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

Summary

EudraCT number	2012-005489-37
Trial protocol	DE IT CZ BG ES AT
Global end of trial date	02 June 2021

Results information

Result version number	v1 (current)
This version publication date	26 November 2021
First version publication date	26 November 2021

Trial information

Trial identification

Sponsor protocol code	CSL654_3003

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02053792
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 Coordinator, CSL Behring GmbH, 049 642139 3304, clinicaltrials@cslbehring.com
Scientific contact	Clinical Trial Coordinator, CSL Behring GmbH, 049 642139 3304, 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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	29 June 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	02 June 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety of rIX-FP as measured by new cases of inhibitors against FIX in subjects with severe hemophilia B.

Protection of trial subjects:

If a subject is withdrawn from the study or further participation is declined, they will continue to have access to medical care and will be treated as per routine medical practice.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 February 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: 5
Country: Number of subjects enrolled	Philippines: 2
Country: Number of subjects enrolled	United States: 6
Country: Number of subjects enrolled	Canada: 1
Country: Number of subjects enrolled	Israel: 15
Country: Number of subjects enrolled	Japan: 9
Country: Number of subjects enrolled	Malaysia: 2
Country: Number of subjects enrolled	South Africa: 2
Country: Number of subjects enrolled	Spain: 6
Country: Number of subjects enrolled	Austria: 5
Country: Number of subjects enrolled	Bulgaria: 4
Country: Number of subjects enrolled	Czechia: 3
Country: Number of subjects enrolled	France: 14
Country: Number of subjects enrolled	Germany: 11
Country: Number of subjects enrolled	Italy: 12
Worldwide total number of subjects	97
EEA total number of subjects	55

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)	13
Children (2-11 years)	25
Adolescents (12-17 years)	5
Adults (18-64 years)	54
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Approximately 115 male PTPs and PUPs with hemophilia B were planned to be enrolled, including all eligible PTPs from CSLB-sponsored rIX-FP lead-in studies, approximately 10 PTPs who required major, nonemergency surgery, and approximately 20 PUPs.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	CSL654 (PTPs)

Arm description:

Previously treated patients (PTPs) will administer CSL654 (rIX-FP) by intravenous infusion as routine prophylaxis, prevention, and on-demand treatment during a treatment period of approximately 5 years or the time it took to reach 100 EDs.

Arm type	Experimental
Investigational medicinal product name	Recombinant fusion protein linking coagulation factor IX with albumin
Investigational medicinal product code	CSL654
Other name	rIX-FP
Pharmaceutical forms	Powder and solvent for solution for injection/infusion
Routes of administration	Intravenous use, Subcutaneous use

Dosage and administration details:

Previously treated patients (PTPs) will administer rIX-FP by intravenous infusion as routine prophylaxis, prevention, and on-demand treatment during a treatment period of approximately 5 years. The dose of rIX-FP administered will be based on the subject's previous rIX-FP use and/or pharmacokinetic data.

Arm title	CSL654 (PUPs)

Arm description:

Previously untreated patients (PUPs) administered CSL654 (rIX-FP) intravenously as weekly prophylaxis and/or on-demand treatment during the first 12 months, and as weekly routine prophylaxis thereafter up to 3 years or the time it takes to achieve 50 EDs..

Arm type	Experimental
Investigational medicinal product name	CSL654
Investigational medicinal product code	
Other name	rIX-FP
Pharmaceutical forms	Powder and solvent for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects will administer rIX-FP by intravenous infusion as routine prophylaxis, prevention, and on-demand treatment during a treatment period of approximately 3 years. The dose of rIX-FP administered will be based on the subject's previous rIX-FP use and/or pharmacokinetic data.

Number of subjects in period 1	CSL654 (PTPs)	CSL654 (PUPs)
Started	83	14
Completed	77	10
Not completed	6	4
Adverse event, serious fatal	1	-
Consent withdrawn by subject	2	2
Physician decision	-	1
Unknown	2	1
Lack of efficacy	1	-

Baseline characteristics

Reporting groups	
Reporting group title	CSL654 (PTPs)
Reporting group description:	
Previously treated patients (PTPs) will administer CSL654 (rIX-FP) by intravenous infusion as routine prophylaxis, prevention, and on-demand treatment during a treatment period of approximately 5 years or the time it took to reach 100 EDs.	
Reporting group title	CSL654 (PUPs)
Reporting group description:	
Previously untreated patients (PUPs) administered CSL654 (rIX-FP) intravenously as weekly prophylaxis and/or on-demand treatment during the first 12 months, and as weekly routine prophylaxis thereafter up to 3 years or the time it takes to achieve 50 EDs..	

Reporting group values	CSL654 (PTPs)	CSL654 (PUPs)	Total
Number of subjects	83	14	97
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	13	13
Children (2-11 years)	24	1	25
Adolescents (12-17 years)	5	0	5
Adults (18-64 years)	54	0	54
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	27.7	1.3	
standard deviation	± 17.81	± 3.11	-
Gender categorical Units: Subjects			
Female	0	0	0
Male	83	14	97

End points

End points reporting groups

Reporting group title	CSL654 (PTPs)

Reporting group description:

Previously treated patients (PTPs) will administer CSL654 (rIX-FP) by intravenous infusion as routine prophylaxis, prevention, and on-demand treatment during a treatment period of approximately 5 years or the time it took to reach 100 EDs.

Reporting group title	CSL654 (PUPs)

Reporting group description:

Previously untreated patients (PUPs) administered CSL654 (rIX-FP) intravenously as weekly prophylaxis and/or on-demand treatment during the first 12 months, and as weekly routine prophylaxis thereafter up to 3 years or the time it takes to achieve 50 EDs..

Primary: Total number of subjects who develop inhibitors against factor IX (FIX)

End point title	Total number of subjects who develop inhibitors against factor IX (FIX)[1]

End point description:

End point type	Primary

End point timeframe:

For PTPs: up to 5 years or the time it takes to achieve 100 exposure days (EDs). For PUPs: up to 3 years or the time it takes to achieve 50 EDs.

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: Descriptive statistics used

End point values	CSL654 (PTPs)	CSL654 (PUPs)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	83	12		
Units: subjects				
number (not applicable)	0	1		

Statistical analyses

No statistical analyses for this end point

Primary: Incremental recovery of 50 IU/kg CSL654 in previously untreated patients (PUPs)

End point title	Incremental recovery of 50 IU/kg CSL654 in previously untreated patients (PUPs)[2][3]

End point description:

End point type	Primary

End point timeframe:

30 minutes after CSL654 infusion

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: Descriptive statistics used because study is per guideline and not powered for this endpoint.
[3] - 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: Only PUPs for this endpoint

End point values	CSL654 (PUPs)			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: (IU/dL)/(IU/kg)				
arithmetic mean (standard deviation)				
Uncorrected FIX Activity	1.295 (± 0.3578)			
Baseline-corrected FIX Activity	1.231 (± 0.3729)			

Statistical analyses

No statistical analyses for this end point

Secondary: Total Annualized Bleeding Rate (ABR) by Prophylaxis Regimen (PTPs)

End point title	Total Annualized Bleeding Rate (ABR) by Prophylaxis Regimen (PTPs)[4]

End point description:

End point type	Secondary

End point timeframe:

For PTPs: up to 5 years or the time it takes to achieve 100 exposure days (EDs).

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: Descriptive statistics derived only for PTPs

End point values	CSL654 (PTPs)			
Subject group type	Reporting group			
Number of subjects analysed	83[5]			
Units: Bleeds/Year/Subject				
arithmetic mean (standard deviation)				
7-Day Regimen (n=41)	2.89 (± 3.115)			
10-Day Regimen (n=23)	2.72 (± 2.827)			
14-Day Regimen (n=48)	2.72 (± 3.395)			
21-Day Regimen (n=11)	1.19 (± 1.572)			

Notes:

[5] - Subjects may be assigned under multiple regimens, but will be counted only once in any given regimen

Statistical analyses

No statistical analyses for this end point

Secondary: Spontaneous ABR by Prophylaxis Regimen (PTPs)

End point title	Spontaneous ABR by Prophylaxis Regimen (PTPs)[6]

End point description:

End point type	Secondary

End point timeframe:

For PTPs: up to 5 years or the time it takes to achieve 100 exposure days (EDs).

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: Only PTPs for this endpoint

End point values	CSL654 (PTPs)			
Subject group type	Reporting group			
Number of subjects analysed	83[7]			
Units: Bleeds/Year/Subject				
arithmetic mean (standard deviation)				
7-Day Regimen (n=41)	0.95 (± 1.672)			
10-Day Regimen (n=23)	0.98 (± 1.689)			
14-Day Regimen (n=48)	1.32 (± 2.205)			
21-Day Regimen (n=11)	0.60 (± 1.408)			

Notes:

[7] - Subjects may be assigned under multiple regimens, but will be counted only once in any given regimen

Statistical analyses

No statistical analyses for this end point

Secondary: Total ABR for On-demand Regimen vs. 14-Day Regimen (PTPs)

End point title	Total ABR for On-demand Regimen vs. 14-Day Regimen

End point description:

End point type	Secondary

End point timeframe:

For PTPs: up to 5 years or the time it takes to achieve 100 exposure days (EDs).

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: Only PTPs for this endpoint

End point values	CSL654 (PTPs)			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: Bleeds/Year/Subject				
arithmetic mean (standard deviation)				
On-demand Regimen (n=14)	17.51 (± 7.130)			
14-Day Regimen (n=14)	3.01 (± 4.204)			

Statistical analyses

No statistical analyses for this end point

Secondary: Spontaneous ABR for On-demand Regimen vs. 14-Day Regimen (PTPs)

End point title	Spontaneous ABR for On-demand Regimen vs. 14-Day Regimen (PTPs)[9]

End point description:

End point type	Secondary

End point timeframe:

For PTPs: up to 5 years or the time it takes to achieve 100 exposure days (EDs).

Notes:

[9] - 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: Only PTPs for this endpoint

End point values	CSL654 (PTPs)			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: Bleeds/Year/Subject				
arithmetic mean (standard deviation)				
On-demand Regimen (n=14)	13.17 (± 5.873)			
14-Day Regimen (n=14)	1.93 (± 3.363)			

Statistical analyses

No statistical analyses for this end point

Secondary: CSL654 consumed per month per subject during routine prophylaxis treatment

End point title	CSL654 consumed per month per subject during routine prophylaxis treatment

End point description:

End point type	Secondary

End point timeframe:

For PTPs: up to 5 years or the time it takes to achieve 100 exposure days (EDs). For PUPs: up to 3 years or the time it takes to achieve 50 EDs.

End point values	CSL654 (PTPs)	CSL654 (PUPs)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	83	12		
Units: IU/kg				
arithmetic mean (standard deviation)	181.8 (± 35.16)	188.53 (± 24.096)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with at least one treatment emergent adverse event (TEAE) and the percentage of participants with at least one CSL654-related TEAE

End point title	Percentage of participants with at least one treatment emergent adverse event (TEAE) and the percentage of participants with at least one CSL654-related TEAE

End point description:

End point type	Secondary

End point timeframe:

For PTPs: up to 5 years or the time it takes to achieve 100 exposure days (EDs). For PUPs: up to 3 years or the time it takes to achieve 50 EDs.

End point values	CSL654 (PTPs)	CSL654 (PUPs)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	83	12		
Units: Percent				
number (not applicable)				
AEs	89.2	91.7		
Related AEs	1.2	16.7		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Investigator's Overall Clinical Assessment of Hemostatic Efficacy for the Treatment of Major Bleeding Events with CSL654 (PUPs)

End point title	Number of Participants with Investigator's Overall Clinical Assessment of Hemostatic Efficacy for the Treatment of Major Bleeding Events with CSL654 (PUPs)[10]

End point description:

The investigator will rate the efficacy of the CSL654 treatment based on a hemostatic efficacy four point rating scale of "excellent, good, moderate or poor/no response

End point type	Secondary

End point timeframe:

Up to 3 years or the time it takes to achieve 50 EDs

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: Only PUPs for this endpoint

End point values	CSL654 (PUPs)			
Subject group type	Reporting group			
Number of subjects analysed	0[11]			
Units: Participants				
number (not applicable)				
Excellent				
Good				
Moderate				
Poor/No response				

Notes:

[11] - No major bleeding events were reported.

Statistical analyses

No statistical analyses for this end point

Secondary: Total ABR for Subjects >=12 years: 7-Day Regimen vs. 14-Day Regimen (PTPs)

End point title	Total ABR for Subjects >=12 years: 7-Day Regimen vs. 14-Day Regimen (PTPs)[12]

End point description:

End point type	Secondary

End point timeframe:

For PTPs: up to 5 years or the time it takes to achieve 100 exposure days (EDs).

Notes:

[12] - 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: Only PTPs for this endpoint

End point values	CSL654 (PTPs)			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: Bleeds/Year/Subject				
arithmetic mean (standard deviation)				
7-Day Regimen	1.12 (± 1.697)			
14-Day Regimen	2.19 (± 3.000)			

Statistical analyses

No statistical analyses for this end point

Secondary: Spontaneous ABR for Subjects >=12 years: 7-Day Regimen vs. 14-Day Regimen (PTPs)

End point title	Spontaneous ABR for Subjects >=12 years: 7-Day Regimen vs. 14-Day Regimen (PTPs)[13]

End point description:

End point type	Secondary

End point timeframe:

For PTPs: up to 5 years or the time it takes to achieve 100 exposure days (EDs).

Notes:

[13] - 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: Only PTPs for this endpoint

End point values	CSL654 (PTPs)			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: Bleeds/Year/Subject				
arithmetic mean (standard deviation)				
7-Day Regimen	0.49 (± 1.135)			
14-Day Regimen	1.33 (± 2.349)			

Statistical analyses

No statistical analyses for this end point

Secondary: Total ABR for Subjects >=12 years: 7-Day Regimen vs. (10 or 14)-Day Regimen (PTPs)

End point title	Total ABR for Subjects >=12 years: 7-Day Regimen vs. (10 or 14)-Day Regimen (PTPs)[14]

End point description:

End point type	Secondary

End point timeframe:

For PTPs: up to 5 years or the time it takes to achieve 100 exposure days (EDs).

Notes:

[14] - 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: Only PTPs for this endpoint

End point values	CSL654 (PTPs)			
Subject group type	Reporting group			
Number of subjects analysed	49			
Units: Bleeds/Year/Subject				
arithmetic mean (standard deviation)				
7-Day Regimen	1.31 (± 1.868)			

(10 or 14)-Day Regimen	2.01 (± 2.700)			

Statistical analyses

No statistical analyses for this end point

Secondary: Spontaneous ABR for Subjects >=12 years: 7-Day Regimen vs. (10 or 14)-Day Regimen (PTPs)

End point title	Spontaneous ABR for Subjects >=12 years: 7-Day Regimen vs. (10 or 14)-Day Regimen (PTPs)[15]

End point description:

End point type	Secondary

End point timeframe:

For PTPs: up to 5 years or the time it takes to achieve 100 exposure days (EDs).

Notes:

[15] - 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: Only PTPs for this endpoint

End point values	CSL654 (PTPs)			
Subject group type	Reporting group			
Number of subjects analysed	49			
Units: Bleeds/Year/Subject				
arithmetic mean (standard deviation)				
7-Day Regimen	0.57 (± 1.192)			
(10 or 14)-Day Regimen	1.05 (± 2.022)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

For PTPs: up to 5 years or the time it takes to achieve 100 exposure days (EDs). For PUPs: up to 3 years or the time it takes to achieve 50 EDs.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups

Reporting group title	CSL654 (PTPs)

Reporting group description:

Subjects will administer CSL654 (rIX-FP) by intravenous infusion as routine prophylaxis, prevention, and on-demand treatment during a treatment period of approximately 5 years.

Reporting group title	CSL654 (PUPs)

Reporting group description:

For previously untreated patients, subjects will administer CSL654 (rIX-FP) intravenously as weekly prophylaxis and/or on-demand treatment during the first 12 months, and as weekly routine prophylaxis thereafter.

Serious adverse events	CSL654 (PTPs)	CSL654 (PUPs)	
Total subjects affected by serious adverse events			
subjects affected / exposed	17 / 83 (20.48%)	5 / 12 (41.67%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	1	0	
Investigations			
Serum ferritin decreased			
subjects affected / exposed	1 / 83 (1.20%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anti factor IX antibody increased			
subjects affected / exposed	0 / 83 (0.00%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Head injury			
subjects affected / exposed	3 / 83 (3.61%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Contusion			
subjects affected / exposed	1 / 83 (1.20%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Extradural Haematoma			
subjects affected / exposed	1 / 83 (1.20%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle injury			
subjects affected / exposed	1 / 83 (1.20%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	1 / 83 (1.20%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	1 / 83 (1.20%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haemorrhage			
subjects affected / exposed	1 / 83 (1.20%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Haematoma			
subjects affected / exposed	1 / 83 (1.20%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral Ischaemia			
subjects affected / exposed	1 / 83 (1.20%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			

Haemorrhage intracranial			
subjects affected / exposed	1 / 83 (1.20%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Blood and lymphatic system disorders			
Iron deficiency anaemia			
subjects affected / exposed	2 / 83 (2.41%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	1 / 83 (1.20%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Haemorrhoids			
subjects affected / exposed	1 / 83 (1.20%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine polyp			
subjects affected / exposed	1 / 83 (1.20%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			
subjects affected / exposed	1 / 83 (1.20%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	1 / 83 (1.20%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Haematuria			

subjects affected / exposed	1 / 83 (1.20%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Haemarthrosis			
subjects affected / exposed	2 / 83 (2.41%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthralgia			
subjects affected / exposed	1 / 83 (1.20%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis			
subjects affected / exposed	1 / 83 (1.20%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemophilic arthropathy			
subjects affected / exposed	1 / 83 (1.20%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint Swelling			
subjects affected / exposed	1 / 83 (1.20%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abscess Jaw			
subjects affected / exposed	1 / 83 (1.20%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	1 / 83 (1.20%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Peritonsillar abscess			
subjects affected / exposed	1 / 83 (1.20%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 83 (0.00%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	0 / 83 (0.00%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	0 / 83 (0.00%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	CSL654 (PTPs)	CSL654 (PUPs)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	69 / 83 (83.13%)	11 / 12 (91.67%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	5 / 83 (6.02%)	0 / 12 (0.00%)	
occurrences (all)	5	0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	15 / 83 (18.07%)	6 / 12 (50.00%)	
occurrences (all)	24	9	
Catheter site bruise			
subjects affected / exposed	0 / 83 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Influenza like illness			

subjects affected / exposed	0 / 83 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 83 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	3	
Selective IgA immunodeficiency			
subjects affected / exposed	0 / 83 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	6 / 83 (7.23%)	2 / 12 (16.67%)	
occurrences (all)	7	2	
Psychiatric disorders			
Irritability			
subjects affected / exposed	0 / 83 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	7 / 83 (8.43%)	2 / 12 (16.67%)	
occurrences (all)	12	6	
Laceration			
subjects affected / exposed	6 / 83 (7.23%)	2 / 12 (16.67%)	
occurrences (all)	7	2	
Fall			
subjects affected / exposed	4 / 83 (4.82%)	4 / 12 (33.33%)	
occurrences (all)	4	6	
Head injury			
subjects affected / exposed	3 / 83 (3.61%)	3 / 12 (25.00%)	
occurrences (all)	4	5	
Mouth injury			
subjects affected / exposed	0 / 83 (0.00%)	2 / 12 (16.67%)	
occurrences (all)	0	2	
Arthropod bite			
subjects affected / exposed	0 / 83 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	3	

Accident			
subjects affected / exposed	0 / 83 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Skin abrasion			
subjects affected / exposed	0 / 83 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Soft tissue injury			
subjects affected / exposed	0 / 83 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Tongue injury			
subjects affected / exposed	0 / 83 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Congenital, familial and genetic disorders			
Factor VII deficiency			
subjects affected / exposed	0 / 83 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Nervous system disorders			
Headache			
subjects affected / exposed	11 / 83 (13.25%)	0 / 12 (0.00%)	
occurrences (all)	21	0	
Tongue biting			
subjects affected / exposed	0 / 83 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Dental caries			
subjects affected / exposed	10 / 83 (12.05%)	1 / 12 (8.33%)	
occurrences (all)	12	1	
Diarrhoea			
subjects affected / exposed	6 / 83 (7.23%)	1 / 12 (8.33%)	
occurrences (all)	6	1	
Toothache			
subjects affected / exposed	5 / 83 (6.02%)	0 / 12 (0.00%)	
occurrences (all)	6	0	
Constipation			
subjects affected / exposed	4 / 83 (4.82%)	2 / 12 (16.67%)	
occurrences (all)	5	3	

Teething			
subjects affected / exposed	0 / 83 (0.00%)	2 / 12 (16.67%)	
occurrences (all)	0	2	
Abdominal pain			
subjects affected / exposed	0 / 83 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Gingival disorder			
subjects affected / exposed	0 / 83 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Vomiting			
subjects affected / exposed	3 / 83 (3.61%)	1 / 12 (8.33%)	
occurrences (all)	3	1	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	2 / 83 (2.41%)	2 / 12 (16.67%)	
occurrences (all)	5	4	
Dermatitis diaper			
subjects affected / exposed	0 / 83 (0.00%)	2 / 12 (16.67%)	
occurrences (all)	0	2	
Urticaria			
subjects affected / exposed	0 / 83 (0.00%)	2 / 12 (16.67%)	
occurrences (all)	0	2	
Ingrowing nail			
subjects affected / exposed	0 / 83 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Nail bed inflammation			
subjects affected / exposed	0 / 83 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	0 / 83 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	25 / 83 (30.12%)	0 / 12 (0.00%)	
occurrences (all)	35	0	
Pain in extremity			

subjects affected / exposed	8 / 83 (9.64%)	0 / 12 (0.00%)	
occurrences (all)	10	0	
Musculoskeletal pain			
subjects affected / exposed	6 / 83 (7.23%)	0 / 12 (0.00%)	
occurrences (all)	8	0	
Soft tissue swelling			
subjects affected / exposed	0 / 83 (0.00%)	2 / 12 (16.67%)	
occurrences (all)	0	5	
Haemophilic arthropathy			
subjects affected / exposed	2 / 83 (2.41%)	1 / 12 (8.33%)	
occurrences (all)	3	1	
Muscle spasms			
subjects affected / exposed	0 / 83 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	15 / 83 (18.07%)	3 / 12 (25.00%)	
occurrences (all)	25	14	
Gastroenteritis			
subjects affected / exposed	10 / 83 (12.05%)	1 / 12 (8.33%)	
occurrences (all)	10	1	
Influenza			
subjects affected / exposed	6 / 83 (7.23%)	1 / 12 (8.33%)	
occurrences (all)	6	2	
Sinusitis			
subjects affected / exposed	5 / 83 (6.02%)	0 / 12 (0.00%)	
occurrences (all)	6	0	
Tonsillitis			
subjects affected / exposed	5 / 83 (6.02%)	0 / 12 (0.00%)	
occurrences (all)	8	0	
Bronchitis			
subjects affected / exposed	4 / 83 (4.82%)	2 / 12 (16.67%)	
occurrences (all)	8	6	
Upper respiratory tract infection			
subjects affected / exposed	4 / 83 (4.82%)	3 / 12 (25.00%)	
occurrences (all)	6	7	

Ear infection			
subjects affected / exposed	3 / 83 (3.61%)	1 / 12 (8.33%)	
occurrences (all)	3	2	
Rhinitis			
subjects affected / exposed	3 / 83 (3.61%)	2 / 12 (16.67%)	
occurrences (all)	3	2	
Viral infection			
subjects affected / exposed	2 / 83 (2.41%)	1 / 12 (8.33%)	
occurrences (all)	2	2	
Pharyngitis streptococcal			
subjects affected / exposed	0 / 83 (0.00%)	2 / 12 (16.67%)	
occurrences (all)	0	3	
Hand-foot-and-mouth disease			
subjects affected / exposed	0 / 83 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	2	
Otitis media			
subjects affected / exposed	0 / 83 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	2	
Croup infectious			
subjects affected / exposed	0 / 83 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Eye infection			
subjects affected / exposed	0 / 83 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Eyelid boil			
subjects affected / exposed	0 / 83 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Gastrointestinal infection			
subjects affected / exposed	0 / 83 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Otitis media chronic			
subjects affected / exposed	0 / 83 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Otitis media viral			
subjects affected / exposed	0 / 83 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	

Paronychia			
subjects affected / exposed	0 / 83 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Respiratory syncytial virus infection			
subjects affected / exposed	0 / 83 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Respiratory tract infection viral			
subjects affected / exposed	0 / 83 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Streptococcal infection			
subjects affected / exposed	0 / 83 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Urinary tract infection			
subjects affected / exposed	0 / 83 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Wound infection			
subjects affected / exposed	0 / 83 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 83 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 September 2013	1. Addition of a third group of subjects (Arm 3) to the study design. Arm 3 comprises subjects who have not previously completed a CSL-sponsored rIX-FP lead-in study and who are scheduled to have a major non-emergency surgery within 8 weeks from the start of the initial pharmacokinetic rIX-FP (100 IU/kg) evaluation period. 2. Change in the sample size from 85 to 95. 3. Clarification that the exploratory objective relating to quality of life is limited to subjects from the CSL654_3002 lead-in study. 4. Minor corrections and clarifications, including word modifications and administrative changes.
03 June 2014	- Per agreement with The Paediatric Committee (PDCO) /European Medicines Agency, study in previously untreated patients (PUPs) is added into this study. 1. To add PUPs with severe hemophilia B (FIX activity ≤2%) who have never been treated with FIX clotting factor products (except previous exposure to blood components) as study Arm 4. 2. Change in the sample size from 95 to 115, to include at least 20 PUPs. 3. Independent Data Monitoring Committee is being utilized to provide an independent evaluation of the study.
14 October 2015	Addition of substudy to assess the pharmacokinetics and safety following subcutaneous administration of rIX-FP in hemophilia B subjects. This substudy will comprise subjects who are currently enrolled in the main study protocol CSL654_3003.
02 December 2016	1. Main study: Addition of the ABR for total treated bleeding episodes to the comparisons between prophylaxis regimens for subjects from Study CSL654_3001. Addition of multiple testing procedure to control the overall Type I error rate for ABR and spontaneous annual bleeding rate (AsBR) comparisons between prophylaxis regimens. 2. Main study: Update of overall study duration and study participation of Arms 1, 2 and 3 subjects to approximately 5 years, and addition of visits beyond 36 months. 3. Main study and subcutaneous (SC) substudy: Addition of final analyses of the a) previously treated patient (PTP) data when all PTPs have completed the study and b) SC substudy data when all subjects have completed the SC substudy. 4. Main study: Minor corrections and clarifications, including word modifications and administrative changes throughout the document. 5. SC substudy: Change in SC dosing in Cohort 3 from single to repeated SC dosing (including home treatment). 6. SC substudy: Addition of optional Cohort 4 for repeated SC dosing that will be opened if additional data are needed to inform further clinical development. 7. SC substudy: Addition of details regarding local tolerability assessments. 8. SC substudy: Addition of SC substudy information to the main study protocol where relevant (eg, objectives and endpoints).
03 February 2020	1. Adjustment of number of PUPs from “at least 20” to “at least 13” to reflect PDCO opinion to allow early termination of PUP enrolment. 2. As study has been completed for PTPs, adjustment of number of PTPs in final PTP analysis (N=83). 3. Adjustment of overall number of subjects to reflect 1 and 2. 4. The frequency of the CSL Safety Management Team meetings has been updated from approximately every 6 months to approximately every 3 months, to reflect an internal process change.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported