



## Clinical trial results:

### **ADVATE Antihemophilic Factor (Recombinant), Plasma/Albumin-Free Method (ADVATE rAHF-PFM): A Phase 4 Study Comparing Two Prophylactic Regimens In Subjects With Severe Or Moderately Severe Hemophilia A**

Due to the EudraCT – Results system being out of service between 31 July 2015 and 12 January 2016, these results have been published in compliance with revised timelines.

#### **Summary**

|                          |                   |
|--------------------------|-------------------|
| EudraCT number           | 2005-000347-29    |
| Trial protocol           | GB AT HU CZ SI IT |
| Global end of trial date | 16 June 2010      |

#### **Results information**

|                                |               |
|--------------------------------|---------------|
| Result version number          | v1 (current)  |
| This version publication date  | 05 March 2016 |
| First version publication date | 05 March 2016 |

#### **Trial information**

##### **Trial identification**

|                       |        |
|-----------------------|--------|
| Sponsor protocol code | 060201 |
|-----------------------|--------|

##### **Additional study identifiers**

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT00243386 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### **Sponsors**

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Baxalta Innovations GmbH   |
| Sponsor organisation address | Industriestrasse 67, Vienna, Austria, 1221   |
| Public contact               | Clinical Trial Registries and Results Disclosure, Baxalta Innovations GmbH, ClinicalTrialsDisclosure@baxalta.com |
| Scientific contact           | Clinical Trial Registries and Results Disclosure, Baxalta Innovations GmbH, ClinicalTrialsDisclosure@baxalta.com |
| Sponsor organisation name    | Baxalta US Inc.  |
| Sponsor organisation address | One Baxter Way, Westlake Village, United States, CA 91362  |
| Public contact               | Clinical Trial Registries and Results Disclosure, Baxalta US Inc., ClinicalTrialsDisclosure@baxalta.com          |
| Scientific contact           | Clinical Trial Registries and Results Disclosure, Baxalta US Inc., ClinicalTrialsDisclosure@baxalta.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? | Yes |

|  |    |
|--|----|
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
|--|----|

Notes:

## Results analysis stage

|  |              |
|--|--------------|
| Analysis stage                                       | Final        |
| Date of interim/final analysis                       | 16 June 2010 |
| Is this the analysis of the primary completion data? | No           |

|                                  |              |
|----------------------------------|--------------|
| Global end of trial reached?     | Yes          |
| Global end of trial date         | 16 June 2010 |
| Was the trial ended prematurely? | No           |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of this study was to compare the rates of bleeding episodes between a standard prophylaxis regimen (20 to 40 IU/kg every  $48 \pm 6$  hours) and a pharmacokinetics (PK)-driven prophylaxis regimen (20 to 80 IU/kg every  $72 \pm 6$  hours).

Protection of trial subjects:

This study was conducted in accordance with the standards of Good Clinical Practice (GCP) in effect at the time of the study.

Background therapy: -

Evidence for comparator: -

|   |                 |
|---|-----------------|
| Actual start date of recruitment                          | 04 January 2006 |
| Long term follow-up planned                               | No              |
| Independent data monitoring committee (IDMC) involvement? | Yes             |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                       |
|--------------------------------------|-----------------------|
| Country: Number of subjects enrolled | Austria: 1            |
| Country: Number of subjects enrolled | Czech Republic: 6     |
| Country: Number of subjects enrolled | Greece: 2             |
| Country: Number of subjects enrolled | Hungary: 9            |
| Country: Number of subjects enrolled | Italy: 4              |
| Country: Number of subjects enrolled | Poland: 26            |
| Country: Number of subjects enrolled | Russian Federation: 8 |
| Country: Number of subjects enrolled | Slovenia: 1           |
| Country: Number of subjects enrolled | United Kingdom: 2     |
| Country: Number of subjects enrolled | United States: 23     |
| Worldwide total number of subjects   | 82                    |
| EEA total number of subjects         | 51                    |

Notes:

| <b>Subjects enrolled per age group</b>    |    |
|---|----|
| 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)                     | 5  |
| Adolescents (12-17 years)                 | 8  |
| Adults (18-64 years)                      | 69 |
| From 65 to 84 years                       | 0  |
| 85 years and over                         | 0  |

## Subject disposition

### Recruitment

Recruitment details:

Subjects were enrolled (signed informed consent) at 21 European and 9 United States clinical sites beginning January 2006 and completing in June 2010

### Pre-assignment

Screening details:

82 subjects were enrolled and screened. 7 were screen failures, 1 was withdrawn for non-compliance, and 1 requested withdrawal. Therefore, 73 of the 82 enrolled were treated with investigational product (rAFH-PFM).

### Pre-assignment period milestones

|                              |    |
|------------------------------|----|
| Number of subjects started   | 82 |
| Number of subjects completed | 73 |

### Pre-assignment subject non-completion reasons

|                            |                                 |
|----------------------------|---------------------------------|
| Reason: Number of subjects | Consent withdrawn by subject: 1 |
| Reason: Number of subjects | Screen Failure: 7               |
| Reason: Number of subjects | Withdrawn for non compliance: 1 |

### Period 1

|                              |  |
|------------------------------|--|
| Period 1 title               | Overall study (Parts 1 and 2) (overall period) |
| Is this the baseline period? | Yes  |
| Allocation method            | Randomised - controlled                        |
| Blinding used                | Not blinded                                    |

Blinding implementation details:

This open-label study had 2 parts

Part 1: Subjects underwent PK evaluation for 48 hours followed by on-demand treatment with rAFH-PFM for 6 months

Part 2: Subjects were randomized either to standard prophylaxis or PK-driven prophylaxis (both with rAFH-PFM) for 12 months.

Randomization in part 2 stratified based on presence of target joints [joint in which at least 4 bleeds occurred within 6 months or > 20 lifetime bleeds (0 target joints; 1-2 target joints;  $\geq$  target joints) to reduce bias

### Arms

|                              |              |
|------------------------------|--------------|
| Are arms mutually exclusive? | No           |
| Arm title                    | All subjects |

Arm description:

All subjects who were exposed to investigational product (rAHF-PFM).

|  |  |
|--|--|
| Arm type                               | Experimental                                 |
| Investigational medicinal product name | ADVATE                                       |
| Investigational medicinal product code | rAHF-PFM                                     |
| Other name                             |  |
| Pharmaceutical forms                   | Powder and solvent for solution for infusion |
| Routes of administration               | Intravenous use                              |

Dosage and administration details:

Standard Prophylaxis - 20-40 IU/kg every 48 $\pm$ 6h; PK-driven Prophylaxis 20-80 IU/kg (determined by PK results) every 72 $\pm$ 6h; On-demand - 10-100 IU/kg - dose and frequency dependent on severity and location of bleed

|  |  |
|--|--|
| <b>Arm title</b>   | On-Demand                                    |
| Arm description:   |  |
| On-demand regimen - rAHF-PFM was to be used for the treatment of bleeding episodes according to the severity and type of episode by the protocol-recommended dosing until the episode resolved: superficial (10-20 IU/kg every 12-14 hours), minor joint (20-40 IU/kg every 12-14 hours), deep muscle (30-60 IU/kg every 12-14 hours), major joint or life-threatening (60-100 IU/kg every 8-12 hours), genitourinary, GI, and intracranial (60-100 IU/kg every 8-12 hours). |  |
| Arm type   | Experimental                                 |
| Investigational medicinal product name   | ADVATE                                       |
| Investigational medicinal product code   | rAHF-PFM                                     |
| Other name   |  |
| Pharmaceutical forms   | Powder and solvent for solution for infusion |
| Routes of administration   | Intravenous use                              |
| Dosage and administration details:   |  |
| Standard Prophylaxis - 20-40 IU/kg every 48±6h; PK-driven Prophylaxis 20-80 IU/kg (determined by PK results) every 72±6h; On-demand - 10-100 IU/kg - dose and frequency dependent on severity and location of bleed  |  |
| <b>Arm title</b>   | Standard Prophylaxis                         |
| Arm description:   |  |
| Standard prophylaxis regimen - subjects dosed at 20-40 IU/kg of rAHF-PFM every 48 ± 6 hours, exact regimen to be determined by the investigator.   |  |
| Arm type   | Experimental                                 |
| Investigational medicinal product name   | ADVATE                                       |
| Investigational medicinal product code   | rAHF-PFM                                     |
| Other name   |  |
| Pharmaceutical forms   | Powder and solvent for solution for infusion |
| Routes of administration   | Intravenous use                              |
| Dosage and administration details:   |  |
| Standard Prophylaxis - 20-40 IU/kg every 48±6h; PK-driven Prophylaxis 20-80 IU/kg (determined by PK results) every 72±6h; On-demand - 10-100 IU/kg - dose and frequency dependent on severity and location of bleed  |  |
| <b>Arm title</b>   | PK-Driven Prophylaxis                        |
| Arm description:   |  |
| Pharmacokinetic (PK)-Driven prophylaxis regimen - subjects dosed at 20-80 IU/kg of rAHF-PFM every 72 ± 6 hours, exact regimen to be determined by the sponsor.   |  |
| Arm type   | Experimental                                 |
| Investigational medicinal product name   | ADVATE                                       |
| Investigational medicinal product code   | rAHF-PFM                                     |
| Other name   |  |
| Pharmaceutical forms   | Powder and solvent for solution for infusion |
| Routes of administration   | Intravenous use                              |
| Dosage and administration details:   |  |
| Standard Prophylaxis - 20-40 IU/kg every 48±6h; PK-driven Prophylaxis 20-80 IU/kg (determined by PK results) every 72±6h; On-demand - 10-100 IU/kg - dose and frequency dependent on severity and location of bleed  |  |
| <b>Arm title</b>   | Any Prophylaxis                              |
| Arm description:   |  |
| Standard Prophylaxis: 20-40 IU/kg of rAHF-PFM every 48 ± 6 hours, exact regimen to be determined by the investigator.  |  |
| PK-Driven Prophylaxis: 20-80 IU/kg of rAHF-PFM every 72 ± 6 hours, exact regimen to be determined by the sponsor   |  |
| Arm type   | Experimental                                 |

|  |  |
|--|--|
| Investigational medicinal product name | ADVATE                                       |
| Investigational medicinal product code | rAHF-PFM                                     |
| Other name                             |  |
| Pharmaceutical forms                   | Powder and solvent for solution for infusion |
| Routes of administration               | Intravenous use                              |

Dosage and administration details:

Standard Prophylaxis - 20-40 IU/kg every 48±6h; PK-driven Prophylaxis 20-80 IU/kg (determined by PK results) every 72±6h; On-demand - 10-100 IU/kg - dose and frequency dependent on severity and location of bleed

| <b>Number of subjects in period 1</b> | All subjects | On-Demand | Standard Prophylaxis |
|---------------------------------------|--------------|-----------|----------------------|
| Started                               | 73           | 73        | 32                   |
| Completed                             | 63           | 66        | 32                   |
| Not completed                         | 10           | 7         | 0                    |
| Consent withdrawn by subject          | 2            | 2         | -                    |
| Lost to follow-up                     | 2            | 2         | -                    |
| Screen-failure                        | 2            | 2         | -                    |
| Withdrawn for non-compliance          | 3            | 1         | -                    |
| Lack of efficacy                      | 1            | -         | -                    |

| <b>Number of subjects in period 1</b> | PK-Driven Prophylaxis | Any Prophylaxis |
|---------------------------------------|-----------------------|-----------------|
| Started                               | 34                    | 66              |
| Completed                             | 31                    | 63              |
| Not completed                         | 3                     | 3               |
| Consent withdrawn by subject          | -                     | -               |
| Lost to follow-up                     | -                     | -               |
| Screen-failure                        | -                     | -               |
| Withdrawn for non-compliance          | 2                     | 2               |
| Lack of efficacy                      | 1                     | 1               |

## Baseline characteristics

### Reporting groups<sup>[1]</sup>

|                       |                               |
|-----------------------|-------------------------------|
| Reporting group title | Overall study (Parts 1 and 2) |
|-----------------------|-------------------------------|

Reporting group description:

Overall study (Parts 1 and 2)

Notes:

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

Justification: The worldwide number of subjects enrolled only included subjects treated with study product (N=73) as per definition of enrolled in EudraCT (Enrolled=Treated). The number of subjects reported in the baseline period includes all subjects enrolled in the study i.e. signed informed consent (N=82).

| Reporting group values         | Overall study (Parts 1 and 2) | Total |  |
|--------------------------------|-------------------------------|-------|--|
| Number of subjects             | 73                            | 73    |  |
| Age categorical                |                               |       |  |
| Units: Subjects                |                               |       |  |
| Age continuous                 |                               |       |  |
| Age continuous description     |                               |       |  |
| Units: years                   |                               |       |  |
| median                         | 26                            |       |  |
| full range (min-max)           | 7 to 59                       | -     |  |
| Gender categorical             |                               |       |  |
| Gender categorical description |                               |       |  |
| Units: Subjects                |                               |       |  |
| Female                         | 0                             | 0     |  |
| Male                           | 73                            | 73    |  |

## End points

### End points reporting groups

|  |  |
|--|--|
| Reporting group title  | All subjects                           |
| Reporting group description:<br>All subjects who were exposed to investigational product (rAHF-PFM).   |  |
| Reporting group title  | On-Demand                              |
| Reporting group description:<br>On-demand regimen - rAHF-PFM was to be used for the treatment of bleeding episodes according to the severity and type of episode by the protocol-recommended dosing until the episode resolved: superficial (10-20 IU/kg every 12-14 hours), minor joint (20-40 IU/kg every 12-14 hours), deep muscle (30-60 IU/kg every 12-14 hours), major joint or life-threatening (60-100 IU/kg every 8-12 hours), genitourinary, GI, and intracranial (60-100 IU/kg every 8-12 hours).   |  |
| Reporting group title  | Standard Prophylaxis                   |
| Reporting group description:<br>Standard prophylaxis regimen - subjects dosed at 20-40 IU/kg of rAHF-PFM every $48 \pm 6$ hours, exact regimen to be determined by the investigator.   |  |
| Reporting group title  | PK-Driven Prophylaxis                  |
| Reporting group description:<br>Pharmacokinetic (PK)-Driven prophylaxis regimen - subjects dosed at 20-80 IU/kg of rAHF-PFM every $72 \pm 6$ hours, exact regimen to be determined by the sponsor.   |  |
| Reporting group title  | Any Prophylaxis                        |
| Reporting group description:<br>Standard Prophylaxis: 20-40 IU/kg of rAHF-PFM every $48 \pm 6$ hours, exact regimen to be determined by the investigator.<br><br>PK-Driven Prophylaxis: 20-80 IU/kg of rAHF-PFM every $72 \pm 6$ hours, exact regimen to be determined by the sponsor  |  |
| Subject analysis set title   | Subjects $\geq 14$ Years               |
| Subject analysis set type  | Sub-group analysis                     |
| Subject analysis set description:<br>Comprised of subjects $\geq 14$ Years   |  |
| Subject analysis set title   | Subjects $< 14$ Years                  |
| Subject analysis set type  | Sub-group analysis                     |
| Subject analysis set description:<br>Comprised of subjects $< 14$ Years  |  |
| Subject analysis set title   | On-Demand Versus Standard Prophylaxis  |
| Subject analysis set type  | Sub-group analysis                     |
| Subject analysis set description:<br>On-demand: rAHF-PFM was to be used for the treatment of bleeding episodes according to the severity and type of episode by the protocol-recommended dosing until the episode resolved: superficial (10-20 IU/kg every 12-14 hours), minor joint (20-40 IU/kg every 12-14 hours), deep muscle (30-60 IU/kg every 12-14 hours), major joint or life-threatening (60-100 IU/kg every 8-12 hours), genitourinary, Gastrointestinal (GI), and intracranial (60-100 IU/kg every 8-12 hours).<br><br>Standard Prophylaxis: 20-40 IU/kg of rAHF-PFM every $48 \pm 6$ hours, exact regimen to be determined by the investigator. |  |
| Subject analysis set title   | On-Demand Versus PK-Driven Prophylaxis |
| Subject analysis set type  | Sub-group analysis                     |
| Subject analysis set description:<br>On-demand: rAHF-PFM was to be used for the treatment of bleeding episodes according to the severity and type of episode by the protocol-recommended dosing until the episode resolved: superficial (10-20 IU/kg every 12-14 hours), minor joint (20-40 IU/kg every 12-14 hours), deep muscle (30-60 IU/kg every 12-14 hours), major joint or life-threatening (60-100 IU/kg every 8-12 hours), genitourinary, GI, and intracranial (60-100 IU/kg every 8-12 hours).<br><br>PK-driven prophylaxis: 20-80 IU/kg of rAHF-PFM every $72 \pm 6$ hours, exact regimen to be determined  |  |



by the sponsor.

|                            |                                  |
|----------------------------|----------------------------------|
| Subject analysis set title | On-Demand Versus Any Prophylaxis |
| Subject analysis set type  | Sub-group analysis               |

Subject analysis set description:

On-demand: rAHF-PFM was to be used for the treatment of bleeding episodes according to the severity and type of episode by the protocol-recommended dosing until the episode resolved: superficial (10-20 IU/kg every 12-14 hours), minor joint (20-40 IU/kg every 12-14 hours), deep muscle (30-60 IU/kg every 12-14 hours), major joint or life-threatening (60-100 IU/kg every 8-12 hours), genitourinary, GI, and intracranial (60-100 IU/kg every 8-12 hours)

Prophylaxis:

- Standard prophylaxis: 20-40 IU/kg of rAHF-PFM every  $48 \pm 6$  hours, exact regimen to be determined by the investigator
- PK-driven prophylaxis: 20-80 IU/kg of rAHF-PFM every  $72 \pm 6$  hours, exact regimen to be determined by the sponsor

|                            |  |
|----------------------------|--|
| Subject analysis set title | Subjects with SAEs outside of 3 Treatment Arms |
| Subject analysis set type  | Safety analysis                                |

Subject analysis set description:

Subjects with SAEs that occurred after exposure to investigational product, but outside of the on-demand, standard prophylaxis and PK-driven prophylaxis treatment arms.

|                            |                                   |
|----------------------------|-----------------------------------|
| Subject analysis set title | On-Demand to Standard Prophylaxis |
| Subject analysis set type  | Sub-group analysis                |

Subject analysis set description:

Comprised of subjects who completed the on-demand and standard prophylaxis regimens.

|                            |                                    |
|----------------------------|------------------------------------|
| Subject analysis set title | On-Demand to PK-Driven Prophylaxis |
| Subject analysis set type  | Sub-group analysis                 |

Subject analysis set description:

Comprised of subjects who completed the on-demand and PK-driven prophylaxis regimens.

|                            |                              |
|----------------------------|------------------------------|
| Subject analysis set title | On-Demand to Any Prophylaxis |
| Subject analysis set type  | Sub-group analysis           |

Subject analysis set description:

Comprised of subjects who completed the on-demand and any prophylaxis regimens.

|                            |                                    |
|----------------------------|------------------------------------|
| Subject analysis set title | Subjects Assessed Before Treatment |
| Subject analysis set type  | Sub-group analysis                 |

Subject analysis set description:

Subjects assessed before treatment with investigational product (rAFH-PFM).

### **Primary: Mean Transformed Annualized Bleed Rate Estimates From Each of the 1-year Prophylaxis Regimens**

|                 |  |
|-----------------|--|
| End point title | Mean Transformed Annualized Bleed Rate Estimates From Each of the 1-year Prophylaxis Regimens <sup>[1]</sup> |
|-----------------|--|

End point description:

Subjects were randomized to receive 1 of the 2 following prophylaxis regimens (Study Part 2):

1. Standard prophylaxis (20-40 IU/kg (every  $48 \pm 6$  hours), exact regimen determined by investigator)
2. PK-driven prophylaxis (20-80 IU/kg (every  $72 \pm 6$  hours), exact regimen determined by sponsor)

Annualized bleed rates were transformed using the square root of the number of bleeding episodes observed ( $X$  = bleeds/year),  $X' = \sqrt{(X + 0.5)}$ . This transformation was performed to stabilize the variance and align the sample distribution with the assumption of normality inherent in using the t-test.

Population: Subjects in the efficacy per-protocol set comprising of all subjects who completed, according to the protocol, both the on-demand treatment regimen and the randomly assigned prophylactic regimen. Subjects did not have major protocol deviations that would impact the assessment of the primary efficacy endpoint.

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

End point timeframe:

12 months  $\pm$  2 weeks

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Arms in the baseline period are not mutually exclusive. Refer to the description of arms in period 1 (baseline period).

Please also note that it is not currently possible to enter statistics for some endpoints in this study due to limitations of EudraCT.

All statistics are available for these study results in ClinicalTrials.gov (NCT00243386).

| End point values                      | Standard Prophylaxis | PK-Driven Prophylaxis |  |  |
|---------------------------------------|----------------------|-----------------------|--|--|
| Subject group type                    | Reporting group      | Reporting group       |  |  |
| Number of subjects analysed           | 30                   | 23                    |  |  |
| Units: (bleeds/year) <sup>(1/2)</sup> |                      |                       |  |  |
| arithmetic mean (standard deviation)  | 1.46 (± 0.98)        | 1.61 (± 1.1)          |  |  |

## Statistical analyses

| Statistical analysis title  | Statistical Analysis 1                       |
|---|--|
| Statistical analysis description:   |  |
| A t-test was used to compare the means of the transformed data. The null-hypothesis tested was H0: X'A(PK-driven prophylaxis) - X'B (standard prophylaxis) = 0 (i.e., no difference for treatment under the 2 prophylactic regimens. $X' = (ABR + 0.5)^{(1/2)}$ |  |
| Comparison groups   | Standard Prophylaxis v PK-Driven Prophylaxis |
| Number of subjects included in analysis   | 53   |
| Analysis specification  | Pre-specified                                |
| Analysis type   | superiority                                  |
| P-value   | = 0.6016                                     |
| Method  | t-test, 2 sided                              |

## Primary: Median Annualized Bleed Rate Estimates From Each of the 1 Year Prophylaxis Regimens

|                 |  |
|-----------------|--|
| End point title | Median Annualized Bleed Rate Estimates From Each of the 1 Year Prophylaxis Regimens <sup>[2]</sup> |
|-----------------|--|

End point description:

Subjects were randomized to receive 1 of the 2 following prophylaxis regimens (part 2 of the study):

1. Standard prophylaxis- infusions every 48 ±6 hours, dosed at 20 to 40 IU/kg.
2. PK-driven prophylaxis- infusions every 72 ±6 hours dosed at 20 to 80 IU/kg.

Population: Subjects in the efficacy intent-to-treat set comprising of all subjects in the prophylaxis treatment regimen who had at least 1 assessment (1 quarterly visit) or who had withdrawn after 3 bleeding episodes prior to reaching the first assessment period.

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

End point timeframe:

12 months ±2 weeks

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Arms in the baseline period are not mutually exclusive. Refer to the description of arms in period 1 (baseline period).

| End point values              | Standard Prophylaxis | PK-Driven Prophylaxis |  |  |
|-------------------------------|----------------------|-----------------------|--|--|
| Subject group type            | Reporting group      | Reporting group       |  |  |
| Number of subjects analysed   | 32                   | 34                    |  |  |
| Units: Bleeds per year        |                      |                       |  |  |
| median (full range (min-max)) | 1 (0 to 25.87)       | 2.01 (0 to 17.06)     |  |  |

## Statistical analyses

| Statistical analysis title              | Statistical analysis 1                       |
|---|--|
| Comparison groups                       | Standard Prophylaxis v PK-Driven Prophylaxis |
| Number of subjects included in analysis | 66   |
| Analysis specification                  | Pre-specified                                |
| Analysis type                           | superiority                                  |
| P-value                                 | = 0.1467                                     |
| Method                                  | Wilcoxon-Rank Sum (Mann-Whitney)             |
| Confidence interval                     |  |
| level                                   | 95 %   |

## Secondary: Mean Difference of Transformed Annualized Bleeding Rate Between On-Demand and Standard Prophylaxis Treatment Regimens

|                 |   |
|-----------------|---|
| End point title | Mean Difference of Transformed Annualized Bleeding Rate Between On-Demand and Standard Prophylaxis Treatment Regimens |
|-----------------|---|

### End point description:

Annualized bleed rates were transformed using the square root of the number of bleeding episodes observed ( $X$  bleeds/year),  $X' = \sqrt{X + 0.5}$ . This transformation was performed to stabilize the variance and align the sample distribution with the assumption of normality inherent in using the paired t-test. Mean Difference of Transformed Annualized Bleeding Rate (TABR) = (On-Demand Treatment TABR) - (Standard Prophylaxis Treatment TABR). Participants from the On-Demand portion of the study were subsequently randomized to either Standard Prophylaxis or PK-Driven Prophylaxis, (i.e the same participants were analyzed across the two measurement time periods).

Population: Subjects in the efficacy intent-to-treat set comprising of all subjects in the prophylaxis treatment regimen who had at least 1 assessment (1 quarterly visit) or who had withdrawn after 3 bleeding episodes prior to reaching the first assessment period.

|   |           |
|---|-----------|
| End point type  | Secondary |
| End point timeframe:  |           |
| On-demand 6 months ( $\pm$ 2 weeks); followed by Prophylaxis 12 months ( $\pm$ 2 weeks) |           |

| End point values                      | On-Demand Versus Standard Prophylaxis |  |  |  |
|---------------------------------------|---------------------------------------|--|--|--|
| Subject group type                    | Subject analysis set                  |  |  |  |
| Number of subjects analysed           | 32                                    |  |  |  |
| Units: (bleeds/year) <sup>(1/2)</sup> |                                       |  |  |  |
| arithmetic mean (standard deviation)  | 5.29 ( $\pm$ 1.46)                    |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Mean Difference of Transformed Annualized Bleeding Rate Between On-Demand and PK-Driven Prophylaxis Treatment Regimens

|                 |  |
|-----------------|--|
| End point title | Mean Difference of Transformed Annualized Bleeding Rate Between On-Demand and PK-Driven Prophylaxis Treatment Regimens |
|-----------------|--|

#### End point description:

Annualized bleed rates were transformed using the square root of the number of bleeding episodes observed ( $X$  bleeds/year),  $X' = \sqrt{(X + 0.5)}$ . This transformation was performed to stabilize the variance and align the sample distribution with the assumption of normality inherent in using the paired t-test. Mean Difference of Transformed Annualized Bleeding Rate (TABR) = (On-Demand Treatment TABR) - (PK-Driven Prophylaxis Treatment TABR) Participants from the On-Demand portion of the study were subsequently randomized to either Standard Prophylaxis or PK-Driven Prophylaxis, (i.e the same participants were analyzed across the two measurement time periods).

Population: Subjects in the efficacy intent-to-treat set comprising of all subjects in the prophylaxis treatment regimen who had at least 1 assessment (1 quarterly visit) or who had withdrawn after 3 bleeding episodes prior to reaching the first assessment period.

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

#### End point timeframe:

On-demand 6 months ( $\pm 2$  weeks); followed by Prophylaxis 12 months ( $\pm 2$  weeks)

| End point values                      | On-Demand Versus PK-Driven Prophylaxis |  |  |  |
|---------------------------------------|--|--|--|--|
| Subject group type                    | Subject analysis set                   |  |  |  |
| Number of subjects analysed           | 34                                     |  |  |  |
| Units: (bleeds/year) <sup>(1/2)</sup> |  |  |  |  |
| arithmetic mean (standard deviation)  | 5 ( $\pm 1.85$ )                       |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Mean Difference of Transformed Annualized Bleeding Rate Between On-Demand and Any Prophylaxis Treatment Regimens

|                 |  |
|-----------------|--|
| End point title | Mean Difference of Transformed Annualized Bleeding Rate Between On-Demand and Any Prophylaxis Treatment Regimens |
|-----------------|--|

#### End point description:

Annualized bleed rates were transformed using the square root of the number of bleeding episodes observed ( $X$  bleeds/year),  $X' = \sqrt{(X + 0.5)}$ . This transformation was performed to stabilize the variance

and align the sample distribution with the assumption of normality inherent in using the paired t-test. Mean Difference of Transformed Annualized Bleeding Rate (TABR) = (On-Demand Treatment TABR) - (Any Prophylaxis Treatment TABR). Any Prophylaxis = Standard or PK-Driven Prophylaxis Participants from the On-Demand portion of the study were subsequently randomized to either Standard Prophylaxis or PK-Driven Prophylaxis, (i.e the same participants were analyzed across the two measurement time periods).

Population: Subjects in the efficacy intent-to-treat set comprising of all subjects in the prophylaxis treatment regimen who had at least 1 assessment (1 quarterly visit) or who had withdrawn after 3 bleeding episodes prior to reaching the first assessment period.

|   |           |
|---|-----------|
| End point type  | Secondary |
| End point timeframe:  |           |
| On-demand 6 months ( $\pm$ 2 weeks); Prophylaxis 12 months ( $\pm$ 2 weeks) |           |

| End point values                      | On-Demand Versus Any Prophylaxis |  |  |  |
|---------------------------------------|----------------------------------|--|--|--|
| Subject group type                    | Subject analysis set             |  |  |  |
| Number of subjects analysed           | 66                               |  |  |  |
| Units: (bleeds/year) <sup>(1/2)</sup> |                                  |  |  |  |
| arithmetic mean (standard deviation)  | 5.14 ( $\pm$ 1.66)               |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Total Weight-Adjusted Dose of rAHF-PFM Used Per Year for Each Prophylaxis Arm

|                 |  |
|-----------------|--|
| End point title | Total Weight-Adjusted Dose of rAHF-PFM Used Per Year for Each Prophylaxis Arm <sup>[3]</sup> |
|-----------------|--|

End point description:

Subjects were randomized to receive 1 of the 2 following prophylaxis regimens (part 2 of the study):

1. Standard prophylaxis- infusions every 48  $\pm$ 6 hours, dosed at 20 to 40 IU/kg.
2. PK-driven prophylaxis- infusions every 72  $\pm$ 6 hours dosed at 20 to 80 IU/kg.

Population: Subjects in the efficacy intent-to-treat set comprising of all subjects in the prophylaxis treatment regimen who had at least 1 assessment (1 quarterly visit) or who had withdrawn after 3 bleeding episodes prior to reaching the first assessment period.

|                         |           |
|-------------------------|-----------|
| End point type          | Secondary |
| End point timeframe:    |           |
| 12 months $\pm$ 2 weeks |           |

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Arms in the baseline period are not mutually exclusive. Refer to the description of arms in period 1 (baseline period).

| End point values                      | Standard Prophylaxis    | PK-Driven Prophylaxis     |  |  |
|---------------------------------------|-------------------------|---------------------------|--|--|
| Subject group type                    | Reporting group         | Reporting group           |  |  |
| Number of subjects analysed           | 32                      | 34                        |  |  |
| Units: IU/kg                          |                         |                           |  |  |
| median (inter-quartile range (Q1-Q3)) | 5768.2 (4728 to 6425.4) | 5197.8 (3268.4 to 8273.5) |  |  |

## Statistical analyses

| Statistical analysis title              | Statistical analysis 1                       |
|---|--|
| Comparison groups                       | PK-Driven Prophylaxis v Standard Prophylaxis |
| Number of subjects included in analysis | 66   |
| Analysis specification                  | Pre-specified                                |
| Analysis type                           | superiority                                  |
| P-value                                 | = 0.4924                                     |
| Method                                  | Wilcoxon-Rank Sum (Mann-Whitney)             |
| Confidence interval                     |  |
| level                                   | 95 %   |

## Secondary: Bleeding Episodes Treated With 1 to ≥4 Infusions

|                 |   |
|-----------------|---|
| End point title | Bleeding Episodes Treated With 1 to ≥4 Infusions <sup>[4]</sup> |
|-----------------|---|

End point description:

The number of bleeding episodes treated with 1, 2, 3, or ≥4 infusions of rAHF-PFM to achieve adequate hemostasis.

Population: Subjects in the efficacy intent-to-treat set comprising of all subjects in the prophylaxis treatment regimen who had at least 1 assessment (1 quarterly visit) or who had withdrawn after 3 bleeding episodes prior to reaching the first assessment period.

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

End point timeframe:

Throughout the study period (4 years and 5 months)

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Arms in the baseline period are not mutually exclusive. Refer to the description of arms in period 1 (baseline period) for this endpoint.

| End point values                   | On-Demand       | Standard Prophylaxis | PK-Driven Prophylaxis |  |
|------------------------------------|-----------------|----------------------|-----------------------|--|
| Subject group type                 | Reporting group | Reporting group      | Reporting group       |  |
| Number of subjects analysed        | 62              | 13                   | 22                    |  |
| Units: Bleeding episodes           |                 |                      |                       |  |
| 1 infusion (n = 62, 13, 22)        | 1168            | 68                   | 90                    |  |
| 2 infusions (n = 51, 6, 9)         | 277             | 12                   | 37                    |  |
| 3 infusions (n = 27, 2, 4)         | 128             | 4                    | 5                     |  |
| 4 or more infusions (n = 21, 5, 5) | 50              | 9                    | 7                     |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Assessment of Hemostasis for Treatment of Bleeding Episodes

|                 |  |
|-----------------|--|
| End point title | Assessment of Hemostasis for Treatment of Bleeding |
|-----------------|--|

End point description:

Number of rAHF-PFM-treated bleeding episodes with an assessment of hemostasis (4-point ordinal scale):

Excellent: Full pain relief & bleeding cessation within ~8 hrs of 1 infusion. Additional infusions may have been given to maintain hemostasis;

Good: Definite pain relief and/or improvement in bleeding within ~8 hrs after infusion. Possibly requires >1 infusion for complete resolution;

Fair: Probable or slight relief of pain & slight improvement in bleeding within ~8 hrs after infusion.

Requires >1 infusion for complete resolution;

None: No improvement or condition worsens.

Population: Subjects in the hemostatic efficacy rating set comprising of subjects who reported a bleeding episode that was treated with rAFH-PFM.

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

End point timeframe:

On-demand 6 months ( $\pm$  2 weeks); Prophylaxis 12 months ( $\pm$  2 weeks)

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Arms in the baseline period are not mutually exclusive. Refer to the description of arms in period 1 (baseline period).

| End point values            | On-Demand       | Standard Prophylaxis | PK-Driven Prophylaxis |  |
|-----------------------------|-----------------|----------------------|-----------------------|--|
| Subject group type          | Reporting group | Reporting group      | Reporting group       |  |
| Number of subjects analysed | 70              | 18                   | 25                    |  |
| Units: Beeding episodes     |                 |                      |                       |  |
| Excellent                   | 547             | 39                   | 33                    |  |
| Good                        | 943             | 38                   | 75                    |  |
| Fair                        | 167             | 16                   | 11                    |  |
| None                        | 3               | 0                    | 20                    |  |
| Unknown                     | 13              | 0                    | 0                     |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Total Area Under the Curve (AUC)

|                 |                                  |
|-----------------|----------------------------------|
| End point title | Total Area Under the Curve (AUC) |
|-----------------|----------------------------------|

End point description:

Total AUC estimated by AUC 0-48h plus an area extrapolated from the log-linear regression model.

Population: Subjects in the pharmacokinetic (PK) intent-to-treat set comprising of subjects who provided at least 1 evaluable PK assessment.

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

End point timeframe:

Pharmacokinetic evaluations: 30 minutes pre-infusion up to 48 hours post-infusion

| End point values                    | Subjects ≥14 Years   | Subjects <14 Years   |  |  |
|-------------------------------------|----------------------|----------------------|--|--|
| Subject group type                  | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed         | 65                   | 6                    |  |  |
| Units: IU*h/dL                      |                      |                      |  |  |
| geometric mean (standard deviation) | 1334.45 (± 454.33)   | 1061.26 (± 452.87)   |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Area Under the Curve

|                 |                      |
|-----------------|----------------------|
| End point title | Area Under the Curve |
|-----------------|----------------------|

End point description:

Area under the factor VIII (FVIII) plasma concentration versus time curve (AUC) from 0 to 48 hours estimated using the linear trapezoidal method.

Population: Subjects in the pharmacokinetic (PK) intent-to-treat set comprising of subjects who provided at least 1 evaluable PK assessment.

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

End point timeframe:

Pharmacokinetic evaluations: 30 minutes pre-infusion up to 48 hours post-infusion

| End point values                    | Subjects ≥14 Years   | Subjects <14 Years   |  |  |
|-------------------------------------|----------------------|----------------------|--|--|
| Subject group type                  | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed         | 65                   | 6                    |  |  |
| Units: IU*h/dL                      |                      |                      |  |  |
| geometric mean (standard deviation) | 1213.98 (± 323.96)   | 966.68 (± 330.83)    |  |  |

### Statistical analyses

No statistical analyses for this end point



## Secondary: Maximum Plasma Concentration (C-max)

|                 |                                      |
|-----------------|--------------------------------------|
| End point title | Maximum Plasma Concentration (C-max) |
|-----------------|--------------------------------------|

End point description:

Maximal Factor VIII Concentration After Infusion.

Population: Subjects in the pharmacokinetic (PK) intent-to-treat set comprising of subjects who provided at least 1 evaluable PK assessment.

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

End point timeframe:

Within 1 hour post-infusion

| End point values                    | Subjects ≥14 Years   | Subjects <14 Years   |  |  |
|-------------------------------------|----------------------|----------------------|--|--|
| Subject group type                  | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed         | 65                   | 6                    |  |  |
| Units: IU/dL                        |                      |                      |  |  |
| geometric mean (standard deviation) | 91.12 (± 20.15)      | 74.47 (± 11.3)       |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Adjusted Incremental Recovery (IR)

|                 |                                    |
|-----------------|------------------------------------|
| End point title | Adjusted Incremental Recovery (IR) |
|-----------------|------------------------------------|

End point description:

Change in factor VIII concentration from pre- to post-infusion at initial and termination study visits.  
Adjusted IR defined as: [Cmax (IU/dL) – pre-infusion FVIII (IU/dL)]/dose (IU/kg).

Population: Subjects in the pharmacokinetic (PK) intent-to-treat set comprising of subjects who provided at least 1 evaluable PK assessment.

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

End point timeframe:

30 minutes pre-infusion to 48 hours post-infusion

| End point values                    | Subjects ≥14 Years   | Subjects <14 Years   |  |  |
|-------------------------------------|----------------------|----------------------|--|--|
| Subject group type                  | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed         | 65                   | 6                    |  |  |
| Units: IU/dL per IU/kg              |                      |                      |  |  |
| geometric mean (standard deviation) | 1.81 (± 0.41)        | 1.47 (± 0.27)        |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Terminal Half-life

|                 |                    |
|-----------------|--------------------|
| End point title | Terminal Half-life |
|-----------------|--------------------|

End point description:

Computed from the regression slope in the terminal phase of the model. Terminal half life is the time it takes for the plasma concentration or the amount of drug in the body to be reduced by 50%.

Population: Subjects in the pharmacokinetic (PK) intent-to-treat set comprising of subjects who provided at least 1 evaluable PK assessment.

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

End point timeframe:

Pharmacokinetic evaluations: 30 minutes pre-infusion up to 48 hours post-infusion

| End point values                     | Subjects ≥14 Years   | Subjects <14 Years   |  |  |
|--------------------------------------|----------------------|----------------------|--|--|
| Subject group type                   | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed          | 65                   | 6                    |  |  |
| Units: Hours                         |                      |                      |  |  |
| arithmetic mean (standard deviation) | 13.91 (± 5.07)       | 14.66 (± 5.21)       |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Weight-Adjusted Clearance

|                 |                           |
|-----------------|---------------------------|
| End point title | Weight-Adjusted Clearance |
|-----------------|---------------------------|

End point description:

Computed as the weight-adjusted dose divided by total area under the curve (AUC).

Population: Subjects in the pharmacokinetic (PK) intent-to-treat set comprising of subjects who provided at least 1 evaluable PK assessment.

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

End point timeframe:

Pharmacokinetic evaluations: 30 minutes pre-infusion up to 48 hours post-infusion

| End point values                     | Subjects ≥14 Years   | Subjects <14 Years   |  |  |
|--------------------------------------|----------------------|----------------------|--|--|
| Subject group type                   | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed          | 65                   | 6                    |  |  |
| Units: mL/(kg*h)                     |                      |                      |  |  |
| arithmetic mean (standard deviation) | 3.89 (± 1.21)        | 5.17 (± 1.94)        |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Mean Residence Time

|                 |                     |
|-----------------|---------------------|
| End point title | Mean Residence Time |
|-----------------|---------------------|

End point description:

Computed as total Area Under the Moment Curve (AUMC) divided by the total area under the curve (AUC).

Population: Subjects in the pharmacokinetic (PK) intent-to-treat set comprising of subjects who provided at least 1 evaluable PK assessment. Population: Comprised of subjects who provided at least 1 evaluable pharmacokinetic (PK) assessment.

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

End point timeframe:

Pharmacokinetic evaluations: 30 minutes pre-infusion up to 48 hours post-infusion

| End point values                     | Subjects ≥14 Years   | Subjects <14 Years   |  |  |
|--------------------------------------|----------------------|----------------------|--|--|
| Subject group type                   | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed          | 65                   | 6                    |  |  |
| Units: Hours                         |                      |                      |  |  |
| arithmetic mean (standard deviation) | 17.71 (± 7.16)       | 17.88 (± 5.67)       |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Volume of Distribution at Steady State

|                 |  |
|-----------------|--|
| End point title | Volume of Distribution at Steady State |
|-----------------|--|

End point description:

Computed as weight-adjusted clearance \* mean residence time.

Population: Subjects in the pharmacokinetic (PK) intent-to-treat set comprising of subjects who provided at least 1 evaluable PK assessment.

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

End point timeframe:

Pharmacokinetic evaluations: 30 minutes pre-infusion up to 48 hours post-infusion

| End point values                     | Subjects ≥14 Years   | Subjects <14 Years   |  |  |
|--------------------------------------|----------------------|----------------------|--|--|
| Subject group type                   | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed          | 65                   | 6                    |  |  |
| Units: dL/kg                         |                      |                      |  |  |
| arithmetic mean (standard deviation) | 0.65 (± 0.19)        | 0.84 (± 0.19)        |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Factor VIII Inhibitor Development

|                 |  |
|-----------------|--|
| End point title | Factor VIII Inhibitor Development <sup>[6]</sup> |
|-----------------|--|

End point description:

Number of treated subjects who developed factor VIII inhibitors.

Population: All subjects in the safety analysis set comprising of all subjects who were exposed to rAHF-PFM.

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

End point timeframe:

Throughout study period (4 years and 5 months)

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Arms in the baseline period are not mutually exclusive. Refer to the description of arms in period 1 (baseline period).

| End point values            | All subjects    |  |  |  |
|-----------------------------|-----------------|--|--|--|
| Subject group type          | Reporting group |  |  |  |
| Number of subjects analysed | 73              |  |  |  |
| Units: Subjects             | 0               |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Subjects with AEs Related to Investigational Product (IP)

|                 |  |
|-----------------|--|
| End point title | Number of Subjects with AEs Related to Investigational Product (IP) <sup>[7]</sup> |
|-----------------|--|

End point description:

Number of treated subjects with AEs judged to be possibly or probably related to treatment with IP.

Population: All subjects in the safety analysis set comprising of all subjects who were exposed to rAHF-PFM.

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

End point timeframe:

Throughout study period (4 years and 5 months)

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Arms in the baseline period are not mutually exclusive. Refer to the description of arms in period 1 (baseline period).

|                             |                 |  |  |  |
|-----------------------------|-----------------|--|--|--|
| <b>End point values</b>     | All subjects    |  |  |  |
| Subject group type          | Reporting group |  |  |  |
| Number of subjects analysed | 73              |  |  |  |
| Units: Subjects             | 4               |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Subjects who reported $\geq 1$ AE Regardless of Relatedness to Investigational Product (IP)

|                 |  |
|-----------------|--|
| End point title | Number of Subjects who reported $\geq 1$ AE Regardless of Relatedness to Investigational Product (IP) <sup>[8]</sup> |
|-----------------|--|

End point description:

Number of treated subjects with 1 or more AE regardless of relatedness to IP.

Population: All subjects in the safety analysis set comprising of all subjects who were exposed to rAHF-PFM.

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

End point timeframe:

Throughout study period (4 years and 5 months)

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Arms in the baseline period are not mutually exclusive. Refer to the description of arms in period 1 (baseline period) .

|                             |                 |  |  |  |
|-----------------------------|-----------------|--|--|--|
| <b>End point values</b>     | All subjects    |  |  |  |
| Subject group type          | Reporting group |  |  |  |
| Number of subjects analysed | 73              |  |  |  |
| Units: Subjects             | 44              |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Subjects who reported $\geq 1$ AE Regardless of Relatedness to Investigational Product (IP) by treatment regimen

|                 |   |
|-----------------|---|
| End point title | Number of Subjects who reported $\geq 1$ AE Regardless of Relatedness to Investigational Product (IP) by treatment regimen <sup>[9]</sup> |
|-----------------|---|

End point description:

Population: All subjects in the safety analysis set comprising of all subjects who were exposed to rAHF-PFM.

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

End point timeframe:

Throughout the study period (4 years and 5 months)

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Arms in the baseline period are not mutually exclusive. Refer to the description of arms in period 1 (baseline period).

| End point values            | On-Demand       | Standard Prophylaxis | PK-Driven Prophylaxis |  |
|-----------------------------|-----------------|----------------------|-----------------------|--|
| Subject group type          | Reporting group | Reporting group      | Reporting group       |  |
| Number of subjects analysed | 72              | 32                   | 34                    |  |
| Units: Subjects             | 33              | 15                   | 19                    |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Subjects with SAEs by Preferred MedDRA Term and Treatment Regimen

|                 |   |
|-----------------|---|
| End point title | Number of Subjects with SAEs by Preferred MedDRA Term and Treatment Regimen <sup>[10]</sup> |
|-----------------|---|

End point description:

Number of Subjects with serious adverse events (SAEs) by Preferred MedDRA Term and Treatment Regimen (On-demand; Standard Prophylaxis and pharmacokinetic (PK)-driven Prophylaxis)

Population: All subjects in the safety analysis set comprising of all subjects who were exposed to rAHF-PFM.

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

End point timeframe:

Throughout the study period (4 years and 5 months)

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Arms in the baseline period are not mutually exclusive. Refer to the description of arms in period 1 (baseline period).

| End point values            | On-Demand       | Standard Prophylaxis | PK-Driven Prophylaxis | Subjects with SAEs outside of 3 Treatment Arms |
|-----------------------------|-----------------|----------------------|-----------------------|--|
| Subject group type          | Reporting group | Reporting group      | Reporting group       | Subject analysis set                           |
| Number of subjects analysed | 72              | 32                   | 34                    | 1  |
| Units: Subjects             |                 |                      |                       |  |
| ABDOMINAL PAIN              | 1               | 0                    | 0                     | 0  |
| NAUSEA                      | 1               | 0                    | 0                     | 0  |
| TOOTH ABSCESS               | 1               | 0                    | 0                     | 0  |
| JOINT DISLOCATION           | 1               | 0                    | 0                     | 0  |
| HAEMOPHILIC ARTHROPATHY     | 1               | 0                    | 1                     | 0  |
| SYNOVITIS                   | 1               | 0                    | 0                     | 0  |
| CALCULUS URINARY            | 1               | 0                    | 0                     | 0  |
| HOSPITALIZATION             | 1               | 0                    | 0                     | 0  |
| PULPITIS DENTAL             | 0               | 1                    | 0                     | 0  |
| SOMNAMBULISM                | 0               | 1                    | 0                     | 0  |

|   |   |   |   |   |
|---|---|---|---|---|
| FACTOR VIII INHIBITION<br>(UNCONFIRMED) | 0 | 0 | 1 | 0 |
| APPENDICITIS                            | 0 | 0 | 1 | 0 |
| PAIN IN EXTREMITY                       | 0 | 0 | 0 | 1 |

## Statistical analyses

No statistical analyses for this end point

### Secondary: AEs with onset ≤1 hour following the end of an infusion, regardless of relatedness

|                 |  |
|-----------------|--|
| End point title | AEs with onset ≤1 hour following the end of an infusion, regardless of relatedness <sup>[11]</sup> |
|-----------------|--|

End point description:

Population: All subjects in the safety analysis set comprising of all subjects who were exposed to rAHF-PFM.

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

End point timeframe:

Throughout study period (4 years and 5 months)

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Arms in the baseline period are not mutually exclusive. Refer to the description of arms in period 1 (baseline period).

|                             |                 |  |  |  |
|-----------------------------|-----------------|--|--|--|
| <b>End point values</b>     | All subjects    |  |  |  |
| Subject group type          | Reporting group |  |  |  |
| Number of subjects analysed | 73              |  |  |  |
| Units: Adverse events       | 39              |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Subjects with Severe SAEs and Severe non-SAEs by Preferred MedDRA Term and Treatment Regimen

|                 |  |
|-----------------|--|
| End point title | Number of Subjects with Severe SAEs and Severe non-SAEs by Preferred MedDRA Term and Treatment Regimen <sup>[12]</sup> |
|-----------------|--|

End point description:

This outcome is focused only on SEVERE serious adverse events (SAEs) and SEVERE non-SAEs.

Population: All subjects in the safety analysis set comprising of all subjects who were exposed to rAHF-PFM.

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

End point timeframe:

Throughout the study period (4 years and 5 months)

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Arms in the baseline period are not mutually exclusive. Refer to the description of arms in period 1 (baseline period).

| End point values                  | On-Demand       | Standard Prophylaxis | PK-Driven Prophylaxis |  |
|-----------------------------------|-----------------|----------------------|-----------------------|--|
| Subject group type                | Reporting group | Reporting group      | Reporting group       |  |
| Number of subjects analysed       | 72              | 32                   | 34                    |  |
| Units: Subjects                   |                 |                      |                       |  |
| TOOTH ABSCESS (SAE)               | 1               | 0                    | 0                     |  |
| HAEMOPHILIC ARTHROPATHY (SAE)     | 0               | 0                    | 1                     |  |
| HAEMOPHILIC ARTHROPATHY (non-SAE) | 1               | 0                    | 1                     |  |
| ABDOMINAL PAIN (non-SAE)          | 1               | 0                    | 0                     |  |
| ARTHRALGIA (non-SAE)              | 1               | 0                    | 0                     |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Baseline Health-related Quality of Life (HRQoL) Scores: PF, RP, BP, GH, VT, SF, RE, MH, PCS, and MCS

|                 |  |
|-----------------|--|
| End point title | Baseline Health-related Quality of Life (HRQoL) Scores: PF, RP, BP, GH, VT, SF, RE, MH, PCS, and MCS |
|-----------------|--|

End point description:

Physical Functioning (PF); Role Limitation Due to Physical Health (RP); Bodily Pain (BP); General Health (GH); Vitality (VT); Social Functioning (SF); Role Limitation Due to Emotional Problems (RE); Mental Health (MH), Physical Component Score (PCS); Mental Component Score (MCS). Baseline SF-36v1 Scores, where data available. Scores range 0-100, higher scores represent better health. There is no total overall score; scoring is done for subscores and summary scores. The raw data from the SF-36 items were transformed to norm based scores for each of the 8 HRQoL/SF-36 health domain scores.

Population: All subjects in pharmacoeconomic (PE) set comprising of subjects who completed a HRQoL assessment.

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

End point timeframe:

Baseline

| End point values              | Subjects Assessed Before Treatment |  |  |  |
|-------------------------------|------------------------------------|--|--|--|
| Subject group type            | Subject analysis set               |  |  |  |
| Number of subjects analysed   | 71                                 |  |  |  |
| Units: Scores on a scale      |                                    |  |  |  |
| median (full range (min-max)) |                                    |  |  |  |
| Physical Functioning (PF)     | 44.56 (17.29 to 57.14)             |  |  |  |



|                                |                        |  |  |  |
|--------------------------------|------------------------|--|--|--|
| Role-Physical (RP)             | 42.1 (27.95 to 56.24)  |  |  |  |
| Bodily Pain (BP)               | 46.48 (25.07 to 62.75) |  |  |  |
| General Health (GH)            | 43.87 (19.52 to 64)    |  |  |  |
| Vitality (VT)                  | 51.42 (25.39 to 67.2)  |  |  |  |
| Social Functioning (SF)        | 46.28 (19.14 to 57.14) |  |  |  |
| Role-Emotional (RE)            | 55.34 (23.74 to 55.34) |  |  |  |
| Mental Health (MH)             | 50.44 (20.91 to 64.07) |  |  |  |
| Physical Component Score (PCS) | 42.32 (20.1 to 67.67)  |  |  |  |
| Mental Component Score (MCS)   | 52.65 (22.56 to 68.1)  |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Health-related Quality of Life (HRQoL) Scores: PF, RP, BP, GH, VT, SF, RE, MH, PCS, and MCS at the End of Treatment Regimens

|                 |  |
|-----------------|--|
| End point title | Health-related Quality of Life (HRQoL) Scores: PF, RP, BP, GH, VT, SF, RE, MH, PCS, and MCS at the End of Treatment Regimens <sup>[13]</sup> |
|-----------------|--|

End point description:

Physical Functioning (PF); Role Limitation Due to Physical Health (RP); Bodily Pain (BP); General Health (GH); Vitality (VT); Social Functioning (SF); Role Limitation Due to Emotional Problems (RE); Mental Health (MH); Physical Component Score (PCS); Mental Component Score (MCS). Baseline SF-36v1 Scores, where data available. Scores range 0-100, higher scores represent better health. There is no total overall score; scoring is done for subscores and summary scores. The raw data from the SF-36 items were transformed to norm based scores for each of the 8 HRQoL/SF-36 health domain scores.

Population: All subjects in pharmacoeconomic (PE) set comprising of subjects who completed a HRQoL assessment.

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

End point timeframe:

End of on-demand treatment period (6 months) and at study termination (approximately 18 months)

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Arms in the baseline period are not mutually exclusive. Refer to the description of arms in period 1 (baseline period).

| End point values              | On-Demand           | Standard Prophylaxis | PK-Driven Prophylaxis | Any Prophylaxis     |
|-------------------------------|---------------------|----------------------|-----------------------|---------------------|
| Subject group type            | Reporting group     | Reporting group      | Reporting group       | Reporting group     |
| Number of subjects analysed   | 63                  | 31                   | 34                    | 65                  |
| Units: Scores on a scale      |                     |                      |                       |                     |
| median (full range (min-max)) |                     |                      |                       |                     |
| Bodily Pain (BP)              | 46.5 (29.4 to 62.8) | 51.6 (19.9 to 62.8)  | 51.6 (29.4 to 62.8)   | 51.6 (19.9 to 62.8) |

|  |                     |                     |                     |                     |
|--|---------------------|---------------------|---------------------|---------------------|
| General Health (GH)                            | 43.9 (19.5 to 64)   | 48.6 (19.5 to 64)   | 46.2 (29.8 to 60.3) | 48.6 (19.5 to 64)   |
| Mental Component Score (MCS), On-Demand n=62   | 54.9 (22.8 to 69.9) | 56.1 (13.3 to 69.6) | 54.5 (11.4 to 62.5) | 55 (11.4 to 69.6)   |
| Mental Health (MH), On-Demand n=62             | 51.6 (14.1 to 64.1) | 50.4 (20.9 to 64.1) | 52.7 (7.3 to 64.1)  | 50.4 (7.3 to 64.1)  |
| Physical Component Score (PCS), On-Demand n=62 | 44 (16.1 to 61.2)   | 50.2 (17.6 to 68.8) | 47.3 (25.3 to 62.3) | 47.8 (17.6 to 68.8) |
| Physical Functioning (PF), On-Demand n=62      | 48.8 (17.3 to 57.1) | 46.7 (21.5 to 57.1) | 46.7 (17.3 to 57.1) | 46.7 (17.3 to 57.1) |
| Role Emotional (RE)                            | 55.3 (23.7 to 55.3) | 55.3 (23.7 to 55.3) | 55.3 (23.7 to 55.3) | 55.3 (23.7 to 55.3) |
| Role Physical (RP)                             | 49.2 (28 to 56.2)   | 56.2 (28 to 56.2)   | 56.2 (28 to 56.2)   | 56.2 (28 to 56.2)   |
| Social Functioning (SF)                        | 46.3 (30 to 57.1)   | 51.7 (24.6 to 57.1) | 51.7 (13.7 to 57.1) | 51.7 (13.7 to 57.1) |
| Vitality (VT)                                  | 53.8 (32.5 to 70.4) | 56.2 (27.8 to 70.4) | 56.2 (23 to 68)     | 56.2 (23 to 70.4)   |

## Statistical analyses

No statistical analyses for this end point

## Secondary: HRQoL Scores Change From On-Demand Treatment Regimen Period Through Prophylaxis Period

|                 |  |
|-----------------|--|
| End point title | HRQoL Scores Change From On-Demand Treatment Regimen Period Through Prophylaxis Period |
|-----------------|--|

End point description:

Differences in health domain scores = (End of on-demand treatment) – (End of prophylaxis regimen). A negative value for the median difference equates to a larger domain score for the prophylaxis regimen.

Physical Functioning (PF); Role Limitation Due to Physical Health (RP); Bodily Pain (BP); General Health (GH); Vitality (VT); Social Functioning (SF); Role Limitation Due to Emotional Problems (RE); Mental Health (MH), Physical Component Score (PCS); Mental Component Score (MCS).

Scores range 0-100, higher scores represent better health. There is no total overall score; scoring is done for subscores and summary scores. The raw data from the SF-36 items were transformed to norm based scores for each of the 8 HRQoL/SF-36 health domain scores.

Population: Subjects ≥14 years in pharmacoeconomic (PE) set comprising of subjects ≥14 years who completed a Health Related Quality of Life (HRQoL) assessment.

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

End point timeframe:

End of on-demand treatment period (6 months) and at study termination (approximately 18 months)

| End point values              | On-Demand to Standard Prophylaxis | On-Demand to PK-Driven Prophylaxis | On-Demand to Any Prophylaxis |  |
|-------------------------------|-----------------------------------|------------------------------------|------------------------------|--|
| Subject group type            | Subject analysis set              | Subject analysis set               | Subject analysis set         |  |
| Number of subjects analysed   | 27                                | 30                                 | 57                           |  |
| Units: Scores on a scale      |                                   |                                    |                              |  |
| median (full range (min-max)) |                                   |                                    |                              |  |
| Physical Functioning (PF)     | 0 (-10.48 to 14.68)               | -2.1 (-18.88 to 20.97)             | -2.1 (-18.88 to 20.97)       |  |

|                                |                         |                         |                         |  |
|--------------------------------|-------------------------|-------------------------|-------------------------|--|
| Role Physical (RP)             | 0 (-28.29 to 21.21)     | 0 (-28.29 to 28.29)     | 0 (-28.29 to 28.29)     |  |
| Bodily Pain (BP)               | 0 (-29.55 to 17.55)     | -4.29 (-25.27 to 13.28) | 0 (-29.55 to 17.55)     |  |
| General Health (GH)            | -3.74 (-21.07 to 18.73) | -2.34 (-20.13 to 17.79) | -2.34 (-21.07 to 18.73) |  |
| Vitality (VT)                  | 0 (-9.47 to 23.67)      | 0 (-16.57 to 30.77)     | 0 (-16.57 to 30.77)     |  |
| Social Functioning (SF)        | 0 (-21.72 to 16.29)     | 0 (-16.29 to 16.29)     | 0 (-21.72 to 16.29)     |  |
| Role Emotional (RE)            | 0 (-10.53 to 31.6)      | 0 (-31.6 to 21.07)      | 0 (-31.6 to 31.6)       |  |
| Mental Health (MH)             | 0 (-13.63 to 15.9)      | -1.13 (-40.9 to 34.08)  | 0 (-40.9 to 34.08)      |  |
| Physical Component Score (PCS) | -2.55 (-20.22 to 8.69)  | -3.14 (-16.78 to 19.7)  | -2.76 (-20.22 to 19.7)  |  |
| Mental Component Score (MCS)   | 1.52 (-8.31 to 21.64)   | 0.79 (-35.25 to 24.56)  | 1.3 (-35.25 to 24.56)   |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Bodily Pain HRQoL Scores Change From On-Demand Period Through Prophylaxis Period

|                 |  |
|-----------------|--|
| End point title | Bodily Pain HRQoL Scores Change From On-Demand Period Through Prophylaxis Period |
|-----------------|--|

End point description:

After an on-demand treatment period, subjects were randomized to 1 of 2 prophylactic regimens for 12 months. The standard prophylactic regimen was dosed at 20 to 40 IU/kg every 48 ±6 hours, and the PK-driven prophylaxis regimen was dosed at 20 to 80 IU/kg every 72 ±6 hours.

Bodily Pain Health Related Quality of Life (HRQoL) Scores Change = (End of on-demand treatment) – (End of prophylaxis regimen). A negative value for the median difference equates to a larger domain score for the prophylaxis regimen.

Scores range 0-100, higher scores represent better health. There is no total overall score; scoring is done for subscores and summary scores. The raw data from the SF-36 items were transformed to norm based scores.

Population: Subjects ≥14 years in pharmacoeconomic (PE) set comprising of subjects ≥14 years who completed a HRQoL assessment.

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

End point timeframe:

End of on-demand treatment period (6 months) and at study termination (approximately 18 months)

|                               |                              |  |  |  |
|-------------------------------|------------------------------|--|--|--|
| <b>End point values</b>       | On-Demand to Any Prophylaxis |  |  |  |
| Subject group type            | Subject analysis set         |  |  |  |
| Number of subjects analysed   | 57                           |  |  |  |
| Units: Scores on a scale      |                              |  |  |  |
| median (full range (min-max)) | 0 (-29.55 to 17.55)          |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Physical Component Scores (PCS) HRQoL Scores Change From On-Demand Period Through Prophylaxis Period

|                 |  |
|-----------------|--|
| End point title | Physical Component Scores (PCS) HRQoL Scores Change From On-Demand Period Through Prophylaxis Period |
|-----------------|--|

End point description:

After an on-demand treatment period, subjects were randomized to 1 of 2 prophylactic regimens for 12 months. The standard prophylactic regimen was dosed at 20 to 40 IU/kg every 48 ±6 hours, and the PK-driven prophylaxis regimen was dosed at 20 to 80 IU/kg every 72 ±6 hours.

PCS Health Related Quality of Life (HRQoL) Scores Change = (End of on-demand treatment) – (End of prophylaxis regimen) A negative value for the median difference equates to a larger domain score for the prophylaxis regimen. Scores range 0-100, higher scores represent better health. There is no total overall score; scoring is done for subscores and summary scores. The raw data from the SF-36 items were transformed to norm based scores.

Population: Subjects ≥14 years in pharmacoeconomic (PE) set comprising of subjects ≥14 years who completed a HRQoL assessment.

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

End point timeframe:

End of on-demand treatment period (6 months) and at study termination (approximately 18 months)

|                               |                              |  |  |  |
|-------------------------------|------------------------------|--|--|--|
| <b>End point values</b>       | On-Demand to Any Prophylaxis |  |  |  |
| Subject group type            | Subject analysis set         |  |  |  |
| Number of subjects analysed   | 57                           |  |  |  |
| Units: Scores on a scale      |                              |  |  |  |
| median (full range (min-max)) | -2.76 (-20.22 to 19.7)       |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Post-hoc: Median (IQR) Annualized Bleed Rates

|                 |   |
|-----------------|---|
| End point title | Median (IQR) Annualized Bleed Rates <sup>[14]</sup> |
|-----------------|---|

End point description:

Bleed rates (number of bleeding episodes per subject) were annualized to account for the varying number of days a subject may have actually been on each regimen.

Population: Subjects in the efficacy intent-to-treat set comprising of all subjects in the prophylaxis

treatment segment who had at least 1 assessment (1 quarterly visit) or who had withdrawn after 3 bleeding episodes prior to reaching the first assessment period.

|                |          |
|----------------|----------|
| End point type | Post-hoc |
|----------------|----------|

End point timeframe:

On-demand 6 months ( $\pm$  2 weeks); Prophylaxis 12 months ( $\pm$  2 weeks)

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Arms in the baseline period are not mutually exclusive. Refer to the description of arms in period 1 (baseline period).

| End point values                      | On-Demand              | Standard Prophylaxis | PK-Driven Prophylaxis | Any Prophylaxis |
|---------------------------------------|------------------------|----------------------|-----------------------|-----------------|
| Subject group type                    | Reporting group        | Reporting group      | Reporting group       | Reporting group |
| Number of subjects analysed           | 53                     | 30                   | 23                    | 53              |
| Units: Bleeding episodes              |                        |                      |                       |                 |
| median (inter-quartile range (Q1-Q3)) | 43.98 (35.73 to 56.53) | 0.99 (0 to 2.14)     | 1 (0 to 4.08)         | 1 (0 to 4.07)   |

## Statistical analyses

| Statistical analysis title              | Statistical analysis 1      |
|---|-----------------------------|
| Comparison groups                       | On-Demand v Any Prophylaxis |
| Number of subjects included in analysis | 106                         |
| Analysis specification                  | Post-hoc                    |
| Analysis type                           | superiority                 |
| P-value                                 | < 0.0001                    |
| Method                                  | Wilcoxon Signed-Rank Test   |
| Confidence interval                     |                             |
| level                                   | 95 %                        |

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Throughout the study period (4 years and 5 months)

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

### Dictionary used

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

|                    |     |
|--------------------|-----|
| Dictionary version | N/A |
|--------------------|-----|

### Reporting groups

|                       |           |
|-----------------------|-----------|
| Reporting group title | On-Demand |
|-----------------------|-----------|

Reporting group description:

On-demand: rAHF-PFM was to be used for the treatment of bleeding episodes according to the severity and type of episode by the protocol-recommended dosing until the episode resolved: superficial (10-20 IU/kg every 12-14 hours), minor joint (20-40 IU/kg every 12-14 hours), deep muscle (30-60 IU/kg every 12-14 hours), major joint or life-threatening (60-100 IU/kg every 8-12 hours), genitourinary, GI, and intracranial (60-100 IU/kg every 8-12 hours)

|                       |                       |
|-----------------------|-----------------------|
| Reporting group title | PK-Driven Prophylaxis |
|-----------------------|-----------------------|

Reporting group description:

PK-driven prophylaxis regimen dosed at 20 to 80 IU/kg (every 72  $\pm$  6 hours) exact regimen to be determined by the sponsor

|                       |                                      |
|-----------------------|--------------------------------------|
| Reporting group title | SAEs Outside of the 3 Treatment Arms |
|-----------------------|--------------------------------------|

Reporting group description:

Participants with SAEs that occurred after exposure to investigational product, but outside of the three treatment arms

|                       |                      |
|-----------------------|----------------------|
| Reporting group title | Standard Prophylaxis |
|-----------------------|----------------------|

Reporting group description:

Standard prophylaxis regimen dosed at 20 to 40 IU/kg (every 48  $\pm$  6 hours), exact regimen to be determined by the investigator

| Serious adverse events                            | On-Demand      | PK-Driven Prophylaxis | SAEs Outside of the 3 Treatment Arms |
|---|----------------|-----------------------|--------------------------------------|
| Total subjects affected by serious adverse events |                |                       |                                      |
| subjects affected / exposed                       | 7 / 73 (9.59%) | 3 / 34 (8.82%)        | 1 / 1 (100.00%)                      |
| number of deaths (all causes)                     | 0              | 0                     | 0                                    |
| number of deaths resulting from adverse events    | 0              | 0                     | 0                                    |
| Injury, poisoning and procedural complications    |                |                       |                                      |
| JOINT DISLOCATION                                 |                |                       |                                      |
| subjects affected / exposed                       | 1 / 73 (1.37%) | 0 / 34 (0.00%)        | 0 / 1 (0.00%)                        |
| occurrences causally related to treatment / all   | 0 / 1          | 0 / 0                 | 0 / 0                                |
| deaths causally related to treatment / all        | 0 / 0          | 0 / 0                 | 0 / 0                                |
| Surgical and medical procedures                   |                |                       |                                      |
| HOSPITALIZATION                                   |                |                       |                                      |

|  |  |                |               |
|--|--|----------------|---------------|
| subjects affected / exposed  | 1 / 73 (1.37%)   | 0 / 34 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all                            | 0 / 1  | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all                                 | 0 / 0  | 0 / 0          | 0 / 0         |
| Blood and lymphatic system disorders<br>FACTOR VIII INHIBITION             | Additional description: This event was unconfirmed and therefore did not meet protocol definition for a Factor VIII inhibitor. |                |               |
| subjects affected / exposed  | 0 / 73 (0.00%)   | 1 / 34 (2.94%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all                            | 0 / 0  | 1 / 1          | 0 / 0         |
| deaths causally related to treatment / all                                 | 0 / 0  | 0 / 0          | 0 / 0         |
| Gastrointestinal disorders<br>ABDOMINAL PAIN                               |  |                |               |
| subjects affected / exposed  | 1 / 73 (1.37%)   | 0 / 34 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all                            | 0 / 1  | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all                                 | 0 / 0  | 0 / 0          | 0 / 0         |
| NAUSEA   |  |                |               |
| subjects affected / exposed  | 1 / 73 (1.37%)   | 0 / 34 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all                            | 0 / 1  | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all                                 | 0 / 0  | 0 / 0          | 0 / 0         |
| Renal and urinary disorders<br>CALCULUS URINARY                            |  |                |               |
| subjects affected / exposed  | 1 / 73 (1.37%)   | 0 / 34 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all                            | 0 / 1  | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all                                 | 0 / 0  | 0 / 0          | 0 / 0         |
| Psychiatric disorders<br>SOMNAMBULISM                                      |  |                |               |
| subjects affected / exposed  | 0 / 73 (0.00%)   | 0 / 34 (0.00%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all                            | 0 / 0  | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all                                 | 0 / 0  | 0 / 0          | 0 / 0         |
| Musculoskeletal and connective tissue disorders<br>HAEMOPHILIC ARTHROPATHY |  |                |               |
| subjects affected / exposed  | 1 / 73 (1.37%)   | 1 / 34 (2.94%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all                            | 0 / 1  | 0 / 1          | 0 / 0         |
| deaths causally related to treatment / all                                 | 0 / 0  | 0 / 0          | 0 / 0         |
| SYNOVITIS  |  |                |               |

|   |                |                |                 |
|---|----------------|----------------|-----------------|
| subjects affected / exposed                     | 1 / 73 (1.37%) | 0 / 34 (0.00%) | 0 / 1 (0.00%)   |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| <b>PAIN IN EXTREMITY</b>                        |                |                |                 |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 0 / 34 (0.00%) | 1 / 1 (100.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| <b>Infections and infestations</b>              |                |                |                 |
| <b>TOOTH ABSCESS</b>                            |                |                |                 |
| subjects affected / exposed                     | 1 / 73 (1.37%) | 0 / 34 (0.00%) | 0 / 1 (0.00%)   |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| <b>PULPITIS DENTAL</b>                          |                |                |                 |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 0 / 34 (0.00%) | 0 / 1 (0.00%)   |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| <b>APPENDICITIS</b>                             |                |                |                 |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 1 / 34 (2.94%) | 0 / 1 (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           |

|   |                      |  |  |
|---|----------------------|--|--|
| <b>Serious adverse events</b>                         | Standard Prophylaxis |  |  |
| Total subjects affected by serious adverse events     |                      |  |  |
| subjects affected / exposed                           | 2 / 32 (6.25%)       |  |  |
| number of deaths (all causes)                         | 0                    |  |  |
| number of deaths resulting from adverse events        | 0                    |  |  |
| <b>Injury, poisoning and procedural complications</b> |                      |  |  |
| <b>JOINT DISLOCATION</b>                              |                      |  |  |
| subjects affected / exposed                           | 0 / 32 (0.00%)       |  |  |
| occurrences causally related to treatment / all       | 0 / 0                |  |  |
| deaths causally related to treatment / all            | 0 / 0                |  |  |
| <b>Surgical and medical procedures</b>                |                      |  |  |
| <b>HOSPITALIZATION</b>                                |                      |  |  |



|   |  |  |  |
|---|--|--|--|
| subjects affected / exposed                     | 0 / 32 (0.00%)   |  |  |
| occurrences causally related to treatment / all | 0 / 0  |  |  |
| deaths causally related to treatment / all      | 0 / 0  |  |  |
| Blood and lymphatic system disorders            |  |  |  |
| FACTOR VIII INHIBITION                          | Additional description: This event was unconfirmed and therefore did not meet protocol definition for a Factor VIII inhibitor. |  |  |
| subjects affected / exposed                     | 0 / 32 (0.00%)   |  |  |
| occurrences causally related to treatment / all | 0 / 0  |  |  |
| deaths causally related to treatment / all      | 0 / 0  |  |  |
| Gastrointestinal disorders                      |  |  |  |
| ABDOMINAL PAIN                                  |  |  |  |
| subjects affected / exposed                     | 0 / 32 (0.00%)   |  |  |
| occurrences causally related to treatment / all | 0 / 0  |  |  |
| deaths causally related to treatment / all      | 0 / 0  |  |  |
| NAUSEA  |  |  |  |
| subjects affected / exposed                     | 0 / 32 (0.00%)   |  |  |
| occurrences causally related to treatment / all | 0 / 0  |  |  |
| deaths causally related to treatment / all      | 0 / 0  |  |  |
| Renal and urinary disorders                     |  |  |  |
| CALCULUS URINARY                                |  |  |  |
| subjects affected / exposed                     | 0 / 32 (0.00%)   |  |  |
| occurrences causally related to treatment / all | 0 / 0  |  |  |
| deaths causally related to treatment / all      | 0 / 0  |  |  |
| Psychiatric disorders                           |  |  |  |
| SOMNAMBULISM                                    |  |  |  |
| subjects affected / exposed                     | 1 / 32 (3.13%)   |  |  |
| occurrences causally related to treatment / all | 0 / 1  |  |  |
| deaths causally related to treatment / all      | 0 / 0  |  |  |
| Musculoskeletal and connective tissue disorders |  |  |  |
| HAEMOPHILIC ARTHROPATHY                         |  |  |  |
| subjects affected / exposed                     | 0 / 32 (0.00%)   |  |  |
| occurrences causally related to treatment / all | 0 / 0  |  |  |
| deaths causally related to treatment / all      | 0 / 0  |  |  |
| SYNOVITIS                                       |  |  |  |

|   |                |  |  |
|---|----------------|--|--|
| subjects affected / exposed                     | 0 / 32 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| <b>PAIN IN EXTREMITY</b>                        |                |  |  |
| subjects affected / exposed                     | 0 / 32 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| <b>Infections and infestations</b>              |                |  |  |
| <b>TOOTH ABSCESS</b>                            |                |  |  |
| subjects affected / exposed                     | 0 / 32 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| <b>PULPITIS DENTAL</b>                          |                |  |  |
| subjects affected / exposed                     | 1 / 32 (3.13%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| <b>APPENDICITIS</b>                             |                |  |  |
| subjects affected / exposed                     | 0 / 32 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |

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

| <b>Non-serious adverse events</b>                            | On-Demand        | PK-Driven Prophylaxis | SAEs Outside of the 3 Treatment Arms |
|--|------------------|-----------------------|--------------------------------------|
| <b>Total subjects affected by non-serious adverse events</b> |                  |                       |                                      |
| subjects affected / exposed                                  | 18 / 73 (24.66%) | 7 / 34 (20.59%)       | 0 / 1 (0.00%)                        |
| <b>Nervous system disorders</b>                              |                  |                       |                                      |
| <b>HEADACHE</b>  |                  |                       |                                      |
| subjects affected / exposed                                  | 4 / 73 (5.48%)   | 3 / 34 (8.82%)        | 0 / 1 (0.00%)                        |
| occurrences (all)  | 6                | 5                     | 0                                    |
| <b>Gastrointestinal disorders</b>                            |                  |                       |                                      |
| <b>DIARRHOEA</b>   |                  |                       |                                      |
| subjects affected / exposed                                  | 4 / 73 (5.48%)   | 0 / 34 (0.00%)        | 0 / 1 (0.00%)                        |
| occurrences (all)  | 4                | 0                     | 0                                    |
| <b>IRRITABLE BOWEL SYNDROME</b>                              |                  |                       |                                      |

|   |  |  |  |
|---|--|--|--|
| subjects affected / exposed<br>occurrences (all)  | 0 / 73 (0.00%)<br>0                            | 2 / 34 (5.88%)<br>4                            | 0 / 1 (0.00%)<br>0                           |
| Respiratory, thoracic and mediastinal disorders<br>COUGH<br>subjects affected / exposed<br>occurrences (all)  | 0 / 73 (0.00%)<br>0                            | 0 / 34 (0.00%)<br>0                            | 0 / 1 (0.00%)<br>0                           |
| Musculoskeletal and connective tissue disorders<br>ARTHRALGIA<br>subjects affected / exposed<br>occurrences (all)   | 0 / 73 (0.00%)<br>0                            | 0 / 34 (0.00%)<br>0                            | 0 / 1 (0.00%)<br>0                           |
| Infections and infestations<br>NASOPHARYNGITIS<br>subjects affected / exposed<br>occurrences (all)<br><br>UPPER RESPIRATORY TRACT INFECTION<br>subjects affected / exposed<br>occurrences (all) | 6 / 73 (8.22%)<br>7<br><br>4 / 73 (5.48%)<br>4 | 0 / 34 (0.00%)<br>0<br><br>2 / 34 (5.88%)<br>2 | 0 / 1 (0.00%)<br>0<br><br>0 / 1 (0.00%)<br>0 |

|   |  |  |  |
|---|--|--|--|
| <b>Non-serious adverse events</b>   | Standard Prophylaxis                           |  |  |
| Total subjects affected by non-serious adverse events<br>subjects affected / exposed  | 4 / 32 (12.50%)                                |  |  |
| Nervous system disorders<br>HEADACHE<br>subjects affected / exposed<br>occurrences (all)  | 0 / 32 (0.00%)<br>0                            |  |  |
| Gastrointestinal disorders<br>DIARRHOEA<br>subjects affected / exposed<br>occurrences (all)<br><br>IRRITABLE BOWEL SYNDROME<br>subjects affected / exposed<br>occurrences (all) | 0 / 32 (0.00%)<br>0<br><br>0 / 32 (0.00%)<br>0 |  |  |
| Respiratory, thoracic and mediastinal disorders<br>COUGH<br>subjects affected / exposed<br>occurrences (all)  | 2 / 32 (6.25%)<br>2                            |  |  |

|   |  |  |  |
|---|--|--|--|
| Musculoskeletal and connective tissue disorders<br>ARTHRALGIA<br>subjects affected / exposed<br>occurrences (all)   | 2 / 32 (6.25%)<br>3                            |  |  |
| Infections and infestations<br>NASOPHARYNGITIS<br>subjects affected / exposed<br>occurrences (all)<br><br>UPPER RESPIRATORY TRACT INFECTION<br>subjects affected / exposed<br>occurrences (all) | 0 / 32 (0.00%)<br>0<br><br>0 / 32 (0.00%)<br>0 |  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date              | Amendment  |
|-------------------|--|
| 30 May 2006       | Provision of criteria for assessing the severity and cause of bleeding episodes and recording the anatomical site(s) affected. |
| 20 September 2007 | Change in inclusion criteria.  |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported

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### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/22212248>