



Clinical trial results:

An Open-Label, Multicenter Evaluation of the Long-Term Safety and Efficacy of Recombinant Human Coagulation Factor VIII Fusion Protein (rFVIII Fc) in the Prevention and Treatment of Bleeding Episodes in Previously Treated Subjects With Hemophilia A

Summary

| | |
|--------------------------|-------------------------------|
| EudraCT number | 2011-003072-37 |
| Trial protocol | SE BE GB DE AT ES IT IE PL NL |
| Global end of trial date | 18 October 2017 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 03 May 2018 |
| First version publication date | 03 May 2018 |

Trial information

Trial identification

| | |
|-----------------------|----------|
| Sponsor protocol code | 8HA01EXT |
|-----------------------|----------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01454739 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Bioverativ Therapeutics Inc. |
| Sponsor organisation address | 225 Second Avenue, Waltham, Massachusetts (MA), United States, 02451 |
| Public contact | Not available, Bioverativ Therapeutics Inc., clinicaltrials@bioverativ.com |
| Scientific contact | Not available, Bioverativ Therapeutics Inc., clinicaltrials@bioverativ.com |

Notes:

Paediatric regulatory details

| | |
|--|---------------------|
| Is trial part of an agreed paediatric investigation plan (PIP) | Yes |
| EMA paediatric investigation plan number(s) | EMA-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 | 18 October 2017 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 18 October 2017 |
| Global end of trial reached? | Yes |
| Global end of trial date | 18 October 2017 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The main objective of this study was to evaluate the long-term safety of Recombinant human Factor VIII (rFVIIIFc) in subjects with hemophilia A.

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and the International Conference on Harmonization guideline E6: Good Clinical Practice. Safety evaluations included monitoring of adverse events (AEs) and serious adverse events (SAEs), physical examination, medical and surgical history (from previous study and updated), height, weight and Concomitant therapy and procedure recording and Laboratory Safety Assessments (hematology, blood chemistry and Nijmegen-modified Bethesda assay).

Background therapy: -

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 15 December 2011 |
| 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 | Netherlands: 1 |
| Country: Number of subjects enrolled | Poland: 3 |
| Country: Number of subjects enrolled | Spain: 2 |
| Country: Number of subjects enrolled | Sweden: 1 |
| Country: Number of subjects enrolled | United Kingdom: 46 |
| Country: Number of subjects enrolled | Austria: 3 |
| Country: Number of subjects enrolled | Germany: 3 |
| Country: Number of subjects enrolled | Ireland: 8 |
| Country: Number of subjects enrolled | Italy: 5 |
| Country: Number of subjects enrolled | Belgium: 1 |
| Country: Number of subjects enrolled | France: 2 |
| Country: Number of subjects enrolled | Australia: 21 |
| Country: Number of subjects enrolled | Brazil: 3 |
| Country: Number of subjects enrolled | Canada: 2 |
| Country: Number of subjects enrolled | Hong Kong: 6 |
| Country: Number of subjects enrolled | India: 14 |
| Country: Number of subjects enrolled | Israel: 3 |

| | |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | Japan: 13 |
| Country: Number of subjects enrolled | New Zealand: 15 |
| Country: Number of subjects enrolled | South Africa: 27 |
| Country: Number of subjects enrolled | Switzerland: 1 |
| Country: Number of subjects enrolled | United States: 60 |
| Worldwide total number of subjects | 240 |
| EEA total number of subjects | 75 |

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) | 59 |
| Adolescents (12-17 years) | 24 |
| Adults (18-64 years) | 155 |
| From 65 to 84 years | 2 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Subjects provided their written informed consent to participate in this study after the Investigator has verified that they are eligible per protocol defined criteria. For subjects, unable to provide written informed consent, parents or legal guardian(s) obtained the informed consent form.

Period 1

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

Arms

| | |
|------------------------------|---|
| Are arms mutually exclusive? | Yes |
| Arm title | rFVIIIFc [Subjects from Study 8HA02PED] |

Arm description:

Tailored Prophylaxis(TP): 25 IU/kg-65 IU/kg rFVIIIFc every 3-5 days or 2 times/week at approximately 20 IU/kg to 65 IU/kg rFVIIIFc on Day 1 & 40 IU/kg-65 IU/kg rFVIIIFc on Day 4 as intravenous (IV) injection. Weekly: rFVIIIFc IV injection once weekly at approximately 65 IU/kg. Personalized P: If optimal prophylaxis dosing not achieved using TP/WP, Investigator personalized dosing to meet individual subjects's needs (options: adding "prevention" dose prior to strenuous activity; targeting FVIII trough level of >3%, if bleeding history &/or activity level requires/dosing less frequently. Episodic (On demand): individual dose of rFVIIIFc IV based on clinical condition, type & severity of bleeding event & if indicated, FVIII levels (per investigator & Sponsor decision). The rate of administration determined by subject's comfort level. For subjects <12 years of age, weekly and episodic treatment regimens were only available once subjects were at least 12 years old.

| | |
|--|----------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Recombinant Factor VIII-Fc |
| Investigational medicinal product code | rFVIIIFc |
| Other name | BIIB031 |
| Pharmaceutical forms | Powder for injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

Subjects received rFVIIIFc as tailored, weekly, personalized prophylaxis or episodic (on-demand regimen). Subjects were allowed to change treatment regimens (for example, from prophylaxis to on-demand, or from on-demand to prophylaxis) per investigator decision.

| | |
|------------------|---|
| Arm title | rFVIIIFc [Subjects from Studies 997HA301/997HA307/997HA309] |
|------------------|---|

Arm description:

Tailored Prophylaxis (TP): 25 IU/kg-65 IU/kg rFVIIIFc every 3-5 days or 2 times/week at approximately 20 IU/kg to 65 IU/kg rFVIIIFc on Day 1 & 40 IU/kg-65 IU/kg rFVIIIFc on Day 4 as intravenous (IV) injection. Weekly: rFVIIIFc IV injection once weekly at approximately 65 IU/kg. Personalized P: If optimal prophylaxis dosing not achieved using TP/WP, Investigator personalized dosing to meet individual subjects's needs (options: adding "prevention" dose prior to strenuous activity; targeting FVIII trough level of >3%, if bleeding history &/or activity level requires/dosing less frequently. Episodic (On demand): individual dose of rFVIIIFc IV based on clinical condition, type & severity of bleeding event & if indicated, FVIII levels (per investigator & Sponsor decision). The rate of administration determined by subject's comfort level.

| | |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

| | |
|--|----------------------------|
| Investigational medicinal product name | Recombinant Factor VIII-Fc |
| Investigational medicinal product code | rFVIIIFc |
| Other name | BIIB031 |
| Pharmaceutical forms | Powder for injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

Subjects received rFVIIIFc as tailored, weekly, personalized prophylaxis or episodic (on-demand regimen). Subjects were allowed to change treatment regimens (for example, from prophylaxis to on-demand, or from on-demand to prophylaxis) per investigator decision.

| Number of subjects in period 1 | rFVIIIFc [Subjects from Study 8HA02PED] | rFVIIIFc [Subjects from Studies 997HA301/997HA307/997HA309] |
|--------------------------------|---|---|
| | | |
| Started | 61 | 179 |
| Completed | 54 | 158 |
| Not completed | 7 | 21 |
| Consent withdrawn by subject | 2 | 6 |
| Physician decision | - | 5 |
| Adverse Event | - | 1 |
| Protocol violation | 2 | 3 |
| Other | 3 | 5 |
| Lost to follow-up | - | 1 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|---|
| Reporting group title | rFVIIIFc [Subjects from Study 8HA02PED] |
|-----------------------|---|

Reporting group description:

Tailored Prophylaxis(TP): 25 IU/kg-65 IU/kg rFVIIIFc every 3-5 days or 2 times/week at approximately 20 IU/kg to 65 IU/kg rFVIIIFc on Day 1 & 40 IU/kg-65 IU/kg rFVIIIFc on Day 4 as intravenous (IV) injection. Weekly: rFVIIIFc IV injection once weekly at approximately 65 IU/kg. Personalized P: If optimal prophylaxis dosing not achieved using TP/WP, Investigator personalized dosing to meet individual subjects's needs (options: adding "prevention" dose prior to strenuous activity; targeting FVIII trough level of >3%, if bleeding history &/or activity level requires/dosing less frequently. Episodic (On demand): individual dose of rFVIIIFc IV based on clinical condition, type & severity of bleeding event & if indicated, FVIII levels (per investigator & Sponsor decision). The rate of administration determined by subject's comfort level. For subjects <12 years of age, weekly and episodic treatment regimens were only available once subjects were at least 12 years old.

| | |
|-----------------------|---|
| Reporting group title | rFVIIIFc [Subjects from Studies 997HA301/997HA307/997HA309] |
|-----------------------|---|

Reporting group description:

Tailored Prophylaxis (TP): 25 IU/kg-65 IU/kg rFVIIIFc every 3-5 days or 2 times/week at approximately 20 IU/kg to 65 IU/kg rFVIIIFc on Day 1 & 40 IU/kg-65 IU/kg rFVIIIFc on Day 4 as intravenous (IV) injection. Weekly: rFVIIIFc IV injection once weekly at approximately 65 IU/kg. Personalized P: If optimal prophylaxis dosing not achieved using TP/WP, Investigator personalized dosing to meet individual subjects's needs (options: adding "prevention" dose prior to strenuous activity; targeting FVIII trough level of >3%, if bleeding history &/or activity level requires/dosing less frequently. Episodic (On demand): individual dose of rFVIIIFc IV based on clinical condition, type & severity of bleeding event & if indicated, FVIII levels (per investigator & Sponsor decision). The rate of administration determined by subject's comfort level.

| Reporting group values | rFVIIIFc [Subjects from Study 8HA02PED] | rFVIIIFc [Subjects from Studies 997HA301/997HA307/997HA309] | Total |
|--|---|---|-------|
| Number of subjects | 61 | 179 | 240 |
| Age categorical Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 59 | 0 | 59 |
| Adolescents (12-17 years) | 2 | 22 | 24 |
| Adults (18-64 years) | 0 | 155 | 155 |
| From 65-84 years | 0 | 2 | 2 |
| 85 years and over | 0 | 0 | 0 |
| Age continuous Units: years | | | |
| arithmetic mean | 6.7 | 33.5 | |
| standard deviation | ± 2.74 | ± 13.48 | - |
| Gender categorical Units: Subjects | | | |
| Female | 0 | 0 | 0 |
| Male | 61 | 179 | 240 |

End points

End points reporting groups

| | |
|--|---|
| Reporting group title | rFVIIIFc [Subjects from Study 8HA02PED] |
| Reporting group description: Tailored Prophylaxis(TP): 25 IU/kg-65 IU/kg rFVIIIFc every 3-5 days or 2 times/week at approximately 20 IU/kg to 65 IU/kg rFVIIIFc on Day 1 & 40 IU/kg-65 IU/kg rFVIIIFc on Day 4 as intravenous (IV) injection. Weekly: rFVIIIFc IV injection once weekly at approximately 65 IU/kg. Personalized P: If optimal prophylaxis dosing not achieved using TP/WP, Investigator personalized dosing to meet individual subjects's needs (options: adding "prevention" dose prior to strenuous activity; targeting FVIII trough level of >3%, if bleeding history &/or activity level requires/dosing less frequently. Episodic (On demand): individual dose of rFVIIIFc IV based on clinical condition, type & severity of bleeding event & if indicated, FVIII levels (per investigator & Sponsor decision). The rate of administration determined by subject's comfort level. For subjects <12 years of age, weekly and episodic treatment regimens were only available once subjects were at least 12 years old. | |
| Reporting group title | rFVIIIFc [Subjects from Studies 997HA301/997HA307/997HA309] |
| Reporting group description: Tailored Prophylaxis (TP): 25 IU/kg-65 IU/kg rFVIIIFc every 3-5 days or 2 times/week at approximately 20 IU/kg to 65 IU/kg rFVIIIFc on Day 1 & 40 IU/kg-65 IU/kg rFVIIIFc on Day 4 as intravenous (IV) injection. Weekly: rFVIIIFc IV injection once weekly at approximately 65 IU/kg. Personalized P: If optimal prophylaxis dosing not achieved using TP/WP, Investigator personalized dosing to meet individual subjects's needs (options: adding "prevention" dose prior to strenuous activity; targeting FVIII trough level of >3%, if bleeding history &/or activity level requires/dosing less frequently. Episodic (On demand): individual dose of rFVIIIFc IV based on clinical condition, type & severity of bleeding event & if indicated, FVIII levels (per investigator & Sponsor decision). The rate of administration determined by subject's comfort level. | |
| Subject analysis set title | rFVIIIFc [8HA02PED (<6 years old age cohort)] |
| Subject analysis set type | Full analysis |
| Subject analysis set description: Subjects enrolled from the study 8HA02PED with <6 years old age. | |
| Subject analysis set title | rFVIIIFc [8HA02PED (6 - <12 years old age cohort)] |
| Subject analysis set type | Full analysis |
| Subject analysis set description: Subjects enrolled from the study 8HA02PED with 6 - <12 years old age. | |
| Subject analysis set title | rFVIIIFc [Subjects from Study 997HA301/997HA307/997HA309] |
| Subject analysis set type | Full analysis |
| Subject analysis set description: Subjects were included from studies 997HA301/997HA307/997HA309. | |

Primary: Number of Subjects with any Positive Inhibitor Development

| | |
|--|---|
| End point title | Number of Subjects with any Positive 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. Safety Analysis Set included subjects who received at least 1 dose of rFVIIIFc in study 8HA01EXT. | |
| End point type | Primary |
| End point timeframe: Approximately 5 years | |
| 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 were done, no inferential statistical analyses were performed.

| End point values | rFVIIIFc [Subjects from Study 8HA02PED] | rFVIIIFc [Subjects from Studies 997HA301/997 HA307/997HA3 09] | | |
|---|--|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 61 | 179 | | |
| Units: subjects with any positive inhibitor | 0 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized Bleeding Rate

| | |
|--|--------------------------|
| End point title | Annualized Bleeding Rate |
| End point description: | |
| Bleeding episodes should be classified as spontaneous if a subject records a bleeding event when there is no known contributing factor such as definite trauma or antecedent strenuous activity. Bleeding episodes should be classified as traumatic if a subject records a bleeding event when there is a known or believed reason for the bleed. Full Analysis Set (FAS) included all subjects who received at least 1 dose of rFVIIIFc. Here, "n" indicates number of subject analyzed in specified treatment regimen. "99999" indicates that the data was not analyzed for the arm in the specified category. Annualized bleeding episodes=(Number of bleeding episodes during the efficacy period/number of days during efficacy period)*365.25. The efficacy period reflects the sum of all intervals of time during which subjects were treated with rFVIIIFc according to the treatment regimens of the study excluding major and minor surgical/rehabilitation periods and large injection intervals. | |
| End point type | Secondary |
| End point timeframe: | |
| Approximately 5 years | |

| End point values | rFVIIIFc [8HA02PED (<6 years old age cohort)] | rFVIIIFc [8HA02PED (6 - <12 years old age cohort)] | rFVIIIFc [Subjects from Study 997HA301/997 HA307/997HA3 09] | |
|--|---|---|--|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 30 | 31 | 179 | |
| Units: episodes per subject per year | | | | |
| median (inter-quartile range (Q1-Q3)) | | | | |
| Tailored Prophylaxis (n= 29, 30, 131) | 1.18 (0.60 to 2.37) | 1.59 (0.55 to 3.55) | 0.64 (0.00 to 2.84) | |
| Weekly Prophylaxis (n= 0, 0, 34) | 99999 (99999 to 99999) | 99999 (99999 to 99999) | 1.90 (0.27 to 4.85) | |
| Personalized Prophylaxis (n= 2, 1, 23) | 3.72 (3.35 to 4.09) | 1.01 (1.01 to 1.01) | 4.11 (0.64 to 8.78) | |
| Episodic (n= 0, 0, 13) | 99999 (99999 to 99999) | 99999 (99999 to 99999) | 19.10 (15.12 to 30.46) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized Spontaneous Joint Bleeding Episodes

| | |
|-----------------|--|
| End point title | Annualized Spontaneous Joint Bleeding Episodes |
|-----------------|--|

End point description:

Bleeding episodes should be classified as spontaneous if a subject records a bleeding event when there is no known contributing factor such as definite trauma or antecedent strenuous activity. In addition of type of bleeding episode (e.g., spontaneous, traumatic), the location of the bleed (joint, internal, skin/mucosa, or muscle) were also collected. FAS included all subjects who received at least 1 dose of rFVIIIFc. Annualized spontaneous joint bleeding episodes = (Number of spontaneous joint bleeding episodes during the efficacy period / number of days during efficacy period) *365.25. Here, "n" indicates number of subject analyzed in specified treatment regimen. "99999" indicates that the data was not analyzed for the arm in the specified category.

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

End point timeframe:

Approximately 5 years

| End point values | rFVIIIFc [8HA02PED (<6 years old age cohort)] | rFVIIIFc [8HA02PED (6 - <12 years old age cohort)] | rFVIIIFc [Subjects from Study 997HA301/997 HA307/997HA3 09] | |
|--|--|---|--|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 30 | 31 | 179 | |
| Units: episodes per subject per year | | | | |
| median (inter-quartile range (Q1-Q3)) | | | | |
| Tailored Prophylaxis (n= 29, 30, 131) | 0.00 (0.00 to 0.55) | 0.00 (0.00 to 0.55) | 0.00 (0.00 to 0.63) | |
| Weekly Prophylaxis (n= 0, 0, 34) | 99999 (99999 to 99999) | 99999 (99999 to 99999) | 0.58 (0.00 to 1.90) | |
| Personalized Prophylaxis (n= 2, 1, 23) | 2.20 (1.34 to 3.07) | 0.00 (0.00 to 0.00) | 0.91 (0.00 to 2.84) | |
| Episodic (n= 0, 0, 13) | 99999 (99999 to 99999) | 99999 (99999 to 99999) | 9.22 (4.35 to 15.70) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Total Number of Days of Exposure

| | |
|-----------------|----------------------------------|
| End point title | Total Number of Days of Exposure |
|-----------------|----------------------------------|

End point description:

An exposure day is a 24-hour period in which one or more rFVIIIFc injections are given. The total number of days of exposure to rFVIIIFc were summarized. Safety Analysis Set included subjects who received at least 1 dose of rFVIIIFc in study 8HA01EXT. Here, "n" indicates number of subject analyzed in specified treatment regimen. "99999" indicates that the data was not analyzed for the arm in the specified category.

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

End point timeframe:
Approximately 5 years

| End point values | rFVIIIFc [Subjects from Study 8HA02PED] | rFVIIIFc [Subjects from Studies 997HA301/997 HA307/997HA3 09] | | |
|-------------------------------------|--|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 61 | 179 | | |
| Units: days | | | | |
| median (full range (min-max)) | | | | |
| Tailored Prophylaxis (n= 59, 131) | 332.00 (18.0 to 467.0) | 257.00 (4.0 to 660.0) | | |
| Weekly Prophylaxis (n= 0, 34) | 99999 (99999 to 99999) | 203.50 (5.0 to 318.0) | | |
| Personalized Prophylaxis (n= 3, 23) | 107.00 (102.0 to 152.0) | 223.00 (14.0 to 535.0) | | |
| Episodic (n= 0, 13) | 99999 (99999 to 99999) | 27.00 (0.0 to 88.0) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized rFVIIIFc Consumption as Total Dose per Kilogram (kg) per Subject per Year

| | |
|--|--|
| End point title | Annualized rFVIIIFc Consumption as Total Dose per Kilogram (kg) per Subject per Year |
| End point description: Annualized consumption = (total IU/kg of study treatment received during the efficacy period / total number of days during the efficacy period) multiplied by 365.25. FAS included all subjects who received at least 1 dose of rFVIIIFc. Here, "n" indicates number of subject analyzed in specified treatment regimen. "99999" indicates that the data was not analyzed for the arm in the specified category. | |
| End point type | Secondary |
| End point timeframe: Approximately 5 years | |

| End point values | rFVIIIFc [8HA02PED (<6 years old age cohort)] | rFVIIIFc [8HA02PED (6 - <12 years old age cohort)] | rFVIIIFc [Subjects from Study 997HA301/997 HA307/997HA3 09] | |
|---|--|---|--|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 30 | 31 | 179 | |
| Units: dose per kilogram per subject per year | | | | |

| median (inter-quartile range (Q1-Q3)) | | | | |
|--|---------------------------|---------------------------|---------------------------|--|
| Tailored Prophylaxis (n= 29, 30, 131) | 5417.9 (4683.4 to 6303.9) | 4989.7 (4293.8 to 5842.4) | 4359.8 (3993.8 to 5630.3) | |
| Weekly Prophylaxis (n= 0, 0, 34) | 99999 (99999 to 99999) | 99999 (99999 to 99999) | 3505.2 (3267.9 to 3639.0) | |
| Personalized Prophylaxis (n= 2, 1, 23) | 5457.1 (4435.0 to 6479.1) | 4572.3 (4572.3 to 4572.3) | 3926.7 (3261.8 to 6194.8) | |
| Episodic (n= 0, 0, 13) | 99999 (99999 to 99999) | 99999 (99999 to 99999) | 801.7 (286.2 to 1057.7) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Physician's Global Assessment of Response to Treatment Using a 4-point Scale

| | |
|-----------------|--|
| End point title | Physician's Global Assessment of Response to Treatment Using a 4-point Scale |
|-----------------|--|

End point description:

Subjects were assessed for response to their rFVIIIFc regimen using the following 4-point scale: Excellent: bleeding episodes responded to less than or equal to (\leq) the usual number of injections or \leq the usual dose of rFVIIIFc, or the rate of breakthrough bleeding during prophylaxis was \leq that usually observed; Effective: most bleeding episodes responded to the same number of injections and dose, but some required more injections or higher doses, or there was a minor increase in the rate of breakthrough; Partially Effective: bleeding episodes most often required more injections and/or higher doses than expected, or adequate breakthrough bleeding prevention during prophylaxis required more frequent injections and/or higher doses and Ineffective: routine failure to control hemostasis or hemostatic control require additional agents. FAS included all subjects who received at least 1 dose of rFVIIIFc. The results were reported based on the efficacy period for overall treatment regimen.

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

End point timeframe:

Approximately 5 years

| End point values | rFVIIIFc [Subjects from Study 8HA02PED] | rFVIIIFc [Subjects from Studies 997HA301/997 HA307/997HA3 09] | | |
|-----------------------------|--|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 61 | 179 | | |
| Units: percentage of visits | | | | |
| number (not applicable) | | | | |
| Excellent | 94.2 | 84.7 | | |
| Effective | 5.6 | 14.9 | | |
| Partially Effective | 0.2 | 0.4 | | |
| Ineffective | 0 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Excellent or Good Response to Treatment Using a 4-Point Scale

| | |
|--|---|
| End point title | Percentage of Subjects with Excellent or Good Response to Treatment Using a 4-Point Scale |
| End point description: Using eDiary, subject received rating for treatment response to any bleeding episode (BE) using 4-point scale-Excellent: Abrupt pain relief and/or improvement in signs of bleeding within approximately (approx.) 8 hours (h) after initial injection (inj.); Good: Definite pain relief and/or improvement in signs of bleeding within approx. 8h after an injection, but possibly requiring more than 1 injection after 24–48h for complete resolution; Moderate: Probable/slight beneficial effect within 8h after initial injection and requires more than 1 injection and None: No improvement, or condition worsens within approx. 8h after initial injection. This assessment was to be made approx. 8 to 12h from time the injection was given to treat BE and prior to any additional doses of rFVIIIFc given for same bleeding episode. FAS population included. "n"=number of subject analyzed in specified treatment regimen during efficacy period. "99999"=data was not analyzed for the arm in the specified category. | |
| End point type | Secondary |
| End point timeframe: Approximately 5 years | |

| End point values | rFVIIIFc [8HA02PED (<6 years old age cohort)] | rFVIIIFc [8HA02PED (6 - <12 years old age cohort)] | rFVIIIFc [Subjects from Study 997HA301/997 HA307/997HA3 09] | |
|--|--|---|--|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 30 | 31 | 179 | |
| Units: % of first inj. with evaluations for BE | | | | |
| number (not applicable) | | | | |
| Tailored Prophylaxis (n= 29, 30, 131) | 88.0 | 90.6 | 74.5 | |
| Weekly Prophylaxis (n= 0, 0, 34) | 99999 | 99999 | 76.2 | |
| Personalized Prophylaxis (n= 2, 1, 23) | 100.0 | 100.0 | 82.2 | |
| Episodic (n= 0, 0, 13) | 99999 | 99999 | 91.8 | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From signing of ICF through follow-up [7 (+7) days after the last dose of rFVIIIFc] or final visit/early termination visit (approximately 5 years)

Adverse event reporting additional description:

The Safety Analysis Set consisted of subjects who received at least 1 dose of rFVIIIFc in study. AEs emergent during major surgical/rehabilitation periods are excluded.

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

Dictionary used

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

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

Reporting groups

| | |
|-----------------------|---|
| Reporting group title | rFVIIIFc [Subjects from Study 8HA02PED] |
|-----------------------|---|

Reporting group description:

Tailored Prophylaxis (TP): 25 IU/kg-65 IU/kg rFVIIIFc every 3-5 days or 2 times/week at approximately 20 IU/kg to 65 IU/kg rFVIIIFc on Day 1 & 40 IU/kg-65 IU/kg rFVIIIFc on Day 4 as intravenous (IV) injection. Weekly: rFVIIIFc IV injection once weekly at approximately 65 IU/kg. Personalized P: If optimal prophylaxis dosing not achieved using TP/WP, Investigator personalized dosing to meet individual subjects's needs (options: adding "prevention" dose prior to strenuous activity; targeting FVIII trough level of >3%, if bleeding history &/or activity level requires/dosing less frequently. Episodic (On demand): individual dose of rFVIIIFc IV based on clinical condition, type & severity of bleeding event & if indicated, FVIII levels (per investigator & Sponsor decision). The rate of administration determined by subject's comfort level. For subjects <12 years of age, weekly and episodic treatment regimens were only available once subjects were at least 12 years old.

| | |
|-----------------------|---|
| Reporting group title | rFVIIIFc [Subjects from studies 997HA301/997HA307/997HA309] |
|-----------------------|---|

Reporting group description:

Tailored Prophylaxis (TP): 25 IU/kg-65 IU/kg rFVIIIFc every 3-5 days or 2 times/week at approximately 20 IU/kg to 65 IU/kg rFVIIIFc on Day 1 & 40 IU/kg-65 IU/kg rFVIIIFc on Day 4 as intravenous (IV) injection. Weekly: rFVIIIFc IV injection once weekly at approximately 65 IU/kg. Personalized P: If optimal prophylaxis dosing not achieved using TP/WP, Investigator personalized dosing to meet individual subjects's needs (options: adding "prevention" dose prior to strenuous activity; targeting FVIII trough level of >3%, if bleeding history &/or activity level requires/dosing less frequently. Episodic (On demand): individual dose of rFVIIIFc IV based on clinical condition, type & severity of bleeding event & if indicated, FVIII levels (per investigator & Sponsor decision). The rate of administration determined by subject's comfort level.

| | |
|-----------------------|------------------|
| Reporting group title | Overall rFVIIIFc |
|-----------------------|------------------|

Reporting group description: -

| Serious adverse events | rFVIIIFc [Subjects from Study 8HA02PED] | rFVIIIFc [Subjects from studies 997HA301/997HA307/997HA309] | Overall rFVIIIFc |
|---|---|---|-------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 20 / 61 (32.79%) | 43 / 179 (24.02%) | 63 / 240 (26.25%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Hepatic Neoplasm Malignant | | | |

| | | | |
|---|----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 179 (0.56%) | 1 / 240 (0.42%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metastases to peritoneum | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 179 (0.56%) | 1 / 240 (0.42%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Bleeding varicose vein | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 179 (0.56%) | 1 / 240 (0.42%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Superior vena cava syndrome | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 179 (0.00%) | 1 / 240 (0.42%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Superior vena cava stenosis | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 179 (0.00%) | 1 / 240 (0.42%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Surgical and medical procedures | | | |
| Bone graft | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 179 (0.56%) | 1 / 240 (0.42%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Carpal tunnel decompression | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 179 (0.56%) | 1 / 240 (0.42%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Central venous catheter removal | | | |
| subjects affected / exposed | 4 / 61 (6.56%) | 0 / 179 (0.00%) | 4 / 240 (1.67%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 0 | 0 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Central venous catheterisation | | | |

| | | | |
|--|----------------|-----------------|-----------------|
| subjects affected / exposed | 2 / 61 (3.28%) | 1 / 179 (0.56%) | 3 / 240 (1.25%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Circumcision | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 179 (0.00%) | 1 / 240 (0.42%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Joint arthroplasty | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 179 (0.56%) | 1 / 240 (0.42%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Knee arthroplasty | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 2 / 179 (1.12%) | 2 / 240 (0.83%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Device breakage | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 179 (0.00%) | 1 / 240 (0.42%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Device dislocation | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 179 (0.56%) | 1 / 240 (0.42%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infusion site mass | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 179 (0.56%) | 1 / 240 (0.42%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 179 (0.00%) | 1 / 240 (0.42%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |

| | | | |
|---|----------------|-----------------|-----------------|
| Epistaxis | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 1 / 179 (0.56%) | 2 / 240 (0.83%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nasal polyps | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 179 (0.56%) | 1 / 240 (0.42%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Depression | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 179 (0.56%) | 1 / 240 (0.42%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Investigations | | | |
| Body temperature increased | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 179 (0.00%) | 1 / 240 (0.42%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nuclear magnetic resonance imaging abnormal | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 179 (0.00%) | 1 / 240 (0.42%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Accident | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 179 (0.56%) | 1 / 240 (0.42%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fall | | | |
| subjects affected / exposed | 6 / 61 (9.84%) | 0 / 179 (0.00%) | 6 / 240 (2.50%) |
| occurrences causally related to treatment / all | 0 / 7 | 0 / 0 | 0 / 7 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Forearm fracture | | | |

| | | | |
|---|----------------|-----------------|-----------------|
| subjects affected / exposed | 2 / 61 (3.28%) | 0 / 179 (0.00%) | 2 / 240 (0.83%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Head injury | | | |
| subjects affected / exposed | 6 / 61 (9.84%) | 1 / 179 (0.56%) | 7 / 240 (2.92%) |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 1 | 0 / 7 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 179 (0.56%) | 1 / 240 (0.42%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Joint dislocation | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 179 (0.56%) | 1 / 240 (0.42%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Periprosthetic fracture | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 179 (0.56%) | 1 / 240 (0.42%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skull fracture | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 179 (0.00%) | 1 / 240 (0.42%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Toxicity to various agents | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 179 (0.56%) | 1 / 240 (0.42%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Transplant failure | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 179 (0.56%) | 1 / 240 (0.42%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Traumatic haematoma | | | |

| | | | |
|---|----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 61 (0.00%) | 2 / 179 (1.12%) | 2 / 240 (0.83%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Traumatic haemorrhage | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 179 (0.00%) | 1 / 240 (0.42%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 179 (0.56%) | 1 / 240 (0.42%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Angina pectoris | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 179 (0.56%) | 1 / 240 (0.42%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myocardial infarction | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 179 (0.56%) | 1 / 240 (0.42%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Cubital tunnel syndrome | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 179 (0.56%) | 1 / 240 (0.42%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Headache | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 179 (0.00%) | 1 / 240 (0.42%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hydrocephalus | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 179 (0.56%) | 1 / 240 (0.42%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nerve compression | | | |

| | | | |
|---|----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 179 (0.56%) | 1 / 240 (0.42%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 179 (0.56%) | 1 / 240 (0.42%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Constipation | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 179 (0.56%) | 1 / 240 (0.42%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Food poisoning | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 179 (0.56%) | 1 / 240 (0.42%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastritis haemorrhagic | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 179 (0.56%) | 1 / 240 (0.42%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rectal haemorrhage | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 179 (0.56%) | 1 / 240 (0.42%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tooth impacted | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 179 (0.56%) | 1 / 240 (0.42%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Varices oesophageal | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 179 (0.56%) | 1 / 240 (0.42%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vomiting | | | |

| | | | |
|---|----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 179 (0.56%) | 1 / 240 (0.42%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Biliary colic | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 179 (0.56%) | 1 / 240 (0.42%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholangitis acute | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 179 (0.56%) | 1 / 240 (0.42%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin and subcutaneous tissue disorders | | | |
| Haemorrhage subcutaneous | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 179 (0.56%) | 1 / 240 (0.42%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urticaria | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 179 (0.00%) | 1 / 240 (0.42%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Calculus ureteric | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 179 (0.56%) | 1 / 240 (0.42%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haematuria | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 179 (0.00%) | 1 / 240 (0.42%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nephrolithiasis | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 179 (0.56%) | 1 / 240 (0.42%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|------------------|------------------|
| Renal impairment | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 179 (0.56%) | 1 / 240 (0.42%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthropathy | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 2 / 179 (1.12%) | 2 / 240 (0.83%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemarthrosis | | | |
| subjects affected / exposed | 2 / 61 (3.28%) | 3 / 179 (1.68%) | 5 / 240 (2.08%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 3 | 0 / 5 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemophilic arthropathy | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 11 / 179 (6.15%) | 11 / 240 (4.58%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 12 | 0 / 12 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intervertebral disc disorder | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 179 (0.56%) | 1 / 240 (0.42%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Osteoarthritis | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 179 (0.56%) | 1 / 240 (0.42%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spinal osteoarthritis | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 2 / 179 (1.12%) | 2 / 240 (0.83%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Synovitis | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 179 (0.56%) | 1 / 240 (0.42%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------------------------|-----------------------------------|-----------------------------------|
| Infections and infestations Appendicitis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 61 (0.00%) 0 / 0 0 / 0 | 1 / 179 (0.56%) 0 / 1 0 / 0 | 1 / 240 (0.42%) 0 / 1 0 / 0 |
| Cellulitis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 61 (1.64%) 0 / 1 0 / 0 | 0 / 179 (0.00%) 0 / 0 0 / 0 | 1 / 240 (0.42%) 0 / 1 0 / 0 |
| Chronic sinusitis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 61 (0.00%) 0 / 0 0 / 0 | 1 / 179 (0.56%) 0 / 1 0 / 0 | 1 / 240 (0.42%) 0 / 1 0 / 0 |
| Device related infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 61 (0.00%) 0 / 0 0 / 0 | 1 / 179 (0.56%) 0 / 1 0 / 0 | 1 / 240 (0.42%) 0 / 1 0 / 0 |
| Hepatitis C subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 61 (0.00%) 0 / 0 0 / 0 | 2 / 179 (1.12%) 0 / 2 0 / 0 | 2 / 240 (0.83%) 0 / 2 0 / 0 |
| Infectious pleural effusion subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 61 (0.00%) 0 / 0 0 / 0 | 1 / 179 (0.56%) 0 / 1 0 / 0 | 1 / 240 (0.42%) 0 / 1 0 / 0 |
| Influenza subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 61 (0.00%) 0 / 0 0 / 0 | 1 / 179 (0.56%) 0 / 1 0 / 0 | 1 / 240 (0.42%) 0 / 1 0 / 0 |
| Pericoronitis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 61 (0.00%) 0 / 0 0 / 0 | 1 / 179 (0.56%) 0 / 1 0 / 0 | 1 / 240 (0.42%) 0 / 1 0 / 0 |
| Pneumonia | | | |

| | | | |
|---|----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 61 (1.64%) | 1 / 179 (0.56%) | 2 / 240 (0.83%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sinusitis | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 179 (0.00%) | 1 / 240 (0.42%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Staphylococcal bacteraemia | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 179 (0.56%) | 1 / 240 (0.42%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Staphylococcal infection | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 179 (0.00%) | 1 / 240 (0.42%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Streptococcal sepsis | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 179 (0.56%) | 1 / 240 (0.42%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Subcutaneous abscess | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 179 (0.56%) | 1 / 240 (0.42%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tooth abscess | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 179 (0.00%) | 1 / 240 (0.42%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 179 (0.00%) | 1 / 240 (0.42%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Viral infection | | | |

| | | | |
|---|----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 179 (0.00%) | 1 / 240 (0.42%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Viral upper respiratory tract infection | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 179 (0.00%) | 1 / 240 (0.42%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 179 (0.56%) | 1 / 240 (0.42%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| 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 | rFVIIIFc [Subjects from Study 8HA02PED] | rFVIIIFc [Subjects from studies 997HA301/997HA307/997HA309] | Overall rFVIIIFc |
|---|---|---|--------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 49 / 61 (80.33%) | 110 / 179 (61.45%) | 159 / 240 (66.25%) |
| Injury, poisoning and procedural complications | | | |
| Fall | | | |
| subjects affected / exposed | 11 / 61 (18.03%) | 14 / 179 (7.82%) | 25 / 240 (10.42%) |
| occurrences (all) | 22 | 14 | 36 |
| Laceration | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 15 / 179 (8.38%) | 16 / 240 (6.67%) |
| occurrences (all) | 1 | 19 | 20 |
| Limb injury | | | |
| subjects affected / exposed | 4 / 61 (6.56%) | 10 / 179 (5.59%) | 14 / 240 (5.83%) |
| occurrences (all) | 4 | 10 | 14 |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 9 / 179 (5.03%) | 9 / 240 (3.75%) |
| occurrences (all) | 0 | 9 | 9 |
| Nervous system disorders | | | |

| | | | |
|---|--|--|--|
| Headache subjects affected / exposed occurrences (all) | 10 / 61 (16.39%) 19 | 15 / 179 (8.38%) 18 | 25 / 240 (10.42%) 37 |
| General disorders and administration site conditions Pyrexia subjects affected / exposed occurrences (all) | 6 / 61 (9.84%) 8 | 5 / 179 (2.79%) 6 | 11 / 240 (4.58%) 14 |
| Immune system disorders Seasonal allergy subjects affected / exposed occurrences (all) | 9 / 61 (14.75%) 12 | 5 / 179 (2.79%) 5 | 14 / 240 (5.83%) 17 |
| Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all) | 5 / 61 (8.20%) 5 2 / 61 (3.28%) 2 8 / 61 (13.11%) 9 | 16 / 179 (8.94%) 17 8 / 179 (4.47%) 8 6 / 179 (3.35%) 6 | 21 / 240 (8.75%) 22 10 / 240 (4.17%) 10 14 / 240 (5.83%) 15 |
| Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) | 8 / 61 (13.11%) 9 | 9 / 179 (5.03%) 10 | 17 / 240 (7.08%) 19 |
| Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Pain in extremity subjects affected / exposed occurrences (all) | 7 / 61 (11.48%) 11 5 / 61 (8.20%) 6 | 20 / 179 (11.17%) 26 11 / 179 (6.15%) 12 | 27 / 240 (11.25%) 37 16 / 240 (6.67%) 18 |
| Infections and infestations Gastroenteritis viral subjects affected / exposed occurrences (all) | 6 / 61 (9.84%) 8 | 2 / 179 (1.12%) 2 | 8 / 240 (3.33%) 10 |

| | | | |
|---|------------------|-------------------|-------------------|
| Influenza | | | |
| subjects affected / exposed | 3 / 61 (4.92%) | 14 / 179 (7.82%) | 17 / 240 (7.08%) |
| occurrences (all) | 3 | 16 | 19 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 6 / 61 (9.84%) | 37 / 179 (20.67%) | 43 / 240 (17.92%) |
| occurrences (all) | 13 | 61 | 74 |
| Pharyngitis | | | |
| subjects affected / exposed | 4 / 61 (6.56%) | 2 / 179 (1.12%) | 6 / 240 (2.50%) |
| occurrences (all) | 9 | 2 | 11 |
| Tonsillitis | | | |
| subjects affected / exposed | 12 / 61 (19.67%) | 2 / 179 (1.12%) | 14 / 240 (5.83%) |
| occurrences (all) | 14 | 2 | 16 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 13 / 61 (21.31%) | 19 / 179 (10.61%) | 32 / 240 (13.33%) |
| occurrences (all) | 34 | 27 | 61 |
| Viral infection | | | |
| subjects affected / exposed | 4 / 61 (6.56%) | 3 / 179 (1.68%) | 7 / 240 (2.92%) |
| occurrences (all) | 4 | 4 | 8 |
| Viral upper respiratory tract infection | | | |
| subjects affected / exposed | 7 / 61 (11.48%) | 0 / 179 (0.00%) | 7 / 240 (2.92%) |
| occurrences (all) | 22 | 0 | 22 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|----------------|---|
| 26 August 2013 | This amendment was commenced to allow interim analyses of safety and/or efficacy data to support regulatory submissions and planning of future clinical studies, mandate tailored or personalized prophylaxis for pediatric subjects <12 years of age, update the maximum dose and minimum interval for prophylaxis dosing in pediatric subjects, mandate that subjects first dosed with rFVIIIFc when <12 years of age would be followed to at least 100 EDs and update the statistical section. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported