# 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<br>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<br>Units: years | | | |
| median | 29 | 31.5 | 34 |
| full range (min-max) | 12 to 65 | 18 to 59 | 13 to 62 |
| Gender categorical<br>Units: Subjects | | | |
| Female | 0 | 0 | 0 |
| Male | 118 | 24 | 23 |

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

| Gender categorical<br>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<br><br>Advate | 52.6 (47.4 to 58.3)<br><br>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<br><br>Advate | 0.55 (0.41 to 0.75)<br>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<br><br>Advate | 47.45 (41.55 to 54.18)<br>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.<br><br>- The inclusion criteria defining the cut-off value in international normalized ratio (INR) was removed.<br><br>- Exclusion Criterion #1 was amended to define a positive inhibitor value. |
| 02 April 2012 | - The end-of-study definition was further clarified.<br><br>- 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