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 Antihaemophilic 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	v1
This version publication date	13 July 2016
First version publication date	10 July 2015

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)	EMEA-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 four 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*(number of spontaneous bleeding episodes requiring treatment) / (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 On-demand v rVIII-SingleChain Prophylaxis
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: AUC0-∞ (Part 3)

End point title	AUC0-∞ (Part 3)[7]

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	Primary

End point timeframe:

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

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: Part 3 PK primary endpoint analyses were summarized as descriptive statistics, as per protocol.

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

Primary: Cmax (Part 3)

End point title	Cmax (Part 3)[8]

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	Primary

End point timeframe:

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

Notes:

[8] - 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: Part 3 PK primary endpoint analyses were summarized as descriptive statistics, as per protocol.

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

Primary: Tmax (Part 3)

End point title	Tmax (Part 3)[9]

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	Primary

End point timeframe:

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

Notes:

[9] - 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: Part 3 PK primary endpoint analyses were summarized as descriptive statistics, as per protocol.

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

Primary: Half-life (t1/2) (Part 3)

End point title	Half-life (t1/2) (Part 3)[10]

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	Primary

End point timeframe:

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

Notes:

[10] - 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: Part 3 PK primary endpoint analyses were summarized as descriptive statistics, as per protocol.

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

Primary: Mean residence time (MRT) (Part 3)

End point title	Mean residence time (MRT) (Part 3)[11]

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	Primary

End point timeframe:

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

Notes:

[11] - 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: Part 3 PK primary endpoint analyses were summarized as descriptive statistics, as per protocol.

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

Primary: Clearance (Cl) (Part 3)

End point title	Clearance (Cl) (Part 3)[12]

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	Primary

End point timeframe:

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

Notes:

[12] - 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: Part 3 PK primary endpoint analyses were summarized as descriptive statistics, as per protocol.

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

Primary: Volume of distribution at steady-state (Vss) (Part 3)

End point title	Volume of distribution at steady-state (Vss) (Part 3)[13]

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	Primary

End point timeframe:

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

Notes:

[13] - 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: Part 3 PK primary endpoint analyses were summarized as descriptive statistics, as per protocol.

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

Primary: Incremental recovery (Part 3)

End point title	Incremental recovery (Part 3)[14]

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	Primary

End point timeframe:

At 30 minutes after infusion

Notes:

[14] - 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: Part 3 PK primary endpoint analyses were summarized as descriptive statistics, as per protocol.

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

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 four 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:

[15] - 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 (± 8.1)			
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 (Cl) (Part 1)

End point title	Clearance (Cl) (Part 1)

End point description:

Clearance (Cl) 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 (± 11.3)			
rVIII-SingleChain	50 (± 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 (± 0.381)			
rVIII-SingleChain	2.24 (± 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[16]	146[17]	173[18]	
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:

[16] - Number of treated bleeding episodes = 590

[17] - Number of treated bleeding episodes = 258

[18] - Number of treated bleeding episodes = 848

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 occurrences (all)	13 / 174 (7.47%) 14		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	20 / 174 (11.49%) 22		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	18 / 174 (10.34%) 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: • 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: • 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: • 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