Clinical trial results:
A Phase III Open, Multicentre Study to Confirm the Safety, Pharmacokinetics and Efficacy of BPL's High Purity Factor X in the Prophylaxis of Bleeding in Factor X Deficient Children Under the Age of 12 Years

Summary

EudraCT number	2012-003093-98
Trial protocol	GB
Global end of trial date	19 October 2016

Results information

Result version number	v1 (current)
This version publication date	26 April 2017
First version publication date	26 April 2017
Summary attachment (see zip file)	Ten02 Clinical Study Report Synopsis (Ten02 CSR synopsis - (28 March 2017)-.pdf)

Trial information

Trial identification

Sponsor protocol code	Ten02

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01721681
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bio Products Laboratory Ltd
Sponsor organisation address	Dagger Lane , Elstree, United Kingdom, WD6 3BX
Public contact	Head of Clinical Research, Bio Products Laboratory Limited, 44 02089572200, medinfo@bpl.co.uk
Scientific contact	Head of Clinical Research, Bio Products Laboratory Limited, 44 02089572200, medinfo@bpl.co.uk

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000971-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	07 November 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 October 2016
Global end of trial reached?	Yes
Global end of trial date	19 October 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy of FACTOR X in the prevention of bleeding when given as routine prophylaxis over 6 months

Protection of trial subjects:

The option of dosing at home, or at a local clinic was given for routine prophylaxis or short-term preventative treatment. Minor bleeds, which did not require additional treatment were allowed to be treated at home.

For the child's convenience, the option was given for some of the unscheduled blood samples to be collected from the patient's home, or school by a trained nurse or phlebotomist trained in the study procedures, or at a local haemophilia clinic.

Background therapy:

The use of antifibrinolytics (e.g. tranexamic acid) were permitted under the protocol for minimal use only to support treatment of bleeds.

Evidence for comparator: -

Actual start date of recruitment	20 April 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 9
Worldwide total number of subjects	9
EEA total number of subjects	9

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)	9

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:

Subject recruitment was in the United Kingdom only across 3 centres.
The first subject was screened for the study on the 08 April 2015 and enrolled on the 20 April 2015.
The last subject was screened for the study on the 17 February 2016 and enrolled on the 18 March 2016.
The last patient last visit was on the 19 October 2016.

Pre-assignment

Screening details:

There were no screen failures. Baseline Visit took place within 4 weeks of the Screening Visit as per the protocol.
Screening included the following medical assessments; Demography, updated medical history including bleed history and history of exposure to blood products, physical examination including height and weight, vital signs, blood samples

Period 1

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

Arms

Arm title	FACTOR X

Arm description:

There was only one treatment arm. All subjects were administered FACTOR X product.

Arm type	Experimental
Investigational medicinal product name	FACTOR X
Investigational medicinal product code	FACTOR X
Other name	Coagadex
Pharmaceutical forms	Concentrate and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

FACTOR X contains a nominal 100 IU/mL human coagulation factor X when reconstituted in Water for Injections.
The initial dose at the Baseline Visit was a recommended 50 IU/kg of FACTOR X.
The second dose of FACTOR X (40-50 IU/kg recommended, was given 72 hours (± 2 hours) after the Baseline Visit (Day 4).
For children in the 0-5 year age group, at the Investigator's discretion, the second dose of FACTOR X may have been given at 48 hours (± 2 hours) after the Baseline Visit (Day 3), if considered necessary to maintain the minimum trough level.
There was a dose adjustment period of up to 6 weeks, thereafter a dosage regimen of 40-50 IU/kg twice a week was recommended, but was not mandatory. Treatment was to be given no more frequently than every 48 hours.
Recommended doses for bleeding episodes was 25 IU/kg for a minor bleed and 50 IU/kg for a major bleed, repeated as often as required based on the FX:C recovery levels and clinical need.

Number of subjects in period 1	FACTOR X
Started	9
Completed	9

Baseline characteristics

Reporting groups

Reporting group title	Overall Trial

Reporting group description: -

Reporting group values	Overall Trial	Total	
Number of subjects	9	9	
Age categorical			
Subjects fell into 2 age groups, 0-5 years and 6-11 years			
Units: Subjects			
Children 2-11 years	9	9	
Gender categorical Units: Subjects			
Female	5	5	
Male	4	4	
Risk Category At Study Entry			
Descriptive statistics were to be presented on the number and percentage of subjects experiencing major and minor bleeds and episodes of excessive bleeding following injury, by risk category of break-through bleeding. Low risk subjects had all the following criteria: • had been on routine prophylaxis for at least one year immediately prior to study entry. • experienced no more than one minor spontaneous bleeding episode (other than gum bleeds or bruising), requiring clinical assessment during the past year. • experienced no major spontaneous bleeds during the past year			
Units: Subjects			
Risk Category At Study Entry	9	9	
Ethnicity			
Demographic data, including and ethnic origin was to be summarised. All subjects were described as 'not Hispanic or Latino'.			
Units: Subjects			
Ethnicity	9	9	
Factor X Deficiency Diagnosis			
Baseline characteristics, including historical disease data and diagnostic information was summarised as appropriate.			
Units: IU/dL median full range (min-max)	 1.7 1 to 5	 -	
Lowest factor X Result			
Baseline characteristics, including historical disease data and diagnostic information was to be summarised as appropriate.			
Units: IU/dL median full range (min-max)	 1 1 to 4	 -	

Subject analysis sets

Subject analysis set title	Per-Protocol
Subject analysis set type	Per protocol

Subject analysis set description:

All subjects who had completed a minimum of 6 months (26 weeks) treatment and a minimum of 50 exposure days.

Subject analysis set title	Safety/ITT
Subject analysis set type	Safety analysis

Subject analysis set description:

All unique subjects who received at least one dose of study medication. For this analysis the data for the 1st and 2nd treatment cycles for the re-screened subjects were merged as they are the same patient, i.e. 01-001 was merged with data for subject 01-007, and data for subject 01-003 was merged with 01-008.

Subject analysis set title	Safety/ITT treatment cycle
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Included data for all treatment cycles, where the data for the 2 re screened subjects was not be merged, and was presented separately.

Reporting group values	Per-Protocol	Safety/ITT	Safety/ITT treatment cycle
Number of subjects	9	9	9
Age categorical			
Subjects fell into 2 age groups, 0-5 years and 6-11 years			
Units: Subjects			
Children 2-11 years	9	9	9
Gender categorical Units: Subjects			
Female	5	5	6
Male	4	4	5
Risk Category At Study Entry			
Descriptive statistics were to be presented on the number and percentage of subjects experiencing major and minor bleeds and episodes of excessive bleeding following injury, by risk category of break-through bleeding. Low risk subjects had all the following criteria: • had been on routine prophylaxis for at least one year immediately prior to study entry. • experienced no more than one minor spontaneous bleeding episode (other than gum bleeds or bruising), requiring clinical assessment during the past year. • experienced no major spontaneous bleeds during the past year			
Units: Subjects			
Risk Category At Study Entry	9	9	11
Ethnicity			
Demographic data, including and ethnic origin was to be summarised. All subjects were described as 'not Hispanic or Latino'.			
Units: Subjects			
Ethnicity	9	9	11
Factor X Deficiency Diagnosis			
Baseline characteristics, including historical disease data and diagnostic information was summarised as appropriate.			
Units: IU/dL			
median	1.7	1.7	1.7
full range (min-max)	1 to 5	1 to 5	1 to 5
Lowest factor X Result			
Baseline characteristics, including historical disease data and diagnostic information was to be summarised as appropriate.			
Units: IU/dL			
median	1	1	1
full range (min-max)	1 to 4	1 to 4	1 to 4

End points

End points reporting groups

Reporting group title	FACTOR X

Reporting group description:

There was only one treatment arm. All subjects were administered FACTOR X product.

Subject analysis set title	Per-Protocol
Subject analysis set type	Per protocol

Subject analysis set description:

All subjects who had completed a minimum of 6 months (26 weeks) treatment and a minimum of 50 exposure days.

Subject analysis set title	Safety/ITT
Subject analysis set type	Safety analysis

Subject analysis set description:

All unique subjects who received at least one dose of study medication. For this analysis the data for the 1st and 2nd treatment cycles for the re-screened subjects were merged as they are the same patient, i.e. 01-001 was merged with data for subject 01-007, and data for subject 01-003 was merged with 01-008.

Subject analysis set title	Safety/ITT treatment cycle
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Included data for all treatment cycles, where the data for the 2 re screened subjects was not be merged, and was presented separately.

Primary: Primary endpoint is investigator assessment of efficacy of FACTOR X in the prevention of bleeding when given as routine prophylaxis over 6 months.

End point title	Primary endpoint is investigator assessment of efficacy of FACTOR X in the prevention of bleeding when given as routine prophylaxis over 6 months.[1]

End point description:

Primary endpoint is investigator assessment of efficacy of FACTOR X in the prevention of bleeding when given as routine prophylaxis over 6 months.

End point type	Primary

End point timeframe:

6 months.

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 formal hypotheses was tested for this endpoint

End point values	FACTOR X	Per-Protocol		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	9	9		
Units: percentage				
number (not applicable)	9	9		

Statistical analyses

No statistical analyses for this end point

Secondary: Number and Percentage of Children Experiencing Major and Minor Bleeds

End point title	Number and Percentage of Children Experiencing Major and Minor Bleeds

End point description:

Descriptive statistics were presented on the number and percentage of children experiencing major and minor bleeds and episodes of excessive bleeding following injury.

End point type	Secondary

End point timeframe:

6 months.

End point values	FACTOR X	Per-Protocol	Safety/ITT	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	9	9	9	
Units: Percentage				
number (not applicable)	9	9	9	

Statistical analyses

No statistical analyses for this end point

Secondary: factor X Incremental Recovery

End point title	factor X Incremental Recovery

End point description:

FX:C incremental recovery was measured 30 minute post-dose at the Visit 1 (Baseline) and the End of Study Visit based on central laboratory results.

End point type	Secondary

End point timeframe:

6 months.

End point values	FACTOR X	Per-Protocol		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	9	9		
Units: IU/dL/IU/Kg				
median (full range (min-max))	1.72 (1.3 to 2.2)	1.72 (1.3 to 2.2)		

Statistical analyses

Statistical analysis title	Incremental Recovery

Statistical analysis description:

Statistical testing of incremental recovery (IR) between age groups

Comparison groups	FACTOR X v Per-Protocol
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	other[2]
P-value	= 0 [3]
Method	Regression, Linear
Parameter estimate	Median difference (final values)
Point estimate	1.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.6
upper limit	1.88
Variability estimate	Standard deviation

Notes:

[2] - linear regression models

[3] - The null hypothesis was that the age group effect was 0.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From after Informed Consent to the last day in the study. Six months plus 28 days (to include safety follow up assessment).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19

Reporting groups

Reporting group title	FACTOR X

Reporting group description:

There was only one treatment arm. All subjects were administered FACTOR X product.

Serious adverse events	FACTOR X		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 9 (11.11%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Infections and infestations			
Influenza			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lower respiratory tract infection			
subjects affected / exposed	1 / 9 (11.11%)		
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	FACTOR X		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 9 (100.00%)		
Investigations			
Temperature Elevation			

subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1		
Nervous system disorders Headache subjects affected / exposed occurrences (all) Lethargy subjects affected / exposed occurrences (all)	 1 / 9 (11.11%) 1 1 / 9 (11.11%) 1		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	 3 / 9 (33.33%) 3		
General disorders and administration site conditions Pyrexia subjects affected / exposed occurrences (all)	 3 / 9 (33.33%) 6		
Reproductive system and breast disorders Dysmenorrhoea subjects affected / exposed occurrences (all)	 1 / 9 (11.11%) 1		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	 3 / 9 (33.33%) 4		
Skin and subcutaneous tissue disorders Vitiligo subjects affected / exposed occurrences (all)	 1 / 9 (11.11%) 1		
Musculoskeletal and connective tissue disorders Pain in extremity subjects affected / exposed occurrences (all)	 1 / 9 (11.11%) 2		
Infections and infestations Bacterial disease carrier			

subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Influenza			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Lower respiratory tract infection			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	2		
Nasopharyngitis			
subjects affected / exposed	3 / 9 (33.33%)		
occurrences (all)	4		
Rhinitis			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	2		
Viral infection			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	2		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 March 2013	Protocol amendment 1 included the following changes: Removal of references to user kits as they are not to be provided for this study. Site will use their own administration supplies.
24 November 2014	Protocol Amendment 2 included a re-write of the study protocol to reduce the study duration, reduce the number of subjects, and reduce the number of sample collection: Administrative changes to BPL personnel, reduced length of study duration from 12 months to 6 months. Inclusion of the term 'retrospective' to the study to enable collection of retrospective FACTOR X use. Adjustment to study design with respect to blood sampling at the baseline visit as follows; 'sample for inhibitor assessment will be collected and only tested if a later sample is positive for inhibitors. Blood samples for factor x activity analysis will be collected pre-dose and at 30 min (+5 min) post-dose for an incremental recovery assessment'. Reduction of the maximum number of children enrolled from 16 to 12.
22 April 2015	Protocol Amendment 3 included the following changes: Additional detail to be collected in the CRF for surgical procedures as follows; name of surgical procedure and surgical technique whether it is a planned or an emergency surgery indication for surgery surgery start and end dates and times extubation date and time date and time post-operative bleeding stabilised discharge date date of last dose of FACTOR X to treat post-operative bleeding number of swabs and pads used whether there were any unusual features of the surgery or complications which might influence bleeding at the time of surgery or later blood loss compared to a patient without a haemostatic disorder undergoing the same type of surgery (more than, equal to, or less than) whether there was excessive bleeding during surgery relevant laboratory assessments FACTOR X infusions administered Deletion of the following text 'For children who turn 6 years old during the study, an assent form is expected to be completed to confirm the child's continued eligibility for the trial' and instead replaced with 'The child will be provided with written information. If considered appropriate by the investigator, an assent will be obtained using the 8-11 year old Assent Form' and 'For children aged 4-7 years if considered appropriate by the investigator, assent will be obtained using the 4-7 year old Assent Form'. Deletion of the following test relating to additional testing if subjects test positive for Parvovirus 'In addition, children who are negative for Parvovirus B19 IgG and IgM at the Baseline Visit will attend the hospital or a local clinic for an additional blood test 7 days after the Baseline Visit.' Text was deleted as there is no strong scientific rationale or regulatory requirement for children to have this additional test. Text added to clarify when an SAE report needs to be completed in case of a planned surgery e.g. if the underlying condition caused the prolonged hospitalisation.
24 August 2015	Protocol Amendment 4 included the following changes: I. Redefinition of factor X severity II. Clarify reporting of laboratory results as adverse events III. Updated Appendix VIII – Trial Plan Flow Chart IV. Clarification of bleeding assessments V. Administrative changes

13 November 2015	Protocol Amendment 5 included the following changes: Addition to the protocol title to include 'Prophylaxis of Bleeding in'. Additional text regarding re-enrollment of subjects who have completed the study early as follows 'Children may be re-consented and re-enrolled in to the study following case by case evaluation and agreement between the Sponsor and the Co-ordinating Investigator. In such cases, children will be assigned a new patient number and treated as new subjects who must repeat all trial procedures from Screening Visit to End of Study Visit'. Additional wording to the primary objective to include 'reduction' as well as 'prevention' of bleeding. Additional text on laboratory sampling to state that a sample for inhibitor assessment will be collected and only tested if, for example, there is a clinical suspicion of inhibitor development or a later sample is positive for inhibitors.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported