EU Clinical Trials Register

Clinical trial results:
A Phase III Study on the Safety, Pharmacokinetics, and Efficacy of Coagulation Factor VIIa (Recombinant) in Congenital Hemophilia A or B Pediatric Patients from birth to <12 years old with Inhibitors to Factor VIII or IX: PerSept 2

Summary

EudraCT number	2015-000958-38
Trial protocol	CZ BG IT
Global end of trial date	30 August 2017

Results information

Result version number	v1 (current)
This version publication date	12 February 2021
First version publication date	12 February 2021

Trial information

Trial identification

Sponsor protocol code	LFB-FVIIa-007-14

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02448680
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	LFB USA, Inc.
Sponsor organisation address	175 Crossing Boulevard, Framingham, United States, 01702
Public contact	Director US Clinical Operations, LFB USA, Inc., 1 5083705166,
Scientific contact	Director US Clinical Operations, LFB USA, Inc., 1 5083705166,

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001203-PIP02-14
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	29 September 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 August 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of the study is to assess the safety, efficacy and pharmacokinetics of 2 separate dose regimens (75 µg/kg and 225 µg/kg) of Coagulation Factor VIIa (Recombinant) for the treatment of bleeding episodes in hemophilia A or B patients with inhibitors to Factor VIII or IX in 13 patients (birth to <6 years old), and 12 patients (≥6 years old to <12 years old).

Protection of trial subjects:

This study was conducted in compliance with good clinical practice (GCP) as described in the International Conference on Harmonisation (ICH) document "Guidance for Industry-E6 Good Clinical Practice: Consolidated Guidance" dated April 1996 and its addendum dated November 2016. These practices were consistent with the principles stated in the Declaration of Helsinki (October 2013 revised version). All other applicable regulations were followed.

Background therapy: -

Evidence for comparator:

This is not an active or placebo-controlled study, as a control arm is not feasible and not ethical.

Actual start date of recruitment	07 December 2015
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	Czech Republic: 1
Country: Number of subjects enrolled	Georgia: 2
Country: Number of subjects enrolled	Mexico: 3
Country: Number of subjects enrolled	South Africa: 6
Country: Number of subjects enrolled	United States: 1
Country: Number of subjects enrolled	Ukraine: 12
Worldwide total number of subjects	25
EEA total number of subjects	1

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)	5
Children (2-11 years)	20
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:

Enrollment was conducted at a total of 10 sites in 7 countries (USA, Czech Republic, Turkey, Ukraine, South Africa, Mexico and Georgia). Ten sites screened subjects and of these, 8 sites randomized a total of 25 subjects.

Pre-assignment

Screening details:

31 Subjects were screened. 25 Subjects were enrolled. Screen failure reasons included: Consent Withdrawal (1), Patient ineligible (3), Other (2)

Period 1

Period 1 title	Active Treatment Period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

No comparator

Arms

Are arms mutually exclusive?	No
Arm title	FVIIa: 75 µg/kg First, Then 225 µg/kg

Arm description:

 Coagulation Factor VIIa (Recombinant) : First Intervention (3 months), Second Intervention (3 months), repeat sequence for entirety of study.

A cross over design to assess the efficacy of 2 separate dose regimens (75 µg/kg and 225 µg/kg) of Coagulation Factor VIIa (Recombinant) for the treatment of bleeding episodes in hemophilia A or B patients with inhibitors to Factor VIII or Factor IX.

Arm type	Experimental
Investigational medicinal product name	Coagulation Factor VIIa (recombinant)
Investigational medicinal product code	LR769
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Two-minute IV push of 75 µg/kg every 3 hours as needed for mild/moderate bleeding episodes. Up to eight administrations within a 24 hour period. Two-minute IV push of 75 µg/kg every 2 hours as needed for severe bleeding episodes.

Arm title	FVIIa: 225 µg/kg First, Then 75 µg/kg

Arm description:

Coagulation Factor VIIa (Recombinant) : First Intervention (3 months), Second Intervention (3 months), repeat sequence for entirety of study.

A cross over design to assess the efficacy of 2 separate dose regimens (75 µg/kg and 225 µg/kg) of Coagulation Factor VIIa (Recombinant) for the treatment of bleeding episodes in hemophilia A or B patients with inhibitors to Factor VIII or Factor IX.

Arm type	Experimental
Investigational medicinal product name	Coagulation Factor VIIa (recombinant)
Investigational medicinal product code	LR769
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Two-minute IV push of 225 µg/kg for mild/moderate bleeding episodes, followed 9 hours later with a two minute IV infusion of 75 µg/kg of LR769 every 3 hours if needed. Up to 6 administrations within a 24 hour period. Two-minute IV push of 225 µg/kg for severe bleeding episodes. This first dose may have been followed 6 hours later with a two-minute IV infusion of 75 µg/kg of LR769. This may have been repeated, if needed, every two hours until improvement of the bleeding episode was observed.

Number of subjects in period 1	FVIIa: 75 µg/kg First, Then 225 µg/kg	FVIIa: 225 µg/kg First, Then 75 µg/kg
Started	12	13
Completed	11	10
Not completed	1	3
Physician decision	1	1
Consent withdrawn by subject	-	2

Baseline characteristics

Reporting groups

Reporting group title	FVIIa: 75 µg/kg First, Then 225 µg/kg

Reporting group description:

Coagulation Factor VIIa (Recombinant) : First Intervention (3 months), Second Intervention (3 months), repeat sequence for entirety of study.

A cross over design to assess the efficacy of 2 separate dose regimens (75 µg/kg and 225 µg/kg) of Coagulation Factor VIIa (Recombinant) for the treatment of bleeding episodes in hemophilia A or B patients with inhibitors to Factor VIII or Factor IX.

Reporting group title	FVIIa: 225 µg/kg First, Then 75 µg/kg

Reporting group description:

Coagulation Factor VIIa (Recombinant) : First Intervention (3 months), Second Intervention (3 months), repeat sequence for entirety of study.

A cross over design to assess the efficacy of 2 separate dose regimens (75 µg/kg and 225 µg/kg) of Coagulation Factor VIIa (Recombinant) for the treatment of bleeding episodes in hemophilia A or B patients with inhibitors to Factor VIII or Factor IX.

Reporting group values	FVIIa: 75 µg/kg First, Then 225 µg/kg	FVIIa: 225 µg/kg First, Then 75 µg/kg	Total
Number of subjects	12	13	25
Age categorical			
Units: Subjects			
Birth to < 6 years old	6	7	13
>= 6 years to < 12 years old	6	6	12
Age continuous			
Units: years			
arithmetic mean	4.9	4.8	
standard deviation	± 3.02	± 3.63	-
Gender categorical			
Units: Subjects			
Female	0	0	0
Male	12	13	25
Race (MIH/OMB)			
Units: Subjects			
Black or African American	4	3	7
White	8	10	18
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	1	2	3
Not hispanic or latino	11	11	22
Weight			
Units: Kg			
arithmetic mean	19.73	21.94	
standard deviation	± 7.432	± 13.391	-
Height			
Units: cm			
arithmetic mean	104.21	108.60	
standard deviation	± 21.210	± 25.904	-

Body Mass Index (BMI) Units: Kg/m2			
arithmetic mean	17.74	17.35	
standard deviation	± 2.505	± 3.842	-

End points

End points reporting groups

Reporting group title	FVIIa: 75 µg/kg First, Then 225 µg/kg

Reporting group description:

 Coagulation Factor VIIa (Recombinant) : First Intervention (3 months), Second Intervention (3 months), repeat sequence for entirety of study.

A cross over design to assess the efficacy of 2 separate dose regimens (75 µg/kg and 225 µg/kg) of Coagulation Factor VIIa (Recombinant) for the treatment of bleeding episodes in hemophilia A or B patients with inhibitors to Factor VIII or Factor IX.

Reporting group title	FVIIa: 225 µg/kg First, Then 75 µg/kg

Reporting group description:

Coagulation Factor VIIa (Recombinant) : First Intervention (3 months), Second Intervention (3 months), repeat sequence for entirety of study.

A cross over design to assess the efficacy of 2 separate dose regimens (75 µg/kg and 225 µg/kg) of Coagulation Factor VIIa (Recombinant) for the treatment of bleeding episodes in hemophilia A or B patients with inhibitors to Factor VIII or Factor IX.

Subject analysis set title	Coagulation Factor VIIa (Recombinant): 75 µg/kg
Subject analysis set type	Full analysis

Subject analysis set description:

Coagulation Factor VIIa (Recombinant): 75 µg/kg Treatment Regimen at Time of Mild/Moderate Bleeding Episode followed if needed subsequent doses of 75 µg/kg. (75 µg/kg treatment regimen for 3 months) . A cross over design to assess the efficacy of 2 separate dose regimens (75 µg/kg and 225 µg/kg) of Coagulation Factor VIIa (Recombinant) for the treatment of bleeding episodes in hemophilia A or B patients with inhibitors to Factor VIII or Factor IX. This is the Treated Population.

Subject analysis set title	Coagulation Factor VIIa (Recombinant): 225 µg/kg
Subject analysis set type	Full analysis

Subject analysis set description:

Coagulation Factor VIIa (Recombinant): 225 µg/kg Treatment Regimen at Time of Mild/Moderate/Severe Bleeding Episode followed if needed subsequent doses of 75 µg/kg. (225 µg/kg treatment regimen for 3 months) .
A cross over design to assess the efficacy of 2 separate dose regimens (75 µg/kg and 225 µg/kg) of Coagulation Factor VIIa (Recombinant) for the treatment of bleeding episodes in hemophilia A or B patients with inhibitors to Factor VIII or Factor IX. This is Treated Population.

Primary: Proportion of Successfully Treated Mild/Moderate Bleeding Per FDA Requirement

End point title	Proportion of Successfully Treated Mild/Moderate Bleeding Per FDA Requirement

End point description:

For the primary efficacy endpoint, successful treatment of mild/moderate bleeding episode was defined as meeting all of the following:
• "Good" or "excellent" response noted by the patient/parent/legal guardian or other caregiver, depending on patient's age and maturity
• Study drug treatment: No further treatment with LR769 beyond timepoint where a "good" or "excellent" response for this bleeding episode was noted.
• No other hemostatic treatment needed for this bleeding episode
• No administration of blood products that would indicate continuation of bleeding beyond timepoint where a "good" or "excellent" response for this bleeding episode was noted
• No increase of pain beyond timepoint where a "good" or "excellent" where a "good" or "excellent" response for this bleeding episode was noted that could not be explained other than as continuation of bleeding

End point type	Primary

End point timeframe:

12 hours after first administration of study drug

End point values	Coagulation Factor VIIa (Recombinant) : 75 µg/kg	Coagulation Factor VIIa (Recombinant) : 225 µg/kg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	23[1]	23[2]		
Units: Proportion of successfully treated BEs				
number (confidence interval 95%)	0.654 (0.523 to 0.785)	0.603 (0.482 to 0.723)		

Notes:

[1] - 239 bleeding episodes analyzed

[2] - 307 Bleeding episodes analyzed

Statistical analyses

Statistical analysis title	Comparing prop with an OPC of 0.55 in 75 µg/kg

Statistical analysis description:

In 75 µg/kg regimen, the null hypothesis (H0) that the true proportion of success (p) ≤0.55 versus Ha that p >0.55 was tested using a 1-sided, 1-sample, normal approximation test and a test statistic obtained by dividing (estimate of p - 0.55) by its estimated SD, taking into account the correlation between BEs for a given patient. The test was conducted at the 0.0125 level (adjusted from 0.025 to 0.0125 to account for multiplicity of testing).
OPC = Objective performance criterion

Comparison groups	Coagulation Factor VIIa (Recombinant): 75 µg/kg v Coagulation Factor VIIa (Recombinant): 225 µg/kg
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	= 0.06
Method	1-sided, 1-sample, normal approximation

Notes:

[3] - The null hypothesis, i.e., comparing the proportion of success with a pre-specified OPC of 0.55, was tested within 75 µg/kg treatment regimen (239 bleeding episodes reported by 23 patients). The results reported (p-value and 95% confidence interval) are not comparing the 2 treatment regimens (i. e., 75 µg/kg and 225 µg/kg regimens).

Statistical analysis title	Comparing prop with an OPC of 0.55 in 225 µg/kg

Statistical analysis description:

In 225 µg/kg regimen, the null hypothesis (H0) that the true proportion of success (p) ≤0.55 versus Ha that p >0.55 was tested using a 1-sided, 1-sample, normal approximation test and a test statistic obtained by dividing (estimate of p - 0.55) by its estimated SD, taking into account the correlation between BEs for a given patient. The test was conducted at the 0.0125 level (adjusted from 0.025 to 0.0125 to account for multiplicity of testing).
OPC = Objective performance criterion

Comparison groups	Coagulation Factor VIIa (Recombinant): 225 µg/kg v Coagulation Factor VIIa (Recombinant): 75 µg/kg

Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	other[4]
P-value	= 0.196
Method	1-sided, 1-sample, normal approximation

Notes:

[4] - The null hypothesis, i.e.,comparing the proportion of success with a pre-specified OPC of 0.55, was tested within 225 µg/kg treatment regimen (307 bleeding episodes reported by 23 patients). The results reported (p-value and 95% confidence interval) are not comparing the 2 treatment regimens (i. e., 75 µg/kg and 225 µg/kg regimens).

Primary: Proportion of Successfully Treated Bleeding Episodes (Mild/Moderate/Severe) Per EMA Definition

End point title	Proportion of Successfully Treated Bleeding Episodes (Mild/Moderate/Severe) Per EMA Definition

End point description:

• "Good" or "excellent" response noted by the patient/caregiver for mild/moderate bleeding episodes,
• "Good" or "excellent" response noted by the physician for severe bleeding episodes.

End point type	Primary

End point timeframe:

12 hours after first administration of study drug

End point values	Coagulation Factor VIIa (Recombinant) : 75 µg/kg	Coagulation Factor VIIa (Recombinant) : 225 µg/kg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	23[5]	24[6]		
Units: Proportion success of BEs				
number (confidence interval 95%)	0.667 (0.533 to 0.800)	0.625 (0.500 to 0.750)		

Notes:

[5] - 239 bleeding episodes analyzed

[6] - 310 Bleeding episodes analyzed

Statistical analyses

Statistical analysis title	Comparing prop with an OPC of 0.55 in 75 µg/kg

Statistical analysis description:

In 75 µg/kg regimen, the null hypothesis (H0) that the true proportion of success (p) ≤0.55 versus Ha that p >0.55 was tested using a 1-sided, 1-sample, normal approximation test and a test statistic obtained by dividing (estimate of p - 0.55) by its estimated SD, taking into account the correlation between BEs for a given patient. The test was conducted at the 0.0125 level (adjusted from 0.025 to 0.0125 to account for multiplicity of testing).
OPC = Objective performance criterion

Comparison groups	Coagulation Factor VIIa (Recombinant): 75 µg/kg v Coagulation Factor VIIa (Recombinant): 225 µg/kg

Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	other[7]
P-value	= 0.043
Method	1-sided, 1-sample, normal approximation

Notes:

[7] - The null hypothesis, i.e., comparing the proportion of success with a pre-specified OPC of 0.55, was tested within 75 μg/kg treatment regimen (239 bleeding episodes reported by 23 patients). The results reported (p-value and 95% confidence interval) are not comparing the 2 treatment regimens (i. e., 75 μg/kg and 225 μg/kg regimens).

Statistical analysis title	Comparing prop with an OPC of 0.55 in 225 μg/kg

Statistical analysis description:

In 225 μg/kg regimen, the null hypothesis (H0) that the true proportion of success (p) ≤0.55 versus Ha that p >0.55 was tested using a 1-sided, 1-sample, normal approximation test and a test statistic obtained by dividing (estimate of p - 0.55) by its estimated SD, taking into account the correlation between BEs for a given patient. The test was conducted at the 0.0125 level (adjusted from 0.025 to 0.0125 to account for multiplicity of testing).
OPC = Objective performance criterion

Comparison groups	Coagulation Factor VIIa (Recombinant): 225 μg/kg v Coagulation Factor VIIa (Recombinant): 75 μg/kg
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	other[8]
P-value	= 0.12
Method	1-sided, 1-sample, normal approximation

Notes:

[8] - The null hypothesis, i.e.,comparing the proportion of success with a pre-specified OPC of 0.55, was tested within 225 μg/kg treatment regimen (310 bleeding episodes reported by 24 patients). The results reported (p-value and 95% confidence interval) are not comparing the 2 treatment regimens (i. e., 75 μg/kg and 225 μg/kg regimens).

Secondary: FDA Definition - Patient-Reported "Good" or "Excellent" Response for Mild/Moderate Bleeding Episodes

End point title	FDA Definition - Patient-Reported "Good" or "Excellent" Response for Mild/Moderate Bleeding Episodes

End point description:

Based on Patient-Reported "Good" or "Excellent" responses as per the below descriptions:
Good: Symptoms of bleed (e.g., swelling, tenderness, and decreased range of motion in the case of musculoskeletal
hemorrhage) had largely been reduced by the treatment, but had not completely disappeared. Symptoms had improved
enough to not require more infusions of the study drug.
Excellent: Full relief of pain and cessation of objective signs of bleed (e.g., swelling, tenderness, and decreased range
of motion in the case of musculoskeletal hemorrhage). No additional infusion of study drug was required.

Statistical analysis : The observed proportion of successfully treated mild/moderate bleeding episodes and the 95% confidence intervals for the true proportion are provided.

End point type	Secondary

End point timeframe:

12 hours after first administration of study drug

End point values	Coagulation Factor VIIa (Recombinant) : 75 μg/kg	Coagulation Factor VIIa (Recombinant) : 225 μg/kg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	23[9]	23[10]		
Units: proportion success of BEs				
number (confidence interval 95%)	0.667 (0.533 to 0.800)	0.629 (0.502 to 0.756)		

Notes:

[9] - 239 Bleeding episodes analyzed

[10] - 307 Bleeding episodes analyzed

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Patient Assessment of a "Good" or "Excellent" Response for Mild/Moderate Bleeding Episodes

End point title	Time to Patient Assessment of a "Good" or "Excellent" Response for Mild/Moderate Bleeding Episodes

End point description:

Categories of Response to Treatment are Described as Follows:
None: No noticeable effect of the treatment on the bleed or worsening of patient's condition. Continuation of treatment
with the study drug was needed.
Moderate: Some effect of the treatment on the bleed was noticed, e.g., pain decreased or bleeding signs improved, but
bleed continued and required continued treatment with the study drug.
Good: Symptoms of bleed (e.g., swelling, tenderness, and decreased range of motion in the case of musculoskeletal
haemorrhage) had largely been reduced by the treatment, but had not completely disappeared. Symptoms had
improved enough to not require more infusions of the study drug.
Excellent: Full relief of pain and cessation of objective signs of bleed (e.g., swelling, tenderness, and decreased range
of motion in the case of musculoskeletal haemorrhage). No additional infusion of study drug was required.

End point type	Secondary

End point timeframe:

Within 24 hours of Bleeding Episode

End point values	Coagulation Factor VIIa (Recombinant) : 75 μg/kg	Coagulation Factor VIIa (Recombinant) : 225 μg/kg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	23[11]	23[12]		
Units: hours				
median (confidence interval 95%)	9.00 (8.92 to 11.83)	12.00 (11.83 to 12.00)		

Notes:

[11] - 233 Bleeding episodes analyzed

[12] - 299 Bleeding episodes analyzed

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Administrations of Study Drug Per Mild/Moderate Bleeding Episode

End point title	Number of Administrations of Study Drug Per Mild/Moderate Bleeding Episode
End point description:	
The number of study drug administrations with non-missing dose information in order to treat one mild/moderate bleeding episode.	
End point type	Secondary
End point timeframe:	
Within 24 hours of Bleeding Episode	

End point values	Coagulation Factor VIIa (Recombinant) : 75 µg/kg	Coagulation Factor VIIa (Recombinant) : 225 µg/kg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	23[13]	23[14]		
Units: Number of Administrations of Study Drug				
arithmetic mean (standard deviation)	3.6 (± 2.27)	2.6 (± 2.48)		

Notes:

[13] - 239 Bleeding episodes analyzed

[14] - 307 Bleeding episodes analyzed

Statistical analyses

No statistical analyses for this end point

Secondary: Total Amount of Study Drug Administered Per Mild/Moderate Bleeding Episode

End point title	Total Amount of Study Drug Administered Per Mild/Moderate Bleeding Episode
End point description:	
The total amount of study drug administered in order to treat one mild/moderate bleeding episode.	
End point type	Secondary
End point timeframe:	
Within 24 hours of Bleeding Episode	

End point values	Coagulation Factor VIIa (Recombinant) : 75 µg/kg	Coagulation Factor VIIa (Recombinant) : 225 µg/kg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	23[15]	23[16]		
Units: mL per bleeding episode				
arithmetic mean (standard deviation)	6.733 (± 6.3693)	8.287 (± 5.6531)		

Notes:

[15] - 239 Bleeding episodes analyzed

[16] - 307 Bleeding episodes analyzed

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Mild/Moderate Bleeding Episodes With Successful Pain Relief

End point title	Mild/Moderate Bleeding Episodes With Successful Pain Relief

End point description:

Successful pain relief was defined as a Visual Analogue Scale (VAS: 0-100; 0 : no pain at all; 100 : the worst pain ever possible) pain score at 12 hours after initial study drug administration that was less than the pain score at the start of treatment with study drug.

End point type	Other pre-specified

End point timeframe:

12 hour after first administration of study drug

End point values	Coagulation Factor VIIa (Recombinant) : 75 µg/kg	Coagulation Factor VIIa (Recombinant) : 225 µg/kg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	23[17]	23[18]		
Units: Bleeding Episodes (BEs)	220	275		

Notes:

[17] - 239 Bleeding episodes analyzed

[18] - 307 Bleeding episodes analyzed

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From signing of the informed consent/assent until resolution or 30 days after the last dose of LR769 or early termination, whichever came first. The average duration for monitoring adverse event is about 11.2 months per patient.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.1

Reporting groups

Reporting group title	Coagulation Factor VIIa (recombinant): 75 µg/kg

Reporting group description:

75 µg/kg treatment regimen for 3 months
Coagulation FVIIa (Recombinant): A cross over design to assess the efficacy of 2 separate dose regimens (75 µg/kg and 225 µg/kg) of Coagulation Factor VIIa (Recombinant) for the treatment of bleeding episodes in hemophilia A or B patients with inhibitors to Factor VIII or Factor IX.

Reporting group title	Coagulation Factor VIIa (recombinant): 225 µg/kg

Reporting group description:

225 µg/kg treatment regimen for 3 months
Coagulation FVIIa (Recombinant): A cross over design to assess the efficacy of 2 separate dose regimens (75 µg/kg and 225 µg/kg) of Coagulation Factor VIIa (Recombinant) for the treatment of bleeding episodes in hemophilia A or B patients with inhibitors to Factor VIII or Factor IX.

Serious adverse events	Coagulation Factor VIIa (recombinant): 75 µg/kg	Coagulation Factor VIIa (recombinant): 225 µg/kg	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 23 (0.00%)	2 / 25 (8.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Nervous system disorders			
Paresis	Additional description: The patient was diagnosed with paresis that was classified as an SAE and resolved. The investigator considered the SAE not related to study drug.		
subjects affected / exposed	0 / 23 (0.00%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Dysentery	Additional description: The patient was diagnosed with dysentery that was classified as an SAE and resolved. The investigator considered the SAE not related to study drug.		
subjects affected / exposed	0 / 23 (0.00%)	1 / 25 (4.00%)	
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	Coagulation Factor VIIa (recombinant): 75 µg/kg	Coagulation Factor VIIa (recombinant): 225 µg/kg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 23 (52.17%)	15 / 25 (60.00%)	
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	2 / 23 (8.70%)	0 / 25 (0.00%)	
occurrences (all)	2	0	
Gastrointestinal disorders			
Diarrhea			
subjects affected / exposed	1 / 23 (4.35%)	3 / 25 (12.00%)	
occurrences (all)	1	3	
Vomiting			
subjects affected / exposed	1 / 23 (4.35%)	2 / 25 (8.00%)	
occurrences (all)	1	2	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 23 (13.04%)	3 / 25 (12.00%)	
occurrences (all)	4	4	
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 23 (4.35%)	3 / 25 (12.00%)	
occurrences (all)	1	4	
Nasopharyngitis			
subjects affected / exposed	4 / 23 (17.39%)	3 / 25 (12.00%)	
occurrences (all)	6	3	
Respiratory Tract Infection Viral			
subjects affected / exposed	1 / 23 (4.35%)	2 / 25 (8.00%)	
occurrences (all)	2	3	
Rhinitis			
subjects affected / exposed	3 / 23 (13.04%)	3 / 25 (12.00%)	
occurrences (all)	3	3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 August 2015	This amendment included the following key changes: -Timing around treatment for severe bleeding episode was added. -Clarifying statement regarding enrollment of patients <12 years old following DMC review of PK, safety and efficacy data. -Table of Total Amount of Blood Taken during the study added to ensure awareness of the maximum allowable blood volume collection in pediatric patients. -Added exclusion criterion #10: hypersensitivity to the active substance or excipients. - Added information regarding required reporting periods for SAEs. - Added weight and dose adjustment at each 6 week visit due to pediatric patient weight fluctuation. -Added signs and symptoms of thromboembolic events as an additional safety precaution unrelated to any safety concern. -Several minor corrections were also made. This amendment was not implemented.
26 August 2015	This amendment included the following key changes: -Timing around treatment for severe bleeding episode was added. -Clarifying statement regarding enrollment of patients <12 years old following DMC review of PK, safety and efficacy data. -Table of Total Amount of Blood Taken during the study added to ensure awareness of the maximum allowable blood volume collection in pediatric patients. -Added exclusion criterion #10: hypersensitivity to the active substance or excipients. - Added information regarding required reporting periods for SAEs. - Added weight and dose adjustment at each 6 week visit due to pediatric patient weight fluctuation. -Added signs and symptoms of thromboembolic events as an additional safety precaution unrelated to any safety concern. -For completeness, "ethnicity" was added to demographics . -Several minor corrections were also made.
09 October 2015	This amendment includes the following key changes: -The LR769 surgical study (LFB-FVIIa-008-14) could only include patients younger than 12 years of age if sufficient PK, efficacy and safety data becomes available and after the DMC has reviewed these data and determined the appropriateness of including this population. This information was included for clarification that patients <12 years old would not be enrolled into the surgical study from this pediatric study until review of PK, safety and efficacy data was reviewed by the DMC.
29 June 2016	This amendment includes the following key changes: -Patient population changed from"≥ 6 months old to <12 years old" to "birth to <12 years old" at the request of regulatory agency.-A number of minor edits were made for clarification. -Slight modifications regarding PK analysis to facilitate investigators' review include details on the way population PK analysis will be performed as described in the PKAP. -Added wording to reflect a single primary efficacy endpoint. -Statement to clarify that patients in a bleeding state would be deferred from the PK part of the study to a later date was added. -Selection and timing of dose for each patient section was updated for clarity. -Statement added, "For subjects < 12 kg, the minimum weight requirement is 10.5 kg ,when blood will be collected by peripheral venipuncture. The investigator must contact the Medical Monitor to discuss enrollment of any subject weighing < 12 kg with an indwelling catheter, Port-a-cath or PICC line". -GEE and GLMM sensitivity analyses were added to align with changes made in the adult study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported