COAGULATION FACTOR X (HUMAN), FACTOR X

TEN03

A PHASE III OPEN, MULTICENTRE STUDY TO INVESTIGATE THE SAFETY AND EFFICACY OF BPL'S HIGH PURITY FACTOR X IN THE TREATMENT OF FACTOR X DEFICIENT SUBJECTS UNDERGOING SURGERY

FINAL CLINICAL STUDY REPORT

Indication studied:	*Hereditary Factor X deficiency*
Developmental phase of study:	*PHASE III*
First patient enrolled:	*29 Jun 2012*
Last patient visit:	*03 Apr 2013*
Release date of final report:	*07 May 2014*

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This trial was conducted in accordance with the ethical principles of Good Clinical Practice, according to the ICH Harmonised Tripartite Guideline.

2. SYNOPSIS

Name of Sponsor/Company: Bio Products Laboratory Ltd	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product: FACTOR X		
Name of Active Ingredient: Coagulation factor X (human)		

Title of Study:

A Phase III Open, Multicentre Study to Investigate the Safety and Efficacy of BPL's High Purity FACTOR X in the Treatment of Factor X Deficient Subjects Undergoing Surgery

Investigators:

USA: Miguel Escobar, MD (study site 22)
UK: Carolyn Millar, MD, PhD (study site 05)

Study Centres:

Subjects were enrolled at two study sites in two countries:

USA: Study site 22: Gulf States Hemophilia and Thrombophilia Center, University of Texas Health Sciences Center, Houston, Texas, USA

UK: Study site 05: Hammersmith Hospital Haemophilia Centre, Hammersmith Hospital, London, UK

Publications (reference):

None

Studied period (years):	**Phase of development:**
Date first patient enrolled: 29 Jun 2012 Date last patient completed: 03 Apr 2013	III

Objectives:

The objective of this study was to investigate the safety and efficacy of FACTOR X in preventing bleeding and achieving haemostasis in factor X-deficient subjects undergoing surgery.

Methodology:

This was an open, multi-centre, non-randomised prospective study in subjects with mild to severe factor X deficiency (factor X activity [FX:C] <20 IU/dL) to assess the safety and efficacy of FACTOR X in preventing bleeding and achieving haemostasis during planned surgery.

Subjects requiring emergency surgery could take part in the study if they had given written informed consent before the emergency surgery and there was sufficient time to perform all of the mandatory screening and pre-surgery assessments before surgery. Pregnant subjects undergoing obstetric delivery (including Caesarean surgery and vaginal delivery) and who were not considering breastfeeding after the birth of the child could enter the study. Subjects who failed screening could be recruited into the study if they met all the inclusion and exclusion criteria on re-screening. Subjects could also take part in this study more than once (for each surgical procedure they undertook). Subjects had to undergo consent and screening assessments for each planned surgical procedure to be assessed in the study.

Entry into the study was based upon the subject's lowest reliable FX:C recorded in the subject's hospital notes or at the Screening Visit, whichever was lower. This FX:C level was used to assign the subject to one of two groups for an analysis of the effect of the severity of factor X deficiency on the efficacy of FACTOR X.

The screening visit could take place up to 4 weeks before surgery. On Day 1, subjects received a pre-surgery bolus dose of FACTOR X between 1 and 4 hours before the surgical procedure that was designed to raise the FX:C level to 7090 IU/dL. If surgery was delayed longer than 8 to 12 hours, or if local laboratory tests indicated that the required FX:C level was not reached, a repeat dose could be given if appropriate. The half-life of FACTOR X is approximately 30 hours, therefore repeat dosing was considered unlikely to be necessary.

Based on the pre-surgery bolus dose, a recovery assessment was performed at which the FX:C was measured pre-dose and at 30 minutes post-dose. After surgery, subjects remained in the hospital receiving maintenance doses of FACTOR X until they were no longer considered to be at risk of significant bleeding as a result of the surgical procedure.

During the hospital stay, the subject underwent regular safety checks, including assessment of bleeding at the surgical site, vital signs, infusion site assessments and adverse event (AE) checks. The subject's FX:C, prothrombin time (PT) and activated partial thromboplastin time (APTT) were measured at the local laboratory to enable appropriate dosing of FACTOR X. The subject's FX:C, factor X antigen (FX:Ag), PT and APTT were also measured at a central laboratory for efficacy analysis.

When, in the investigator's opinion, the subject was no longer considered to be at risk of significant bleeding from the surgical procedure, an End-of-Treatment Assessment, which included a factor X inhibitor screen and assay, was performed after which the subject could be discharged from hospital (Option A). However, as determined to be appropriate by the investigator, the final few doses of FACTOR X to control bleeding from the surgical procedure could be self-administered by the subject after an early discharge from hospital (Option B). In this case, a subject who had previously been trained in self-administration was supplied with FACTOR X to use at home according to a regimen assigned by the investigator. The subject was also supplied with FACTOR X to treat any spontaneous bleeds not related to the surgical procedure that occurred after early discharge from hospital but before the repeat End-of-Treatment Assessment. Alternatively, a subject who was not trained in self-administration returned to the investigational site for further doses of FACTOR X, or may have had FACTOR X administered at home by a member of the study team. In this case, the subject was to return to the clinic for a repeat End-of-Treatment Assessment as soon as possible after the final dose of FACTOR X (Early Discharge Follow-up visit). If a subject who was discharged early had a bleed at the surgical site or an unmanageable bleed at any location before the Early Discharge Follow up visit, the subject was to return to the investigational site for an unscheduled visit to assess the bleed. An unmanageable bleed was defined as a bleed that unacceptably restricted a subject's day-to-day life such that the subject could not cope with the bleed at home.

Subjects who were discharged early were given a subject diary to complete at home. The subject was to be instructed to record the details of each dose administered if the subject was self-administering FACTOR X, any reactions or AEs experienced, concomitant medications taken and details of any bleeds. The diary was returned to the investigator at the subject's next visit, at which time the investigator was to review the diary and the data were to be transcribed into the subject's case report form. If a subject was unable to complete the diary correctly, for any reason, a member of the study staff was to contact the subject on a weekly basis and record in the subject's diary the data as relayed verbally by the subject. The diary would then be maintained at the investigational site on the subject's behalf. Subject diaries were only required for subjects who were discharged early.

Number of subjects (planned and analyzed):

It was intended that a minimum of five and a maximum of ten subjects would be enrolled in order to achieve a minimum of ten evaluable surgical procedures. However, data collected on surgical procedures from BPL's FACTOR X pharmacokinetic study (Protocol Ten01) may have been combined with the data collected in this BPL Ten03 surgery study to form a consolidated report of surgical experiences. In this case, the number of subjects and procedures required in the Ten03 could be reduced accordingly. Subjects could also take part in this study more than once (for each surgical procedure they undertook).

Two subjects, with two surgical procedures each, took part in this study. Subjects were consented for each separate surgery, therefore the total enrolment overall was four study subjects.

Diagnosis and main criteria for inclusion:

Included subjects were 12 years of age or older, with a diagnosis of hereditary mild to severe factor X deficiency (<20 IU/dL), including previously untreated subjects OR subjects currently treated with fresh frozen plasma (FFP), prothrombin complex concentrate (PCC) or factor IX/X concentrate by prophylaxis or on demand. Subjects were to undergo surgery in which the investigator believed a factor X concentrate was required due to a prior history of unusual bleeding, either spontaneously or after surgery or trauma in the absence of treatment with a factor X-containing product.

Test product, dose and mode of administration, batch number:

Product: FACTOR X, a high-purity, plasma-derived human coagulation factor X concentrate.

Dosage and administration: FACTOR X was administered by intravenous infusion to all eligible subjects as recommended. Subjects were administered a loading dose before the surgical procedure to raise factor X levels to 70-90 IU/dL, and subsequent doses after the surgical procedure were given to maintain the factor X level above 50 IU/dL, until the subject was considered to be no longer at risk of post-operative bleeding.

The dose for each subject was calculated based on the actual factor X content per vial and the subject's weight on the day of surgery, or at the screening visit for emergency cases where weight could not be taken on the day of surgery, and a nominal recovery of 1.5 IU/dL per IU/kg.

Batch numbers: FXSN8788, FXSN8968, FXSN8968B, FXSN8968G.

Duration of treatment:

The duration of treatment for most subjects was anticipated to be 5 to 10 days, including one or more pre-surgery loading doses, followed by maintenance doses. Subjects could receive treatment for a shorter period for minor procedures.

The maximum treatment period was generally expected to be up to 14 days in total. However, if complications occurred, the treatment period could be extended to a maximum of 21 days.

The total duration of subject's participation in the study was a maximum of 10 weeks.

Reference therapy, dose and mode of administration, batch number:

None

Criteria for evaluation:

Efficacy:

Primary Efficacy Endpoint

The primary efficacy endpoint was blood loss during and after surgery; this endpoint was based upon the regulatory advice received.

The primary efficacy variable was assessed using the following parameters:

1. Clinical estimation of volume of blood loss during surgery
2. Requirement for blood transfusion (units of packed red blood cells or units of whole blood)

or infusion of autologous red cells during and after surgery

3. Number and duration of post-operative bleeding episodes
4. Measurements of haemoglobin pre-operatively, post-operatively and at discharge

The variables above were combined into an overall assessment of blood loss during and after surgery relative to blood loss typically expected in a normal patient (i.e. someone without a bleeding disorder) undergoing the same surgical procedure.

Secondary Efficacy Endpoints

The secondary efficacy endpoints were as follows:

1. Assessment of incremental recovery of FX:C and FX:Ag after the pre-surgery bolus infusion
2. Assessment of FX:C and FX:Ag levels on each day post-surgery
3. Assessment of the cumulative weight-adjusted doses of FACTOR X as measured by FX:C (IU/kg body weight) administered to each subject to maintain haemostasis
4. Assessment of the cumulative doses of FACTOR X as measured by FX:C (IU) administered to each subject to maintain haemostasis
5. Amount of weight-adjusted FACTOR X as measured by FX:C (IU/kg body weight) administered daily (day of surgery and each post-operative day) to maintain haemostasis

Safety:

The following safety assessments were used to evaluate the safety of FACTOR X:

- AEs
- Haematology
- Serum biochemistry
- PT and APTT
- Viral serology
- Factor X inhibitor screen and Nijmegen-Bethesda assay
- Vital signs
- Physical examination
- Infusion site observations

The following additional tests may have also been performed:

- Genotype analysis (optional)
- Pregnancy test (for females of childbearing potential)
- APGAR score and neonatal safety assessment (if the subject was in the study for obstetric delivery)

Statistical methods:

Efficacy analyses were performed for the ITT and per-protocol populations. The per-protocol population was analysed for surgical procedures eligible for the primary analysis and surgical procedures eligible for the secondary analysis. The safety analysis was based on the safety population.

Primary Efficacy Analysis:

The primary efficacy endpoint was blood loss during and after surgery. This assessment was made by the investigator at the subject's End-of-Treatment Assessment (after the last dose of FACTOR X). The final assessment was made by the Data Review Committee (DRC) after all other factors which might affect the blood loss had been taken into account.

Efficacy categories (excellent, good, poor, or unassessable) at discharge were summarised descriptively by the type of surgery (major or minor) as decided by the DRC, and overall.

The following variables, contributing to this efficacy endpoint, were also tabulated:

1. Clinical estimation of volume of blood loss during surgery: Expected blood loss in a subject without a bleeding disorder undergoing that procedure, and estimated actual blood loss in the study subject, were summarised by type of surgery (major or minor) as decided by the DRC, and overall. The assessment of blood loss during surgery (blood loss less than expected, blood loss as expected, blood loss more than expected, blood loss excessive) was summarised descriptively by type of surgery (major or minor) as decided by the DRC, and overall.
2. Requirement for blood transfusion (units of packed red blood cells or units of whole blood) or infusion of autologous red cells during and after surgery: The number of units of whole blood, packed red cells, or autologous cells was summarised descriptively by type of surgery (major or minor) as decided by the DRC, and overall.
3. Number and duration of post-operative bleeding episodes: The number and duration of bleeding episodes while the subject was at risk of bleeding during surgery were summarised descriptively by type of surgery (major or minor) as decided by the DRC, and overall. The assessment of FACTOR X in the control of bleeding episodes (excellent, good, poor or unassessable) was summarised descriptively by location, cause, type of surgery (major or minor) as decided by the DRC and overall.
4. Measurements of haemoglobin pre-operatively, post-operatively and at discharge: Changes in haemoglobin (g/dL) from the pre-operative value were summarised by type of surgery (major or minor) as decided by the DRC and overall.

Secondary Efficacy Analysis

The following endpoints were tabulated:

1. Incremental recovery after the pre-surgery intravenous infusion: Total FX:C (IU) and FX:Ag levels administered for the bolus injection(s), normalised for body weight, were to be calculated for each surgical procedure. The factor X increment at 30 minutes post-dose infusion was calculated by subtracting the pre-infusion factor X level from the post-dose value.

   Recovery = factor X increment (IU/dL) ÷ factor X dose (IU/kg)
2. Assessment of FX:C and FX:Ag levels on each day post-surgery: FX:C and FX:Ag levels on each day post-surgery (Day 1, Day 2, etc) were summarised by type of surgery (major or minor) and overall. Factor X values of ≤0.01 IU/dL were regarded as zero.
3. Assessment of the cumulative weight-adjusted doses of FACTOR X as measured by FX:C (IU/kg body weight) administered to each subject to maintain haemostasis: Sum of total weight-adjusted FX:C adjusted to maintain haemostasis were summarised by type of surgery (major or minor) and overall.
4. Assessment of the cumulative doses of FACTOR X as measured by FX:C (IU) administered to each subject to maintain haemostasis: Sum of total FX:C (IU) administered to maintain haemostasis were summarised by type of surgery (major or minor) and overall.
5. Amount of weight-adjusted FX:C (IU/kg body weight) administered daily (day of surgery and each post-operative day, defined as calendar days) to maintain haemostasis: Daily weight-adjusted FX:C (IU/kg body weight) administered to maintain haemostasis were summarised by study day, type of surgery (major or minor) and overall.

Safety Analysis

The safety analysis was based on the safety population. The general strategy of the safety evaluation was to examine the summaries for any trends. No formal hypothesis testing was carried out.

SUMMARY – CONCLUSIONS

EFFICACY RESULTS:

Four surgical procedures in two subjects, all of which were classified by the DRC as major, were included in the ITT population. Two of the procedures were excluded from the primary efficacy analysis due to significant differences observed between the local and central laboratory measurements of plasma FX:C. However, all four procedures were eligible for the secondary efficacy analysis.

For all surgical procedures, FACTOR X was assessed by investigators and by the DRC as 'excellent' in the control of bleeding during and after surgery.

The estimated volume of blood loss was as expected in three of the four surgical procedures (75.0%) and less than expected in one surgical procedure (25.0%).The mean and median estimates of actual blood loss in the surgical procedures in the secondary analysis were 160.5 mL and 100.0 mL, respectively; the estimates of expected blood loss in the same type of surgical procedure in a subject without a bleeding disorder were 247.5 mL and 100.0 mL, respectively.

None of the subjects had any bleeds during the study. None of the subjects required any blood transfusions during the study.

The median total dose of FACTOR X infused pre-surgery was 38.65 IU/kg.

The median number of infusions was 13. The median number of exposure days until a subject was no longer at risk of bleeding due to the surgical procedure was 11.5.

The median total dose of FACTOR X to maintain haemostasis was 180.65 IU/kg.

In three out of four surgical procedures, haemoglobin and haematocrit decreased below the lower limit of the normal range post-surgery; however, none of the levels were considered clinically significant by the Investigator.

The subjects' FX:C levels were maintained in the range of 0.23 to 0.69 IU/mL (23-69 IU/dL) from Day 2 up to and including discharge.

The mean incremental recovery for FX:C was calculated as 2.14 and 1.98 IU/mL per IU/kg using the clotting and chromogenic assays, respectively and 2.5 IU/dL per IU/kg for FX:Ag.

SAFETY RESULTS:

Overall, a total of 26 treatment-emergent AEs (TEAEs) were reported for the four surgical procedures included in this study. Subjects in three surgical procedures (75.0%), reported at least one TEAE. There were no TEAEs reported for one surgical procedure (25%). The system organ classes with the most commonly reported TEAEs were gastrointestinal disorders (seven events, [26.9%]) and injury, poisoning and procedural complications (six events [23.1%]). The most commonly reported TEAEs overall were constipation and dyspepsia (three events [11.5%] each) and peripheral oedema and procedural pain (two events [7.7%] each). There were no serious AEs (SAEs). None of the TEAEs were considered related to the investigational medicinal product, and none of the events led to early discontinuation of the study drug.

Test results for haematology, serum biochemistry did not indicate any clinically significant values. However, one TEAE of mild anaemia and one TEAE of mild decreased haemoglobin were reported, both of which were considered related to surgery. One subject had TEAEs of hypokalaemia, hypomagnesaemia, and hypoglycaemia that were mild and considered very likely or probably related to surgery. There were no product-related seroconversions.

One subject had a blood pressure reading that was high at Screening, but was within normal limits during the rest of the study. Vital signs for all subjects were within normal limits otherwise. There were no outstanding physical examination findings or changes from baseline

CONCLUSION:

Two subjects, with two surgical procedures each, took part in this study. Subjects were consented for each separate surgical procedure, therefore the total enrolment overall was four study subjects. For clarity, results of efficacy and safety analyses are reported in terms of surgical procedures rather than subjects.

Four surgical procedures in two subjects were included in the ITT population. Two of the procedures were excluded from the per-protocol primary analysis due to significant differences observed between the local and central laboratory measurements of plasma FX:C. However, all four procedures were eligible for the per-protocol secondary analysis.

For all surgical procedures, FACTOR X was assessed by investigators and by the DRC as 'excellent' in the control of bleeding during and after surgery. The estimated volume of blood loss was as expected in three of the four surgical procedures (75.0%) and less than expected in one surgical procedure (25.0%). None of the subjects had any bleeds during the study. None of the subjects required any blood transfusions during the study. For the secondary per-protocol population, the median total weight-adjusted dose to maintain haemostasis was 180.65 IU/kg, and the mean incremental recovery for FX:C was calculated as 2.14 and 1.98 IU/mL per IU/kg using the clotting and chromogenic assays, respectively and 2.5 IU/mL per IU/kg for FX:Ag.

Overall, a total of 26 TEAEs were reported for the four surgical procedures included in this study. Subjects in three surgical procedures (75.0%), reported at least one TEAE. There were no TEAEs reported for one surgical procedure (25%). The system organ classes with the most commonly reported TEAEs were gastrointestinal disorders (seven events, [26.9%]) and injury, poisoning and procedural complications (six events [23.1%]). The most commonly reported TEAEs overall were constipation and dyspepsia (three events [11.5%] each) and peripheral oedema, procedural pain and procedural discomfort (two events [7.7%] each). There were no SAEs. None of the TEAEs were considered related to the investigational medicinal product, and none of the events led to early discontinuation of the study drug.

FACTOR X was shown to be effective in maintaining haemostasis in patients undergoing surgery at the dosage level used in this study. FACTOR X was well tolerated and there were no safety concerns.

Date of the report:

07 May 2014