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| Applicant | Bio Products Laboratory Limited |
| Established Name | Coagulation Factor X (Human) |
| (Proposed) Trade Name | |
| Pharmacologic Class | |
| Formulation(s), including Adjuvants, etc | |
| Dosage Form(s) and Route(s) of Administration | |
| Dosing Regimen | |
| Indication(s) and Intended Population(s) | The treatment of bleeding episodes and controlling bleeding during surgical procedures in patients with hereditary factor X deficiency. |

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GLOSSARY

| | | |
|------|-----------------------------------|---------------------|
| AE | adverse event | |
| BLA | biologics license application | |
| DRC | data review committee | FFP |
| PCC | prothrombin complex concentrates | fresh-frozen plasma |
| PK | pharmacokinetics | |
| SAE | serious adverse event | |
| TEAE | treatment-emergent adverse events | |

1. EXECUTIVE SUMMARY

FACTOR X has shown a favorable benefit-to-risk ratio for the treatment of bleeding episodes and for controlling bleeding and maintaining haemostasis during and after surgical procedures in subjects 12 years or older with hereditary factor X deficiency.

The submission is founded on two studies: a PK, safety and efficacy study (Ten01), and a surgery study (Ten03). In the Ten01 study, 12 subjects received FACTOR X intravenous infusions at investigational sites, clinics, or at home to treat a total of 96 bleeding episodes. Of the total of 96 bleeding episodes treated with FACTOR X, 68 (71%) were treated with a single infusion and 18 (19%) required two infusions. Seven bleeds (7%) required more than 2 infusions and 3 bleeding episodes (3%) were not included in the assessment as these bleeds had no records in the clinical database at the time of database lock for the interim analysis. The mean \pm SD total dose of FACTOR X given per bleed was 37.0 ± 23.4 IU/kg, similar to the total dose per bleed in the 50 assessable bleeds. Of the 50 assessable on-demand FACTOR X-treated bleeds, 45 (90.0%) bleeds yielded excellent response to FACTOR X treatment as assessed by the subjects. The treatment success rate was 96.0% (95% confidence interval [CI]: 86.3% to 99.5%). Fifteen of the 50 assessable on-demand bleeds were also rated by investigators; 13 (86.7%) of these bleeds had an excellent response to FACTOR X.

In the Ten03 study, one subject who had knee replacement surgery has been included for analysis. The overall efficacy of FACTOR X in preventing blood loss during and after surgery was assessed by the investigator as excellent. No blood transfusion was needed for this subject, and he did not experience any post-operative bleeding.

The safety data showed that FACTOR X intravenous infusions were well tolerated with few adverse drug reactions. No SAE was possibly related to FACTOR X. There was no evidence to suggest that FACTOR X induced factor X inhibitors. No drug-drug or drug-food interactions were reported in the studies. The sample size of the trials was very small. From a statistical point of view, the results may not be conceded as being statistically proven. There were no statistical issues in these trials.

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied

Hereditary factor X deficiency is a rare haemophilia caused by the inherited lack of coagulation factor X. Factor X deficiency can result in bleeding patterns similar to, if less frequent than, those seen in males with haemophilia A or B. Unlike haemophilias A and B, both genders can be carriers and both can develop factor X deficiency. The prevalence of severe factor X deficiency in the general population is approximately 1 in 1 million.

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

Factor X deficiency is currently treated with replacement therapy, specifically fresh-frozen plasma (FFP) or prothrombin complex concentrates (PCC). Both of these treatments have disadvantages for factor X-deficient patients in terms of the infusion of additional plasma proteins other than the required coagulation factor, which may lead to adverse events.

2.4 Previous Human Experience with the Product (Including Foreign Experience)

Orphan drug designation was requested from the EMA in 2007, and was granted on 18 September 2007.

2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission

Orphan drug designation was requested from the FDA in 2007, and was granted on 08 November 2007.

Regulatory advice was requested from the FDA and EMA in the form of parallel Scientific Advice / Protocol Assistance in October 2007. FDA and EMA responded on 29 April 2008 and 07 May 2008, respectively.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission was adequately organized for conducting a complete statistical review without unreasonable difficulty.

4. SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES

4.1 Chemistry, Manufacturing, and Controls

On request of the committee chair, the statistical methods used in the process validation of the individual established manufacturing steps were reviewed. The sponsor imported data into the statistical analysis software (b) (4) and ran their analysis using this software. Analyzed outputs are presented in various graphical forms (Summary of fit; X/Y Overview Plot Principle Component Analysis (PCA); Score Scatter Plot; DModX plot; Contribution plot; Hotelling's T2 Plot, Statistical Process Control (SPC) charts, in the form of Shewhart plots). CBER has no access to the proprietary software (b) (4) and cannot evaluate the correctness of the results. The statistical interpretation of the software output was correct.

4.6 Pharmacovigilance

A Type B Pre-submission meeting was held with CBER on 23 October 2012 which included a discussion on the need for Risk Evaluation and Mitigation strategies (REMS) and Medication Guide. FDA agreed that a REMS or Medication Guide was not required for this BLA.

5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

5.1 Review Strategy

The sources of this review were two extremely small clinical trials. Both of these trials were reviewed. For the consultation on Chemistry, Manufacturing, and Controls, three files with Continued Process Verification were used.

5.2 BLA/IND Documents That Serve as the Basis for the Statistical Review

The following documents were reviewed: 2.5 Clinical Overview, 2.7.3 Summary of Clinical Efficacy (Control Bleeding in Surgery), 2.7.3 Summary of Clinical Summary (Treat Bleeding), 2.7.4 Summary of Clinical Safety, 3.2.P.3.5.2 Continued Process Verification: Established Step 1: (b) (4), 3.2.P.3.5.3 Continued Process Verification: Established Step 2: Solvent-Detergent Treatment, 3.2.P.3.5.4 Continued Process Verification: Established Step 3: (b) (4), 5.3.3 Reports of Human PK Studies, 5.3.5 Report on Efficacy and Safety Studies.
(b) (4)

5.3 Table of Studies/Clinical Trials

The submission is founded on two studies: a PK, safety and efficacy study (Ten01), and a surgery study (Ten03).

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

The efficacy of FACTOR X for on-demand treatment of bleeds and to control bleeding during surgical procedures in subjects aged 12 and older with hereditary factor X deficiency is supported by the Ten01 PK, safety and efficacy study (Trial #1) and Ten03 surgery study (Trial #2).

6.1 Trial #1

In the Ten01 study up to and including the cut-off date of 10 Aug 2012, 12 subjects received FACTOR X intravenous infusions at investigational sites, clinics, or at home to treat a total of 96 bleeding episodes. At the time of the database lock for the interim analysis, 58 bleeds in 12 subjects had been reviewed by the data review committee (DRC). Each of these 12 subjects had at least one significant bleed. Of the 58 bleeds, 50 bleeds were deemed assessable by the DRC. The remaining 8 bleeds in one subject were considered not assessable by the DRC.

6.1.1 Objectives (Primary, Secondary, etc)

The primary objective was to assess the PK of FACTOR X after a single dose of 25 IU/kg in subjects with severe or moderate factor X deficiency. The secondary objectives were:

- 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.

6.1.2 Design Overview

This was a phase III open-label, multicenter, first-in-human study to investigate the PK, safety and efficacy of FACTOR X in the treatment of severe and moderate factor X deficiency. 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.

6.1.3 Population

Included subjects were 12 years of age or older, with a diagnosis of hereditary mild to severe factor X deficiency (<20% basal level of FX:C), including previously untreated subjects or subjects currently treated with FFP), PCC or factor IX/X concentrate by prophylaxis or on demand.

6.1.4 Study Treatments or Agents Mandated by the Protocol

After an initial dose of 25 IU/kg and PK assessment at the Baseline Visit, subjects received FACTOR X as a bolus injection for spontaneous or traumatic bleeds or for specific short-term preventative use.

6.1.6 Sites and Centers

UK (two sites): St. George's Haemophilia Centre, London; Leicester Haemophilia Comprehensive Care Centre, Leicester.

Spain (two sites): Hospital Universitario La Paz Madrid; Hospital San Pedro de Alcantara, Caceres.

USA (one site): New York Presbyterian Hospital, Weill Cornell Center, New York, NY.

Germany (one site): Klinikum Bremen-Mitte, Ambulanz fuer Thrombose und Haemostasestoerungen, Bremen.

Turkey (two sites): Ege Universitesi Tip Fakultesi, Bornova, Izmir; Yizuncu Yil University Faculty of Medicine, Van.

6.1.8 Endpoints and Criteria for Study Success

Clinical efficacy was measured using the following endpoints:

1. Subject's assessment of efficacy (all bleeds) as 'excellent', 'good', 'poor' or 'unassessable';
2. Investigator's assessment of efficacy (bleeds requiring assessment at the hospital) as 'excellent', 'good', 'poor' or 'unassessable'. 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.

PK efficacy was evaluated using incremental recovery (IR), half-life (non-compartmental), AUC(0-144h), AUC(0-∞), AUC(0-t), clearance, mean residence time

[MRT(0-∞)], volume of distribution, C₀, C_{max}(obs), T_{max} and terminal elimination rate constant for FX:C at the Baseline Visit and the Repeat PK assessment (usually at the 6-Month Visit).

Safety was measured using the following endpoints:

Adverse events, Thrombogenicity markers, Haematology, Biochemistry, PT and APTT, Viral serology, Factor X inhibitor screen and Nijmegen-Bethesda assay, Vital signs, Physical examination, Infusion site observations,

6.1.9 Statistical Considerations & Statistical Analysis Plan

Unless otherwise stated, categorical variables were presented using counts and percentages, whilst continuous variables were presented using the mean, 95% confidence interval for the mean, standard deviation (SD), median, minimum, maximum, number of surgeries and number of missing surgeries or data points. Minima and maxima were quoted to the number of decimal places as recorded in the CRF; means, SDs, and medians were quoted to one further decimal place. Percentages were rounded to one decimal place. The efficacy analysis was to be performed for the intent-to-treat population, and the safety population used to report all safety data, in accordance with the statistical analysis plan. Demographic data were to be reported for the safety population. The primary population for the purposes of analysis was defined as the intent-to-treat population.

6.1.10 Study Population and Disposition

Nine (69.2%) of the 13 enrolled subjects were female and 4 were male. Nine (69.2%) subjects were white/Caucasian, two (15.4%) were Asian and two (15.4%) were African American. The mean age was approximately 30 years with a maximum years of 55.

| | Safety Population (N=13) |
|---|-------------------------------------|
| | Mean (± SD) |
| Age (yr) | 29.9 (± 15.45) |
| Weight (kg) | 69.59 (± 19.087) |
| | Number (%) |
| Sex | |
| Male | 4 (30.8%) |
| Female | 9 (69.2%) |
| Race | |
| American Indian or Alaska Native | 0 |
| Asian | 2 (15.4%) |
| Black or African American | 2 (15.4%) |
| Native Hawaiian or other Pacific Islander | 0 |
| White or Caucasian | 9 (69.2%) |
| Other | 0 |
| Ethnicity | |
| Hispanic or Latino | 4 (30.8%) |
| Not Hispanic or Latino | 9 (69.2%) |

Of the 13 subjects, 12 received FACTOR X to treat bleeds. The bleeds in one subject were considered not assessable by the DRC because of the use of other factor X containing products. Therefore, the efficacy analysis for on-demand treatment of bleeds included only 11 subjects with assessable bleeds treated with FACTOR X.

By the cut-off date, 2 subjects had completed the study, 1 subject discontinued because of death (not related to the study treatment), and the rest of the subjects were remaining in the study (Table 15). No subject withdrew consent, discontinued the study due to an AE, or was withdrawn by the investigator or sponsor.

Table 15: Disposition of all subjects

| | Number |
|--|---------------|
| Enrolled | 13 |
| Completed study | 2 |
| Withdrew from study | 1 |
| AE | 0 |
| Withdrew consent | 0 |
| Investigator judgment | 0 |
| Protocol noncompliance | 0 |
| Lost to follow-up | 0 |
| Termination of study or withdrawn by sponsor | 0 |
| Death | 1 |
| SAE | 0 |
| Pregnancy | 0 |
| Other | 0 |

Population wise, the disease history was as follows: factor X activity at diagnosis (IU/dL) 4.0 (\pm 3.74), time since lowest factor X activity recorded (yr) 7.6 (\pm 11.10) , and lowest factor X activity recorded (IU/dL) 0.92 (\pm 1.04).

The sample size was too small to allow subgroup analysis on the effects of demographics and baseline clinical characteristics on FACTOR X safety.

6.1.11 Efficacy Analyses

Of the 50 assessable on-demand FACTOR X-treated bleeds, 45 (90.0%) bleeds yielded excellent response to FACTOR X treatment, 3 (6.0%) yielded good response, and 2 (4.0%) yielded poor response, as assessed by the subjects. The treatment failure rate was 4.0%. The treatment success rate was 96.0% (95% confidence interval [CI]: 86.3% to 99.5%). Fifteen of the 50 assessable on-demand bleeds were also rated by investigators; 13 (86.7%) of these bleeds had an excellent response to FACTOR X, 1 bleed (6.7%) had good response, and 1 bleed (6.7%) had poor response. The other bleeds were not rated by investigators, as the subjects had not needed to visit the investigational site for assessments.

For the 50 assessable bleeds, the mean \pm SD unit dose of FACTOR X given per infusion to treat a bleed was 25.4 ± 2.58 IU/kg. On average, 1.3 ± 0.63 infusions were needed to treat a bleed, with a mean \pm SD total dose of FACTOR X of 34.2 ± 16.14 IU/kg.

Of the total of 96 bleeding episodes treated with FACTOR X, 68 (71%) were treated with a single infusion and 18 (19%) required two infusions. Seven bleeds (7%) required more than 2 infusions and 3 bleeding episodes (3%) were not included in the assessment as these bleeds had no records in the clinical database at the time of database lock for the interim analysis. The mean \pm SD total dose of FACTOR X given per bleed was 37.0 ± 23.4 IU/kg, similar to the total dose per bleed in the 50 assessable bleeds.

6.1.12 Safety Analyses

6.1.12.3 Deaths

During the study period, one subject ((b) (6)) died of pneumonia. This serious adverse event (SAE) was considered unrelated to FACTOR X treatment.

6.1.12.4 Nonfatal Serious Adverse Events

Treatment-emergent adverse events (TEAEs) occurred in 12 (85.7%) of the 13 subjects during the study period. The most common TEAEs were headache (28.6%), nasopharyngitis (21.4%), nausea (21.4%), and pain in extremities (21.4%), each occurring in 3 or more subjects. Two of the 13 (15.4%) subjects experienced a total of 6 TEAEs considered by the investigator to be possibly related to the study drug (i.e., adverse drug reactions [ADR]): fatigue (2 events in 1 subject), infusion site erythema (2 events in 1 subject), infusion site pain (1 event in 1 subject), and back pain (1 event in 1 subject). None of the FACTOR X related TEAEs were serious.

Three of the 13 (21.4%) subjects experienced a total of 5 SAEs (haemorrhage, dysmenorrhoea, menorrhagia, pneumonia, and syncope) and were considered by the investigators as unrelated to the study treatment. No subject discontinued participation due to an AE. As the majority of doses were approximately 25 IU/kg, it is not possible to assess whether there was a dose-AE relationship.

6.2 Trial #2

6.2.1 Objectives (Primary, Secondary, etc)

The primary objective was 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 surgery.

6.2.2 Design Overview

This was a phase III open-label, multicenter study to investigate the safety and efficacy of FACTOR X in the treatment of factor X deficient subjects undergoing surgery.

6.2.4 Study Treatments or Agents Mandated by the Protocol

FACTOR X was given by intravenous infusion. Subjects were administered a loading dose before surgery. The loading dose was calculated to raise the subject's factor X level to 70% to 90% of normal. The post-surgery maintenance dose was calculated to maintain the subject's factor X level at least 50% of normal.

6.2.9 Statistical Considerations & Statistical Analysis Plan

One white male patient of age 55 was enrolled in this study. The overall efficacy was estimated as excellent. There are no statistical issues.

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

The sample size was very small. The sponsor used descriptive statistics.

10.2 Conclusions and Recommendations

In conclusion, FACTOR X has shown a favorable benefit-to-risk ratio for the treatment of bleeding episodes and for controlling bleeding and maintaining haemostasis during and after surgical procedures in subjects 12 years or older with hereditary factor X deficiency.

Of the 50 assessable on-demand FACTOR X-treated bleeds in study Ten01, 45 (90.0%) bleeds yielded excellent response to FACTOR X treatment, 3 (6.0%) yielded good response, and 2 (4.0%) yielded poor response, as assessed by the subjects. The treatment failure rate was 4.0%. The treatment success rate was 96.0% (95% confidence interval [CI]: 86.3% to 99.5%). Fifteen of the 50 assessable on-demand bleeds were also rated by investigators; 13 (86.7%) of these bleeds had an excellent response to FACTOR X, 1 bleed (6.7%) had good response, and 1 bleed (6.7%) had poor response. The other bleeds were not rated by investigators, as the subjects had not needed to visit the investigational site for assessments.

Two subjects in study Ten01 received FACTOR X treatment for controlling bleeding during surgical procedures. Up to and including the cut-off dates, 3 subjects had received FACTOR X to control bleeding during surgical procedures and maintain haemostasis after the surgical procedures in the Ten01 and Ten03 studies. The overall efficacy was estimated as excellent.

The safety data of FACTOR X in the 14 subjects in studies Ten01 and Ten03 showed that FACTOR X intravenous infusions were well tolerated with few adverse drug reactions (fatigue, infusion site erythema, infusion site pain, and back pain). No SAE was possibly related to FACTOR X. FACTOR X use was not associated with any abnormality in clinical laboratory parameters or physical signs. There was no evidence to suggest that FACTOR X induced factor X inhibitor. No clinical signs or symptoms of thrombosis

were observed in any subject in the Ten01 and Ten03 studies. No drug-drug or drug-food interactions were reported in the studies.

The sample size of the trials was very small. From a statistical point of view, the results may not be conceded as being statistically proven. There were no statistical issues in these trials.