



## Clinical trial results:

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

#### Summary

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

#### Results information

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

#### Trial information

##### Trial identification

|                       |          |
|-----------------------|----------|
| Sponsor protocol code | 997HA307 |
|-----------------------|----------|

##### Additional study identifiers

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

Notes:

#### Sponsors

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

Notes:

#### Paediatric regulatory details

|                                                                      |     |
|----------------------------------------------------------------------|-----|
| Is trial part of an agreed paediatric investigation plan (PIP)       | No  |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No  |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | Yes |

Notes:

## Results analysis stage

|                                                      |             |
|------------------------------------------------------|-------------|
| Analysis stage                                       | Final       |
| Date of interim/final analysis                       | 20 May 2015 |
| Is this the analysis of the primary completion data? | No          |
| Global end of trial reached?                         | Yes         |
| Global end of trial date                             | 20 May 2015 |
| Was the trial ended prematurely?                     | No          |

Notes:

## General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

|                                                           |               |
|-----------------------------------------------------------|---------------|
| Actual start date of recruitment                          | 24 March 2014 |
| Long term follow-up planned                               | No            |
| Independent data monitoring committee (IDMC) involvement? | No            |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                   |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | United Kingdom: 9 |
| Country: Number of subjects enrolled | Australia: 5      |
| Country: Number of subjects enrolled | United States: 5  |
| Worldwide total number of subjects   | 19                |
| EEA total number of subjects         | 9                 |

Notes:

### Subjects enrolled per age group

|                                           |   |
|-------------------------------------------|---|
| In utero                                  | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days)                      | 0 |
| Infants and toddlers (28 days-23 months)  | 0 |

|                           |    |
|---------------------------|----|
| Children (2-11 years)     | 0  |
| Adolescents (12-17 years) | 10 |
| Adults (18-64 years)      | 9  |
| From 65 to 84 years       | 0  |
| 85 years and over         | 0  |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

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

### Period 1

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

### Arms

|                              |                    |
|------------------------------|--------------------|
| Are arms mutually exclusive? | Yes                |
| <b>Arm title</b>             | rFVIIIFc 1000/3000 |

Arm description:

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

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

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

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

Dosage and administration details:

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

|                  |                    |
|------------------|--------------------|
| <b>Arm title</b> | rFVIIIFc 3000/1000 |
|------------------|--------------------|

Arm description:

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

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

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

bleeding

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

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

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

Dosage and administration details:

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

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

## Baseline characteristics

### Reporting groups

|                       |                    |
|-----------------------|--------------------|
| Reporting group title | rFVIIIFc 1000/3000 |
|-----------------------|--------------------|

Reporting group description:

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

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

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

|                       |                    |
|-----------------------|--------------------|
| Reporting group title | rFVIIIFc 3000/1000 |
|-----------------------|--------------------|

Reporting group description:

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

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

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

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

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

## End points

### End points reporting groups

|                       |                    |
|-----------------------|--------------------|
| Reporting group title | rFVIIIFc 1000/3000 |
|-----------------------|--------------------|

Reporting group description:

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

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2. A prophylaxis regimen of 65 IU/kg administered every 7 days was considered for appropriate subjects who were selected based on the opinion of the Investigator
3. An episodic (on-demand) treatment with rFVIIIFc at 20 to 50 IU/kg, depending on the severity of the bleeding episode.

|                       |                    |
|-----------------------|--------------------|
| Reporting group title | rFVIIIFc 3000/1000 |
|-----------------------|--------------------|

Reporting group description:

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

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

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

|                            |                                                |
|----------------------------|------------------------------------------------|
| Subject analysis set title | Pharmacokinetic Analysis Set: rFVIIIFc 1000 IU |
|----------------------------|------------------------------------------------|

|                           |              |
|---------------------------|--------------|
| Subject analysis set type | Per protocol |
|---------------------------|--------------|

Subject analysis set description:

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

|                            |                                                |
|----------------------------|------------------------------------------------|
| Subject analysis set title | Pharmacokinetic Analysis Set: rFVIIIFc 3000 IU |
|----------------------------|------------------------------------------------|

|                           |              |
|---------------------------|--------------|
| Subject analysis set type | Per protocol |
|---------------------------|--------------|

Subject analysis set description:

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

|                            |                     |
|----------------------------|---------------------|
| Subject analysis set title | Safety Analysis Set |
|----------------------------|---------------------|

|                           |                 |
|---------------------------|-----------------|
| Subject analysis set type | Safety analysis |
|---------------------------|-----------------|

Subject analysis set description:

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

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

|                 |                                                                                                                                                                       |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Area Under the Concentration-time Curve From Time Zero to Infinity (AUCinf) as Measured by Activated Partial Thromboplastin Time (aPTT) Clotting Assay <sup>[1]</sup> |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

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

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Up to 96 hours ( $\pm 60$  minutes) after each of 2 injections

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Descriptive statistics are presented, per protocol.

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

Notes:

[2] - subjects with sufficient PK data

## Statistical analyses

No statistical analyses for this end point

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

|                 |                                                                                                                             |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------|
| End point title | Incremental Recovery (IR, K value) as Estimated From the FVIII Activity Data Measured by aPTT Clotting Assay <sup>[3]</sup> |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------|

End point description:

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

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Up to 96 hours ( $\pm 60$  minutes) after each of 2 injections

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Descriptive statistics are presented, per protocol.

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

## Statistical analyses

No statistical analyses for this end point

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

|                 |                                                                |
|-----------------|----------------------------------------------------------------|
| End point title | Maximum Activity (Cmax) as Measured by the aPTT Clotting Assay |
|-----------------|----------------------------------------------------------------|

End point description:

Maximum measured concentration of rFVIIIFc.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

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

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

## Statistical analyses

No statistical analyses for this end point

### Secondary: Half-life (t<sub>1/2</sub>) as Measured by aPTT Clotting Assay

|                 |                                                                  |
|-----------------|------------------------------------------------------------------|
| End point title | Half-life (t <sub>1/2</sub> ) as Measured by aPTT Clotting Assay |
|-----------------|------------------------------------------------------------------|

End point description:

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

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

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

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

Notes:

[4] - subjects with sufficient PK data

## Statistical analyses

No statistical analyses for this end point

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

|                 |                                                       |
|-----------------|-------------------------------------------------------|
| End point title | Clearance (CL) as Measured by the aPTT Clotting Assay |
|-----------------|-------------------------------------------------------|

End point description:

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

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Up to 96 hours ( $\pm 60$  minutes) after each of 2 injections

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

Notes:

[5] - subjects with sufficient PK data

## Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Up to 96 hours ( $\pm 60$  minutes) after each of 2 injections

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

Notes:

[6] - subjects with sufficient PK data

### Statistical analyses

No statistical analyses for this end point

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

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

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

Notes:

[7] - subjects with sufficient PK data

### Statistical analyses

No statistical analyses for this end point

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

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

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

### Statistical analyses

No statistical analyses for this end point

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

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

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

Notes:

[8] - subjects with sufficient PK data

### Statistical analyses

No statistical analyses for this end point

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

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

End point description:

First order rate constant associated with the terminal portion of the curve ( $\lambda_z$ ).

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Up to 96 hours ( $\pm 60$  minutes) after each of 2 injections

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

Notes:

[9] - subjects with sufficient PK data

### Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Up to 96 hours ( $\pm 60$  minutes) after each of 2 injections

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

Notes:

[10] - subjects with sufficient PK data

### Statistical analyses

No statistical analyses for this end point

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

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

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

Notes:

[11] - subjects with sufficient PK data

### Statistical analyses

No statistical analyses for this end point

### Secondary: Terminal Exponential Volume of Distribution (V<sub>z</sub>) as Measured by aPTT Clotting Assay

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

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

Notes:

[12] - subjects with sufficient PK data

## Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Up to 96 hours ( $\pm 60$  minutes) after each of 2 injections

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

Notes:

[13] - subjects with sufficient PK data

[14] - subjects with sufficient PK data

## Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Up to 96 hours ( $\pm 60$  minutes) after each of 2 injections

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

Notes:

[15] - subjects with sufficient PK data

### Statistical analyses

No statistical analyses for this end point

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

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

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

Notes:

[16] - subjects with sufficient PK data

### Statistical analyses

No statistical analyses for this end point

### Secondary: t<sub>1/2</sub> as Measured by Two-Stage Chromogenic Clotting Assay

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

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

Notes:

[17] - subjects with sufficient PK data

[18] - subjects with sufficient PK data

### Statistical analyses

No statistical analyses for this end point

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

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

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

Notes:

[19] - subjects with sufficient PK data

[20] - subjects with sufficient PK data

### Statistical analyses

No statistical analyses for this end point

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

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

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

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

Notes:

[21] - subjects with sufficient PK data

[22] - subjects with sufficient PK data

### Statistical analyses

No statistical analyses for this end point

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

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

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

Notes:

[23] - subjects with sufficient PK data

[24] - subjects with sufficient PK data

### Statistical analyses

No statistical analyses for this end point

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

|                 |                                                          |
|-----------------|----------------------------------------------------------|
| End point title | Tmax as Measured by Two-Stage Chromogenic Clotting Assay |
|-----------------|----------------------------------------------------------|

|                                                         |           |
|---------------------------------------------------------|-----------|
| End point description:                                  |           |
| Time at which maximum activity (Cmax) is observed.      |           |
| End point type                                          | Secondary |
| End point timeframe:                                    |           |
| Up to 96 hours (±60 minutes) after each of 2 injections |           |

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

Notes:

[25] - subjects with sufficient PK data

### Statistical analyses

No statistical analyses for this end point

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

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

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

Notes:

[26] - subjects with sufficient PK data

[27] - subjects with sufficient PK data

### Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Up to 96 hours ( $\pm 60$  minutes) after each of 2 injections

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

Notes:

[28] - subjects with sufficient PK data

[29] - subjects with sufficient PK data

**Statistical analyses**

No statistical analyses for this end point

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

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

End point description:

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

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Up to 96 hours ( $\pm 60$  minutes) after each of 2 injections

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

Notes:

[30] - subjects with sufficient PK data

[31] - subjects with sufficient PK data

## Statistical analyses

No statistical analyses for this end point

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

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

End point description:

Dose normalized area under the FVIII activity-time curve.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Up to 96 hours ( $\pm 60$  minutes) after each of 2 injections

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

Notes:

[32] - subjects with sufficient PK data

[33] - subjects with sufficient PK data

## Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Up to 96 hours ( $\pm 60$  minutes) after each of 2 injections

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

Notes:

[34] - subjects with sufficient PK data

[35] - subjects with sufficient PK data

## Statistical analyses

No statistical analyses for this end point

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

|                 |                                                                                                            |
|-----------------|------------------------------------------------------------------------------------------------------------|
| End point title | Percentage of Subjects Developing Confirmed Inhibitors as Measured by the Nijmegen-modified Bethesda Assay |
|-----------------|------------------------------------------------------------------------------------------------------------|

End point description:

An inhibitor test result  $\geq 0.6$  Bethesda units (BU)/mL, confirmed on 2 separate samples drawn 2 to 4 weeks apart, was considered positive. Both tests were to be performed by the central laboratory using the Nijmegen-modified Bethesda Assay. An exact 95% CI for the percentage of subjects with a confirmed inhibitor was calculated using the Clopper-Pearson exact method.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

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

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

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

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

Adverse event reporting additional description:

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

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |      |
|--------------------|------|
| Dictionary version | 15.0 |
|--------------------|------|

### Reporting groups

|                       |              |
|-----------------------|--------------|
| Reporting group title | Total active |
|-----------------------|--------------|

Reporting group description:

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

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

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

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

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

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

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

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

## **More information**

### **Substantial protocol amendments (globally)**

Were there any global substantial amendments to the protocol? No

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### **Interruptions (globally)**

Were there any global interruptions to the trial? No

### **Limitations and caveats**

None reported