

**Clinical trial results:****A Phase III Open, Multicentre Study to Investigate the Pharmacokinetics, Safety and Efficacy of BPL's High Purity Factor X in the Treatment of Severe and Moderate Factor X Deficiency****Summary**

| | |
|--------------------------|-----------------|
| EudraCT number | 2009-011145-18 |
| Trial protocol | GB ES DE |
| Global end of trial date | 30 October 2013 |

Results information

| | |
|-----------------------------------|---|
| Result version number | v2 (current) |
| This version publication date | 17 July 2016 |
| First version publication date | 17 July 2014 |
| Version creation reason | <ul style="list-style-type: none">• New data added to full data set• Correction of full data set List of non-serious AE's - some SAEs have been listed in here in error, as they are reported in the SAE section they will be removed from here. Spain is listed as ongoing, this is not correct so will be changed to completed. Change of public contact to Head of Medical Affairs. |
| Summary attachment (see zip file) | Final CSR Ten01 (final-clinical-summary-report-ten01.pdf) |

Trial information**Trial identification**

| | |
|-----------------------|-------|
| Sponsor protocol code | TEN01 |
|-----------------------|-------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT00930176 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Bio Products Laboratory Limited |
| Sponsor organisation address | Dagger Lane, Elstree, United Kingdom, |
| Public contact | Head of Medical Affairs, Bio Products Laboratory Limited, +44 0208957 2200, medinfo@bpl.co.uk |
| Scientific contact | Head of Medical Affairs, Bio Products Laboratory Limited, +44 0208957 2200, 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) | EMA-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 | 30 October 2013 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 30 October 2013 |
| Global end of trial reached? | Yes |
| Global end of trial date | 30 October 2013 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To assess the pharmacokinetics of Factor X after a single dose of 25 IU/kg in subjects with severe or moderate FX deficiency

Protection of trial subjects:

The number of blood samples collected for the PK profile is the minimum recommended by the regulatory authorities and the International Society for Thrombosis and Haemostasis (ISTH)

Background therapy: -

Evidence for comparator:

Not applicable

| | |
|---|-------------|
| Actual start date of recruitment | 05 May 2010 |
| 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 | Turkey: 6 |
| Country: Number of subjects enrolled | United States: 2 |
| Country: Number of subjects enrolled | Germany: 1 |
| Country: Number of subjects enrolled | Spain: 4 |
| Country: Number of subjects enrolled | United Kingdom: 3 |
| Worldwide total number of subjects | 16 |
| EEA total number of subjects | 8 |

Notes:

Subjects enrolled per age group

| | |
|--|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 | 0 |

| | |
|--|----|
| wk | |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 6 |
| Adults (18-64 years) | 10 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

17 subjects were screened for the study. One subject was ineligible; 16 subjects were enrolled to the study.

Period 1

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

Arms

| | |
|-----------|------------------|
| Arm title | Active treatment |
|-----------|------------------|

Arm description:

FACTOR X 25 IU/kg to treat a bleed

| | |
|--|---|
| Arm type | Experimental |
| Investigational medicinal product name | FACTOR X |
| Investigational medicinal product code | |
| Other name | Human coagulation factor X |
| Pharmaceutical forms | Powder and solvent for solution for injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

25 IU/kg to treat a bleed and for any preventative use.

Raise plasma FX to 70-90 IU/dL pre-surgery and maintain >50 IU/dL post-surgery until no longer at risk of bleeding due to surgery.

| Number of subjects in period 1 | Active treatment |
|--------------------------------|------------------|
| Started | 16 |
| Completed | 15 |
| Not completed | 1 |
| Adverse event, serious fatal | 1 |

Baseline characteristics

Reporting groups

| | |
|--------------------------------|---------------|
| Reporting group title | Overall Trial |
| Reporting group description: - | |

| Reporting group values | Overall Trial | Total | |
|--|---------------|-------|--|
| Number of subjects | 16 | 16 | |
| Age categorical | | | |
| Age at screening for the study | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 0 | 0 | |
| Children (2-11 years) | 0 | 0 | |
| Adolescents (12-17 years) | 6 | 6 | |
| Adults (18-64 years) | 10 | 10 | |
| From 65-84 years | 0 | 0 | |
| 85 years and over | 0 | 0 | |
| Age continuous | | | |
| Age at study entry | | | |
| Units: years | | | |
| arithmetic mean | 27.1 | | |
| full range (min-max) | 12 to 58 | - | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 10 | 10 | |
| Male | 6 | 6 | |
| FXD severity | | | |
| Severe = plasma FX:C <1 IU/dL Moderate = plasma FX:C 1-<5 IU/dL | | | |
| Units: Subjects | | | |
| Severe | 14 | 14 | |
| Moderate | 2 | 2 | |

End points

End points reporting groups

| | |
|--|------------------|
| Reporting group title | Active treatment |
| Reporting group description: FACTOR X 25 IU/kg to treat a bleed | |

Primary: FX:C Incremental recovery

| | |
|---|--|
| End point title | FX:C Incremental recovery ^[1] |
| End point description: Combined incremental recovery (peak increment within the first hour post-dose) for 31 PK assessments. | |
| End point type | Primary |
| End point timeframe: At Baseline and Repeat PK Assessment | |

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: This was not a statistically powered study

| End point values | Active treatment | | | |
|---|---------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 16 ^[2] | | | |
| Units: IU/dL per IU/kg | | | | |
| geometric mean (geometric coefficient of variation) | 2.07 (\pm 21.01) | | | |

Notes:

[2] - Value given is the mean of 31 results: 16 for Baseline Visit + 15 for Repeat PK assessment

Statistical analyses

No statistical analyses for this end point

Primary: FX:C Half-life

| | |
|--|-------------------------------|
| End point title | FX:C Half-life ^[3] |
| End point description: Half-life of FX:C after bolus dose of 25 IU/kg | |
| End point type | Primary |
| End point timeframe: Baseline Visit and Repeat PK Assessment | |

Notes:

[3] - 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: This was not a statistically powered study

| | | | | |
|---|-------------------|--|--|--|
| End point values | Active treatment | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 16 ^[4] | | | |
| Units: hours | | | | |
| geometric mean (geometric coefficient of variation) | 29.36 (± 22.89) | | | |

Notes:

[4] - Value is the mean of 31 results: 16 for Baseline Visit + 15 for Repeat PK assessment

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Consent to 30 days post-last dose of IMP

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 13.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|------------------|
| Reporting group title | Active treatment |
|-----------------------|------------------|

Reporting group description:

All subjects receiving FACTOR X

| Serious adverse events | Active treatment | | |
|---|------------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 6 / 16 (37.50%) | | |
| number of deaths (all causes) | 1 | | |
| number of deaths resulting from adverse events | 0 | | |
| Injury, poisoning and procedural complications | | | |
| Post procedural haemorrhage | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |
| Syncope | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 2 / 16 (12.50%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Reproductive system and breast disorders | | | |
| Dysmenorrhoea | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 1 / 16 (6.25%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Menorrhagia | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Gastritis | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Muscle haemorrhage | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Pneumonia | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Nosocomial infection | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Tooth abscess | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastric ulcer helicobacter | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | | |
| 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 | Active treatment | | |
|---|-------------------|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 16 / 16 (100.00%) | | |
| Vascular disorders | | | |
| Haematoma | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | | |
| occurrences (all) | 2 | | |
| Hypotension | | | |
| subjects affected / exposed | 4 / 16 (25.00%) | | |
| occurrences (all) | 4 | | |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | | |
| occurrences (all) | 2 | | |
| Infusion site erythema | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | | |
| occurrences (all) | 2 | | |
| Infusion site pain | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | | |
| occurrences (all) | 1 | | |
| Malaise | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | | |
| occurrences (all) | 2 | | |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | | |
| occurrences (all) | 1 | | |
| Oedema peripheral | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | | |
| occurrences (all) | 2 | | |
| Pyrexia | | | |

| | | | |
|---|--|--|--|
| <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Swelling</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Ulcer</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Vessel puncture site haematoma</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>1 / 16 (6.25%)</p> <p>2</p> <p>1 / 16 (6.25%)</p> <p>1</p> <p>2 / 16 (12.50%)</p> <p>2</p> <p>1 / 16 (6.25%)</p> <p>1</p> | | |
| <p>Immune system disorders</p> <p>Urticaria</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>1 / 16 (6.25%)</p> <p>2</p> | | |
| <p>Respiratory, thoracic and mediastinal disorders</p> <p>Cough</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Dyspnoea</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Nasal congestion</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Oropharyngeal pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Tachypnoea</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>1 / 16 (6.25%)</p> <p>1</p> <p>1 / 16 (6.25%)</p> <p>1</p> <p>1 / 16 (6.25%)</p> <p>1</p> <p>1 / 16 (6.25%)</p> <p>1</p> <p>1 / 16 (6.25%)</p> <p>1</p> | | |
| <p>Psychiatric disorders</p> <p>Insomnia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>1 / 16 (6.25%)</p> <p>1</p> | | |
| <p>Injury, poisoning and procedural complications</p> | | | |

| | | | |
|--|-----------------------|--|--|
| Contusion subjects affected / exposed occurrences (all) | 1 / 16 (6.25%) 2 | | |
| Fall subjects affected / exposed occurrences (all) | 1 / 16 (6.25%) 1 | | |
| Head injury subjects affected / exposed occurrences (all) | 1 / 16 (6.25%) 1 | | |
| Joint injury subjects affected / exposed occurrences (all) | 2 / 16 (12.50%) 2 | | |
| Thermal burn subjects affected / exposed occurrences (all) | 1 / 16 (6.25%) 1 | | |
| Nervous system disorders Dizziness subjects affected / exposed occurrences (all) | 1 / 16 (6.25%) 1 | | |
| Headache subjects affected / exposed occurrences (all) | 8 / 16 (50.00%) 14 | | |
| Migraine subjects affected / exposed occurrences (all) | 1 / 16 (6.25%) 2 | | |
| Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) | 2 / 16 (12.50%) 4 | | |
| Iron deficiency anaemia subjects affected / exposed occurrences (all) | 1 / 16 (6.25%) 1 | | |
| Gastrointestinal disorders Abdominal pain upper subjects affected / exposed occurrences (all) | 1 / 16 (6.25%) 1 | | |
| Constipation | | | |

| | | | |
|--|-----------------|--|--|
| subjects affected / exposed | 1 / 16 (6.25%) | | |
| occurrences (all) | 2 | | |
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | | |
| occurrences (all) | 1 | | |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 2 / 16 (12.50%) | | |
| occurrences (all) | 2 | | |
| Gingivitis | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | | |
| occurrences (all) | 1 | | |
| Nausea | | | |
| subjects affected / exposed | 2 / 16 (12.50%) | | |
| occurrences (all) | 6 | | |
| Odynophagia | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | | |
| occurrences (all) | 3 | | |
| Toothache | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | | |
| occurrences (all) | 1 | | |
| Vomiting | | | |
| subjects affected / exposed | 2 / 16 (12.50%) | | |
| occurrences (all) | 2 | | |
| Skin and subcutaneous tissue disorders | | | |
| Acne | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | | |
| occurrences (all) | 2 | | |
| Dermatitis allergic | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | | |
| occurrences (all) | 1 | | |
| Pruritus | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | | |
| occurrences (all) | 1 | | |
| Renal and urinary disorders | | | |
| Nephrolithiasis | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 16 (6.25%) | | |
| occurrences (all) | 1 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 5 / 16 (31.25%) | | |
| occurrences (all) | 14 | | |
| Back pain | | | |
| subjects affected / exposed | 6 / 16 (37.50%) | | |
| occurrences (all) | 10 | | |
| Groin pain | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | | |
| occurrences (all) | 1 | | |
| Joint stiffness | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | | |
| occurrences (all) | 1 | | |
| Muscle spasms | | | |
| subjects affected / exposed | 2 / 16 (12.50%) | | |
| occurrences (all) | 2 | | |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 3 / 16 (18.75%) | | |
| occurrences (all) | 3 | | |
| Musculoskeletal stiffness | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | | |
| occurrences (all) | 1 | | |
| Myalgia | | | |
| subjects affected / exposed | 2 / 16 (12.50%) | | |
| occurrences (all) | 2 | | |
| Neck pain | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | | |
| occurrences (all) | 4 | | |
| Osteoarthritis | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | | |
| occurrences (all) | 1 | | |
| Pain in extremity | | | |

| | | | |
|-----------------------------------|-----------------|--|--|
| subjects affected / exposed | 6 / 16 (37.50%) | | |
| occurrences (all) | 8 | | |
| Infections and infestations | | | |
| Bronchitis | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | | |
| occurrences (all) | 1 | | |
| Cystitis | | | |
| subjects affected / exposed | 2 / 16 (12.50%) | | |
| occurrences (all) | 2 | | |
| Fungal infection | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | | |
| occurrences (all) | 1 | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 7 / 16 (43.75%) | | |
| occurrences (all) | 11 | | |
| Oral infection | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | | |
| occurrences (all) | 1 | | |
| Osteomyelitis | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | | |
| occurrences (all) | 1 | | |
| Otitis media | | | |
| subjects affected / exposed | 2 / 16 (12.50%) | | |
| occurrences (all) | 2 | | |
| Respiratory tract infection | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | | |
| occurrences (all) | 1 | | |
| Tooth infection | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | | |
| occurrences (all) | 1 | | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 4 / 16 (25.00%) | | |
| occurrences (all) | 9 | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | | |
| occurrences (all) | 1 | | |

| | | | |
|------------------------------------|----------------|--|--|
| Metabolism and nutrition disorders | | | |
| Fluid overload | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | | |
| occurrences (all) | 1 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 13 July 2010 | First bleeding episode to be treated under the supervision of a physician. Addition of definition of treatment failure. Update in definition of efficacy criteria. Clarification of the assessments of bleeds to be used in the efficacy evaluation. Addition of success criteria. Addition of the definition of excessive blood loss in surgery. Update in efficacy assessment criteria for menorrhagic bleeds. Change to the washout period before PK assessments. Amendments to selected PK parameters & analyses. |
| 03 November 2010 | Addition of blood sample collections for thrombogenicity marker assays. Change to infusion rate. Change to instructions regarding assessments of bleeds if subject was sleeping at the defined timepoint. Clarification on the efficacy assessment of FACTOR X in treating a bleed if the investigator's and subject's assessments differed. |
| 08 April 2011 | Addition of table listing number of bleeds required to meet the criteria for treatment success. Addition of PK parameter AUC(0-t) Change of CRO. Change in name and status of Sponsor. |
| 15 October 2012 | Change to primary and secondary efficacy endpoints for the surgery component of the protocol. Change to study procedures for subjects undergoing surgery, as a consequence of changes to the primary and secondary endpoints. Update to definitions of efficacy populations. Update to definitions of major and minor surgeries. Updates to data analysis for consistency with updated efficacy endpoints. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported