



Clinical trial results:

A Phase I/III Open-label, Multicenter, Crossover Safety, Efficacy and Pharmacokinetic Study of Recombinant Coagulation Factor VIII (rFVIII) Compared to Recombinant Human Antihemophilic Factor VIII (rFVIII; INN: octocog alfa) in Subjects with Hemophilia A, and a Repeat PK, Safety and Efficacy Study

Summary

| | |
|--------------------------|-------------------------------|
| EudraCT number | 2011-002393-23 |
| Trial protocol | DE SE AT IT PL GB ES HU NL CZ |
| Global end of trial date | 12 December 2014 |

Results information

| | |
|--------------------------------|---|
| Result version number | v2 (current) |
| This version publication date | 29 July 2016 |
| First version publication date | 10 July 2015 |
| Version creation reason | • Correction of full data set Minor corrections made |

Trial information

Trial identification

| | |
|-----------------------|-------------|
| Sponsor protocol code | CSL627_1001 |
|-----------------------|-------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01486927 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | CSL Behring GmbH |
| Sponsor organisation address | Emil-von-Behring-Str. 76, Marburg, Germany, 35041 |
| Public contact | Clin.Trial Registration Coordinator, CSL Behring GmbH, clinicaltrials@cslbehring.com |
| Scientific contact | Clin.Trial Registration Coordinator, CSL Behring GmbH, clinicaltrials@cslbehring.com |

Notes:

Paediatric regulatory details

| | |
|--|---------------------|
| Is trial part of an agreed paediatric investigation plan (PIP) | Yes |
| EMA paediatric investigation plan number(s) | EMA-001215-PIP01-11 |
| 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? | No |

Notes:

Results analysis stage

| | |
|--|------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 23 January 2015 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 12 December 2014 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To characterize the pharmacokinetic (PK) profile of rVIII-SingleChain
To demonstrate efficacy in the prevention and treatment of bleeding events
To demonstrate the efficacy of routine prophylaxis treatment over on-demand treatment
To demonstrate the efficacy of rVIII-SingleChain in surgical prophylaxis
To characterize the rate of inhibitor formation

Protection of trial subjects:

This study was carried out in accordance with the International Conference on Harmonisation (ICH) Good Clinical Practice guidelines, and standard operating procedures for clinical research and development at CSL Behring (CSLB). The study protocol and all amendments were approved by the Independent Ethics Committee(s) (IECs) / Institutional Review Board(s) (IRBs) of the participating centers. Before undergoing screening procedures for possible enrollment into the study, subjects or the subject's legally acceptable representative (ie, for subjects ≥ 12 to < 18 years), were informed, in an understandable form, about the nature, scope, and possible consequences of the study. The investigator was responsible for obtaining a subject's written informed consent to participate in the study. The investigator could cease study treatment and withdraw the subject, or the subject could withdraw himself from participation in the study at any time. The decision to withdraw consent and discontinue participation in the study could not prejudice the subject's future medical treatment in any way.

Background therapy: -

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 15 February 2012 |
| 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 | Netherlands: 4 |
| Country: Number of subjects enrolled | Poland: 24 |
| Country: Number of subjects enrolled | Spain: 3 |
| Country: Number of subjects enrolled | South Africa: 16 |
| Country: Number of subjects enrolled | United Kingdom: 3 |
| Country: Number of subjects enrolled | Austria: 5 |
| Country: Number of subjects enrolled | Ukraine: 11 |
| Country: Number of subjects enrolled | Czech Republic: 2 |
| Country: Number of subjects enrolled | United States: 22 |

| | |
|--------------------------------------|-----------------------|
| Country: Number of subjects enrolled | Germany: 19 |
| Country: Number of subjects enrolled | Hungary: 2 |
| Country: Number of subjects enrolled | Italy: 10 |
| Country: Number of subjects enrolled | Australia: 8 |
| Country: Number of subjects enrolled | Canada: 1 |
| Country: Number of subjects enrolled | Japan: 10 |
| Country: Number of subjects enrolled | Lebanon: 3 |
| Country: Number of subjects enrolled | Malaysia: 9 |
| Country: Number of subjects enrolled | Philippines: 10 |
| Country: Number of subjects enrolled | Romania: 3 |
| Country: Number of subjects enrolled | Russian Federation: 9 |
| Worldwide total number of subjects | 174 |
| EEA total number of subjects | 75 |

Notes:

Subjects enrolled per age group

| | |
|---|-----|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 14 |
| Adults (18-64 years) | 160 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

This multicenter, multinational study enrolled subjects at 54 participating study centers in the United States, Japan, Europe, Australia, Canada, Lebanon, Malaysia, Philippines, Russian Federation, South Africa, and Ukraine.

Pre-assignment

Screening details:

Screening took place 4 to 28 days prior to first dose of study product (rVIII-SingleChain). A total of 204 subjects were screened, 29 of these did not fulfill all eligibility criteria and were therefore screening failures. A total of 175 subjects were enrolled; 174 subjects were exposed to treatment with rVIII-SingleChain.

Period 1

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

Arms

| | |
|-----------|----------------------------------|
| Arm title | Recombinant Factor VIII (rFVIII) |
|-----------|----------------------------------|

Arm description:

In Part 1 of the study (a single-sequence crossover pharmacokinetic [PK] analysis), 27 subjects received a single injection of octocog alfa followed by a single injection of rVIII-SingleChain. Twenty-six of the 27 subjects from Part 1 then entered Part 2 of the study where they were assigned either to an on-demand or prophylaxis regimen with repeat injections of rVIII-SingleChain until they reached 50 exposure days (EDs). In Part 3 of the study, 148 additional subjects were enrolled and were assigned either to an on-demand or prophylaxis regimen with repeat injections of rVIII-SingleChain until they reached 50 EDs; 64 of these subjects participated in additional PK analyses. Overall, 174 subjects received rVIII-SingleChain as either on-demand or prophylaxis regimens, and 13 subjects participated in the surgical substudy.

| | |
|--|---|
| Arm type | Experimental |
| Investigational medicinal product name | rVIII-SingleChain |
| Investigational medicinal product code | CSL627 |
| Other name | |
| Pharmaceutical forms | Powder and solvent for solution for injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

In Part 1 of the study, subjects received a single infusion of 50 IU/kg rVIII-SingleChain preceded by a 4-day washout period. In Parts 2 and 3 of the study, subjects received repeat injections of rVIII-SingleChain either as an on-demand or prophylaxis regimen at a dose and frequency determined by their study doctor. Subjects participating in the Part 3 PK analyses received a single infusion of 50 IU/kg rVIII-SingleChain and a repeat dose of the same strength of rVIII-SingleChain, after 3 to 6 months. Subjects from Parts 2 and 3 participating in the surgical substudy received an individualized dose regimen of rVIII-SingleChain, based on the type of surgery and the clinical status of the subject.

| | |
|--|---|
| Investigational medicinal product name | Octocog alfa |
| Investigational medicinal product code | |
| Other name | Human coagulation factor VIII (rDNA) |
| Pharmaceutical forms | Powder and solvent for solution for injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

In Part 1 of the study, subjects received a single infusion of 50 IU/kg of octocog alfa preceded by a 4-day washout period.

| Number of subjects in period 1 | Recombinant Factor VIII (rFVIII) |
|--|---|
| Started | 174 |
| Completed | 161 |
| Not completed | 13 |
| 50 Exposure days not reached | 2 |
| Subject did not reach 6 months of treatment | 1 |
| Consent withdrawn by subject | 8 |
| Physician decision | 1 |
| Right knee surgery (prior to surgery substudy) | 1 |

Baseline characteristics

Reporting groups

| | |
|--------------------------------|---------------|
| Reporting group title | Overall trial |
| Reporting group description: - | |

| Reporting group values | Overall trial | Total | |
|---|---------------|-------|--|
| Number of subjects | 174 | 174 | |
| Age categorical | | | |
| Units: Subjects | | | |
| Adolescents (12-17 years) | 14 | 14 | |
| Adults (18-65 years) | 160 | 160 | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 31.3 | | |
| standard deviation | ± 11.77 | - | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 0 | 0 | |
| Male | 174 | 174 | |
| Type of FVIII product used before enrollment | | | |
| Type of FVIII product used by the subjects before enrollment into the study. This could have been a plasma-derived FVIII product or a recombinant FVIII product. | | | |
| Units: Subjects | | | |
| Plasma-derived Product | 83 | 83 | |
| Recombinant Product | 91 | 91 | |
| Treatment modality of FVIII therapy before enrollment | | | |
| Treatment modality of FVIII therapy before enrollment, ie, routine prophylaxis or on-demand treatment. If a subject used both modalities, only the most recent one was counted. | | | |
| Units: Subjects | | | |
| Prophylaxis | 82 | 82 | |
| On-demand | 92 | 92 | |

End points

End points reporting groups

| | |
|--|--|
| Reporting group title | Recombinant Factor VIII (rFVIII) |
| Reporting group description: In Part 1 of the study (a single-sequence crossover pharmacokinetic [PK] analysis), 27 subjects received a single injection of octocog alfa followed by a single injection of rVIII-SingleChain. Twenty-six of the 27 subjects from Part 1 then entered Part 2 of the study where they were assigned either to an on-demand or prophylaxis regimen with repeat injections of rVIII-SingleChain until they reached 50 exposure days (EDs). In Part 3 of the study, 148 additional subjects were enrolled and were assigned either to an on-demand or prophylaxis regimen with repeat injections of rVIII-SingleChain until they reached 50 EDs; 64 of these subjects participated in additional PK analyses. Overall, 174 subjects received rVIII-SingleChain as either on-demand or prophylaxis regimens, and 13 subjects participated in the surgical substudy. | |
| Subject analysis set title | PK population (Part 1) |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: The PK population (Part 1) consisted of subjects who had received 1 dose of 50 IU/kg of rVIII-SingleChain and for whom a sufficient number of analyzable PK samples were obtained to permit the evaluation of the PK profile. In the Part 1 PK analysis, these subjects also received 1 dose of 50 IU/kg octocog alfa. There were 27 subjects in the PK population (Part 1). | |
| Subject analysis set title | rVIII-SingleChain PK population (Part 3) |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: The rVIII-SingleChain PK population (Part 3) consisted of subjects who received rVIII-SingleChain during Part 3 of the study (initial and repeat dose) and for whom a sufficient number of analyzable PK samples were obtained to permit the evaluation of the PK profile. In Part 3, 64 subjects participated in the initial PK, of whom 30 also participated in the repeat PK. | |
| Subject analysis set title | rVIII-SingleChain On-demand |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: The rVIII-SingleChain On-demand group consisted of all subjects in the efficacy population who received at least 1 dose rVIII-SingleChain as part of on-demand treatment during Parts 2 or 3 of the study. There were 27 subjects in the rVIII-SingleChain On-demand group. | |
| Subject analysis set title | rVIII-SingleChain Prophylaxis |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: The rVIII-SingleChain Prophylaxis group consisted of all subjects in the efficacy population who received at least 1 dose rVIII-SingleChain as part of routine prophylaxis treatment during Parts 2 or 3 of the study. There were 146 subjects in the rVIII-SingleChain Prophylaxis group. | |
| Subject analysis set title | rVIII-SingleChain Surgical |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: The rVIII-SingleChain Surgical group included all subjects enrolled in the surgical sub-study who received at least 1 dose of rVIII-SingleChain during the surgical sub-study. There were 13 subjects in the rVIII-SingleChain Surgical group. | |
| Subject analysis set title | rVIII-SingleChain |
| Subject analysis set type | Per protocol |
| Subject analysis set description: The Efficacy population consisted of all subjects who received at least one dose of rVIII-SingleChain as part of either routine prophylaxis treatment or on-demand treatment during Parts 2 or 3 of the study. There were 173 subjects in the Efficacy population. | |

Primary: Treatment success

| | |
|-----------------|----------------------------------|
| End point title | Treatment success ^[1] |
|-----------------|----------------------------------|

End point description:

The investigator rated the efficacy of the treatment based on a 4-point rating scale "excellent, good, moderate or poor/no response". Efficacy ratings of "excellent" or "good" were considered treatment success for this end point; the percentage of bleeding events with a rating of excellent or good and the 95% confidence interval are presented. The denominator includes all treated bleeding events. The 95% confidence interval is based on a model to account for within-subject correlation.

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

End point timeframe:

Up to 24 months

Notes:

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

Justification: Data were analyzed using descriptive statistics only.

| End point values | rVIII- SingleChain On-demand | rVIII- SingleChain Prophylaxis | rVIII- SingleChain | |
|---|------------------------------------|--------------------------------------|-----------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 27 ^[2] | 146 ^[3] | 173 ^[4] | |
| Units: % bleeding events successfully treated | | | | |
| number (confidence interval 95%) | 92.4 (87.8 to 95.3) | 92.2 (86.3 to 95.8) | 92.3 (88.9 to 94.8) | |

Notes:

[2] - Number of treated bleeding events = 590

[3] - Number of treated bleeding events = 258

[4] - Number of treated bleeding events = 848

Statistical analyses

No statistical analyses for this end point

Primary: Inhibitor formation to FVIII

| | |
|-----------------|---|
| End point title | Inhibitor formation to FVIII ^[5] |
|-----------------|---|

End point description:

Number of subjects who develop inhibitors to FVIII

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

End point timeframe:

Up to 24 months

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: Data were analyzed using descriptive statistics only.

| End point values | Recombinant Factor VIII (rFVIII) | | | |
|-----------------------------|--|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 174 | | | |
| Units: Subjects | 0 | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Annualized spontaneous bleeding rate

| | |
|-----------------|--------------------------------------|
| End point title | Annualized spontaneous bleeding rate |
|-----------------|--------------------------------------|

End point description:

The annualized spontaneous bleeding rate (AsBR) was derived for each subject as follows:

$365.25 \times (\text{number of spontaneous bleeding episodes requiring treatment}) / (\text{observed treatment period of interest})$.

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

End point timeframe:

Up to 24 months

| End point values | rVIII- SingleChain On-demand | rVIII- SingleChain Prophylaxis | | |
|--|------------------------------------|--------------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 27 | 146 | | |
| Units: Number of spontaneous bleeds per year | | | | |
| median (inter-quartile range (Q1-Q3)) | 11.73 (2.8 to 36.5) | 0 (0 to 2.4) | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Prophylaxis/On-demand |
| Comparison groups | rVIII-SingleChain Prophylaxis v rVIII-SingleChain On-demand |
| Number of subjects included in analysis | 173 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[6] |
| P-value | < 0.0001 |
| Method | Poisson, regression |
| Parameter estimate | Rate ratio |
| Point estimate | 0.08 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.07 |
| upper limit | 0.1 |

Notes:

[6] - A test of the null hypothesis of no difference on AsBR between the 2 comparison groups was based on the Poisson Regression method. The corresponding prophylaxis/on-demand ratio with 95% CI was calculated.

Primary: Treatment success during the peri-operative surgical sub-study

| | |
|-----------------|---|
| End point title | Treatment success during the peri-operative surgical sub- |
|-----------------|---|

End point description:

Subjects received rVIII-SingleChain before and during surgery based on the type of surgery and the

clinical status of the subject. The investigator rated the efficacy of the treatment based on a 4-point surgical treatment rating scale of "excellent, good, moderate or poor/no response". Efficacy ratings of "excellent" or "good" were considered treatment success for this endpoint. The rate of success, defined as the percentage of surgeries with a rating of excellent or good for hemostatic efficacy on the surgical treatment scale is presented for the Surgical Population, based on the total number of surgeries (N=16) as denominator.

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

End point timeframe:

From the start of surgery through the post-operative recovery (generally up to 14 days after surgery)

Notes:

[7] - 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: Data were analyzed using descriptive statistics only.

| | | | | |
|---|----------------------------|--|--|--|
| End point values | rVIII-SingleChain Surgical | | | |
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 13 | | | |
| Units: % of surgeries with successful treatment | | | | |
| number (not applicable) | 100 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: AUC0-∞ (Part 1)

| | |
|-----------------|-----------------|
| End point title | AUC0-∞ (Part 1) |
|-----------------|-----------------|

End point description:

AUC0-∞ (AUC from 0 extrapolated to infinity) of a single infusion of octocog alfa and rVIII-SingleChain without correction for subject's predose plasma FVIII activity. FVIII activity values for octocog alfa are dose-adjusted for chromogenic potency.

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

End point timeframe:

Before infusion and at up to 10 time points within 72 hours of infusion

| | | | | |
|--------------------------------------|------------------------|--|--|--|
| End point values | PK population (Part 1) | | | |
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 27 | | | |
| Units: IU*h/dL | | | | |
| arithmetic mean (standard deviation) | | | | |
| Octocog alfa | 1550 (± 552) | | | |
| rVIII-SingleChain | 2090 (± 650) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Cmax (Part 1)

| | |
|--|---------------|
| End point title | Cmax (Part 1) |
| End point description: Cmax of a single infusion of octocog alfa and rVIII-SingleChain with correction for subject's predose plasma FVIII activity. FVIII activity values for octocog alfa are dose-adjusted for chromogenic potency. | |
| End point type | Secondary |
| End point timeframe: Before infusion and at up to 10 time points within 72 hours of infusion | |

| End point values | PK population (Part 1) | | | |
|--------------------------------------|------------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 27 | | | |
| Units: IU/dL | | | | |
| arithmetic mean (standard deviation) | | | | |
| Octocog alfa | 116 (± 18.1) | | | |
| rVIII-SingleChain | 113 (± 17.4) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Tmax (Part 1)

| | |
|--|---------------|
| End point title | Tmax (Part 1) |
| End point description: Tmax = time of Cmax (with correction for subject's predose plasma FVIII activity) after a single infusion of octocog alfa and rVIII-SingleChain. | |
| End point type | Secondary |
| End point timeframe: Before infusion and at up to 10 time points within 72 hours of infusion | |

| End point values | PK population (Part 1) | | | |
|-------------------------------|------------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 27 | | | |
| Units: hours | | | | |
| median (full range (min-max)) | | | | |
| Octocog alfa | 0.583 (0.45 to 0.8) | | | |
| rVIII-SingleChain | 0.683 (0.467 to 1.25) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Half-life (t1/2) (Part 1)

| | |
|-----------------|---------------------------|
| End point title | Half-life (t1/2) (Part 1) |
|-----------------|---------------------------|

End point description:

Half-life (t1/2) of a single infusion of octocog alfa and rVIII-SingleChain without correction for subject's predose plasma FVIII activity.

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

End point timeframe:

Before infusion and at up to 10 time points within 72 hours of infusion.

| End point values | PK population (Part 1) | | | |
|--------------------------------------|------------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 27 | | | |
| Units: hours | | | | |
| arithmetic mean (standard deviation) | | | | |
| Octocog alfa | 13.3 (± 4.36) | | | |
| rVIII-SingleChain | 14.5 (± 3.77) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Mean residence time (MRT) (Part 1)

| | |
|-----------------|------------------------------------|
| End point title | Mean residence time (MRT) (Part 1) |
|-----------------|------------------------------------|

End point description:

Mean residence time (MRT) of a single infusion of octocog alfa and rVIII-SingleChain without correction for subject's predose plasma FVIII activity.

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

End point timeframe:

Before infusion and at up to 10 time points within 72 hours of infusion

| End point values | PK population (Part 1) | | | |
|--------------------------------------|------------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 27 | | | |
| Units: hours | | | | |
| arithmetic mean (standard deviation) | | | | |
| Octocog alfa | 17.1 (± 5.57) | | | |
| rVIII-SingleChain | 20.4 (± 5.49) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Clearance (CI) (Part 1)

| | |
|---|-------------------------|
| End point title | Clearance (CI) (Part 1) |
| End point description: | |
| Clearance (CI) of a single infusion of octocog alfa and rVIII-SingleChain without correction for subject's predose plasma FVIII activity. FVIII activity values for octocog alfa are dose-adjusted for chromogenic potency. | |
| End point type | Secondary |
| End point timeframe: | |
| Before infusion and at up to 10 time points within 72 hours of infusion | |

| End point values | PK population (Part 1) | | | |
|--------------------------------------|------------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 27 | | | |
| Units: mL/h/kg | | | | |
| arithmetic mean (standard deviation) | | | | |
| Octocog alfa | 3.68 (± 1.41) | | | |
| rVIII-SingleChain | 2.64 (± 0.846) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Volume of distribution at steady-state (Vss) (Part 1)

| | |
|---|---|
| End point title | Volume of distribution at steady-state (Vss) (Part 1) |
| End point description: | |
| Volume of distribution at steady-state (Vss) of a single infusion of octocog alfa and rVIII-SingleChain without correction for subject's predose plasma FVIII activity. FVIII activity values for octocog alfa are dose-adjusted for chromogenic potency. | |
| End point type | Secondary |
| End point timeframe: | |
| Before infusion and at up to 10 time points within 72 hours of infusion | |

| End point values | PK population (Part 1) | | | |
|--------------------------------------|------------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 27 | | | |
| Units: mL/kg | | | | |
| arithmetic mean (standard deviation) | | | | |
| Octocog alfa | 57.1 (\pm 11.3) | | | |
| rVIII-SingleChain | 50 (\pm 7.51) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Incremental recovery (Part 1)

| | |
|--|-------------------------------|
| End point title | Incremental recovery (Part 1) |
| End point description: | |
| Incremental recovery of a single infusion of octocog alfa and rVIII-SingleChain with correction for subject's predose plasma FVIII activity. FVIII activity values for octocog alfa are dose-adjusted for chromogenic potency. | |
| End point type | Secondary |
| End point timeframe: | |
| At 30 minutes after infusion | |

| End point values | PK population (Part 1) | | | |
|--------------------------------------|------------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 27 | | | |
| Units: [IU/dL]/[IU/kg] | | | | |
| arithmetic mean (standard deviation) | | | | |
| Octocog alfa | 2.32 (\pm 0.381) | | | |
| rVIII-SingleChain | 2.24 (\pm 0.357) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized bleeding rate for total bleeds and traumatic bleeds

| | |
|---|--|
| End point title | Annualized bleeding rate for total bleeds and traumatic bleeds |
| End point description: | |
| The annualized bleeding rate was derived for each subject as follows: 365.25*(number of bleeding episodes requiring treatment) / (observed treatment period of interest). | |

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Up to 24 months | |

| End point values | rVIII- SingleChain On-demand | rVIII- SingleChain Prophylaxis | | |
|---------------------------------------|------------------------------------|--------------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 27 | 146 | | |
| Units: Number of bleeds per year | | | | |
| median (inter-quartile range (Q1-Q3)) | | | | |
| Total Bleeds | 19.64 (6.2 to 46.5) | 1.14 (0 to 4.2) | | |
| Traumatic Bleeds | 3.12 (0 to 8.4) | 0 (0 to 0.9) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of bleeding episodes requiring 1, 2, 3 or > 3 infusions of rVIII-SingleChain to achieve hemostasis

| | |
|---|---|
| End point title | Proportion of bleeding episodes requiring 1, 2, 3 or > 3 infusions of rVIII-SingleChain to achieve hemostasis |
| End point description: | |
| Percentage of bleeding episodes requiring 1, 2, 3 or > 3 infusions of rVIII-SingleChain (rVIII-SC) to achieve hemostasis. The denominator includes all treated bleeding episodes. | |
| End point type | Secondary |
| End point timeframe: | |
| During the study (up to 24 months; assessed at Months 1, 2, 3, 4, 5, 6, 9, 12, 15, 18, 21 and 24) | |

| End point values | rVIII- SingleChain On-demand | rVIII- SingleChain Prophylaxis | rVIII- SingleChain | |
|--|------------------------------------|--------------------------------------|-----------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 27 ^[8] | 146 ^[9] | 173 ^[10] | |
| Units: Percentage of bleeding episodes | | | | |
| number (not applicable) | | | | |
| Requiring 1 rVIII-SC infusion for hemostasis | 82.7 | 76.7 | 80.9 | |
| Requiring 2 rVIII-SC infusions for hemostasis | 12 | 14 | 12.6 | |
| Requiring 3 rVIII-SC infusions for hemostasis | 3.22 | 3.88 | 3.42 | |
| Requiring >3 rVIII-SC infusions for hemostasis | 2.03 | 5.43 | 3.07 | |

Notes:

[8] - Number of treated bleeding episodes = 590

[9] - Number of treated bleeding episodes = 258

[10] - Number of treated bleeding episodes = 848

Statistical analyses

No statistical analyses for this end point

Other pre-specified: AUC0-∞ (Part 3)

| | |
|-----------------|-----------------|
| End point title | AUC0-∞ (Part 3) |
|-----------------|-----------------|

End point description:

AUC0-∞ (AUC from 0 extrapolated to infinity) of an initial and repeat infusion of rVIII-SingleChain without correction for subject's predose plasma FVIII activity.

| | |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

Before infusion and at up to 12 time points within 96 hours of infusion

| End point values | rVIII-SingleChain PK population (Part 3) | | | |
|--------------------------------------|--|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 64 | | | |
| Units: IU*h/dL | | | | |
| arithmetic mean (standard deviation) | | | | |
| Initial, n = 64 | 1830 (± 640) | | | |
| Repeat, n = 30 | 1880 (± 649) | | | |

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Cmax (Part 3)

| | |
|-----------------|---------------|
| End point title | Cmax (Part 3) |
|-----------------|---------------|

End point description:

Cmax of an initial and repeat infusion of rVIII-SingleChain with correction for subject's predose plasma FVIII activity.

| | |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

Before infusion and at up to 12 time points within 96 hours of infusion

| End point values | rVIII-SingleChain PK population (Part 3) | | | |
|--------------------------------------|--|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 63 | | | |
| Units: IU/dL | | | | |
| arithmetic mean (standard deviation) | | | | |
| Initial, n = 63 | 99.9 (± 19.9) | | | |
| Repeat, n = 29 | 108 (± 18.5) | | | |

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Tmax (Part 3)

| | |
|--|---------------------|
| End point title | Tmax (Part 3) |
| End point description: Tmax = time of Cmax (with correction for subject's predose plasma FVIII activity) after an initial and repeat infusion of rVIII-SingleChain. | |
| End point type | Other pre-specified |
| End point timeframe: Before infusion and at up to 12 time points within 96 hours of infusion. | |

| End point values | rVIII-SingleChain PK population (Part 3) | | | |
|-------------------------------|--|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 63 | | | |
| Units: hours | | | | |
| median (full range (min-max)) | | | | |
| Initial, n = 63 | 0.333 (0.117 to 1.22) | | | |
| Repeat, n = 29 | 0.317 (0.117 to 0.667) | | | |

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Half-life (t1/2) (Part 3)

| | |
|---|---------------------------|
| End point title | Half-life (t1/2) (Part 3) |
| End point description: Half-life (t1/2) of an initial and repeat infusion of rVIII-SingleChain without correction for subject's predose plasma FVIII activity. | |
| End point type | Other pre-specified |

End point timeframe:

Before infusion and at up to 12 time points within 96 hours of infusion.

| End point values | rVIII- SingleChain PK population (Part 3) | | | |
|--------------------------------------|--|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 64 | | | |
| Units: hours | | | | |
| arithmetic mean (standard deviation) | | | | |
| Initial, n = 64 | 14.1 (± 3.82) | | | |
| Repeat, n = 30 | 12.9 (± 3.7) | | | |

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Mean residence time (MRT) (Part 3)

| | |
|--|------------------------------------|
| End point title | Mean residence time (MRT) (Part 3) |
| End point description: Mean residence time (MRT) of an initial and repeat infusion of rVIII-SingleChain without correction for subject's predose plasma FVIII activity. | |
| End point type | Other pre-specified |
| End point timeframe: Before infusion and at up to 12 time points within 96 hours of infusion. | |

| End point values | rVIII- SingleChain PK population (Part 3) | | | |
|--------------------------------------|--|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 64 | | | |
| Units: hours | | | | |
| arithmetic mean (standard deviation) | | | | |
| Initial, n = 64 | 20.3 (± 5.36) | | | |
| Repeat, n = 30 | 18.9 (± 5.39) | | | |

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Clearance (Cl) (Part 3)

| | |
|---|-------------------------|
| End point title | Clearance (Cl) (Part 3) |
| End point description: Clearance (Cl) of an initial and repeat infusion of rVIII-SingleChain without correction for subject's predose plasma FVIII activity. | |
| End point type | Other pre-specified |
| End point timeframe: Before infusion and at up to 12 time points within 96 hours of infusion. | |

| End point values | rVIII-SingleChain PK population (Part 3) | | | |
|--------------------------------------|--|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 64 | | | |
| Units: mL/h/kg | | | | |
| arithmetic mean (standard deviation) | | | | |
| Initial, n = 64 | 3.15 (± 1.21) | | | |
| Repeat, n = 30 | 3.05 (± 1.1) | | | |

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Volume of distribution at steady-state (Vss) (Part 3)

| | |
|---|---|
| End point title | Volume of distribution at steady-state (Vss) (Part 3) |
| End point description: Volume of distribution at steady-state (Vss) of an initial and repeat infusion of rVIII-SingleChain without correction for subject's predose plasma FVIII activity. | |
| End point type | Other pre-specified |
| End point timeframe: Before infusion and at up to 12 time points within 96 hours of infusion. | |

| End point values | rVIII-SingleChain PK population (Part 3) | | | |
|--------------------------------------|--|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 64 | | | |
| Units: mL/kg | | | | |
| arithmetic mean (standard deviation) | | | | |
| Initial, n = 64 | 59.5 (± 14.2) | | | |
| Repeat, n = 30 | 53.1 (± 8.74) | | | |

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Incremental recovery (Part 3)

| | |
|-----------------|-------------------------------|
| End point title | Incremental recovery (Part 3) |
|-----------------|-------------------------------|

End point description:

Incremental recovery of an initial and repeat infusion of rVIII-SingleChain with correction for subject's predose plasma FVIII activity.

| | |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

At 30 minutes after infusion

| End point values | rVIII-SingleChain PK population (Part 3) | | | |
|--------------------------------------|--|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 63 | | | |
| Units: [IU/dL]/[IU/kg] | | | | |
| arithmetic mean (standard deviation) | | | | |
| Initial, n = 63 | 1.85 (± 0.404) | | | |
| Repeat, n = 29 | 1.99 (± 0.352) | | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

For the duration of the study, approximately 2 years, 10 months.

Adverse event reporting additional description:

The Safety Population comprised all subjects treated with rVIII-SingleChain. A total of 14592 rVIII-SingleChain infusions were administered to 174 subjects during the study.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 14.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|-------------------|
| Reporting group title | Safety Population |
|-----------------------|-------------------|

Reporting group description:

The Safety Population comprised all subjects treated with rVIII-SingleChain.

| Serious adverse events | Safety Population | | |
|---|-------------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 8 / 174 (4.60%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | 0 | | |
| Investigations | | | |
| Blood uric acid increased | | | |
| subjects affected / exposed | 1 / 174 (0.57%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Injury, poisoning and procedural complications | | | |
| Ankle fracture | | | |
| subjects affected / exposed | 1 / 174 (0.57%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 1 / 174 (0.57%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Thrombocytopenia | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 174 (0.57%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Immune system disorders | | | |
| Hypersensitivity | | | |
| subjects affected / exposed | 1 / 174 (0.57%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Varices oesophageal | | | |
| subjects affected / exposed | 1 / 174 (0.57%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Tonsillar haemorrhage | | | |
| subjects affected / exposed | 1 / 174 (0.57%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Psychiatric disorders | | | |
| Suicidal ideation | | | |
| subjects affected / exposed | 1 / 174 (0.57%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Postoperative wound infection | | | |
| subjects affected / exposed | 1 / 174 (0.57%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Viral infection | | | |
| subjects affected / exposed | 1 / 174 (0.57%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| Non-serious adverse events | Safety Population | | |
|---|-------------------|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 45 / 174 (25.86%) | | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 13 / 174 (7.47%) | | |
| occurrences (all) | 14 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 20 / 174 (11.49%) | | |
| occurrences (all) | 22 | | |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 18 / 174 (10.34%) | | |
| occurrences (all) | 22 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 29 February 2012 | Protocol Amendment 1 included the following main change: PK sample collection time in Part 1 changed from 28 to 32 h post dose throughout protocol. |
| 06 July 2012 | Protocol Amendment 2 included the following main changes: <ul style="list-style-type: none">• PK sample collection time points changed in Part 3• Statement of inclusion of Japanese centers in Part 3• Schedule of Assessment tables revised for clarity• IMP reconstitution table updated for multiple presentations and concentrations• Number of evaluable subjects required clarified• Exclusion of subjects not capable of home treatment added• Additional safety criteria added• Prior FVIII half-life and recovery collection specified for Part 3• Clarification of pharmacokinetic population |
| 24 May 2013 | Protocol Amendment 3 included the following main changes: <ul style="list-style-type: none">• The duration of the subject study participation was clarified to allow subjects to be treated with rVIII-SingleChain for 50 EDs and continue on treatment until the end of study visit or extension study.• Cohort screening size was increased to ensure sufficient evaluable subjects.• Laboratory assessments and confirmation of results were clarified for central and local laboratories.• The roles and responsibilities of the IDMC were updated to provide increased subject safety.• Recording of actual dosing over nominal dosing was clarified to accurately reflect dosing.• Definitions of overdose, treatment compliance, and retention of samples were added to guide sites in proper study conduct.• Additional subject information (gene defect and blood group, if available) was collected.• Assessment for antibodies against CHO cells was added for subject safety.• Assessment for antibodies against FVIII at screening / Day 1 for subject safety.• AE reporting processes were updated.• Statistical analyses and methods were clarified. |
| 10 March 2014 | Protocol Amendment 4 included the following main changes: <ul style="list-style-type: none">• Addition of a co-primary objective of efficacy of routine prophylaxis treatment over on-demand treatment.• Addition of AsBR as a primary endpoint.• Addition of annualized bleeding rate as a secondary endpoint.• The statistical methodology was updated. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported