



## Clinical trial results:

**Randomized, controlled, parallel, prospective trial to evaluate the effect of secondary prophylaxis with rFVIII therapy in severe hemophilia A adult and/or adolescent subjects, as applicable, compared to that of episodic treatment (SPINART)**

### Summary

|                          |                  |
|--------------------------|------------------|
| EudraCT number           | 2008-000985-21   |
| Trial protocol           | BG               |
| Global end of trial date | 22 November 2013 |

### Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1           |
| This version publication date  | 12 July 2016 |
| First version publication date | 03 May 2015  |

### Trial information

#### Trial identification

|                       |                  |
|-----------------------|------------------|
| Sponsor protocol code | BAY14-2222/12800 |
|-----------------------|------------------|

#### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT00623480 |
| WHO universal trial number (UTN)   | -           |

Notes:

### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Bayer HealthCare AG   |
| Sponsor organisation address | Kaiser-Wilhelm-Allee, Leverkusen, Germany, D-51368                                      |
| Public contact               | Therapeutic Area Head, Bayer HealthCare AG, clinical-trials-contact@bayerhealthcare.com |
| Scientific contact           | Therapeutic Area Head, Bayer HealthCare AG, clinical-trials-contact@bayerhealthcare.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                       | 22 November 2013 |
| Is this the analysis of the primary completion data? | No               |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 22 November 2013 |
| Was the trial ended prematurely?                     | No               |

Notes:

## General information about the trial

Main objective of the trial:

To evaluate the effect of secondary prophylaxis on bleeding frequency (number of all bleeds per year) compared to on-demand (episodic) treatment.

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. Only after the subject voluntarily signed the informed consent form was he able to enter the study. In case of participation of adolescent subjects (12-17 years, in applicable countries), parents/legal representatives were informed first and upon their agreement, the information was presented to the subject. If the subject agreed, the formal consent was collected from parents/legal representatives and the subject.

Background therapy: -

Evidence for comparator: -

|   |               |
|---|---------------|
| Actual start date of recruitment                          | 27 March 2008 |
| Long term follow-up planned                               | Yes           |
| Long term follow-up rationale                             | Safety        |
| Long term follow-up duration                              | 1 Months      |
| Independent data monitoring committee (IDMC) involvement? | Yes           |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                   |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | Bulgaria: 31      |
| Country: Number of subjects enrolled | Romania: 14       |
| Country: Number of subjects enrolled | United States: 54 |
| Country: Number of subjects enrolled | Argentina: 7      |
| Worldwide total number of subjects   | 106               |
| EEA total number of subjects         | 45                |

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          | 0 |

|                           |     |
|---------------------------|-----|
| months)                   |     |
| Children (2-11 years)     | 0   |
| Adolescents (12-17 years) | 3   |
| Adults (18-64 years)      | 103 |
| From 65 to 84 years       | 0   |
| 85 years and over         | 0   |

## Subject disposition

### Recruitment

Recruitment details:

The study was conducted between 27 March 2008 (first subject first visit) and 22 November 2013 (last subject last visit) at 31 investigational centers in 4 countries.

### Pre-assignment

Screening details:

Out of a total of 106 screened subjects and 84 subjects were randomized to either prophylaxis treatment with Kogenate formulated with sucrose (FS) or on-demand treatment with Kogenate FS using a 1:1 assignment ratio.

### Period 1

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

### Arms

|                              |   |
|------------------------------|---|
| Are arms mutually exclusive? | Yes   |
| <b>Arm title</b>             | Recombinant Factor VIII Prophylaxis treatment |

Arm description:

Subjects received 25 international units per kilogram (IU/kg) of Recombinant Factor VIII (Kogenate FS, BAY14-2222) intravenously (IV), 3 times per week. Dose escalation steps by 5 IU/kg (to 30 IU/kg or 35 IU/kg maximum) for subjects exhibiting a bleeding frequency of 12 bleeding episodes per year or greater.

|  |                         |
|--|-------------------------|
| Arm type                               | Experimental            |
| Investigational medicinal product name | Recombinant Factor VIII |
| Investigational medicinal product code | BAY14-2222              |
| Other name                             | Kogenate FS             |
| Pharmaceutical forms                   | Injection               |
| Routes of administration               | Intravenous use         |

Dosage and administration details:

Subjects received 25 IU/kg of Recombinant Factor VIII (Kogenate FS, BAY14-2222) IV, 3 times per week. Dose escalation steps by 5 IU/kg (to 30 IU/kg or 35 IU/kg maximum) for subjects exhibiting a bleeding frequency of 12 bleeding episodes per year or greater.

|                  |   |
|------------------|---|
| <b>Arm title</b> | Recombinant Factor VIII On-demand Treatment |
|------------------|---|

Arm description:

Subjects received Recombinant Factor VIII (Kogenate FS, BAY14-2222) IV for bleeds in accordance with package insert instructions and study physician recommendations.

|  |                         |
|--|-------------------------|
| Arm type                               | Experimental            |
| Investigational medicinal product name | Recombinant Factor VIII |
| Investigational medicinal product code | BAY14-2222              |
| Other name                             | Kogenate FS             |
| Pharmaceutical forms                   | Injection               |
| Routes of administration               | Intravenous use         |

Dosage and administration details:

Subjects received Recombinant Factor VIII (Kogenate FS, BAY14-2222) IV for bleeds in accordance with package insert instructions and study physician recommendations.

| <b>Number of subjects in period 1<sup>[1]</sup></b> | Recombinant Factor VIII Prophylaxis treatment | Recombinant Factor VIII On-demand Treatment |
|---|---|---|
| Started   | 42  | 42  |
| Completed   | 35  | 35  |
| Not completed                                       | 7   | 7   |
| Consent withdrawn by subject                        | 2   | 4   |
| Site closed by sponsor                              | -   | 1   |
| Protocol violation                                  | -   | 1   |
| 'Non-compliant with study medication '              | 4   | -   |
| Lost to follow-up                                   | -   | 1   |
| Lack of efficacy                                    | 1   | -   |

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Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: All enrolled subjects were not treated with study drugs. As baseline included only treated subjects, the worldwide number enrolled in the trial differs with the number of subjects reported in the baseline period.

## Baseline characteristics

### Reporting groups

|                       |   |
|-----------------------|---|
| Reporting group title | Recombinant Factor VIII Prophylaxis treatment |
|-----------------------|---|

Reporting group description:

Subjects received 25 international units per kilogram (IU/kg) of Recombinant Factor VIII (Kogenate FS, BAY14-2222) intravenously (IV), 3 times per week. Dose escalation steps by 5 IU/kg (to 30 IU/kg or 35 IU/kg maximum) for subjects exhibiting a bleeding frequency of 12 bleeding episodes per year or greater.

|                       |   |
|-----------------------|---|
| Reporting group title | Recombinant Factor VIII On-demand Treatment |
|-----------------------|---|

Reporting group description:

Subjects received Recombinant Factor VIII (Kogenate FS, BAY14-2222) IV for bleeds in accordance with package insert instructions and study physician recommendations.

| Reporting group values             | Recombinant Factor VIII Prophylaxis treatment | Recombinant Factor VIII On-demand Treatment | Total |
|------------------------------------|---|---|-------|
| Number of subjects                 | 42  | 42  | 84    |
| Age categorical<br>Units: Subjects |   |   |       |

|   |               |               |    |
|---|---------------|---------------|----|
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation | 30.6<br>± 8.8 | 30.7<br>± 9.7 | -  |
| Gender categorical<br>Units: Subjects                                   |               |               |    |
| Male  | 42            | 42            | 84 |

|                                       |  |  |  |
|---------------------------------------|--|--|--|
| Number of subjects with target joints |  |  |  |
|---------------------------------------|--|--|--|

A 'target joint' is a particular joint that has experienced repeated bleeds or at least four bleeds into one joint within a six month period.

|                 |    |    |    |
|-----------------|----|----|----|
| Units: Subjects |    |    |    |
| Yes             | 28 | 31 | 59 |
| No              | 14 | 11 | 25 |

|   |             |               |   |
|---|-------------|---------------|---|
| Number of bleeds during last 6 months<br>Units: Bleeds<br>arithmetic mean<br>standard deviation | 10<br>± 4.4 | 12.2<br>± 5.1 | - |
|---|-------------|---------------|---|

## End points

### End points reporting groups

|   |   |
|---|---|
| Reporting group title   | Recombinant Factor VIII Prophylaxis treatment |
| Reporting group description:<br>Subjects received 25 international units per kilogram (IU/kg) of Recombinant Factor VIII (Kogenate FS, BAY14-2222) intravenously (IV), 3 times per week. Dose escalation steps by 5 IU/kg (to 30 IU/kg or 35 IU/kg maximum) for subjects exhibiting a bleeding frequency of 12 bleeding episodes per year or greater. |   |
| Reporting group title   | Recombinant Factor VIII On-demand Treatment   |
| Reporting group description:<br>Subjects received Recombinant Factor VIII (Kogenate FS, BAY14-2222) IV for bleeds in accordance with package insert instructions and study physician recommendations.   |   |

### Primary: Bleeding Frequency (Number of Total Bleeds)

|   |   |
|---|---|
| End point title   | Bleeding Frequency (Number of Total Bleeds) |
| End point description:  |   |
| End point type  | Primary                                     |
| End point timeframe:<br>After the last enrolled subject has been in the study for 1 year. At the cut-off, the median follow-up duration was 616 days (minimum was 111 days and maximum was 1109 days) |   |

| End point values              | Recombinant Factor VIII Prophylaxis treatment | Recombinant Factor VIII On-demand Treatment |  |  |
|-------------------------------|---|---|--|--|
| Subject group type            | Reporting group                               | Reporting group                             |  |  |
| Number of subjects analysed   | 42 <sup>[1]</sup>                             | 42 <sup>[2]</sup>                           |  |  |
| Units: bleeds                 |   |   |  |  |
| median (full range (min-max)) | 0 (0 to 57)                                   | 54.5 (0 to 149)                             |  |  |

Notes:

[1] - The intent-to-treat (ITT) population included all randomized subjects who received any study drug

[2] - The ITT population included all randomized subjects who received any study drug

### Statistical analyses

|   |   |
|---|---|
| Statistical analysis title              | Statistical analysis 1  |
| Comparison groups                       | Recombinant Factor VIII On-demand Treatment v Recombinant Factor VIII Prophylaxis treatment |
| Number of subjects included in analysis | 84  |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | superiority   |
| P-value                                 | < 0.0001 <sup>[3]</sup>   |
| Method                                  | Negative Binomial Regression Model  |
| Parameter estimate                      | Ratio   |
| Point estimate                          | 14.7  |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | 8.1     |
| upper limit         | 26.5    |

Notes:

[3] - Adjusted for time of follow-up.

## Secondary: Change From Baseline to 3 Years in the MRI (Magnetic Resonance Imaging) Scale

|                 |   |
|-----------------|---|
| End point title | Change From Baseline to 3 Years in the MRI (Magnetic Resonance Imaging) Scale |
|-----------------|---|

End point description:

The Extended MRI Scale total score had a range between 0 (normal unaffected joint) to 45 (maximal joint damage) points. It was composed of 2 domains, the soft tissue domain with a maximum of 9 points and the osteochondral domain with a maximum of 36 points. A single score for each subject was to be calculated from the sum of both domains and the average over all joints for the Extended MRI endpoint. Higher MRI score denotes greater joint structure damage thus a positive change from baseline means worsening.

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

End point timeframe:

Baseline and 3 years

| End point values                             | Recombinant Factor VIII Prophylaxis treatment | Recombinant Factor VIII On-demand Treatment |  |  |
|--|---|---|--|--|
| Subject group type                           | Reporting group                               | Reporting group                             |  |  |
| Number of subjects analysed                  | 41 <sup>[4]</sup>                             | 38 <sup>[5]</sup>                           |  |  |
| Units: scores on a scale                     |   |   |  |  |
| least squares mean (confidence interval 95%) | 0.79 (0.27 to 1.32)                           | 0.96 (0.34 to 1.58)                         |  |  |

Notes:

[4] - Full analysis set (FAS): all randomized subjects who had a baseline and/or post-baseline measurement

[5] - FAS: all randomized subjects who had a baseline and/or post-baseline measurement

## Statistical analyses

|   |   |
|---|---|
| Statistical analysis title              | Statistical analysis 1  |
| Comparison groups                       | Recombinant Factor VIII Prophylaxis treatment v Recombinant Factor VIII On-demand Treatment |
| Number of subjects included in analysis | 79  |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | superiority   |
| P-value                                 | = 0.6614 <sup>[6]</sup>   |
| Method                                  | cLDA model  |
| Parameter estimate                      | Estimated difference  |
| Point estimate                          | -0.17   |



|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | -0.92   |
| upper limit         | 0.59    |

Notes:

[6] - Adjusted for presence/absence of target joint and prior 6 month bleeding frequency

## Secondary: Change From Baseline to 3 Years in the Colorado Adult Joint Assessment Scale (CAJAS)

|                 |  |
|-----------------|--|
| End point title | Change From Baseline to 3 Years in the Colorado Adult Joint Assessment Scale (CAJAS) |
|-----------------|--|

End point description:

The total joint score was derived for each of six joints: left and right sides for knees (score: 0-25), ankles (score: 0-25), and elbows (score: 0-21). Higher CAJAS score denotes greater joint structure damage thus a positive change from baseline means worsening. CAJAS total score is the sum of all 6 joints, ranging from 0 (best possible outcome) to 142 (worst possible outcome).

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

End point timeframe:

Baseline and 3 years

| End point values                             | Recombinant Factor VIII Prophylaxis treatment | Recombinant Factor VIII On-demand Treatment |  |  |
|--|---|---|--|--|
| Subject group type                           | Reporting group                               | Reporting group                             |  |  |
| Number of subjects analysed                  | 42 <sup>[7]</sup>                             | 42 <sup>[8]</sup>                           |  |  |
| Units: scores on a scale                     |   |   |  |  |
| least squares mean (confidence interval 95%) | -0.31 (-0.79 to 0.18)                         | 0.63 (0.08 to 1.18)                         |  |  |

Notes:

[7] - FAS: all randomized subjects who had a baseline and/or post-baseline measurement

[8] - FAS: all randomized subjects who had a baseline and/or post-baseline measurement

## Statistical analyses

|   |   |
|---|---|
| Statistical analysis title              | Statistical analysis 1  |
| Comparison groups                       | Recombinant Factor VIII Prophylaxis treatment v Recombinant Factor VIII On-demand Treatment |
| Number of subjects included in analysis | 84  |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | superiority   |
| P-value                                 | = 0.0072 <sup>[9]</sup>   |
| Method                                  | cLDA model  |
| Parameter estimate                      | Estimated difference  |
| Point estimate                          | -0.94   |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | -1.61   |
| upper limit                             | -0.26   |

Notes:

[9] - Adjusted for presence/absence of target joint and prior 6 month bleeding frequency.

### **Other pre-specified: Change From Baseline to 3 Years in the Physical Functioning Domain of the Haemo-Quality of Life (QoL)-A**

|   |   |
|---|---|
| End point title   | Change From Baseline to 3 Years in the Physical Functioning Domain of the Haemo-Quality of Life (QoL)-A |
| End point description:<br>The Haemo-QoL-A total score as well as each of its domains have a range between 0 (worst QoL) and 100 (best QoL) points. Therefore, a higher Haemo-QoL-A score denotes greater QoL. |   |
| End point type  | Other pre-specified   |
| End point timeframe:<br>Baseline and 3 years  |   |

| <b>End point values</b>                      | Recombinant Factor VIII Prophylaxis treatment | Recombinant Factor VIII On-demand Treatment |  |  |
|--|---|---|--|--|
| Subject group type                           | Reporting group                               | Reporting group                             |  |  |
| Number of subjects analysed                  | 41 <sup>[10]</sup>                            | 42 <sup>[11]</sup>                          |  |  |
| Units: scores on a scale                     |   |   |  |  |
| least squares mean (confidence interval 95%) | 7.86 (1.79 to 13.92)                          | -5.3 (-11.97 to 1.37)                       |  |  |

Notes:

[10] - FAS: all randomized subjects who had a baseline and/or post-baseline measurement

[11] - FAS: all randomized subjects who had a baseline and/or post-baseline measurement

### **Statistical analyses**

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Statistical analysis 1  |
| Comparison groups                       | Recombinant Factor VIII Prophylaxis treatment v Recombinant Factor VIII On-demand Treatment |
| Number of subjects included in analysis | 83  |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | superiority   |
| Method                                  | cLDA model  |
| Parameter estimate                      | Estimated difference  |
| Point estimate                          | 13.15   |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | 5.23  |
| upper limit                             | 21.08   |

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From randomization until Month 37

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 16.1 |
|--------------------|------|

### Reporting groups

|                       |   |
|-----------------------|---|
| Reporting group title | Recombinant Factor VIII Prophylaxis treatment |
|-----------------------|---|

Reporting group description:

Subjects received 25 international units per kilogram (IU/kg) of Recombinant Factor VIII (Kogenate FS, BAY14-2222) intravenously (IV), 3 times per week. Dose escalation steps by 5 IU/kg (to 30 IU/kg or 35 IU/kg maximum) for subjects exhibiting a bleeding frequency of 12 bleeding episodes per year or greater.

|                       |   |
|-----------------------|---|
| Reporting group title | Recombinant Factor VIII On-demand Treatment |
|-----------------------|---|

Reporting group description:

Subjects received Recombinant Factor VIII (Kogenate FS, BAY14-2222) IV for bleeds in accordance with package insert instructions and study physician recommendations.

| Serious adverse events                            | Recombinant Factor VIII Prophylaxis treatment | Recombinant Factor VIII On-demand Treatment |  |
|---|---|---|--|
| Total subjects affected by serious adverse events |   |   |  |
| subjects affected / exposed                       | 9 / 42 (21.43%)                               | 10 / 42 (23.81%)                            |  |
| number of deaths (all causes)                     | 0   | 0   |  |
| number of deaths resulting from adverse events    | 0   | 0   |  |
| Injury, poisoning and procedural complications    |   |   |  |
| Humerus fracture                                  |   |   |  |
| subjects affected / exposed                       | 0 / 42 (0.00%)                                | 1 / 42 (2.38%)                              |  |
| occurrences causally related to treatment / all   | 0 / 0   | 1 / 1                                       |  |
| deaths causally related to treatment / all        | 0 / 0   | 0 / 0                                       |  |
| Meniscus injury                                   |   |   |  |
| subjects affected / exposed                       | 1 / 42 (2.38%)                                | 0 / 42 (0.00%)                              |  |
| occurrences causally related to treatment / all   | 1 / 1   | 0 / 0                                       |  |
| deaths causally related to treatment / all        | 0 / 0   | 0 / 0                                       |  |
| Stab wound  |   |   |  |
| subjects affected / exposed                       | 0 / 42 (0.00%)                                | 1 / 42 (2.38%)                              |  |
| occurrences causally related to treatment / all   | 0 / 0   | 1 / 1                                       |  |
| deaths causally related to treatment / all        | 0 / 0   | 0 / 0                                       |  |

|   |                |                |  |
|---|----------------|----------------|--|
| Tibia fracture                                  |                |                |  |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 1 / 42 (2.38%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Congenital, familial and genetic disorders      |                |                |  |
| Phimosis  |                |                |  |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 1 / 42 (2.38%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Vascular disorders                              |                |                |  |
| Haematoma                                       |                |                |  |
| subjects affected / exposed                     | 1 / 42 (2.38%) | 0 / 42 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Nervous system disorders                        |                |                |  |
| Migraine  |                |                |  |
| subjects affected / exposed                     | 1 / 42 (2.38%) | 0 / 42 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Blood and lymphatic system disorders            |                |                |  |
| Anaemia   |                |                |  |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 1 / 42 (2.38%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Gastrointestinal disorders                      |                |                |  |
| Peritoneal haemorrhage                          |                |                |  |
| subjects affected / exposed                     | 1 / 42 (2.38%) | 0 / 42 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Retroperitoneal haematoma                       |                |                |  |
| subjects affected / exposed                     | 1 / 42 (2.38%) | 0 / 42 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Tooth impacted                                  |                |                |  |

|   |                |                |  |
|---|----------------|----------------|--|
| subjects affected / exposed                     | 1 / 42 (2.38%) | 0 / 42 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Reproductive system and breast disorders        |                |                |  |
| Balanitis                                       |                |                |  |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 1 / 42 (2.38%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Psychiatric disorders                           |                |                |  |
| Suicidal ideation                               |                |                |  |
| subjects affected / exposed                     | 1 / 42 (2.38%) | 0 / 42 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Musculoskeletal and connective tissue disorders |                |                |  |
| Haemarthrosis                                   |                |                |  |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 2 / 42 (4.76%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 2 / 2          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Joint contracture                               |                |                |  |
| subjects affected / exposed                     | 1 / 42 (2.38%) | 0 / 42 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Joint lock                                      |                |                |  |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 1 / 42 (2.38%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Joint range of motion decreased                 |                |                |  |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 1 / 42 (2.38%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Muscle haemorrhage                              |                |                |  |

|   |                |                |  |
|---|----------------|----------------|--|
| subjects affected / exposed                     | 0 / 42 (0.00%) | 1 / 42 (2.38%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Osteoarthritis                                  |                |                |  |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 1 / 42 (2.38%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Infections and infestations                     |                |                |  |
| Appendicitis                                    |                |                |  |
| subjects affected / exposed                     | 2 / 42 (4.76%) | 1 / 42 (2.38%) |  |
| occurrences causally related to treatment / all | 2 / 2          | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Device related infection                        |                |                |  |
| subjects affected / exposed                     | 1 / 42 (2.38%) | 0 / 42 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Peritonsillar abscess                           |                |                |  |
| subjects affected / exposed                     | 1 / 42 (2.38%) | 0 / 42 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Pilonidal cyst                                  |                |                |  |
| subjects affected / exposed                     | 1 / 42 (2.38%) | 0 / 42 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Metabolism and nutrition disorders              |                |                |  |
| Dehydration                                     |                |                |  |
| subjects affected / exposed                     | 0 / 42 (0.00%) | 1 / 42 (2.38%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |

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

| <b>Non-serious adverse events</b>   | Recombinant Factor VIII Prophylaxis treatment                             | Recombinant Factor VIII On-demand Treatment                               |  |
|---|---|---|--|
| Total subjects affected by non-serious adverse events<br>subjects affected / exposed  | 13 / 42 (30.95%)  | 27 / 42 (64.29%)  |  |
| Vascular disorders<br>Hypertension<br>subjects affected / exposed<br>occurrences (all)  | 0 / 42 (0.00%)<br>0   | 3 / 42 (7.14%)<br>3   |  |
| Nervous system disorders<br>Headache<br>subjects affected / exposed<br>occurrences (all)  | 2 / 42 (4.76%)<br>2   | 7 / 42 (16.67%)<br>12   |  |
| General disorders and administration site conditions<br>Pyrexia<br>subjects affected / exposed<br>occurrences (all)   | 1 / 42 (2.38%)<br>2   | 5 / 42 (11.90%)<br>6  |  |
| Gastrointestinal disorders<br>Dental caries<br>subjects affected / exposed<br>occurrences (all)<br><br>Toothache<br>subjects affected / exposed<br>occurrences (all)<br><br>Dyspepsia<br>subjects affected / exposed<br>occurrences (all) | 0 / 42 (0.00%)<br>0<br><br>3 / 42 (7.14%)<br>3<br><br>0 / 42 (0.00%)<br>0 | 4 / 42 (9.52%)<br>4<br><br>2 / 42 (4.76%)<br>3<br><br>3 / 42 (7.14%)<br>3 |  |
| Respiratory, thoracic and mediastinal disorders<br>Cough<br>subjects affected / exposed<br>occurrences (all)  | 0 / 42 (0.00%)<br>0   | 3 / 42 (7.14%)<br>3   |  |
| Musculoskeletal and connective tissue disorders<br>Arthralgia<br>subjects affected / exposed<br>occurrences (all)<br><br>Back pain<br>subjects affected / exposed<br>occurrences (all)  | 5 / 42 (11.90%)<br>7<br><br>1 / 42 (2.38%)<br>1                           | 5 / 42 (11.90%)<br>5<br><br>4 / 42 (9.52%)<br>5                           |  |

|   |                     |                       |  |
|---|---------------------|-----------------------|--|
| Myalgia<br>subjects affected / exposed<br>occurrences (all)                           | 3 / 42 (7.14%)<br>3 | 1 / 42 (2.38%)<br>1   |  |
| Infections and infestations   |                     |                       |  |
| Influenza<br>subjects affected / exposed<br>occurrences (all)                         | 2 / 42 (4.76%)<br>2 | 7 / 42 (16.67%)<br>7  |  |
| Pharyngitis<br>subjects affected / exposed<br>occurrences (all)                       | 0 / 42 (0.00%)<br>0 | 4 / 42 (9.52%)<br>5   |  |
| Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)                   | 2 / 42 (4.76%)<br>2 | 9 / 42 (21.43%)<br>10 |  |
| Upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all) | 2 / 42 (4.76%)<br>2 | 3 / 42 (7.14%)<br>4   |  |
| Metabolism and nutrition disorders  |                     |                       |  |
| Vitamin D deficiency<br>subjects affected / exposed<br>occurrences (all)              | 0 / 42 (0.00%)<br>0 | 3 / 42 (7.14%)<br>3   |  |



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date              | Amendment  |
|-------------------|--|
| 30 September 2008 | Age listed on inclusion criteria changed from 25-50 to 20-50 years. Requirements for some study procedures were clarified, including joint assessment and timing of MRIs.  |
| 09 January 2009   | Added countries and increased the number of investigational centers. Exclusion criteria for poor joint status was clarified. Data Monitoring Committee description was added.  |
| 05 November 2009  | Allowed for changes in Inclusion/Exclusion criteria: subjects were included who experienced more frequent bleeding events, more severe joint damage, as well as the existence of a single transient FVIII inhibitor more than 10 years prior to enrollment into the trial. Maximum limit of 12 subjects per site was removed. Elimination of the dose adjustment for subjects with a body mass index of greater than 30 in order to prevent suboptimal dosing resulting in a trough level that may fall below the target level of 1 percent for effective prophylaxis of spontaneous bleeding. Elimination of the requirement of a follow-up MRI for those subjects who discontinued the study prior to 18 months from the time of their enrollment. |
| 22 November 2011  | Changes in the primary and secondary objectives and inclusion and exclusion criteria. Requirement of recruitment limit per site was removed. Details of assessments were revised and endpoints were clarified. Elimination of the requirement of a follow-up MRI for those subjects who discontinued the study prior to 18 months from the time of their enrollment. Quality of life measurements were updated. Two new instruments for assessments of hypersensitivity and lack of drug effect were added.  |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported