



Clinical trial results:

A Prospective Study to Evaluate the Effect of rFVIII-FS in Different Prophylactic Regimens on Bleeding Events Frequency and Development of Arthropathy in Previously Treated and Minimally Treated Hemophilia A Pediatric Population

Summary

| | |
|--------------------------|-------------------|
| EudraCT number | 2014-005253-39 |
| Trial protocol | Outside EU/EEA |
| Global end of trial date | 28 September 2009 |

Results information

| | |
|--------------------------------|---|
| Result version number | v2 (current) |
| This version publication date | 07 September 2016 |
| First version publication date | 20 June 2015 |
| Version creation reason | <ul style="list-style-type: none">• New data added to full data set• Correction of full data set Bayer sponsor contact information to be updated |

Trial information

Trial identification

| | |
|-----------------------|------------------|
| Sponsor protocol code | BAY14-2222/12684 |
|-----------------------|------------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT00632814 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Bayer AG |
| Sponsor organisation address | Kaiser-Wilhelm-Allee, D-51368, Leverkusen, Germany, |
| Public contact | Therapeutic Area Head, Bayer AG, clinical-trials-contact@bayer.com |
| Scientific contact | Therapeutic Area Head, Bayer AG, clinical-trials-contact@bayer.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 | 02 August 2010 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 28 September 2009 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To evaluate and compare the effect of 3 different prophylactic regimens (once per week, twice per week, and three times per week; dose escalation in case of insufficient bleeding protection) on frequency of joint bleeds in severe and moderate pediatric hemophilia A subjects.

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. Before entering the study, the informed consent form was read by and explained to all subjects and/or their legally authorized representatives. Participating subjects and/or their legally authorized representatives signed informed consent form and could withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. Only investigators qualified by training and experience were selected as appropriate experts to investigate the study drug.

Background therapy: -

Evidence for comparator: -

| | |
|---|--------------|
| Actual start date of recruitment | 28 June 2007 |
| 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 | Russian Federation: 32 |
| Worldwide total number of subjects | 32 |
| EEA total number of subjects | 0 |

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) | 3 |
| Children (2-11 years) | 27 |
| Adolescents (12-17 years) | 2 |

| | |
|----------------------|---|
| Adults (18-64 years) | 0 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

The recruitment period took from first subject first visit 28 Jun 2007 to last subject first visit 26 Dec 2008. The study period took from first subject first visit 28 Jun 2007 to last subject last visit 28 Sep 2009. All 4 sites were medical clinics. Assignment to a group was based on subjects previous treatment schedule (non-randomized).

Pre-assignment

Screening details:

There was an indefinite time period between screening and baseline. Study treatment started at visit 2 (baseline).

Period 1

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

Arms

| | |
|------------------------------|--|
| Are arms mutually exclusive? | Yes |
| Arm title | rFVIII-FS (Kogenate FS, BAY14-2222), 70 IU/kg qw |

Arm description:

rFVIII-FS (Octocog-alfa, antihemophilic factor [recombinant]) 70 international units per kilogram (IU/kg), dosing by injection once per week (qw) (weekly on Day 7 + 1 after previous injection) for 9 months. Dose escalation was permitted due to joint bleeding (escalation to 35 IU/kg twice a week [biw] or further escalation to 25 IU/kg three times a week [tiw]).

| | |
|--|---|
| Arm type | Experimental |
| Investigational medicinal product name | Recombinant FVIII formulated with sucrose (rFVIII-FS) |
| Investigational medicinal product code | BAY14-2222 |
| Other name | Octocog alfa, Kogenate® FS |
| Pharmaceutical forms | Injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

rFVIII-FS (Octocog-alfa, antihemophilic factor [recombinant]) 70 IU/kg, dosing by injection qw (weekly on Day 7 + 1 after previous injection) for 9 months. Dose escalation was permitted due to joint bleeding (escalation to 35 IU/kg biw or further escalation to 25 IU/kg tiw).

| | |
|------------------|--|
| Arm title | rFVIII-FS (Kogenate FS, BAY14-2222), biw (30 IU/kg + 40 IU/kg) |
|------------------|--|

Arm description:

rFVIII-FS (Octocog-alfa, antihemophilic factor [recombinant]) 70 IU/kg, dosing by injection biw (30 IU/kg [day 1] + 40 IU/kg [day 4]) for 9 months. Dose escalation was permitted due to joint bleeding (escalation to 25 IU/kg tiw).

| | |
|--|---|
| Arm type | Experimental |
| Investigational medicinal product name | Recombinant FVIII formulated with sucrose (rFVIII-FS) |
| Investigational medicinal product code | BAY14-2222 |
| Other name | Octocog alfa, Kogenate® FS |
| Pharmaceutical forms | Injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

rFVIII-FS (Octocog-alfa, antihemophilic factor [recombinant]) 70 IU/kg, dosing by injection biw (30 IU/kg [day 1] + 40 IU/kg [day 4]) for 9 months. Dose escalation was permitted due to joint bleeding (escalation to 25 IU/kg tiw).

| | |
|------------------|---|
| Arm title | rFVIII-FS (Kogenate FS, BAY14-2222), tiw (3 x 25 IU/kg) |
|------------------|---|

Arm description:

rFVIII-FS (Octocog-alfa, antihemophilic factor [recombinant]) 75 IU/kg, dosing by injection tiw (3 x 25 IU/kg [day 1, 3, 5]) for 9 months. No escalation opportunity for subjects in this group.

| | |
|--|---|
| Arm type | Experimental |
| Investigational medicinal product name | Recombinant FVIII formulated with sucrose (rFVIII-FS) |
| Investigational medicinal product code | BAY14-2222 |
| Other name | Octocog alfa, Kogenate® FS |
| Pharmaceutical forms | Injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

rFVIII-FS (Octocog-alfa, antihemophilic factor [recombinant]) 75 IU/kg, dosing by injection tiw (3 x 25 IU/kg [day 1, 3, 5]) for 9 months. No escalation opportunity for subjects in this group.

| Number of subjects in period 1 | rFVIII-FS (Kogenate FS, BAY14-2222), 70 IU/kg qw | rFVIII-FS (Kogenate FS, BAY14-2222), biw (30 IU/kg + 40 IU/kg) | rFVIII-FS (Kogenate FS, BAY14-2222), tiw (3 x 25 IU/kg) |
|---------------------------------------|--|--|---|
| | | | |
| Started | 11 | 13 | 8 |
| Completed | 11 | 13 | 8 |

Baseline characteristics

Reporting groups

| | |
|--|--|
| Reporting group title | rFVIII-FS (Kogenate FS, BAY14-2222), 70 IU/kg qw |
| Reporting group description: rFVIII-FS (Octocog-alfa, antihemophilic factor [recombinant]) 70 international units per kilogram (IU/kg), dosing by injection once per week (qw) (weekly on Day 7 + 1 after previous injection) for 9 months. Dose escalation was permitted due to joint bleeding (escalation to 35 IU/kg twice a week [biw] or further escalation to 25 IU/kg three times a week [tiw]). | |
| Reporting group title | rFVIII-FS (Kogenate FS, BAY14-2222), biw (30 IU/kg + 40 IU/kg) |
| Reporting group description: rFVIII-FS (Octocog-alfa, antihemophilic factor [recombinant]) 70 IU/kg, dosing by injection biw (30 IU/kg [day 1] + 40 IU/kg [day 4]) for 9 months. Dose escalation was permitted due to joint bleeding (escalation to 25 IU/kg tiw). | |
| Reporting group title | rFVIII-FS (Kogenate FS, BAY14-2222), tiw (3 x 25 IU/kg) |
| Reporting group description: rFVIII-FS (Octocog-alfa, antihemophilic factor [recombinant]) 75 IU/kg, dosing by injection tiw (3 x 25 IU/kg [day 1, 3, 5]) for 9 months. No escalation opportunity for subjects in this group. | |

| Reporting group values | rFVIII-FS (Kogenate FS, BAY14-2222), 70 IU/kg qw | rFVIII-FS (Kogenate FS, BAY14-2222), biw (30 IU/kg + 40 IU/kg) | rFVIII-FS (Kogenate FS, BAY14-2222), tiw (3 x 25 IU/kg) |
|------------------------------------|--|--|---|
| Number of subjects | 11 | 13 | 8 |
| Age categorical Units: Subjects | | | |

| | | | |
|---|---------------|---------------|-------------|
| Age continuous Units: years arithmetic mean standard deviation | 3.27 ± 3.2 | 6.08 ± 3.5 | 6 ± 3.12 |
| Gender Categorical Units: subjects | | | |
| Male | 11 | 13 | 8 |
| Ethnicity Units: Subjects | | | |
| Caucasian | 11 | 13 | 7 |
| Asian | 0 | 0 | 1 |
| Number of subjects on prophylaxis versus on-demand therapy prior to screening | | | |
| Number of subjects on prophylaxis versus on-demand therapy before screening | | | |
| Units: Subjects | | | |
| On demand | 9 | 6 | 5 |
| Prophylaxis | 2 | 7 | 3 |
| Number of subjects with different exposure days (ED) Units: Subjects | | | |
| 0 ED | 1 | 0 | 0 |
| 1 to <20 ED | 0 | 0 | 0 |
| 20 to <100 ED | 5 | 2 | 4 |
| ≥100 ED | 5 | 11 | 4 |

| | | | |
|--|---------|---------|---------|
| Number of subjects with target joint present Units: Subjects | | | |
| Target joint present | 4 | 7 | 7 |
| Target joint absent | 7 | 6 | 1 |
| Number of subjects with bleeding rates in previous 6-9 Months Units: Subjects | | | |
| No bleedings | 1 | 2 | 0 |
| Any bleedings | 10 | 11 | 8 |
| Number of subjects with joint bleeding in previous 6-9 Months Units: Subjects | | | |
| Any joint bleeding | 9 | 11 | 6 |
| No joint bleeding | 2 | 2 | 2 |
| Body weight Units: kilograms | | | |
| arithmetic mean | 17.48 | 24.39 | 25.45 |
| standard deviation | ± 10.43 | ± 11.35 | ± 9.87 |
| Height Units: centimeters | | | |
| arithmetic mean | 98.09 | 120.31 | 122 |
| standard deviation | ± 22.88 | ± 23.75 | ± 20.74 |
| FVIII trough level at Baseline Units: percentage of FVIII activity | | | |
| arithmetic mean | 1.43 | 1.62 | 0.78 |
| standard deviation | ± 0.7 | ± 1.79 | ± 0.24 |
| Stockholm Joint Score | | | |
| The assessment of joint function using Stockholm Joint Score. The minimum value is 0 (the best condition), and the maximum value is 140 (the worst condition). | | | |
| Units: scores on a scale | | | |
| arithmetic mean | 3.9 | 5.9 | 7.1 |
| standard deviation | ± 4.8 | ± 5.8 | ± 4.6 |

| | | | |
|------------------------------------|-------|--|--|
| Reporting group values | Total | | |
| Number of subjects | 32 | | |
| Age categorical Units: Subjects | | | |

| | | | |
|---|----|--|--|
| Age continuous Units: years | | | |
| arithmetic mean | | | |
| standard deviation | - | | |
| Gender Categorical Units: subjects | | | |
| Male | 32 | | |
| Ethnicity Units: Subjects | | | |
| Caucasian | 31 | | |
| Asian | 1 | | |
| Number of subjects on prophylaxis versus on-demand therapy prior to | | | |

| | | | |
|--|----|--|--|
| screening | | | |
| Number of subjects on prophylaxis versus on-demand therapy before screening | | | |
| Units: Subjects | | | |
| On demand | 20 | | |
| Prophylaxis | 12 | | |
| Number of subjects with different exposure days (ED) | | | |
| Units: Subjects | | | |
| 0 ED | 1 | | |
| 1 to <20 ED | 0 | | |
| 20 to <100 ED | 11 | | |
| >=100 ED | 20 | | |
| Number of subjects with target joint present | | | |
| Units: Subjects | | | |
| Target joint present | 18 | | |
| Target joint absent | 14 | | |
| Number of subjects with bleeding rates in previous 6-9 Months | | | |
| Units: Subjects | | | |
| No bleedings | 3 | | |
| Any bleedings | 29 | | |
| Number of subjects with joint bleeding in previous 6-9 Months | | | |
| Units: Subjects | | | |
| Any joint bleeding | 26 | | |
| No joint bleeding | 6 | | |
| Body weight | | | |
| Units: kilograms | | | |
| arithmetic mean | | | |
| standard deviation | - | | |
| Height | | | |
| Units: centimeters | | | |
| arithmetic mean | | | |
| standard deviation | - | | |
| FVIII trough level at Baseline | | | |
| Units: percentage of FVIII activity | | | |
| arithmetic mean | | | |
| standard deviation | - | | |
| Stockholm Joint Score | | | |
| The assessment of joint function using Stockholm Joint Score. The minimum value is 0 (the best condition), and the maximum value is 140 (the worst condition). | | | |
| Units: scores on a scale | | | |
| arithmetic mean | | | |
| standard deviation | - | | |

End points

End points reporting groups

| | |
|--|--|
| Reporting group title | rFVIII-FS (Kogenate FS, BAY14-2222), 70 IU/kg qw |
| Reporting group description: rFVIII-FS (Octocog-alfa, antihemophilic factor [recombinant]) 70 international units per kilogram (IU/kg), dosing by injection once per week (qw) (weekly on Day 7 + 1 after previous injection) for 9 months. Dose escalation was permitted due to joint bleeding (escalation to 35 IU/kg twice a week [biw] or further escalation to 25 IU/kg three times a week [tiw]). | |
| Reporting group title | rFVIII-FS (Kogenate FS, BAY14-2222), biw (30 IU/kg + 40 IU/kg) |
| Reporting group description: rFVIII-FS (Octocog-alfa, antihemophilic factor [recombinant]) 70 IU/kg, dosing by injection biw (30 IU/kg [day 1] + 40 IU/kg [day 4]) for 9 months. Dose escalation was permitted due to joint bleeding (escalation to 25 IU/kg tiw). | |
| Reporting group title | rFVIII-FS (Kogenate FS, BAY14-2222), tiw (3 x 25 IU/kg) |
| Reporting group description: rFVIII-FS (Octocog-alfa, antihemophilic factor [recombinant]) 75 IU/kg, dosing by injection tiw (3 x 25 IU/kg [day 1, 3, 5]) for 9 months. No escalation opportunity for subjects in this group. | |

Primary: Percentage of Subjects With Less Than 2 Joint Bleeds During the 9-month Treatment Period

| | |
|--|---|
| End point title | Percentage of Subjects With Less Than 2 Joint Bleeds During the 9-month Treatment Period ^[1] |
| End point description: | |
| End point type | Primary |
| End point timeframe: Up to 9 months | |
| 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 | rFVIII-FS (Kogenate FS, BAY14-2222), 70 IU/kg qw | rFVIII-FS (Kogenate FS, BAY14-2222), biw (30 IU/kg + 40 IU/kg) | rFVIII-FS (Kogenate FS, BAY14-2222), tiw (3 x 25 IU/kg) | |
|-------------------------------|--|--|---|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 11 | 13 | 8 | |
| Units: Percentage of subjects | | | | |
| number (not applicable) | 72.7 | 84.6 | 75 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Bleeds per Subject During the 9-month Treatment Period

| | |
|-----------------|---|
| End point title | Number of Bleeds per Subject During the 9-month Treatment |
|-----------------|---|

| | |
|------------------------|-----------|
| | Period |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Up to 9 months | |

| End point values | rFVIII-FS (Kogenate FS, BAY14-2222), 70 IU/kg qw | rFVIII-FS (Kogenate FS, BAY14-2222), biw (30 IU/kg + 40 IU/kg) | rFVIII-FS (Kogenate FS, BAY14-2222), tiw (3 x 25 IU/kg) | |
|-------------------------------|---|--|---|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 11 | 13 | 8 | |
| Units: bleeds per subject | | | | |
| median (full range (min-max)) | | | | |
| All bleeds | 3 (0 to 12) | 2 (0 to 6) | 1.5 (0 to 8) | |
| Joint bleeds | 0 (0 to 2) | 0 (0 to 3) | 0 (0 to 8) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Bleeding Events During the 9-month Treatment Period

| | |
|------------------------|---|
| End point title | Number of Subjects With Bleeding Events During the 9-month Treatment Period |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Up to 9 months | |

| End point values | rFVIII-FS (Kogenate FS, BAY14-2222), 70 IU/kg qw | rFVIII-FS (Kogenate FS, BAY14-2222), biw (30 IU/kg + 40 IU/kg) | rFVIII-FS (Kogenate FS, BAY14-2222), tiw (3 x 25 IU/kg) | |
|-----------------------------|---|--|---|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 11 | 13 | 8 | |
| Units: subjects | | | | |
| number (not applicable) | | | | |
| no bleeds | 3 | 4 | 4 | |
| bleeds at all | 8 | 9 | 4 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Joint Bleeds During the 9-month Treatment Period

| | |
|-----------------|--|
| End point title | Number of Subjects With Joint Bleeds During the 9-month Treatment Period |
|-----------------|--|

End point description:

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

End point timeframe:

Up to 9 months

| End point values | rFVIII-FS (Kogenate FS, BAY14-2222), 70 IU/kg qw | rFVIII-FS (Kogenate FS, BAY14-2222), biw (30 IU/kg + 40 IU/kg) | rFVIII-FS (Kogenate FS, BAY14-2222), tiw (3 x 25 IU/kg) | |
|-----------------------------|---|--|---|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 11 | 13 | 8 | |
| Units: subjects | | | | |
| number (not applicable) | | | | |
| no bleeds | 8 | 9 | 6 | |
| bleeds at all | 3 | 4 | 2 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects in Each Group at the End of the Study

| | |
|-----------------|--|
| End point title | Number of Subjects in Each Group at the End of the Study |
|-----------------|--|

End point description:

Subjects were allowed to switch treatment groups upon occurrence of joint bleed. Therefore, the number of subjects per group at the end of the study is different from the number of subjects per group at baseline.

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

End point timeframe:

Up to 9 months

| End point values | rFVIII-FS (Kogenate FS, BAY14-2222), 70 IU/kg qw | rFVIII-FS (Kogenate FS, BAY14-2222), biw (30 IU/kg + 40 IU/kg) | rFVIII-FS (Kogenate FS, BAY14-2222), tiw (3 x 25 IU/kg) | |
|-----------------------------|---|--|---|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 11 | 13 | 8 | |
| Units: Subjects | 8 | 14 | 10 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Actual Monthly rFVIII-FS Consumption

| | |
|------------------------|--------------------------------------|
| End point title | Actual Monthly rFVIII-FS Consumption |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Up to 9 months | |

| End point values | rFVIII-FS (Kogenate FS, BAY14-2222), 70 IU/kg qw | rFVIII-FS (Kogenate FS, BAY14-2222), biw (30 IU/kg + 40 IU/kg) | rFVIII-FS (Kogenate FS, BAY14-2222), tiw (3 x 25 IU/kg) | |
|--------------------------------------|---|--|---|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 11 | 13 | 8 | |
| Units: IU/kg | | | | |
| arithmetic mean (standard deviation) | 390.8 (± 106.9) | 422.3 (± 138.2) | 501.4 (± 241.2) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Stockholm Hemophilia Joint Score at 9 Months of Treatment

| | |
|--|---|
| End point title | Change From Baseline in Stockholm Hemophilia Joint Score at 9 Months of Treatment |
| End point description: | |
| The assessment of joint function using Stockholm Joint Score. The minimum value is 0 (the best condition), and the maximum value is 140 (the worst condition). | |

| | |
|---|-----------|
| End point type | Secondary |
| End point timeframe: baseline and 9 months | |

| End point values | rFVIII-FS (Kogenate FS, BAY14-2222), 70 IU/kg qw | rFVIII-FS (Kogenate FS, BAY14-2222), biw (30 IU/kg + 40 IU/kg) | rFVIII-FS (Kogenate FS, BAY14-2222), tiw (3 x 25 IU/kg) | |
|--------------------------------------|---|--|---|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 11 | 13 | 8 | |
| Units: Scores on a scale | | | | |
| arithmetic mean (standard deviation) | -1.4 (± 2.4) | -2 (± 4.5) | -1.8 (± 2.2) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Haemo-Quality of Life (QoL) Standardized Total Score at 9 Months of Treatment (Completed by Subjects in the Total Group)

| | |
|-----------------|--|
| End point title | Haemo-Quality of Life (QoL) Standardized Total Score at 9 Months of Treatment (Completed by Subjects in the Total Group) |
|-----------------|--|

End point description:

QoL was measured by the Haemo-QoL standardized total Score, which ranged from 0 (the best condition) to 100 (the worst condition).

| | |
|----------------------------------|-----------|
| End point type | Secondary |
| End point timeframe: 9 months | |

| End point values | rFVIII-FS (Kogenate FS, BAY14-2222), 70 IU/kg qw | rFVIII-FS (Kogenate FS, BAY14-2222), biw (30 IU/kg + 40 IU/kg) | rFVIII-FS (Kogenate FS, BAY14-2222), tiw (3 x 25 IU/kg) | |
|--------------------------------------|---|--|---|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 3 ^[2] | 10 ^[3] | 7 ^[4] | |
| Units: Scores on a scale | | | | |
| arithmetic mean (standard deviation) | 30.28 (± 13.09) | 39.07 (± 23.5) | 30.27 (± 11.95) | |

Notes:

[2] - Subjects who completed the questionnaire.

[3] - subjects who completed the questionnaire.

[4] - Subjects who completed the questionnaire.

Statistical analyses

No statistical analyses for this end point

Secondary: Haemo-Quality of Life (QoL) Standardized Total Score (Completed by Parents/Caregivers in the Total Group) at 9 Months of Treatment

| | |
|-----------------|--|
| End point title | Haemo-Quality of Life (QoL) Standardized Total Score (Completed by Parents/Caregivers in the Total Group) at 9 Months of Treatment |
|-----------------|--|

End point description:

QoL was measured by the Haemo-QoL standardized total Score, which ranged from 0 (the best condition) to 100 (the worst condition).

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

End point timeframe:

9 months

| End point values | rFVIII-FS (Kogenate FS, BAY14-2222), 70 IU/kg qw | rFVIII-FS (Kogenate FS, BAY14-2222), biw (30 IU/kg + 40 IU/kg) | rFVIII-FS (Kogenate FS, BAY14-2222), tiw (3 x 25 IU/kg) | |
|--------------------------------------|---|--|---|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 3 ^[5] | 10 ^[6] | 7 ^[7] | |
| Units: Scores on a scale | | | | |
| arithmetic mean (standard deviation) | 29.13 (± 17.4) | 28.43 (± 10.27) | 31.38 (± 13.06) | |

Notes:

[5] - Subjects who completed the questionnaire.

[6] - subjects who completed the questionnaire.

[7] - Subjects who completed the questionnaire.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the start of study drug administration until the end of study (9 months +/- 2 weeks)

| | |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 13.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|--|
| Reporting group title | rFVIII-FS (Kogenate FS, BAY14-2222), 70 IU/kg qw |
|-----------------------|--|

Reporting group description:

rFVIII-FS (Octocog-alfa, antihemophilic factor [recombinant]) 70 IU/kg, dosing by injection once per week [qw] (weekly on Day 7 + 1 after previous injection) for 9 months. Dose escalation was permitted due to joint bleeding (escalation to 35 IU/kg twice a week or further escalation to 25 IU/kg three times a week).

| | |
|-----------------------|--|
| Reporting group title | rFVIII-FS (Kogenate FS, BAY14-2222), biw (30 IU/kg + 40 IU/kg) |
|-----------------------|--|

Reporting group description:

rFVIII-FS (Octocog-alfa, antihemophilic factor [recombinant]) 70 IU/kg, dosing by injection twice per week [biw] (30 IU/kg [day 1] + 40 IU/kg [day 4]) for 9 months. Dose escalation was permitted due to joint bleeding (escalation to 25 IU/kg three times a week).

| | |
|-----------------------|---|
| Reporting group title | rFVIII-FS (Kogenate FS, BAY14-2222), tiw (3 x 25 IU/kg) |
|-----------------------|---|

Reporting group description:

rFVIII-FS (Octocog-alfa, antihemophilic factor [recombinant]) 75 IU/kg, dosing by injection three times per week [tiw] (3 x 25 IU/kg [day 1, 3, 5]) for 9 months. No escalation opportunity for subjects in this group.

| Serious adverse events | rFVIII-FS (Kogenate FS, BAY14-2222), 70 IU/kg qw | rFVIII-FS (Kogenate FS, BAY14-2222), biw (30 IU/kg + 40 IU/kg) | rFVIII-FS (Kogenate FS, BAY14-2222), tiw (3 x 25 IU/kg) |
|---|--|--|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 2 / 13 (15.38%) | 0 / 8 (0.00%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Blood and lymphatic system disorders | | | |
| FACTOR VIII INHIBITION | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 13 (0.00%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| ABDOMINAL PAIN | | | |

| | | | |
|---|----------------|----------------|---------------|
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 13 (7.69%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| VOMITING | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 13 (7.69%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| EAR INFECTION | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 13 (7.69%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| RESPIRATORY TRACT INFECTION VIRAL | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 13 (7.69%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

Frequency threshold for reporting non-serious adverse events: 0 %

| Non-serious adverse events | rFVIII-FS (Kogenate FS, BAY14-2222), 70 IU/kg qw | rFVIII-FS (Kogenate FS, BAY14-2222), biw (30 IU/kg + 40 IU/kg) | rFVIII-FS (Kogenate FS, BAY14-2222), tiw (3 x 25 IU/kg) |
|--|--|--|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 4 / 11 (36.36%) | 3 / 13 (23.08%) | 3 / 8 (37.50%) |
| Injury, poisoning and procedural complications | | | |
| LOWER LIMB FRACTURE | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 13 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Blood and lymphatic system disorders | | | |
| IRON DEFICIENCY ANAEMIA | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 13 (0.00%) | 1 / 8 (12.50%) |
| occurrences (all) | 0 | 0 | 1 |
| General disorders and administration site conditions | | | |
| CHILLS | | | |

| | | | |
|---|---------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 1 / 13 (7.69%) 1 | 1 / 8 (12.50%) 1 |
| PYREXIA subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 0 / 13 (0.00%) 0 | 1 / 8 (12.50%) 4 |
| Respiratory, thoracic and mediastinal disorders EPISTAXIS subjects affected / exposed occurrences (all) | 1 / 11 (9.09%) 2 | 0 / 13 (0.00%) 0 | 0 / 8 (0.00%) 0 |
| LARYNGOSPASM subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 1 / 13 (7.69%) 1 | 0 / 8 (0.00%) 0 |
| RESPIRATORY DISORDER subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 1 / 13 (7.69%) 1 | 0 / 8 (0.00%) 0 |
| Skin and subcutaneous tissue disorders DERMATITIS ALLERGIC subjects affected / exposed occurrences (all) | 1 / 11 (9.09%) 1 | 0 / 13 (0.00%) 0 | 0 / 8 (0.00%) 0 |
| Infections and infestations ADENOIDITIS subjects affected / exposed occurrences (all) | 1 / 11 (9.09%) 1 | 0 / 13 (0.00%) 0 | 0 / 8 (0.00%) 0 |
| RESPIRATORY TRACT INFECTION VIRAL subjects affected / exposed occurrences (all) | 1 / 11 (9.09%) 1 | 0 / 13 (0.00%) 0 | 1 / 8 (12.50%) 1 |
| TONSILLITIS subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 0 / 13 (0.00%) 0 | 1 / 8 (12.50%) 1 |
| TUBERCULOSIS subjects affected / exposed occurrences (all) | 1 / 11 (9.09%) 1 | 0 / 13 (0.00%) 0 | 0 / 8 (0.00%) 0 |
| VARICELLA subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 0 / 13 (0.00%) 0 | 1 / 8 (12.50%) 1 |
| YERSINIA INFECTION | | | |

| | | | |
|-----------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 13 (0.00%) | 1 / 8 (12.50%) |
| occurrences (all) | 0 | 0 | 1 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|--|
| 12 December 2006 | Modification of the study design from a single-center study into a multicenter study with 3 study centers. 1. The number of subjects to be enrolled was increased from 20 to 40. 2. The planned enrolment period was extended from 3 months to 8 months. 3. An additional vial size containing 1000 IU FVIII/milliliter was introduced. 4. It was specified that the sterile water for injection was provided in a prefilled syringe in the treatment kit. |
| 22 September 2008 | 1. The number of study centers was increased from 3 to 6. 2. The number of subjects to be enrolled was reduced from 40 to 36 in order to balance the sizes of the 3 treatment groups (12 per treatment group). |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Protocol deviations were not excluded: For example, a previously untreated subject developed the transitory inhibitor; change to a higher group did not always occur according protocol; there was temporary lack of smaller vial sizes at the centers.

Notes: