Clinical trial results:
A Phase 3 Open-label, Multicenter, Pharmacokinetics, Safety, and Efficacy Study of a Recombinant Fusion Protein Linking Coagulation Factor IX with Albumin (rIX-FP) in Previously Treated Children with Hemophilia B

Summary

EudraCT number	2011-006032-23
Trial protocol	AT ES CZ IT
Global end of trial date	05 October 2014

Results information

Result version number	v2 (current)
This version publication date	29 July 2016
First version publication date	21 April 2015
Version creation reason	• Correction of full data set Minor clarifications made

Trial information

Trial identification

Sponsor protocol code	CSL654_3002

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01662531
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	CSL Behring GmbH
Sponsor organisation address	Emil-von-Behring Strasse 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	24 October 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	05 October 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

• To evaluate the pharmacokinetics (PK) of a single dose of rIX-FP.
• To evaluate the safety of rIX-FP with respect to the development of inhibitors to Factor IX (FIX) in patients with severe hemophilia B (FIX: ≤ 2%).

Protection of trial subjects:

To ensure the safety of the subjects, this study did not start until after 50 exposure days (EDs) were accrued in at least 10 subjects ≥12 years of age in the rIX-FP clinical program. Study enrollment was limited to subjects 6 to <12 years of age with at least 150 EDs to previous FIX products and subjects <6 years of age with at least 50 EDs to previous FIX products. Subjects with a history (including family history) of inhibitors against FIX were excluded to further reduce the risk of inhibitor formation during the study.

This study was carried out in accordance with the International Conference on Harmonisation (ICH) Good Clinical Practice guidelines, the Declaration of Helsinki (2008), 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 and/or their legally acceptable representative were informed, in an understandable form, about the nature, scope, and possible consequences of the study. This information was given orally to subjects by a physician or medically qualified person; written information about the study was also provided in a Subject Information Sheet.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 January 2013
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: 1
Country: Number of subjects enrolled	Austria: 2
Country: Number of subjects enrolled	Czech Republic: 3
Country: Number of subjects enrolled	France: 6
Country: Number of subjects enrolled	Germany: 3
Country: Number of subjects enrolled	Italy: 3
Country: Number of subjects enrolled	Australia: 2
Country: Number of subjects enrolled	Canada: 1
Country: Number of subjects enrolled	Israel: 4

Country: Number of subjects enrolled	Russian Federation: 2
Worldwide total number of subjects	27
EEA total number of subjects	18

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)	3
Children (2-11 years)	24
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:

Of the 18 sites that were activated, subjects were enrolled from 17 sites in 10 countries.

Pre-assignment

Screening details:

Patients <12 years of age with severe hemophilia B (FIX activity of ≤2%) were planned to be enrolled in the study, including 11 to 12 subjects in each age group (6 to <12 years and <6 years of age).
Of 29 subjects screened, 27 subjects were enrolled and treated with rIX-FP.

Period 1

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

Arms

Arm title	rIX-FP

Arm description:

All subjects received a single dose of 50 IU/kg rIX-FP on Day 1 during the pharmacokinetic phase of the study.
Subjects received weekly (7-day) routine prophylaxis treatment with an initial weekly dose of 35 to 50 IU/kg rIX-FP, which may have been adjusted based on protocol-specified criteria.
All 27 subjects were included in the Safety, Pharmacokinetic and Efficacy populations.

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

Dosage and administration details:

Subjects received weekly (7-day) routine prophylaxis treatment with an initial weekly dose of 35 to 50 IU/kg rIX-FP, which may have been adjusted based on protocol-specified criteria.

Number of subjects in period 1	rIX-FP
Started	27
Completed	27

Baseline characteristics

Reporting groups

Reporting group title	rIX-FP

Reporting group description:

All subjects received a single dose of 50 IU/kg rIX-FP on Day 1 during the pharmacokinetic phase of the study.
Subjects received weekly (7-day) routine prophylaxis treatment with an initial weekly dose of 35 to 50 IU/kg rIX-FP, which may have been adjusted based on protocol-specified criteria.
All 27 subjects were included in the Safety, Pharmacokinetic and Efficacy populations.

Reporting group values	rIX-FP	Total	
Number of subjects	27	27	
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 5.9 ± 2.93	 -	
Gender categorical Units: Subjects			
Female	0	0	
Male	27	27	

Subject analysis sets

Subject analysis set title	Age < 6 Years
Subject analysis set type	Sub-group analysis

Subject analysis set description:

All subjects received a single dose of 50 IU/kg rIX-FP on Day 1 during the pharmacokinetic phase of the study.
Subjects received weekly (7-day) routine prophylaxis treatment with an initial weekly dose of 35 to 50 IU/kg rIX-FP, which may have been adjusted based on protocol-specified criteria.

Subject analysis set title	Age 6 to <12 Years
Subject analysis set type	Sub-group analysis

Subject analysis set description:

All subjects received a single dose of 50 IU/kg rIX-FP on Day 1 during the pharmacokinetic phase of the study.
Subjects received weekly (7-day) routine prophylaxis treatment with an initial weekly dose of 35 to 50 IU/kg rIX-FP, which may have been adjusted based on protocol-specified criteria.

Reporting group values	Age < 6 Years	Age 6 to <12 Years	
Number of subjects	12	15	
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 3.2 ± 1.7	 8.1 ± 1.41	

Gender categorical Units: Subjects			
Female	0	0	
Male	12	15	

End points

End points reporting groups

Reporting group title	rIX-FP

Reporting group description:

All subjects received a single dose of 50 IU/kg rIX-FP on Day 1 during the pharmacokinetic phase of the study.
Subjects received weekly (7-day) routine prophylaxis treatment with an initial weekly dose of 35 to 50 IU/kg rIX-FP, which may have been adjusted based on protocol-specified criteria.
All 27 subjects were included in the Safety, Pharmacokinetic and Efficacy populations.

Subject analysis set title	Age < 6 Years
Subject analysis set type	Sub-group analysis

Subject analysis set description:

All subjects received a single dose of 50 IU/kg rIX-FP on Day 1 during the pharmacokinetic phase of the study.
Subjects received weekly (7-day) routine prophylaxis treatment with an initial weekly dose of 35 to 50 IU/kg rIX-FP, which may have been adjusted based on protocol-specified criteria.

Subject analysis set title	Age 6 to <12 Years
Subject analysis set type	Sub-group analysis

Subject analysis set description:

All subjects received a single dose of 50 IU/kg rIX-FP on Day 1 during the pharmacokinetic phase of the study.
Subjects received weekly (7-day) routine prophylaxis treatment with an initial weekly dose of 35 to 50 IU/kg rIX-FP, which may have been adjusted based on protocol-specified criteria.

Primary: Incremental recovery following a single intravenous dose of 50 IU/kg rIX-FP or previous FIX product

End point title	Incremental recovery following a single intravenous dose of 50 IU/kg rIX-FP or previous FIX product[1]

End point description:

Incremental recovery (IU/dL/IU/kg) is defined as the FIX activity (IU/dL) 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.
Incremental recovery was measured following a single intravenous dose of 50 IU/kg rIX-FP on Day 1.
Analysis of previous FIX product was conducted at the beginning of the study in a subset of subjects who had no historical PK data of their previous FIX product. For the PK assessment, the previous FIX product was administered by IV infusion after approximately 4 days following the last FIX treatment, prior to any dosing of rIX-FP.
The formal PK population consisted of subjects who received at least 1 dose of rIX-FP for PK assessment and for whom a sufficient number of analyzable PK samples had been obtained to permit the evaluation of the PK profile of rIX-FP.

End point type	Primary

End point timeframe:

30 minutes after infusion

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	rIX-FP	Age < 6 Years	Age 6 to <12 Years	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	27[2]	12[3]	15[4]	
Units: (IU/dL)/(IU/kg)				
arithmetic mean (standard deviation)				
rIX-FP Assessment (n=27, 12, 15)	1.0114 (± 0.22711)	0.9506 (± 0.20432)	1.06 (± 0.23934)	

Previous FIX Assessment (n=17, 8, 9)	0.7379 (± 0.19768)	0.6764 (± 0.1398)	0.7925 (± 0.23219)	

Notes:

[2] - PK population

[3] - PK population

[4] - PK population

Statistical analyses

No statistical analyses for this end point

Primary: Half-life (t1/2) following a single intravenous dose of 50 IU/kg rIX-FP or previous FIX product

End point title	Half-life (t1/2) following a single intravenous dose of 50 IU/kg rIX-FP or previous FIX product[5]

End point description:

FIX activity was measured at a central laboratory using validated one-stage clotting method. FIX levels were not corrected for baseline values.

End point type	Primary

End point timeframe:

Pre-dose, 30 minutes, 3, 24, 48, 72 120, 168, 240 and 336 hours post-dose

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: No statistical analyses were conducted for this end point.

End point values	rIX-FP	Age < 6 Years	Age 6 to <12 Years	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	27[6]	12[7]	15[8]	
Units: hours				
arithmetic mean (standard deviation)				
rIX-FP Assessment (n=26, 11, 15)	91.4492 (± 15.9754)	89.6124 (± 11.17364)	92.7962 (± 19.02537)	
Previous FIX Assessment (n=16, 7, 9)	18.6291 (± 6.15551)	19.8816 (± 8.01073)	17.655 (± 4.52497)	

Notes:

[6] - PK population

[7] - PK population

[8] - PK population

Statistical analyses

No statistical analyses for this end point

Primary: Area under the concentration versus time curve from time point zero to the last sample with quantifiable drug concentration (AUClast)

End point title	Area under the concentration versus time curve from time point zero to the last sample with quantifiable drug concentration (AUClast)[9]

End point description:

AUClast following a single intravenous dose of 50 IU/kg rIXFP or previous FIX product.
FIX activity was measured at a central laboratory using validated one-stage clotting method. FIX levels were not corrected for baseline values.

End point type	Primary

End point timeframe:

Pre-dose, 30 minutes, 3, 24, 48, 72 120, 168, 240 and 336 hours post-dose

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: No statistical analyses were conducted for this end point.

End point values	rIX-FP	Age < 6 Years	Age 6 to <12 Years	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	27[10]	12[11]	15[12]	
Units: IU*hr/dL				
arithmetic mean (standard deviation)				
rIX-FP Assessment (n=27, 12, 15)	4156.704 (± 1204.095)	3891.482 (± 1252.994)	4368.881 (± 1162.1)	
Previous FIX Assessment (n=16, 7, 9)	718.9386 (± 230.5288)	676.5414 (± 316.9138)	751.9143 (± 146.7045)	

Notes:

[10] - PK population

[11] - PK population

[12] - PK population

Statistical analyses

No statistical analyses for this end point

Primary: Clearance for FIX activity following a single intravenous dose of 50 IU/kg rIX-FP or previous FIX product

End point title	Clearance for FIX activity following a single intravenous dose of 50 IU/kg rIX-FP or previous FIX product[13]

End point description:

FIX activity was measured at a central laboratory using validated one-stage clotting method. FIX levels were not corrected for baseline values. Clearance is normalized for body weight.

End point type	Primary

End point timeframe:

Pre-dose, 30 minutes, 3, 24, 48, 72 120, 168, 240 and 336 hours post-dose

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: No statistical analyses were conducted for this end point.

End point values	rIX-FP	Age < 6 Years	Age 6 to <12 Years	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	27[14]	12[15]	15[16]	
Units: mL/hr/kg				
arithmetic mean (standard deviation)				
rIX-FP Assessment (n=26, 11, 15)	1.1119 (± 0.31373)	1.1841 (± 0.32924)	1.0589 (± 0.30203)	
Previous FIX Assessment (n=16, 7, 9)	6.4007 (± 2.14434)	7.1576 (± 2.78944)	5.8119 (± 1.37641)	

Notes:

[14] - PK population

[15] - PK population

[16] - PK population

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects developing inhibitors to Factor IX (FIX)

End point title	Number of subjects developing inhibitors to Factor IX (FIX)[17]

End point description:

Inhibitor formation was defined as any inhibitor (≥0.6 BU [Bethesda Units]/mL) identified and confirmed by retesting.

End point type	Primary

End point timeframe:

12 months

Notes:

[17] - 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	rIX-FP			
Subject group type	Reporting group			
Number of subjects analysed	27[18]			
Units: participants	0			

Notes:

[18] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with treatment-related adverse events

End point title	Number of subjects with treatment-related adverse events

End point description:

End point type	Secondary

End point timeframe:

12 months

End point values	rIX-FP			
Subject group type	Reporting group			
Number of subjects analysed	27[19]			
Units: participants				
Any adverse event	26			
Treatment-related adverse event	0			

Notes:

[19] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Bleeding Episodes Requiring One, Two or More Than Two Infusions of rIX-FP to Achieve Hemostasis

End point title	Number of Bleeding Episodes Requiring One, Two or More Than Two Infusions of rIX-FP to Achieve Hemostasis

End point description:

For each bleeding episode that required treatment, the number of episodes that required one, two or more than two infusions of rIX-FP to achieve hemostasis

End point type	Secondary

End point timeframe:

12 months

End point values	rIX-FP	Age < 6 Years	Age 6 to <12 Years	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	27[20]	12[21]	15[22]	
Units: bleeding episodes				
1 infusion	94	40	54	
2 infusions	9	5	4	
> 2 infusions	3	0	3	
1 or 2 infusions	103	45	58	

Notes:

[20] - Efficacy Population

[21] - Efficacy Population

[22] - Efficacy Population

Statistical analyses

No statistical analyses for this end point

Secondary: Consumption of rIX-FP during routine prophylaxis

End point title	Consumption of rIX-FP during routine prophylaxis

End point description:

Consumption of rIX-FP during routine prophylaxis is expressed as the total prophylaxis dose per month.

End point type	Secondary

End point timeframe:

12 months

End point values	rIX-FP	Age < 6 Years	Age 6 to <12 Years	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	27[23]	12[24]	15[25]	
Units: IU/kg/month				
arithmetic mean (standard deviation)	205.071 (± 41.155)	213.517 (± 44.3848)	198.314 (± 38.5693)	

Notes:

[23] - Efficacy Population

[24] - Efficacy Population

[25] - Efficacy Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects developing antibodies against rIX-FP

End point title	Number of subjects developing antibodies against rIX-FP

End point description:

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

End point type	Secondary

End point timeframe:

12 months

End point values	rIX-FP			
Subject group type	Reporting group			
Number of subjects analysed	27[26]			
Units: participants	0			

Notes:

[26] - Safety Population

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

12 months

Adverse event reporting additional description:

Treatment-emergent AEs (TEAEs), defined as AEs present prior to the first dose of rIX-FP that subsequently worsened in severity or those that were not present prior to the first dose but subsequently appeared are summarized.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	14.1

Reporting groups

Reporting group title	rIX-FP

Reporting group description:

All subjects received a single dose of 50 IU/kg rIX-FP on Day 1 during the pharmacokinetic phase of the study.
Subjects received weekly (7-day) routine prophylaxis treatment with an initial weekly dose of 35 to 50 IU/kg rIX-FP, which may have been adjusted based on protocol-specified criteria.

Serious adverse events	rIX-FP		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 27 (14.81%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Forearm fracture			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Head injury			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tongue injury			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue			

disorders			
arthralgia			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Groin pain			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	rIX-FP		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	23 / 27 (85.19%)		
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	5 / 27 (18.52%)		
occurrences (all)	9		
Injury			
subjects affected / exposed	2 / 27 (7.41%)		
occurrences (all)	4		
Head injury			
subjects affected / exposed	2 / 27 (7.41%)		
occurrences (all)	2		
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 27 (7.41%)		
occurrences (all)	4		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	9 / 27 (33.33%)		
occurrences (all)	14		
Blood and lymphatic system disorders			

Anaemia subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 2		
Gastrointestinal disorders Dental discomfort subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Toothache subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	 2 / 27 (7.41%) 2 2 / 27 (7.41%) 2 2 / 27 (7.41%) 2 2 / 27 (7.41%) 2		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Oropharyngeal pain subjects affected / exposed occurrences (all)	 4 / 27 (14.81%) 4 2 / 27 (7.41%) 2		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Pain in extremity subjects affected / exposed occurrences (all)	 3 / 27 (11.11%) 3 2 / 27 (7.41%) 2		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) Bronchitis	 4 / 27 (14.81%) 6 		

subjects affected / exposed	3 / 27 (11.11%)		
occurrences (all)	4		
Ear infection			
subjects affected / exposed	3 / 27 (11.11%)		
occurrences (all)	4		
Gastroenteritis			
subjects affected / exposed	3 / 27 (11.11%)		
occurrences (all)	3		
Pharyngitis			
subjects affected / exposed	2 / 27 (7.41%)		
occurrences (all)	3		
Viral infection			
subjects affected / exposed	2 / 27 (7.41%)		
occurrences (all)	3		
Molluscum contagiosum			
subjects affected / exposed	2 / 27 (7.41%)		
occurrences (all)	2		
Upper respiratory tract infection			
subjects affected / exposed	2 / 27 (7.41%)		
occurrences (all)	2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported