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-label 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

Coordinating Investigator:

Dr Ri Liesner (Investigator Site 01), London, UK

Other Investigators:

Dr Michael Gattens (Investigator Site 02), Cambridge, UK

Dr Jeanette Payne (Investigator Site 03), Sheffield, UK

Study centres: A total of three sites participated in the study:

Site 01 Great Ormond Street Hospital, London, UK

Site 02, Addenbrooke's Hospital , Cambridge, UK

Site 03 Sheffield Children's Hospital, Sheffield, UK

Publications (reference):

None

Studied period:	**Phase of development:**
Date first subject enrolled: 20 Apr 2015 Date last subject completed: 19 Oct 2016	III

Objectives:

Primary:

- to assess the efficacy of FACTOR X in the reduction/prevention of bleeding when given as routine prophylaxis over 6 months (26 weeks)

Secondary:

- to assess the pharmacokinetics (factor X [(FX] incremental recovery and trough levels) of FACTOR X after a single dose of 50 IU/kg
- to assess the safety of FACTOR X when given as routine prophylaxis over 6 months (26 weeks).

Methodology:

This was an open-label, multi-centre, phase III, prospective and retrospective study in subjects under the age of 12 years with severe or moderate FX deficiency.

Eligibility of subjects was assessed at the Screening Visit, which was conducted within 4 weeks of Visit 1 (Baseline). During Screening a medical assessment, including physical examination was conducted and blood samples for haematology and biochemistry were taken.

In the case of eligible subjects who had received FACTOR X prior to study entry on compassionate use, retrospective data on FACTOR X dosing, adverse events and break-through bleeds were collected, from the time the subject commenced treatment with FACTOR X.

After screening subjects had a Visit 1 (Baseline) conducted, at this visit subjects received their first dose of FACTOR X. Pre-dose blood samples were collected for:

- long-term archive.
- Viral serology.
- FX inhibitor assay, which would be assayed at a later date, if an inhibitor was suspected.

FX activity (defined as FX:C levels in the blood) blood samples were collected at pre-dose and 30 min (± 5 min) post-dose for incremental recovery (IR) assessment.

The second dose of FACTOR X was administered at the Investigator Site 72 hours post first dose under the supervision of site staff (Visit 2, Day 4). If required (to maintain adequate trough levels) and at the Investigator's discretion Visit 2 for subjects aged 0-5 years was conducted 48 hours post first dose (Day 3).

Subjects commenced using FACTOR X as routine prophylaxis after Visit 2 and attended a minimum of 2 additional visits during the first 6 weeks of treatment:

- Visit 3 during weeks 2-4 (Days 9-28)
- Visit 4 during weeks 5-6 (Days 29-42)

At Visits 2 to 4 blood samples to measure FX trough were collected within 1 hour pre-dose. Vital signs were performed prior to each blood sample collection.

The subject's weight was measured at Week 16 and as required to assess if IU/kg dosing needed to be adjusted to ensure the correct routine prophylactic dose was administered. It was recommended that this measurement was taken at the Investigator Site. If the subject continued past week 28 to achieve 50 exposure days, their weight was checked at 3-monthly intervals (week 29 and week 42) until the End of Study Visit.

At least six months (26 weeks) after the Visit 1 (Baseline), with a minimum of 50 exposure days, subjects underwent an End of Study Visit, which included a physical examination, collection of blood samples for FX:C levels (pre-dose and at 30 min (± 5 min) post-dose for an incremental recovery assessment), viral serology, haematology, biochemistry and FX inhibitors. At this visit the Investigator made an overall clinical assessment of efficacy of prophylactic therapy with FACTOR X in reducing/preventing bleeding during the study.

A follow up safety assessment (visit or by telephone) was performed 28 days after the End of Study dose of FACTOR X; this included a check of any new serious adverse events.

Number of subjects: It was planned to enrol a minimum of 8 and a maximum of 12 subjects in the study to achieve a minimum of 8 evaluable children.

Two subjects (01-001 and 01-003) completed 50 exposure days, but completed less than 26 weeks in the study. The subjects were re-screened and then completed the study as subject numbers 01-007 and 01-008. The data from their first treatment cycle (*i.e.* as 01-001 and 01-003) was excluded from the Per-Protocol analysis but included in the other analysis population (Safety/ITT and Safety/ITT treatment population).

Therefore 9 unique subjects were enrolled. Eleven treatment cycles were initiated (*i.e.* 11 subject numbers issued).

Diagnosis and main criteria for inclusion:

The study included subjects who were under 12 years of age, had hereditary severe or moderate FX deficiency with <5% (<5 IU/dL) basal FX:C at diagnosis, had a history of severe bleeding (*e*.g. intracranial haemorrhage, before starting prophylactic therapy, OR a mutation in the F10 gene causing a documented severe bleeding phenotype).

Test product, dose and mode of administration:

Product: FACTOR X, a high-purity, plasma-derived human coagulation FX concentrate. The reconstituted solution was given through intravenous (IV) infusion at a rate not exceeding 3 mL/minute.

Bolus dose for Incremental Recovery assessment

At Visit 1 (Baseline) and the End of Study Visit (V5), eligible subjects received a recommended bolus dose of 50 IU/kg FACTOR X to calculate incremental recovery.

Routine prophylaxis

After Visit 1 (Baseline) a prophylaxis dose of 40-50 IU/kg was recommended and the second dose of FACTOR X was given 72 hours ± 2 hours, (Day 4) after the first dose under clinical supervision. For subjects in the 0-5 year age group, at the Investigator's discretion, the dose could be given at 48 hours ± 2 hours (Day 3) after the Visit 1 (Baseline). The dose and frequency was adjusted over the first 6 weeks of treatment to maintain a minimum trough level of 5 IU/dL. A dosing regimen of 40-50 IU/kg twice a week was recommended, but was not mandatory. Treatment was given no more frequently than every 48 hours, and a maximum peak FX:C level of 120 IU/dL was recommended. The maximum dose per infusion was advised as 60 IU/kg.

Treatment of bleeds

The recommended dosage for minor bleeds was 25 IU/kg and 50 IU/kg for a major/life-threatening bleed. Treatment could be repeated as often as required based on the FX:C recovery levels and clinical need.

Preventative therapy

Subjects received a recommended dose of 40-50 IU/kg as short-term preventative treatment (eg. prior to exercise or joint rehabilitation).

Surgery

If subjects required surgery (elective or emergency**)** the dosage of FACTOR X was calculated based on the subject's FX:C level, body weight and the subject's observed recovery at the Visit 1 (Baseline). The loading dose was to be calculated to raise the subject's FX:C level to 70 to 90 IU/dL. The post-surgery maintenance doses were to be calculated to maintain the subject's FX:C level of at least 50 IU/dL.

Batch numbers: FXSN0257G, FXSN0504, FXSN0504A

Duration of treatment:

Subjects were to be treated with FACTOR X for a minimum of 6 months (26 weeks) and for a minimum of 50 exposure days, whichever came later. The duration of the study for an individual subject, assuming twice-weekly dosing, and taking into account screening and the safety follow up 4 weeks after the last dose of FACTOR X, would be approximately 34 weeks in total.

In addition, subjects requiring a surgical or invasive procedure during the study were to receive 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 endpoint:

The Investigator's assessment of the efficacy of FACTOR X in the reduction/prevention of bleeding when given as routine prophylaxis over 6 months (26 weeks), taking into account the subject's risk of break-through bleeding (due to bleeding history, treatment history and genetic mutation) and other relevant factors (*e.g*. compliance with the protocol, attainment of required FX:C trough levels).

Secondary efficacy endpoints:

- Number of bleeds per month including severity, duration, location and cause.
- Investigators' assessment of efficacy in treating major bleeds or life-threatening break-through bleeds and excessive bleeding following injury.
- Parents'/guardians' assessment of efficacy in treating a bleed (conducted for all bleeds).
- FX:C trough levels at all scheduled study visits and at all Bleed Assessment and Trough Measurement unscheduled visits.
- FX:C level 30 minute post-dose incremental recovery at the Visit 1 (Baseline) and the End of Study Visit.
- FX:C incremental recovery and trough levels following any change in dosing regimen required for clinical reasons/insufficient trough levels.
- Dose of FACTOR X to treat a bleed (IU/kg) (including initial dose for new bleeds and any repeated doses for ongoing bleeds), number of infusions to treat a bleed and dose per infusion; all analysed on a per-bleed and a per-subject basis.
- Total of FACTOR X dose in IU/kg, total number of infusions and average dose per infusion for: prophylactic use, to treat a bleed, any additional preventative use, any surgical use and overall use; all analysed on a per subject basis.
- Average monthly dose of FACTOR X in IU/kg, and average monthly number of infusions for: prophylactic use, to treat a bleed, any additional preventative use, any surgical use and overall use; all analysed on a per subject basis.

Safety endpoints

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

- Adverse events (AEs), related and unrelated AEs.
- Haematology.
- Serum Biochemistry.
- Viral serology.
- FX inhibitor screen and Nijmegen-Bethesda assay.
- Vital signs.
- Physical examination.
- Infusion site observations.
- Number of exposure days.

Retrospective data collection (compassionate use of FACTOR X)

Subjects may have received FACTOR X prior to the Ten02 study on a compassionate use basis. Retrospective data during compassionate use with FACTOR X and treatment of bleeds/surgeries was collected and included in the analysis as supportive data.

Statistical methods:

Three analysis population groups were defined:

Per-Protocol (PP) analysis set, which included all subjects who had completed a minimum of 6 months (26 weeks) treatment and a minimum of 50 exposure days.

Safety/ITT analysis set, which included 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.

Safety/ITT treatment cycle analysis set, included data for all treatment cycles, where the data for the re-screened subjects was not be merged, and was presented separately.

Efficacy Analyses:

The primary endpoint was the Investigator's assessment of efficacy of FACTOR X in the reduction/prevention of bleeding when given as routine prophylaxis over 6 months (26 weeks) in the Per-Protocol population (PP). The efficacy criteria were set at 'excellent', 'good', 'poor', or 'unassessable' taking into account the risk category of break-through bleeding.

Risk of break-through bleeding was defined as follows:

Low risk: 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) which required clinical assessment and no major spontaneous bleeds in the past year prior to study entry.

High risk: any subjects who had not met any of the above criteria.

Secondary endpoints are tabulated.

FACTOR X Exposure and Bleed Data

Descriptive statistics for FACTOR X dosing (bolus/prophylactic/preventative or to treat bleeds) and bleed data were presented.

Recovery Analyses

Descriptive statistics for FX:C incremental recovery and trough levels were calculated. Incremental recovery was defined as the rise in FX:C level recorded at 30 min (± 5 min) after the infusion. Units in which FX:C levels were converted to IU/dL, in order that the recovery could be reported in IU/dL per IU/kg. Incremental recovery was calculated using the central laboratory FX:C result.

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 on the safety data.

SUMMARY OF RESULTS

Eleven treatment cycles were initiated in 9 unique subjects. Data on 2 treatment cycles were excluded from the Per-Protocol (PP) analysis as 2 subjects (01-001, 01-003) completed 50 exposure days (EDs), but completed less than 26 weeks in the study. The subjects were re-screened and issued with new subject numbers (01-007, 01-008) and they completed a second treatment cycle as per protocol (50 EDs and 26 weeks treatment).

The mean age was 7.3 years, ranging from 2.6 to 11.9 years (PP population). Four subjects were between the ages of 0 and 5 years old and five were between 6 and 11 years old. The majority of subjects were Asian (7, 77.8%) and the remainder were Caucasian/White (2, 22.2%). All except one subject suffered from severe FX deficiency, the remaining subject (11.1%) had moderate FX deficiency.

All subjects were considered by the investigator to be at low risk (as defined in the protocol) of bleeding at study entry.

EFFICACY RESULTS:

Nine subjects and 9 treatment cycles were included in the PP analysis.

Primary Efficacy variable

Investigators' assessment of FACTOR X in reducing or preventing bleeding following 6 months (26 weeks) of prophylactic treatment was rated excellent in all subjects (N=9, 100%).

Secondary Efficacy variables

Incremental Recovery (IR) and FX trough levels

The mean IR at Visit 1 (Baseline) was 1.66 IU/dL per IU/kg (range: 1.3 to 2.2) and at End of Study Visit was 1.82 IU/dL per IU/kg (range: 1.3 to 2.2) respectively. Overall mean IR was 1.74 IU/dL per IU/kg (range: 1.3 to 2.2). The overall IR for the younger age group (0-5 years) was statistically lower than the IR observed for the older subjects (p=0.0013): mean IR of 1.53 (95% CI: 1.36, 1.70) and 1.91 (95% CI: 1.76, 2.06) IU/dL per IU/kg respectively. This difference in IR between the age groups was also statistically different at each visit.

No dose adjustment visits were required to maintain the FX;C trough at the target level of 5 IU/dL. In all the subjects the FX:C trough levels were maintained above the target (5 IU/dL) after steady state (Visit 4).

Overall FACTOR X usage

A total of 559 infusions of FACTOR X were administered to 9 subjects in the PP population. Overall the total mean dose per subject was 2416.8 IU/kg, and ranged from 1205.0 to 3082.2 IU/kg. The mean dose per infusion per subject in the 0 to 5 year old group was slightly higher than the older subjects; 40.45 IU/kg (95% CI: 31.32, 49.57) and 37.94 IU/kg (95% CI: 24.11, 51.77) respectively.

Prophylactic therapy

A total of 537 prophylactic infusions were administered in the PP population, with a mean (SD) per subject of 59.7 ($\pm$5.1). The median dosing interval per subject was 3.0 days with a range of 2 to 8 days. The prophylactic doses used in the study were varied and slightly lower than those recommended in the protocol (40-50 IU/kg), the median dose per infusion per subject was 39.06 IU/kg, which ranged from 18.0 to 47.3 IU/kg. This equates to a mean (SD) dose per month per subject of 357.95 IU/kg ($\pm$79.84). The younger subjects (0 to 5 year group) were infused with slightly higher prophylactic doses compared to the older subjects; a mean of 40.13 (95% CI: 30.70, 49.57) and 37.66 (95% CI: 23.42, 51.91) IU/kg respectively, but the 95% confidence intervals (CI) overlap considerably.

No short term preventative doses were administered during the prospective study.

Bleeding episodes

A total of 10 bleeds in 3 (33.3%) subjects were reported in the PP population after the Visit 1 (Baseline), 6 were minor, 3 major and for one bleed the severity was not recorded. Across the whole PP population this equates to 0.178 bleeding episodes per month. Three of the bleeds were spontaneous nose bleeds (all in one subject) with a duration ranging from 10 minutes (0.17 hrs) to 1 hour and 30 minutes (1.5 hrs), the remainder were caused by injury or menorrhagia. Four bleeds in 2 subjects (both in the 6 to 11 age group) required treatment with FACTOR X: 1 minor bleed, 3 major bleeds. All bleeds were treated with a single infusion of FACTOR X, the mean (SD) dose per subjects was 31.70 ($\pm$10.08) IU/kg. Only 1 subject also administered tranexamic acid to treat a bleed, this was for a menorrhagic bleed. Lower doses (range 24.6 to 38.0 IU/kg) than those recommended in the protocol (50 IU/kg) were used to treat major bleeds. For 3 (75%) of these bleeds FACTOR X therapy was rated as excellent by the parents/guardians; the remaining bleed was not assessed by the subject's parent(s)/guardian(s). As Per-Protocol, Investigators only had to assess efficacy for major bleeds or life-threatening break-through bleeds and excessive bleeding following injury. No life-threatening bleeds or excessive bleeding was reported. Two out of the 3 major bleeds were assessed by the clinicians, in both cases these were rated as excellent. There was an additional minor bleed reported in the Safety/ITT treatment cycle population (subject 01-003). This was a spontaneous nose bleed which was not treated with FACTOR X and resolved in 3 minutes.

Surgery

There were no surgical interventions in the prospective arm of the study.

SAFETY RESULTS:

The mean duration (from screening until safety follow-up) in the prospective study for the 9 unique subjects in the Safety/ITT population was 9.4 (SD±3.0) months per subject, this equates to 84.6 subject.months (number of subjects times mean months). In the prospective arm of the study, no more than one infusion was administered per day, therefore the number of exposure days (EDs) is equal to the number of infusions.

A total of 665 EDs were experienced by 9 unique subjects in the Safety/ITT population, with a mean of 73.9 EDs per subject, which equates to a mean of 9.71 infusions per month per subject. The mean dose per infusion was 38.99 IU/kg (926.69 IU). Therefore, a total of 25,928.4 IU/kg (616,248.9 IU) of FACTOR X was consumed in the prospective study. In addition to the 10 bleeds reported in the PP population another bleed was report in the Safety/ITT population, the bleed was minor and was not treated with FACTOR X or any other medication. Therefore, a total of 11 bleeds were reported in 4 unique subjects in the Safety/ITT population.

Of the 665 EDs administered in the prospective study, 22 (3.3%) were bolus doses for IR assessments, 4 (0.6%) to treat bleeds and the remaining (639, 96.1%) for routine prophylactic treatment.

Subjects in the younger age group (0-5 years) experienced more EDs than the older age group, 353 and 312 EDs respectively. This was due to 2 subjects in the 0-5 year age group re-entering the study for a second treatment cycle.

A total of 28 treatment-emergent AEs (TEAEs) were reported in 8 (88.9%) unique subjects in the Safety/ITT population, including 2 serious TEAEs in 1 subject. The majority of TEAEs reported were of mild intensity (92.9%). There were no withdrawals due to an AE or death. All the TEAEs were considered unrelated to FACTOR X.

There were no clinically significant trends or changes from baseline in vital signs, physical examination or changes in clinical laboratory measurements from screening. Six of the 9 unique subjects infused FACTOR X via a venous access device (Portacath). No infusion site reactions were observed in any subjects. The FX inhibitor results were all negative at the End of Study Visit and there were no reported inhibitor developments or changes in viral serology.

Compassionate use

Three subjects received FACTOR X on compassionate use prior to enrolling on the Ten02 study.

There were no reports of bleeding episodes, AEs related to FACTOR X, inhibitor development or any other safety concern during this period.

One surgical intervention was reported in the retrospective data collection (insertion of venous access device, Portacath). An estimated total of 2,750 IU (267 IU/kg) of FACTOR X was administered across 6 infusions for the surgery over a period of 5 days, no bleeding complication or any safety concerns were raised.

During compassionate use, an estimated grand total of 554,150 IU of FACTOR X was administered across 780 infusions (779 EDs) in 3 subjects.

CONCLUSION

FACTOR X was rated excellent at reducing/preventing bleeding when given to 9 unique children as routine prophylaxis for 6 months.

The mean age was 7.3 years in the PP population (range 2.6 to 11.9 years).

For bleeding episodes (PP group):

- 10 bleeds in 3 subjects were reported, which equates to a rate of 0.178 bleeding episodes per month per subject across 9 subjects. The remaining bleeds were due to injury or menorrhagia.
- 3 out of the 10 bleeds were spontaneous nose bleeds with a duration ranging from 0.17 to 1.5 hours.
- 4 bleeds were treated with FACTOR X, a mean (SD) dose per subjects of 31.7 (±10.08) IU/kg was used. Only 1 subject also administered tranexamic acid to treat a bleed, this was for a menorrhagic bleed.
- FACTOR X efficacy was rated excellent by the parent(s)/guardian(s) in 3 out of the 4 bleeds and by the Investigators for 2 major bleeds. For the remaining bleeds efficacy was not assessed.
- Lower doses (range: 24.6 to 38.0 IU/kg) than those recommended in the protocol (50 IU/kg) were used to treat major bleeds. However, all the bleeds in the study were treated by a single infusion of FACTOR X, thus suggesting that the doses used were sufficient to control a bleed.

In the PP group prophylactic dosing regimens varied across the study and lower prophylactic doses than those recommended in the protocol (40-50 IU/kg twice a week) were administered.

- Median routine prophylaxis dose of FACTOR X was 39.06 IU/kg (range: 18.0, 47.3) which equates to mean (SD) dose per month per subject 357.95 IU/kg (±79.84).
- Median dosing interval was 3.0 days.

The younger subjects (0-5 years) administered slightly higher doses than the older age group. Overall the prophylactic doses and dosing frequencies were well-tolerated and no safety concerns were raised.

The mean IR was 1.53 IU/dL per IU/kg and 1.91 IU/dL per IU/kg in the 0-5 year and 6-11 year age groups, respectively. This difference was observed to be statistically different (p=0.0013). This age difference was statistically significant for IR across all visits. No dose adjustments visit were required to maintain FX:C at the target levels of 5 IU/dL. After Visit 4 (steady state) all the FX:C trough levels were >5 IU/dL.

A total of 25,928.4 IU/kg (616,248.9 IU) of FACTOR X was consumed across 665 infusions (665 EDs) in the prospective study and an estimated total of 554,150 IU across 780 infusions (779 EDs) during compassionate use.

Subjects in both the prospective arm of the study and retrospective data collection (compassionate use) reported:

- no AEs related to FACTOR X,
- no clinically significant changes in laboratory measurements, vital signs or physical examination.
- no reports of sero-conversions or development of FX inhibitors.

In addition to bleeds reported in the PP population, one minor bleed was reported in the Safety/ITT population; this was not treated with FACTOR X or any other medication. No bleeds were reported in the compassionate use period.

In conclusion, the data from this study shows routine prophylactic doses of FACTOR X ranging from 18.0 to 47.3 IU/kg administered approximately twice weekly (median dosing interval of 3 days) to be efficacious and safe in treating children <12 years suffering from hereditary FX deficiency.

Date of the report: 28 March 2017