



Clinical trial results:

A Phase III Open-label Pharmacokinetic, Efficacy and Safety Study of rVIII-SingleChain in a Pediatric Population with Severe Hemophilia A Summary

EudraCT number	2012-001336-65
Trial protocol	HU DE ES NL IT PT PL AT IE FR
Global end of trial date	24 August 2015

Results information

Result version number	v2 (current)
This version publication date	06 April 2017
First version publication date	09 September 2016
Version creation reason	<ul style="list-style-type: none">• Correction of full data setMinor clarifications made

Trial information

Trial identification

Sponsor protocol code	CSL627_3002
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02093897
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	21 September 2015
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	24 August 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of recombinant single-chain FVIII (rVIII-SingleChain) in the treatment of major and minor bleeding episodes based on the investigator's 4-point assessment scale.

Protection of trial subjects:

This study was carried out in accordance with the International Conference on Harmonisation Good Clinical Practice guidelines, standard operating procedures for clinical research and development at CSL Behring and any other relevant procedures and applicable international and national regulatory requirements. The study protocol and all amendments were approved by the Independent Ethics Committee / Institutional Review Board of the participating centers. Before undergoing Screening procedures for possible enrollment into the study, the subjects' legally acceptable representative was informed, in an understandable form, about the nature, scope, and possible consequences of the study. The investigator was responsible for obtaining a subject's legally acceptable representative 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. If a subject was withdrawn from the study or further participation was declined, the subject would continue to have access to medical care and would be treated according to routine medical practice, but would no longer receive the investigational medicinal product.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 March 2014
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	Australia: 3
Country: Number of subjects enrolled	Georgia: 5
Country: Number of subjects enrolled	Lebanon: 6
Country: Number of subjects enrolled	Malaysia: 4
Country: Number of subjects enrolled	Philippines: 8
Country: Number of subjects enrolled	Romania: 1
Country: Number of subjects enrolled	Switzerland: 1
Country: Number of subjects enrolled	Thailand: 10
Country: Number of subjects enrolled	Turkey: 8
Country: Number of subjects enrolled	Ukraine: 6
Country: Number of subjects enrolled	United States: 4
Country: Number of subjects enrolled	Netherlands: 6
Country: Number of subjects enrolled	Poland: 2

Country: Number of subjects enrolled	Portugal: 2
Country: Number of subjects enrolled	Spain: 2
Country: Number of subjects enrolled	Austria: 3
Country: Number of subjects enrolled	France: 7
Country: Number of subjects enrolled	Germany: 5
Country: Number of subjects enrolled	Italy: 1
Worldwide total number of subjects	84
EEA total number of subjects	29

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)	2
Children (2-11 years)	82
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:

This multicenter, multinational study enrolled subjects at 37 participating study centers in Australia, Europe, Georgia, Lebanon, Malaysia, Philippines, Switzerland, Thailand, Turkey, Ukraine, and the United States.

Pre-assignment

Screening details:

Screening took place 4 to 28 days prior to first dose of study product (rVIII-SingleChain). A total of 88 subjects were screened, 4 of these did not fulfill all eligibility criteria and were therefore screening failures.

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	rVIII-SingleChain
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Arm description:

Subjects were assigned to either an on-demand or prophylaxis regimen and received rVIII-SingleChain as an intravenous (IV) infusion. Subjects assigned to a prophylaxis regimen were treated with 15 to 50 IU/kg of rVIII-SingleChain every second day or 2 to 3 times per week, or at the investigator's discretion, based on available PK data, the FVIII treatment regimen used before enrollment and/or the subject's bleeding phenotype. The dose for on-demand treatment of a bleeding episode was based on the recommendations of the World Federation of Hemophilia (WFH), with a minimum dose of 15 IU/kg. All subjects were to be treated for a minimum of 50 EDs. For the PK evaluation, the subjects received a single IV dose of 50 IU/kg of rVIII-SingleChain on Day 1 at the start of the PK evaluation period. A total of 5313 CSL627 infusions were administered to 84 subjects during the study. As planned, groups were closed and subjects discontinued when 25 subjects reached 50 EDs per group.

Arm type	Experimental
Investigational medicinal product name	rVIII-SingleChain
Investigational medicinal product code	CSL627
Other name	Recombinant Single-Chain Factor VIII
Pharmaceutical forms	Powder and solvent for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects were assigned to either an on-demand or prophylaxis regimen and received rVIII-SingleChain as an intravenous (IV) infusion. Subjects assigned to a prophylaxis regimen were treated with 15 to 50 IU/kg of rVIII-SingleChain every second day or 2 to 3 times per week, or at the investigator's discretion, based on available PK data, the FVIII treatment regimen used before enrollment and/or the subject's bleeding phenotype. The dose for on-demand treatment of a bleeding episode was based on the recommendations of the World Federation of Hemophilia (WFH), with a minimum dose of 15 IU/kg. All subjects were to be treated for a minimum of 50 EDs. For the PK evaluation, the subjects received a single IV dose of 50 IU/kg of rVIII-SingleChain on Day 1 at the start of the PK evaluation period.

Number of subjects in period 1	rVIII-SingleChain
Started	84
Completed	65
Not completed	19
Physician decision	1
Adverse event, non-fatal	1
Planned age group closure once numbers reached	17

Baseline characteristics

Reporting groups

Reporting group title	Overall trial
Reporting group description: -	

Reporting group values	Overall trial	Total	
Number of subjects	84	84	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	2	2	
Children (2-11 years)	82	82	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous			
Units: years			
arithmetic mean	6.6		
standard deviation	± 3.11	-	
Gender categorical			
Units: Subjects			
Female	0	0	
Male	84	84	
Type of FVIII product used before enrollment			
Type of FVIII product used by the subjects within the 12 months before enrollment into the study. This could have been a plasma FVIII product or a recombinant FVIII product.			
Units: Subjects			
Plasma product	33	33	
Recombinant Product	49	49	
Unknown	2	2	
Treatment modality of FVIII therapy before enrollment			
Treatment modality of FVIII therapy within the 12 months 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	60	60	
On-Demand	24	24	

End points

End points reporting groups

Reporting group title	rVIII-SingleChain
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Reporting group description:

Subjects were assigned to either an on-demand or prophylaxis regimen and received rVIII-SingleChain as an intravenous (IV) infusion. Subjects assigned to a prophylaxis regimen were treated with 15 to 50 IU/kg of rVIII-SingleChain every second day or 2 to 3 times per week, or at the investigator's discretion, based on available PK data, the FVIII treatment regimen used before enrollment and/or the subject's bleeding phenotype. The dose for on-demand treatment of a bleeding episode was based on the recommendations of the World Federation of Hemophilia (WFH), with a minimum dose of 15 IU/kg. All subjects were to be treated for a minimum of 50 EDs. For the PK evaluation, the subjects received a single IV dose of 50 IU/kg of rVIII-SingleChain on Day 1 at the start of the PK evaluation period. A total of 5313 CSL627 infusions were administered to 84 subjects during the study. As planned, groups were closed and subjects discontinued when 25 subjects reached 50 EDs per group.

Subject analysis set title	On-demand
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Subject analysis set type	Sub-group analysis
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Subject analysis set description:

The Efficacy Population consisted of all subjects who received at least 1 dose of rVIII-SingleChain as part of either a routine prophylaxis or on-demand regimen during the study. One subject was excluded from the efficacy population because of a pre-existing inhibitor to FVIII (confirmed by reexamination of a screening sample initially reported as negative due to laboratory error).

Subjects assigned to the on-demand treatment regimen treated themselves, or were treated by a caregiver/guardian, as needed for any bleeding episode and did not receive routine assigned infusions. Preventative and additional doses of rVIII-SingleChain were allowed; data from such doses are included in the analysis of 'Consumption of rVIII-SingleChain' end points. "Preventative dose" was defined as a dose taken before an activity or a minor procedure to prevent or minimize a bleeding episode, and "additional dose" was defined as a dose taken beyond the need to control hemostasis.

Subject analysis set title	Prophylaxis
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Subject analysis set type	Sub-group analysis
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Subject analysis set description:

The Efficacy Population consisted of all subjects who received at least 1 dose of rVIII-SingleChain as part of either a routine prophylaxis or on-demand regimen during the study (1 subject was excluded from the efficacy population as described previously). Subjects receiving routine prophylaxis treatment were initially treated with 15-50 IU/kg of rVIII-SingleChain every 2nd day or 2 to 3 times per week, or at the investigator's discretion, based upon available PK data, the FVIII treatment regimen used before enrollment and/or the subject's bleeding phenotype. The dose or dosing frequency may have been adjusted if necessary.

Preventative and additional doses of rVIII-SingleChain were allowed; data from such doses are included in the analysis of 'Consumption of rVIII-SingleChain' end points. "Preventative dose" was a dose taken before an activity or a minor procedure to prevent or minimize a bleeding episode and "additional dose" was a dose taken beyond the need to control hemostasis.

Subject analysis set title	Efficacy Population
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Subject analysis set type	Sub-group analysis
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Subject analysis set description:

The Efficacy Population consisted of all subjects who received at least 1 dose of rVIII-SingleChain as part of either a routine prophylaxis or on-demand regimen during the study. One subject was excluded from the efficacy population because of a pre-existing inhibitor to FVIII (confirmed by reexamination of a screening sample initially reported as negative due to laboratory error).

Subject analysis set title	Pharmacokinetic Population
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Subject analysis set type	Sub-group analysis
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Subject analysis set description:

The PK Population comprised those subjects who participated in the PK assessment and received at least 1 dose of rVIII-SingleChain and for whom a sufficient number of analyzable PK samples were obtained to permit the evaluation of the PK profile of rVIII-SingleChain.

Primary: Treatment success

End point title	Treatment success ^[1]
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End point description:

Rate of treatment success where treatment success of a bleeding episode is defined as a rating of "excellent" or "good" based on the investigator's overall clinical assessment of hemostatic efficacy (using a 4-point scale of excellent, good, moderate or poor/no response) on the on-demand and prophylaxis regimens combined. The rate of success was based on the number of treated bleeding events; there were 347 treated bleeding events in the Efficacy Population.

End point type	Primary
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End point timeframe:

Up to 1 year

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: Primary endpoint data were analysed descriptively and no statistical analyses were planned or conducted.

End point values	Efficacy Population			
Subject group type	Subject analysis set			
Number of subjects analysed	83			
Units: Percentage of treated bleeding events				
number (confidence interval 95%)	96.3 (91.3 to 98.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized bleeding rate

End point title	Annualized bleeding rate
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End point description:

The annualized bleeding rate was defined as the number of bleeding episodes requiring treatment divided by the efficacy evaluation period in days, x 365.25, and is presented separately for the on-demand regimen and the prophylaxis regimens.

End point type	Secondary
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End point timeframe:

Up to 1 year

End point values	On-demand	Prophylaxis		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	3	80		
Units: Treated bleeding episodes per year				
median (inter-quartile range (Q1-Q3))	78.56 (35.12 to 86.62)	3.69 (0 to 7.2)		

Statistical analyses

No statistical analyses for this end point

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

End point title	Percentage of bleeding episodes requiring 1, 2, 3 or > 3 infusions of rVIII-SingleChain to achieve hemostasis
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End point description:

End point type	Secondary
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End point timeframe:

Up to 1 year

End point values	Efficacy Population			
Subject group type	Subject analysis set			
Number of subjects analysed	83 ^[2]			
Units: Percentage (%) of bleeding episodes				
number (not applicable)				
Requiring 1 infusion	85.9			
Requiring 2 infusions	9.8			
Requiring 3 infusions	2.3			
Requiring > 3 infusions	2			

Notes:

[2] - Number of treated bleeds = 347

Statistical analyses

No statistical analyses for this end point

Secondary: Consumption of rVIII-SingleChain - IU/kg per subject per month

End point title	Consumption of rVIII-SingleChain - IU/kg per subject per month
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End point description:

End point type	Secondary
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End point timeframe:

Up to 1 year

End point values	On-demand	Prophylaxis		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	3	80		
Units: IU/kg per subject per month				
median (full range (min-max))	202 (126 to 231)	378 (153 to 1394)		

Statistical analyses

No statistical analyses for this end point

Secondary: Consumption of rVIII-SingleChain - IU/kg per subject per year

End point title	Consumption of rVIII-SingleChain - IU/kg per subject per year
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End point description:

End point type	Secondary
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End point timeframe:

Up to 1 year

End point values	On-demand	Prophylaxis		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	3	80		
Units: IU/kg per subject per year				
median (full range (min-max))	2429 (1508 to 2771)	4541 (1839 to 16727)		

Statistical analyses

No statistical analyses for this end point

Secondary: Consumption of rVIII-SingleChain - IU/kg per bleeding event

End point title	Consumption of rVIII-SingleChain - IU/kg per bleeding event
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End point description:

End point type	Secondary
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End point timeframe:

Up to 1 year

End point values	On-demand	Prophylaxis		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	3	80		
Units: IU/kg per event				
median (full range (min-max))	25.9 (21 to 78)	37 (16 to 282)		

Statistical analyses

No statistical analyses for this end point

Secondary: Consumption of rVIII-SingleChain (on-demand regimen) - number of infusions per subject per month

End point title	Consumption of rVIII-SingleChain (on-demand regimen) - number of infusions per subject per month
End point description:	
End point type	Secondary
End point timeframe:	
Up to 1 year	

End point values	On-demand			
Subject group type	Subject analysis set			
Number of subjects analysed	3			
Units: number of infusion per subject per month				
median (full range (min-max))	7.58 (5.1 to 7.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Consumption of rVIII-SingleChain (on-demand regimen) - number of infusions per subject per year

End point title	Consumption of rVIII-SingleChain (on-demand regimen) - number of infusions per subject per year
End point description:	
End point type	Secondary
End point timeframe:	
Up to 1 year	

End point values	On-demand			
Subject group type	Subject analysis set			
Number of subjects analysed	3 ^[3]			
Units: number of infusions per subject per year				
median (full range (min-max))	90.95 (60.9 to 92.3)			

Notes:

[3] - Subjects assigned to the on-demand treatment regimen.

Statistical analyses

No statistical analyses for this end point

Secondary: Incremental recovery

End point title	Incremental recovery
End point description: Incremental recovery expressed as (IU/dL)/(IU/kg) corrected for subject's predose plasma FVIII activity measured using the chromogenic substrate assay.	
End point type	Secondary
End point timeframe: At 1 hour after the start of infusion	

End point values	Pharmacokinetic Population			
Subject group type	Subject analysis set			
Number of subjects analysed	39			
Units: (IU/dL)/(IU/kg)				
arithmetic mean (standard deviation)	1.63 (± 0.329)			

Statistical analyses

No statistical analyses for this end point

Secondary: Half-life (t_{1/2}) of rVIII-SingleChain

End point title	Half-life (t _{1/2}) of rVIII-SingleChain
End point description: Half-life (t _{1/2}) of rVIII-SingleChain, baseline uncorrected; plasma FVIII activity measured using the chromogenic substrate assay.	
End point type	Secondary
End point timeframe: Immediately before dosing, and at approximately 1, 5, 10, 24, and 48 hours after dosing.	

End point values	Pharmacokinetic Population			
Subject group type	Subject analysis set			
Number of subjects analysed	39			
Units: hour				
arithmetic mean (standard deviation)	10.3 (± 2.51)			

Statistical analyses

No statistical analyses for this end point

Secondary: Area under the concentration curve (AUC)

End point title	Area under the concentration curve (AUC)
End point description: AUC to the last sample with quantifiable drug concentration (AUC _{0-t}), baseline uncorrected; plasma FVIII activity measured using the chromogenic substrate assay.	
End point type	Secondary
End point timeframe: Immediately before dosing, and at approximately 1, 5, 10, 24, and 48 hours after dosing.	

End point values	Pharmacokinetic Population			
Subject group type	Subject analysis set			
Number of subjects analysed	39			
Units: IU*h/dL				
arithmetic mean (standard deviation)	1050 (± 286)			

Statistical analyses

No statistical analyses for this end point

Secondary: Clearance (Cl) of rVIII-SingleChain

End point title	Clearance (Cl) of rVIII-SingleChain
End point description: Clearance (Cl) of rVIII-SingleChain, baseline uncorrected; plasma FVIII activity measured using the chromogenic substrate assay.	
End point type	Secondary
End point timeframe: Immediately before dosing, and at approximately 1, 5, 10, 24, and 48 hours after dosing.	

End point values	Pharmacokinetic Population			
Subject group type	Subject analysis set			
Number of subjects analysed	39			
Units: mL/h/kg				
arithmetic mean (standard deviation)	4.86 (± 1.43)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with inhibitor formation to rVIII-SingleChain

End point title	Number of subjects with inhibitor formation to rVIII-SingleChain
End point description: The number of subjects who develop inhibitors to rVIII-SingleChain, defined as a rVIII-SingleChain antibody titer of at least 0.6 Bethesda Units (BU) per mL after receiving study drug.	
End point type	Secondary
End point timeframe: At screening, then after dosing at approximately monthly intervals for 6 months, then every 3 months until reaching 50 EDs, and at the end of study visit (up to approximately 12 months).	

End point values	rVIII-SingleChain			
Subject group type	Reporting group			
Number of subjects analysed	84			
Units: subjects	0			

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 1 year, 5 months.

Adverse event reporting additional description:

The Safety Population comprised all subjects treated with rVIII-SingleChain. A total of 5313 CSL627 infusions were administered to 84 subjects during the study.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	16.1
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Reporting groups

Reporting group title	rVIII-SingleChain
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Reporting group description: -

Serious adverse events	rVIII-SingleChain		
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 84 (10.71%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Investigations			
Inhibiting antibodies positive	Additional description: Subject identified with pre-existing inhibitor to FVIII confirmed by reexamination of screening sample initially reported as negative due to laboratory error. Therefore, event is not a de-novo inhibitor developed during exposure to rVIII-SingleChain.		
subjects affected / exposed	1 / 84 (1.19%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Hand fracture			
subjects affected / exposed	1 / 84 (1.19%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Laceration			
subjects affected / exposed	1 / 84 (1.19%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Splenic rupture			

subjects affected / exposed	1 / 84 (1.19%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Device occlusion			
subjects affected / exposed	1 / 84 (1.19%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Systemic inflammatory response syndrome			
subjects affected / exposed	1 / 84 (1.19%)		
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 / 84 (1.19%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Dyspepsia			
subjects affected / exposed	1 / 84 (1.19%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Bacteraemia			
subjects affected / exposed	1 / 84 (1.19%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 84 (1.19%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Non-serious adverse events	rVIII-SingleChain		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	31 / 84 (36.90%)		
Injury, poisoning and procedural complications			
Head injury			
subjects affected / exposed	5 / 84 (5.95%)		
occurrences (all)	6		
Nervous system disorders			
Headache			
subjects affected / exposed	7 / 84 (8.33%)		
occurrences (all)	9		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	5 / 84 (5.95%)		
occurrences (all)	5		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	7 / 84 (8.33%)		
occurrences (all)	10		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	8 / 84 (9.52%)		
occurrences (all)	8		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	14 / 84 (16.67%)		
occurrences (all)	15		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 May 2013	<ul style="list-style-type: none">- Extended duration of study participation to allow at least 50 EDs- Increased cohort size of subjects screened for participation- Added assessment for Chinese hamster ovary (CHO) antibodies- Defined preventative dosing and additional dosing- Added collection of additional subject information including blood group and hemophilia A gene defect- Updated Independent Data and Safety Monitoring Committee responsibilities
28 March 2014	<ul style="list-style-type: none">- Identified change in Coordinating Investigator- Incorporated a change in PK collection time points as recommended by Food and Drug Administration (FDA)- Updated Independent Data and Safety Monitoring Committee data review information

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported