



## Clinical trial results:

**FEIBA NF: a prospective, open-label, randomized, parallel study to evaluate efficacy and safety of prophylactic versus on-demand treatment in subjects with hemophilia A or B and a high titer inhibitor**

### Summary

|                          |                 |
|--------------------------|-----------------|
| EudraCT number           | 2008-003855-65  |
| Trial protocol           | FR BG IT PL     |
| Global end of trial date | 17 October 2012 |

### Results information

|                                |                |
|--------------------------------|----------------|
| Result version number          | v1             |
| This version publication date  | 23 May 2016    |
| First version publication date | 06 August 2015 |

### Trial information

#### Trial identification

|                       |        |
|-----------------------|--------|
| Sponsor protocol code | 090701 |
|-----------------------|--------|

#### Additional study identifiers

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

Notes:

### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Baxalta US Inc.  |
| Sponsor organisation address | One Baxter Way, Westlake Village CA, United States, 91362-3811   |
| 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          |
| 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 |

Notes:

### Paediatric regulatory details

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

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

Notes:

## Results analysis stage

|  |                 |
|--|-----------------|
| Analysis stage                                       | Final           |
| Date of interim/final analysis                       | 17 October 2012 |
| Is this the analysis of the primary completion data? | Yes             |
| Primary completion date                              | 17 October 2012 |
| Global end of trial reached?                         | Yes             |
| Global end of trial date                             | 17 October 2012 |
| Was the trial ended prematurely?                     | No              |

Notes:

## General information about the trial

Main objective of the trial:

To demonstrate that the annualized rate of all types of bleeds in subjects on the prophylaxis arm is less than that of the subjects in the on-demand arm

Protection of trial subjects:

This study was conducted in accordance with the protocol, the International Conference on Harmonisation Guideline for Good Clinical Practice (ICH GCP), Title 21 of the US Code of Federal Regulations (US CFR), the European Clinical Trial Directive (2001/20/EC and 2005/28/EC), and national and local requirements.

Background therapy: -

Evidence for comparator: -

|   |               |
|---|---------------|
| Actual start date of recruitment                          | 31 March 2009 |
| 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 | United States: 2       |
| Country: Number of subjects enrolled | Poland: 2              |
| Country: Number of subjects enrolled | Brazil: 5              |
| Country: Number of subjects enrolled | Ukraine: 8             |
| Country: Number of subjects enrolled | Romania: 1             |
| Country: Number of subjects enrolled | Croatia: 1             |
| Country: Number of subjects enrolled | Russian Federation: 11 |
| Country: Number of subjects enrolled | Bulgaria: 2            |
| Country: Number of subjects enrolled | Japan: 2               |
| Country: Number of subjects enrolled | New Zealand: 2         |
| Worldwide total number of subjects   | 36                     |
| EEA total number of subjects         | 6                      |

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)                 | 7  |
| Adults (18-64 years)                      | 24 |
| From 65 to 84 years                       | 0  |
| 85 years and over                         | 0  |

## Subject disposition

### Recruitment

Recruitment details:

Enrollment was conducted in Europe, North America, Asia-Pacific, and South America at 17 clinical sites beginning in March 2009.

### Pre-assignment

Screening details:

52 participants were enrolled. Sixteen participants discontinued, (ten were screen failures and six were withdrawn before randomization (2 sponsor's decision- inhibitors, 3 withdrew consent, and 1 due to investigator decision to have participant on prophylaxis). Therefore 36 participants were randomized.

### Period 1

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

### Arms

|  |   |
|--|---|
| Are arms mutually exclusive?           | No  |
| <b>Arm title</b>                       | On-demand arm   |
| Arm description: -                     |   |
| Arm type                               | Experimental  |
| Investigational medicinal product name | FEIBA NF  |
| Investigational medicinal product code |   |
| Other name                             | Anti-Inhibitor Coagulant Complex (AICC), Nanofiltered |
| Pharmaceutical forms                   | Infusion  |
| Routes of administration               | Intravenous bolus use                                 |

Dosage and administration details:

On demand: Subjects will be treated with the standard FEIBA NF dose and dosing interval prescribed by the treating physician throughout the 12-month study period. The recommended target dose of FEIBA NF for on-demand therapy will be based on the type of bleeding episode and the product will be infused as needed at the discretion of the investigator.

|  |   |
|--|---|
| <b>Arm title</b>                       | Prophylaxis arm                                       |
| Arm description: -                     |   |
| Arm type                               | Experimental  |
| Investigational medicinal product name | FEIBA NF  |
| Investigational medicinal product code |   |
| Other name                             | Anti-Inhibitor Coagulant Complex (AICC), Nanofiltered |
| Pharmaceutical forms                   | Infusion  |
| Routes of administration               | Intravenous bolus use                                 |

Dosage and administration details:

Prophylaxis: 85 ± 15 U/kg (70-100 U/kg) every other day

|  |                                      |
|--|--------------------------------------|
| <b>Arm title</b>   | On-demand arm versus Prophylaxis arm |
| Arm description:   |                                      |
| Please note that all uniquely titled arms defined in the results posted in ClinicalTrials.gov are imported into EU results as well. Period arm 'On-demand arm versus Prophylaxis arm' is used for some endpoints and in the statistical analysis section. Baseline characteristics for this period arm contain on-demand and prophylaxis subjects. |                                      |
| Arm type   | Experimental                         |

|  |   |
|--|---|
| Investigational medicinal product name | FEIBA NF  |
| Investigational medicinal product code |   |
| Other name                             | Anti-Inhibitor Coagulant Complex (AICC), Nanofiltered |
| Pharmaceutical forms                   | Infusion  |
| Routes of administration               | Intravenous bolus use                                 |

Dosage and administration details:

Prophylaxis: 85 ± 15 U/kg (70-100 U/kg) every other day

|  |   |
|--|---|
| Investigational medicinal product name | FEIBA NF  |
| Investigational medicinal product code |   |
| Other name                             | Anti-Inhibitor Coagulant Complex (AICC), Nanofiltered |
| Pharmaceutical forms                   | Infusion  |
| Routes of administration               | Intravenous bolus use                                 |

Dosage and administration details:

On demand: Subjects will be treated with the standard FEIBA NF dose and dosing interval prescribed by the treating physician throughout the 12-month study period. The recommended target dose of FEIBA NF for on-demand therapy will be based on the type of bleeding episode and the product will be infused as needed at the discretion of the investigator.

|                  |           |
|------------------|-----------|
| <b>Arm title</b> | On-demand |
|------------------|-----------|

Arm description:

Please note that all uniquely titled arms defined in the results posted in ClinicalTrials.gov are imported into EU results as well. 'On-demand' is the same as 'On-demand arm'.

|  |   |
|--|---|
| Arm type                               | Experimental  |
| Investigational medicinal product name | FEIBA NF  |
| Investigational medicinal product code |   |
| Other name                             | Anti-Inhibitor Coagulant Complex (AICC), Nanofiltered |
| Pharmaceutical forms                   | Infusion  |
| Routes of administration               | Intravenous bolus use                                 |

Dosage and administration details:

On demand: Subjects will be treated with the standard FEIBA NF dose and dosing interval prescribed by the treating physician throughout the 12-month study period. The recommended target dose of FEIBA NF for on-demand therapy will be based on the type of bleeding episode and the product will be infused as needed at the discretion of the investigator.

|                  |             |
|------------------|-------------|
| <b>Arm title</b> | Prophylaxis |
|------------------|-------------|

Arm description:

Please note that all uniquely titled arms defined in the results posted in ClinicalTrials.gov are imported into EU results as well. 'Prophylaxis' is the same as 'Prophylaxis arm'.

|  |   |
|--|---|
| Arm type                               | Experimental  |
| Investigational medicinal product name | FEIBA NF  |
| Investigational medicinal product code |   |
| Other name                             | Anti-Inhibitor Coagulant Complex (AICC), Nanofiltered |
| Pharmaceutical forms                   | Infusion  |
| Routes of administration               | Intravenous bolus use                                 |

Dosage and administration details:

Prophylaxis: 85 ± 15 U/kg (70-100 U/kg) every other day

| Number of subjects in period 1 | On-demand arm | Prophylaxis arm | On-demand arm versus Prophylaxis arm |
|--------------------------------|---------------|-----------------|--------------------------------------|
|                                |               |                 |                                      |
| Started                        | 19            | 17              | 36                                   |
| Completed                      | 17            | 16              | 33                                   |
| Not completed                  | 2             | 1               | 3                                    |
| Adverse event, serious fatal   | 1             | -               | 1                                    |
| Adverse event, non-fatal       | -             | 1               | 1                                    |
| planned surgery                | 1             | -               | 1                                    |

| Number of subjects in period 1 | On-demand | Prophylaxis |
|--------------------------------|-----------|-------------|
| Started                        | 19        | 17          |
| Completed                      | 17        | 16          |
| Not completed                  | 2         | 1           |
| Adverse event, serious fatal   | 1         | -           |
| Adverse event, non-fatal       | -         | 1           |
| planned surgery                | 1         | -           |

## Baseline characteristics

### Reporting groups

|  |                                      |
|--|--------------------------------------|
| Reporting group title  | On-demand arm                        |
| Reporting group description: -   |                                      |
| Reporting group title  | Prophylaxis arm                      |
| Reporting group description: -   |                                      |
| Reporting group title  | On-demand arm versus Prophylaxis arm |
| Reporting group description:   |                                      |
| Please note that all uniquely titled arms defined in the results posted in ClinicalTrials.gov are imported into EU results as well. Period arm 'On-demand arm versus Prophylaxis arm' is used for some endpoints and in the statistical analysis section. Baseline characteristics for this period arm contain on-demand and prophylaxis subjects. |                                      |
| Reporting group title  | On-demand                            |
| Reporting group description:   |                                      |
| Please note that all uniquely titled arms defined in the results posted in ClinicalTrials.gov are imported into EU results as well. 'On-demand' is the same as 'On-demand arm'.  |                                      |
| Reporting group title  | Prophylaxis                          |
| Reporting group description:   |                                      |
| Please note that all uniquely titled arms defined in the results posted in ClinicalTrials.gov are imported into EU results as well. 'Prophylaxis' is the same as 'Prophylaxis arm'.  |                                      |

| Reporting group values | On-demand arm | Prophylaxis arm | On-demand arm versus Prophylaxis arm |
|------------------------|---------------|-----------------|--------------------------------------|
| Number of subjects     | 19            | 17              | 36                                   |
| Age categorical        |               |                 |                                      |
| Units: Subjects        |               |                 |                                      |

|                                |        |        |        |
|--------------------------------|--------|--------|--------|
| Age continuous                 |        |        |        |
| Age continuous description     |        |        |        |
| Units: years                   |        |        |        |
| arithmetic mean                | 29.1   | 25.6   | 27.4   |
| standard deviation             | ± 15.2 | ± 15.4 | ± 15.2 |
| Gender categorical             |        |        |        |
| Gender categorical description |        |        |        |
| Units: Subjects                |        |        |        |
| Female                         | 0      | 0      | 0      |
| Male                           | 19     | 17     | 36     |
| Region of Enrollment           |        |        |        |
| Units: Subjects                |        |        |        |
| United States                  | 1      | 1      | 2      |
| Poland                         | 1      | 1      | 2      |
| Brazil                         | 3      | 2      | 5      |
| Ukraine                        | 4      | 4      | 8      |
| Romania                        | 0      | 1      | 1      |
| Croatia                        | 0      | 1      | 1      |
| Russian Federation             | 8      | 3      | 11     |
| Bulgaria                       | 0      | 2      | 2      |
| Japan                          | 1      | 1      | 2      |

|             |   |   |   |
|-------------|---|---|---|
| New Zealand | 1 | 1 | 2 |
|-------------|---|---|---|

| Reporting group values             | On-demand | Prophylaxis | Total |
|------------------------------------|-----------|-------------|-------|
| Number of subjects                 | 19        | 17          | 108   |
| Age categorical<br>Units: Subjects |           |             |       |

|   |        |        |     |
|---|--------|--------|-----|
| Age continuous                          |        |        |     |
| Age continuous description              |        |        |     |
| Units: years                            |        |        |     |
| arithmetic mean                         | 29.1   | 25.6   |     |
| standard deviation                      | ± 15.2 | ± 15.4 | -   |
| Gender categorical                      |        |        |     |
| Gender categorical description          |        |        |     |
| Units: Subjects                         |        |        |     |
| Female                                  | 0      | 0      | 0   |
| Male                                    | 19     | 17     | 108 |
| Region of Enrollment<br>Units: Subjects |        |        |     |
| United States                           | 1      | 1      | 6   |
| Poland                                  | 1      | 1      | 6   |
| Brazil                                  | 3      | 2      | 15  |
| Ukraine                                 | 4      | 4      | 24  |
| Romania                                 | 0      | 1      | 3   |
| Croatia                                 | 0      | 1      | 3   |
| Russian Federation                      | 8      | 3      | 33  |
| Bulgaria                                | 0      | 2      | 6   |
| Japan                                   | 1      | 1      | 6   |
| New Zealand                             | 1      | 1      | 6   |



## End points

### End points reporting groups

|  |                                      |
|--|--------------------------------------|
| Reporting group title  | On-demand arm                        |
| Reporting group description: -   |                                      |
| Reporting group title  | Prophylaxis arm                      |
| Reporting group description: -   |                                      |
| Reporting group title  | On-demand arm versus Prophylaxis arm |
| Reporting group description:<br>Please note that all uniquely titled arms defined in the results posted in ClinicalTrials.gov are imported into EU results as well. Period arm 'On-demand arm versus Prophylaxis arm' is used for some endpoints and in the statistical analysis section. Baseline characteristics for this period arm contain on-demand and prophylaxis subjects. |                                      |
| Reporting group title  | On-demand                            |
| Reporting group description:<br>Please note that all uniquely titled arms defined in the results posted in ClinicalTrials.gov are imported into EU results as well. 'On-demand' is the same as 'On-demand arm'.  |                                      |
| Reporting group title  | Prophylaxis                          |
| Reporting group description:<br>Please note that all uniquely titled arms defined in the results posted in ClinicalTrials.gov are imported into EU results as well. 'Prophylaxis' is the same as 'Prophylaxis arm'.  |                                      |

### Primary: Reduction in annualized bleeding episode rate (ABR) among participants receiving prophylactic treatment as compared to those treated on-demand

|  |   |
|--|---|
| End point title  | Reduction in annualized bleeding episode rate (ABR) among participants receiving prophylactic treatment as compared to those treated on-demand <sup>[1]</sup> |
| End point description:<br>Participants were Randomized to Receive 1 of the 2 Following Treatment Regimens: 1.On-Demand: FEIBA NF dose & dosing interval as prescribed by treating physician 2.Prophylaxis: 85 ± 15 U/kg of FEIBA NF every other day during 12-month prophylactic period Annualized rate of bleeding episodes was calculated as: (Number of bleeding episodes/observed treatment period in days) * 365.25 |   |
| End point type   | Primary   |
| End point timeframe:<br>12 months ± 14 days  |   |

#### 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: Baseline period arms are not mutually exclusive. Details see under description of period arms.

| End point values                      | On-demand arm     | Prophylaxis arm |  |  |
|---------------------------------------|-------------------|-----------------|--|--|
| Subject group type                    | Reporting group   | Reporting group |  |  |
| Number of subjects analysed           | 19                | 17              |  |  |
| Units: bleeds/year                    |                   |                 |  |  |
| median (inter-quartile range (Q1-Q3)) | 28.7 (17.7 to 50) | 7.9 (2.9 to 11) |  |  |

## Statistical analyses

|  |                                 |
|--|---------------------------------|
| <b>Statistical analysis title</b>  | Statistical analysis 1          |
| Statistical analysis description:  |                                 |
| H0: $\mu(\text{on-demand}) = \mu(\text{prophylaxis})$ Versus H1: $\mu(\text{on-demand}) \neq \mu(\text{prophylaxis})$ (Where H0 implies no difference in mean bleeding episode rate between prophylaxis and on-demand treatment arms and H1 implies otherwise. This test was performed at a significance level of 5%, two-sided, two sample) |                                 |
| Comparison groups  | On-demand arm v Prophylaxis arm |
| Number of subjects included in analysis  | 36                              |
| Analysis specification   | Pre-specified                   |
| Analysis type  |                                 |
| P-value  | = 0.0003                        |
| Method   | Two-sample, two-sided t-test    |
| Confidence interval  |                                 |
| level  | 95 %                            |

## Secondary: Annualized Bleeding Rate by Treatment Regimen, Bleeding Etiology, and Bleed Type

|  |   |
|--|---|
| End point title                                  | Annualized Bleeding Rate by Treatment Regimen, Bleeding Etiology, and Bleed Type <sup>[2]</sup> |
| End point description:                           |   |
| Spontaneous includes unknown/undermined etiology |   |
| End point type                                   | Secondary   |
| End point timeframe:                             |   |
| 12 months $\pm$ 14 days                          |   |

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: Baseline period arms are not mutually exclusive. Details see under description of period arms.

| End point values                         | On-demand arm       | Prophylaxis arm |  |  |
|--|---------------------|-----------------|--|--|
| Subject group type                       | Reporting group     | Reporting group |  |  |
| Number of subjects analysed              | 19                  | 17              |  |  |
| Units: Bleeds per year                   |                     |                 |  |  |
| median (inter-quartile range (Q1-Q3))    |                     |                 |  |  |
| Spontaneous                              | 18.9 (10.9 to 43.5) | 5.6 (2.9 to 8)  |  |  |
| Traumatic                                | 4.7 (1.9 to 10.7)   | 2.5 (0 to 3.1)  |  |  |
| Joint                                    | 22.9 (14.1 to 46.9) | 6 (2.9 to 10)   |  |  |
| Non-Joint                                | 2.9 (1 to 4.9)      | 0.5 (0 to 2)    |  |  |
| Spontaneous Joint                        | 16.6 (9.9 to 40.8)  | 4.5 (2.9 to 8)  |  |  |
| Spontaneous Non-Joint                    | 1 (1 to 2.9)        | 0 (0 to 1)      |  |  |
| Traumatic Joint                          | 4 (1 to 7.1)        | 1 (0 to 3.1)    |  |  |
| Traumatic Non-Joint                      | 0 (0 to 1.9)        | 0 (0 to 1)      |  |  |
| All Bleeding Etiologies, and Bleed Types | 28.7 (17.7 to 50)   | 7.9 (2.9 to 11) |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Differences in Mean Transformed Annualized Bleeding Rate Between On-Demand and Prophylaxis Treatment Regimens by Bleeding Etiology, and Bleeding Type

|                 |  |
|-----------------|--|
| End point title | Differences in Mean Transformed Annualized Bleeding Rate Between On-Demand and Prophylaxis Treatment Regimens by Bleeding Etiology, and Bleeding Type <sup>[3]</sup> |
|-----------------|--|

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 t-test. The difference in mean transformed ABRs was used to perform statistical tests and generate p-values at a significance level of 5%. Participants were Randomized to Receive 1 of the 2 Following Treatment Regimens: 1.On-Demand: FEIBA NF dose & dosing interval as prescribed by treating physician 2.Prophylaxis: 85 ± 15 U/kg of FEIBA NF every other day during 12-month prophylactic period

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

End point timeframe:

12 months ± 14 days

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: Baseline period arms are not mutually exclusive. Details see under description of period arms.

|  |                                      |  |  |  |
|--|--------------------------------------|--|--|--|
| <b>End point values</b>                | On-demand arm versus Prophylaxis arm |  |  |  |
| Subject group type                     | Reporting group                      |  |  |  |
| Number of subjects analysed            | 36                                   |  |  |  |
| Units: (bleeds/year) <sup>^(1/2)</sup> |                                      |  |  |  |
| arithmetic mean (standard deviation)   |                                      |  |  |  |
| Spontaneous Bleeds                     | 2.2 (± 1.8)                          |  |  |  |
| Traumatic Bleeds                       | 1 (± 1.2)                            |  |  |  |
| Joint Bleeds                           | 2.4 (± 1.9)                          |  |  |  |
| Non-Joint Bleeds                       | 0.8 (± 0.9)                          |  |  |  |
| Spontaneous Joint Bleeds               | 2.1 (± 1.8)                          |  |  |  |
| Spontaneous Non-Joint Bleeds           | 0.8 (± 0.8)                          |  |  |  |
| Traumatic Joint Bleeds                 | 0.9 (± 1.2)                          |  |  |  |
| Traumatic Non-Joint Bleeds             | 0 (± 0.9)                            |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Annualized Bleeding Rate for New Target Joints

|                 |   |
|-----------------|---|
| End point title | Annualized Bleeding Rate for New Target Joints <sup>[4]</sup> |
|-----------------|---|

End point description:

Target joints are ≥4 bleeds/6 months in any one of the following joints: ankles, knees, elbows, and hips; a target joint bleeding episode refers to an individual anatomical location.

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

End point timeframe:

12 months  $\pm$  14 days

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: Baseline period arms are not mutually exclusive. Details see under description of period arms.

| End point values                      | On-demand arm   | Prophylaxis arm |  |  |
|---------------------------------------|-----------------|-----------------|--|--|
| Subject group type                    | Reporting group | Reporting group |  |  |
| Number of subjects analysed           | 19              | 17              |  |  |
| Units: Bleeds per year                |                 |                 |  |  |
| median (inter-quartile range (Q1-Q3)) | 5.9 (0 to 12.9) | 0 (0 to 4.1)    |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Differences in Mean Transformed Annualized Bleeding Rate Between On-Demand and Prophylaxis Treatment Regimens: New Target Joints

|                 |   |
|-----------------|---|
| End point title | Differences in Mean Transformed Annualized Bleeding Rate Between On-Demand and Prophylaxis Treatment Regimens: New Target Joints <sup>[5]</sup> |
|-----------------|---|

End point description:

Annualized bleed rates (ABRs) 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 a two-sample, two-sided t-test. The difference in mean transformed ABRs was used to perform statistical tests and generate p-values at a significance level of 5%

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

End point timeframe:

12 months  $\pm$  14 days

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: Baseline period arms are not mutually exclusive. Details see under description of period arms.

| End point values                      | On-demand arm versus Prophylaxis arm |  |  |  |
|---------------------------------------|--------------------------------------|--|--|--|
| Subject group type                    | Reporting group                      |  |  |  |
| Number of subjects analysed           | 36                                   |  |  |  |
| Units: (bleeds/year) <sup>(1/2)</sup> |                                      |  |  |  |
| arithmetic mean (standard deviation)  | 1.6 ( $\pm$ 2.2)                     |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of New Target Joints

|  |  |
|--|--|
| End point title  | Number of New Target Joints <sup>[6]</sup> |
| End point description:<br>Target Joints are defined as $\geq 4$ bleeds/6 months in any one of the following joints: ankles, knees, elbows and hips |  |
| End point type   | Secondary                                  |
| End point timeframe:<br>12 months $\pm$ 14 days  |  |

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: Baseline period arms are not mutually exclusive. Details see under description of period arms.

| End point values            | On-demand arm   | Prophylaxis arm |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 19              | 17              |  |  |
| Units: new target joints    | 23              | 7               |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Assessment of Objective Clinical Symptoms- Visual Analog Scale (VAS): Pain in Adolescents and Adults ( $\geq 12$ years old)

|   |  |
|---|--|
| End point title   | Assessment of Objective Clinical Symptoms- Visual Analog Scale (VAS): Pain in Adolescents and Adults ( $\geq 12$ years old) <sup>[7]</sup> |
| End point description:<br>Pain caused by a bleeding episode in adolescents and adults ( $\geq 12$ years old) was measured at pre-infusion (pre-inf) and at $6 \pm 0.5$ hours (h) and $24 \pm 1$ h post-infusion (post-inf) (after the last infusion given to treat a bleeding episode) on the VAS pain scale in millimeters from 0 (no pain) to 100 (worst possible pain). For analysis purposes, if short acting analgesics (duration of activity approximately $6 \pm 0.5$ h) were used, pain was assigned the highest possible score (100). Pain assessment occurred after each infusion related to single bleeding episodes. In case participants required an additional infusion within 24h, pain was assessed $6 \pm 0.5$ h and $24 \pm 1$ h following the subsequent infusion. Change in VAS scores at $6 \pm 0.5$ h and $24 \pm 1$ h post-infusion were also compared relative to pre-infusion VAS scores (ie, (pre-infusion VAS score) - (post-infusion VAS score)). |  |
| End point type  | Secondary  |
| End point timeframe:<br>Throughout the study period, 12 months $\pm$ 14 days  |  |

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: Baseline period arms are not mutually exclusive. Details see under description of period arms.

| End point values                      | On-demand arm   | Prophylaxis arm |  |  |
|---------------------------------------|-----------------|-----------------|--|--|
| Subject group type                    | Reporting group | Reporting group |  |  |
| Number of subjects analysed           | 17              | 12              |  |  |
| Units: Scores on a scale              |                 |                 |  |  |
| median (inter-quartile range (Q1-Q3)) |                 |                 |  |  |

|  |                |                     |  |  |
|--|----------------|---------------------|--|--|
| Pre-Infusion (N= 513, 130)                     | 29 (12 to 55)  | 49.5 (34.7 to 81.6) |  |  |
| 6 ± 0.5 hours post-infusion (N= 522, 158)      | 10 (4 to 37)   | 33.8 (8 to 52.6)    |  |  |
| 24 ± 1 hours post-infusion (N= 512,131)        | 3 (1 to 14)    | 6.2 (1 to 20)       |  |  |
| Change (Pre-Inf to 6h post-inf) (N= 509, 129)  | 10 (4 to 21.8) | 19.4 (5 to 41.6)    |  |  |
| Change (Pre-Inf to 24h post-inf) (N= 489, 102) | 18 (8 to 39.6) | 37.8 (17 to 75.5)   |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Assessment of Clinical Symptoms - Visual Analog Scale (VAS): Pain in Pediatrics (<12 years old)

|                 |  |
|-----------------|--|
| End point title | Assessment of Clinical Symptoms - Visual Analog Scale (VAS): Pain in Pediatrics (<12 years old) <sup>[8]</sup> |
|-----------------|--|

End point description:

Pain caused by a bleeding episode (BE) in pediatric participants (<12 years old) was measured at pre-infusion (pre-inf) and at 6 ± 0.5 h and 24 ± 1 h post-infusion (post-inf) (after the last infusion given to treat a bleeding episode) using the children's VAS pain scale (a facial expression scale with one end marked as no pain and the opposite end marked as the worst possible pain). For analysis purposes, if short acting analgesics (duration of activity approximately 6 ± 0.5 h) were used, pain was assigned the highest possible score (worst possible pain). Scores on the children's VAS scale are presented as: -No Pain -Mild Pain -Moderate pain -Severe pain -Very severe pain

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

End point timeframe:

12 months ± 14 days

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: Baseline period arms are not mutually exclusive. Details see under description of period arms.

| End point values                                 | On-demand arm   | Prophylaxis arm |  |  |
|--|-----------------|-----------------|--|--|
| Subject group type                               | Reporting group | Reporting group |  |  |
| Number of subjects analysed                      | 2               | 2               |  |  |
| Units: Bleeding episodes                         |                 |                 |  |  |
| Pre-Infusion (N= 54, 8) - No Pain                | 27              | 3               |  |  |
| Pre-Infusion (N= 54, 8) - Mild Pain              | 3               | 1               |  |  |
| Pre-Infusion (N= 54, 8) - Moderate Pain          | 12              | 3               |  |  |
| Pre-Infusion (N= 54, 8) - Severe Pain            | 10              | 1               |  |  |
| Pre-Infusion (N= 54, 8) - Very Severe Pain       | 2               | 0               |  |  |
| 6 ± 0.5 h post-infusion (N= 74, 8) - No Pain     | 47              | 3               |  |  |
| ± 0.5 h post-infusion (N= 74, 8) - Mild Pain     | 9               | 3               |  |  |
| ± 0.5 h post-infusion (N= 74, 8) - Moderate Pain | 15              | 2               |  |  |
| ± 0.5 h post-infusion (N= 74, 8) - Severe Pain   | 3               | 0               |  |  |

|  |    |   |  |  |
|--|----|---|--|--|
| ± 0.5 h post-infusion (N= 74, 8)- Very Severe Pain | 0  | 0 |  |  |
| 24 ± 1 h post-infusion (N= 77, 9) - No Pain        | 60 | 7 |  |  |
| 24 ± 1 h post-infusion (N= 77, 9) - Mild Pain      | 11 | 1 |  |  |
| 24 ± 1 h post-infusion (N= 77, 9) - Moderate Pain  | 6  | 1 |  |  |
| 24 ± 1 h post-infusion (N= 77, 9) - Severe Pain    | 0  | 0 |  |  |
| 24± 1h post-infusion (N = 77, 9) -Very Severe Pain | 0  | 0 |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Assessment of Clinical Symptoms - Range of Motion (ROM)

|  |  |
|--|--|
| End point title  | Assessment of Clinical Symptoms - Range of Motion (ROM) <sup>[9]</sup> |
| End point description:   |  |
| ROM was measured using a goniometer for 3 key joints (ie, ankles, knees, and elbows) at screening, month 6, and termination (end of study visit) |  |
| End point type   | Secondary  |
| End point timeframe:   |  |
| 12 months ± 14 days  |  |

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: Baseline period arms are not mutually exclusive. Details see under description of period arms.

| End point values                                | On-demand arm   | Prophylaxis arm     |  |  |
|---|-----------------|---------------------|--|--|
| Subject group type                              | Reporting group | Reporting group     |  |  |
| Number of subjects analysed                     | 19              | 17                  |  |  |
| Units: degrees                                  |                 |                     |  |  |
| median (inter-quartile range (Q1-Q3))           |                 |                     |  |  |
| Left Elbow - Extension: Screening               | 15 (0 to 45)    | 10 (0 to 25)        |  |  |
| Left Elbow - Extension: Month 6 (n = 18,16)     | 10 (0 to 41)    | 8 (0 to 42.5)       |  |  |
| Left Elbow - Extension: Termination (n = 17,16) | 20 (0 to 41)    | 15.5 (0 to 40)      |  |  |
| Left Elbow - Flexion: Screening (n = 19,17)     | 125 (90 to 140) | 115 (80 to 140)     |  |  |
| Left Elbow - Flexion: Month 6 (n = 18,16)       | 130 (90 to 140) | 125 (72.5 to 143)   |  |  |
| Left Elbow - Flexion: Termination (n = 17,16)   | 110 (90 to 140) | 125 (75 to 145)     |  |  |
| Left Elbow - Pronation: Screening (n = 18,16)   | 64 (55 to 90)   | 55 (22.5 to 77.5)   |  |  |
| Left Elbow - Pronation: Month 6 (n = 17,14)     | 80 (60 to 90)   | 67.5 (35 to 80)     |  |  |
| Left Elbow - Pronation: Termination (n = 17,15) | 68 (60 to 90)   | 65 (30 to 80)       |  |  |
| Left Elbow - Supination: Screening (n = 18,16)  | 75 (50 to 90)   | 42.5 (17.5 to 77.5) |  |  |

|  |                    |                    |  |  |
|--|--------------------|--------------------|--|--|
| Left Elbow - Supination: Month 6 (n = 17,14)       | 80 (50 to 90)      | 60 (35 to 80)      |  |  |
| Left Elbow - Supination: Termination (n = 17,15)   | 70 (50 to 90)      | 70 (35 to 80)      |  |  |
| Right Elbow - Extension: Screening (n = 19,17)     | 20 (0 to 50)       | 10 (0 to 50)       |  |  |
| Right Elbow - Extension: Month 6 (n = 18,16)       | 17.5 (0 to 50)     | 10 (0 to 42.5)     |  |  |
| Right Elbow - Extension: Termination (n = 18,16)   | 22.5 (0 to 45)     | 20 (0 to 62.5)     |  |  |
| Right Elbow - Flexion: Screening (n = 19,17)       | 120 (105 to 140)   | 100 (80 to 130)    |  |  |
| Right Elbow - Flexion: Month 6 (n = 18,16)         | 122.5 (110 to 140) | 100 (85 to 136)    |  |  |
| Right Elbow - Flexion: Termination (n = 18,16)     | 121 (110 to 140)   | 99 (70 to 127.5)   |  |  |
| Right Elbow - Pronation: Screening (n = 18,16)     | 75 (55 to 90)      | 57.5 (27.5 to 80)  |  |  |
| Right Elbow - Pronation: Month 6 (n = 17,14)       | 80 (55 to 90)      | 72.5 (40 to 80)    |  |  |
| Right Elbow - Pronation: Termination (n = 18,15)   | 67.5 (55 to 90)    | 70 (40 to 80)      |  |  |
| Right Elbow - Supination: Screening (n = 18,16)    | 75 (45 to 90)      | 52.5 (20 to 80)    |  |  |
| Right Elbow - Supination: Month 6 (n = 17,14)      | 70 (45 to 90)      | 72.5 (30 to 80)    |  |  |
| Right Elbow - Supination: Termination (n = 18,15)  | 75 (45 to 90)      | 70 (30 to 80)      |  |  |
| Left Knee - Extension: Screening (n = 18,16)       | 15 (5 to 90)       | 1.5 (0 to 55.5)    |  |  |
| Left Knee - Extension: Month 6 (n = 17,14)         | 15 (5 to 70)       | 0 (0 to 20)        |  |  |
| Left Knee - Extension: Termination (n = 18,15)     | 15 (5 to 90)       | 0 (0 to 70)        |  |  |
| Left Knee - Flexion: Screening (n = 19,17)         | 100 (80 to 130)    | 90 (65 to 115)     |  |  |
| Left Knee - Flexion: Month 6 (n = 18,16)           | 112.5 (80 to 130)  | 97.5 (65 to 125)   |  |  |
| Left Knee - Flexion: Termination (n = 18,16)       | 105 (60 to 130)    | 92.5 (70 to 125)   |  |  |
| Right Knee - Extension: Screening (n = 18,16)      | 35 (10 to 90)      | 5 (0 to 30)        |  |  |
| Right Knee - Extension: Month 6 (n = 17,14)        | 20 (10 to 90)      | 10 (2 to 30)       |  |  |
| Right Knee - Extension: Termination (n = 18,15)    | 17.5 (10 to 90)    | 5 (0 to 30)        |  |  |
| Right Knee - Flexion: Screening (n = 19,17)        | 90 (20 to 122)     | 80 (60 to 125)     |  |  |
| Right Knee - Flexion: Month 6 (n = 18,16)          | 90 (20 to 130)     | 82.5 (56 to 127.5) |  |  |
| Right Knee - Flexion: Termination (n = 18,16)      | 85 (20 to 120)     | 87.5 (56 to 127.5) |  |  |
| Left Ankle - Dorsiflexion: Screening (n = 18,16)   | 20 (15 to 30)      | 17.5 (9 to 37.5)   |  |  |
| Left Ankle - Dorsiflexion: Month 6 (n = 17,14)     | 20 (11 to 35)      | 17.5 (8 to 50)     |  |  |
| Left Ankle - Dorsiflexion: Termination (n = 17,15) | 15 (11 to 25)      | 20 (5 to 50)       |  |  |
| Left Ankle - Plantarflexion: Screening (n = 18,16) | 34.5 (30 to 40)    | 30 (10 to 35)      |  |  |
| Left Ankle - Plantarflexion: Month 6 (n = 17,14)   | 34 (25 to 35)      | 30 (15 to 40)      |  |  |



|  |               |                   |  |  |
|--|---------------|-------------------|--|--|
| Left Ankle - Plantarflexion: Termination (n=17,15) | 35 (30 to 40) | 30 (15 to 35)     |  |  |
| Left Ankle - Pronation: Screening (n = 19,17)      | 14 (10 to 20) | 15 (10 to 15)     |  |  |
| Left Ankle - Pronation: Month 6 (n = 18,15)        | 15 (10 to 20) | 15 (10 to 16)     |  |  |
| Left Ankle - Pronation: Termination (n = 18,16)    | 15 (10 to 20) | 12.5 (10 to 15.5) |  |  |
| Left Ankle - Supination: Screening (n = 19,17)     | 25 (10 to 30) | 15 (10 to 27)     |  |  |
| Left Ankle - Supination: Month 6 (n = 18,15)       | 25 (20 to 30) | 25 (10 to 30)     |  |  |
| Left Ankle - Supination: Termination (n = 18,16)   | 25 (16 to 30) | 20 (10 to 27.5)   |  |  |
| Right Ankle - Dorsiflexion: Screening (n = 18,16)  | 15 (10 to 20) | 20 (7.5 to 35)    |  |  |
| Right Ankle - Dorsiflexion: Month 6 (n = 17,14)    | 15 (15 to 20) | 25 (6 to 40)      |  |  |
| Right Ankle - Dorsiflexion: Termination (n= 17,15) | 15 (14 to 20) | 20 (10 to 40)     |  |  |
| Right Ankle - Plantarflexion: Screening (n= 18,16) | 35 (30 to 40) | 20 (9 to 39)      |  |  |
| Right Ankle - Plantarflexion: Month 6 (n= 17,14)   | 30 (25 to 40) | 23 (10 to 40)     |  |  |
| Right Ankle - Plantarflexion: Termination(n=17,15) | 30 (25 to 40) | 21 (10 to 40)     |  |  |
| Right Ankle - Pronation: Screening (n = 19,17)     | 10 (10 to 15) | 10 (10 to 20)     |  |  |
| Right Ankle - Pronation: Month 6 (n= 18,15)        | 10 (10 to 20) | 10 (10 to 20)     |  |  |
| Right Ankle - Pronation: Termination (n= 18,16)    | 10 (10 to 17) | 11 (10 to 17.5)   |  |  |
| Right Ankle - Supination: Screening (n = 19,17)    | 17 (10 to 30) | 20 (10 to 30)     |  |  |
| Right Ankle - Supination: Month 6 (n= 18,15)       | 20 (10 to 30) | 20 (10 to 30)     |  |  |
| Right Ankle - Supination: Termination (n= 18,16)   | 20 (10 to 30) | 20 (10 to 30)     |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Assessment of Hemostasis for Treatment of Bleeding Episodes- Overall Efficacy Rating at 6 hours

|                 |   |
|-----------------|---|
| End point title | Assessment of Hemostasis for Treatment of Bleeding Episodes- Overall Efficacy Rating at 6 hours <sup>[10]</sup> |
|-----------------|---|

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 ~6 hours of 1 infusion. Additional infusions may have been given to maintain hemostasis; Good: Definite pain relief and/or improvement in bleeding within ~6 hours after infusion. Possibly requires >1 infusion for complete resolution; Fair: Probable or slight relief of pain & slight improvement in bleeding within ~6 hours after infusion. Requires >1 infusion for complete resolution; None: No improvement or condition worsens

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

End point timeframe:

6 h ± 30 min post-infusion

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: Baseline period arms are not mutually exclusive. Details see under description of period arms.

| End point values            | On-demand arm   | Prophylaxis arm |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 19              | 14              |  |  |
| Units: bleeding episodes    |                 |                 |  |  |
| Excellent (n = 16, 5)       | 109             | 16              |  |  |
| Good (n = 19, 14)           | 355             | 106             |  |  |
| Fair (n = 15, 6)            | 142             | 42              |  |  |
| None (n = 6, 2)             | 14              | 5               |  |  |
| Rating Not Done (n = 3, 2)  | 3               | 2               |  |  |
| Not Available (n = 0, 1)    | 0               | 2               |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Assessment of Hemostasis for Treatment of Bleeding Episodes- Overall Efficacy Rating at 24 hours

|                 |  |
|-----------------|--|
| End point title | Assessment of Hemostasis for Treatment of Bleeding Episodes- Overall Efficacy Rating at 24 hours <sup>[11]</sup> |
|-----------------|--|

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 ~24 hours of 1 infusion. Additional infusions may have been given to maintain hemostasis; Good: Definite pain relief and/or improvement in bleeding within ~24 hours after infusion. Possibly requires >1 infusion for complete resolution; Fair: Probable or slight relief of pain & slight improvement in bleeding within ~24 hours after infusion. Requires >1 infusion for complete resolution; None: No improvement or condition worsens

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

End point timeframe:

24 ± 1 h post-infusion

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: Baseline period arms are not mutually exclusive. Details see under description of period arms.

| End point values            | On-demand arm   | Prophylaxis arm |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 19              | 14              |  |  |
| Units: bleeding episodes    |                 |                 |  |  |
| Excellent (n = 16, 6)       | 282             | 42              |  |  |
| Good (n = 19, 14)           | 280             | 89              |  |  |
| Fair (n = 9, 3)             | 36              | 12              |  |  |
| None (n = 1,0)              | 1               | 0               |  |  |
| Rating Not Done (n = 8, 3)  | 24              | 28              |  |  |

|                          |   |   |  |  |
|--------------------------|---|---|--|--|
| Not Available (n = 0, 1) | 0 | 2 |  |  |
|--------------------------|---|---|--|--|

## Statistical analyses

No statistical analyses for this end point

### Secondary: Total Weight Adjusted Dose to Control a Bleeding Episode

|                 |  |
|-----------------|--|
| End point title | Total Weight Adjusted Dose to Control a Bleeding Episode <sup>[12]</sup> |
|-----------------|--|

End point description:

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

End point timeframe:

12 months  $\pm$  14 days

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: Baseline period arms are not mutually exclusive. Details see under description of period arms.

| End point values                      | On-demand arm             | Prophylaxis arm          |  |  |
|---------------------------------------|---------------------------|--------------------------|--|--|
| Subject group type                    | Reporting group           | Reporting group          |  |  |
| Number of subjects analysed           | 19                        | 14                       |  |  |
| Units: Units/kg                       |                           |                          |  |  |
| median (inter-quartile range (Q1-Q3)) | 4049.7 (2324.5 to 7408.4) | 1524.9 (293.2 to 2883.5) |  |  |

## Statistical analyses

|                            |                        |
|----------------------------|------------------------|
| Statistical analysis title | Statistical analysis 1 |
|----------------------------|------------------------|

|                   |                                 |
|-------------------|---------------------------------|
| Comparison groups | Prophylaxis arm v On-demand arm |
|-------------------|---------------------------------|

|   |    |
|---|----|
| Number of subjects included in analysis | 33 |
|---|----|

|                        |               |
|------------------------|---------------|
| Analysis specification | Pre-specified |
|------------------------|---------------|

|               |  |
|---------------|--|
| Analysis type |  |
|---------------|--|

|         |          |
|---------|----------|
| P-value | = 0.0067 |
|---------|----------|

|        |  |
|--------|--|
| Method | Mann-Whitney tests (Wilcoxon-Rank Sum) |
|--------|--|

|                     |  |
|---------------------|--|
| Confidence interval |  |
|---------------------|--|

|       |      |
|-------|------|
| level | 95 % |
|-------|------|

### Secondary: The Number of Bleeding Episode (BE) Which Required 1, 2, 3, or $\geq 4$ Infusions to Control Bleeding

|                 |   |
|-----------------|---|
| End point title | The Number of Bleeding Episode (BE) Which Required 1, 2, 3, or $\geq 4$ Infusions to Control Bleeding <sup>[13]</sup> |
|-----------------|---|

End point description:

|                         |           |
|-------------------------|-----------|
| End point type          | Secondary |
| End point timeframe:    |           |
| 12 months $\pm$ 14 days |           |

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: Baseline period arms are not mutually exclusive. Details see under description of period arms.

| End point values               | On-demand arm   | Prophylaxis arm |  |  |
|--------------------------------|-----------------|-----------------|--|--|
| Subject group type             | Reporting group | Reporting group |  |  |
| Number of subjects analysed    | 19              | 14              |  |  |
| Units: Bleeding Episodes (BEs) |                 |                 |  |  |
| 1 infusion                     | 352             | 98              |  |  |
| 2 infusions                    | 134             | 41              |  |  |
| 3 infusions                    | 62              | 13              |  |  |
| $\geq 4$ infusions             | 75              | 21              |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Abnormal Activated Partial Thromboplastin Time (aPTT) Assay Results

|                 |   |
|-----------------|---|
| End point title | Abnormal Activated Partial Thromboplastin Time (aPTT) Assay Results <sup>[14]</sup> |
|-----------------|---|

End point description:

The normal reference range of values for aPTT is 22.8 – 31 seconds.

|   |           |
|---|-----------|
| End point type  | Secondary |
| End point timeframe:  |           |
| Screening visit, Month 3, Month 6, Month 9, and Termination visit |           |

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: Baseline period arms are not mutually exclusive. Details see under description of period arms.

| End point values                      | On-demand arm       | Prophylaxis arm     |  |  |
|---------------------------------------|---------------------|---------------------|--|--|
| Subject group type                    | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed           | 19                  | 16                  |  |  |
| Units: seconds                        |                     |                     |  |  |
| median (inter-quartile range (Q1-Q3)) |                     |                     |  |  |
| Screening visit (n= 19, 16)           | 67.3 (63.1 to 75.1) | 68.5 (61 to 73.1)   |  |  |
| Month 3 (n= 14, 15)                   | 68 (62.7 to 76.2)   | 62.7 (57.5 to 67.2) |  |  |
| Month 6 (n= 17, 15)                   | 68.2 (64.6 to 72.1) | 65.6 (62.6 to 69.5) |  |  |

|                               |                     |                     |  |  |
|-------------------------------|---------------------|---------------------|--|--|
| Month 9 (n= 17, 15)           | 70 (64.6 to 77.9)   | 68.1 (58.1 to 73.9) |  |  |
| Termination visit (n= 18, 16) | 69.8 (63.4 to 75.6) | 69.4 (60.5 to 77.1) |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Abnormal D-Dimer Assay Results

|                        |   |
|------------------------|---|
| End point title        | Abnormal D-Dimer Assay Results <sup>[15]</sup>                    |
| End point description: | The normal reference range of values for D-dimers is <500 ng/mL.  |
| End point type         | Secondary   |
| End point timeframe:   | Screening visit, Month 3, Month 6, Month 9, and Termination visit |

Notes:

[15] - 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: Baseline period arms are not mutually exclusive. Details see under description of period arms.

| End point values                      | On-demand arm       | Prophylaxis arm        |  |  |
|---------------------------------------|---------------------|------------------------|--|--|
| Subject group type                    | Reporting group     | Reporting group        |  |  |
| Number of subjects analysed           | 9                   | 9                      |  |  |
| Units: ng/mL                          |                     |                        |  |  |
| median (inter-quartile range (Q1-Q3)) |                     |                        |  |  |
| Screening visit (n= 7, 6)             | 862 (647 to 1035)   | 833.5 (644 to 1164)    |  |  |
| Month 3 (n= 7, 8)                     | 690 (561 to 830)    | 1021.5 (730 to 1633.5) |  |  |
| Month 6 (n= 9, 8)                     | 969 (753 to 1103)   | 1032 (652 to 1442.5)   |  |  |
| Month 9 (n= 6, 8)                     | 731.5 (592 to 1398) | 1121 (942.5 to 1448.5) |  |  |
| Termination visit (n= 5, 9)           | 813 (695 to 1386)   | 1031 (872 to 1258)     |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Abnormal Fibrinogen Assay Results

|                        |   |
|------------------------|---|
| End point title        | Abnormal Fibrinogen Assay Results <sup>[16]</sup>   |
| End point description: | The normal reference range of values for fibrinogen is 200-400 mg/dL.<br>Note: 99999 entered where there were no abnormal fibrinogen assay results for this arm/group at this time point. |
| End point type         | Secondary   |

End point timeframe:

Screening visit, Month 3, Month 6, Month 9, and Termination visit

Notes:

[16] - 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: Baseline period arms are not mutually exclusive. Details see under description of period arms.

| End point values                      | On-demand arm          | Prophylaxis arm        |  |  |
|---------------------------------------|------------------------|------------------------|--|--|
| Subject group type                    | Reporting group        | Reporting group        |  |  |
| Number of subjects analysed           | 4                      | 6                      |  |  |
| Units: mg/dL                          |                        |                        |  |  |
| median (inter-quartile range (Q1-Q3)) |                        |                        |  |  |
| Screening visit (n= 4, 6)             | 428 (414 to 478.5)     | 422 (411 to 428)       |  |  |
| Month 3 (n= 0, 2)                     | 99999 (99999 to 99999) | 402 (199 to 605)       |  |  |
| Month 6 (n= 3, 1)                     | 415 (412 to 418)       | 759 (759 to 759)       |  |  |
| Month 9 (n= 1, 4)                     | 508 (508 to 508)       | 326.5 (183.5 to 635.5) |  |  |
| Termination visit (n= 2, 2)           | 456.5 (425 to 488)     | 522.5 (414 to 631)     |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Abnormal Fibrin Degradation Products (FDP) Assay Results

|                 |  |
|-----------------|--|
| End point title | Abnormal Fibrin Degradation Products (FDP) Assay Results <sup>[17]</sup> |
|-----------------|--|

End point description:

The normal reference range of values for FDP is 0-5 ug/mL.

Note: 99999 entered where there were no abnormal fibrin degradation products assay results for this arm/group at this time point

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

End point timeframe:

Screening visit, Month 3, Month 6, Month 9, and Termination visit

Notes:

[17] - 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: Baseline period arms are not mutually exclusive. Details see under description of period arms.

| End point values                      | On-demand arm          | Prophylaxis arm |  |  |
|---------------------------------------|------------------------|-----------------|--|--|
| Subject group type                    | Reporting group        | Reporting group |  |  |
| Number of subjects analysed           | 3                      | 2               |  |  |
| Units: ug/mL                          |                        |                 |  |  |
| median (inter-quartile range (Q1-Q3)) |                        |                 |  |  |
| Screening visit (n= 1, 2)             | 16 (16 to 16)          | 12 (8 to 16)    |  |  |
| Month 3 (n= 0, 2)                     | 99999 (99999 to 99999) | 8 (8 to 8)      |  |  |

|                             |            |            |  |  |
|-----------------------------|------------|------------|--|--|
| Month 6 (n= 1, 1)           | 8 (8 to 8) | 8 (8 to 8) |  |  |
| Month 9 (n= 1, 2)           | 8 (8 to 8) | 8 (8 to 8) |  |  |
| Termination visit (n= 3, 1) | 8 (8 to 8) | 8 (8 to 8) |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Abnormal Prothrombin Fragment F 1.2 Assay Results

|                 |   |
|-----------------|---|
| End point title | Abnormal Prothrombin Fragment F 1.2 Assay Results <sup>[18]</sup> |
|-----------------|---|

End point description:

The normal reference range of values for prothrombin fragment F 1.2 is 69-229 pmol/L.

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

End point timeframe:

Screening visit, Month 3, Month 6, Month 9, and Termination visit

Notes:

[18] - 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: Baseline period arms are not mutually exclusive. Details see under description of period arms.

| End point values                      | On-demand arm      | Prophylaxis arm   |  |  |
|---------------------------------------|--------------------|-------------------|--|--|
| Subject group type                    | Reporting group    | Reporting group   |  |  |
| Number of subjects analysed           | 6                  | 9                 |  |  |
| Units: pmol/L                         |                    |                   |  |  |
| median (inter-quartile range (Q1-Q3)) |                    |                   |  |  |
| Screening visit (n= 2, 1)             | 284 (278 to 290)   | 308 (308 to 308)  |  |  |
| Month 3 (n= 6, 7)                     | 336.5 (267 to 414) | 579 (354 to 972)  |  |  |
| Month 6 (n= 3, 9)                     | 448 (272 to 714)   | 430 (366 to 504)  |  |  |
| Month 9 (n= 4, 9)                     | 382 (313 to 405.5) | 415 (272 to 472)  |  |  |
| Termination visit (n= 4, 7)           | 252.5 (250 to 265) | 643 (376 to 1679) |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Abnormal Prothrombin Time Assay Results

|                 |   |
|-----------------|---|
| End point title | Abnormal Prothrombin Time Assay Results <sup>[19]</sup> |
|-----------------|---|

End point description:

The normal reference range of values for PT is 9.7-12.3 sec.

Note: 99999 entered where there were no abnormal prothrombin time assay results for this arm/group at this time point

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

End point timeframe:

Screening visit, Month 3, Month 6, Month 9, and Termination visit

Notes:

[19] - 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: Baseline period arms are not mutually exclusive. Details see under description of period arms.

| End point values                      | On-demand arm          | Prophylaxis arm        |  |  |
|---------------------------------------|------------------------|------------------------|--|--|
| Subject group type                    | Reporting group        | Reporting group        |  |  |
| Number of subjects analysed           | 1                      | 1                      |  |  |
| Units: seconds                        |                        |                        |  |  |
| median (inter-quartile range (Q1-Q3)) |                        |                        |  |  |
| Screening visit (n= 1, 1)             | 9.4 (9.4 to 9.4)       | 9.6 (9.6 to 9.6)       |  |  |
| Month 3 (n= 1, 0)                     | 9.5 (9.5 to 9.5)       | 99999 (99999 to 99999) |  |  |
| Month 6 (n= 0, 1)                     | 99999 (99999 to 99999) | 12.5 (12.5 to 12.5)    |  |  |
| Month 9 (n= 1, 1)                     | 12.7 (12.7 to 12.7)    | 13.6 (13.6 to 13.6)    |  |  |
| Termination visit (n= 0, 1)           | 99999 (99999 to 99999) | 13.4 (13.4 to 13.4)    |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Abnormal Thrombin-Antithrombin III (TAT) Assay Results

|                 |  |
|-----------------|--|
| End point title | Abnormal Thrombin-Antithrombin III (TAT) Assay Results <sup>[20]</sup> |
|-----------------|--|

End point description:

The normal reference range of values for TAT is 1-4.1 ug/L.

Note: 99999 entered where there were no abnormal Abnormal Thrombin-Antithrombin II assay results for this arm/group at this time point

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

End point timeframe:

Screening visit, Month 3, Month 6, Month 9, and Termination visit

Notes:

[20] - 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: Baseline period arms are not mutually exclusive. Details see under description of period arms.

| End point values                      | On-demand arm    | Prophylaxis arm    |  |  |
|---------------------------------------|------------------|--------------------|--|--|
| Subject group type                    | Reporting group  | Reporting group    |  |  |
| Number of subjects analysed           | 4                | 7                  |  |  |
| Units: ug/L                           |                  |                    |  |  |
| median (inter-quartile range (Q1-Q3)) |                  |                    |  |  |
| Screening visit (n= 4, 1)             | 5.1 (4.4 to 5.9) | 5.6 (5.6 to 5.6)   |  |  |
| Month 3 (n= 3, 7)                     | 4.7 (4.5 to 5.9) | 12.3 (4.4 to 40.8) |  |  |



|                             |                        |                  |  |  |
|-----------------------------|------------------------|------------------|--|--|
| Month 6 (n= 3, 6)           | 7.9 (6.3 to 10.5)      | 5.6 (4.4 to 6.1) |  |  |
| Month 9 (n= 0, 3)           | 99999 (99999 to 99999) | 6 (5.6 to 52.9)  |  |  |
| Termination visit (n= 2, 5) | 10.3 (8 to 12.5)       | 5.6 (5.1 to 7.3) |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Viral Serology from Screening Visit and Study Termination Visit: Hepatitis A, Hepatitis B, and Hepatitis C

|                 |  |
|-----------------|--|
| End point title | Viral Serology from Screening Visit and Study Termination Visit: Hepatitis A, Hepatitis B, and Hepatitis C <sup>[21]</sup> |
|-----------------|--|

End point description:

-Hepatitis A Virus Antibody (HAV Ab) -Hepatitis B Virus Core Antibody (HBcAb) -Hepatitis B Virus Surface Antibody (HBsAb) -Hepatitis B Virus Surface Antigen (HBsAg) -Hepatitis C Virus (HCV)

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

End point timeframe:

12 months ± 14 days

Notes:

[21] - 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: Baseline period arms are not mutually exclusive. Details see under description of period arms.

| End point values                                 | On-demand arm   | Prophylaxis arm |  |  |
|--|-----------------|-----------------|--|--|
| Subject group type                               | Reporting group | Reporting group |  |  |
| Number of subjects analysed                      | 19              | 17              |  |  |
| Units: participants                              |                 |                 |  |  |
| HAV Ab: Screening Negative; Termination Positive | 1               | 0               |  |  |
| HAV Ab: Screening Negative; Termination Negative | 8               | 11              |  |  |
| HAV Ab: Screening Positive; Termination Positive | 8               | 4               |  |  |
| HAV Ab: Screening Positive; Termination Negative | 1               | 1               |  |  |
| HAV Ab: Serology not available                   | 1               | 1               |  |  |
| HBcAb: Screening Negative; Termination Positive  | 0               | 1               |  |  |
| HBcAb: Screening Negative; Termination Negative  | 8               | 11              |  |  |
| HBcAb: Screening Positive; Termination Positive  | 9               | 4               |  |  |
| HBcAb: Screening Positive; Termination Negative  | 1               | 0               |  |  |
| HBcAb: Serology not available                    | 1               | 1               |  |  |
| HBsAb: Screening Negative; Termination Positive  | 2               | 5               |  |  |
| HBsAb: Screening Negative; Termination Negative  | 2               | 2               |  |  |

|   |    |    |  |  |
|---|----|----|--|--|
| HBsAb: Screening Positive; Termination Positive | 13 | 9  |  |  |
| HBsAb: Screening Positive; Termination Negative | 1  | 0  |  |  |
| HBsAb: Serology not available                   | 1  | 1  |  |  |
| HBsAg: Screening Negative; Termination Positive | 0  | 0  |  |  |
| HBsAg: Screening Negative; Termination Negative | 18 | 16 |  |  |
| HBsAg: Serology not available                   | 1  | 1  |  |  |
| HCV: Screening Negative; Termination Positive   | 0  | 0  |  |  |
| HCV: Screening Negative; Termination Negative   | 6  | 10 |  |  |
| HCV: Screening Positive; Termination Positive   | 12 | 6  |  |  |
| HCV: Screening Positive; Termination Negative   | 0  | 0  |  |  |
| HCV: Serology not available                     | 1  | 1  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Viral Serology From Screening Visit and Study Termination Visit: HIV-1/2 Antibody (Ab)

|                 |  |
|-----------------|--|
| End point title | Viral Serology From Screening Visit and Study Termination Visit: HIV-1/2 Antibody (Ab) <sup>[22]</sup> |
|-----------------|--|

End point description:

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

End point timeframe:

12 months ± 14 days

Notes:

[22] - 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: Baseline period arms are not mutually exclusive. Details see under description of period arms.

| End point values                                  | On-demand       | Prophylaxis     |  |  |
|---|-----------------|-----------------|--|--|
| Subject group type                                | Reporting group | Reporting group |  |  |
| Number of subjects analysed                       | 19              | 17              |  |  |
| Units: participants                               |                 |                 |  |  |
| HIV 1/2 Ab: Screen Negative; Termination Positive | 0               | 0               |  |  |
| HIV 1/2 Ab: Screen Negative; Termination Negative | 18              | 16              |  |  |
| HIV 1/2 Ab: : Serology not available              | 1               | 1               |  |  |

## Statistical analyses

No statistical analyses for this end point

---

**Secondary: Viral Serology From Screening Visit and Study Termination Visit: Parvovirus B19 IgG Antibody [IV]**

---

|                 |   |
|-----------------|---|
| End point title | Viral Serology From Screening Visit and Study Termination Visit: Parvovirus B19 IgG Antibody [IV] <sup>[23]</sup> |
|-----------------|---|

End point description:

Normal range (0 - 0.89 IV); High (> 0.89 IV) - Parvovirus B19 IgG Antibody [IV] (Parvo IgG Ab)

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

End point timeframe:

12 months ± 14 days

Notes:

[23] - 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: Baseline period arms are not mutually exclusive. Details see under description of period arms.

| End point values                                   | On-demand       | Prophylaxis     |  |  |
|--|-----------------|-----------------|--|--|
| Subject group type                                 | Reporting group | Reporting group |  |  |
| Number of subjects analysed                        | 19              | 17              |  |  |
| Units: participants                                |                 |                 |  |  |
| Parvo IgG Ab: Screening High ; Termination Normal  | 3               | 1               |  |  |
| Parvo IgG Ab: Screening High ; Termination High    | 14              | 13              |  |  |
| Parvo IgG Ab: Screening Normal; Termination Normal | 0               | 2               |  |  |
| Parvo IgG Ab: Screening Normal ; Termination High  | 1               | 0               |  |  |
| Parvo IgG Ab: Serology not available               | 1               | 1               |  |  |

---

**Statistical analyses**

---

No statistical analyses for this end point

---

**Secondary: Viral Serology From Screening Visit and Study Termination Visit: Parvovirus B19 IgM Antibody [IV]**

---

|                 |   |
|-----------------|---|
| End point title | Viral Serology From Screening Visit and Study Termination Visit: Parvovirus B19 IgM Antibody [IV] <sup>[24]</sup> |
|-----------------|---|

End point description:

Normal range (0 - 0.89 IV); High (> 0.89 IV) - Parvovirus B19 IgM Antibody [IV] (Parvo IgM Ab)

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

End point timeframe:

12 months ± 14 days

Notes:

[24] - 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: Baseline period arms are not mutually exclusive. Details see under description of period arms.

| End point values                                      | On-demand       | Prophylaxis     |  |  |
|---|-----------------|-----------------|--|--|
| Subject group type                                    | Reporting group | Reporting group |  |  |
| Number of subjects analysed                           | 19              | 17              |  |  |
| Units: participants                                   |                 |                 |  |  |
| Parvo IgM Ab: Screening High ;<br>Termination Normal  | 0               | 0               |  |  |
| Parvo IgM Ab: Screening High ;<br>Termination High    | 1               | 0               |  |  |
| Parvo IgM Ab: Screening Normal;<br>Termination Normal | 17              | 16              |  |  |
| Parvo IgM Ab: Screening Normal ;<br>Termination High  | 0               | 0               |  |  |
| Parvo IgM Ab: Serology not available                  | 1               | 1               |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Rate of Related Adverse Events (AEs) per Year

|                        |   |
|------------------------|---|
| End point title        | Rate of Related Adverse Events (AEs) per Year <sup>[25]</sup> |
| End point description: |   |

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

End point timeframe:

12 months ± 14 days

Notes:

[25] - 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: Baseline period arms are not mutually exclusive. Details see under description of period arms.

| End point values                      | On-demand arm   | Prophylaxis arm |  |  |
|---------------------------------------|-----------------|-----------------|--|--|
| Subject group type                    | Reporting group | Reporting group |  |  |
| Number of subjects analysed           | 19              | 17              |  |  |
| Units: Related AEs per year           |                 |                 |  |  |
| median (inter-quartile range (Q1-Q3)) | 0 (0 to 0)      | 0 (0 to 0.979)  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Rate of Related Adverse Events (AEs) during or within 1 Hour of Infusion per Year

|                        |   |
|------------------------|---|
| End point title        | Rate of Related Adverse Events (AEs) during or within 1 Hour of Infusion per Year <sup>[26]</sup> |
| End point description: |   |

|  |           |
|--|-----------|
| End point type   | Secondary |
| End point timeframe:   |           |
| 12 months $\pm$ 14 days  |           |
| Notes:   |           |
| [26] - 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: Baseline period arms are not mutually exclusive. Details see under description of period arms.  |           |

| End point values                              | On-demand arm   | Prophylaxis arm |  |  |
|---|-----------------|-----------------|--|--|
| Subject group type                            | Reporting group | Reporting group |  |  |
| Number of subjects analysed                   | 19              | 17              |  |  |
| Units: Related AEs within/during 1hr per year |                 |                 |  |  |
| median (inter-quartile range (Q1-Q3))         | 0 (0 to 0)      | 0 (0 to 0)      |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Related Thromboembolic Adverse Events (AEs)

|                 |   |
|-----------------|---|
| End point title | Number of Related Thromboembolic Adverse Events (AEs) <sup>[27]</sup> |
|-----------------|---|

End point description:

|  |           |
|--|-----------|
| End point type   | Secondary |
| End point timeframe:   |           |
| 12 months $\pm$ 14 days  |           |
| Notes:   |           |
| [27] - 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: Baseline period arms are not mutually exclusive. Details see under description of period arms.  |           |

| End point values                  | On-demand arm   | Prophylaxis arm |  |  |
|-----------------------------------|-----------------|-----------------|--|--|
| Subject group type                | Reporting group | Reporting group |  |  |
| Number of subjects analysed       | 19              | 17              |  |  |
| Units: Related thromboembolic AEs | 0               | 0               |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Absolute Changes in Inhibitor Titer of Hemophilia A Participants with Shifts in Factor VIII (FVIII) Inhibitor Titer Levels

|                 |  |
|-----------------|--|
| End point title | Absolute Changes in Inhibitor Titer of Hemophilia A Participants with Shifts in Factor VIII (FVIII) Inhibitor Titer Levels <sup>[28]</sup> |
|-----------------|--|

End point description:

Absolute Changes in Inhibitor Titer (or no change in low or high titer status): -Inhibitor Titer went from Low ( $\leq 5$  BU) to Low ( $\leq 5$  BU) -Inhibitor Titer went from Low ( $\leq 5$  BU) to High ( $> 5$  BU) -Inhibitor Titer went from High ( $> 5$  BU) to Low ( $\leq 5$  BU) -Inhibitor Titer went from High ( $> 5$  BU) to High ( $> 5$  BU)  
Note: 99999 entered where there were no inhibitor titer shifts for this arm/group at this time point

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

End point timeframe:

12 months  $\pm$  14 days

Notes:

[28] - 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: Baseline period arms are not mutually exclusive. Details see under description of period arms.

| End point values                               | On-demand arm          | Prophylaxis arm        |  |  |
|--|------------------------|------------------------|--|--|
| Subject group type                             | Reporting group        | Reporting group        |  |  |
| Number of subjects analysed                    | 17                     | 16                     |  |  |
| Units: Bethesda Units (BU)                     |                        |                        |  |  |
| median (inter-quartile range (Q1-Q3))          |                        |                        |  |  |
| Screening to 3 Month- Low to High (N=2, 3)     | 12.1 (12.1 to 12.1)    | 4 (0.7 to 16.8)        |  |  |
| Screening to 3 Month- High to Low (N=1, 0)     | 2 (2 to 2)             | 99999 (99999 to 99999) |  |  |
| Screening to 6 Month- Low to High (N=2, 1)     | 12.9 (4.9 to 20.8)     | 5.3 (5.3 to 5.3)       |  |  |
| Screening to 6 Month- High to Low (N=1, 0)     | 3.4 (3.4 to 3.4)       | 99999 (99999 to 99999) |  |  |
| Screening to 9 Month- Low to High (N=2, 1)     | 5 (4.3 to 5.6)         | 3.7 (3.7 to 3.7)       |  |  |
| Screening to 9 Month- High to Low (N=0, 2)     | 99999 (99999 to 99999) | 2.1 (0.9 to 3.2)       |  |  |
| Screening to Termination- Low to High (N=2, 1) | 39.2 (3.8 to 74.7)     | 5.8 (5.8 to 5.8)       |  |  |
| Screening to Termination- High to Low (N=1, 2) | 14.6 (14.6 to 14.6)    | 3.3 (3.3 to 3.3)       |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Absolute Changes in Inhibitor Titer of Hemophilia B Participants with Shifts in Factor IX (FIX) Inhibitor Titer Levels

|                 |  |
|-----------------|--|
| End point title | Absolute Changes in Inhibitor Titer of Hemophilia B Participants with Shifts in Factor IX (FIX) Inhibitor Titer Levels <sup>[29]</sup> |
|-----------------|--|

End point description:

Absolute Changes in Inhibitor Titer (or no change in low or high titer status): -Inhibitor Titer went from Low ( $\leq 5$  BU) to Low ( $\leq 5$  BU) -Inhibitor Titer went from Low ( $\leq 5$  BU) to High ( $> 5$  BU) -Inhibitor Titer went from High ( $> 5$  BU) to Low ( $\leq 5$  BU) -Inhibitor Titer went from High ( $> 5$  BU) to High ( $> 5$  BU)  
Note: 99999 entered where there were no inhibitor titer shifts for this arm/group at this time point

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

End point timeframe:

12 months  $\pm$  14 days

Notes:

[29] - 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: Baseline period arms are not mutually exclusive. Details see under description of period arms.

| End point values                                 | On-demand arm          | Prophylaxis arm        |  |  |
|--|------------------------|------------------------|--|--|
| Subject group type                               | Reporting group        | Reporting group        |  |  |
| Number of subjects analysed                      | 1                      | 1                      |  |  |
| Units: Bethesda Units (BU)                       |                        |                        |  |  |
| median (inter-quartile range (Q1-Q3))            |                        |                        |  |  |
| Screening to 3 Month- Low to Low (N=1, 0)        | 3.2 (3.2 to 3.2)       | 99999 (99999 to 99999) |  |  |
| Screening to 3 Month- Low to High (N=0, 0)       | 99999 (99999 to 99999) | 99999 (99999 to 99999) |  |  |
| Screening to 3 Month- High to Low (N=0, 0)       | 99999 (99999 to 99999) | 99999 (99999 to 99999) |  |  |
| Screening to 3 Month- High to High (N=1, 1)      | 0.3 (0.3 to 0.3)       | 10.7 (10.7 to 10.7)    |  |  |
| Screening to 6 Month- Low to Low (N=1, 0)        | 1.5 (1.5 to 1.5)       | 99999 (99999 to 99999) |  |  |
| Screening to 6 Month- Low to High (N=0, 0)       | 99999 (99999 to 99999) | 99999 (99999 to 99999) |  |  |
| Screening to 6 Month- High to Low (N=0, 0)       | 99999 (99999 to 99999) | 99999 (99999 to 99999) |  |  |
| Screening to 6 Month- High to High (N=1, 1)      | 1.7 (1.7 to 1.7)       | 23.2 (23.2 to 23.2)    |  |  |
| Screening to 9 Month- Low to Low (N=1, 0)        | 3.2 (3.2 to 3.2)       | 99999 (99999 to 99999) |  |  |
| Screening to 9 Month- Low to High (N=0, 0)       | 99999 (99999 to 99999) | 99999 (99999 to 99999) |  |  |
| Screening to 9 Month- High to Low (N=0, 0)       | 99999 (99999 to 99999) | 99999 (99999 to 99999) |  |  |
| Screening to 9 Month- High to High (N=0, 1)      | 99999 (99999 to 99999) | 37 (37 to 37)          |  |  |
| Screening to Termination - Low to Low (N=0, 0)   | 99999 (99999 to 99999) | 99999 (99999 to 99999) |  |  |
| Screening to Termination- Low to High (N=0, 0)   | 99999 (99999 to 99999) | 99999 (99999 to 99999) |  |  |
| Screening to Termination- High to Low (N=0, 0)   | 99999 (99999 to 99999) | 99999 (99999 to 99999) |  |  |
| Screening to Termination - High to High (N=1, 1) | 11.3 (11.3 to 11.3)    | 21.4 (21.4 to 21.4)    |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Pharmacoeconomics: Annual total length of hospitalization for indwelling line

|                 |   |
|-----------------|---|
| End point title | Pharmacoeconomics: Annual total length of hospitalization for indwelling line <sup>[30]</sup> |
|-----------------|---|

End point description:

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

End point timeframe:

12 months  $\pm$  14 days

Notes:

[30] - 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: Baseline period arms are not mutually exclusive. Details see under description of period arms.

| End point values                     | On-demand arm     | Prophylaxis arm   |  |  |
|--------------------------------------|-------------------|-------------------|--|--|
| Subject group type                   | Reporting group   | Reporting group   |  |  |
| Number of subjects analysed          | 18                | 16                |  |  |
| Units: Days                          |                   |                   |  |  |
| arithmetic mean (standard deviation) | 0.7 ( $\pm$ 2.61) | 0.7 ( $\pm$ 2.75) |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Pharmacoeconomics: Annual total number of days lost (work or school)

|                 |  |
|-----------------|--|
| End point title | Pharmacoeconomics: Annual total number of days lost (work or school) <sup>[31]</sup> |
|-----------------|--|

End point description:

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

End point timeframe:

12 months  $\pm$  14 days

Notes:

[31] - 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: Baseline period arms are not mutually exclusive. Details see under description of period arms.

| End point values                     | On-demand arm       | Prophylaxis arm     |  |  |
|--------------------------------------|---------------------|---------------------|--|--|
| Subject group type                   | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed          | 17                  | 16                  |  |  |
| Units: Days                          |                     |                     |  |  |
| arithmetic mean (standard deviation) | 17.4 ( $\pm$ 25.42) | 15.4 ( $\pm$ 24.28) |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Health-Related Quality of Life (HRQoL): EuroQoL (Quality of Life)-5 Dimensions (EQ-5D) Index Scores

|                 |   |
|-----------------|---|
| End point title | Health-Related Quality of Life (HRQoL): EuroQoL (Quality of |
|-----------------|---|



## End point description:

EQ-5D is a participant answered questionnaire scoring 5 dimensions - mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The EQ-5D total score ranges from 0 (worst health state) to 1 (perfect health state) and 1 reflects the best outcome. EQ-5D Index scores based on EQ-5D questionnaire were calculated for participants  $\geq 14$  years of age, at screening, 6 months, and at termination visit. Changes in scores at 6 months and termination were also calculated. A relatively higher score represents better quality of life.

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

End point timeframe:

12 months  $\pm$  14 days

## Notes:

[32] - 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: Baseline period arms are not mutually exclusive. Details see under description of period arms.

| End point values                             | On-demand arm          | Prophylaxis arm        |  |  |
|--|------------------------|------------------------|--|--|
| Subject group type                           | Reporting group        | Reporting group        |  |  |
| Number of subjects analysed                  | 16                     | 12                     |  |  |
| Units: Scores on a scale                     |                        |                        |  |  |
| arithmetic mean (standard deviation)         |                        |                        |  |  |
| Screening (N= 16, 12)                        | 0.627 ( $\pm$ 0.2067)  | 0.62 ( $\pm$ 0.1841)   |  |  |
| 6 Months (N= 15, 11)                         | 0.621 ( $\pm$ 0.188)   | 0.729 ( $\pm$ 0.1392)  |  |  |
| Termination (N= 15, 10)                      | 0.605 ( $\pm$ 0.2146)  | 0.7 ( $\pm$ 0.1233)    |  |  |
| Change (Screening - Month 6) (N= 15, 11)     | -0.006 ( $\pm$ 0.2088) | -0.096 ( $\pm$ 0.2403) |  |  |
| Change (Screening - Termination) (N= 15, 10) | 0.01 ( $\pm$ 0.247)    | -0.075 ( $\pm$ 0.2594) |  |  |
| Change (Month 6 - Termination) (N= 15, 10)   | 0.016 ( $\pm$ 0.1765)  | 0.001 ( $\pm$ 0.1493)  |  |  |

## Statistical analyses

No statistical analyses for this end point

**Secondary: Hemophilia-specific Quality of Life questionnaire for adults (Haem-A-QoL)  $\geq$  16 Years Old**

|                 |   |
|-----------------|---|
| End point title | Hemophilia-specific Quality of Life questionnaire for adults (Haem-A-QoL) $\geq$ 16 Years Old <sup>[33]</sup> |
|-----------------|---|

## End point description:

The Haem-A-QoL instrument has been developed and used in Hemophilia A patients. As a hemophilia-specific instrument, this measure assesses very specific aspects of dealing with hemophilia. The areas covered by this instrument are: Physical Health (PH), Sports & Leisure (S&L), School & Work (W&S), Dealing with Hemophilia (Dealing), Family Planning (FP), Feeling, Relationships (R'ships), Treatment, View, and Outlook for the Future (Future). A Haem-A-QoL Total Score (Total) was also calculated. For the Haem-A-QoL, higher scores indicate a worse quality of life. Scores on a scale range between 0 and 100. Haem-A-QoL scores at screening, 6 months, and at termination visit were collected. Changes in scores at 6 months and termination were also calculated.

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

End point timeframe:

12 months  $\pm$  14 days

Notes:

[33] - 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: Baseline period arms are not mutually exclusive. Details see under description of period arms.

| End point values                                   | On-demand arm       | Prophylaxis arm     |  |  |
|--|---------------------|---------------------|--|--|
| Subject group type                                 | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed                        | 15                  | 12                  |  |  |
| Units: Scores on a scale                           |                     |                     |  |  |
| arithmetic mean (standard deviation)               |                     |                     |  |  |
| Dealing- Screening (N=15, 12)                      | 35 ( $\pm$ 19.72)   | 26 ( $\pm$ 15.84)   |  |  |
| Dealing- Month 6 (N=14, 11)                        | 25 ( $\pm$ 16.67)   | 18.9 ( $\pm$ 21.11) |  |  |
| Dealing- Termination (N=14, 11)                    | 25.6 ( $\pm$ 25.21) | 23.7 ( $\pm$ 22.15) |  |  |
| Dealing- Change (Screening - Month 6) (N=14, 11)   | 10.7 ( $\pm$ 18.61) | 3.4 ( $\pm$ 22.62)  |  |  |
| Dealing- Change(Screening - Termination)(N=14, 11) | 10.1 ( $\pm$ 27.19) | -1.4 ( $\pm$ 21.37) |  |  |
| Dealing- Change (Month 6 - Termination)(N=14, 11)  | -0.6 ( $\pm$ 16.81) | -4.8 ( $\pm$ 21.26) |  |  |
| FP- Screening (N=9, 8)                             | 16.7 ( $\pm$ 20.49) | 34.9 ( $\pm$ 31.31) |  |  |
| FP- Month 6 (N=12, 7)                              | 20.5 ( $\pm$ 26.71) | 14.3 ( $\pm$ 11.25) |  |  |
| FP- Termination (N=13, 8)                          | 19.1 ( $\pm$ 16.25) | 21.1 ( $\pm$ 22.14) |  |  |
| FP- Change (Screening - Month 6) (N=9, 7)          | -3.7 ( $\pm$ 26.94) | 14.9 ( $\pm$ 28.73) |  |  |
| FP- Change(Screening - Termination)(N=9, 7)        | -2.5 ( $\pm$ 25.57) | 13.1 ( $\pm$ 20.26) |  |  |
| FP- Change (Month 6 - Termination)(N=11, 6)        | -0.8 ( $\pm$ 32.68) | -8.3 ( $\pm$ 28.41) |  |  |
| Feeling- Screening (N=15, 12)                      | 39.6 ( $\pm$ 28.22) | 48.2 ( $\pm$ 29.02) |  |  |
| Feeling- Month 6 (N=14, 11)                        | 33.9 ( $\pm$ 28.77) | 29 ( $\pm$ 17.29)   |  |  |
| Feeling- Termination (N=14, 11)                    | 30.8 ( $\pm$ 28.53) | 26.1 ( $\pm$ 20.69) |  |  |
| Feeling- Change (Screening - Month 6) (N=14, 11)   | 4.9 ( $\pm$ 27.75)  | 17.3 ( $\pm$ 34.72) |  |  |
| Feeling- Change(Screening - Termination)(N=14, 11) | 8 ( $\pm$ 31.91)    | 20.2 ( $\pm$ 24.58) |  |  |
| Feeling- Change (Month 6 - Termination)(N=14, 11)  | 3.1 ( $\pm$ 16.4)   | 2.8 ( $\pm$ 23.94)  |  |  |
| Future- Screening (N=14, 12)                       | 46.8 ( $\pm$ 28.46) | 48.6 ( $\pm$ 23.32) |  |  |
| Future- Month 6 (N=14, 11)                         | 40.2 ( $\pm$ 26.14) | 46 ( $\pm$ 18.03)   |  |  |
| Future- Termination (N=14, 11)                     | 47.9 ( $\pm$ 25.47) | 46.8 ( $\pm$ 18.74) |  |  |
| Future- Change (Screening - Month 6) (N=13, 11)    | 4 ( $\pm$ 26.84)    | 1.1 ( $\pm$ 24.34)  |  |  |
| Future- Change(Screening - Termination)(N=13, 11)  | -3.8 ( $\pm$ 20.53) | 0.3 ( $\pm$ 16.58)  |  |  |
| Future- Change (Month 6 - Termination)(N=14, 11)   | -7.7 ( $\pm$ 20.25) | -0.8 ( $\pm$ 16.3)  |  |  |
| PH- Screening (N=15, 12)                           | 64 ( $\pm$ 22.46)   | 66.4 ( $\pm$ 24.21) |  |  |
| PH- Month 6 (N=14, 11)                             | 50.8 ( $\pm$ 27.55) | 43.1 ( $\pm$ 25.24) |  |  |
| PH- Termination (N=14, 11)                         | 56.1 ( $\pm$ 24.98) | 42.3 ( $\pm$ 18.86) |  |  |
| PH- Change (Screening - Month 6) (N=14, 11)        | 14.6 ( $\pm$ 21.7)  | 21.1 ( $\pm$ 28.77) |  |  |
| PH- Change(Screening - Termination)(N=14, 11)      | 9.3 ( $\pm$ 23.93)  | 21.9 ( $\pm$ 24.79) |  |  |

|   |                 |                |  |  |
|---|-----------------|----------------|--|--|
| PH- Change (Month 6 - Termination)(N=14, 11)        | -5.3 (± 10.65)  | 0.8 (± 20.2)   |  |  |
| R'ships- Screening (N=15, 11)                       | 28.3 (± 36.57)  | 26.9 (± 28.83) |  |  |
| R'ships- Month 6 (N=14, 11)                         | 19 (± 28.2)     | 15.2 (± 13.85) |  |  |
| R'ships- Termination (N=14, 10)                     | 17.9 (± 22.13)  | 15 (± 17.48)   |  |  |
| R'ships- Change (Screening - Month 6) (N=14, 10)    | 7.7 (± 34.04)   | 10.4 (± 27.45) |  |  |
| R'ships- Change(Screening - Termination)(N=14, 10)  | 8.9 (± 30.57)   | 12.1 (± 25.49) |  |  |
| R'ships- Change (Month 6 - Termination)(N=14, 10)   | 1.2 (± 21.4)    | 1.7 (± 16.57)  |  |  |
| S&L- Screening (N=12, 8)                            | 69.3 (± 17.11)  | 83.1 (± 14.13) |  |  |
| S&L- Month 6 (N=12, 8)                              | 63.1 (± 23.09)  | 69.7 (± 19.75) |  |  |
| S&L- Termination (N=12, 8)                          | 72.3 (± 17.3)   | 78.1 (± 12.52) |  |  |
| S&L- Change (Screening - Month 6) (N=9, 5)          | 9.9 (± 19.75)   | 20.5 (± 27.97) |  |  |
| S&L- Change(Screening - Termination)(N=9, 5)        | 1.2 (± 15.91)   | 7 (± 21.68)    |  |  |
| S&L- Change (Month 6 - Termination)(N=11, 7)        | -10.2 (± 13.44) | -2.5 (± 15.61) |  |  |
| Treatment- Screening (N=15, 12)                     | 36.9 (± 13.32)  | 39.6 (± 20.7)  |  |  |
| Treatment- Month 6 (N=14, 11)                       | 30.4 (± 19.82)  | 40.9 (± 16.96) |  |  |
| Treatment- Termination (N=14, 11)                   | 34.8 (± 14.87)  | 42.6 (± 17.8)  |  |  |
| Treatment- Change (Screening - Month 6) (N=14, 11)  | 6.5 (± 23.72)   | 0 (± 16.74)    |  |  |
| Treatment-Change(Screening - Termination)(N=14, 11) | 2.1 (± 17.81)   | -1.7 (± 23.86) |  |  |
| Treatment- Change (Month 6- Termination)(N=14, 11)  | -4.4 (± 15.07)  | -1.7 (± 18.7)  |  |  |
| View- Screening (N=15, 12)                          | 52.3 (± 24.49)  | 55.6 (± 11.97) |  |  |
| View- Month 6 (N=14, 11)                            | 44.3 (± 27.66)  | 40 (± 13.23)   |  |  |
| View- Termination (N=14, 11)                        | 47.9 (± 22.59)  | 37.7 (± 21.26) |  |  |
| View- Change (Screening - Month 6) (N=14, 11)       | 7.5 (± 23.68)   | 14.3 (± 17.25) |  |  |
| View- Change (Screening - Termination)(N=14, 11)    | 3.9 (± 23.79)   | 16.6 (± 15.01) |  |  |
| View- Change (Month 6- Termination)(N=14, 11)       | -3.6 (± 17.03)  | 2.3 (± 20.78)  |  |  |
| W&S-Screening (N=13, 10)                            | 43.8 (± 25.9)   | 57.7 (± 17.87) |  |  |
| W&S- Month 6 (N=13, 9)                              | 31.7 (± 26.82)  | 37.5 (± 20.73) |  |  |
| W&S- Termination (N=12, 9)                          | 28.6 (± 22.53)  | 36.8 (± 19.63) |  |  |
| W&S- Change (Screening - Month 6) (N=12, 8)         | 10.9 (± 30.98)  | 25.3 (± 25.6)  |  |  |
| W&S- Change (Screening - Termination)(N=12, 8)      | 16.1 (± 33.86)  | 25.3 (± 19.01) |  |  |
| W&S- Change (Month 6- Termination)(N=12, 9)         | 5.2 (± 15.95)   | 0.7 (± 21.75)  |  |  |
| Total- Screening (N=14, 12)                         | 44 (± 15.5)     | 49.2 (± 15.43) |  |  |
| Total- Month 6 (N=14, 11)                           | 37.4 (± 19.37)  | 38.1 (± 11.34) |  |  |
| Total- Termination (N=14, 11)                       | 40.2 (± 17.55)  | 38.7 (± 14.21) |  |  |
| Total- Change (Screening - Month 6) (N=13, 11)      | 9.2 (± 18.44)   | 10.2 (± 17.84) |  |  |
| Total- Change (Screening - Termination)(N=13, 11)   | 6.1 (± 15.41)   | 9.5 (± 12.77)  |  |  |
| Total- Change (Month 6- Termination)(N=14, 11)      | -2.7 (± 9.21)   | -0.7 (± 14.4)  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Hemophilia-specific Quality of Life questionnaire for Children and Adolescents < 16 Years Old (Haemo-QoL) - Parent's Evaluation

|                 |   |
|-----------------|---|
| End point title | Hemophilia-specific Quality of Life questionnaire for Children and Adolescents < 16 Years Old (Haemo-QoL) - Parent's Evaluation <sup>[34]</sup> |
|-----------------|---|

End point description:

The Haemo-QoL is a quality of life (QoL) assessment instrument for children and adolescents with haemophilia. As a hemophilia-specific instrument, this measure assesses very specific aspects of dealing with hemophilia. The areas covered by this instrument are: Physical Health (PH), Sports & School (S&S), Dealing with Hemophilia (Dealing), Family, Feeling, Relationships (R'ships), Treatment, View, Outlook for the Future (Future), Friends, Others, and Support. A Haemo-QoL Total Score (Total) was also calculated. For the Haemo-QoL, higher scores indicate a worse quality of life. Scores on a scale range between 0 and 100. Haemo-QoL scores at screening, 6 months, and at termination visit were collected. Changes in scores at 6 months and termination were also calculated.

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

End point timeframe:

12 months ± 14 days

Notes:

[34] - 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: Baseline period arms are not mutually exclusive. Details see under description of period arms.

| End point values                                 | On-demand arm   | Prophylaxis arm |  |  |
|--|-----------------|-----------------|--|--|
| Subject group type                               | Reporting group | Reporting group |  |  |
| Number of subjects analysed                      | 4               | 5               |  |  |
| Units: Scores on a scale                         |                 |                 |  |  |
| arithmetic mean (standard deviation)             |                 |                 |  |  |
| Dealing- Screening (N=4, 4)                      | 25.9 (± 11.8)   | 39.3 (± 17)     |  |  |
| Dealing- Month 6 (N=4, 4)                        | 25.6 (± 19.31)  | 36.6 (± 16.07)  |  |  |
| Dealing- Termination (N=4, 5)                    | 21.4 (± 16.24)  | 28.6 (± 13.36)  |  |  |
| Dealing- Change (Screening - Month 6) (N=4, 4)   | 0.3 (± 8.61)    | 2.7 (± 7.92)    |  |  |
| Dealing- Change(Screening - Termination)(N=4, 4) | 4.5 (± 7.92)    | 13.4 (± 5.36)   |  |  |
| Dealing- Change (Month 6 - Termination)(N=4, 4)  | 4.2 (± 11.85)   | 10.7 (± 7.72)   |  |  |
| Family- Screening (N=4, 5)                       | 55.3 (± 19.05)  | 50.9 (± 8.72)   |  |  |
| Family- Month 6 (N=4, 5)                         | 50.3 (± 27.65)  | 49.1 (± 10.27)  |  |  |
| Family- Termination (N=4, 5)                     | 45.8 (± 31.03)  | 39.8 (± 13.77)  |  |  |
| Family- Change (Screening - Month 6) (N=4, 5)    | 5 (± 9.26)      | 1.7 (± 15.65)   |  |  |
| Family- Change(Screening - Termination)(N=4, 5)  | 9.5 (± 15.52)   | 11.1 (± 19.22)  |  |  |

|  |                 |                 |  |  |
|--|-----------------|-----------------|--|--|
| Family- Change (Month 6 - Termination)(N=4, 5)   | 4.5 (± 12.16)   | 9.3 (± 5.24)    |  |  |
| Feeling- Screening (N=4, 5)                      | 44.1 (± 14.25)  | 38.2 (± 2.77)   |  |  |
| Feeling- Month 6 (N=4, 5)                        | 50.3 (± 27.02)  | 37.5 (± 22.21)  |  |  |
| Feeling- Termination (N=4, 5)                    | 33.6 (± 36.07)  | 27.8 (± 16.97)  |  |  |
| Feeling- Change (Screening - Month 6) (N=4, 5)   | -6.3 (± 24.27)  | 0.7 (± 24.02)   |  |  |
| Feeling- Change(Screening - Termination)(N=4, 5) | 10.5 (± 27.92)  | 10.5 (± 19.45)  |  |  |
| Feeling- Change (Month 6 - Termination)(N=4, 5)  | 16.7 (± 13.85)  | 9.7 (± 20.64)   |  |  |
| Friends- Screening (N=4, 5)                      | 35.9 (± 20.65)  | 52.1 (± 17.18)  |  |  |
| Friends- Month 6 (N=4, 5)                        | 26.6 (± 17.95)  | 36.3 (± 29.78)  |  |  |
| Friends- Termination (N=4, 5)                    | 34.4 (± 14.88)  | 66.3 (± 20.06)  |  |  |
| Friends- Change (Screening - Month 6) (N=4, 5)   | 9.4 (± 27.72)   | 15.8 (± 21.88)  |  |  |
| Friends- Change(Screening - Termination)(N=4, 5) | 1.6 (± 17.95)   | -14.2 (± 28.31) |  |  |
| Friends- Change (Month 6 - Termination)(N=4, 5)  | -7.8 (± 22.46)  | -30 (± 31.68)   |  |  |
| Future- Screening (N=2, 2)                       | 53.1 (± 13.26)  | 43.8 (± 17.68)  |  |  |
| Future- Month 6 (N=2, 2)                         | 40.6 (± 13.26)  | 37.5 (± 8.84)   |  |  |
| Future- Termination (N=2, 2)                     | 31.3 (± 0)      | 43.8 (± 8.84)   |  |  |
| Future- Change (Screening - Month 6) (N=2, 2)    | 12.5 (± 0)      | 6.3 (± 8.84)    |  |  |
| Future- Change(Screening - Termination)(N=2, 2)  | 21.9 (± 13.26)  | 0 (± 8.84)      |  |  |
| Future- Change (Month 6 - Termination)(N=2, 2)   | 9.4 (± 13.26)   | -6.3 (± 0)      |  |  |
| Others- Screening (N=4, 5)                       | 27.1 (± 34.44)  | 29.2 (± 16.67)  |  |  |
| Others- Month 6 (N=4, 5)                         | 42.7 (± 39.14)  | 24.2 (± 15.7)   |  |  |
| Others- Termination (N=4, 5)                     | 28.1 (± 32.87)  | 25.8 (± 13.63)  |  |  |
| Others- Change (Screening - Month 6) (N=4, 5)    | -15.6 (± 16.8)  | 5 (± 20.28)     |  |  |
| Others- Change(Screening - Termination)(N=4, 5)  | -1 (± 15.36)    | 3.3 (± 15.98)   |  |  |
| Others- Change (Month 6 - Termination)(N=4, 5)   | 14.6 (± 19.98)  | -1.7 (± 10.87)  |  |  |
| PH- Screening (N=4, 5)                           | 58 (± 11.06)    | 52.1 (± 23.23)  |  |  |
| PH- Month 6 (N=4, 5)                             | 53.6 (± 13.98)  | 48 (± 17.23)    |  |  |
| PH- Termination (N=4, 5)                         | 41.1 (± 11.85)  | 40.4 (± 17.02)  |  |  |
| PH- Change (Screening - Month 6) (N=4, 5)        | 4.5 (± 12.16)   | 4.1 (± 32.71)   |  |  |
| PH- Change(Screening - Termination)(N=4, 5)      | 17 (± 17.1)     | 11.8 (± 29.6)   |  |  |
| PH- Change (Month 6 - Termination)(N=4, 5)       | 12.5 (± 22.87)  | 7.7 (± 22.25)   |  |  |
| R'ships- Screening (N=2, 2)                      | 12.5 (± 17.68)  | 43.8 (± 8.84)   |  |  |
| R'ships- Month 6 (N=2, 2)                        | 25 (± 35.36)    | 43.8 (± 8.84)   |  |  |
| R'ships- Termination (N=2, 2)                    | 0 (± 0)         | 37.5 (± 17.68)  |  |  |
| R'ships- Change (Screening - Month 6) (N=2, 2)   | -12.5 (± 17.68) | 0 (± 0)         |  |  |
| R'ships-Change(Screening - Termination)(N=2, 2)  | 12.5 (± 17.68)  | 6.3 (± 8.84)    |  |  |
| R'ships- Change (Month 6- Termination)(N=2, 2)   | 25 (± 35.36)    | 6.3 (± 8.84)    |  |  |
| S&S- Screening (N=4, 5)                          | 67.1 (± 10.68)  | 59.1 (± 23.73)  |  |  |
| S&S- Month 6 (N=4, 5)                            | 62.5 (± 7.74)   | 56.5 (± 9.07)   |  |  |

|  |                 |                |  |  |
|--|-----------------|----------------|--|--|
| S&S- Termination (N=4, 5)                          | 55.6 (± 17.16)  | 57.2 (± 17.29) |  |  |
| S&S- Change (Screening - Month 6) (N=4, 5)         | 4.6 (± 6.89)    | 2.6 (± 16.32)  |  |  |
| S&S- Change (Screening - Termination)(N=4, 5)      | 11.5 (± 12.02)  | 1.9 (± 10.22)  |  |  |
| S&S- Change (Month 6- Termination)(N=4, 5)         | 6.9 (± 18.07)   | -0.8 (± 8.94)  |  |  |
| Support-Screening (N=4, 4)                         | 28.1 (± 25.77)  | 51.6 (± 9.38)  |  |  |
| Support-Month 6 (N=4, 4)                           | 18.8 (± 29.32)  | 42.2 (± 17.95) |  |  |
| Support- Termination (N=4, 5)                      | 32.8 (± 32.02)  | 48.8 (± 20.44) |  |  |
| Support- Change (Screening - Month 6) (N=4, 4)     | 9.4 (± 24.21)   | 9.4 (± 10.83)  |  |  |
| Support- Change (Screening - Termination)(N=4, 4)  | -4.7 (± 13.86)  | 3.1 (± 15.73)  |  |  |
| Support- Change (Month 6- Termination)(N=4, 4)     | -14.1 (± 21.27) | -6.3 (± 8.84)  |  |  |
| Treatment- Screening (N=4, 5)                      | 29 (± 13.23)    | 64.2 (± 22.6)  |  |  |
| Treatment- Month 6 (N=4, 5)                        | 21.9 (± 6.9)    | 54.8 (± 14.53) |  |  |
| Treatment- Termination (N=4, 5)                    | 17.1 (± 22.12)  | 41 (± 13.34)   |  |  |
| Treatment- Change (Screening - Month 6) (N=4, 5)   | 7.1 (± 10.1)    | 9.4 (± 13.06)  |  |  |
| Treatment- Change(Screening - Termination)(N=4, 5) | 11.9 (± 17.16)  | 23.2 (± 16.94) |  |  |
| Treatment- Change (Month 6- Termination)(N=4, 5)   | 4.8 (± 22.47)   | 13.8 (± 11.14) |  |  |
| View-Screening (N=4, 5)                            | 47.4 (± 18.25)  | 36.7 (± 16.94) |  |  |
| View-Month 6 (N=4, 5)                              | 46.3 (± 24.45)  | 36.4 (± 22.04) |  |  |
| View- Termination (N=4, 5)                         | 32.8 (± 35.68)  | 30.8 (± 12.85) |  |  |
| View- Change (Screening - Month 6) (N=4, 5)        | 1.1 (± 6.38)    | 0.3 (± 7.63)   |  |  |
| View- Change (Screening - Termination)(N=4, 5)     | 14.7 (± 18.62)  | 5.9 (± 10.08)  |  |  |
| View- Change (Month 6- Termination)(N=4, 5)        | 13.5 (± 13.02)  | 5.6 (± 16.7)   |  |  |
| Total-Screening (N=4, 5)                           | 43.7 (± 13.67)  | 48.1 (± 8.84)  |  |  |
| Total-Month 6 (N=4, 5)                             | 42 (± 13.84)    | 42.3 (± 11.08) |  |  |
| Total- Termination (N=4, 5)                        | 34.5 (± 21.83)  | 39.5 (± 8.52)  |  |  |
| Total- Change (Screening - Month 6) (N=4, 5)       | 1.7 (± 1.19)    | 5.7 (± 14.97)  |  |  |
| Total- Change (Screening - Termination)(N=4, 5)    | 9.1 (± 8.57)    | 8.6 (± 8.72)   |  |  |
| Total- Change (Month 6- Termination)(N=4, 5)       | 7.4 (± 8.91)    | 2.8 (± 7.06)   |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Hemophilia-specific Quality of Life questionnaire for Children and Adolescents < 16 Years Old (Haemo-QoL) - Child's Evaluation

|                 |  |
|-----------------|--|
| End point title | Hemophilia-specific Quality of Life questionnaire for Children and Adolescents < 16 Years Old (Haemo-QoL) - Child's Evaluation <sup>[35]</sup> |
|-----------------|--|

End point description:

The Haemo-QoL is a quality of life (QoL) assessment instrument for children and adolescents with

haemophilia. As a hemophilia-specific instrument, this measure assesses very specific aspects of dealing with hemophilia. The areas covered by this instrument are: Physical Health (PH), Sports & School (S&S), Dealing with Hemophilia (Dealing), Family, Feeling, Relationships (R'ships), Treatment, View, Outlook for the Future (Future), Friends, Others, and Support. A Haemo-QoL Total Score (Total) was also calculated. For the Haemo-QoL, higher scores indicate a worse quality of life. Scores on a scale range between 0 and 100. Haemo-QoL scores at screening, 6 months, and at termination visit were collected. Changes in scores at 6 months and termination were also calculated.

|                         |           |
|-------------------------|-----------|
| End point type          | Secondary |
| End point timeframe:    |           |
| 12 months $\pm$ 14 days |           |

Notes:

[35] - 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: Baseline period arms are not mutually exclusive. Details see under description of period arms.

| End point values                                 | On-demand arm       | Prophylaxis arm      |  |  |
|--|---------------------|----------------------|--|--|
| Subject group type                               | Reporting group     | Reporting group      |  |  |
| Number of subjects analysed                      | 4                   | 5                    |  |  |
| Units: Scores on a scale                         |                     |                      |  |  |
| arithmetic mean (standard deviation)             |                     |                      |  |  |
| Dealing- Screening (N=4, 4)                      | 33 ( $\pm$ 17.1)    | 44.6 ( $\pm$ 20.72)  |  |  |
| Dealing- Month 6 (N=4, 4)                        | 21.4 ( $\pm$ 2.92)  | 37.5 ( $\pm$ 13.2)   |  |  |
| Dealing- Termination (N=4, 5)                    | 25 ( $\pm$ 9.22)    | 32.9 ( $\pm$ 12.73)  |  |  |
| Dealing- Change (Screening - Month 6) (N=4, 4)   | 11.6 ( $\pm$ 15.26) | 7.1 ( $\pm$ 8.75)    |  |  |
| Dealing- Change(Screening - Termination)(N=4, 4) | 8 ( $\pm$ 15.26)    | 14.3 ( $\pm$ 12.37)  |  |  |
| Dealing- Change (Month 6 - Termination)(N=4, 4)  | -3.6 ( $\pm$ 6.52)  | 7.1 ( $\pm$ 6.52)    |  |  |
| Family- Screening (N=4, 5)                       | 50.5 ( $\pm$ 23.94) | 35.6 ( $\pm$ 22.05)  |  |  |
| Family- Month 6 (N=4, 5)                         | 43.4 ( $\pm$ 28.78) | 36.4 ( $\pm$ 23.06)  |  |  |
| Family- Termination (N=4, 5)                     | 38.3 ( $\pm$ 21.25) | 32.5 ( $\pm$ 21.09)  |  |  |
| Family- Change (Screening - Month 6) (N=4, 5)    | 7 ( $\pm$ 20.31)    | -0.7 ( $\pm$ 16.38)  |  |  |
| Family- Change(Screening - Termination)(N=4, 5)  | 12.2 ( $\pm$ 25.72) | 3.1 ( $\pm$ 15.51)   |  |  |
| Family- Change (Month 6 - Termination)(N=4, 5)   | 5.2 ( $\pm$ 13.66)  | 3.9 ( $\pm$ 12.2)    |  |  |
| Feeling- Screening (N=4, 5)                      | 54.8 ( $\pm$ 31.91) | 34.9 ( $\pm$ 12.89)  |  |  |
| Feeling- Month 6 (N=4, 5)                        | 41.4 ( $\pm$ 43.03) | 22 ( $\pm$ 18.68)    |  |  |
| Feeling- Termination (N=4, 5)                    | 34.4 ( $\pm$ 39.48) | 19.2 ( $\pm$ 15.39)  |  |  |
| Feeling- Change (Screening - Month 6) (N=4, 5)   | 13.4 ( $\pm$ 16.91) | 12.9 ( $\pm$ 27.77)  |  |  |
| Feeling- Change(Screening - Termination)(N=4, 5) | 20.4 ( $\pm$ 11.77) | 15.7 ( $\pm$ 23.2)   |  |  |
| Feeling- Change (Month 6 - Termination)(N=4, 5)  | 7 ( $\pm$ 7.79)     | 2.8 ( $\pm$ 15.26)   |  |  |
| Friends- Screening (N=4, 5)                      | 34.4 ( $\pm$ 25.26) | 58.8 ( $\pm$ 20.54)  |  |  |
| Friends- Month 6 (N=4, 5)                        | 28.1 ( $\pm$ 15.73) | 42.5 ( $\pm$ 29.78)  |  |  |
| Friends- Termination (N=4, 5)                    | 32.8 ( $\pm$ 12.88) | 56.3 ( $\pm$ 27.24)  |  |  |
| Friends- Change (Screening - Month 6) (N=4, 5)   | 6.3 ( $\pm$ 25.52)  | 16.3 ( $\pm$ 24.84)  |  |  |
| Friends- Change(Screening - Termination)(N=4, 5) | 1.6 ( $\pm$ 28.58)  | 2.5 ( $\pm$ 22.79)   |  |  |
| Friends- Change (Month 6 - Termination)(N=4, 5)  | -4.7 ( $\pm$ 17.95) | -13.8 ( $\pm$ 20.44) |  |  |

|  |                    |                |  |  |
|--|--------------------|----------------|--|--|
| Future- Screening (N=2, 2)                           | 40.6 (± 13.26)     | 43.8 (± 17.68) |  |  |
| Future- Month 6 (N=2, 2)                             | 43.8 (± 17.68)     | 43.8 (± 17.68) |  |  |
| Future- Termination (N=2, 2)                         | 46.9 (± 22.1)      | 28.1 (± 22.1)  |  |  |
| Future- Change (Screening - Month 6)<br>(N=2, 2)     | -3.1 (± 4.42)      | 0 (± 0)        |  |  |
| Future- Change(Screening -<br>Termination)(N=2, 2)   | -6.3 (± 8.84)      | 15.6 (± 4.42)  |  |  |
| Future- Change (Month 6 -<br>Termination)(N=2, 2)    | -3.1 (± 4.42)      | 15.6 (± 4.42)  |  |  |
| Others- Screening (N=4, 5)                           | 42.7 (± 33.74)     | 26.7 (± 20.11) |  |  |
| Others- Month 6 (N=4, 5)                             | 33.3 (± 40.11)     | 16.7 (± 15.02) |  |  |
| Others- Termination (N=4, 5)                         | 18.8 (± 21.11)     | 13.3 (± 12.64) |  |  |
| Others- Change (Screening - Month 6)<br>(N=4, 5)     | 9.4 (± 8.59)       | 10 (± 25.79)   |  |  |
| Others- Change(Screening -<br>Termination)(N=4, 5)   | 24 (± 14.18)       | 13.3 (± 23.09) |  |  |
| Others- Change (Month 6 -<br>Termination)(N=4, 5)    | 14.6 (± 19.39)     | 3.3 (± 16.24)  |  |  |
| PH- Screening (N=4, 5)                               | 67 (± 24.98)       | 42.1 (± 32.28) |  |  |
| PH- Month 6 (N=4, 5)                                 | 49.1 (± 14.69)     | 33.9 (± 16.66) |  |  |
| PH- Termination (N=4, 5)                             | 41.1 (± 23.05)     | 25.7 (± 10.83) |  |  |
| PH- Change (Screening - Month 6)<br>(N=4, 5)         | 17.9 (± 19.56)     | 8.2 (± 34.43)  |  |  |
| PH- Change(Screening -<br>Termination)(N=4, 5)       | 25.9 (± 14.4)      | 16.4 (± 29.73) |  |  |
| PH- Change (Month 6 -<br>Termination)(N=4, 5)        | 8 (± 12.16)        | 8.2 (± 20.66)  |  |  |
| R'ships- Screening (N=2, 2)                          | 6.3 (± 8.84)       | 43.8 (± 8.84)  |  |  |
| R'ships- Month 6 (N=2, 2)                            | 18.8 (± 26.52)     | 43.8 (± 8.84)  |  |  |
| R'ships- Termination (N=2, 2)                        | 6.3 (± 8.84)       | 18.8 (± 26.52) |  |  |
| R'ships- Change (Screening - Month 6)<br>(N=2, 2)    | -12.5 (±<br>17.68) | 0 (± 0)        |  |  |
| R'ships-Change(Screening -<br>Termination)(N=2, 2)   | 0 (± 0)            | 25 (± 17.68)   |  |  |
| R'ships- Change (Month 6-<br>Termination)(N=2, 2)    | 12.5 (± 17.68)     | 25 (± 17.68)   |  |  |
| S&S- Screening (N=4, 5)                              | 53.3 (± 14.74)     | 51.3 (± 19.82) |  |  |
| S&S- Month 6 (N=4, 5)                                | 46.8 (± 13.42)     | 54.2 (± 5.53)  |  |  |
| S&S- Termination (N=4, 5)                            | 33.2 (± 5.64)      | 49.8 (± 18.49) |  |  |
| S&S- Change (Screening - Month 6)<br>(N=4, 5)        | 6.5 (± 11.42)      | -2.8 (± 18.53) |  |  |
| S&S- Change (Screening -<br>Termination)(N=4, 5)     | 20.1 (± 14.74)     | 1.5 (± 18.74)  |  |  |
| S&S- Change (Month 6-<br>Termination)(N=4, 5)        | 13.5 (± 9.1)       | 4.4 (± 15.19)  |  |  |
| Support-Screening (N=4, 4)                           | 32.8 (± 3.13)      | 62.5 (± 31.04) |  |  |
| Support-Month 6 (N=4, 4)                             | 28.1 (± 10.83)     | 56.3 (± 31.87) |  |  |
| Support- Termination (N=4, 5)                        | 17.2 (± 17.21)     | 65 (± 15.69)   |  |  |
| Support- Change (Screening - Month 6)<br>(N=4, 4)    | 4.7 (± 12.88)      | 6.3 (± 31.46)  |  |  |
| Support- Change (Screening -<br>Termination)(N=4, 4) | 15.6 (± 18.75)     | -3.1 (± 18.75) |  |  |
| Support- Change (Month 6-<br>Termination)(N=4, 4)    | 10.9 (± 10.67)     | -9.4 (± 25.77) |  |  |
| Treatment- Screening (N=4, 5)                        | 27.3 (± 15.38)     | 69.6 (± 25.63) |  |  |
| Treatment- Month 6 (N=4, 5)                          | 30.6 (± 16.5)      | 56.8 (± 15.89) |  |  |
| Treatment- Termination (N=4, 5)                      | 35.9 (± 26.1)      | 44.2 (± 27.1)  |  |  |



|  |                |                |  |  |
|--|----------------|----------------|--|--|
| Treatment- Change (Screening - Month 6) (N=4, 5)   | -3.2 (± 4.43)  | 12.9 (± 21.22) |  |  |
| Treatment- Change(Screening - Termination)(N=4, 5) | -8.6 (± 13.86) | 25.4 (± 28)    |  |  |
| Treatment- Change (Month 6- Termination)(N=4, 5)   | -5.3 (± 11.25) | 12.6 (± 15.53) |  |  |
| View-Screening (N=4, 5)                            | 46 (± 19.33)   | 31.9 (± 14.36) |  |  |
| View-Month 6 (N=4, 5)                              | 39.3 (± 33.02) | 32.4 (± 19.41) |  |  |
| View- Termination (N=4, 5)                         | 32.5 (± 32.75) | 32.2 (± 8.6)   |  |  |
| View- Change (Screening - Month 6) (N=4, 5)        | 6.7 (± 14.96)  | -0.5 (± 18.94) |  |  |
| View- Change (Screening - Termination)(N=4, 5)     | 13.5 (± 16.56) | -0.3 (± 10.77) |  |  |
| View- Change (Month 6- Termination)(N=4, 5)        | 6.8 (± 8.67)   | 0.2 (± 13.48)  |  |  |
| Total-Screening (N=4, 5)                           | 44.9 (± 12.28) | 45.1 (± 9.16)  |  |  |
| Total-Month 6 (N=4, 5)                             | 37.4 (± 17.91) | 37.7 (± 9.87)  |  |  |
| Total- Termination (N=4, 5)                        | 32.2 (± 17.96) | 35.3 (± 9.06)  |  |  |
| Total- Change (Screening - Month 6) (N=4, 5)       | 7.5 (± 7.21)   | 7.4 (± 16.57)  |  |  |
| Total- Change (Screening - Termination)(N=4, 5)    | 12.7 (± 8.69)  | 9.8 (± 12.35)  |  |  |
| Total- Change (Month 6- Termination)(N=4, 5)       | 5.2 (± 3.55)   | 2.5 (± 9.46)   |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Health-Related Quality of Life (HRQoL) - General Pain Assessment Using a Visual Analogue Scale (VAS) in Adults and Adolescents ≥12 Years Old

|                 |  |
|-----------------|--|
| End point title | Health-Related Quality of Life (HRQoL) - General Pain Assessment Using a Visual Analogue Scale (VAS) in Adults and Adolescents ≥12 Years Old <sup>[36]</sup> |
|-----------------|--|

End point description:

General pain was assessed using a VAS pain scale at screening, 6 months, and at termination. Unlike the VAS pain assessment for pain of bleeding episodes (Outcome above), this general pain assessment did not take use of analgesics into account. For the pain scale, a higher number indicates worse pain. The visual analog scale ranges from 0 to 100 where the endpoints are labeled 'Worst imaginable health state' (=0) and 'Best imaginable health state' (=100). A positive change from baseline indicates improvement. Change in VAS scores at 6 months and study termination were also compared relative to Baseline/Screening scores (ie, (Baseline/Screening VAS score) - (VAS score at 6 months and study termination)).

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

End point timeframe:

Baseline, 6 months and 12 months ± 14 days

Notes:

[36] - 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: Baseline period arms are not mutually exclusive. Details see under description of period arms.

| End point values                             | On-demand arm   | Prophylaxis arm |  |  |
|--|-----------------|-----------------|--|--|
| Subject group type                           | Reporting group | Reporting group |  |  |
| Number of subjects analysed                  | 17              | 15              |  |  |
| Units: Scores on a scale                     |                 |                 |  |  |
| arithmetic mean (standard deviation)         |                 |                 |  |  |
| Screening (N= 17, 15)                        | 35.2 (± 30.15)  | 55.5 (± 23.68)  |  |  |
| Month 6 (N= 16, 14)                          | 36.6 (± 25.81)  | 32.7 (± 26.24)  |  |  |
| Termination (N= 16, 14)                      | 32.4 (± 21.97)  | 29.8 (± 30.48)  |  |  |
| Change (Screening - Month 6) (N= 16, 14)     | 0.8 (± 31.77)   | 20.3 (± 38.91)  |  |  |
| Change (Screening - Termination) (N= 16, 14) | 5 (± 28.7)      | 23.2 (± 46.61)  |  |  |
| Change (Month 6 - Termination) (N= 16, 14)   | 4.2 (± 21.82)   | 2.9 (± 19.62)   |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Health-Related Quality of Life (HRQoL) - General Pain Assessment Using a Visual Analogue Scale (VAS) in Pediatrics <12 Years Old

|                 |  |
|-----------------|--|
| End point title | Health-Related Quality of Life (HRQoL) - General Pain Assessment Using a Visual Analogue Scale (VAS) in Pediatrics <12 Years Old <sup>[37]</sup> |
|-----------------|--|

End point description:

General pain was assessed using the children's VAS pain scale (a facial expression scale with one end marked as no pain and the opposite end marked as the worst possible pain). Assessments were done at the screening, 6 months, and termination visits. Scores on the children's VAS scale are presented as: - No Pain -Mild Pain -Moderate pain -Severe pain -Very severe pain Unlike the VAS pain assessment for pain of bleeding episodes (Outcome above), this general pain assessment did not take use of analgesics into account. Change in VAS scores at 6 months and study termination were also compared relative to Baseline/Screening scores (ie, (Baseline/Screening VAS score) - (VAS score at 6 months and study termination)).

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

End point timeframe:

Baseline, 6 months and 12 months ± 14 days

Notes:

[37] - 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: Baseline period arms are not mutually exclusive. Details see under description of period arms.

| End point values             | On-demand arm   | Prophylaxis arm |  |  |
|------------------------------|-----------------|-----------------|--|--|
| Subject group type           | Reporting group | Reporting group |  |  |
| Number of subjects analysed  | 2               | 2               |  |  |
| Units: participants          |                 |                 |  |  |
| Screening - No Pain          | 1               | 0               |  |  |
| Screening - Mild Pain        | 0               | 1               |  |  |
| Screening - Moderate Pain    | 1               | 0               |  |  |
| Screening - Severe Pain      | 0               | 1               |  |  |
| Screening - Very Severe Pain | 0               | 0               |  |  |
| Month 6 - No Pain            | 0               | 0               |  |  |

|                                      |   |   |  |  |
|--------------------------------------|---|---|--|--|
| Month 6 - Mild Pain                  | 1 | 2 |  |  |
| Month 6 - Moderate Pain              | 1 | 0 |  |  |
| Month 6 - Severe Pain                | 0 | 0 |  |  |
| Month 6 - Very Severe Pain           | 0 | 0 |  |  |
| Termination visit - No Pain          | 0 | 1 |  |  |
| Termination visit - Mild Pain        | 0 | 0 |  |  |
| Termination visit - Moderate Pain    | 1 | 1 |  |  |
| Termination visit - Severe Pain      | 0 | 0 |  |  |
| Termination visit - Very Severe Pain | 1 | 0 |  |  |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Throughout the study period of 3 years and 7 months

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

### Dictionary used

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

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

### Reporting groups

|                       |               |
|-----------------------|---------------|
| Reporting group title | On-demand arm |
|-----------------------|---------------|

Reporting group description:

Factor VIII Inhibitor Bypassing Activity (nanofiltered, vapor heat-treated) : Standard FEIBA NF dose and dosing interval as prescribed by the treating physician

|                       |                 |
|-----------------------|-----------------|
| Reporting group title | Prophylaxis arm |
|-----------------------|-----------------|

Reporting group description:

Factor VIII Inhibitor Bypassing Activity (nanofiltered, vapor heat-treated) : 85 ± 15 U/kg of FEIBA NF every other day during the 12-month ± 14 days prophylactic period

| Serious adverse events                            | On-demand arm   | Prophylaxis arm |  |
|---|-----------------|-----------------|--|
| Total subjects affected by serious adverse events |                 |                 |  |
| subjects affected / exposed                       | 7 / 19 (36.84%) | 6 / 17 (35.29%) |  |
| number of deaths (all causes)                     | 1               | 0               |  |
| number of deaths resulting from adverse events    |                 |                 |  |
| Investigations                                    |                 |                 |  |
| Hepatitis B Surface Antibody Positive             |                 |                 |  |
| subjects affected / exposed                       | 1 / 19 (5.26%)  | 2 / 17 (11.76%) |  |
| occurrences causally related to treatment / all   | 1 / 1           | 2 / 2           |  |
| deaths causally related to treatment / all        | 0 / 0           | 0 / 0           |  |
| Injury, poisoning and procedural complications    |                 |                 |  |
| Femoral Neck Fracture                             |                 |                 |  |
| subjects affected / exposed                       | 1 / 19 (5.26%)  | 0 / 17 (0.00%)  |  |
| occurrences causally related to treatment / all   | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all        | 0 / 0           | 0 / 0           |  |
| Vascular disorders                                |                 |                 |  |
| Arteriosclerosis                                  |                 |                 |  |
| subjects affected / exposed                       | 1 / 19 (5.26%)  | 0 / 17 (0.00%)  |  |
| occurrences causally related to treatment / all   | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all        | 0 / 1           | 0 / 0           |  |

|   |                |                |  |
|---|----------------|----------------|--|
| Haematoma                                       |                |                |  |
| subjects affected / exposed                     | 0 / 19 (0.00%) | 1 / 17 (5.88%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Haemorrhage                                     |                |                |  |
| subjects affected / exposed                     | 1 / 19 (5.26%) | 0 / 17 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Hypertensive Crisis                             |                |                |  |
| subjects affected / exposed                     | 1 / 19 (5.26%) | 0 / 17 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Surgical and medical procedures                 |                |                |  |
| Catheter Removal                                |                |                |  |
| subjects affected / exposed                     | 1 / 19 (5.26%) | 0 / 17 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Gastrointestinal disorders                      |                |                |  |
| Abdominal Wall Haematoma                        |                |                |  |
| subjects affected / exposed                     | 0 / 19 (0.00%) | 1 / 17 (5.88%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Hepatobiliary disorders                         |                |                |  |
| Cholecystitis Acute                             |                |                |  |
| subjects affected / exposed                     | 1 / 19 (5.26%) | 0 / 17 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Respiratory, thoracic and mediastinal disorders |                |                |  |
| Epistaxis                                       |                |                |  |
| subjects affected / exposed                     | 1 / 19 (5.26%) | 0 / 17 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Renal and urinary disorders                     |                |                |  |
| Haematuria                                      |                |                |  |

|  |                |                 |  |
|--|----------------|-----------------|--|
| subjects affected / exposed                            | 1 / 19 (5.26%) | 0 / 17 (0.00%)  |  |
| occurrences causally related to treatment / all        | 0 / 1          | 0 / 0           |  |
| deaths causally related to treatment / all             | 0 / 0          | 0 / 0           |  |
| <b>Musculoskeletal and connective tissue disorders</b> |                |                 |  |
| Arthropathy  |                |                 |  |
| subjects affected / exposed                            | 1 / 19 (5.26%) | 0 / 17 (0.00%)  |  |
| occurrences causally related to treatment / all        | 0 / 1          | 0 / 0           |  |
| deaths causally related to treatment / all             | 0 / 0          | 0 / 0           |  |
| Haemarthrosis  |                |                 |  |
| subjects affected / exposed                            | 1 / 19 (5.26%) | 2 / 17 (11.76%) |  |
| occurrences causally related to treatment / all        | 0 / 3          | 0 / 8           |  |
| deaths causally related to treatment / all             | 0 / 0          | 0 / 0           |  |
| Muscle Haemorrhage                                     |                |                 |  |
| subjects affected / exposed                            | 0 / 19 (0.00%) | 1 / 17 (5.88%)  |  |
| occurrences causally related to treatment / all        | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all             | 0 / 0          | 0 / 0           |  |
| <b>Infections and infestations</b>                     |                |                 |  |
| Haematoma Infection                                    |                |                 |  |
| subjects affected / exposed                            | 1 / 19 (5.26%) | 0 / 17 (0.00%)  |  |
| occurrences causally related to treatment / all        | 0 / 1          | 0 / 0           |  |
| deaths causally related to treatment / all             | 0 / 0          | 0 / 0           |  |

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

| <b>Non-serious adverse events</b>                            | On-demand arm   | Prophylaxis arm |  |
|--|-----------------|-----------------|--|
| <b>Total subjects affected by non-serious adverse events</b> |                 |                 |  |
| subjects affected / exposed                                  | 4 / 19 (21.05%) | 3 / 17 (17.65%) |  |
| <b>Blood and lymphatic system disorders</b>                  |                 |                 |  |
| Anaemia  |                 |                 |  |
| subjects affected / exposed                                  | 2 / 19 (10.53%) | 0 / 17 (0.00%)  |  |
| occurrences (all)  | 2               | 0               |  |
| <b>General disorders and administration site conditions</b>  |                 |                 |  |
| Pyrexia  |                 |                 |  |

|  |                      |                     |  |
|--|----------------------|---------------------|--|
| subjects affected / exposed<br>occurrences (all) | 2 / 19 (10.53%)<br>4 | 0 / 17 (0.00%)<br>0 |  |
| Gastrointestinal disorders                       |                      |                     |  |
| Diarrhoea  |                      |                     |  |
| subjects affected / exposed                      | 1 / 19 (5.26%)       | 1 / 17 (5.88%)      |  |
| occurrences (all)                                | 2                    | 1                   |  |
| Nausea   |                      |                     |  |
| subjects affected / exposed                      | 2 / 19 (10.53%)      | 0 / 17 (0.00%)      |  |
| occurrences (all)                                | 2                    | 0                   |  |
| Vomiting   |                      |                     |  |
| subjects affected / exposed                      | 2 / 19 (10.53%)      | 0 / 17 (0.00%)      |  |
| occurrences (all)                                | 2                    | 0                   |  |
| Respiratory, thoracic and mediastinal disorders  |                      |                     |  |
| Cough  |                      |                     |  |
| subjects affected / exposed                      | 1 / 19 (5.26%)       | 1 / 17 (5.88%)      |  |
| occurrences (all)                                | 1                    | 1                   |  |
| Oropharyngeal Pain                               |                      |                     |  |
| subjects affected / exposed                      | 1 / 19 (5.26%)       | 1 / 17 (5.88%)      |  |
| occurrences (all)                                | 1                    | 1                   |  |
| Skin and subcutaneous tissue disorders           |                      |                     |  |
| Acne   |                      |                     |  |
| subjects affected / exposed                      | 1 / 19 (5.26%)       | 1 / 17 (5.88%)      |  |
| occurrences (all)                                | 1                    | 1                   |  |
| Musculoskeletal and connective tissue disorders  |                      |                     |  |
| Arthralgia                                       |                      |                     |  |
| subjects affected / exposed                      | 2 / 19 (10.53%)      | 1 / 17 (5.88%)      |  |
| occurrences (all)                                | 3                    | 1                   |  |
| Arthropathy                                      |                      |                     |  |
| subjects affected / exposed                      | 1 / 19 (5.26%)       | 0 / 17 (0.00%)      |  |
| occurrences (all)                                | 1                    | 0                   |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

---

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported