Clinical trial results:
A Phase III Study on the Safety, Pharmacokinetics and Efficacy of Coagulation Factor VIIa (Recombinant) in Congenital Hemophilia A or B Patients with Inhibitors to Factor VIII or IX

Summary

EudraCT number	2013-004779-11
Trial protocol	GB BG RO PL
Global end of trial date	31 July 2015

Results information

Result version number	v1 (current)
This version publication date	29 July 2016
First version publication date	29 July 2016

Trial information

Trial identification

Sponsor protocol code	RB-FVIIa-006-13

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02020369
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	LFB USA, Inc.
Sponsor organisation address	175 Crossing Blvd, Framingham, United States, 01702
Public contact	Jeffry Lawrence, MD, LFB USA, 1 508 370 5113, jeffry.lawrence@lfb-usa.com
Scientific contact	Jeffry Lawrence, MD, LFB USA, 1 508 370 5113, jeffry.lawrence@lfb-usa.com

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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	01 March 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 July 2015
Global end of trial reached?	Yes
Global end of trial date	31 July 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy of 2 separate dose regimens (75 µg/kg and 225 µg/kg) of LR769 for the treatment of bleeding episodes in hemophilia A or B patients with inhibitors to factor VIII or IX.
To assess the safety of LR769. This included the immunogenic potential of the drug product.

Protection of trial subjects:

Safety was assessed by physical examinations, vital signs, electrocardiograms (ECGs), clinical laboratory tests, immunogenicity testing, and assessment of AEs.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	29 April 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	Poland: 1
Country: Number of subjects enrolled	United Kingdom: 1
Country: Number of subjects enrolled	Bulgaria: 2
Country: Number of subjects enrolled	United States: 4
Country: Number of subjects enrolled	Georgia: 2
Country: Number of subjects enrolled	Russian Federation: 5
Country: Number of subjects enrolled	Ukraine: 12
Worldwide total number of subjects	27
EEA total number of subjects	4

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)	0
Children (2-11 years)	0

Adolescents (12-17 years)	5
Adults (18-64 years)	22
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was initiated on 29 April 2014 (first patient, date of first assessment). The study was completed on 31 July 2015 (last patient, last date recorded). 27 patients experienced a total of 468 bleeding episodes (465 mild/moderate and 3 severe bleeding episodes) that were treated with LR769.

Pre-assignment

Screening details:

29 patients were screened and 2 of these patients screen failed.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Coagulation Factor VIIa (Recombinant): 75 µg/kg

Arm description:

Coagulation Factor VIIa (Recombinant): 75 µg/kg for 3 months

Coagulation Factor VIIa (Recombinant): A cross over design to assess the efficacy of 2 separate dose regimens (75µg/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/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:

2-minute IV push of 75 µg/kg every 3 hours as needed for mild/moderate bleeding episodes. Up to 8 administrations within a 24 hour period.
2-minute IV push of 75 µg/kg every 2 hours as needed for Severe bleeding episodes.

Arm title	Coagulation Factor VIIa (Recombinant): 225 µg/kg

Arm description:

Coagulation Factor VIIa (Recombinant) : 225 µg/kg for 3 months

Coagulation Factor VIIa (Recombinant): A cross over design to assess the efficacy of 2 separate dose regimens (75µg/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/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:

2-minute IV push of 225 µg/kg needed for mild/moderate bleeding episodes.
followed 9 hours later with a 2 minute IV infusion of 75 µg/kg of LR769 if needed.
Up to 6 administrations within a 24 hour period.

2-minute IV push of 225 µg/kg for Severe bleeding episodes.

This first dose may have been followed 6 hours later with a 2 minute IV infusion of 75 µg/kg of LR769. This may have been repeated, if needed, every 2 hours until improvement of the bleeding episode was observed.

Number of subjects in period 1	Coagulation Factor VIIa (Recombinant): 75 µg/kg	Coagulation Factor VIIa (Recombinant): 225 µg/kg
Started	13	14
Completed	11	11
Not completed	2	3
Consent withdrawn by subject	1	1
Physician decision	-	1
Patient non-compliant	1	-
patient non compliant	-	1

Baseline characteristics

Reporting groups

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

Reporting group description:

Coagulation Factor VIIa (Recombinant): 75 µg/kg for 3 months

Coagulation Factor VIIa (Recombinant): A cross over design to assess the efficacy of 2 separate dose regimens (75µg/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/IX

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

Reporting group description:

Coagulation Factor VIIa (Recombinant) : 225 µg/kg for 3 months

Coagulation Factor VIIa (Recombinant): A cross over design to assess the efficacy of 2 separate dose regimens (75µg/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/IX

Reporting group values	Coagulation Factor VIIa (Recombinant): 75 µg/kg	Coagulation Factor VIIa (Recombinant): 225 µg/kg	Total
Number of subjects	13	14	27
Age categorical Units: Subjects			
Adolescents (12-17 years)	2	3	5
Adults (18-64 years)	11	11	22
Age continuous Units: years			
median	31	30.5	
full range (min-max)	13 to 51	12 to 54	-
Gender categorical Units: Subjects			
Male	13	14	27

Subject analysis sets

Subject analysis set title	Treated bleeding episodes at 75 µg/kg
Subject analysis set type	Per protocol

Subject analysis set description:

25 patients analysed in this set (dose 75 µg/kg)

Subject analysis set title	Treated bleeding episode at 225 µg/kg
Subject analysis set type	Per protocol

Subject analysis set description:

25 patients analysed in this set (dose 225 µg/kg)

Reporting group values	Treated bleeding episodes at 75 µg/kg	Treated bleeding episode at 225 µg/kg	
Number of subjects	25	25	
Age categorical Units: Subjects			
Adolescents (12-17 years)	5	5	
Adults (18-64 years)	20	20	

Age continuous Units: years median full range (min-max)			
Gender categorical Units: Subjects			
Male	25	25	

End points

End points reporting groups

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

Reporting group description:

Coagulation Factor VIIa (Recombinant): 75 µg/kg for 3 months

Coagulation Factor VIIa (Recombinant): A cross over design to assess the efficacy of 2 separate dose regimens (75µg/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/IX

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

Reporting group description:

Coagulation Factor VIIa (Recombinant) : 225 µg/kg for 3 months

Coagulation Factor VIIa (Recombinant): A cross over design to assess the efficacy of 2 separate dose regimens (75µg/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/IX

Subject analysis set title	Treated bleeding episodes at 75 µg/kg
Subject analysis set type	Per protocol

Subject analysis set description:

25 patients analysed in this set (dose 75 µg/kg)

Subject analysis set title	Treated bleeding episode at 225 µg/kg
Subject analysis set type	Per protocol

Subject analysis set description:

25 patients analysed in this set (dose 225 µg/kg)

Primary: percentage of successfully treated mild/moderate bleeding episodes

End point title	percentage of successfully treated mild/moderate bleeding episodes[1]

End point description:

End point type	Primary

End point timeframe:

The pre-specified primary efficacy endpoint was the proportion of successfully treated mild/moderate bleeding episodes at 12 hours (bleeding episode level) after initial administration of study drug .

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: The primary efficacy analysis was performed based on data-as-observed approach. Descriptive analyse.

End point values	Treated bleeding episodes at 75 µg/kg	Treated bleeding episode at 225 µg/kg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	25[2]	25[3]		
Units: percentage				
success	80	90		
failure	14	6		
missing	6	4		

Notes:

[2] - 252 Treated (Mild/Moderate) Bleeding Episodes at 12 Hours After Initial Administration of Study Drug

[3] - 213 Treated (Mild/Moderate) Bleeding Episodes at 12 Hours After Initial Administration of Study Drug

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: April 29, 2014 through July 31, 2015	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	15.1

Reporting groups	
Reporting group title	Overall patients

Reporting group description: -

Serious adverse events	Overall patients		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 27 (3.70%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Nervous system disorders			
Subarachnoid haemorrhage			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Tonsillitis	Additional description: Acute tonsillitis		
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	Overall patients		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 27 (14.81%)		
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 27 (11.11%)		
occurrences (all)	4		

Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	 3 / 27 (11.11%) 3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 February 2014	Added a 3 week visit to the protocol.
27 March 2014	This amendment included the following key changes: • Upon request of several European countries an immunogenicity sample was added for each 6-week period after the initial 3- and 6-week visits. Several minor corrections were also made. • Correction of a discrepancy in the number of bleeding episodes and number of patients that determined the study duration.
31 July 2014	Amendment contained the following changes to the study: • Investigational product produced at a larger manufacturing scale was introduced. • Changes throughout the protocol related to the addition of a repeat PK analysis with Process B study drug. • Change to procedures at follow-up visits in Phase B to allow some follow-up visits during Phase B to be conducted outside the hospital/hemophilia care center by qualified staff or qualified healthcare professionals.
23 April 2015	Amendment contained the following changes to the protocol: • Change in the medical monitor, his title and contact information. • Deletion of the requirement in the synopsis for 10 severe bleeding episodes to have occurred before the end of the study. The rationale for this change was as follows: -Considering the low incidence of severe bleeding episodes during the study and the absence of any specific regulatory requirement for a certain number of severe bleeding episodes, the text requiring 10 severe bleeding episodes has been deleted. The low incidence of severe bleeding episodes in the patients treated to date reflects the actual incidence of severe bleeding episodes in this population. The company’s intent was to treat a full range of bleeding episodes (from mild to severe), which had been accomplished.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported