kingdom: 20
Country: Number of subjects enrolled	Austria: 5
Country: Number of subjects enrolled	Belgium: 1
Country: Number of subjects enrolled	France: 2
Country: Number of subjects enrolled	Germany: 4
Country: Number of subjects enrolled	Italy: 5
Worldwide total number of subjects	165
EEA total number of subjects	40

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	13
Adults (18-64 years)	151
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The screening period to determine subject eligibility was to last for up to 8 weeks and included at least a 96-hour washout from Factor VIII (FVIII) prior to initial study dosing. A 72-hour washout was allowed for adolescent subjects (i.e., 12 to 17 years old).

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm 1: Individualized (Tailored) Prophylaxis

Arm description:

On rFVIIIFc Day 0, all subjects underwent PK analysis with 50 IU/kg rFVIIIFc to estimate their PK parameters and guide the appropriate dose or interval of dosing. A subset of subjects (Sequential PK subgroup) also had PK analyses performed with a single dose of 50 IU/kg Advate (Advate Day 0) within 8 weeks prior to rFVIIIFc Day 0. A >= 96 hour washout was performed before the PK dose of Advate or rFVIIIFc was administered. Repeat PK profiling with a single dose of 50 IU/kg rFVIIIFc was conducted at Week 14 or after 12 to 24 weeks of prophylaxis with rFVIIIFc.

After PK assessments, all subjects started twice weekly treatment with 25 IU/kg of rFVIIIFc via intravenous (IV) injection on Day 1 and 50 IU/kg on Day 4, followed by individualized dose and interval modification within the range of 25 to 65 IU/kg every 3 to 5 days, as determined by rFVIIIFc PK analysis, to maintain a trough level of 1% to 3% (or higher, as clinically indicated) FVIII activity.

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

Dosage and administration details:

Study site staff members were instructed to refer to the Directions for Handling and Administration located in the Investigator Site File and/or the Pharmacy Manual for specific instructions on the handling, preparation, administration, and disposal of the study treatment.

Investigational medicinal product name	Advate®
Investigational medicinal product code	
Other name	octocog alfa, Antihemophilic Factor [Recombinant] Plasma/Albumin Free Method
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Study site staff members were instructed to refer to the Directions for Handling and Administration located in the Investigator Site File and/or the Pharmacy Manual for specific instructions on the handling, preparation, administration, and disposal of the study treatment.

Arm title	Arm 2: Weekly Prophylaxis

Arm description:

65 IU/kg of rFVIIIFc via IV injection every 7 days

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

Dosage and administration details:

Study site staff members were instructed to refer to the Directions for Handling and Administration located in the Investigator Site File and/or the Pharmacy Manual for specific instructions on the handling, preparation, administration, and disposal of the study treatment.

Arm title	Arm 3: Episodic (On-Demand) Dosing

Arm description:

10 to 50 IU/kg rFVIIIFc via IV injection, as required to treat a bleeding episode

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

Dosage and administration details:

Study site staff members were instructed to refer to the Directions for Handling and Administration located in the Investigator Site File and/or the Pharmacy Manual for specific instructions on the handling, preparation, administration, and disposal of the study treatment.

Number of subjects in period 1	Arm 1: Individualized (Tailored) Prophylaxis	Arm 2: Weekly Prophylaxis	Arm 3: Episodic (On-Demand) Dosing
Started	118	24	23
Pharmacokinetic (PK) Subgroup	30 [1]	0 [2]	0 [3]
Perioperative Management Subgroup	8 [4]	1 [5]	0 [6]
Completed	112	19	22
Not completed	6	5	1
Adverse event, serious fatal	1	-	-
Consent withdrawn by subject	2	2	-
Physician decision	2	-	-
Adverse event, non-fatal	-	2	-
Not specified	1	1	1

Notes:

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

Justification: Milestones are provided to account for PK Subgroup and Perioperative Management Subgroup populations.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Milestones are provided to account for PK Subgroup and Perioperative Management Subgroup populations.
[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Milestones are provided to account for PK Subgroup and Perioperative Management Subgroup populations.
[4] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Milestones are provided to account for PK Subgroup and Perioperative Management Subgroup populations.
[5] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Milestones are provided to account for PK Subgroup and Perioperative Management Subgroup populations.
[6] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Milestones are provided to account for PK Subgroup and Perioperative Management Subgroup populations.

Baseline characteristics

Reporting groups	
Reporting group title	Arm 1: Individualized (Tailored) Prophylaxis

Reporting group description:

On rFVIIIFc Day 0, all subjects underwent PK analysis with 50 IU/kg rFVIIIFc to estimate their PK parameters and guide the appropriate dose or interval of dosing. A subset of subjects (Sequential PK subgroup) also had PK analyses performed with a single dose of 50 IU/kg Advate (Advate Day 0) within 8 weeks prior to rFVIIIFc Day 0. A >= 96 hour washout was performed before the PK dose of Advate or rFVIIIFc was administered. Repeat PK profiling with a single dose of 50 IU/kg rFVIIIFc was conducted at Week 14 or after 12 to 24 weeks of prophylaxis with rFVIIIFc.

After PK assessments, all subjects started twice weekly treatment with 25 IU/kg of rFVIIIFc via intravenous (IV) injection on Day 1 and 50 IU/kg on Day 4, followed by individualized dose and interval modification within the range of 25 to 65 IU/kg every 3 to 5 days, as determined by rFVIIIFc PK analysis, to maintain a trough level of 1% to 3% (or higher, as clinically indicated) FVIII activity.

Reporting group title	Arm 2: Weekly Prophylaxis

Reporting group description:

65 IU/kg of rFVIIIFc via IV injection every 7 days

Reporting group title	Arm 3: Episodic (On-Demand) Dosing

Reporting group description:

10 to 50 IU/kg rFVIIIFc via IV injection, as required to treat a bleeding episode

Reporting group values	Arm 1: Individualized (Tailored) Prophylaxis	Arm 2: Weekly Prophylaxis	Arm 3: Episodic (On-Demand) Dosing
Number of subjects	118	24	23
Age categorical Units: Subjects			
Adolescents (12-17 years)	11	0	2
Adults (18-64 years)	106	24	21
From 65-84 years	1	0	0
Age continuous Units: years			
median	29	31.5	34
full range (min-max)	12 to 65	18 to 59	13 to 62
Gender categorical Units: Subjects			
Female	0	0	0
Male	118	24	23

Reporting group values	Total		
Number of subjects	165		
Age categorical Units: Subjects			
Adolescents (12-17 years)	13		
Adults (18-64 years)	151		
From 65-84 years	1		
Age continuous Units: years			
median			
full range (min-max)	-		

Gender categorical Units: Subjects			
Female	0		
Male	165		

End points

End points reporting groups

Reporting group title	Arm 1: Individualized (Tailored) Prophylaxis

Reporting group description:

On rFVIIIFc Day 0, all subjects underwent PK analysis with 50 IU/kg rFVIIIFc to estimate their PK parameters and guide the appropriate dose or interval of dosing. A subset of subjects (Sequential PK subgroup) also had PK analyses performed with a single dose of 50 IU/kg Advate (Advate Day 0) within 8 weeks prior to rFVIIIFc Day 0. A >= 96 hour washout was performed before the PK dose of Advate or rFVIIIFc was administered. Repeat PK profiling with a single dose of 50 IU/kg rFVIIIFc was conducted at Week 14 or after 12 to 24 weeks of prophylaxis with rFVIIIFc.

After PK assessments, all subjects started twice weekly treatment with 25 IU/kg of rFVIIIFc via intravenous (IV) injection on Day 1 and 50 IU/kg on Day 4, followed by individualized dose and interval modification within the range of 25 to 65 IU/kg every 3 to 5 days, as determined by rFVIIIFc PK analysis, to maintain a trough level of 1% to 3% (or higher, as clinically indicated) FVIII activity.

Reporting group title	Arm 2: Weekly Prophylaxis

Reporting group description:

65 IU/kg of rFVIIIFc via IV injection every 7 days

Reporting group title	Arm 3: Episodic (On-Demand) Dosing

Reporting group description:

10 to 50 IU/kg rFVIIIFc via IV injection, as required to treat a bleeding episode

Subject analysis set title	Arm 1: Individualized (Tailored) Prophylaxis, Advate
Subject analysis set type	Safety analysis

Subject analysis set description:

Subjects in the Individualized (Tailored) Prophylaxis arm who received at least 1 dose of Advate.

Subject analysis set title	Arm 1: Individualized (Tailored) Prophylaxis, rFVIIIFc Only
Subject analysis set type	Safety analysis

Subject analysis set description:

Subjects in the Individualized (Tailored) Prophylaxis arm who received at least 1 dose of rFVIIIFc.

Subject analysis set title	Any Arm: Perioperative Management (Surgery) Subgroup
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects from any arm who underwent major surgery. The surgical period and dosing were dependent on the type of surgery the subject underwent.

Subject analysis set title	Arm 1: Individualized Prophylaxis: Sequential PK Subgroup
Subject analysis set type	Sub-group analysis

Subject analysis set description:

On rFVIIIFc Day 0, all subjects underwent pharmacokinetic (PK) analysis with 50 IU/kg rFVIIIFc to estimate their PK parameters and guide the appropriate dose or interval of dosing. A subset of subjects (Sequential PK subgroup) also had PK analyses performed with a single dose of 50 IU/kg Advate (Advate Day 0) within 8 weeks prior to rFVIIIFc Day 0. A >= 96 hour washout was performed before the PK dose of Advate or rFVIIIFc was administered. Repeat PK profiling with a single dose of 50 IU/kg rFVIIIFc was conducted at Week 14 or after 12 to 24 weeks of prophylaxis with rFVIIIFc.

Analysis set includes subjects who had evaluable one- or two-stagePK profiles for both Advate and baseline rFVIIIFc.

Subject analysis set title	Arm 1: Individualized Prophylaxis, Prestudy Prophylaxis
Subject analysis set type	Sub-group analysis

Subject analysis set description:

On rFVIIIFc Day 0, all subjects underwent pharmacokinetic (PK) analysis with 50 IU/kg rFVIIIFc to estimate their PK parameters and guide the appropriate dose or interval of dosing. A subset of subjects (Sequential PK subgroup) also had PK analyses performed with a single dose of 50 IU/kg Advate (Advate Day 0) within 8 weeks prior to rFVIIIFc Day 0. A >= 96 hour washout was performed before the PK dose of Advate or rFVIIIFc was administered. Repeat PK profiling with a single dose of 50 IU/kg rFVIIIFc was conducted at Week 14 or after 12 to 24 weeks of prophylaxis with rFVIIIFc.

After PK assessments, all subjects started twice weekly treatment with 25 IU/kg of rFVIIIFc via

intravenous (IV) injection on Day 1 and 50 IU/kg on Day 4, followed by individualized dose and interval modification within the range of 25 to 65 IU/kg every 3 to 5 days, as determined by rFVIIIFc PK analysis, to maintain a trough level of 1% to 3% (or higher, as clinically indicated) FVIII activity.

Subject analysis set title	Arm 1: Individualized Prophylaxis, Prestudy On-demand
Subject analysis set type	Sub-group analysis

Subject analysis set description:

On rFVIIIFc Day 0, all subjects underwent pharmacokinetic (PK) analysis with 50 IU/kg rFVIIIFc to estimate their PK parameters and guide the appropriate dose or interval of dosing. A subset of subjects (Sequential PK subgroup) also had PK analyses performed with a single dose of 50 IU/kg Advate (Advate Day 0) within 8 weeks prior to rFVIIIFc Day 0. A >= 96 hour washout was performed before the PK dose of Advate or rFVIIIFc was administered. Repeat PK profiling with a single dose of 50 IU/kg rFVIIIFc was conducted at Week 14 or after 12 to 24 weeks of prophylaxis with rFVIIIFc.

After PK assessments, all subjects started twice weekly treatment with 25 IU/kg of rFVIIIFc via intravenous (IV) injection on Day 1 and 50 IU/kg on Day 4, followed by individualized dose and interval modification within the range of 25 to 65 IU/kg every 3 to 5 days, as determined by rFVIIIFc PK analysis, to maintain a trough level of 1% to 3% (or higher, as clinically indicated) FVIII activity.

Subject analysis set title	All Arms: Total
Subject analysis set type	Full analysis

Subject analysis set description:

All subjects from the Individualized (Tailored) Prophylaxis, Weekly Prophylaxis, and Episodic (On-Demand)
Dosing arms.

Primary: Incidence Rate of FVIII Inhibitor Development

End point title	Incidence Rate of FVIII Inhibitor Development[1]

End point description:

An inhibitor test result ≥0.6 Bethesda units (BU)/mL, identified and confirmed by re-testing of a second sample obtained within 2 to 4 weeks, was considered positive. Both tests were to be performed using the Nijmegen-modified Bethesda Assay by the central laboratory. The incidence rates along with the 95% confidence interval (CI) were summarized for all titers for subjects with 50 or more exposure days (EDs) to rFVIIIFc and a valid inhibitor test after the 50th exposure. In addition, the incidence rates for all subjects regardless of their EDs to rFVIIIFc were also summarized. The 95% CI was calculated using Clopper-Pearson exact method. Safety Analysis Set: subjects who received at least 1 dose of Advate or at least 1 dose of rFVIIIFc.

End point type	Primary

End point timeframe:

up to 52 weeks ± 2 weeks

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Per protocol, descriptive statistics were collected for this endpoint.

End point values	Arm 1: Individualized (Tailored) Prophylaxis	Arm 2: Weekly Prophylaxis	Arm 3: Episodic (On-Demand) Dosing	All Arms: Total
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	118[2]	24[3]	23[4]	165[5]
Units: percentage of subjects				
number (confidence interval 95%)				
Subjects with>=50 EDs; n=107, 1, 2, 110	0 (0 to 3.4)	0 (0 to 97.5)	0 (0 to 84.2)	0 (0 to 3.3)
All subjects; n=117, 24, 23, 164	0 (0 to 3.1)	0 (0 to 14.2)	0 (0 to 14.8)	0 (0 to 2.2)

Notes:

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

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

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

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

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Treatment-emergent Adverse Events (TEAEs) and Treatment-emergent Serious Adverse Events (TESAEs)

End point title	Number of Subjects With Treatment-emergent Adverse Events (TEAEs) and Treatment-emergent Serious Adverse Events (TESAEs)[6][7]

End point description:

AE=any untoward medical occurrence that did not necessarily have a causal relationship with treatment. TEAE=AE present prior to receiving the first injection of Advate or rFVIIIFc that subsequently worsened in severity or not present prior to receiving the first injection but subsequently appeared before the last visit on study. Serious AE (SAE)=AE resulting in death, immediate risk of death, inpatient hospitalization or prolongation of existing hospitalization, persistent or significant disability/incapacity, or a congenital anomaly/birth defect, or any other medically important event. For Arm 1, AEs emergent between the first on-study Advate dose and 1st rFVIIIFc dose are reported as treatment-emergent to Advate (first column); AEs emergent after the first rFVIIIFc injection are reported as treatment-emergent to rFVIIIFc (2nd column). Safety Analysis Set: subjects who received at least 1 dose of Advate or at least 1 dose of rFVIIIFc.

End point type	Primary

End point timeframe:

up to 52 weeks + 30 days ± 1 week

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Per protocol, descriptive statistics were collected for this endpoint.

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: For Arm 1, AEs emergent between the first on-study Advate dose and the first rFVIIIFc dose are reported as treatment-emergent to Advate; AEs emergent after the first rFVIIIFc injection are reported as treatment-emergent to rFVIIIFc (2 separate columns).

End point values	Arm 2: Weekly Prophylaxis	Arm 3: Episodic (On-Demand) Dosing	Arm 1: Individualized (Tailored) Prophylaxis, Advate	Arm 1: Individualized (Tailored) Prophylaxis, rFVIIIFc Only
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	24	23	30	117
Units: subjects				
>=1 TEAE	18	10	3	80
>=1 Related TEAE	3	2	0	5
>=1 TESAE	2	0	0	10
>=1 Related TESAE	0	0	0	0

End point values	Any Arm: Perioperative Management			

	(Surgery) Subgroup			
Subject group type	Subject analysis set			
Number of subjects analysed	9			
Units: subjects				
>=1 TEAE	4			
>=1 Related TEAE	0			
>=1 TESAE	2			
>=1 Related TESAE	0			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Potentially Clinically Significant Abnormal Laboratory Values From Baseline

End point title	Number of Subjects With Potentially Clinically Significant Abnormal Laboratory Values From Baseline[8]

End point description:

Clinical laboratory evaluations included hematology and blood chemistry. Table does not include laboratory tests evaluated during the surgical/rehabilitation period. ULN=upper limit of normal. Safety Analysis Set: subjects who received at least 1 dose of Advate or at least 1 dose of rFVIIIFc.

End point type	Primary

End point timeframe:

up to 52 weeks ± 2 weeks

Notes:

[8] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Per protocol, descriptive statistics were collected for this endpoint.

End point values	Arm 1: Individualized (Tailored) Prophylaxis	Arm 2: Weekly Prophylaxis	Arm 3: Episodic (On-Demand) Dosing	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	118[9]	24[10]	23[11]	
Units: subjects				
Leukocytes <3.0*10^9/L; n=117, 24, 23	2	0	2	
Leukocytes >=16*10^9/L; n=117, 24, 23	1	0	0	
Lymphocytes <0.8*10^9/L; n=104, 22, 21	3	1	1	
Lymphocytes >12*10^9/L; n=104, 22, 21	0	0	0	
Neutrophils <1.5*10^9/L; n=104, 22, 21	4	0	1	
Neutrophils >13.5*10^9/L; n=104, 22, 21	1	0	0	
Monocytes >2.5*10^9/L; n=104, 22, 21	0	0	0	
Eosinophils >1.6*10^9/L; n=104, 22, 21	0	0	0	
Basophils >1.6*10^9/L; n=104, 22, 21	0	0	0	

Erythrocytes <=3.5*10^12/L; n=117, 24, 23	1	0	0	
Erythrocytes >=6.4*10^12/L; n=117, 24, 23	1	0	1	
Hemoglobin <=115 g/L; n=117, 24, 23	3	0	1	
Hemoglobin >=190 g/L; n=117, 24, 23	0	0	0	
Hematocrit <=37%; n=117, 24, 23	5	2	1	
Hematocrit >=60%; n=117, 24, 23	0	0	0	
Platelets <=75*10^9/L; n=117, 24, 23	0	0	0	
Platelets >=700*10^9/L; n=117, 24, 23	0	0	0	
Alanine Aminotransferase >=3*ULN; n=117, 24, 23	4	0	0	
Aspartate Aminotransferase >=3*ULN; n=117, 24, 23	4	1	0	
Alkaline Phosphatase >=3*ULN; n=117, 24, 23	0	0	0	
Total Bilirubin >=34.2 µmol/L; n=117, 24, 23	3	0	2	
Blood Urea Nitrogen >=10.7 mmol/L; n=117, 24, 23	1	1	0	
Creatinine >=176.8 µmol/L; n=117, 24, 23	0	0	0	
Sodium <=126 mmol/L; n=117, 24, 23	0	0	0	
Sodium >=156 mmol/L; n=117, 24, 23	1	0	0	
Potassium <=3 mmol/L; n=117, 24, 23	0	0	0	
Potassium >=6 mmol/L; n=117, 24, 23	0	0	0	
Chloride <=90 mmol/L; n=117, 24, 23	1	0	0	
Chloride >=118 mmol/L; n=117, 24, 23	0	0	0	
Phosphate <=0.55 mmol/L n=117, 24, 23	1	0	0	
Phosphate >=1.71 mmol/L; n=117, 24, 23	0	0	0	
Glucose <=2.22 mmol/L; n=117, 24, 23	0	0	0	
Glucose >=9.71 mmol/L; n=117, 24, 23	2	1	0	
Total Protein <=45 g/L; n=117, 24, 23	0	0	0	
Total Protein >=100 g/L; n=117, 24, 23	0	0	0	

Notes:

[9] - n=the number of subjects with at least one postbaseline value.

[10] - n=the number of subjects with at least one postbaseline value.

[11] - n=the number of subjects with at least one postbaseline value.

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Clinically Relevant Abnormalities in Vital Signs or Relevant Changes From Baseline in Vital Signs

End point title	Number of Subjects With Clinically Relevant Abnormalities in Vital Signs or Relevant Changes From Baseline in Vital Signs[12]

End point description:

Number of subjects with clinically relevant abnormalities or relevant changes from baseline in temperature, pulse (beats per minute [bpm]), systolic blood pressure (SBP), and diastolic blood pressure (DBP) are presented. Baseline (BL) is defined as the last non-missing evaluable assessment taken prior and closest to the first rFVIIIFc dose. signifies increase and signifies decrease. Safety Analysis Set: subjects who received at least 1 dose of Advate or at least 1 dose of rFVIIIFc and had a baseline assessment and at least 1 postbaseline assessment for temperature or at least 1 postbaseline assessment for pulse, SBP, and DBP.

End point type	Primary

End point timeframe:

up to 52 weeks ± 2 weeks

Notes:

[12] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Per protocol, descriptive statistics were collected for this endpoint.

End point values	Arm 1: Individualized (Tailored) Prophylaxis	Arm 2: Weekly Prophylaxis	Arm 3: Episodic (On-Demand) Dosing	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	113	24	23	
Units: subjects				
Temperature: >38°C and ≥1°C from BL	1	0	0	
Pulse: >120 bpm or >20 bpm from BL	11	2	0	
Pulse: <50 bpm or >20 bpm from BL	11	2	1	
SBP: >180 mm Hg or >40 mm Hg from BL	0	1	0	
SBP: <90 mm Hg or >30 mm Hg from BL	5	1	1	
DBP: >105 mm Hg or >30 mm Hg from BL	1	0	0	
DBP: <50 mm Hg or >20 mm Hg from BL	5	0	1	

Statistical analyses

No statistical analyses for this end point

Primary: Annualized Bleeding Rate

End point title	Annualized Bleeding Rate[13]

End point description:

Annualized bleeding episodes = (number of bleeding episodes during the efficacy period / number of days during the efficacy period)*365.25. The efficacy period in Arms 1 and 2 began with the first prophylactic dose of rFVIIIFc and ended with the last dose (regardless of reason for dosing). The efficacy period in Arm 3 began at the time of last PK rFVIIIFc sampling timepoint and ended at the date of the last study visit. Periods of PK evaluations and surgery/rehabilitation are not included in the efficacy period. A bleeding episode started from the first sign of a bleed, and ended 72 hours after the last treatment for the bleeding, within which any symptoms of bleeding at the same location, or injections less than or equal to 72 hours apart, were considered the same bleeding episode. Full Analysis Set: subjects who received at least 1 dose of rFVIIIFc with an efficacy assessment.

End point type	Primary

End point timeframe:

up to 52 weeks ± 2 weeks (efficacy period as defined in description)

Notes:

[13] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: See "Comparison of Annualized Bleeding Rates: Arm 1 Versus Arm 3" endpoint for statistical analysis.

End point values	Arm 1: Individualized (Tailored) Prophylaxis	Arm 2: Weekly Prophylaxis	Arm 3: Episodic (On-Demand) Dosing	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	117	23	23	
Units: episodes per subject per year				
median (inter-quartile range (Q1-Q3))	1.6 (0 to 4.69)	3.59 (1.86 to 8.36)	33.57 (21.14 to 48.69)	

Statistical analyses

No statistical analyses for this end point

Primary: Comparison of Annualized Bleeding Rates: Arm 1 Versus Arm 3

End point title	Comparison of Annualized Bleeding Rates: Arm 1 Versus Arm

End point description:

Estimated using the negative binomial model with treatment arm as covariate, based on whole study duration for all subjects. Annualized bleeding episodes = (number of bleeding episodes / number of days in the respective period)*365.25.The efficacy period in Arm 1 began with the first prophylactic dose of rFVIIIFc and ended with the last dose (regardless of reason for dosing). The efficacy period in Arm 3 began at the time of last PK rFVIIIFc sampling timepoint and ended at the date of the last study visit. Periods of PK evaluations and surgery/rehabilitation are not included in the efficacy period. A bleeding episode started from the first sign of a bleed, and ended 72 hours after the last treatment for the bleeding, within which any symptoms of bleeding at the same location, or injections less than or equal to 72 hours apart, were considered part of the same bleeding episode. Full Analysis Set: subjects who received at least 1 dose of rFVIIIFc with an efficacy assessment.

End point type	Primary

End point timeframe:

up to 52 weeks ± 2 weeks (efficacy period as defined in description)

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Per protocol, Arm 1 versus Arm 3 only was analyzed as a primary endpoint. Arm 2 versus Arm 3 only was analyzed as a secondary endpoint. Both are included in this record.

End point values	Arm 1: Individualized (Tailored) Prophylaxis	Arm 3: Episodic (On-Demand) Dosing		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	117	23		
Units: episodes per subject per year				
number (confidence interval 95%)	2.91 (2.3 to 3.68)	37.25 (24.03 to 57.74)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

The null hypothesis for the primary endpoint is no difference between the individualized (tailored) prophylaxis regimen and the on-demand regimen. The sample size of this study was mainly based on

clinical rather than statistical considerations. However it was projected to have > 90% power at the 2-sided 0.05 level of significance to detect a 60% reduction in annualized bleeding episodes, based upon this hypothesis test.

Comparison groups	Arm 1: Individualized (Tailored) Prophylaxis v Arm 3: Episodic (On-Demand) Dosing
Number of subjects included in analysis	140
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	negative binomial model
Parameter estimate	Bleeding Rate Ratio
Point estimate	0.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.05
upper limit	0.13

Primary: Area Under the Curve (AUC) Per Dose (One-stage Clotting Assay)

End point title	Area Under the Curve (AUC) Per Dose (One-stage Clotting Assay)[15]

End point description:

Dose normalized area under the drug concentration-time curve. Sampling for Advate PK profiling was conducted, following at least 96 hours of washout, at these timepoints: preinjection and at either 30 (±3) minutes or 10 (±3) minutes, 1 hour (±15 minutes), 6 (±1) hours, 24 (±2) hours (Day 1), 48 (±2) hours (Day 2), and 72 (±2) hours (Day 3) from the start of the injection. Sampling for rFVIIIFc PK profiling was conducted at Day 0 (directly following at least 96 hours washout from Advate PK profiling or within 4 weeks of the Advate dose or other rFVIII product) and repeated 12 to 24 weeks later at the following timepoints: preinjection and at 30 (±3) minutes (or 10 (±3) minutes), 1 hour (±15 minutes), 6 (±1) hours, 24 (±2) hours (Day 1), 72 (±2) hours (Day 3), 96 (±2) hours (Day 4), and 120 (±2) hours (Day 5) from the start of the injection.

End point type	Primary

End point timeframe:

See endpoint description for complete time frame.

Notes:

[15] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analysis for this endpoint cannot be entered due EudraCT system restrictions for within-group comparison.

End point values	Arm 1: Individualized Prophylaxis: Sequential PK Subgroup			
Subject group type	Subject analysis set			
Number of subjects analysed	28[16]			
Units: IU*h/dL per IU/kg				
geometric mean (confidence interval 95%)				
rFVIIIFc Baseline	51.24 (44.97 to 58.38)			
Advate	32.88 (29.31 to 36.88)			

Notes:

[16] - Subjects who had evaluable one-stage PK profiles for both Advate and baseline rFVIIIFc.

Statistical analyses

No statistical analyses for this end point

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

End point title	Elimination Half Life (t1/2; One-stage Clotting Assay)[17]

End point description:

Time required for the activity of the drug to reach half of its original value. Sampling for Advate PK profiling was conducted, following at least 96 hours of washout, at these timepoints: preinjection and at either 30 (±3) minutes or 10 (±3) minutes, 1 hour (±15 minutes), 6 (±1) hours, 24 (±2) hours (Day 1), 48 (±2) hours (Day 2), and 72 (±2) hours (Day 3) from the start of the injection. Sampling for rFVIIIFc PK profiling was conducted at Day 0 (directly following at least 96 hours washout from Advate PK profiling or within 4 weeks of the Advate dose or other rFVIII product) and repeated 12 to 24 weeks later at the following timepoints: preinjection and at 30 (±3) minutes (or 10 (±3) minutes), 1 hour (±15 minutes), 6 (±1) hours, 24 (±2) hours (Day 1), 72 (±2) hours (Day 3), 96 (±2) hours (Day 4), and 120 (±2) hours (Day 5) from the start of the injection.

End point type	Primary

End point timeframe:

See endpoint description for complete time frame.

Notes:

[17] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analysis for this endpoint cannot be entered due EudraCT system restrictions for within-group comparison.

End point values	Arm 1: Individualized Prophylaxis: Sequential PK Subgroup			
Subject group type	Subject analysis set			
Number of subjects analysed	28[18]			
Units: hours				
geometric mean (confidence interval 95%)				
rFVIIIFc Baseline	18.97 (17.03 to 21.12)			
Advate	12.43 (11.14 to 13.86)			

Notes:

[18] - Subjects who had evaluable one-stage PK profiles for both Advate and baseline rFVIIIFc.

Statistical analyses

No statistical analyses for this end point

Primary: Clearance (CL; One-stage Clotting Assay)

End point title	Clearance (CL; One-stage Clotting Assay)[19]

End point description:

Rate at which the body removes the drug, measured as the volume of the plasma cleared of drug per

unit time per unit weight. Sampling for Advate PK profiling was conducted, following at least 96 hours of washout, at these timepoints: preinjection and at either 30 (±3) minutes or 10 (±3) minutes, 1 hour (±15 minutes), 6 (±1) hours, 24 (±2) hours (Day 1), 48 (±2) hours (Day 2), and 72 (±2) hours (Day 3) from the start of the injection. Sampling for rFVIIIFc PK profiling was conducted at Day 0 (directly following at least 96 hours washout from Advate PK profiling or within 4 weeks of the Advate dose or other rFVIII product) and repeated 12 to 24 weeks later at the following timepoints: preinjection and at 30 (±3) minutes (or 10 (±3) minutes), 1 hour (±15 minutes), 6 (±1) hours, 24 (±2) hours (Day 1), 72 (±2) hours (Day 3), 96 (±2) hours (Day 4), and 120 (±2) hours (Day 5) from the start of the injection.

End point type	Primary

End point timeframe:

See endpoint description for complete time frame.

Notes:

[19] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analysis for this endpoint cannot be entered due EudraCT system restrictions for within-group comparison.

End point values	Arm 1: Individualized Prophylaxis: Sequential PK Subgroup			
Subject group type	Subject analysis set			
Number of subjects analysed	28[20]			
Units: mL/h/kg				
geometric mean (confidence interval 95%)				
rFVIIIFc Baseline	1.952 (1.713 to 2.224)			
Advate	3.041 (2.711 to 3.412)			

Notes:

[20] - Subjects who had evaluable one-stage PK profiles for both Advate and baseline rFVIIIFc.

Statistical analyses

No statistical analyses for this end point

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

End point title	Mean Residence Time (MRT; One-stage Clotting Assay)[21]

End point description:

The average time that a drug molecule is present in the systemic circulation. Sampling for Advate PK profiling was conducted, following at least 96 hours of washout, at these timepoints: preinjection and at either 30 (±3) minutes or 10 (±3) minutes, 1 hour (±15 minutes), 6 (±1) hours, 24 (±2) hours (Day 1), 48 (±2) hours (Day 2), and 72 (±2) hours (Day 3) from the start of the injection. Sampling for rFVIIIFc PK profiling was conducted at Day 0 (directly following at least 96 hours washout from Advate PK profiling or within 4 weeks of the Advate dose or other rFVIII product) and repeated 12 to 24 weeks later at the following timepoints: preinjection and at 30 (±3) minutes (or 10 (±3) minutes), 1 hour (±15 minutes), 6 (±1) hours, 24 (±2) hours (Day 1), 72 (±2) hours (Day 3), 96 (±2) hours (Day 4), and 120 (±2) hours (Day 5) from the start of the injection.

End point type	Primary

End point timeframe:

See endpoint description for complete time frame.

Notes:

[21] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analysis for this endpoint cannot be entered due EudraCT system restrictions for within-group comparison.

End point values	Arm 1: Individualized Prophylaxis: Sequential PK Subgroup			
Subject group type	Subject analysis set			
Number of subjects analysed	28[22]			
Units: hours				
geometric mean (confidence interval 95%)				
rFVIIIFc Baseline	25.15 (22.65 to 27.91)			
Advate	16.84 (15.22 to 18.63)			

Notes:

[22] - Subjects who had evaluable one-stage PK profiles for both Advate and baseline rFVIIIFc.

Statistical analyses

No statistical analyses for this end point

Primary: Incremental Recovery (One-stage Clotting Assay)

End point title	Incremental Recovery (One-stage Clotting Assay)[23]

End point description:

The rise in FVIII activity in IU/dL per unit dose administered in IU/kg. Sampling for Advate PK profiling was conducted, following at least 96 hours of washout, at these timepoints: preinjection and at either 30 (±3) minutes or 10 (±3) minutes, 1 hour (±15 minutes), 6 (±1) hours, 24 (±2) hours (Day 1), 48 (±2) hours (Day 2), and 72 (±2) hours (Day 3) from the start of the injection. Sampling for rFVIIIFc PK profiling was conducted at Day 0 (directly following at least 96 hours washout from Advate PK profiling or within 4 weeks of the Advate dose or other rFVIII product) and repeated 12 to 24 weeks later at the following timepoints: preinjection and at 30 (±3) minutes (or 10 (±3) minutes), 1 hour (±15 minutes), 6 (±1) hours, 24 (±2) hours (Day 1), 72 (±2) hours (Day 3), 96 (±2) hours (Day 4), and 120 (±2) hours (Day 5) from the start of the injection.

End point type	Primary

End point timeframe:

See endpoint description for complete time frame.

Notes:

[23] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analysis for this endpoint cannot be entered due EudraCT system restrictions for within-group comparison.

End point values	Arm 1: Individualized Prophylaxis: Sequential PK Subgroup			
Subject group type	Subject analysis set			
Number of subjects analysed	28[24]			
Units: IU/dL per IU/kg				
geometric mean (confidence interval 95%)				
rFVIIIFc Baseline	2.2395 (2.1116 to 2.3753)			
Advate	2.3516 (2.211 to 2.501)			

Notes:

[24] - Subjects who had evaluable one-stage PK profiles for both Advate and baseline rFVIIIFc.

Statistical analyses

No statistical analyses for this end point

Secondary: Comparison of Annualized Bleeding Rates: Arm 2 Versus Arm 3

End point title	Comparison of Annualized Bleeding Rates: Arm 2 Versus Arm

End point description:

Estimated using the negative binomial model with treatment arm as covariate, based on whole study duration for all subjects. Annualized bleeding episodes = (number of bleeding episodes / number of days in the respective period)*365.25.The efficacy period in Arm 2 began with the first prophylactic dose of rFVIIIFc and ended with the last dose (regardless of reason for dosing). The efficacy period in Arm 3 began at the time of last PK rFVIIIFc sampling timepoint and ended at the date of the last study visit. Periods of PK evaluations and surgery/rehabilitation are not included in the efficacy period. A bleeding episode started from the first sign of a bleed, and ended 72 hours after the last treatment for the bleeding, within which any symptoms of bleeding at the same location, or injections less than or equal to 72 hours apart, were considered the same bleeding episode. Full Analysis Set: subjects who received at least 1 dose of rFVIIIFc with an efficacy assessment.

End point type	Secondary

End point timeframe:

up to 52 weeks ± 2 weeks (efficacy period as defined in description)

Notes:

[25] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Per protocol, Arm 1 versus Arm 3 only was analyzed as a primary endpoint. Arm 2 versus Arm 3 only was analyzed as a secondary endpoint. Both are included in this record.

End point values	Arm 2: Weekly Prophylaxis	Arm 3: Episodic (On-Demand) Dosing		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	23		
Units: episodes per subject per year				
number (confidence interval 95%)	8.92 (5.48 to 14.51)	37.25 (24.03 to 57.74)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Arm 2: Weekly Prophylaxis v Arm 3: Episodic (On-Demand) Dosing

Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	negative binomial model
Parameter estimate	Bleeding Rate Ratio
Point estimate	0.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.12
upper limit	0.46

Secondary: Annualized rFVIIIFc Consumption Per Subject

End point title	Annualized rFVIIIFc Consumption Per Subject

End point description:

Consumption is calculated for the efficacy period. The efficacy period in Arms 1 and 2 began with the first prophylactic dose of rFVIIIFc and ended with the last dose (regardless of reason for dosing). The efficacy period in Arm 3 began at the time of last PK rFVIIIFc sampling timepoint and ended at the date of the last study visit. Periods of PK evaluations and surgery/rehabilitation are not included in the efficacy period. Overall units (IU/kg) of annualized rFVIIIFc consumption = [Total rFVIIIFc IU/kg received during the efficacy period / number of days in efficacy period] x 365.25. Full Analysis Set: subjects who received at least 1 dose of rFVIIIFc. 'Overall' n=subjects in the Full Analysis Set with evaluable data in the efficacy period; 'Last 3 Months on Study' n=subjects in the Full Analysis Set with evaluable data and >=6 months on study.

End point type	Secondary

End point timeframe:

up to 52 weeks ± 2 weeks (efficacy period as defined in description)

End point values	Arm 1: Individualized (Tailored) Prophylaxis	Arm 2: Weekly Prophylaxis	Arm 3: Episodic (On-Demand) Dosing	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	117	24	23	
Units: IU/kg rFVIIIFc per subject per year				
arithmetic mean (standard deviation)				
Overall; n=117, 23, 23	4631.98 (± 1041.608)	4003.69 (± 652.573)	1304.36 (± 874.361)	
Last 3 months on study; n=112, 16, 18	4868.35 (± 1365.108)	3882.89 (± 583.344)	1225.8 (± 848.656)	

Statistical analyses

No statistical analyses for this end point

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

Episode

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

End point description:

Subject's assessment of the response to the first rFVIIIFc injection for each bleeding episode. Percentages were based on the number of bleeding episodes for which a response was provided for the first injection, using the following 4-point scale: excellent; good; moderate; no response. Full Analysis Set: subjects who received at least 1 dose of rFVIIIFc and had at least 1 evaluable bleeding episode; based on the number of injections with an evaluation.

End point type	Secondary

End point timeframe:

up to 52 weeks ± 2 weeks

End point values	Arm 1: Individualized (Tailored) Prophylaxis	Arm 2: Weekly Prophylaxis	Arm 3: Episodic (On-Demand) Dosing	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	63[26]	19[27]	23[28]	
Units: percentage of responses				
number (not applicable)				
Excellent or Good	79.7	64	80.2	
Excellent	33.7	18	30.8	
Good	46	46.1	49.3	
Moderate	18.8	34.8	19.6	
No Response	1.5	1.1	0.2	

Notes:

[26] - Number of bleeding episodes analyzed=202

[27] - Number of bleeding episodes analyzed=89

[28] - Number of bleeding episodes analyzed=454

Statistical analyses

No statistical analyses for this end point

Secondary: Investigator's Assessment of Subjects' Bleeding Response to rFVIIIFc Injection

End point title	Investigator's Assessment of Subjects' Bleeding Response to rFVIIIFc Injection

End point description:

The investigator was given the opportunity to record an assessment of a subject’s response to treatment, if the subject was treated in the hospital for a major bleed, using the following 4-point scale: excellent; good; moderate; no response.

End point type	Secondary

End point timeframe:

up to 52 weeks ± 2 weeks

End point values	Arm 1: Individualized (Tailored) Prophylaxis	Arm 2: Weekly Prophylaxis	Arm 3: Episodic (On-Demand) Dosing	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[29]	0[30]	0[31]	
Units: percentage of responses				
number (not applicable)				

Notes:

[29] - This supplemental assessment was not summarized because of insufficient data.

[30] - This supplemental assessment was not summarized because of insufficient data.

[31] - This supplemental assessment was not summarized because of insufficient data.

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized Bleeding Rate by Location of Bleed (Joint, Muscle, Internal, Skin/Mucosa)

End point title	Annualized Bleeding Rate by Location of Bleed (Joint, Muscle, Internal, Skin/Mucosa)

End point description:

Annualized bleeding episodes = (Number of bleeding episodes at the specified location / number of days in efficacy period) x 365.25. The efficacy period in Arms 1 and 2 began with the first prophylactic dose of rFVIIIFc and ended with the last dose (regardless of reason for dosing). The efficacy period in Arm 3 began at the time of last PK rFVIIIFc sampling timepoint and ended at the date of the last study visit. Periods of PK evaluations and surgery/rehabilitation were not included in the efficacy period. A bleeding episode started from the first sign of a bleed, and ended 72 hours after the last treatment for the bleeding, within which any symptoms of bleeding at the same location, or injections less than or equal to 72 hours apart, were considered the same bleeding episode. Any bleeding at a different location was a separate bleeding episode regardless of time from the last injection. Full Analysis Set: subjects who received at least 1 dose of rFVIIIFc with evaluable data.

End point type	Secondary

End point timeframe:

up to 52 weeks ± 2 weeks (efficacy period as defined in description)

End point values	Arm 1: Individualized (Tailored) Prophylaxis	Arm 2: Weekly Prophylaxis	Arm 3: Episodic (On-Demand) Dosing	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	117	23	23	
Units: episodes per subject per year				
median (inter-quartile range (Q1-Q3))				
Joint	0 (0 to 3.11)	1.93 (0 to 7.62)	22.76 (15.07 to 39.02)	
Muscle	0 (0 to 0)	0 (0 to 2.01)	5.57 (1.86 to 10.05)	
Internal	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)	
Soft Tissue	0 (0 to 0)	0 (0 to 0)	0 (0 to 1.86)	
Skin/Mucosa	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)	

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized Joint Bleeding Rate (Spontaneous and Traumatic)

End point title	Annualized Joint Bleeding Rate (Spontaneous and Traumatic)

End point description:

Annualized bleeding episodes = (Number of bleeding episodes of the specified type / number of days in efficacy period) x 365.25. The efficacy period in Arms 1 and 2 began with the first prophylactic dose of rFVIIIFc and ended with the last dose (regardless of reason for dosing). The efficacy period in Arm 3 began at the time of last PK rFVIIIFc sampling timepoint and ended at the date of the last study visit. Periods of PK evaluations and surgery/rehabilitation were not included in the efficacy period. A bleeding episode started from the first sign of a bleed, and ended 72 hours after the last treatment for the bleeding, within which any symptoms of bleeding at the same location, or injections less than or equal to 72 hours apart, were considered the same bleeding episode. Full Analysis Set: subjects who received at least 1 dose of rFVIIIFc with evaluable data.

End point type	Secondary

End point timeframe:

up to 52 weeks ± 2 weeks (efficacy period as defined in description)

End point values	Arm 1: Individualized (Tailored) Prophylaxis	Arm 2: Weekly Prophylaxis	Arm 3: Episodic (On-Demand) Dosing	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	117	23	23	
Units: bleeding episodes per subject per year				
median (inter-quartile range (Q1-Q3))				
Spontaneous	0 (0 to 1.73)	0 (0 to 3.81)	18.59 (7.59 to 29.59)	
Traumatic	0 (0 to 1.16)	0 (0 to 2.01)	3.93 (0 to 8.56)	
Unknown	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)	

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

Number of days from the last injection to treat a bleeding episode to a new bleeding episode, analyzed for per evaluable bleeding episode and per subject. For "per subject" values, number of days from last injection to treat a bleed to a new bleeding episode is averaged across all evaluable bleeding episodes for each subject first, and then descriptive statistics were calculated across subjects. A follow-up injection administered >72 hours after the most recent injection given to treat a bleed was considered a new bleed at the same location and was classified as type=Unknown (not evaluable). Please see the endpoint "Annualized Bleeding Rate" for a definition of the efficacy period. Full Analysis Set: subjects who received at least 1 dose of rFVIIIFc and had at least 1 evaluable bleeding episode. The first bleed for each subject could not be included in this analysis since there was no previous bleed from which to

measure time.

End point type	Secondary

End point timeframe:

up to 52 weeks ± 2 weeks (efficacy period as defined in description).

End point values	Arm 1: Individualized (Tailored) Prophylaxis	Arm 2: Weekly Prophylaxis	Arm 3: Episodic (On-Demand) Dosing	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	48[32]	12[33]	23[34]	
Units: days				
median (inter-quartile range (Q1-Q3))				
Per bleeding episode	19.83 (8.58 to 55.46)	8 (5.35 to 15.38)	6.55 (4.46 to 10.27)	
Per subject	42.9 (20.25 to 65.93)	40.71 (11.75 to 52.39)	10.12 (7.42 to 16.37)	

Notes:

[32] - Number of evaluable bleeding episodes analyzed=149

[33] - Number of evaluable bleeding episodes analyzed=76

[34] - Number of evaluable bleeding episodes analyzed=430

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

A bleeding episode started from the first sign of a bleed, and ended 72 hours after the last treatment for the bleeding, within which any symptoms of bleeding at the same location, or injections less than or equal to 72 hours apart, were considered the same bleeding episode. All injections given from the initial sign of a bleed until the last date/time within the bleed window are counted. The resolution of a bleed is defined as no sign of bleeding following injection for the bleed. The efficacy period in Arms 1 and 2 began with the first prophylactic dose of rFVIIIFc and ended with the last dose (regardless of reason for dosing). The efficacy period in Arm 3 began at the time of last PK rFVIIIFc sampling timepoint and ended at the date of the last study visit. Periods of PK evaluations and surgery/rehabilitation are not included in the efficacy period. Full Analysis Set: subjects who received at least 1 dose of rFVIIIFc and had at least 1 bleeding episode.

End point type	Secondary

End point timeframe:

up to 52 weeks ± 2 weeks (efficacy period as defined in description)

End point values	Arm 1: Individualized (Tailored) Prophylaxis	Arm 2: Weekly Prophylaxis	Arm 3: Episodic (On-Demand) Dosing	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	64[35]	19[36]	23[37]	
Units: injections				

median (inter-quartile range (Q1-Q3))				
Per bleeding episode	1 (1 to 1)	1 (1 to 1)	1 (1 to 1)	
Per subject	1 (1 to 1.33)	1 (1 to 1.43)	1.03 (1 to 1.17)	

Notes:

[35] - Number of bleeding episodes analyzed=209

[36] - Number of bleeding episodes analyzed=92

[37] - Number of bleeding episodes analyzed=456

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Injections Required for Resolution of a Bleeding Episode by Location of Bleed

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

End point description:

Please see previous Endpoint for a definition of the efficacy period. A bleeding episode started from the first sign of a bleed, and ended 72 hours after the last treatment for the bleeding, within which any symptoms of bleeding at the same location, or injections less than or equal to 72 hours apart, were considered the same bleeding episode. All injections given from the initial sign of a bleed until the last date/time within the bleed window were counted. The resolution of a bleed was defined as no sign of bleeding following injection for the bleed. Bleeding episodes that presented in multiple locations are included as a single event in the overall summary for the number of injections to resolve that bleeding episode but are included in summaries for each location. Full Analysis Set: subjects who received at least 1 dose of rFVIIIFc and had evaluable efficacy assessments; n=total number of bleeds at given location.

End point type	Secondary

End point timeframe:

up to 52 weeks ± 2 weeks (efficacy period as defined in description)

End point values	Arm 1: Individualized (Tailored) Prophylaxis	Arm 2: Weekly Prophylaxis	Arm 3: Episodic (On-Demand) Dosing	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	64	19	23	
Units: injections				
median (inter-quartile range (Q1-Q3))				
Joint; n=151, 67, 366	1 (1 to 1)	1 (1 to 1)	1 (1 to 1)	
Muscle; n=35, 23, 82	1 (1 to 1)	1 (1 to 1)	1 (1 to 1)	
Soft Tissue; n=24, 5, 25	1 (1 to 1)	1 (1 to 2)	1 (1 to 1)	
Internal; n=3, 2, 6	1 (1 to 1)	1 (1 to 1)	1 (1 to 1)	
Skin/Mucosa; n=11, 6, 8	1 (1 to 1)	1 (1 to 1)	1 (1 to 1)	

Statistical analyses

No statistical analyses for this end point

Secondary: Total Dose Per Injection Required for Resolution of a Bleeding Episode

by Location of Bleed

End point title	Total Dose Per Injection Required for Resolution of a Bleeding Episode by Location of Bleed

End point description:

For each bleeding episode at one location, the total dose is the sum of the doses (IU/kg) administered across all injections given to treat that bleeding episode. Please see the above Endpoint for a definition of the efficacy period. A bleeding episode started from the first sign of a bleed, and ended 72 hours after the last treatment for the bleeding, within which any symptoms of bleeding at the same location, or injections less than or equal to 72 hours apart, were considered part of the same bleeding episode. Bleeding episodes that presented in multiple locations are included as a single event in the overall summary for dose administered to resolve that bleeding episode but are included in the individual summaries for each location. Full Analysis Set: subjects who received at least 1 dose of rFVIIIFc and had complete information on the dose administered to treat a bleeding episode; n=total number of bleeding episodes at this location.

End point type	Secondary

End point timeframe:

up to 52 weeks ± 2 weeks (efficacy period as defined in description)

End point values	Arm 1: Individualized (Tailored) Prophylaxis	Arm 2: Weekly Prophylaxis	Arm 3: Episodic (On-Demand) Dosing	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	63	19	23	
Units: IU/kg				
median (inter-quartile range (Q1-Q3))				
Joint; n=151, 67, 366	29.69 (24.1 to 53.44)	28.23 (20.16 to 40.32)	27.35 (22.73 to 39.22)	
Muscle; n=35, 23, 82	40.98 (26.79 to 53.1)	32.12 (26.98 to 32.47)	27.78 (23.47 to 31.01)	
Soft Tissue; n=23, 5, 25	30.6 (24.51 to 53.13)	51.88 (20.16 to 54.88)	27.78 (23.44 to 31.45)	
Internal; n=3, 2, 6	32.63 (23.39 to 51.72)	58.4 (48.08 to 68.73)	32.54 (30 to 49.18)	
Skin/Mucosa; n=11, 6, 8	33.9 (28.23 to 53.19)	28.34 (21.65 to 44.35)	21.37 (19.95 to 25.16)	

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

Volume of distribution at steady state. Sampling for Advate PK profiling was conducted, following at least 96 hours of washout, at these timepoints: preinjection and at either 30 (±3) minutes or 10 (±3) minutes, 1 hour (±15 minutes), 6 (±1) hours, 24 (±2) hours (Day 1), 48 (±2) hours (Day 2), and 72 (±2) hours (Day 3) from the start of the injection. Sampling for rFVIIIFc PK profiling was conducted at Day 0 (directly following at least 96 hours washout from Advate PK profiling or within 4 weeks of the Advate dose or other rFVIII product) and repeated 12 to 24 weeks later at the following timepoints: preinjection and at 30 (±3) minutes (or 10 (±3) minutes), 1 hour (±15 minutes), 6 (±1) hours, 24 (±2) hours (Day 1), 72 (±2) hours (Day 3), 96 (±2) hours (Day 4), and 120 (±2) hours (Day 5) from the start of the injection.

End point type	Secondary

End point timeframe:

See endpoint description for complete time frame.

End point values	Arm 1: Individualized Prophylaxis: Sequential PK Subgroup			
Subject group type	Subject analysis set			
Number of subjects analysed	28[38]			
Units: mL/kg				
geometric mean (confidence interval 95%)				
rFVIIIFc Baseline	49.1 (46.6 to 51.7)			
Advate	51.2 (47.2 to 55.5)			

Notes:

[38] - Subjects who had evaluable one-stage PK profiles for both Advate and baseline rFVIIIFc.

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

Volume of distribution at steady state. Sampling for Advate PK profiling was conducted, following at least 96 hours of washout, at these timepoints: preinjection and at either 30 (±3) minutes or 10 (±3) minutes, 1 hour (±15 minutes), 6 (±1) hours, 24 (±2) hours (Day 1), 48 (±2) hours (Day 2), and 72 (±2) hours (Day 3) from the start of the injection. Sampling for rFVIIIFc PK profiling was conducted at Day 0 (directly following at least 96 hours washout from Advate PK profiling or within 4 weeks of the Advate dose or other rFVIII product) and repeated 12 to 24 weeks later at the following timepoints: preinjection and at 30 (±3) minutes (or 10 (±3) minutes), 1 hour (±15 minutes), 6 (±1) hours, 24 (±2) hours (Day 1), 72 (±2) hours (Day 3), 96 (±2) hours (Day 4), and 120 (±2) hours (Day 5) from the start of the injection.

End point type	Secondary

End point timeframe:

See endpoint description for complete time frame.

End point values	Arm 1: Individualized Prophylaxis: Sequential PK Subgroup			
Subject group type	Subject analysis set			
Number of subjects analysed	27[39]			
Units: mL/kg				
geometric mean (confidence interval 95%)				

rFVIIIFc Baseline Advate	52.6 (47.4 to 58.3) 56.8 (51.5 to 62.7)			

Notes:

[39] - Subjects who had evaluable two-stage PK profiles for both Advate and baseline rFVIIIFc.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to 1% and 3% FVIII Activity (One-stage Clotting Assay)

End point title	Time to 1% and 3% FVIII Activity (One-stage Clotting Assay)

End point description:

Estimated time after dose (in days) when FVIII activity has declined to approximately 1 or 3 IU/dL (1% or 3%) above baseline, respectively. Sampling for Advate PK profiling was conducted, following at least 96 hours of washout, at these timepoints: preinjection and at either 30 (±3) minutes or 10 (±3) minutes, 1 hour (±15 minutes), 6 (±1) hours, 24 (±2) hours (Day 1), 48 (±2) hours (Day 2), and 72 (±2) hours (Day 3) from the start of the injection. Sampling for rFVIIIFc PK profiling was conducted at Day 0 (directly following at least 96 hours washout from Advate PK profiling or within 4 weeks of the Advate dose or other rFVIII product) and repeated 12 to 24 weeks later at the following timepoints: preinjection and at 30 (±3) minutes (or 10 (±3) minutes), 1 hour (±15 minutes), 6 (±1) hours, 24 (±2) hours (Day 1), 72 (±2) hours (Day 3), 96 (±2) hours (Day 4), and 120 (±2) hours (Day 5) from the start of the injection.

End point type	Secondary

End point timeframe:

See endpoint description for complete time frame.

End point values	Arm 1: Individualized Prophylaxis: Sequential PK Subgroup			
Subject group type	Subject analysis set			
Number of subjects analysed	28[40]			
Units: days				
geometric mean (confidence interval 95%)				
Advate: Time 1%	3.298 (2.985 to 3.645)			
Advate: Time 3%	2.478 (2.242 to 2.738)			
rFVIIIFc Baseline: Time 1%	4.918 (4.434 to 5.455)			
rFVIIIFc Baseline: Time 3%	3.707 (3.325 to 4.133)			

Notes:

[40] - Subjects who had evaluable one-stage PK profiles for both Advate and baseline rFVIIIFc.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to 1% and 3% FVIII Activity (Two-stage Chromogenic Assay)

End point title	Time to 1% and 3% FVIII Activity (Two-stage Chromogenic Assay)

End point description:

Estimated time after dose (in days) when FVIII activity has declined to approximately 1 or 3 IU/dL (1% or 3%) above baseline, respectively. Sampling for Advate PK profiling was conducted, following at least 96 hours of washout, at these timepoints: preinjection and at either 30 (±3) minutes or 10 (±3) minutes, 1 hour (±15 minutes), 6 (±1) hours, 24 (±2) hours (Day 1), 48 (±2) hours (Day 2), and 72 (±2) hours (Day 3) from the start of the injection. Sampling for rFVIIIFc PK profiling was conducted at Day 0 (directly following at least 96 hours washout from Advate PK profiling or within 4 weeks of the Advate dose or other rFVIII product) and repeated 12 to 24 weeks later at the following timepoints: preinjection and at 30 (±3) minutes (or 10 (±3) minutes), 1 hour (±15 minutes), 6 (±1) hours, 24 (±2) hours (Day 1), 72 (±2) hours (Day 3), 96 (±2) hours (Day 4), and 120 (±2) hours (Day 5) from the start of the injection.

End point type	Secondary

End point timeframe:

See endpoint description for complete time frame.

End point values	Arm 1: Individualized Prophylaxis: Sequential PK Subgroup			
Subject group type	Subject analysis set			
Number of subjects analysed	27[41]			
Units: days				
geometric mean (confidence interval 95%)				
Advate: Time 1%	3.22 (2.97 to 3.491)			
Advate: Time 3%	2.306 (2.12 to 2.509)			
rFVIIIFc Baseline: Time 1%	5.01 (4.525 to 5.548)			
rFVIIIFc Baseline: Time 3%	3.612 (3.25 to 4.015)			

Notes:

[41] - Subjects who had evaluable two-stage PK profiles for both Advate and baseline rFVIIIFc.

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

Time at which maximum activity (Cmax) is observed. Sampling for Advate PK profiling was conducted, following at least 96 hours of washout, at these timepoints: preinjection and at either 30 (±3) minutes or 10 (±3) minutes, 1 hour (±15 minutes), 6 (±1) hours, 24 (±2) hours (Day 1), 48 (±2) hours (Day 2), and 72 (±2) hours (Day 3) from the start of the injection. Sampling for rFVIIIFc PK profiling was conducted at Day 0 (directly following at least 96 hours washout from Advate PK profiling or within 4 weeks of the Advate dose or other rFVIII product) and repeated 12 to 24 weeks later at the following timepoints: preinjection and at 30 (±3) minutes (or 10 (±3) minutes), 1 hour (±15 minutes), 6 (±1) hours, 24 (±2) hours (Day 1), 72 (±2) hours (Day 3), 96 (±2) hours (Day 4), and 120 (±2) hours (Day 5) from the start of the injection.

End point type	Secondary

End point timeframe:

See endpoint description for complete time frame.

End point values	Arm 1: Individualized Prophylaxis: Sequential PK Subgroup			
Subject group type	Subject analysis set			
Number of subjects analysed	28[42]			
Units: hours				
geometric mean (confidence interval 95%)				
rFVIIIFc Baseline	0.49 (0.37 to 0.63)			
Advate	0.48 (0.33 to 0.68)			

Notes:

[42] - Subjects who had evaluable one-stage PK profiles for both Advate and baseline rFVIIIFc.

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

Time at which the maximum activity (Cmax) is observed. Sampling for Advate PK profiling was conducted, following at least 96 hours of washout, at these timepoints: preinjection and at either 30 (±3) minutes or 10 (±3) minutes, 1 hour (±15 minutes), 6 (±1) hours, 24 (±2) hours (Day 1), 48 (±2) hours (Day 2), and 72 (±2) hours (Day 3) from the start of the injection. Sampling for rFVIIIFc PK profiling was conducted at Day 0 (directly following at least 96 hours washout from Advate PK profiling or within 4 weeks of the Advate dose or other rFVIII product) and repeated 12 to 24 weeks later at the following timepoints: preinjection and at 30 (±3) minutes (or 10 (±3) minutes), 1 hour (±15 minutes), 6 (±1) hours, 24 (±2) hours (Day 1), 72 (±2) hours (Day 3), 96 (±2) hours (Day 4), and 120 (±2) hours (Day 5) from the start of the injection.

End point type	Secondary

End point timeframe:

See endpoint description for complete time frame.

End point values	Arm 1: Individualized Prophylaxis: Sequential PK Subgroup			
Subject group type	Subject analysis set			
Number of subjects analysed	27[43]			
Units: hours				
geometric mean (confidence interval 95%)				

rFVIIIFc Baseline Advate	0.55 (0.41 to 0.75) 0.46 (0.35 to 0.61)			

Notes:

[43] - Subjects who had evaluable two-stage PK profiles for both Advate and baseline rFVIIIFc.

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Curve (AUC) Per Dose (Two-stage Chromogenic Assay)

End point title	Area Under the Curve (AUC) Per Dose (Two-stage Chromogenic Assay)

End point description:

Dose normalized area under the drug concentration-time curve. Sampling for Advate PK profiling was conducted, following at least 96 hours of washout, at these timepoints: preinjection and at either 30 (±3) minutes or 10 (±3) minutes, 1 hour (±15 minutes), 6 (±1) hours, 24 (±2) hours (Day 1), 48 (±2) hours (Day 2), and 72 (±2) hours (Day 3) from the start of the injection. Sampling for rFVIIIFc PK profiling was conducted at Day 0 (directly following at least 96 hours washout from Advate PK profiling or within 4 weeks of the Advate dose or other rFVIII product) and repeated 12 to 24 weeks later at the following timepoints: preinjection and at 30 (±3) minutes (or 10 (±3) minutes), 1 hour (±15 minutes), 6 (±1) hours, 24 (±2) hours (Day 1), 72 (±2) hours (Day 3), 96 (±2) hours (Day 4), and 120 (±2) hours (Day 5) from the start of the injection.

End point type	Secondary

End point timeframe:

See endpoint description for complete time frame.

End point values	Arm 1: Individualized Prophylaxis: Sequential PK Subgroup			
Subject group type	Subject analysis set			
Number of subjects analysed	27[44]			
Units: IU*h/dL per IU/kg				
geometric mean (confidence interval 95%)				
rFVIIIFc Baseline Advate	47.45 (41.55 to 54.18) 28.05 (24.85 to 31.65)			

Notes:

[44] - Subjects who had evaluable two-stage PK profiles for both Advate and baseline rFVIIIFc.

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

Time required for the activity of the drug to reach half of its original value. Sampling for Advate PK

profiling was conducted, following at least 96 hours of washout, at these timepoints: preinjection and at either 30 (±3) minutes or 10 (±3) minutes, 1 hour (±15 minutes), 6 (±1) hours, 24 (±2) hours (Day 1), 48 (±2) hours (Day 2), and 72 (±2) hours (Day 3) from the start of the injection. Sampling for rFVIIIFc PK profiling was conducted at Day 0 (directly following at least 96 hours washout from Advate PK profiling or within 4 weeks of the Advate dose or other rFVIII product) and repeated 12 to 24 weeks later at the following timepoints: preinjection and at 30 (±3) minutes (or 10 (±3) minutes), 1 hour (±15 minutes), 6 (±1) hours, 24 (±2) hours (Day 1), 72 (±2) hours (Day 3), 96 (±2) hours (Day 4), and 120 (±2) hours (Day 5) from the start of the injection.

End point type	Secondary

End point timeframe:

See endpoint description for complete time frame.

End point values	Arm 1: Individualized Prophylaxis: Sequential PK Subgroup			
Subject group type	Subject analysis set			
Number of subjects analysed	27[45]			
Units: hours				
geometric mean (confidence interval 95%)				
rFVIIIFc Baseline	20.89 (18.23 to 23.93)			
Advate	13.67 (12.31 to 15.18)			

Notes:

[45] - Subjects who had evaluable two-stage PK profiles for both Advate and baseline rFVIIIFc.

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

Rate at which the body removes the drug, measured as the volume of the plasma cleared of drug per unit time per unit weight. Sampling for Advate PK profiling was conducted, following at least 96 hours of washout, at these timepoints: preinjection and at either 30 (±3) minutes or 10 (±3) minutes, 1 hour (±15 minutes), 6 (±1) hours, 24 (±2) hours (Day 1), 48 (±2) hours (Day 2), and 72 (±2) hours (Day 3) from the start of the injection. Sampling for rFVIIIFc PK profiling was conducted at Day 0 (directly following at least 96 hours washout from Advate PK profiling or within 4 weeks of the Advate dose or other rFVIII product) and repeated 12 to 24 weeks later at the following timepoints: preinjection and at 30 (±3) minutes (or 10 (±3) minutes), 1 hour (±15 minutes), 6 (±1) hours, 24 (±2) hours (Day 1), 72 (±2) hours (Day 3), 96 (±2) hours (Day 4), and 120 (±2) hours (Day 5) from the start of the injection.

End point type	Secondary

End point timeframe:

See endpoint description for complete time frame.

End point values	Arm 1: Individualized Prophylaxis: Sequential PK Subgroup			
Subject group type	Subject analysis set			
Number of subjects analysed	27[46]			
Units: mL/h/kg				
geometric mean (confidence interval 95%)				
rFVIIIFc Baseline	2.108 (1.846 to 2.407)			
Advate	3.566 (3.159 to 4.024)			

Notes:

[46] - Subjects who had evaluable two-stage PK profiles for both Advate and baseline rFVIIIFc.

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

The average time that a drug molecule is present in the systemic circulation. Sampling for Advate PK profiling was conducted, following at least 96 hours of washout, at these timepoints: preinjection and at either 30 (±3) minutes or 10 (±3) minutes, 1 hour (±15 minutes), 6 (±1) hours, 24 (±2) hours (Day 1), 48 (±2) hours (Day 2), and 72 (±2) hours (Day 3) from the start of the injection. Sampling for rFVIIIFc PK profiling was conducted at Day 0 (directly following at least 96 hours washout from Advate PK profiling or within 4 weeks of the Advate dose or other rFVIII product) and repeated 12 to 24 weeks later at the following timepoints: preinjection and at 30 (±3) minutes (or 10 (±3) minutes), 1 hour (±15 minutes), 6 (±1) hours, 24 (±2) hours (Day 1), 72 (±2) hours (Day 3), 96 (±2) hours (Day 4), and 120 (±2) hours (Day 5) from the start of the injection.

End point type	Secondary

End point timeframe:

See endpoint description for complete time frame.

End point values	Arm 1: Individualized Prophylaxis: Sequential PK Subgroup			
Subject group type	Subject analysis set			
Number of subjects analysed	27[47]			
Units: hours				
geometric mean (confidence interval 95%)				
rFVIIIFc Baseline	24.96 (22.41 to 27.8)			
Advate	15.94 (14.7 to 17.27)			

Notes:

[47] - Subjects who had evaluable two-stage PK profiles for both Advate and baseline rFVIIIFc.

Statistical analyses

No statistical analyses for this end point

Secondary: Incremental Recovery (Two-stage Chromogenic Assay)

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

End point description:

The rise in FVIII activity in IU/dL per unit dose administered in IU/kg. Sampling for Advate PK profiling was conducted, following at least 96 hours of washout, at these timepoints: preinjection and at either 30 (±3) minutes or 10 (±3) minutes, 1 hour (±15 minutes), 6 (±1) hours, 24 (±2) hours (Day 1), 48 (±2) hours (Day 2), and 72 (±2) hours (Day 3) from the start of the injection. Sampling for rFVIIIFc PK profiling was conducted at Day 0 (directly following at least 96 hours washout from Advate PK profiling or within 4 weeks of the Advate dose or other rFVIII product) and repeated 12 to 24 weeks later at the following timepoints: preinjection and at 30 (±3) minutes (or 10 (±3) minutes), 1 hour (±15 minutes), 6 (±1) hours, 24 (±2) hours (Day 1), 72 (±2) hours (Day 3), 96 (±2) hours (Day 4), and 120 (±2) hours (Day 5) from the start of the injection.

End point type	Secondary

End point timeframe:

See endpoint description for complete time frame.

End point values	Arm 1: Individualized Prophylaxis: Sequential PK Subgroup			
Subject group type	Subject analysis set			
Number of subjects analysed	27[48]			
Units: IU/dL per IU/kg				
geometric mean (confidence interval 95%)				
rFVIIIFc Baseline	2.4912 (2.2762 to 2.7265)			
Advate	2.5589 (2.3247 to 2.8168)			

Notes:

[48] - Subjects who had evaluable two-stage PK profiles for both Advate and baseline rFVIIIFc.

Statistical analyses

No statistical analyses for this end point

Secondary: Hemophilia-Specific Quality of Life Index for Adults (Haem-A-QoL) Questionnaire: Change From Baseline to Week 14

End point title	Hemophilia-Specific Quality of Life Index for Adults (Haem-A-QoL) Questionnaire: Change From Baseline to Week 14[49]

End point description:

The Haem-A-QoL consists of items pertaining to 10 domains specific to living with hemophilia and was administered to adult subjects (17 years and older). The 10 domains are: physical health, feeling, view of yourself, sports/leisure, school/work, dealing with hemophilia, and treatment (time frame for all 7 domains, during the last month) and future, family planning, and outlook for the future (time frame for all 3 domains, recently). Lower scores represent better QoL; therefore, a negative change from baseline represents improvement during the course of the study. Scores on a scale range between 0 and 100. Subjects in Arm 1 were stratified by their prestudy regimen (either prophylaxis or on demand). Full Analysis Set: subjects over 17 years of age who received at least 1 dose of rFVIIIFc and had an

assessment; n=subjects who had specified assessment at given timepoint.

End point type	Secondary

End point timeframe:

Baseline, Week 14

Notes:

[49] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: For this endpoint, the Individualized Prophylaxis arm (Arm 1) is broken down by the subject's prestudy treatment regimen (either Prestudy Prophylaxis or Prestudy On-demand). Both are presented here.

End point values	Arm 2: Weekly Prophylaxis	Arm 3: Episodic (On-Demand) Dosing	Arm 1: Individualized Prophylaxis, Prestudy Prophylaxis	Arm 1: Individualized Prophylaxis, Prestudy On-demand
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	15	17	69	22
Units: units on a scale				
median (full range (min-max))				
Total Score; n=57, 17, 14, 14	-4.73 (-30.5 to 3.2)	-2.09 (-25.1 to 5.4)	-2.18 (-25 to 20.9)	-1.48 (-28.6 to 5.1)
Physical Health; n=68, 22, 15, 17	-10 (-40 to 10)	0 (-55 to 40)	-5 (-70 to 75)	-12.5 (-42.5 to 45)
Feeling; n=68, 22, 15, 17	-6.25 (-50 to 6.3)	-6.25 (-37.5 to 6.3)	0 (-43.8 to 43.8)	-6.25 (-37.5 to 12.5)
View of Yourself; n=68, 22, 15, 17	0 (-30 to 15)	-5 (-40 to 20)	0 (-70 to 25)	5 (-30 to 25)
Sports and Leisure; n=48, 12, 12, 8	-10 (-30 to 0)	-2.5 (-30 to 15)	0 (-55 to 40)	-2.5 (-25 to 18.8)
Work and School; n=53, 17,13, 14	0 (-31.3 to 39.6)	0 (-58.3 to 12.5)	-6.25 (-56.3 to 25)	-6.25 (-37.5 to 25)
Dealing with Hemophilia; n=65, 22, 15, 17	0 (-25 to 41.7)	0 (-50 to 100)	0 (-33.3 to 50)	0 (-25 to 16.7)
Treatment; n=68, 21, 15, 16	-3.13 (-31.3 to 18.8)	0 (-21.9 to 18.8)	-3.13 (-37.1 to 21.9)	-3.13 (-43.8 to 31.3)
Future; n=66, 21, 15, 17	-5 (-35 to 15)	-5 (-55 to 25)	2.5 (-35 to 25)	0 (-30 to 55)
Family Planning; n=38, 10, 8, 7	0 (-50 to 8.3)	-2.08 (-31.3 to 0)	0 (-31.3 to 18.8)	0 (-18.8 to 31.3)
Partnership and Sexuality; n=62, 20, 15, 17	0 (-41.7 to 0)	0 (-100 to 25)	0 (-25 to 41.7)	0 (-25 to 58.3)

Statistical analyses

No statistical analyses for this end point

Secondary: Hemophilia-Specific Quality of Life Index for Adults (Haem-A-QoL) Questionnaire: Change From Baseline to Week 28

End point title	Hemophilia-Specific Quality of Life Index for Adults (Haem-A-QoL) Questionnaire: Change From Baseline to Week 28[50]

End point description:

The Haem-A-QoL consists of items pertaining to 10 domains specific to living with hemophilia and was administered to adult subjects (17 years and older). The 10 domains are: physical health, feeling, view of yourself, sports/leisure, school/work, dealing with hemophilia, and treatment (time frame for all 7 domains, during the last month) and future, family planning, and outlook for the future (time frame for all 3 domains, recently). Lower scores represent better QoL; therefore, a negative change from baseline

represents improvement during the course of the study. Scores on a scale range between 0 and 100. Subjects in Arm 1 were stratified by their prestudy regimen (either prophylaxis or on demand). Full Analysis Set: subjects over 17 years of age who received at least 1 dose of rFVIIIFc and had an assessment; n=subjects who had specified assessment at given timepoint.

End point type	Secondary

End point timeframe:

Baseline, Week 28

Notes:

[50] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: For this endpoint, the Individualized Prophylaxis arm (Arm 1) is broken down by the subject's prestudy treatment regimen (either Prestudy Prophylaxis or Prestudy On-demand). Both are presented here.

End point values	Arm 2: Weekly Prophylaxis	Arm 3: Episodic (On-Demand) Dosing	Arm 1: Individualized Prophylaxis, Prestudy Prophylaxis	Arm 1: Individualized Prophylaxis, Prestudy On-demand
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	3	7	42	17
Units: units on a scale				
median (full range (min-max))				
Total Score; n=34, 12, 3, 5	-5.81 (-9.8 to 5.4)	-0.56 (-11.2 to 3.4)	-1.03 (-26.7 to 11.5)	-4.31 (-35.6 to 13.9)
Physical Health; n=40, 17, 3, 7	-5 (-45 to -5)	0 (-15 to 20)	0 (-31.3 to 60)	-25 (-65 to 25)
Feeling; n=40, 17, 3, 7	-6.25 (-18.8 to 6.3)	0 (-12.5 to 18.8)	-3.13 (-50 to 25)	-6.25 (-50 to 18.8)
View of Yourself; n=42, 17, 3, 7	0 (-5 to 5)	0 (-5 to 15)	0 (-40 to 35)	0 (-40 to 20)
Sports and Leisure; n=29, 10, 2, 5	-10 (-25 to 5)	5 (-8.8 to 5)	0 (-68.8 to 45)	-5 (-50 to 5)
Work and School; n=34, 15, 2, 6	-9.38 (-18.8 to 0)	-3.13 (-25 to 6.3)	0 (-50 to 37.5)	-6.25 (-56.3 to 25)
Dealing with Hemophilia; n=40, 17, 3, 7	0 (-16.7 to 25)	0 (-16.7 to 8.3)	0 (-33.3 to 33.3)	0 (-25 to 58.3)
Treatment; n=42, 14, 3, 7	6.25 (-12.5 to 28.1)	0 (-18.8 to 6.3)	0 (-28.1 to 18.8)	-4.69 (-43.8 to 12.5)
Future; n=40, 17, 3, 6	-5 (-20 to -5)	7.5 (-15 to 10)	0 (-45 to 35)	-5 (-45 to 60)
Family Planning; n=19, 10, 2, 2	0 (0 to 0)	9.38 (0 to 18.8)	0 (-25 to 16.7)	0 (-18.8 to 33.3)
Partnership and Sexuality; n=37, 14, 3, 7	0 (-8.3 to 0)	0 (-25 to 8.3)	0 (-25 to 66.7)	0 (-25 to 91.7)

Statistical analyses

No statistical analyses for this end point

Secondary: Hemophilia-Specific Quality of Life Index for Children (Haemo-QoL) Questionnaire: Change From Baseline to Week 14 and Week 28 in Haemo-QoL III Total Score

End point title	Hemophilia-Specific Quality of Life Index for Children (Haemo-QoL) Questionnaire: Change From Baseline to Week 14 and Week 28 in Haemo-QoL III Total Score

End point description:

The Haemo-QoL III, a quality of life assessment instrument for adolescents with hemophilia, was administered to subjects from 13 to 16 years old. This instrument assesses domains specific to living

with hemophilia and consists of 12 domains: physical health, feeling, view of yourself, family, friends, others, sports and school, treatment, perceived support, dealing with hemophilia, future, and relationships. Total HAEMO-QoL score is the sum of all raw scores for all subscales for subjects for whom at least the minimum number of required questions have been answered. Total scores are presented as the Transformed Scale Score (TSS) from 0-100%, with lower scores indicating a better quality of life. A negative change indicates improvement. Full Analysis Set: subjects 13 to 16 years of age who received at least 1 dose of rFVIIIFc and had an assessment; n=subjects who had specified assessment at given timepoint.

End point type	Secondary

End point timeframe:

Baseline, Week 14, Week 28

End point values	Arm 1: Individualized (Tailored) Prophylaxis	Arm 2: Weekly Prophylaxis	Arm 3: Episodic (On-Demand) Dosing	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	0[51]	2[52]	
Units: units on a scale				
median (full range (min-max))				
Baseline; n=8, 0, 2	11.2 (-6.2 to -1.3)	(to)	26.3 (16.2 to 36.4)	
Change from Baseline at Week 14; n=8, 0, 1	-3.25 (6.5 to 38.3)	(to)	-5.01 (-5.01 to -5.01)	
Change from Baseline at Week 28; n=4, 0, 0	-3.73 (-21.9 to 2.3)	(to)	0 (0 to 0)	

Notes:

[51] - No subjects had an assessment for this reporting group.

[52] - All values of '0' for Week 28 are actually 'NA', since there were no subjects analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Investigators'/Surgeons' Assessment of Subjects' Response to rFVIIIFc for Major Surgery

End point title	Investigators'/Surgeons' Assessment of Subjects' Response to rFVIIIFc for Major Surgery

End point description:

Based on the first assessment of hemostasis by the surgeon/investigator 24 hours or later post-surgery. Scaled responses: Excellent = 1, Good = 2, Fair = 3, Poor/none = 4. Subjects in the Full Analysis Set who received at least 1 dose of rFVIIIFc and underwent major surgery.

End point type	Secondary

End point timeframe:

up to 52 weeks

End point values	Any Arm: Perioperative Management (Surgery) Subgroup			
Subject group type	Subject analysis set			
Number of subjects analysed	9[53]			
Units: responses				
Excellent or Good	9			
Excellent	8			
Good	1			
Fair	0			
Poor/None	0			

Notes:

[53] - Number of major surgeries analyzed=9

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Injections Required to Maintain Hemostasis During Major Surgery

End point title	Number of Injections Required to Maintain Hemostasis During Major Surgery

End point description:

The number of injections to maintain hemostasis during surgery includes all injections for surgery purposes, including from the loading dose to the end date/time of surgery. Subjects in the Full Analysis Set who received at least 1 dose of rFVIIIFc and underwent major surgery.

End point type	Secondary

End point timeframe:

up to 52 weeks

End point values	Any Arm: Perioperative Management (Surgery) Subgroup			
Subject group type	Subject analysis set			
Number of subjects analysed	9[54]			
Units: injections				
median (full range (min-max))	1 (1 to 1)			

Notes:

[54] - Number of major surgeries analyzed=9

Statistical analyses

No statistical analyses for this end point

Secondary: Dose Per Injection and Total Dose Required to Maintain Hemostasis During Major Surgery

End point title	Dose Per Injection and Total Dose Required to Maintain Hemostasis During Major Surgery

End point description:

Mean dose per injection is the average dose for all injections (including loading dose) needed to maintain hemostasis during surgery. Total dose is the sum across all injections (including loading dose) needed to maintain hemostasis during surgery. Subjects in the Full Analysis Set who received at least 1 dose of rFVIIIFc and underwent major surgery.

End point type	Secondary

End point timeframe:

up to 52 weeks ± 2 weeks

End point values	Any Arm: Perioperative Management (Surgery) Subgroup			
Subject group type	Subject analysis set			
Number of subjects analysed	9[55]			
Units: IU/kg				
median (full range (min-max))				
Dose per Injection	51.4 (50 to 77)			
Total Dose	51.4 (50 to 77)			

Notes:

[55] - Number of major surgeries analyzed=9

Statistical analyses

No statistical analyses for this end point

Secondary: Estimated Total Blood Loss During Major Surgery

End point title	Estimated Total Blood Loss During Major Surgery

End point description:

Subjects in the Full Analysis Set who received at least 1 dose of rFVIIIFc, underwent major surgery, and had blood loss during surgery information available.

End point type	Secondary

End point timeframe:

up to 52 weeks ± 2 weeks

End point values	Any Arm: Perioperative Management (Surgery) Subgroup			
Subject group type	Subject analysis set			
Number of subjects analysed	9[56]			
Units: mL				
median (full range (min-max))	15 (0 to 600)			

Notes:

[56] - Number of major surgeries analyzed=7

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Transfusions Required Per Surgery

End point title	Number of Transfusions Required Per Surgery

End point description:

Number of blood component transfusions during a single surgery. Subjects in the Full Analysis Set who received at least 1 dose of rFVIIIFc and underwent major surgery.

End point type	Secondary

End point timeframe:

up to 52 weeks ± 2 weeks

End point values	Any Arm: Perioperative Management (Surgery) Subgroup			
Subject group type	Subject analysis set			
Number of subjects analysed	9[57]			
Units: surgeries				
0 transfusions	8			
1 transfusion	0			
2 transfusions	1			
3 transfusions	0			
> 3 transfusions	0			

Notes:

[57] - Number of major surgeries analyzed=9

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

up to 52 weeks + 30 days ± 1 week

Adverse event reporting additional description:

Based on subjects treated with rFVIIIFc in each arm. One subject in Individualized (Tailored) Prophylaxis arm received only Advate and was not included in the treatment-emergent AE table. Does not include SAEs emergent during surgical/rehabilitation period (see Endpoint 2 for a summary of treatment-emergent events for this subgroup).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.0

Reporting groups

Reporting group title	Arm 1: Individualized (Tailored) Prophylaxis, rFVIIIFc

Reporting group description:

Initial twice weekly dosing with 25 IU/kg of rFVIIIFc via IV injection on Day 1 and 50 IU/kg on Day 4, followed by individualized dose and interval modification within the range of 25 to 65 IU/kg every 3 to 5 days to maintain a trough level of 1% to 3% (or higher, as clinically indicated) rFVIIIFc activity.

Prior to rFVIIIFc treatment, on rFVIIIFc Day 0, all subjects underwent PK analysis with rFVIIIFc in order to estimate subject's PK parameters and guide the appropriate dose or interval of dosing. Repeat PK profiling with a single dose of 50 IU/kg rFVIIIFc was conducted at Week 14 or after 12 to 24 weeks of prophylaxis with rFVIIIFc.

A subset of subjects (Sequential PK Subgroup) also had PK profiling performed with a single dose of 50 IU/kg Advate (Advate Day 0) within 8 weeks prior to rFVIIIFc Day 0. A >= 96 hour washout from Advate or any other FVIII product was performed before the first PK dose of rFVIIIFc was administered.

Reporting group title	Arm 2: Weekly Prophylaxis

Reporting group description:

65 IU/kg of rFVIIIFc via IV injection every 7 days

Reporting group title	Arm 3: Episodic (On-Demand) Dosing

Reporting group description:

Initial single dose of 50 IU/kg of rFVIIIFc via IV injection followed by 10 to 50 IU/kg rFVIIIFc, as required to treat a bleeding episode.

Serious adverse events	Arm 1: Individualized (Tailored) Prophylaxis, rFVIIIFc	Arm 2: Weekly Prophylaxis	Arm 3: Episodic (On-Demand) Dosing
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 117 (8.55%)	2 / 24 (8.33%)	0 / 23 (0.00%)
number of deaths (all causes)	1	0	0
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Face injury			

subjects affected / exposed	1 / 117 (0.85%)	0 / 24 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	0 / 117 (0.00%)	1 / 24 (4.17%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Overdose			
subjects affected / exposed	1 / 117 (0.85%)	0 / 24 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Vascular disorders			
Hypertensive emergency			
subjects affected / exposed	1 / 117 (0.85%)	0 / 24 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Tachycardia			
subjects affected / exposed	1 / 117 (0.85%)	0 / 24 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Restless legs syndrome			
subjects affected / exposed	1 / 117 (0.85%)	0 / 24 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	1 / 117 (0.85%)	0 / 24 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Inguinal hernia			

subjects affected / exposed	1 / 117 (0.85%)	0 / 24 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tooth disorder			
subjects affected / exposed	1 / 117 (0.85%)	0 / 24 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Respiratory distress			
subjects affected / exposed	1 / 117 (0.85%)	0 / 24 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Completed suicide			
subjects affected / exposed	1 / 117 (0.85%)	0 / 24 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 117 (0.00%)	1 / 24 (4.17%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 117 (0.85%)	0 / 24 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemarthrosis			
subjects affected / exposed	1 / 117 (0.85%)	0 / 24 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar spinal stenosis			

subjects affected / exposed	1 / 117 (0.85%)	0 / 24 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myalgia			
subjects affected / exposed	1 / 117 (0.85%)	0 / 24 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Arm 1: Individualized (Tailored) Prophylaxis, rFVIIIFc	Arm 2: Weekly Prophylaxis	Arm 3: Episodic (On-Demand) Dosing
Total subjects affected by non-serious adverse events			
subjects affected / exposed	32 / 117 (27.35%)	8 / 24 (33.33%)	7 / 23 (30.43%)
Nervous system disorders			
Headache			
subjects affected / exposed	5 / 117 (4.27%)	6 / 24 (25.00%)	2 / 23 (8.70%)
occurrences (all)	6	7	2
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	10 / 117 (8.55%)	2 / 24 (8.33%)	1 / 23 (4.35%)
occurrences (all)	11	3	1
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	16 / 117 (13.68%)	1 / 24 (4.17%)	3 / 23 (13.04%)
occurrences (all)	24	1	3
Upper respiratory tract infection			
subjects affected / exposed	6 / 117 (5.13%)	0 / 24 (0.00%)	3 / 23 (13.04%)
occurrences (all)	7	0	3

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 June 2011	- The required washout period from any FVIII product before collecting blood samples for PK assessment was reduced from 96 hours to 72 hours for adolescent subjects. - The inclusion criteria defining the cut-off value in international normalized ratio (INR) was removed. - Exclusion Criterion #1 was amended to define a positive inhibitor value.
02 April 2012	- The end-of-study definition was further clarified. - The criteria for recommending a modification of dose or dosing interval for subjects in Arm 1 were clarified.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/25196897

http://www.ncbi.nlm.nih.gov/pubmed/24227821