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

Title of Study:

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

Coordinating Investigator:

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Investigators:

Eleven principal investigators:

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Study centres:

Eleven investigative centres in 5 countries:

UK: Study Site 03: St. George's Haemophilia Centre, London. Study Site 04: Leicester Haemophilia Comprehensive Care Centre, Leicester.

Spain: Study Site 11: Hospital Universitario La Paz, Madrid. Study Site 12: Hospital San Pedro de Alcantara, Caceres.

USA: Study Site 21: New York Presbyterian Hospital, Weill Cornell Center, New York, NY. Study Site 23: UCSF Pediatric Hematology/Oncology, San Francisco, CA.

Turkey: Study Site 31: Ege Universitesi Tip Fakultesi, Bornova, Izmir. Study Site 32: Yizuncu Yil University Faculty of Medicine, Van. Study Site 34: İstanbul Üniversitesi Cerrahpaşa Tıp Fakültesi Çocuk Sağlığı ve Hastalıkları Anabilim Dalı, Instanbul. Study Site 35: İstanbul Göztepe Eğitim ve Araştırma Hastanesi, Istanbul.

Germany: Study Site 41:Klinikum Bremen-Mitte, Ambulanz fuer Thrombose und Haemostasestoerungen, Bremen.

Publications (reference):

None.

Studied period:	**Phase of development:**
Date first patient enrolled: 05 May 2010 Date last patient completed: 30 Oct 2013	III

Objectives:

Primary:

- To assess the pharmacokinetics (PK) of BPL's FACTOR X after a single dose of 25 IU/kg in subjects with severe or moderate factor X deficiency.

Secondary:

- To assess the efficacy of FACTOR X in the treatment of bleeding episodes over at least 6 months.
- To assess the safety of FACTOR X in the treatment of bleeding episodes over at least 6 months.
- To investigate the safety and efficacy of FACTOR X, administered by bolus infusion, to prevent bleeding and achieve haemostasis in factor X-deficient subjects undergoing surgical procedures.

Methodology:

This was an open-label, multi-centre, nonrandomised, prospective study in subjects with severe and moderate factor X deficiency to assess the PK, safety and efficacy of FACTOR X, a high-purity factor X concentrate manufactured by Bio Products Laboratory, Ltd (BPL).

A minimum of 12 and a maximum of 16 subjects were planned for enrollment to ensure a minimum of 12 evaluable PK profiles were obtained at the Baseline Visit and at the 6-Month Visit as well as a minimum of 12 bleeding episodes treated with FACTOR X (at least one bleed per subject).

After an initial dose and PK assessment at the Baseline Visit, subjects received FACTOR X for spontaneous or traumatic bleeds or for specific short-term preventative use. The duration of the study for each subject was at least 27 weeks: at least 1 week between the Screening Visit and the Baseline Visit to allow for analyses, at least 25 weeks through the 6-Month Visit, and an End-of-Study Visit at least 1 week after the 6-Month Visit. The study duration might be extended up to a maximum of 2 years.

Excluding the Screening Visit, subjects attended the hospital for a minimum of five study visits: Baseline/Day 1, 1-Month, 3-Month, 6-Month and End-of-Study visits. Other visits in the study extension might be added between the 6-Month and End-of-Study visits at an interval of every 3 months. If a subject had not experienced a bleed requiring treatment with FACTOR X by 5 months following the Baseline Visit, the Repeat PK assessment was postponed until a Study Extension Visit.

All scheduled visits and any batch-change and study extension visits took place at the main investigational sites (hospitals). Visits for preventative treatment or treatment of a bleed might take place at the main investigational sites or at a clinic closer to the subject's home (if the subject did not self-administer at home) to enable easy access to medical care and treatment with FACTOR X (in case of a major bleed. For subjects' convenience, the later PK blood samples might be collected at home or at work by a trained nurse or a phlebotomist who knew the study procedures.

Between visits, subjects were contacted by site staff at regular intervals to monitor their clinical status, concomitant medications, and any bleeds and associated treatment. Every effort was made by the study staff to speak to each subject by telephone.

<u>Subjects undergoing surgery:</u>

Subjects requiring any surgical or invasive procedure during the course of the trial, whether planned or emergency, could do so using FACTOR X if the local laboratory at the main investigational site or other hospital at which the surgery was performed had the facilities to accurately monitor the subject's factor X activity (FX:C) levels. Subjects might undergo more than one such procedure during the study. Before the commencement of any surgical procedure, a subject must have attended Day 1 of the Baseline Visit and should ideally have completed a PK assessment to 144 hours post-dose.

An objective assessment of the severity of the surgical procedures (major or minor) was made by an

independent Data Review Committee (DRC) on receipt of all relevant information about the procedure.

Number of patients (planned and analysed):

A minimum of 12 subjects and a maximum of 16 subjects were planned for the study.

A total of 16 subjects were enrolled in the study from 17 who attended the Screening Visit. All 16 received at least one dose of FACTOR X during the study. Subjects included in the analysed populations are as follows:

Safety analysis: 16 subjects received at least 1 dose of FACTOR X.

PK analysis: 15 subjects received FACTOR X for treatment of bleeds and had sufficient FX:C data to characterise the time course of FACTOR X in plasma at the Baseline and the Repeat PK assessments.

Efficacy in treatment of bleeds: 15 subjects had at least 1 bleed selected by the DRC for analysis.

Efficacy in the control of bleeding during surgical procedures: three subjects were included in the surgery population, two of whom were included in the per-protocol surgery primary analysis and per-protocol surgery secondary analysis. One subject was included in the surgery population but excluded from the per-protocol primary and secondary analyses populations because the subject's FX:C levels pre-dose at the pre-surgery visit was ≥20 IU/dL, as measured by the central laboratory, due to a recent dose of factor X-containing product.

Diagnosis and main criteria for inclusion:

Included subjects were 12 years of age or older, had hereditary severe or moderate factor X deficiency with <5% (<5 IU/dL) basal FX:C at diagnosis, were currently treated with fresh frozen plasma (FFP), a prothrombin complex concentrate (PCC), or a factor IX/X concentrate, and who, in the 12 months immediately before enrollment, had had a minimum of one spontaneous or menorrhagic bleed that required treatment with FFP, PCC, or a factor IX/X concentrate.

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: 25 IU of factor X per kg body weight (25 IU/kg). The reconstituted solution was given through intravenous infusion at a suggested rate of 10 mL/min but no more than 20 mL/minute.

In addition, the dosage of FACTOR X for subjects requiring surgical or invasive procedure during the study was calculated based on the subject's factor X level and body weight and a nominal recovery of 1.5 IU/dL per IU/Kg. The loading dose was calculated to raise the subject's factor X level to 70 to 90 IU/dL. The post-surgery maintenance dose was calculated to maintain the subject's factor X level at least 50 IU/dL.

Batch numbers: FXSN8788, FXSN8788A, FXSN8788C, FXSN8062, FXSN8569, FXSN8569A, FXSN8569B, FXSN9724D, FXSN9724N.

Duration of treatment:

Each subject received one dose of FACTOR X at the Baseline Visit and additional doses of FACTOR X to treat spontaneous or traumatic bleeds or for short-term preventative use as needed for at least 6 months. If a subject did not experience a bleed that required FACTOR X treatment within the first 5 months, the study could be extended at 3 month intervals for the subject, until a bleed occurred, for up to a total duration of 2 years. The study was to be extended for all subjects until a minimum of 12 assessable bleeds in 12 subjects treated with FACTOR X was available, up to a maximum duration of 2 years for each subject.

In addition, subjects requiring a surgical or invasive procedure during the study received FACTOR X treatment until they were considered to be no longer at risk of post-operative bleeding, which was expected to be approximately 5 to 10 days post-surgery.

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

None.

Criteria for evaluation:

Efficacy:

Primary Efficacy Endpoints

The primary efficacy endpoints were incremental recovery (IR) at 30 minutes post-dose IR_{30min}, apparent terminal half-life ($t_{1/2}$) (non-compartmental), area under the concentration versus time curve (AUC) from time zero to 144 hours (AUC_{0-144h}), AUC estimated from time zero to infinity ($AUC_{0-\infty}$), AUC from time zero to sampling time at the last quantifiable concentration (AUC_{0-t}), systemic clearance (CL), mean residence time (MRT) estimated from time zero to infinity ($MRT_{0-\infty}$), volume of distribution (V_d), concentration at time zero (C_0), maximum observed concentration (C_{max}), time at which C_{max} was apparent (t_{max}) and terminal elimination rate constant (λ_z) for FX:C at the Baseline Visit and the Repeat PK assessment (usually at the 6-Month Visit).

Secondary Efficacy Endpoints

Other PK endpoints were IR_{30min}, $t_{1/2}$ (non-compartmental), AUC_{0-144h}, $AUC_{0-\infty}$, AUC_{0-t}, CL, $MRT_{0-\infty}$, V_d, C_0, C_{max}, t_{max} and λ_z for factor X antigen (FX:Ag) at the Baseline Visit and the Repeat PK assessment.

Other efficacy endpoints included the following:

- Total dose of FACTOR X (IU and IU/kg FX:C), total number of infusions and average dose per infusion to treat a new bleed and ongoing bleeds, for any additional preventative use and overall use per subject;
- Total dose of FACTOR X (IU/kg FX:C) to treat a bleed (including initial dose for new bleeds and any repeated doses for ongoing bleeds), number of infusions and dose per infusion on a per bleed and a per subject basis;
- Dose of FACTOR X per infusion for all infusions, all infusions to treat bleeds, all first infusions to treat bleeds, all subsequent infusions to treat bleeds and all infusions taken as a preventative measure;
- Average monthly and yearly dose of FACTOR X (IU/kg FX:C) and average monthly and yearly number of infusions to treat a bleed, for any additional preventative use and overall use per subject;
- Investigator's overall assessment of efficacy as 'excellent', 'good', 'poor' or 'unassessable';
- Number of exposure days overall and per subject;
- Average number of bleeds per subject per month;
- Number of bleeds including severity, duration, location and cause;
- Subject's assessment of efficacy (all bleeds) as 'excellent', 'good', 'poor' or 'unassessable';
- Investigator's assessment of efficacy (bleeds requiring assessment at the hospital) as 'excellent', 'good', 'poor' or 'unassessable'.

Primary Efficacy Endpoints for Surgery:

The primary efficacy endpoint for surgery was the blood loss during and after surgery. The following parameters were assessed by the investigator at the subject's End of Treatment assessment, and contributed to an assessment of efficacy as 'excellent', 'good', 'poor' or 'unassessable':

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.

Secondary Efficacy Endpoints for Surgery:

The following parameters were assessed:

1. Assessment of IR of FX:C and FX:Ag at 30 minutes 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 FACTOR X (IU/kg body weight FX:C) administered to each subject to maintain haemostasis.
4. Assessment of the cumulative doses of FACTOR X (IU FX:C) administered to each subject to maintain haemostasis.
5. Amount of weight-adjusted FX:C (IU/kg body weight FX:C) administered daily (day of surgery and each post-operative day) to maintain haemostasis.

Safety:

The following parameters were measured to assess the safety of FACTOR X:

- Adverse events (AEs)
- Thrombogenicity markers
- Haematology
- Biochemistry
- Prothrombin time (PT) and activated partial thromboplastin time (APTT)
- Viral serology
- Factor X inhibitor screen and Nijmegen-Bethesda assay
- Vital signs
- Physical examination
- Infusion site observations

The following additional tests were performed:

- Genotype analysis (optional)
- Pregnancy test (for females of childbearing potential)

Safety Assessments for Surgery:

- AEs
- Haemoglobin and haematocrit
- Serum ferritin
- PT and APTT
- Factor X inhibitor screen and Nijmegen-Bethesda assay
- Vital signs
- Physical examination

- Infusion site observations

Statistical methods:

Pharmacokinetic Analyses:

Plasma concentration-versus-time curves were produced for FX:C (assayed using both the one-stage clotting and chromogenic assays) and FX:Ag, for the Baseline Visit (first PK) and the Repeat PK assessment (usually at the 6-Month Visit) for each subject with sufficient data points on both linear/linear and log10/linear scales. Actual post-dose sampling times were used. Mean plasma concentration-versus-time curves were produced for each visit. Summary statistics were calculated for plasma concentrations for each PK visit.

For the purpose of estimating PK parameters relevant to exogenously administered factor X, the concentration of FX:C and FX:Ag at pre-dose was subtracted from all subsequent post-dose concentrations. The first post-dose occurrence of a negative concentration following subtraction of pre-dose would generally be deemed to signify the return of concentrations to baseline (pre-dose) levels, and subsequent time points would be ignored for PK purposes. However, each concentration-versus-time profile was reviewed by a BPL pharmacokineticist to confirm that this approach was appropriate for that profile.

PK parameters for each subject were estimated using WinNonlin PK software (Pharsight Corp., Mountain View, California, USA.) as appropriate. An assumption was made that data would most closely adhere to an intravenous bolus administration and a non-compartmental model in WinNonlin was used. Any use of alternative models would be detailed in the clinical study report.

Whether an individual plasma concentration-versus-time curve was evaluable was determined using the r^2 (adjusted) value assigned by the WinNonlin PK software to the curve fit for the non-compartmental analysis. If the r^2 (adjusted) value was ≥ 0.8, the curve would automatically be considered evaluable. For any plasma concentration-versus-time profiles with r^2 (adjusted) <0.8, the BPL pharmacokineticist assessed whether the profile was evaluable and could be included in the PK analysis.

The dose used in calculation of PK parameters was taken from the dose administered as measured at the coagulation laboratory. The mean potency for each batch of FACTOR X across all PK visits was calculated and this value, for the batch administered to the subject, was used in the calculation of dose administered to the subject.

The DRC reviewed each subject's Baseline and Repeat PK data to assess the possible development of covert inhibitors.

Since very little published data are available on the PK of factor X in factor X-deficient patients, the analyses might be modified on review of the data. Any modifications to this approach or additional analyses performed would be detailed in the clinical study report and in communications with the DRC before their review of the interim PK data.

The PK parameters evaluated were IR_{30min}, terminal elimination $t_{1/2}$ (non-compartmental), $AUC_{0\text{-}144h}$, $AUC_{0\text{-}\infty}$, $AUC_{0\text{-}t}$, CL, $MRT_{0\text{-}\infty}$, V_d, C_0, C_{max}, t_{max} and λ_z.

Efficacy Analyses:

Efficacy of FACTOR X in treating bleeds was assessed by the subject (for all bleeds) and by the investigator (for bleeds assessed at the hospital). In cases where a discrepancy existed between the two ratings, the DRC would review the data and make the final decision, which would be considered the primary efficacy rating for analysis. All ratings would be presented. All primary and secondary endpoints were tabulated.

The success criteria for the effectiveness of FACTOR X are based on the following:

The hypothesis for the PK parameters was that, over at least eight PK assessments of $t_{1/2}$ at the Baseline Visit, the lower 95% confidence interval of the $t_{1/2}$ estimate was greater than 20 hours. The hypothesis for the efficacy of FACTOR X was based on the subject's assessment of each new bleed. FACTOR X

would be deemed effective if 80% of treated new assessable bleeds were found to have an excellent or good response. A treatment failure was defined as the need for more than two doses of FACTOR X to treat an overt bleed or menorrhagia or more than three doses of FACTOR X to treat a covert bleed.

For subjects undergoing surgery, the primary and secondary endpoints for surgery were tabulated.

Safety Analyses:

The general strategy of the safety evaluation was to examine the data summaries of all safety assessments for any trends. No formal hypothesis testing was carried out.

SUMMARY – CONCLUSIONS

PK RESULTS:

The PK parameters for factor X obtained in this analysis are consistent with published data. The criterion for treatment success was met, as the 95% CI lower limit of the $t_{1/2}$ for FX:C at the Baseline Visit, using the clotting assay, was 26.9 and 26.8 hours using the geometric and arithmetic means, respectively, and therefore greater than 20 hours.

Based on data from the one-stage clotting assay, after a single intravenous infusion of nominally 25 IU/kg FACTOR X, the mean C_{max} of FX:C was 0.504 IU/mL (50.4 IU/dL) at the Baseline Visit and 0.495 IU/mL (49.5 IU/dL) at the Repeat PK assessment visit. The mean $t_{1/2}$ was approximately 30 and 28 hours at the Baseline and Repeat PK visits, respectively. The overall mean $t_{1/2}$ calculated by combining $t_{1/2}$ values from all subjects' PK visits was 29.36 hours.

The mean IR, calculated using the factor X levels at 1 hour post-dose (IR_{1h}), was 2.08 IU/dL per IU/kg administered at the Baseline Visit and 2.06 IU/kg per IU/kg at the Repeat PK assessment visit. The overall mean IR calculated by combining IR values from all subjects' PK visits was 2.07 IU/dL per IU/kg administered.

Systemic exposure to FX:C (clotting) and FX:C (chromogenic) at the Repeat PK visit was equivalent to that at the Baseline Visit. The DRC concluded that there was no evidence of development of covert inhibitors to FACTOR X.

For FX:Ag, equivalence between baseline and repeat dose exposure could not be concluded.

The systemic exposure to FX:C did not differ substantially between the clotting and the chromogenic assays. The systemic exposure to FX:Ag was slightly larger and the CL and V_d were slightly lower than the values observed for FX:C.

The CL rates of FX:C and FX:Ag indicate that FACTOR X did not undergo appreciable hepatic elimination. The apparent volume of distribution at steady state (V_{ss}) values of FX:C and FX:Ag indicate that FACTOR X appeared to be largely confined to plasma and did not extensively distribute to tissues.

The between-patient variability in systemic exposure to FX:C (clotting and chromogenic) and FX:Ag was low.

EFFICACY RESULTS:

On-Demand Treatment of Bleeds:

Of the 186 FACTOR X-treated bleeds in 15 subjects that were selected by the DRC and were considered assessable, 170 (91.4%) bleeds yielded excellent response to FACTOR X treatment, 14 (7.5%) yielded good response and 2 (1.1%) yielded poor response.

For the 187 bleeds selected by the DRC, the mean ± standard deviation (SD) unit dose of FACTOR X given per infusion to treat a bleed was 25.25 ± 2.449 IU/kg. The treatment failure rate was 2.1%.

On average, 1.2 ± 0.47 infusions were needed to treat a bleed.

The mean ± SD total dose of FACTOR X given to treat a bleed was 30.25 ± 12.406 IU/kg.

Controlling Bleeding During Surgery

In three subjects undergoing tooth extraction procedures, haemostasis was maintained during and after the surgical procedures with no bleeding complications or blood transfusion. The investigators assessed the overall efficacy of FACTOR X to be excellent in all subjects. All surgical procedures were judged as minor by the DRC.

For the two surgical procedures in the per-protocol analysis, the mean cumulative dose of FACTOR X administered to maintain haemostasis was 89.2 IU/kg or 5,885 IU.

Other Efficacy Endpoints

For the 16 subjects in the safety population, there was a mean (range) of 13.0 (1 to 59) bleeds treated with FACTOR X per subject. The mean number of bleeds per subject per month was 0.85.

Of the 15 subjects for whom an investigator's overall assessment of efficacy of FACTOR X during the study was recorded, efficacy was assessed as excellent in 12 subjects (80%) and good in 3 subjects (20%).

SAFETY RESULTS:

During the study period, 16 subjects (100%) experienced at least one treatment-emergent AE. A total of 176 treatment-emergent AEs were reported. The most common AEs were headache (8 subjects [50.0%]), nasopharyngitis (7 subjects [43.8%]), back pain (6 subjects [37.5%]) and pain in extremity (6 subjects [37.5%]).

Two subjects (12.5%) experienced a total of six treatment-emergent AEs that were considered by the investigator to be possibly related to the study drug (i.e. adverse drug reactions): fatigue (two events in one subject), infusion site erythema (two events in one subject), infusion site pain (one event in one subject) and back pain (one event in one subject. None of the treatment-emergent, product-related AEs were classified as serious.

Six subjects (37.5%) experienced the 13 treatment-emergent serious adverse events (SAEs), including one death (pneumonia and nosocomial infection). All of these SAEs were considered by the investigators to be unrelated to FACTOR X.

Subjects' clinical laboratory measurements, vital signs and physical examinations showed no clinically significant trends of abnormality or change from Baseline. No subject had seroconversion in virology tests.

All study subjects were tested negative for factor X inhibitors at the Baseline Visit and remained negative during the study period. The DRC reviewed the PK parameters of FX:C over time and found no indication of the development of covert inhibitors.

Thrombogenicity markers (D-dimer, thrombin-antithrombin [TAT] and prothrombin fragments F1 and F2 [F1+2]) were reviewed by BPL for spurious data and significant increases from pre-dose at the Baseline and Repeat PK assessment visits. After exclusion of spurious data, there were significant elevations in all three parameters at one or both visits in three of the 16 subjects in the safety population. All thrombogenicity profiles in which any one result exceeded the upper limit of the normal range were reviewed by the DRC, and, in the absence of any clinical signs or symptoms of thrombosis in any subject in the safety population, the DRC did not consider any subject's thrombogenicity results to be of clinical significance

No discomfort, induration, tenderness, or warmth was reported in any subject at post-dose time points. One subject had mild erythema 15 minutes post-dose and 30 minutes post-dose at the Baseline Visit. One subject had moderate discomfort, mild erythema and mild warmth pre-dose at the Repeat PK visit.

Data on the specific F10 gene mutation resulting in factor X deficiency was collected in all 16 subjects in the safety population. Twelve separate mutations in the F10 gene were identified. Nine of the 12 mutations were missense mutations resulting in amino acid substitutions, one was a deletion, one

was a nonsense mutation and one was a splice site mutation. Four subjects had compound heterozygous mutations, one subject was heterozygous for a single mutation, and the remaining 11 subjects were homozygous for a single mutation.

CONCLUSION:

Results of this study indicate that FACTOR X is effective in providing on-demand treatment for bleeds and controlling bleeding in minor surgical procedures in subjects with hereditary factor X deficiency at a nominal dose of 25 IU/kg per infusion. The safety profile of FACTOR X is positive, and the benefit-risk ratio is favorable for the intended clinical use.

Date of the report: 07 Apr 2014