



Clinical trial results:

A Non-randomized, Open-label Study To Evaluate The Pharmacokinetics, Safety And Efficacy Of Refacto Af In Previously Treated Pediatric Subjects Less Than Twelve Years Of Age With Severe Hemophilia A (Fviii:c <1%)

Summary

| | |
|--------------------------|----------------------------|
| EudraCT number | 2008-008435-29 |
| Trial protocol | FR ES IT GR CZ SE DK FI BG |
| Global end of trial date | 05 April 2016 |

Results information

| | |
|--------------------------------|-------------------|
| Result version number | v1 (current) |
| This version publication date | 02 September 2016 |
| First version publication date | 02 September 2016 |

Trial information

Trial identification

| | |
|-----------------------|-------------|
| Sponsor protocol code | 3082B2-4433 |
|-----------------------|-------------|

Additional study identifiers

| | |
|------------------------------------|-----------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT00914459 |
| WHO universal trial number (UTN) | - |
| Other trial identifiers | Alias: B1831005 |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Pfizer, Inc. |
| Sponsor organisation address | 235 E 42nd Street, New York, United States, 10017 |
| Public contact | Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc., 001 800--718-1021, ClinicalTrials.gov_Inquiries@pfizer.com |
| Scientific contact | Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc., 001 800--718-1021, ClinicalTrials.gov_Inquiries@pfizer.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 | 20 July 2016 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 05 April 2016 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to evaluate the PK and incremental recovery of ReFacto AF in pediatric subjects less than 12 years of age after a single exposure to ReFacto AF. The secondary objectives of this study are to evaluate the efficacy of ReFacto AF in pediatric subjects less than 12 years of age, including the frequency of less-than-expected therapeutic effect (LETE) and to evaluate the safety of ReFacto AF in these subjects.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy: -

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 11 December 2009 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|------------|
| Country: Number of subjects enrolled | Finland: 1 |
| Country: Number of subjects enrolled | Georgia: 1 |
| Country: Number of subjects enrolled | Italy: 1 |
| Country: Number of subjects enrolled | Romania: 9 |
| Country: Number of subjects enrolled | Serbia: 9 |
| Country: Number of subjects enrolled | Spain: 4 |
| Country: Number of subjects enrolled | Sweden: 2 |
| Country: Number of subjects enrolled | Turkey: 5 |
| Country: Number of subjects enrolled | Ukraine: 5 |
| Worldwide total number of subjects | 37 |
| EEA total number of subjects | 17 |

Notes:

Subjects enrolled per age group

| | |
|--|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 | 0 |

| | |
|--|----|
| wk | |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 1 |
| Children (2-11 years) | 36 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 0 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The study was started in 11 Dec 2009 and completed on 05 Apr 2016.

Period 1

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

Arms

| | |
|------------------------------|-------------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | ReFacto AF: Less Than 6 Years |

Arm description:

Subjects below 6 years of age were treated with IV injections of ReFacto AF at a dose and frequency prescribed by the investigator (minimum dose of 17 international units per kilogram [IU/kg] up to maximum dose of 51 IU/kg) as per local standard of care in accordance with the Summary of Product Characteristics (SmPC).

| | |
|--|--|
| Arm type | Experimental |
| Investigational medicinal product name | ReFacto AF |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder and solution for solution for injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

Subjects received Refacto AF IV infusion as a single dose (minimum dose of 17 IU/kg up to maximum dose of 51 IU/kg) and frequency prescribed by the investigator as per local standard of care in accordance with the Summary of Product Characteristics (SmPC). A single 50 IU/kg dose was administered for assessment of PK parameters, including recovery.

| | |
|------------------|-------------------------------------|
| Arm title | ReFacto AF: 6 to Less Than 12 Years |
|------------------|-------------------------------------|

Arm description:

Subjects of 6 to 12 years of age were treated with IV injections of ReFacto AF at a dose and frequency prescribed by the investigator (minimum dose of 17 IU/kg up to maximum dose of 51 IU/kg) as per local standard of care in accordance with the SmPC.

| | |
|--|--|
| Arm type | Experimental |
| Investigational medicinal product name | ReFacto AF |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder and solution for solution for injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

Subjects received Refacto AF IV infusion as a single dose (minimum dose of 17 IU/kg up to maximum dose of 51 IU/kg) and frequency prescribed by the investigator as per local standard of care in accordance with the Summary of Product Characteristics (SmPC). A single 50 IU/kg dose was administered for assessment of PK parameters, including recovery.

| Number of subjects in period 1 | ReFacto AF: Less Than 6 Years | ReFacto AF: 6 to Less Than 12 Years |
|---------------------------------------|-------------------------------|-------------------------------------|
| Started | 18 | 19 |
| Completed | 17 | 18 |
| Not completed | 1 | 1 |
| Parent/Legal guardian request | 1 | - |
| Protocol deviation | - | 1 |

Baseline characteristics

Reporting groups

| | |
|---|-------------------------------------|
| Reporting group title | ReFacto AF: Less Than 6 Years |
| Reporting group description: Subjects below 6 years of age were treated with IV injections of ReFacto AF at a dose and frequency prescribed by the investigator (minimum dose of 17 international units per kilogram [IU/kg] up to maximum dose of 51 IU/kg) as per local standard of care in accordance with the Summary of Product Characteristics (SmPC). | |
| Reporting group title | ReFacto AF: 6 to Less Than 12 Years |
| Reporting group description: Subjects of 6 to 12 years of age were treated with IV injections of ReFacto AF at a dose and frequency prescribed by the investigator (minimum dose of 17 IU/kg up to maximum dose of 51 IU/kg) as per local standard of care in accordance with the SmPC. | |

| Reporting group values | ReFacto AF: Less Than 6 Years | ReFacto AF: 6 to Less Than 12 Years | Total |
|--|-------------------------------|-------------------------------------|-------|
| Number of subjects | 18 | 19 | 37 |
| Age categorical Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 1 | 0 | 1 |
| Children (2-11 years) | 17 | 19 | 36 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 0 | 0 | 0 |
| From 65-84 years | 0 | 0 | 0 |
| 85 years and over | 0 | 0 | 0 |
| Age Continuous Units: years | | | |
| arithmetic mean | 3.6 | 9.2 | - |
| standard deviation | ± 1.42 | ± 1.47 | - |
| Gender, Male/Female Units: participants | | | |
| Female | 0 | 0 | 0 |
| Male | 18 | 19 | 37 |

Subject analysis sets

| | |
|---|--------------------------|
| Subject analysis set title | ReFacto AF: All Subjects |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: All subjects (aged less than or equal to [\leq] 12 years of age) were treated with IV injections of ReFacto AF at a dose and frequency prescribed by the investigator (minimum dose of 17 IU/kg up to maximum dose of 51 IU/kg) as per local standard of care in accordance with the SmPC. | |

| Reporting group values | ReFacto AF: All Subjects | | |
|--|--------------------------|--|--|
| Number of subjects | 37 | | |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | | |
| Newborns (0-27 days) | 0 | | |
| Infants and toddlers (28 days-23 months) | 1 | | |
| Children (2-11 years) | 36 | | |
| Adolescents (12-17 years) | 0 | | |
| Adults (18-64 years) | 0 | | |
| From 65-84 years | 0 | | |
| 85 years and over | 0 | | |
| Age Continuous | | | |
| Units: years | | | |
| arithmetic mean | 6.5 | | |
| standard deviation | ± 3.2 | | |
| Gender, Male/Female | | | |
| Units: participants | | | |
| Female | 0 | | |
| Male | 37 | | |

End points

End points reporting groups

| | |
|---|-------------------------------------|
| Reporting group title | ReFacto AF: Less Than 6 Years |
| Reporting group description: Subjects below 6 years of age were treated with IV injections of ReFacto AF at a dose and frequency prescribed by the investigator (minimum dose of 17 international units per kilogram [IU/kg] up to maximum dose of 51 IU/kg) as per local standard of care in accordance with the Summary of Product Characteristics (SmPC). | |
| Reporting group title | ReFacto AF: 6 to Less Than 12 Years |
| Reporting group description: Subjects of 6 to 12 years of age were treated with IV injections of ReFacto AF at a dose and frequency prescribed by the investigator (minimum dose of 17 IU/kg up to maximum dose of 51 IU/kg) as per local standard of care in accordance with the SmPC. | |
| Subject analysis set title | ReFacto AF: All Subjects |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: All subjects (aged less than or equal to [\leq] 12 years of age) were treated with IV injections of ReFacto AF at a dose and frequency prescribed by the investigator (minimum dose of 17 IU/kg up to maximum dose of 51 IU/kg) as per local standard of care in accordance with the SmPC. | |

Primary: Percentage of Subjects With Clinically Significant Factor VIII Inhibitor Development

| | |
|--|---|
| End point title | Percentage of Subjects With Clinically Significant Factor VIII Inhibitor Development ^[1] |
| End point description: Clinically significant factor VIII (FVIII) inhibitors were defined as a central laboratory confirmed positive inhibitor of greater than or equal to (\geq) 0.6 Bethesda units (BU) using the Nijmegen modification of the Bethesda assay present at 2 consecutive blood draws within a 6-week interval and one of the following within 4 weeks before the initial or within 4 weeks following the second positive FVIII inhibitor sample collection: the need for the subject to administer alternative hemostatic products in order to achieve sufficient efficacy, or ≥ 2 events indicating a decrease in the efficacy of the study treatment. Percentage of subjects who developed clinically significant Factor VIII inhibitor after study drug administration were reported. Safety analysis population included all enrolled subjects who received at least 1 dose of ReFacto AF. | |
| End point type | Primary |
| End point timeframe: Baseline up to Month 24 | |
| Notes: [1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point. Justification: Only descriptive data was planned to be reported for this endpoint. | |

| End point values | ReFacto AF: Less Than 6 Years | ReFacto AF: 6 to Less Than 12 Years | | |
|----------------------------------|-------------------------------|-------------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 18 | 19 | | |
| Units: percentage of subjects | | | | |
| number (confidence interval 95%) | 0 (0 to 18.53) | 0 (0 to 17.65) | | |

Statistical analyses

No statistical analyses for this end point

Primary: Incremental Recovery

| | |
|-----------------|-------------------------------------|
| End point title | Incremental Recovery ^[2] |
|-----------------|-------------------------------------|

End point description:

Incremental recovery was the increase in circulating FVIII activity for every international unit (IU) of ReFacto AF administered per kilogram of body weight. It was measured in international units per deciliter (IU/dL) per international units per kilogram (IU/kg). The pharmacokinetic (PK) parameter analysis population included all enrolled subjects who received at least 1 dose of ReFacto AF. Here, "n" signifies subjects who were evaluable at the specified time point for each reporting group respectively.

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

End point timeframe:

Days 1, 15, 50, Months 6, 18 and Final visit (up to Month 24)

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only descriptive data was planned to be reported for this endpoint.

| End point values | ReFacto AF: Less Than 6 Years | ReFacto AF: 6 to Less Than 12 Years | | |
|--------------------------------------|-------------------------------|-------------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 18 | 19 | | |
| Units: (IU/dL)/(IU/kg) | | | | |
| arithmetic mean (standard deviation) | | | | |
| Day 1 (n= 17, 18) | 1.67 (± 0.361) | 1.97 (± 0.437) | | |
| Day 15 (n= 18, 17) | 1.23 (± 0.65) | 1.91 (± 0.423) | | |
| Day 50 (n= 17, 18) | 1.66 (± 0.626) | 1.96 (± 0.586) | | |
| Month 6 (n= 2, 5) | 1.69 (± 0.21) | 2.17 (± 0.379) | | |
| Month 18 (n= 4, 5) | 1.81 (± 0.405) | 1.8 (± 0.493) | | |
| Final Visit (n= 17, 17) | 1.98 (± 1.454) | 1.89 (± 0.503) | | |

Statistical analyses

No statistical analyses for this end point

Primary: Terminal Elimination Half Life of ReFacto AF (t_{1/2})

| | |
|-----------------|--|
| End point title | Terminal Elimination Half Life of ReFacto AF (t _{1/2}) ^[3] ^[4] |
|-----------------|--|

End point description:

T_{1/2} was the time for the plasma concentration of drug to decrease by one-half of its original concentration. PK parameter analysis population included all enrolled subjects who received at least 1 dose of ReFacto AF. Here, "number of subjects analysed" signifies subjects who were evaluable for this endpoint. Data was not planned to be collected and analysed for reporting arm "ReFacto AF: Less Than 6 Years", as pre-specified in protocol.

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

End point timeframe:

Pre-dose, 0.5, 1, 3, 6, 9, 24, 28, 32, 48 hours post-dose on Day 1

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only descriptive data was planned to be reported for this endpoint.

[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: The endpoint was planned to be assessed for "ReFacto AF: 6 to Less Than 12 Years" reporting group only.

| | | | | |
|--------------------------------------|-------------------------------------|--|--|--|
| End point values | ReFacto AF: 6 to Less Than 12 Years | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 14 | | | |
| Units: hours | | | | |
| arithmetic mean (standard deviation) | 9.12 (± 1.9429) | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Clearance (CL)

| | |
|-----------------|----------------------------------|
| End point title | Clearance (CL) ^{[5][6]} |
|-----------------|----------------------------------|

End point description:

Drug clearance is a quantitative measure of the rate at which a drug substance is removed from the blood. PK parameter analysis population included all enrolled subjects who received at least 1 dose of ReFacto AF. Here, "number of subjects analysed" signifies subjects who were evaluable for this endpoint. Data was not planned to be collected and analysed for reporting arm "ReFacto AF: Less Than 6 Years", as pre-specified in protocol.

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

End point timeframe:

Pre-dose, 0.5, 1, 3, 6, 9, 24, 28, 32, 48 hours post-dose on Day 1

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only descriptive data was planned to be reported for this endpoint.

[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: The endpoint was planned to be assessed for "ReFacto AF: 6 to Less Than 12 Years" reporting group only.

| | | | | |
|---|-------------------------------------|--|--|--|
| End point values | ReFacto AF: 6 to Less Than 12 Years | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 14 | | | |
| Units: milliliter per hour per kilogram | | | | |
| geometric mean (geometric coefficient of variation) | 4.406 (± 30) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Annualized Bleeding Rates (ABRs): All Subjects

| | |
|--|---|
| End point title | Mean Annualized Bleeding Rates (ABRs): All Subjects |
| End point description: | |
| ABR for each subject was calculated as the number of bleeds requiring administration of FVIII replacement product (taken from the Infusion Log Diary case report form), divided by the total therapy duration (in days), then multiplied by 365.25. ABR for the participants who reported following a primary or secondary prophylaxis, on-demand regimen or preventive regimen at baseline were reported. Efficacy analysis population included all enrolled subjects who received at least 1 dose of ReFacto AF. Here, "number of subjects analysed" signifies subjects who were evaluable for this endpoint and "n" signifies subjects who were evaluable at the specified time points. Here "99999" for mean and "+/-99999" for standard deviation signifies "not available" as the data was not calculated and reported because none of the subjects were reported at baseline as following a preventive regimen. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline up to Month 24 | |

| End point values | ReFacto AF: All Subjects | | | |
|---|--------------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 36 | | | |
| Units: bleeds per year | | | | |
| arithmetic mean (standard deviation) | | | | |
| On-demand regimen (n=14) | 27.51 (± 20.387) | | | |
| Preventive regimen (n=0) | 99999 (± 99999) | | | |
| Primary or secondary prophylaxis regimen (n=22) | 4.18 (± 3.849) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Response to the First On-Demand Treatment for all New Bleeds: All Subjects

| | |
|--|--|
| End point title | Response to the First On-Demand Treatment for all New Bleeds: All Subjects |
| End point description: | |
| Scale for assessment of 'on-demand' treatment is defined as: 1.Excellent:Definite pain relief and/or improvement (improve.)in signs of bleeding starting within 8 hours after an infusion (inf.),with no additional inf. Administered (adm.). 2.Good: Definite pain relief and/or improve. in signs of bleeding starting within 8 hours after an inf.,with at least 1 additional inf. adm. for complete resolution of bleeding episode;or,Definite pain relief and/or improve. in signs of bleeding starting after 8 hours following inf.,with no additional inf. adm. 3.Moderate:Probable or slight improve. starting after 8 hours following inf.,with at least 1 additional inf. adm. for complete resolution of bleeding episode. 4.No Response:No improve. at all between inf. or during 24-hour interval following inf.,or condition worsens.Efficacy population.Number of subjects analysed signifies subjects who were evaluable for this endpoint and received at least 1 dose of ReFacto AF for at least 1 bleeding episode. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline up to Month 24 | |

| End point values | ReFacto AF: All Subjects | | | |
|-----------------------------|--------------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 30 | | | |
| Units: responses | | | | |
| Excellent | 713 | | | |
| Good | 73 | | | |
| Moderate | 16 | | | |
| Data Not Recorded | 2 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of On-Demand ReFacto AF Infusions to Treat a New Bleed: All Subjects

| | |
|-----------------|---|
| End point title | Number of On-Demand ReFacto AF Infusions to Treat a New Bleed: All Subjects |
|-----------------|---|

End point description:

The infusion log diary case report form (CRF) was used to determine the number of on-demand (administration of an unscheduled bolus infusion of Refacto-AF to stop bleeding) ReFacto AF infusions administered to treat a new bleed. This was calculated by adding the initial for a new bleed (on-demand) infusion to any subsequent (on-demand) infusions for the same "previously treated bleed" (same bleed with same start date/time). Efficacy analysis population included all enrolled subjects who received at least 1 dose of ReFacto AF. Here, "number of subjects analysed" signifies subjects who were evaluable for this endpoint.

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

End point timeframe:

Baseline up to Month 24

| End point values | ReFacto AF: All Subjects | | | |
|--------------------------------------|--------------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 30 | | | |
| Units: infusions | | | | |
| arithmetic mean (standard deviation) | 1.1 (± 0.55) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Breakthrough Bleeds Within 48 Hours of a Prophylaxis Dose of ReFacto AF: All Subjects

| | |
|--|---|
| End point title | Number of Breakthrough Bleeds Within 48 Hours of a Prophylaxis Dose of ReFacto AF: All Subjects |
| End point description: | |
| The number of breakthrough bleeds within 48 hours following a prophylaxis dose of ReFacto AF was summarized. The infusion log diary CRF was used to determine the number of infusions administered to treat a new bleed counting only those infusions which were administered less than or equal to (\leq) 48 hours after an infusion marked as "prophylaxis" (which had no associated bleed). Efficacy analysis population included all enrolled subjects who received at least 1 dose of ReFacto AF. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline up to Month 24 | |

| | | | | |
|--------------------------------------|--------------------------|--|--|--|
| End point values | ReFacto AF: All Subjects | | | |
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 37 | | | |
| Units: breakthrough bleeds | | | | |
| arithmetic mean (standard deviation) | 2 (\pm 1.15) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Average Infusion Dose of ReFacto AF: All Subjects

| | |
|--|---|
| End point title | Average Infusion Dose of ReFacto AF: All Subjects |
| End point description: | |
| The average infusion dose (by weight) for each subject was calculated as his total factor FVIII consumption (in IU) divided by weight (in kg) divided by the number of infusions administered in total study duration. Data was reported separately for subjects classified at baseline as following non-prophylaxis regimen (for example: on-demand regimen, preventive, or not specified), and subjects classified at baseline following a primary or secondary prophylaxis regimen. Efficacy analysis population included all enrolled subjects who received at least 1 dose of ReFacto AF. Here, "n" signifies subjects who were evaluable for each specified baseline category. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline up to Month 24 | |

| | | | | |
|--|--------------------------|--|--|--|
| End point values | ReFacto AF: All Subjects | | | |
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 37 | | | |
| Units: IU/kg | | | | |
| arithmetic mean (standard deviation) | | | | |
| With prophylaxis regimen at baseline (n= 22) | 37 (\pm 8.7) | | | |
| With non-prophylaxis regimen at baseline (n= 15) | 29.5 (\pm 7.61) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Total Factor VIII Consumption: All Subjects

| | |
|-----------------|---|
| End point title | Total Factor VIII Consumption: All Subjects |
|-----------------|---|

End point description:

Total factor VIII consumption for each subject was calculated by sum of the total amount of ReFacto AF (in IU) infused for each ReFacto AF infusion (recorded in the infusion log diary CRF) divided by the weight (kg) recorded at the previous visit for each subject. Data was reported separately for subjects classified at baseline as following non-prophylaxis regimen (for example: on-demand regimen, preventive, or not specified), and subjects classified at baseline following a primary or secondary prophylaxis regimen. Efficacy analysis population included all enrolled subjects who received at least 1 dose of ReFacto AF. Here, "n" signifies subjects who were evaluable for each specified baseline category.

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

End point timeframe:

Baseline up to Month 24

| End point values | ReFacto AF: All Subjects | | | |
|--|--------------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 37 | | | |
| Units: IU | | | | |
| arithmetic mean (standard deviation) | | | | |
| With Prophylaxis regimen at baseline (n= 22) | 97959.4 (± 48474.09) | | | |
| With non-prophylaxis regimen at baseline (n= 15) | 84051.7 (± 47362.6) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Less-Than-Expected-Therapeutic Effect (LETE) Bleeds in the On-Demand Setting: All Subjects

| | |
|-----------------|--|
| End point title | Number of Less-Than-Expected-Therapeutic Effect (LETE) Bleeds in the On-Demand Setting: All Subjects |
|-----------------|--|

End point description:

LETE was based on response to treatment of bleeding episode and occurred if subject recorded 2 successive "no response" ratings after 2 ReFacto AF infusions (inf.) which were administered (admin.) at interval of 24 hours for treatment of same bleeding event in absence of confounding factor which included: known presence or identification of a FVIII inhibitor, known inadequate dose for type and/or severity of bleed in opinion of investigator, delay of greater than (>) 4 hours between onset of bleed to inf., delay of >24 hours before admin. of a follow-up inf., known compromised ReFacto AF, faulty admin.

of ReFacto AF, subject had underlying, predisposing condition responsible for bleed in opinion of investigator (kidney stones or medications which impair platelet function like aspirin or NSAIDs), or ongoing trauma responsible for continued bleeding. Efficacy analysis population. "Number of subjects analysed" are subjects who were evaluable for this endpoint and received treatment for at least 1 bleed.

| | |
|-------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline up to Month 24 | |

| | | | | |
|-----------------------------|--------------------------|--|--|--|
| End point values | ReFacto AF: All Subjects | | | |
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 30 | | | |
| Units: LETE bleeds | | | | |
| LETE bleeds | 0 | | | |
| Bleeding episodes | 804 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Less-Than-Expected-Therapeutic Effect (LETE) Bleeds in the Prophylaxis Setting: All Subjects

| | |
|-----------------|--|
| End point title | Number of Less-Than-Expected-Therapeutic Effect (LETE) Bleeds in the Prophylaxis Setting: All Subjects |
|-----------------|--|

End point description:

LETE in the prophylaxis setting occurred if there was a spontaneous bleed within 48 hours (≤ 48 hours) after a regularly scheduled prophylactic dose of ReFacto AF (which was not used to treat a bleed) in the absence of confounding factors. Therefore, LETE in the prophylaxis setting is the occurrence of a bleed. Confounding factors include: Known presence or subsequent identification of a FVIII inhibitor, known inadequate prophylactic dose, known lack of adherence to the prescribed prophylaxis regimen, bleed occurs in a target joint identified at the start of the study, known compromised ReFacto AF, faulty administration of ReFacto AF, an underlying, predisposing condition responsible for the bleed in the opinion of the investigator (e.g., kidney stones or use of medications known to impair platelet function, such as aspirin or NSAIDs) or traumatic injury responsible for bleeding. Efficacy analysis population. Subjects who received at least 1 prophylaxis dose of ReFacto AF were reported.

| | |
|-------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline up to Month 24 | |

| | | | | |
|-----------------------------|--------------------------|--|--|--|
| End point values | ReFacto AF: All Subjects | | | |
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 37 | | | |
| Units: LETE bleeds | | | | |
| LETE bleeds | 2 | | | |
| Prophylaxis infusions | 2457 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Occurrences of Less-Than-Expected-Therapeutic Effect (LETE) in the Low Recovery Setting: All Subjects

| | |
|-----------------|---|
| End point title | Number of Occurrences of Less-Than-Expected-Therapeutic Effect (LETE) in the Low Recovery Setting: All Subjects |
|-----------------|---|

End point description:

LETE in the low recovery setting was defined as lower than expected recovery of FVIII (in the opinion of investigator), following the infusion of ReFacto AF in the absence of confounding factors for the low recovery. The only confounding factors for low recovery are as follows: known presence or subsequent identification of a FVIII inhibitor, known compromised ReFacto AF, faulty administration of ReFacto AF, including inadequate dosing. Efficacy analysis population included all enrolled subjects who received at least 1 dose of ReFacto AF.

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

End point timeframe:

Baseline up to Month 24

| | | | | |
|-----------------------------|--------------------------|--|--|--|
| End point values | ReFacto AF: All Subjects | | | |
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 37 | | | |
| Units: LETE bleeds | 9 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Requiring Escalated Dose of Prescribed Regimen During the Treatment Period: All Subjects

| | |
|-----------------|---|
| End point title | Number of Subjects Requiring Escalated Dose of Prescribed Regimen During the Treatment Period: All Subjects |
|-----------------|---|

End point description:

Subjects who met the dose escalation criteria were prescribed a higher dose and/or more frequent doses as per the investigator's discretion. Efficacy analysis population included all enrolled subjects who received at least 1 dose of ReFacto AF. Subjects who used a prophylaxis regimen were analysed for this endpoint.

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

End point timeframe:

Baseline up to Month 24

| | | | | |
|-----------------------------|--------------------------|--|--|--|
| End point values | ReFacto AF: All Subjects | | | |
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 37 | | | |
| Units: subjects | 5 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentration of Factor VIII at 0.5 Hour Post-dose (C0.5)

| | |
|---|--|
| End point title | Plasma Concentration of Factor VIII at 0.5 Hour Post-dose (C0.5) |
| End point description: PK parameter analysis population included all enrolled subjects who received at least 1 dose of ReFacto AF. | |
| End point type | Secondary |
| End point timeframe: 0.5 hour post-dose on Day 1 | |

| | | | | |
|---|-------------------------------|-------------------------------------|--|--|
| End point values | ReFacto AF: Less Than 6 Years | ReFacto AF: 6 to Less Than 12 Years | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 18 | 19 | | |
| Units: IU/mL | | | | |
| geometric mean (geometric coefficient of variation) | 0.752 (\pm 18) | 0.903 (\pm 45) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Plasma Time Curve From Time 0 Extrapolated to Infinite Time (AUCinf)

| | |
|-----------------|--|
| End point title | Area Under the Plasma Time Curve From Time 0 Extrapolated to Infinite Time (AUCinf) ^[7] |
|-----------------|--|

End point description:

AUCinf is the area under the plasma concentration-time profile from time 0 extrapolated to infinite time. It was calculated as International units*hour per milliliter (IU*hr/mL). PK parameter analysis population included all enrolled subjects who received at least 1 dose of ReFacto AF. Here, "number of subjects analysed" signifies subjects who were evaluable for this endpoint. Data was not planned to be collected and analysed for reporting group "ReFacto AF: Less Than 6 Years", as pre-specified in protocol.

| | |
|---|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Pre-dose, 0.5, 1, 3, 6, 9, 24, 28, 32, 48 hours post-dose on Day 1 | |
| 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: The endpoint was planned to be assessed for "ReFacto AF: 6 to Less Than 12 Years" reporting group only. | |

| | | | | |
|---|-------------------------------------|--|--|--|
| End point values | ReFacto AF: 6 to Less Than 12 Years | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 14 | | | |
| Units: IU*hr/mL | | | | |
| geometric mean (geometric coefficient of variation) | 9.89 (± 41) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Plasma Time Curve From Time Zero to Time of Last Measurable Concentration (AUClast)

| | |
|---|---|
| End point title | Area Under the Plasma Time Curve From Time Zero to Time of Last Measurable Concentration (AUClast) ^[8] |
| End point description: | |
| AUClast is the area under the plasma versus time curve from time zero to time of last measurable concentration (AUClast). PK parameter analysis population included all enrolled subjects who received at least 1 dose of ReFacto AF. Here, "number of subjects analysed" signifies subjects who were evaluable for this endpoint. Data was not planned to be collected and analysed for reporting group "ReFacto AF: Less Than 6 Years", as pre-specified in protocol. | |
| End point type | Secondary |
| End point timeframe: | |
| Pre-dose, 0.5, 1, 3, 6, 9, 24, 28, 32, 48 hours post-dose on Day 1 | |
| 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: The endpoint was planned to be assessed for "ReFacto AF: 6 to Less Than 12 Years" reporting group only. | |

| | | | | |
|---|-------------------------------------|--|--|--|
| End point values | ReFacto AF: 6 to Less Than 12 Years | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 14 | | | |
| Units: IU*hr/mL | | | | |
| geometric mean (geometric coefficient of variation) | 9.49 (± 41) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Volume of Distribution at Steady State (Vss)

| | |
|---|---|
| End point title | Volume of Distribution at Steady State (Vss) ^[9] |
| End point description: Volume of distribution was defined as the theoretical volume in which the total amount of drug was uniformly distributed to produce the desired blood concentration of a drug. Steady state volume of distribution (Vss) was the apparent volume of distribution at steady-state. PK parameter analysis population included all enrolled subjects who received at least 1 dose of ReFacto AF. Here, "number of subjects analysed" signifies subjects who were evaluable for this endpoint. Data was not planned to be collected and analysed for reporting group "ReFacto AF: Less Than 6 Years", as pre-specified in protocol. | |
| End point type | Secondary |

End point timeframe:

Pre-dose, 0.5, 1, 3, 6, 9, 24, 28, 32, 48 hours post-dose on Day 1

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: The endpoint was planned to be assessed for "ReFacto AF: 6 to Less Than 12 Years" reporting group only.

| | | | | |
|---|-------------------------------------|--|--|--|
| End point values | ReFacto AF: 6 to Less Than 12 Years | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 14 | | | |
| Units: mL/kg | | | | |
| geometric mean (geometric coefficient of variation) | 56.42 (± 15) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Residence Time (MRT) of ReFacto AF

| | |
|---|---|
| End point title | Mean Residence Time (MRT) of ReFacto AF ^[10] |
| End point description: MRT was calculated as $AUMC_{inf} / AUC_{inf-TI/2}$, where $AUMC_{inf}$ is the area under the first moment curve from time zero to infinity and TI was the duration of infusion. PK parameter analysis population included all enrolled subjects who received at least 1 dose of ReFacto AF. Here, "number of subjects analysed" signifies subjects who were evaluable for this endpoint. Data was not planned to be collected and analysed for reporting group "ReFacto AF: Less Than 6 Years", as pre-specified in protocol. | |
| End point type | Secondary |

End point timeframe:

Pre-dose, 0.5, 1, 3, 6, 9, 24, 28, 32, 48 hours post-dose on Day 1

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: The endpoint was planned to be assessed for "ReFacto AF: 6 to Less Than 12 Years" reporting group only.

| | | | | |
|-------------------------------|-------------------------------------|--|--|--|
| End point values | ReFacto AF: 6 to Less Than 12 Years | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 14 | | | |
| Units: hour | | | | |
| median (full range (min-max)) | 13.91 (8.51 to 18.3) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Treatment-Emergent Adverse Events (AEs) and Serious Adverse Events (SAEs): All Subjects

| | |
|-----------------|---|
| End point title | Number of Subjects With Treatment-Emergent Adverse Events (AEs) and Serious Adverse Events (SAEs): All Subjects |
|-----------------|---|

End point description:

An adverse event (AE) was any untoward medical occurrence in a subject who received study treatment without regard to possibility of causal relationship. An SAE was an AE resulting in any of the following outcomes or deemed significant for any other reason: death, initial or prolonged inpatient hospitalization, life-threatening experience (immediate risk of dying), persistent or significant disability or incapacity, congenital anomaly. Treatment-emergent are events between first dose of study drug and up to 30 days after last dose that were absent before treatment or that worsened relative to pretreatment state. AEs included both serious and non-serious adverse events.

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

End point timeframe:

Baseline up to 30 days after last study visit (Month 25)

| | | | | |
|-----------------------------|--------------------------|--|--|--|
| End point values | ReFacto AF: All Subjects | | | |
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 37 | | | |
| Units: subjects | | | | |
| AEs | 28 | | | |
| SAEs | 6 | | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to 30 days after last study visit (Month 25)

Adverse event reporting additional description:

Same event may appear both as an AE and a SAE. However, what is presented are distinct events. An event may be categorized as serious in one subject and as nonserious in another subject, or one subject may have experienced both serious and nonserious event during the study. Adverse events data was planned to be reported for the overall population.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 18.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|--------------------------|
| Reporting group title | ReFacto AF: All Subjects |
|-----------------------|--------------------------|

Reporting group description:

All subjects (aged less than or equal to [\leq] 12 years of age) were treated with IV injections of ReFacto AF at a dose and frequency prescribed by the investigator (minimum dose of 17 IU/kg up to maximum dose of 51 IU/kg) as per local standard of care in accordance with the SmPC.

| Serious adverse events | ReFacto AF: All Subjects | | |
|---|--------------------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 6 / 37 (16.22%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | | | |
| Injury, poisoning and procedural complications | | | |
| Head injury | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood and lymphatic system disorders | | | |
| Factor VIII inhibition | | | |
| subjects affected / exposed | 4 / 37 (10.81%) | | |
| occurrences causally related to treatment / all | 4 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Reproductive system and breast disorders | | | |
| Scrotal disorder | | | |

| | | | |
|--|----------------|--|--|
| subjects affected / exposed | 1 / 37 (2.70%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Acute respiratory failure | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Laryngitis | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumonia | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Rhinitis | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| | | | |
|---|--------------------------|--|--|
| Non-serious adverse events | ReFacto AF: All Subjects | | |
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 28 / 37 (75.68%) | | |
| Injury, poisoning and procedural complications | | | |
| Fall | | | |
| subjects affected / exposed | 4 / 37 (10.81%) | | |
| occurrences (all) | 6 | | |
| Head injury | | | |
| subjects affected / exposed | 4 / 37 (10.81%) | | |
| occurrences (all) | 5 | | |

| | | | |
|---------------------------------|----------------|--|--|
| Joint injury | | | |
| subjects affected / exposed | 3 / 37 (8.11%) | | |
| occurrences (all) | 3 | | |
| Limb injury | | | |
| subjects affected / exposed | 2 / 37 (5.41%) | | |
| occurrences (all) | 6 | | |
| Tooth fracture | | | |
| subjects affected / exposed | 2 / 37 (5.41%) | | |
| occurrences (all) | 2 | | |
| Arthropod sting | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | | |
| occurrences (all) | 1 | | |
| Contusion | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | | |
| occurrences (all) | 3 | | |
| Craniocerebral injury | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | | |
| occurrences (all) | 1 | | |
| Laceration | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | | |
| occurrences (all) | 1 | | |
| Lip injury | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | | |
| occurrences (all) | 1 | | |
| Mouth injury | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | | |
| occurrences (all) | 1 | | |
| Vascular disorders | | | |
| Hypotension | | | |
| subjects affected / exposed | 2 / 37 (5.41%) | | |
| occurrences (all) | 2 | | |
| Haematoma | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | | |
| occurrences (all) | 1 | | |
| Surgical and medical procedures | | | |

| | | | |
|---|--|--|--|
| Tooth extraction subjects affected / exposed occurrences (all) | 1 / 37 (2.70%) 1 | | |
| Nervous system disorders Headache subjects affected / exposed occurrences (all) | 2 / 37 (5.41%) 10 | | |
| General disorders and administration site conditions Pyrexia subjects affected / exposed occurrences (all) | 3 / 37 (8.11%) 6 | | |
| Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all) Dental caries subjects affected / exposed occurrences (all) Dyspepsia subjects affected / exposed occurrences (all) Lip haemorrhage subjects affected / exposed occurrences (all) Mouth haemorrhage subjects affected / exposed occurrences (all) Oral cavity fistula subjects affected / exposed occurrences (all) Tooth pulp haemorrhage subjects affected / exposed occurrences (all) | 1 / 37 (2.70%) 2 3 / 37 (8.11%) 3 1 / 37 (2.70%) 2 1 / 37 (2.70%) 1 1 / 37 (2.70%) 1 1 / 37 (2.70%) 1 1 / 37 (2.70%) 1 1 / 37 (2.70%) 1 | | |

| | | | |
|---|---|--|--|
| Toothache subjects affected / exposed occurrences (all) | 1 / 37 (2.70%) 1 | | |
| Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Epistaxis subjects affected / exposed occurrences (all) Obstructive airways disorder subjects affected / exposed occurrences (all) | 3 / 37 (8.11%) 3 2 / 37 (5.41%) 2 1 / 37 (2.70%) 1 | | |
| Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all) Skin mass subjects affected / exposed occurrences (all) Solar urticaria subjects affected / exposed occurrences (all) | 1 / 37 (2.70%) 1 1 / 37 (2.70%) 1 1 / 37 (2.70%) 1 | | |
| Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Pain in extremity subjects affected / exposed occurrences (all) Haemarthrosis subjects affected / exposed occurrences (all) Joint swelling subjects affected / exposed occurrences (all) | 7 / 37 (18.92%) 19 4 / 37 (10.81%) 7 2 / 37 (5.41%) 2 2 / 37 (5.41%) 2 | | |

| | | | |
|-----------------------------------|------------------|--|--|
| Groin pain | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | | |
| occurrences (all) | 1 | | |
| Joint range of motion decreased | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | | |
| occurrences (all) | 2 | | |
| Muscle haemorrhage | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | | |
| occurrences (all) | 1 | | |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 12 / 37 (32.43%) | | |
| occurrences (all) | 16 | | |
| Influenza | | | |
| subjects affected / exposed | 3 / 37 (8.11%) | | |
| occurrences (all) | 4 | | |
| Adenoiditis | | | |
| subjects affected / exposed | 2 / 37 (5.41%) | | |
| occurrences (all) | 6 | | |
| Bronchitis | | | |
| subjects affected / exposed | 2 / 37 (5.41%) | | |
| occurrences (all) | 4 | | |
| Otitis media acute | | | |
| subjects affected / exposed | 2 / 37 (5.41%) | | |
| occurrences (all) | 2 | | |
| Respiratory tract infection viral | | | |
| subjects affected / exposed | 2 / 37 (5.41%) | | |
| occurrences (all) | 2 | | |
| Rhinitis | | | |
| subjects affected / exposed | 2 / 37 (5.41%) | | |
| occurrences (all) | 6 | | |
| Cestode infection | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | | |
| occurrences (all) | 1 | | |
| Gastroenteritis | | | |

| | | | |
|------------------------------------|----------------|--|--|
| subjects affected / exposed | 1 / 37 (2.70%) | | |
| occurrences (all) | 1 | | |
| Infectious mononucleosis | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | | |
| occurrences (all) | 1 | | |
| Laryngitis | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | | |
| occurrences (all) | 1 | | |
| Otitis media | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | | |
| occurrences (all) | 1 | | |
| Pharyngitis | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | | |
| occurrences (all) | 1 | | |
| Pyoderma streptococcal | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | | |
| occurrences (all) | 1 | | |
| Sinusitis | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | | |
| occurrences (all) | 1 | | |
| Tonsillitis | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | | |
| occurrences (all) | 2 | | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | | |
| occurrences (all) | 1 | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | | |
| occurrences (all) | 1 | | |
| Varicella | | | |
| subjects affected / exposed | 1 / 37 (2.70%) | | |
| occurrences (all) | 1 | | |
| Metabolism and nutrition disorders | | | |
| Underweight | | | |
| subjects affected / exposed | 2 / 37 (5.41%) | | |
| occurrences (all) | 2 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---------------|--|
| 27 May 2009 | The purpose of this amendment was to update safety section to provide further details of the primary and secondary safety outcome measures. |
| 27 May 2009 | The purpose of this amendment was to modify the definition of "clinically significant FVIII inhibitor" to remove any association of this definition with LETEs |
| 24 March 2011 | The purpose of this amendment was to clarify the the timing of the follow-up call and the SAE reporting time lines |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported