



Clinical trial results:

An Open-label, Multicenter, Dose-escalation Safety and Pharmacokinetic Study of a Recombinant Coagulation Factor IX Albumin Fusion Protein (rIX-FP) in subjects with Hemophilia B

Summary

EudraCT number	2010-018477-38
Trial protocol	DE AT ES GB IT FR
Global end of trial date	18 July 2011

Results information

Result version number	v1 (current)
This version publication date	13 July 2016
First version publication date	06 August 2015

Trial information

Trial identification

Sponsor protocol code	CSL654_2001
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01233440
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	Clinical Trial Disclosure Manager, CSL Behring, clinicaltrials@cslbehring.com
Scientific contact	Clinical Trial Disclosure Manager, CSL Behring, 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-001107-PIP01-10
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	09 August 2011
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	18 July 2011
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to assess the safety of intravenous (IV) administration of rIX-FP. Safety was evaluated by adverse events and laboratory changes over time.

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 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.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	21 October 2010
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	Spain: 3
Country: Number of subjects enrolled	Austria: 3
Country: Number of subjects enrolled	France: 6
Country: Number of subjects enrolled	Germany: 5
Country: Number of subjects enrolled	Italy: 5
Country: Number of subjects enrolled	Israel: 3
Worldwide total number of subjects	25
EEA total number of subjects	22

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	1
Adults (18-64 years)	24
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

In the dose-escalation safety part of the study 4 subjects per cohort were tested sequentially at 25, 50, and 75 IU/kg of rIX-FP. For the PK evaluation at least 13 subjects were to be tested at 50 IU/kg and up to 8 subjects each in the 25 and/or 75 IU/kg rIX-FP dosing groups. The initial 12 subjects could be dosed a second time for PK testing.

Pre-assignment

Screening details:

Males with severe hemophilia B (Factor IX [FIX] activity \leq 2%), 12-65 years old, who had received FIX products for > 150 exposure days were screened.

Seven subjects received 2 doses of rIX-FP; 3 subjects received 25 and 50 IU/kg rIX-FP, 1 subject received 25 and 75 IU/kg rIX-FP, and 3 subjects received 50 and 75 IU/kg rIX-FP.

Period 1

Period 1 title	rIX-FP Safety and PK Period
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	No
Arm title	25 IU/kg rIX-FP

Arm description:

Subjects received a single dose of 25 IU/kg rIX-FP by bolus intravenous injection.

Arm type	Experimental
Investigational medicinal product name	Recombinant Coagulation Factor IX Albumin Fusion Protein (rIX-FP)
Investigational medicinal product code	CSL654
Other name	rIX-FP
Pharmaceutical forms	Powder for concentrate for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects were administered the dose as a bolus IV injection at a rate of approximately 250 IU per minute or complete the infusion in approximately 10 to 15 minutes. Subjects were to receive rIX-FP at least 2 weeks after a non life-threatening bleeding episode, at least 3 months after a life-threatening bleeding episode, at least 4 days after receiving their previous FIX product dose and were not actively bleeding.

Arm title	50 IU/kg rIX-FP
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Arm description:

Subjects received a single dose of 50 IU/kg rIX-FP by bolus intravenous injection.

Arm type	Experimental
Investigational medicinal product name	Recombinant Coagulation Factor IX Albumin Fusion Protein (rIX-FP)
Investigational medicinal product code	CSL654
Other name	rIX-FP
Pharmaceutical forms	Powder for concentrate for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects were administered the dose as a bolus IV injection at a rate of approximately 250 IU per minute or complete the infusion in approximately 10 to 15 minutes. Subjects were to receive rIX-FP at least 2 weeks after a non life-threatening bleeding episode, at least 3 months after a life-threatening bleeding episode, at least 4 days after receiving their previous FIX product dose and were not actively bleeding.

Arm title	75 IU/kg rIX-FP
Arm description: Subjects received a single dose of 75 IU/kg rIX-FP by bolus intravenous injection.	
Arm type	Experimental
Investigational medicinal product name	Recombinant Coagulation Factor IX Albumin Fusion Protein (rIX-FP)
Investigational medicinal product code	CSL654
Other name	rIX-FP
Pharmaceutical forms	Powder for concentrate for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects were administered the dose as a bolus IV injection at a rate of approximately 250 IU per minute or complete the infusion in approximately 10 to 15 minutes. Subjects were to receive rIX-FP at least 2 weeks after a non life-threatening bleeding episode, at least 3 months after a life-threatening bleeding episode, at least 4 days after receiving their previous FIX product dose and were not actively bleeding.

Number of subjects in period 1	25 IU/kg rIX-FP	50 IU/kg rIX-FP	75 IU/kg rIX-FP
Started	9	14	9
Completed	9	14	9

Period 2

Period 2 title	FIX PK Period
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	50 IU/kg FIX
Arm description: Participants received a single dose of 50 IU/kg of their previous Factor IX (FIX) product.	
Arm type	Experimental
Investigational medicinal product name	Factor IX (recombinant or plasma derived)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

50 IU/kg by IV infusion, at least 4 days following the previous FIX treatment or at least 14 days following the rIX-FP dose.

Number of subjects in period 2	50 IU/kg FIX
Started	15
Completed	15

Baseline characteristics

Reporting groups

Reporting group title	rIX-FP Safety and PK Period
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Reporting group description: -

Reporting group values	rIX-FP Safety and PK Period	Total	
Number of subjects	25	25	
Age categorical Units: Subjects			
< 18 years	1	1	
≥ 18 years	24	24	
Age continuous Units: years			
arithmetic mean	35		
standard deviation	± 11.69	-	
Gender categorical Units: Subjects			
Female	0	0	
Male	25	25	

End points

End points reporting groups

Reporting group title	25 IU/kg rIX-FP
Reporting group description:	
Subjects received a single dose of 25 IU/kg rIX-FP by bolus intravenous injection.	
Reporting group title	50 IU/kg rIX-FP
Reporting group description:	
Subjects received a single dose of 50 IU/kg rIX-FP by bolus intravenous injection.	
Reporting group title	75 IU/kg rIX-FP
Reporting group description:	
Subjects received a single dose of 75 IU/kg rIX-FP by bolus intravenous injection.	
Reporting group title	50 IU/kg FIX
Reporting group description:	
Participants received a single dose of 50 IU/kg of their previous Factor IX (FIX) product.	

Primary: Number of subjects with adverse events and serious adverse events after administration of rIX-FP

End point title	Number of subjects with adverse events and serious adverse events after administration of rIX-FP ^[1]
End point description:	
An adverse event (AE) was defined as any untoward medical occurrence in a subject administered an Investigational Medicinal Product (IMP) (whether it was the study or any reference product[s]). An AE could have been any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the IMP, whether or not causally related to the IMP.	
A serious adverse event was defined as any untoward medical occurrence that at any dose	
<ul style="list-style-type: none">• resulted in death,• was life-threatening,• required in-patient hospitalization or prolongation of existing hospitalization,• resulted in persistent or significant disability/incapacity,• was a congenital anomaly/birth defect,• or was considered according to the investigator's judgment to be a medically significant event.	
End point type	Primary
End point timeframe:	
From the first dose of rIX-FP until 28 days after the last dose.	

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: No statistical analyses were conducted for this end point.

End point values	25 IU/kg rIX-FP	50 IU/kg rIX-FP	75 IU/kg rIX-FP	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	9	14	9	
Units: subjects				
Any adverse events	3	6	5	
Serious adverse events	0	0	0	

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects developing inhibitors against FIX

End point title	Number of subjects developing inhibitors against FIX ^[2]
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End point description:

Assessing the neutralizing capacity of antibodies was achieved via a FIX potency assay. For this assay, the respective subject sample was mixed and pre-incubated with the same volume of FIX containing plasma. Subsequently, the remaining FIX activity was assessed by a one-stage clotting assay.

End point type	Primary
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End point timeframe:

From the first dose of IMP until 28 days after the last dose.

Notes:

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

Justification: No statistical analyses were conducted for this end point.

End point values	25 IU/kg rIX-FP	50 IU/kg rIX-FP	75 IU/kg rIX-FP	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	9	14	9	
Units: subjects	0	0	0	

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects developing antibodies against rIX-FP

End point title	Number of subjects developing antibodies against rIX-FP ^[3]
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End point description:

Antibodies against rIX-FP were detected using a direct binding enzyme-linked immunosorbent assay (ELISA).

End point type	Primary
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End point timeframe:

From the first dose of IMP until 28 days after the last dose.

Notes:

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

Justification: No statistical analyses were conducted for this end point.

End point values	25 IU/kg rIX-FP	50 IU/kg rIX-FP	75 IU/kg rIX-FP	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	9	14	9	
Units: subjects	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Incremental recovery following a single intravenous dose of 50 IU/kg rIX-FP

End point title	Incremental recovery following a single intravenous dose of 50 IU/kg rIX-FP ^[4]
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End point description:

Incremental recovery (IU/mL/IU/kg) is defined as FIX activity (IU/mL) obtained 30 minutes following infusion, per dose of (IU/kg) infusion.

FIX activity was measured at a central laboratory using validated one-stage clotting method.

Recovery values were baseline-corrected for pre-infusion plasma FIX activity.

End point type	Secondary
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End point timeframe:

Pre-dose and at 30 minutes after infusion

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Per the protocol, secondary endpoints included pharmacokinetic analyses following a single intravenous dose of 50 IU/kg rIX-FP.

End point values	50 IU/kg rIX-FP			
Subject group type	Reporting group			
Number of subjects analysed	13 ^[5]			
Units: IU/dL/IU/kg				
arithmetic mean (standard deviation)	1.376 (± 0.28)			

Notes:

[5] - Pharmacokinetic (PK) population

Statistical analyses

No statistical analyses for this end point

Secondary: Half Life of FIX activity following a single intravenous dose of 50 IU/kg rIX-FP

End point title	Half Life of FIX activity following a single intravenous dose of 50 IU/kg rIX-FP ^[6]
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End point description:

FIX activity was measured at a central laboratory using validated one-stage clotting method. FIX levels were baseline adjusted by subtracting the pre-dose values.

End point type	Secondary
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End point timeframe:

Pre-dose and 30 minutes, 3, 6 24, 48, 72, 120, 168, 240 and 336 hours after the end of infusion.

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Per the protocol, secondary endpoints included pharmacokinetic analyses following a single intravenous dose of 50 IU/kg rIX-FP.

End point values	50 IU/kg rIX-FP			
Subject group type	Reporting group			
Number of subjects analysed	13 ^[7]			
Units: hours				
arithmetic mean (standard deviation)	91.57 (± 20.74)			

Notes:

[7] - PK population

Statistical analyses

No statistical analyses for this end point

Secondary: Area under the curve extrapolated to infinity (AUC0-inf) following a single intravenous dose of 50 IU/kg rIX-FP

End point title	Area under the curve extrapolated to infinity (AUC0-inf) following a single intravenous dose of 50 IU/kg rIX-FP ^[8]
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End point description:

FIX activity was measured at a central laboratory using validated one-stage clotting method. FIX levels were baseline adjusted by subtracting the pre-dose values.

End point type	Secondary
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End point timeframe:

Pre-dose and 30 minutes, 3, 6 24, 48, 72, 120, 168, 240 and 336 hours after the end of infusion.

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Per the protocol, secondary endpoints included pharmacokinetic analyses following a single intravenous dose of 50 IU/kg rIX-FP.

End point values	50 IU/kg rIX-FP			
Subject group type	Reporting group			
Number of subjects analysed	13 ^[9]			
Units: hr*IU/dL				
arithmetic mean (standard deviation)	7089.87 (± 1622.83)			

Notes:

[9] - PK population

Statistical analyses

No statistical analyses for this end point

Secondary: Clearance for FIX activity following a single intravenous dose of 50 IU/kg rIX-FP

End point title	Clearance for FIX activity following a single intravenous dose of 50 IU/kg rIX-FP ^[10]
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End point description:

FIX activity was measured at a central laboratory using validated one-stage clotting method. FIX levels were baseline adjusted by subtracting the pre-dose values.

End point type	Secondary
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End point timeframe:

Pre-dose and 30 minutes, 3, 6 24, 48, 72, 120, 168, 240 and 336 hours after the end of infusion.

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Per the protocol, secondary endpoints included pharmacokinetic analyses following a single intravenous dose of 50 IU/kg rIX-FP.

End point values	50 IU/kg rIX-FP			
Subject group type	Reporting group			
Number of subjects analysed	13 ^[11]			
Units: mL/hr/kg)				
arithmetic mean (standard deviation)	0.75 (± 0.19)			

Notes:

[11] - PK population

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the first dose of IMP until 28 days after the last dose.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	13.1
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Reporting groups

Reporting group title	25 IU/kg rIX-FP
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Reporting group description:

Subjects received a single dose of 25 IU/kg rIX-FP by bolus intravenous injection.

Reporting group title	50 IU/kg rIX-FP
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Reporting group description:

Subjects received a single dose of 50 IU/kg rIX-FP by bolus intravenous injection.

Reporting group title	75 IU/kg rIX-FP
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Reporting group description:

Subjects received a single dose of 75 IU/kg rIX-FP by bolus intravenous injection.

Reporting group title	50 IU/kg FIX
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Reporting group description:

Participants received a single dose of 50 IU/kg of their previous Factor IX (FIX) product.

Serious adverse events	25 IU/kg rIX-FP	50 IU/kg rIX-FP	75 IU/kg rIX-FP
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 9 (0.00%)	0 / 14 (0.00%)	0 / 9 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	50 IU/kg FIX		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 15 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	25 IU/kg rIX-FP	50 IU/kg rIX-FP	75 IU/kg rIX-FP
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 9 (33.33%)	6 / 14 (42.86%)	5 / 9 (55.56%)
Injury, poisoning and procedural complications			
Joint injury			
subjects affected / exposed	1 / 9 (11.11%)	0 / 14 (0.00%)	1 / 9 (11.11%)
occurrences (all)	1	0	1
Limb injury			
subjects affected / exposed	1 / 9 (11.11%)	1 / 14 (7.14%)	0 / 9 (0.00%)
occurrences (all)	1	1	0
Muscle rupture			
subjects affected / exposed	0 / 9 (0.00%)	1 / 14 (7.14%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Muscle strain			
subjects affected / exposed	0 / 9 (0.00%)	0 / 14 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Vascular disorders			
Peripheral coldness			
subjects affected / exposed	0 / 9 (0.00%)	0 / 14 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 9 (0.00%)	1 / 14 (7.14%)	1 / 9 (11.11%)
occurrences (all)	0	1	1
Dizziness			
subjects affected / exposed	0 / 9 (0.00%)	0 / 14 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Feeling hot			
subjects affected / exposed	0 / 9 (0.00%)	1 / 14 (7.14%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Inflammation			
subjects affected / exposed	0 / 9 (0.00%)	1 / 14 (7.14%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Injection site erythema			

subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 14 (0.00%) 0	1 / 9 (11.11%) 1
Injection site haematoma subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 14 (0.00%) 0	1 / 9 (11.11%) 1
Gastrointestinal disorders			
Abdominal pain subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 14 (0.00%) 0	1 / 9 (11.11%) 1
Constipation subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	0 / 14 (0.00%) 0	0 / 9 (0.00%) 0
Musculoskeletal and connective tissue disorders			
Arthralgia subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 14 (7.14%) 1	2 / 9 (22.22%) 3
Back pain subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 14 (0.00%) 0	1 / 9 (11.11%) 1
Joint range of motion decreased subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 14 (0.00%) 0	0 / 9 (0.00%) 0
Myalgia subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 14 (7.14%) 1	0 / 9 (0.00%) 0
Pain in extremity subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 14 (7.14%) 1	0 / 9 (0.00%) 0
Infections and infestations			
Nasopharyngitis subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	1 / 14 (7.14%) 1	0 / 9 (0.00%) 0
Influenza subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 14 (0.00%) 0	0 / 9 (0.00%) 0

Non-serious adverse events	50 IU/kg FIX		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 15 (33.33%)		
Injury, poisoning and procedural complications			
Joint injury			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Limb injury			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Muscle rupture			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Muscle strain			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Vascular disorders			
Peripheral coldness			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Dizziness			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
General disorders and administration site conditions			
Feeling hot			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Inflammation			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences (all)	0		
Injection site erythema			

<p>subjects affected / exposed occurrences (all)</p> <p>Injection site haematoma subjects affected / exposed occurrences (all)</p>	<p>0 / 15 (0.00%) 0</p> <p>0 / 15 (0.00%) 0</p>		
<p>Gastrointestinal disorders</p> <p>Abdominal pain subjects affected / exposed occurrences (all)</p> <p>Constipation subjects affected / exposed occurrences (all)</p>	<p>0 / 15 (0.00%) 0</p> <p>0 / 15 (0.00%) 0</p>		
<p>Musculoskeletal and connective tissue disorders</p> <p>Arthralgia subjects affected / exposed occurrences (all)</p> <p>Back pain subjects affected / exposed occurrences (all)</p> <p>Joint range of motion decreased subjects affected / exposed occurrences (all)</p> <p>Myalgia subjects affected / exposed occurrences (all)</p> <p>Pain in extremity subjects affected / exposed occurrences (all)</p>	<p>1 / 15 (6.67%) 1</p> <p>0 / 15 (0.00%) 0</p> <p>1 / 15 (6.67%) 1</p> <p>0 / 15 (0.00%) 0</p> <p>0 / 15 (0.00%) 0</p>		
<p>Infections and infestations</p> <p>Nasopharyngitis subjects affected / exposed occurrences (all)</p> <p>Influenza subjects affected / exposed occurrences (all)</p>	<p>0 / 15 (0.00%) 0</p> <p>1 / 15 (6.67%) 1</p>		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 June 2010	Protocol Amendment 1 was issued before the enrolment of the first subject. Main changes to the protocol included: <ul style="list-style-type: none">- Adding central laboratory tests for FIX inhibitor, albumin and FIX activity at the Screening visit.- Adding a test for rIX-FP antigen level following rIX-FP administration as a study endpoint.- Adding 2 additional rIX-FP PK blood sample collection time points.
17 August 2010	Protocol Amendment 2 was issued before the enrollment of the first subject. Main changes to the protocol included the addition of information related to the testing for antibody against albumin: a sample to be collected prior to rIX-FP infusion and tested together with the Day 28 post-infusion blood sample; a tiered approach to immunogenicity testing for rIX-FP was to be employed; and a finding of non-inhibitory antibody against albumin was not to be considered an exclusion criterion.
20 December 2010	Protocol Amendment 3 included the following main changes: <ul style="list-style-type: none">• Pharmacokinetics (PK) of 75 IU/kg rIX-FP was to be tested in the 3rd safety cohort study subjects, and up to 4 more subjects per each dose of 25 and 75 IU/kg of rIX-FP could be included for PK assessment.• Change to the PK sampling time points after rIX-FP infusion: 2 time points were omitted and 1 optional time point was added.
21 December 2010	Protocol Amendment 4 included a change in the age requirement from 12 – 65 years to 18 – 65 years for sites in France, Germany and UK. For sites in Germany and the UK aged 12 – 17 years could be enrolled after the safety data from the first 2 safety cohorts have been reviewed with no safety concerns identified by Data Review Committee.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported