28 January 2016
EMA/CHMP/139881/2016
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Coagadex

International non-proprietary name: human coagulation factor X

Procedure No. EMEA/H/C/003855/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Table of contents

List of abbreviations

AE	Adverse event
ALT	Alanine aminotransferase
APTT	Activated partial thromboplastin time
ATC	Anatomical Therapeutic Chemical (Classification System)
AUC	Area under the concentration versus time curve
BPL	Bio Products Laboratory Limited
BU	Bethesda Units
b.w.	body weight
CIP	Clean in place
CFU	Colony Forming Units
CL	Systemic clearance
Cmax	Maximum observed concentration
C0	Concentration at time zero
CPS	Cryoprecipitate-depleted plasma supernatant
CT	Computed tomography
CTD	Common technical document
CV	Coefficient of variation
DoE	Design of Experiment
DP	Drug product
DRC	Data review committee
DS	Drug substance
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency
F1+2	Prothrombin Fragments F1 and F2
FACTOR X	syn. for Coagadex
FCT	Fibrinogen Clotting Time
FII	Coagulation factor II
FIX	Coagulation factor IX
FX	Coagulation factor X
FXa	Activated coagulation factor X
FX:Ag	Factor X antigen
FX:C	Factor X activity
FFP	Fresh frozen plasma
GC	Gas chromatography
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HAV	Hepatitis A virus
HBV	Hepatitis B virus
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HPLC	High pressure liquid chromatography
IA	intra-arterial
ICH	International Conference of Harmonization
IMP	Investigational medicinal product

IR	Incremental recovery
IR1h	Incremental recovery at 1 hour post-dose
IS	International Standard
ISTH	International Society of Thrombosis and Haemostasis
IU	International unit
IV	intra-venous
λz	Terminal elimination rate constant
MA	Material attribute
MAA	Marketing authorisation application
Mr	Molecular Weight
NA	Not Applicable
NaCl	Sodium chloride
NAPTT	Non-activated Partial Thromboplastin Time
NGT	Not greater than
NOEL	No Observed Effect Level
OOS	Out-of-specification
PCC	Prothrombin Complex Concentrate
Ph Eur	European Pharmacopoeia
PK	Pharmacokinetic
PT	Prothrombin Time
SAE	Serious adverse event
S/D	Solvent/detergent
SOP	Standard Operating Procedure
TAT	Thrombin-antithrombin complex
TEG	Thromboelastography
TGA	Thrombin Generation Assay
tmax	Time at which maximum concentration is apparent
TVAC	total viable aerobic counts
USP	United States Pharmacopoeia
Vd	Volume of distribution
Vss	Volume of distribution at steady state
WFI	Water for Injections
WHO	World Health Organisation

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Bio Products Laboratory Limited submitted on 6 May 2015 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Coagadex, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 19 September 2013.

Coagadex was designated as an orphan medicinal product EU/3/07/471 on 17 September 2007 in the following indication: Treatment of hereditary factor X deficiency.

The applicant applied for the following indication: Treatment and prophylaxis of bleeding in patients with hereditary factor X deficiency;

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Coagadex as an orphan medicinal product in the approved indication. The outcome of the COMP review can be found on the Agency's website: ema.europa.eu/Find medicine/Rare disease designations.

Control and Prevention of Bleeding Episodes: Coagadex is a blood coagulation factor indicated for control and prevention of bleeding episodes in adults and children (aged 12 years and above) with hereditary factor X deficiency.

Perioperative Management: Coagadex is indicated in the perioperative management in adults and children (aged 12 years and above) with hereditary factor X deficiency.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that human coagulation factor X was considered to be a known active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included EMA Decision P/0188/2014 on the agreement of a paediatric investigation plan (PIP). At the time of submission of the application, the P/0188/2014 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Protocol Assistance

The applicant received Protocol Assistance from the CHMP on 24/04/2008, 13/10/2008, 25/07/2013 and 12/12/2013. The Protocol Assistance pertained to quality, non-clinical and clinical aspects of the

dossier.

Licensing status

The product was not licensed in any country at the time of submission of the application.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Andrea Laslop Co-Rapporteur: Jan Mueller-Berghaus

- The application was received by the EMA on 6 May 2015.
- Accelerated Assessment procedure was agreed-upon by CHMP on 26 March 2015.
- The procedure started on 23 July 2015.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 12 October 2015. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 12 October 2015.
- The PRAC Rapporteur Risk Management Plan (RMP) Assessment Report was adopted by PRAC on 6 November 2015.
- During the meeting on 19 November 2015, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 20 November 2015.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 22 December 2015.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Questions to all CHMP members on 14 January 2016.
- The Rapporteurs circulated the updated Joint Assessment Report on the applicant’s responses to the List of Questions to all CHMP members on 22 January 2016.
- During the meeting on 28 January 2016, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Coagadex.

2. Scientific discussion

2.1. Introduction

Hereditary factor X deficiency is a rare type of bleeding disorder due to an inherited lack of Human Coagulation Factor X. The gene for factor X is located on the long arm of chromosome 13, so unlike haemophilias A and B, both genders can be carriers of the genetic mutation and/or develop the condition. The prevalence in the general population is approximately 1 in 1 million (Uprichard and Perry, 2002; Peyvandi *et al*, 2002).

Hereditary factor X deficiency varies in its severity, which is defined according to the endogenous level of factor X in the plasma. Severe factor X deficiency refers to an endogenous factor X concentration of <1 IU/dL; moderate factor X deficiency refers to an endogenous factor X concentration of 1 to <5 IU/dL, and mild factor X deficiency refers to factor X activity of 5 to 20 IU/dL. The level of endogenous factor X activity in the general population has been reported to be from 65 to 120 IU/dL. The bleeding pattern of subjects with severe factor X deficiency may have similarities to those of male patients with haemophilias A and B, with joint and muscle bleeds being common. However, patients with factor X deficiency also experience significant bleeding from mucous membranes such as nose, lungs and gastrointestinal tract. Females of childbearing age may experience menorrhagia, and bleeding from the umbilical cord after childbirth is also common (Herrmann *et al*, 2006). Bleeding can occur spontaneously, follow minor trauma, or occur during surgical interventions. Important co-morbidities of the patient population are likely to be those related to the complications of the condition such as arthropathy.

Approximately 95 variants of the factor X gene have been described, giving rise to different phenotypes. Type I deficiency, in which a mutation in the factor X gene leads to production of truncated proteins, reduces factor X coagulant activity (FX:C) and antigen (FX:Ag) levels, and results in a more severe clinical manifestation. Type II deficiency, in which the FX:C is reduced but FX:Ag levels are near normal, is a qualitative defect of the factor X protein and often results in more mild symptoms. However, caution has been raised about categorising patients according to their endogenous levels of factor X, as the clinical phenotype does not correlate well with the laboratory phenotype. It is generally accepted that a factor X level of 10-20 IU/dL is required for adequate haemostasis, and patients with the severe disorder require more aggressive treatment than those who have mild disorder, based on the published data of surveys of cohorts of patients and other publications.

Factor X deficiency is currently treated with replacement therapy, specifically fresh-frozen plasma (FFP) or, more recently, prothrombin complex concentrates (PCC). Both of these treatments have disadvantages as they contain additional plasma proteins other than the required coagulation factor, factor X, which may lead to adverse events. PCC products have the advantage over FFP as the coagulation factors in PCC are concentrated, thus requiring smaller infusion volumes (approximately 50 mL).

Three types of PCC products are available: 3-factor complex containing factors II, IX and X; 4-factor complex additionally containing factor VII; and, available in some countries, a complex combining factor IX and X. These products were traditionally used to treat patients with haemophilia B, but the complexes containing factor II have been associated with thromboembolic complications with repeated use. Prothrombin (factor II) has a longer half-life (t1/2) than other clotting factors. The repeated use may result in progressive elevation of prothrombin levels and move the haemostatic equilibrium

toward thrombin generation, fibrin deposition, and thrombotic sequelae. However, no evidence of thrombotic events has been seen in factor X deficient patients who received repeated PCC administrations. In addition, FFP and PCC products often contain unknown and variable amounts of factor X, making it difficult to provide precise dosages and a predictable response. The efficacy of a PCC product can be compromised by these uncertainties, fluctuating levels of factor X and other coagulation factors in the patient, inconsistent dosing, and unpredictable dosing frequencies. The dual factor concentrate, factor IX/X contains a high concentration of factor X with specified content. Patients who receive this product show increased levels of factor IX as well as factor X. Dosing in treatment of factor X deficiency is derived from individual case reports, which may vary by product or batch used.

Coagadex (Factor X) is a human plasma-derived, high-purity factor X concentrate developed to specifically replace deficient factor X and restore hemostasis in patients with factor X deficiency when given either to treat bleeding episodes or prophylactically to maintain circulating levels of factor X sufficient for hemostasis.

It is intended for the treatment and prophylaxis of bleeding episodes and for perioperative management in patients with hereditary factor X deficiency.

2.2. Quality aspects

2.2.1. Introduction

Coagadex contains concentrated human coagulation factor X derived from pooled human plasma for fractionation as active substance (ATC code: B02BD13) representing the factor X molecular species of the healthy normal population. Factor X belongs to the procoagulant vitamin-K-dependent prothrombin complex factors (FII, FVII, FIX and FX) and presents the zymogen of the serine protease for activated factor X (FXa), also known as prethrombokinase or by the eponym Stuart factor, Stuart-Prower factor.

The finished product is presented as a white or off-white freeze-dried plug or powder in two dose sizes of 250 IU and 500 IU of Factor X (nominal). Coagadex is supplied with 2.5 mL (250 IU dose) or 5 mL (500 IU dose) sterilized Water for Injections (WFI) as solvent for reconstitution of the freeze-dried powder. After reconstitution, concentration of the active ingredient is 100 IU FX/mL.

A CE marked disposable medical device (Mix2Vial) is supplied allowing transfer of WFI to Coagadex freeze-dried product and of the reconstituted product into a syringe for administration.

2.2.2. Active Substance

General Information

Factor X is a glycoprotein of 59 kD composed of a light (17 kD) and a heavy chain (42 kD) linked by a single disulphide bond. Two posttranslational amino acid modifications facilitate calcium binding, which is necessary for functional activity: i) Gamma-carboxylation of eleven glutamic acid residues on the light chain and (ii) Beta-Hydroxylation of an aspartic acid on the epidermal growth factor-like regions of the light chain. Factor X is synthesised in the liver and secreted into the plasma as a precursor.

Activation of factor X is catalysed by either the intrinsic factor Xase complex (FIXa, FVIIIa, membrane surface and calcium ions) or the extrinsic factor Xase complex (FVIIa, tissue factor, membrane surface and calcium ions) resulting in cleavage and release of an activation peptide. In the prothrombinase complex, FXa catalyses the conversion of prothrombin to thrombin.

Manufacture, characterisation and process controls

Manufacturer

Manufacture of STABILISED FACTOR X Bulk Drug Substance is performed at a single location:

Bio Products Laboratory Limited. (BPL), Dagger Lane, Elstree, Hertfordshire, WD6 3BX, United Kingdom

Description of manufacturing process and process controls

The STABILISED FACTOR X bulk active substance manufacturing process is presented.

These comprise the following stages:

• Separation of cryoprecipitate and cryoprecipitate-depleted plasma (CPS) by controlled thawing of frozen plasma, followed by centrifugation.

• Isolation of vitamin K-dependent proteins, including factors II, IX and X, from cryoprecipitate-depleted plasma by adsorption on gel.

• Virus inactivation by incubation with solvent and detergent

• Partial separation of factors II, IX and X by chromatography.

• Purification of factor X by chromatography.

• Filtration of factor X through a virus-retentive filter and stabilisation.

Control of Materials

PMF (Plasma Master File)

Coagadex active substance human coagulation factor X is manufactured from plasma for fractionation complying with Ph Eur (0853). A copy of the current EMA PMF Certificate of compliance with Community legislation (EMEA/H/PMF/000014/08/AU/009/G), issued by the EMA on 22 January 2015, has been provided in Module 1 of the application dossier. The PMF Certificate Holder is the Coagadex manufacturer: Bio Products Laboratory (BPL), Dagger Lane, Elstree, Herts, WD6 3BX. A clear reference to PMF, covering plasma for fractionation used for manufacture of Coagadex, has been included.

Raw materials

Raw materials used are pharmacopoeial (having reference to a monograph) with the exception of the three chromatography resins utilized. For these non-compendial raw materials internal specifications have been established. A certificate of analysis has been provided for each of the non-compendial raw materials.

According to Guideline on plasma-derived medicinal products, manufacture of plasma-derived medicinal products starts from defined plasma pools and specifications of the plasma pool should be stated in the application dossier of the respective medicinal product. A clear reference to the PMF is acceptable with respect to the description and testing of the plasma pool for viral markers. The Applicant provided specifications of the plasma pools (e.g. protein concentration, bioburden) upon request. Overall, raw materials are controlled and comply with either Ph Eur or specifications of BPL.

Control of critical steps

Critical process steps of the Coagadex drug substance manufacturing process identified by Failure Mode Effects Analysis (FMEA) risk assessment (with regard to the quality target product profile and quality attributes) are limited to the virus inactivating steps.

In-process controls (IPC) with defined acceptance limits for the critical steps have been established to ensure product quality and safety.

Process validation and / or evaluation

Elements of Process Validation

Process Validation for FACTOR X has adopted the principles of Process Design, Process Qualification and retrospective statistical process qualification.

Process Design

Process Design, based on the target product profile and quality attributes, is described as part of pharmaceutical development.

Process Qualification

Process performance qualification has been performed and is reported for the dedicated steps of FACTOR X bulk drug substance manufacture.

Retrospective statistical process qualification

Retrospective statistical process qualification has been performed on the established fractionation process steps according to process- and product- monitoring procedures using the data from historical batches. This retrospective approach was used due to the absence of a prospective process performance qualification protocol when these established steps were first introduced.

The chosen methodological approach was Principal Component Analysis (PCA) to project high-dimensional data clouds to lower dimensional spaces. Analysed outputs have been presented in various graphical forms (Summary of fit; X/Y Overview Plot PCA; Score Scatter Plot; Hotelling's T2 Plot) derived from an optimized model. Although, generally, this approach is considered acceptable, for ease of understanding a number of questions regarding presentation and explanation of the results of Principal Component Analysis were addressed and further clarified.

Additionally, statistical process control charts (in form of Shewhart plots) displaying data measured on the process or product over time to detect e.g. process shifts, trends have been provided.

Process Validation of Dedicated FACTOR X manufacturing steps

Validation of the dedicated steps of FACTOR X bulk drug substance manufacture was performed by process performance qualification (PPQ) for three batches of FACTOR X bulk drug substance produced at commercial scale for provision of clinical material.

A detailed Process Performance Qualification Protocol summarising process parameters and quality attributes to be tested has been provided. The Applicant stated in the Process Validation Report that the results were within the acceptance criteria without presenting the respective data. The relevant data was provided supporting the conclusion that FACTOR X is manufactured in a controlled and consistent manner.

Validation of repeat virus-filtration

Exposure of FACTOR X intermediate to repeated filtration through virus-filters has been evaluated.

Two studies have been reported: the first evaluated the effect of repeat small-scale virus-filtrations of virus-filtered factor X intermediates from 3 batches which had been manufactured at full commercial scale; the second study evaluated the effect of repeated virus-filtrations at full commercial scale using one batch.

Based on the validation data provided and taking into consideration that potential thrombogenicity is tested for at drug substance and drug product batch release, two consecutive (one-fold repeated) virus filtrations during manufacture of STABILISED FACTOR X drug substance are considered acceptable in the event of a technical failure. Furthermore, criteria have been presented which may prompt a repeat (reprocessing) of the virus-filtration step.

Reprocessing of process filtration

Reprocessing step claimed for filtration of prothrombin complex solution has been justified by the respective experimental data. Nevertheless, the reprocessing of the filtration step was restricted to one-fold (total of two consecutive filtrations).

Storage Stability of Process Intermediates

Hold times for process intermediates were confirmed with relevant provided stability data.

Manufacturing process development

The purification process of factor X utilises initial steps which were originally developed for the purification of other products. Factor X enriched intermediate ("Partially-Purified Factor X") for FX production is a "by product" obtained during these process steps, thus complying with guideline on plasma-derived medicinal products (EMA/CHMP/BWP/706271/2010) which encourages the best use of plasma donations.

Developmental studies on separation of prothrombin complex concentrate from cryoprecipitate-depleted plasma by chromatography and Solvent/detergent treatment were performed using factor IX as substitute for the proteins of the prothrombin complex (including factor X). This approach is considered acceptable, since the studies are relevant for factor X as well.

Evaluation Methods

Each step of the FACTOR X bulk drug substance manufacturing process underwent two stages of pharmaceutical development. In the first stage, the process was derived by empirical experimentation, based on prior knowledge and experience. In the second stage, the robustness of the process step (also known as the design space) was determined by experimental design. These studies have been conducted using small-scale processes which are representative of the commercial-scale operation.

The pharmaceutical manufacturing process development of each step is described according to these two stages.

Additional data have been provided concerning manufacturing process development (rationale for selection of critical quality attributes, material attributes, presence of absence of significant changes in the manufacturing process development, meaning of design space on the manufacturing process).

Characterisation

Elucidation of structure and other characteristics

Biological properties and Factor X Purity

Seven batches of FACTOR X bulk drug substance were tested for biological properties and purity using factor X chromogenic, clotting and antigen assays, factor X specific activity, SDS PAGE and Western blotting.

Use of three different assays to determine the concentration of factor X in seven FACTOR X bulk drug substance batches including two potency assays (chromogenic assay according to Ph Eur; clotting method and a Sandwich ELISA measuring factor X antigen) revealed differences in the results for the concentrations of factor X. The Applicant states that the bias between the assays all fall within a range considered being normal assay variation. This seems acceptable.

Routinely, FACTOR X bulk drug substance potency is assigned using the chromogenic activity assay complying with the current Ph Eur compendial method (01/2008:20719). Validity of the assay to measure the biological activity has been demonstrated.

Immunochemical properties

An immunochemical method was developed to detect atypical factor X antigens (neo-antigens) which may be exposed or generated due to modification of the native molecule during the manufacturing process. Seven batches of FACTOR X bulk drug substance tested for evidence of neo-antigens using this method showed only trace amounts of neo-antigens.

Impurities

The purity of FACTOR X bulk drug substance, batches manufactured during process performance qualification (PPQ) were compared with previous batches which were manufactured to support pre-clinical and clinical development of the FACTOR X product by using gel electrophoresis methods as well as tests for potential thrombogenicity.

Characterisation of FACTOR X bulk drug substance impurities included testing for the presence of other plasma proteins which are co-purified during the FACTOR X manufacturing process.

Based on the results of the potency assays used, published values for the plasma concentrations of these plasma proteins were used to calculate the contribution of each by weight to the overall composition of FACTOR X bulk drug substance. According to this, factor X is the predominant protein in FACTOR X bulk drug substance. The remaining protein is mostly factor II. Other plasma proteins comprise less than 1% of the total protein.

Further clarification and data have been given concerning aggregates, process related intermediates and contaminants.

Specification

There are no pharmacopoeial monographs for human coagulation factor X. Thus compliance standards have been set by Bio Products Laboratory Limited (BPL) in line with ICH Q6B. The selection of tests to be part of the active substance batch release includes potency assay (factor X activity), excipients ranges (chloride and sucrose) and methods to control product-related impurities and process-related impurities.

Pharmacopoeial methods are identified as such but not described, except for the active ingredient. Modified pharmacopoeial methods and non-pharmacopoeial methods are described.

The potency (IU factor X/mL) of Coagadex drug substance and drug product is determined using the European Pharmacopoeia chromogenic assay indicated for human coagulation factor X

(01/2008:20719). This assay method consists of activation of factor X by Russell's viper venom specific factor X activator, followed by enzymatic cleavage of a chromogenic factor Xa substrate to release a chromophore quantifiable by spectrophotometry. Under appropriate assay conditions, there is a linear relation between factor Xa activity and cleavage of the chromogenic substrate.

Validation data for methods not applicable to drug product have been shown in the active substance section. Validation data for methods that are the same for bulk drug substance as for FACTOR X final drug product have been shown in the drug product section.

Stability

The FACTOR X bulk drug substance is stored frozen prior to manufacture of FACTOR X final drug product. A study was conducted to determine the storage stability of this bulk drug substance, using samples taken from commercial-scale batches. Samples were stored in at three temperatures (-20°C, -30°C and -40°C) over a 9-month period.

In both studies, stability-indicating parameters of functional activity, purity, potential thrombogenicity and physical chemistry were measured in samples stored between -20°C and -40°C. Three commercial-scale batches were tested for periods up to 9 months and one pilot scale batch (derived from commercial-scale manufacture) was tested for periods up to 12 months.

The FACTOR X bulk drug substance factor X potency was within the control for all three batches under all storage conditions. Protein concentration, pH and conductivity remained consistent throughout the study for all samples and storage conditions, with no apparent trends. All samples passed tests for potential thrombogenicity throughout the study, with no apparent trends.

The specific activity of all three batches remained within 80-120% of the time zero throughout the study and specific activity was considered to show no time dependent or temperature-dependent trend.

Further clarification/data was requested with regard to storage of the active substance and has been provided.

Based on both stability studies reviewed (commercial and pilot scale study), storage conditions proposed for FACTOR X bulk drug substance of up to 9 months, when stored at ≤ -20°C, are considered acceptable.

Comparability exercise for Active Substance

The Applicant demonstrated that the drug substance manufactured by the validated process intended for commercial production is representative of drug substance manufactured for clinical use.

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical Development

The active substance, FACTOR X of Coagadex is from human plasma.

FACTOR X is a sterile, freeze-dried concentrate of human coagulation factor X. FACTOR X is presented as two dose sizes of 250 International Units (IU) and 500 IU of factor X (nominal).

FACTOR X is supplied with Sterilised Water for Injections as solvent for reconstitution of the freeze-dried powder. 2.5mL Sterilised Water for Injections is supplied with the 250 IU dose and 5mL Sterilised Water for Injections is supplied with the 500 IU dose.

A Mix2Vial is also supplied (CE mark Certificate: 346 EC and 510(k) number: K031861). This is a sterile, non-pyrogenic, single-use fluid transfer device that allows quick transfer of Water for Injection solvent to FACTOR X freeze-dried product, and of the reconstituted FACTOR X product into a syringe for administration.

The composition of active substance in FACTOR X is 100 IU/mL (nominal) in both the 250 IU and 500 IU dose size presented in Table 4 below:

Table 1: Composition of FACTOR X active ingredient

Name of Active Ingredient	Function	Reference	Quantity		
			per mL	per 250 IU vial	per 500 IU vial
Human coagulation factor X	Active	BPL [a]	100 IU	250	500

[a] There is no USP or Ph.Eur. monograph for factor X

The choice of excipients is justified and their functions explained.

The components are filled in type I glass vials with halobutyl rubber stoppers. The container closure system complies with Ph Eur requirements.

Pharmaceutical Development

The formulation of FACTOR X final drug product has been derived from the composition of elution buffers used during chromatographic purification and stabilization of FACTOR X bulk drug substance. During development of those chromatographic steps, citrate and phosphate salts were used to buffer the pH and ionic strength was controlled using these salts in combination with sodium chloride.

Additional formulation studies were performed to ensure that FACTOR X final drug product and the factor X active ingredient was stable during final freeze-drying, terminal heat-treatment, and subsequent long-term storage.

Physicochemical properties:

FACTOR X is a friable white or off-white freeze-dried powder which is readily soluble (not greater than 5 min) in solvent (Sterilized Water for Injections). The re-dissolved solution is clear and colourless.

After reconstitution, FACTOR X contains a low concentration of protein stabilized with buffer counter ions and sucrose.

FACTOR X final drug product has been characterized using non-routine analytical methods, to evaluate the aggregates and degradation products in the reconstituted drug product. Based on this data, a specification for “Aggregates” at Coagadex drug product batch release may not be necessary.

Biological properties:

FACTOR X has been quantified by chromogenic activity assay, clotting assay and determination of factor X binding to an anti-factor X antibody. Results of the different assays showed that chromogenic assay and the clotting assay were equivalent. The bias between the chromogenic assays and the clotting assay was attributed to the individual assay accuracy and inter-assay variation.

The protein composition and characterization of FACTOR X were described at pilot scale and at full commercial scale by different assays to measure factor X and protein impurities. Factor X is the predominant protein in FACTOR X final product. With the submitted data the remaining protein is mostly factor X. Other plasma proteins were only detected in small amounts.

With the non-activated partial thromboplastin time (NAPTT) assay clotting time after re-calcification was tested to look for possible activated coagulation factors, which would shorten the clotting time.

Manufacturing process development

The process of formulation development was an iterative process which embraced the three contiguous elements of formulation, freeze-drying and heat-treatment. This section describes the simultaneous pharmaceutical development of these three steps.

A Quality Target Product Profile (QTPP) and quality attributes were defined to include the relevant aspects of existing monographs for other coagulation factor products and the clinical and product characteristics required for a safe and efficacious treatment of factor X deficiency. The Applicant explained that each step of the FACTOR X manufacturing process underwent two stages of pharmaceutical development. In the first stage, the process was derived by empirical experimentation, based on prior knowledge and experience. In the second stage, the robustness of the process step (also known as the design space) was determined by experimental design. The design space robustness was determined by assessment of product outputs in response to adjustment of process control inputs over a pre-defined range.

These studies have been conducted using small-scale processes which are representative of the commercial-scale operation. The starting material for such small-scale studies was drawn from an intermediate pilot-scale process or from the full commercial-scale manufacturing operation.

Extensive examinations on the optimal Factor X intermediate and final product formulation, with different excipients, stability studies of FX with different pH conditions or different sugar/salt combinations were performed in order to get a formulation which provides sufficient product stability.

The Applicant decided to pursue the development of a lyophilised dosage form. Therefore the formulation was optimized to get an appropriate lyophilised cake appearance. The heat treatment step was optimized and results of different studies confirm that most of the factor X functional activity is preserved across the heat-treatment process step.

Manufacture of the product and process controls

Manufacturer of the FDP (final drug product) as well as names and addresses of testing laboratories are provided. Furthermore a representative batch formula has been provided that includes a list of all components to be used in the manufacturing process and their upper and lower limit of the amounts per batch has been provided.

A description and detailed flow chart of the manufacturing process of FACTOR X Drug Product were provided.

Critical steps in the FACTOR X final drug product manufacturing process were identified by Failure Mode Effects Analysis (FMEA) risk assessment, with regard to the quality target product profile and quality attributes. Critical steps in the manufacturing process of FACTOR X Drug Product are defined and seem to be controlled by appropriate test methods with the exception of bioburden testing.

Process Validation for FACTOR X follows the structure of Process Design and Process Qualification. Process Design, based on the target product profile and quality attributes, is described as part of pharmaceutical development. Validation of the manufacturing steps in general: The whole manufacturing process was evaluated in order to demonstrate that the process is capable to deliver a product that constantly meets predefined acceptance criteria. Deviations during process validation were identified and explained.

To review consistency of the manufacturing process of drug product of FACTOR X different PPQ batches and clinical batches with different test systems were tested. The Applicant compared the test results of the different non routine assays with data of previous studies.

The Applicant restricted the reprocessing to two sterile filtrations and provided the criteria for reprocessing.

Characterisation of impurities

The impurities in FACTOR X were grouped into three classifications and tested in between 7 and 14 batches:

Plasma proteins impurities

Plasma proteins impurities are the impurities in drug substance which are co-purified throughout the manufacturing process. The impurities in this group were analysed with non-routine methods and the concentration of all identified protein impurities was below reported concentration of those proteins in normal plasma.

Non-protein impurities

Non-protein impurities are introduced during the manufacturing process and may not be completely removed in the drug product.

Chemicals which are added during the FACTOR X manufacturing process are measured in the routine testing of final product against specification. These comprise excipients (salts and stabiliser) present within specified limits and impurities added and then substantially removed during the manufacturing process.

Protein activation, degradation or aggregation products

The methods used to look for the presence of protein activation, degradation or aggregation products in FACTOR X batches were briefly described and results of tested FACTOR X batches were provided.

Product specification

There are no pharmacopoeial monographs for human coagulation factor X. Thus compliance standards have been set by Bio Products Laboratory Limited (BPL) in line with ICH Q6B.

The finished product specification includes test for general attributes, potency (Factor X activity determined by the European Pharmacopeia chromogenic assay indicated for human coagulation factor X (01/2008:20719)), identity, purity, excipients ranges (chloride, phosphate, citrate, sucrose and sodium) and microbiological safety (sterility and endotoxins).

The selection of tests for finished product batch release is acceptable. The proposed finished product specification raised some questions that were satisfactorily addressed. The proposed specifications are considered adequate.

Analytical procedures

Pharmacopoeial methods were identified as such but not described. Modified pharmacopoeial methods and non-pharmacopoeial methods were shortly described.

Detailed method descriptions were provided. The use of the endotoxin test instead of the pyrogen test has been justified based on provided data as requested by the Guideline on the replacement of rabbit pyrogen testing by an alternative test for plasma derived medicinal products (EMEA/CHMP/BWP/452081/2007).

Reference Standard

Issues concerning reference standards used have been adequately described by the Applicant.

The Applicant states that factor X activity in the final drug product is measured against a factor X standard preparation. This is either the WHO International Standard for Factors II and X Concentrate (4th International Standard) (#11/126), or a local standard (6th British Working Standard for Blood Coagulation Factors II, IX, X, Concentrate (07/326) which has been calibrated against the contemporaneous WHO International Standard.

The Applicant provided information on the characterisation of the in-house secondary standards and on their calibration against the WHO International Standard for Factors II and X Concentrate (4th International Standard).

Stability of the product

The Applicant claims a shelf-life of 36 months at+2°C to +30°C for the lyophilisate.

Long term stability data from 6 manufacturing batches in the final container stored under the temperatures of +5°C, +25°C, +30°C for 36 months and +40°C for 12 months, with protection from light, have been provided.

For one batch, which was used in the long time stability studies, the intermediate was stored frozen within 6 months.

Two pilot scale batches were further tested for long term stability at +5°C, +25°C, +30°C for 36 months and +40°C for 12 months.

Additionally, all these batches were stored for 36 months at -40°C for use as a reference when estimating biological activity.

Furthermore two reconstitution studies were presented.

Study 1 was performed on FACTOR X 500 IU final drug product (2 commercial scale batches and 1 pilot scale batch), in accordance with batch availability and monitored stability of the reconstituted product for up to 1 hour at 25°C ± 2°C after reconstitution.

Study 2 included the FACTOR X 250 IU final drug product (2 commercial scale batches) and extended the monitoring period to up to 2 hours at 25°C ± 2°C after reconstitution.

Compatibility between FACTOR X and the Mix2VialTM needle-less transfer device, has been demonstrated.

Issues were identified concerning storage of drug product and the reconstituted product that have been answered sufficiently.

The results generated during the stability studies support the proposed shelf life of 3 years at+2°C to +30°C. After reconstitution, from a microbiological point of view, the product should be used immediately.

However, chemical and physical in-use stability has been demonstrated for 1 hour at room temperature (25°C ± 2°C).

Finished product - Solvent WFI in 5 ml glass vials

The information provided in the dossier for the solvent shows that the solvent Water for Injections (sWFI) is manufactured by Bio Product Laboratories Ltd, Elstree under GMP compliant conditions using

a validated process. sWFI is provided as 2.5 ml and 5.0 fill sizes in 5 ml type I glass vials. The vials are stoppered using a Halobutyl rubber stopper with Flurotec coating compliant with the requirements of the Ph Eur 3.2.9. The overseals are made of aluminium with a polypropylene flip off tamper evident cap. The sWFI meets Ph Eur requirements for sterile WFI and has a shelf life of 48 months when stored at +5°C to +30°C. The proposed shelf life conditions are supported by real time stability data.

Adventitious agents

Transmissible Spongiform Encephalopathies (TSE)

Plasma is purchased from approved suppliers in the USA included in the Applicant's centrally certified Plasma Master File (PMF).

None of the FACTOR X excipients or manufacturing ingredients is of human or animal origin.

Risk estimation with regard to TSE transmission was performed to a certain extent.

TSE removal studies were performed for several manufacturing process steps.

The results show that the different studied steps seem to be adequate to remove TSE. The global reduction factors were satisfactory.

Viral Safety

Plasma is purchased from approved suppliers in the USA included in the Applicant's centrally certified Plasma Master File (PMF).

An updated virus risk assessment was submitted to estimate the residual risk of viral transmission.

Virus validation studies were performed for several manufacturing process steps.

The results show that the different studied steps are effective and robust to inactivate/eliminate the model viruses.

The manufacturing process has been sufficiently investigated for virus reduction. The global reduction factors were satisfactory.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends some points for investigation.

2.3. Non-clinical aspects

2.3.1. Introduction

The pharmacological properties of FACTOR X have been investigated in several in vitro studies. Safety pharmacology comprised investigation of thrombogenicity in vitro and in vivo in rats and rabbits. Toxicological studies have been conducted in rats and NZW rabbits.

2.3.2. Pharmacology

Primary pharmacodynamic studies

Primary pharmacodynamic studies have been conducted in four *in vitro* test systems. In vivo efficacy studies have not been performed in animals due the lack of an available animal model for factor X deficiency. FACTOR X was able to correct the coagulation defect in plasma in a dose dependent manner in several coagulation test systems (PT, APTT, TGA, TEG), which measured different characteristics of the coagulation pathway (table 14).

Table 2: Tabulated summary of Primary Pharmacodynamics *In Vitro* Studies

Test system	Test material	Control material	Reference material	Result
Prothrombin Time	FACTOR X (n=7)	Factor X-deficient plasma (negative); Normal pool plasma (positive)	Reference plasma	1 IU/mL FACTOR X corrected the prolonged PT of deficient plasma.
Activated Partial Thromboplastin Time	FACTOR X (n=7)	Factor X-deficient plasma (negative); Normal pool plasma (positive)	Reference plasma	1 IU/mL FACTOR X corrected the prolonged APTT of deficient plasma.
Thrombin Generation Assay	FACTOR X (n=3)	Factor X-deficient plasma (negative); Normal pool plasma (positive)	N/A	Thrombin generation in factor X-deficient plasma corrected to normal by dose-dependent addition of FACTOR X
Thrombin Generation Assay	FACTOR X (n=4)	Factor X-deficient plasma (negative)	Reference plasma	1 IU/mL FACTOR X corrected the absent thrombin generation in deficient plasma close to the reference plasma range.
Thrombo-elastography	FACTOR X (n=4)	Factor X-deficient plasma (negative); Normal pool plasma (positive)	N/A	1 IU/mL FACTOR X corrected the suppressed TEG parameters in deficient plasma close to the normal plasma range.

Secondary pharmacodynamic studies

Secondary pharmacodynamic studies of FACTOR X have not been submitted (see discussion on non-clinical aspects). Secondary pharmacodynamics of the excipients and impurities were presented as a bibliographic review of data and revealed no safety concerns.

Safety pharmacology programme

Eight in vitro safety pharmacology studies derived from 6 complementary in vitro test systems and 3 in vivo studies in rats and rabbits were conducted to assess the thrombogenic potential of FACTOR X. In vivo hypercoagulability was investigated in a modified Wessler Test in rabbits, whereas the PT and APTT determination was part of the single dose (B74250) and repeat dose (C16823) toxicity studies in rats.

The highest dose tested (2400 IU/kg BW) in animals with normal haemostasis was 40 times the intended maximum human prophylactic clinical dose (60 IU/kg BW).

Table 3: in vitro Safety Pharmacology Studies

Type	Test / Study report	Detects	Result	Study Number
Global haemostasis	Non-activated partial thromboplastin time (NAPTT)	Thrombogenic activity	No evidence of increased thrombogenic activity	FXR309, FXR320
Specific clotting assay	Fibrinogen clotting time (FCT)	Thrombin	All assays within the reference range	FXR329
Activated factor X	Xa assay (SDS PAGE Western blot; Specific clotting factor assay)	Endogenous activated factor X	Very low levels detected – approximately 0.001% of t total factor X is in the activated form	FXR349
Thrombin	Thrombin assay (SDS PAGE Western blot; Specific clotting factor assay)	Endogenous activated prothrombin		FXR344
Global haemostasis	Thrombin Generation Assay (TGA)	Prothrombotic activity	No greater reactivity than normal plasma	FXR355
Global haemostasis	Thromboelastography (TEG)	Thrombogenic activity	No greater reactivity than normal plasma	FXR307
General proteolytic activity	Generic activity	Endogenous protease activity against substrates	No greater reactivity than normal plasma	FXR310

Table 4: in vivo safety pharmacology studies

Organ Systems Evaluated	Species/ Strain	Method of Admin.	Doses [a]	Gender and No per group	Noteworthy findings	GLP Compliance	Study Number.
Hemostasis	Rat Han:RCC WIST (SPF)	Intravenous bolus in caudal vein	Test article: 60, 600 and 2400 IU/kg b.w Buffered saline with sucrose: 20mL/kg b.w	3M: 3F	No dose-dependent change in PT ratio or APTT at day 2 or day 14. No difference between FACTOR X, saline control and historical reference data. No difference between response of males and females. No evidence of acute or chronic thrombotic response after single treatment with FACTOR X.	Yes	B74250
Hemostasis	Rat Han:RCC WIST (SPF)	Intravenous bolus in caudal vein	Test article: 30, 120 and 360 IU/kg b.w. repeated every other day Buffered saline with sucrose: 20mL/kg b.w repeated every other day	10M: 10F	No dose-dependent difference in PT ratio or APTT between FACTOR X groups and saline control group at day 28. No difference between test results and historical reference data. No difference between response of males and females. No evidence of acute or chronic thrombotic response after repeated treatment with FACTOR X.	Yes	C16823
Hemostasis - Thromboenicity	Rabbit New Zealand White	Intravenous	Test article: 100, 200 and 400 IU/kg b.w. Thrombin: 50 IU/kg b.w. PCC: 200 IU/kg b.w. Saline: 1mL/kg b.w.	3M: 3F	At doses which exceeded the intended maximum dose in man, there was no statistically significant difference in thrombogenicity scores between FACTOR X treated groups and saline negative control	Yes	S07740

In the in vivo studies there was no dose-dependent change in PT or APTT at day 2, 14 or 28 in male or female rats was detected.FACTOR X did not induce an acute thrombotic response or a chronic thrombotic response, even after high and repeated doses and no statistical significant difference in thrombogenicity scores could be detected between FACTOR X and control group.

Pharmacodynamic drug interactions

No pharmacodynamic drug interaction studies were submitted (see discussion on non-clinical aspects).

2.3.3. Pharmacokinetics

Non–clinical pharmacokinetic studies were not submitted (see discussion on non-clinical aspects).

2.3.4. Toxicology

Single dose toxicity

Single dose (IV) study in rats - B74250 (GLP):

This was designed as a single IV administration of buffered saline (control), 60 IU/kg, 600 IU/kg and 2400 IU/kg BW to 6 M/6 F HannRcc: WIST (SPF) rats

There were 2 deaths: 1 animal died before treatment; 1 animal (60 IU/kg BW) died on day 15 during blood sampling, the administrations well tolerated. Single intravenous administration of FACTOR X at a dose level of 60, 600 and 2400 IU/kg BW had no influence on survival, body weight and food consumption. Early-onset and transient clinical signs were recorded in one isolated animal at the high dose group of 2400 IU/kg BW and had no impact on the macroscopic and microscopic findings.

FACTOR X at the low, mid and high dose caused no morphological alterations in the organs and tissues examined. The gross organ findings noted at necropsy were considered to be within the range of normal background lesions that may be seen in rats of this strain and age and were considered incidental, reflecting the usual individual variability. The no-observed-effect-level (NOEL) in this study was established at 2400 IU/kg BW, the highest dose used. The mode of administration reflected the clinical use (IV). No adverse effects were evident at the selected doses of 60 IU/kg, 600 IU/kg and 2400 IU/kg BW.

Repeat dose toxicity

A repeat dose, 29 days, GLP compliant sub-acute toxicity study was conducted in Sprague Dawley rats (C16823) with IV dosing every other day of 0 IU/kg, 30 IU/kg, 120 IU/kg and 360 IU/kg BW to study toxicity, toxicokinetics and immunogenicity.

Species/ Strain	Method of Administration (Vehicle/Formulation	Duration of Dosing	Doses	Gender and No per group	NOAEL	Noteworthy findings	Study Number.
Rat Han:RCC WIST (SPF)	Intravenous bolus in caudal vein	Every other day for 29 days	0, 30, 120, 360 IU/kg b.w.	10M: 10F	>360 IU/kg b.w/dose	Significant ($p<0.01$) change in WBC in females dosed at 360 IU/kg b.w possibly test item related but not adverse. Significantly ($p<0.01$) elevated sodium in males dosed at 120 IU/kg b.w. and both males and females at 360 IU/kg b.w.. Significantly ($p<0.01$) elevated calcium and phosphorus in females dosed at 360 IU/kg b.w. Considered to be test item related. Inflammation/haemorrhage at the injection sites in all groups – not considered test item related. NOEL: 30 IU/kg b.w./dose	C16823

Groups' allocation was as follows:

Table 5: Allocation of Tests: 28-Day Repeat Dose Toxicity Study

Allocation	males:females per dose group	Test [a]	Test Frequency
A	10:10	**Mortality/Viability**	**Twice daily**
		Clinical signs	**2x daily (1-3); Daily (4-29)**
		Ophthalmoscopy (high dose & control groups only)	**Week 4**
		Food consumption/body weight	**Weekly**
		Clinical laboratory investigations (blood and urine)	**Week 4**
		Immunotoxic potential (by leucocyte population in 6 male and 6 female per group)	Week 4
		Post-mortem pathology	29
B	3:3 (control group) 9:9 (test groups)	**Toxicokinetics**	**Week 1; Week 4**
		Mortality/Viability	**2x daily**
		Clinical signs	**2x daily (1-3); Daily (4-29)**
		Food consumption/body weight	**Weekly**
		Blood sampling for antigenicity study (3m:3f)	Day 25 (group 1); Day 29 (group 2-4)
C	6:6	Immunotoxic potential (by IgM primary immune response to immunogen) (immunise/test)	Immunize day 24; test day 29
		Mortality/Viability	**Twice daily**
		Clinical signs	**2x daily (1-3); Daily (4-29)**
		Food consumption/body weight	**Weekly**
		Blood sampling for antigenicity study	Day 14

[a] Tests reported in this section are highlighted

Figure 1: Mean Plasma Concentrations of FACTOR X in Male Rats on Day 1

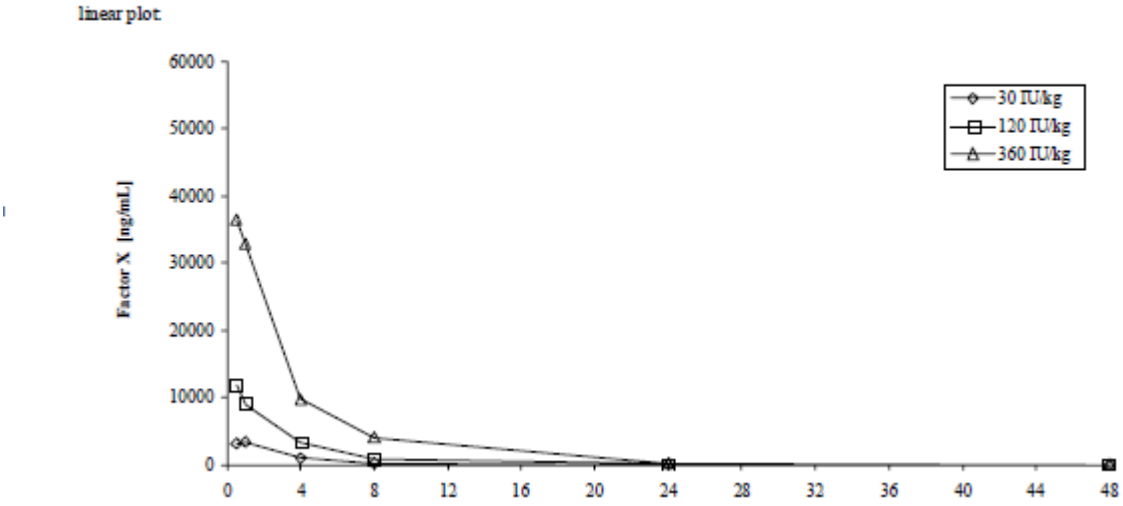
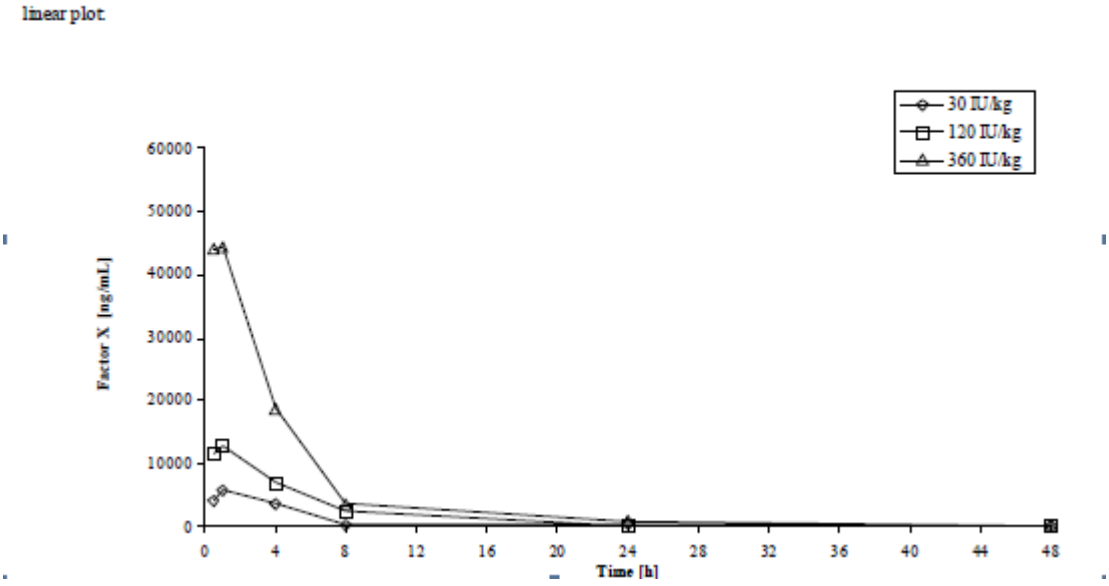


Figure 2: Mean Plasma Concentrations of FACTOR X in Male Rats on Day 29



In overall, repeated doses up to 360 IU/kg BW (14 applications) within 29 days were well tolerated in rats. There were no test item-related effects on mortality, viability, clinical signs, food consumption, body weight, ophthalmoscopy, urine analysis, organ weights, macroscopic findings or microscopic findings.

Sodium, calcium and phosphorus were elevated in some animals (male and female) in the mid- and high-dose groups (120 IU/kg BW and 360 IU/kg BW). In the absence of clinical findings or findings in related biochemistry parameters or microscopic findings of the kidneys or bones, these findings were considered to be not adverse.

The toxicokinetics of factor X were dose-dependent, without gender difference. Dose dependency was reduced after repeated treatment. This may be due to the presence of rat antihuman factor X antibodies, which could mask the detection of factor X.

Genotoxicity

No genotoxicity studies were conducted (See discussion on non-clinical aspects).

Carcinogenicity

No carcinogenicity studies have been conducted (See discussion on non-clinical aspects).

Reproduction Toxicity

No reproductive and developmental toxicity studies have been conducted (See discussion on non-clinical aspects).

Toxicokinetic data

Toxicokinetic data were obtained from the repeated dose toxicity studies and are discussed in the relevant section above.

Local Tolerance

Local tolerance study in NZW rabbits - Study No.: C7092

In this study coagadex was administered as I.V. in the right marginal ear vein; intraarterial: central right ear artery; paravenous injection: adjacent to right marginal ear vein; in one male / 2 females per group.

Study and results are described in Table 18.

Table 6

Species/ Strain	Method of Admin.	Doses	Gender and No per group	Noteworthy findings	Study Number.
Rabbit New Zealand White	Single pumped infusion over 30 minutes via: •Intravenous injection •Paravenous injection •Intra-arterial injection	0, 600 IU/kg b.w (5mL/kg b.w) (1.76-3.09mL/kg b.w for paravenous injection, due to overflow)	1M : 2F	Paravenous injection: Transient local findings in test and control ears. Slight erythema (male and one female) resolved by days 4 and 3, respectively. No local signs in one female. Intra-arterial injection: Early-onset, fully-reversible local findings: slight-to-severe erythema (more pronounced in test ears than in control ears); slight-to-severe oedema in test ears; slight-to-moderate reversible oedema in one female control ear. Peri-arterial, dermal inflammation increased, with minimal-to-moderate fibrosis, acanthosis and scab formation, in test ears compared to control ears. One female test ear artery showed minimal arteritis/periarteritis. Evaluated as showing an effect from the test item.	C7092

Other toxicity studies

The antigenicity of FACTOR X has been evaluated by in vitro and ex vivo studies.

Antigenicity test in vitro– Study Number: FXR361

Antibodies which reacted with neoantigens associated with damaged factor X in preference to native factor X were raised in sheep and used in a semi-quantitative ELISA assay which was developed to differentiate between native factor X (negative response) and heat-damaged factor X. At equivalent

concentrations of factor X, the batches of FACTOR X were negative in the neo-antigen test, whereas different prothrombin complex concentrate products were positive to varying degrees. At equivalent concentrations of total protein, the batches of FACTOR X were slightly positive in the neo-antigen test and the responses were similar for the different prothrombin complex concentrate products tested for comparison.

Based on in vitro antigenicity testing no neo-antigens were detected in FACTOR X, but to varying degrees in other clinical PCC products.

Antigenicity ex vivo test – Study Number: FXR244

A repeat dose, 29 days, toxicity study of FACTOR X was conducted in rats (C16823), (see repeat dose toxicity studies) in which, the formation of rat antibodies to human factor X was investigated and their neutralising (inhibitory) activity was measured by a semi-quantitative ELISA for antibodies to human factor X and a Bethesda assay (Nijmegen modification) for neutralising (inhibitory) antibodies

At day 14 antibodies were detected in all test groups treated with FACTOR X, the response was slightly less in the lowest dose group (30 IU/kg) and some of the females in this group did not give a positive response. At doses of 120 IU/kg and 360 IU/kg the incidence of a positive response was 100%. After 28 days the antibody response and incidence were similar for all FACTOR X dose groups, although females receiving the highest dose (360 IU/kg) showed a slightly higher response than the males.

Using the Bethesda assay for neutralising antibodies, at 14 days all groups showed the same small inhibitory response, including the control group which did not receive FACTOR X. At 28 days, the average result was lower than at 14 days and the control group was found to be negative for inhibitory antibodies. However, the purpose of these studies was to determine whether there was a difference between the control rats and the rats receiving FACTOR X at various doses. There was no difference between the test and control samples at either the 14 day time-point or the 28 day time-point.

Antibodies to human factor X were developed in nearly all rats of the verum groups. Development of antibody formation was not dose dependent and no neutralising antibodies were detected. However, this humoral immune response is an expected reaction reflecting the rat immune response to a foreign (human) factor X protein and is not considered an immunotoxic effect of FACTOR X.

Immune response was not modified by treatment with FACTOR X. White blood cell count was normal in males. White blood cell count (lymphocytes and monocytes) and CD45RA+ were elevated and relative neutrophils were decreased in some females receiving the high dose of FACTOR X (360 IU/kg BW), possibly related to test item but of non-adverse character. The primary immune response (IgM) to sheep erythrocyte suspension was not impaired in any animals (treated as well as control animals).

Excipients

Excipients of FACTOR X are sodium citrate, mannitol, citric acid, sodium phosphate and sucrose. All excipients were within the specification limits, are well known and used widely in dietary and pharmaceutical products.

The potential process impurities during manufacturing are small amounts. Residual impurities were within the specification limits.

The content of product-related impurities was within the specification limits. Furthermore, the company evaluated the hazard about the impact and potential toxicity of these impurities on the basis of publicly available data. There was no indication of any hazard for human exposure.

2.3.5. Ecotoxicity / environmental risk assessment

According to the European Medicines Agency Guideline *"Guideline on the environmental risk assessment of medicinal products for human use"* products containing vitamins, electrolytes, amino acids, peptides, proteins, carbohydrates and lipids as active pharmaceutical ingredient(s), can be exempted from the submission of an ERA.

2.3.6. Discussion on non-clinical aspects

The applicant conducted primary pharmacodynamic studies in four *in vitro* test systems to demonstrate efficacy of FACTOR X. FACTOR X was able to correct the coagulation defect in plasma in a dose dependent manner in several coagulation test systems (PT, APTT, TGA, TEG) with different characteristics of the coagulation pathway. A bibliographic review of literature was presented for the excipients and impurities.

In vivo efficacy studies have not been performed in animals due the lack of an available animal model for factor X deficiency. Furthermore, no secondary pharmacodynamic studies and no studies on pharmacodynamic drug interactions were performed since factor X is a plasma derived protein, which is agreed.

No safety concerns were identified in safety pharmacology investigations examining thrombogenicity in several in vitro tests and 3 in vivo studies. The in vivo studies comprised one Wessler test in rabbits and thrombogenicity potential as part of the single dose and repeat dose toxicity studies in rats. No separate in vivo safety pharmacology study was performed, which is acceptable.

The presented pharmacology studies reveal evidence that FACTOR X will exert haemostatic effects as desired. No potential risk of thrombogenicity and proteolytic activity in FACTOR X has been evaluated.

The toxicology program covered *in vivo* toxicity studies in rats and evaluation of local tolerance in the rabbit.

Single application of up to 2400 IU/kg to rats revealed no treatment related findings. A GLP compliant repeat dose toxicity study was performed in rats with IV dosing every other day (29 days 14 applications). The limited duration of the study is acceptable due to the species specific immunogenicity, although clinically chronic administration is intended. Administration of FACTOR X up to 360 IU/kg was well tolerated. Sodium, calcium and phosphorus were elevated in some animals (male and female) in the mid- and high-dose groups (120 IU/kg BW and 360 IU/kg BW). In the absence of clinical findings or findings in related biochemistry parameters or microscopic findings of the kidneys or bones, those were considered to be not adverse.

Adequate justification for not performing safety studies in higher animals species in accordance with the current guideline "Preclinical safety evaluation of biotechnology-derived pharmaceuticals (CPMP/ICH/302/95, ICH topic S6)" was provided recognizing the plasma derived nature of active ingredient. This was also already addressed in the frame of an initial scientific advice procedure.

No effects (macroscopically and histopathological) on the reproductive organs neither in male nor in female rats were seen. Plasma-derived coagulation factors have been widely used clinically and no adverse effects concerning fertility and reproduction have been reported.
Due to the rarity of hereditary Factor X deficiency, experience regarding the use of Coagadex during pregnancy and breast-feeding is not available. Therefore, Coagadex should be used during pregnancy or breast feeding only if clearly indicated (see SmPC section 4.6).

Coagulation factor X is a plasma derived protein and is not expected to reveal carcinogenic potential therefore studies on carcinogenicity are not required, moreover proteins are not expected to interact directly with DNA or other chromosomal material and with reference to Guideline ICH S6(R1) mutagenicity studies are not to be performed.

Coagulation factor X is a human protein and is not expected to cause reproductive and developmental toxicity. No morphological/histological changes in the reproductive organs in male or female rats were observed during the repeat dose toxicity study. Animal reproduction studies have not been conducted with Coagadex (see SmPC section 4.6).

Toxicokinetic analysis, as part of the repeat dose toxicity study revealed that all animals in all dose groups were exposed to FACTOR X. Systemic exposure of factor X increased in an approximately dose-proportional manner across the dose range. There was no apparent gender-related difference in the extent of systemic exposure of factor X activity. Dose dependency was reduced after repeated treatment. This may be due to the presence of rat antihuman factor X antibodies, which could mask the detection of factor X.

Based on in vitro antigenicity testing no neo-antigens were detected in FACTOR X, but to varying degrees in other clinical PCC products. Although clinical predictivity of this study may be considered questionable, the risk for antigenicity seems to be comparatively low for FACTOR X. Testing of antigenicity as part of the repeat dose toxicity study revealed antibodies to human factor X in nearly all rats of the verum groups. Nevertheless, development of antibody formation was not dose dependent and no neutralising antibodies were detected. However, this humoral immune response is an expected reaction reflecting the rat immune response to a foreign (human) factor X protein and is not considered an immunotoxic effect of FACTOR X.

The immunotoxicity of FACTOR X was evaluated as part of the 29 day repeat dose toxicity study in rats. The expected immune response to sheep erythrocytes was not altered by treatment with FACTOR X: White blood cell count was normal in males, but slightly modified in some females in the highest dose group (360 IU/kg BW). Nonetheless, these changes are rather a response to repeated dosing with foreign human protein over 29 days than a compound specific immunotoxic effect. The primary immune response (IgM) to sheep erythrocyte suspension was not impaired in any animal.

Based on results from the repeat-dose toxicity study in rats, a no effect level (NOEL) of 30 IU/kg BW and a no observed adverse effect level (NOAEL) was identified above the highest dose tested (360 IU/kg BW). The dose of 360 IU/kg BW was 6 times higher than the maximum intended prophylactic clinical dose of 60 IU/kg BW in humans.

Local tolerance of FACTOR X was evaluated in a separate local tolerance study after IV, IA and paravenous injections in rabbits. FACTOR X was well tolerated after IV application at potencies of 600 IU/kg BW. Intraarterial and paravenous application caused local tissue reactions, which were fully reversible and are not considered to warrant concerns regarding clinical safety. The excipients and impurities warrant no specific concerns.

The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, FACTOR X is not expected to pose a risk to the environment.

Overall, the preclinical testing strategy is regarded as appropriate in view of the facts that the product is a preparation of a plasma derived protein. Clinical experience has already been obtained with prothrombin complex concentrates, where Factor X is a component together with other plasma derived products. As such by design – enrichment for Factor X and depletion of other (coagulation) proteins –

an increased safety profile is expected. The applicable regulatory guidelines were taken into consideration adequately.

2.3.7. Conclusion on the non-clinical aspects

The preclinical testing of factor X has been satisfactory, also in view of the nature of the product, a preparation of a plasma derived protein. Relevant information has been included in the SmPC.

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, single and repeat-dose toxicity, thrombogenicity and local tolerability (see SmPC section 5.3).

No investigations on genotoxicity, carcinogenicity and reproductive or developmental toxitcity have been conducted since human plasma coagulation Factor X (as contained in Coagadex) is an endogenous protein (see SmPC section 5.3).

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Study ID	No. of study centres / locations	Design	Study Posology	Study Objective	Subj. by arm entered / compl.	Duration	Diagnosis Incl. criteria	Primary Endpoint
Ten01	2/UK, 2/ES, 2 USA, 4/Turkey, 1/DE	A phase III open, multicentre study	25 IU/kg BW for PK assessment, bleeding events and preventative infusions; Dose for surgical or invasive procedures was based on subject's FX level and BW and a nominal recovery of 1.5 IU/dL per IU/Kg.	Investigation of the PK, safety and efficacy of factor X in the treatment of severe and moderate factor X deficiency; prevent bleeding and achieve haemostasis in surgical procedures	17*/15 * one patient was withdrawn during screening and did not receive FX	At least 27 weeks per subject; could be extended to a maximum of 2 years	Subjects 12 years or older with hereditary severe or moderate factor X deficiency (<5% basal FX:C at diagnosis)	**PK** IR_{30min}; $t_{1/2}$; AUC_{0-144}; $AUC_{0-\infty}$, AUC_{0-t}, CL; $MRT_{0-\infty}$; Vd; C_0; C_{max}; t_{max}; λz
Ten03	1/UK, 1/USA	A phase III open,	Loading dose before surgery to raise FX levels	Investigation of safety and efficacy of	2 patients undergoing 4 procedures	The total duration of subject's participatio	Subjects 12 years or older with hereditary	Blood loss during and after surgery

		multicentre Study	to 70-90 IU/dL, and doses after surgery to maintain the FX level above 50 IU/dL	FX in preventing bleeding and achieving haemostasis in factor X-deficient subjects undergoing surgery	(2 each)	n in the study was a maximum of 10 weeks	mild to severe factor X deficiency (basal FX:C <20 IU/dL) at diagnosis who were to undergo surgery	

2.4.2. Pharmacokinetics

The pharmacokinetics of FACTOR X, measured in terms of FX:C (using one-stage clotting and chromogenic assays) and FX:Ag activities, has been studied in two trials: Ten01 and Ten03.

Ten01 was a phase III open, multicenter study to investigate the pharmacokinetics, safety and efficacy of BPL's FACTOR X in the treatment of severe and moderate factor X deficiency (basal FX:C level <5%). The PK of FACTOR X was investigated in 16 subjects with moderate or severe factor X deficiency in the Ten01 study, 15 of whom had repeat PK profiles according to the protocol. (See Clinical efficacy).

Pharmacokinetic data analysis

Plasma concentration-versus-time curves were produced for FX:C (assayed using the one-stage clotting and the 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. PK parameters for each subject were estimated using WinNonlin PK software 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 r2 (adjusted) value assigned by the WinNonlin PK software to the curve fit for the non-compartmental analysis. If the r2 (adjusted) value was ≥0.8, the curve would automatically be considered evaluable. For any plasma concentration-versus-time profiles with r2 (adjusted) <0.8, an assessment was made whether the profile was evaluable and could be included in the PK analysis.

Pharmacokinetic data analysis

Plasma concentration data (pre-dose adjusted and unadjusted) were planned to be summarised by patient, sampling time and Visit (Baseline or Repeat PK Assessment), as appropriate; PK parameters (based on pre-dose adjusted data only) were summarised by Visit Day. All individual plasma (pre-dose adjusted and unadjusted) and PK parameter estimates were listed and summarised. Mean and individual plasma concentration versus time profiles were illustrated using both linear-linear and logarithmic-linear scales.

The protocol of the TEN01 study foresaw evaluation of single dose PK as the primary objective, evaluation of efficacy and safety 'only' as secondary objectives. The TEN01 protocol defined 'treatment success' based on two criteria, one of them being to demonstrate that the lower limit of 95% CI of t1/2 was greater than 20 hours.

Primary endpoints were Incremental recovery (IR) at 30 minutes post-dose (IR30min), apparent terminal t1/2 (non-compartmental), area under the concentration versus time curve (AUC) from time zero to 144 hours (AUC0-144h), AUC estimated from time zero to infinity (AUC0-∞), AUC from time zero to sampling time at the last quantifiable concentration (AUC0-t), systemic clearance (CL), mean residence time (MRT) estimated from time zero to infinity (MRT0-∞), volume of distribution (Vd), concentration at time zero (C0), maximum observed concentration (Cmax), time at which Cmax was apparent (tmax) and terminal elimination rate constant (λz) for FX:C (clotting and chromogenic) at the Baseline Visit and the Repeat PK assessment (usually at the 6-Month Visit).

Summary statistics included number of patients (n), arithmetic mean and standard deviation (SD). Summaries for the PK parameters were displayed the median, minimum and maximum. In addition, with the exception of tmax, the geometric mean and geometric coefficient of variation (CV) were reported for all PK parameters except tmax.

Subjects had a blood sample for FX:C and FX:Ag assays collected at the Screening Visit and blood samples for FX:C and FX:Ag assays collected at the Baseline Visit and Repeat PK assessment (usually at the 6-Month Visit), pre-dose and at the following time points, for PK assessment: 15 minutes (± 5 minutes) / 30 minutes (± 5 minutes) / 1 hour (± 10 minutes) / 3 hours (± 15 minutes)/ 6 hours (± 15 minutes)/ 24 hours (± 60 minutes) (Day 2)/ 48 hours (± 2 hours) (Day 3)/ 72 hours (± 2 hours) (Day 4)/ 96 hours (± 2 hours) (Day 5) / 120 hours (± 2 hours) (Day 6) / 144 hours (± 2 hours) (Day 7).

Pharmacokinetics in target population

Primary PK Endpoints Results

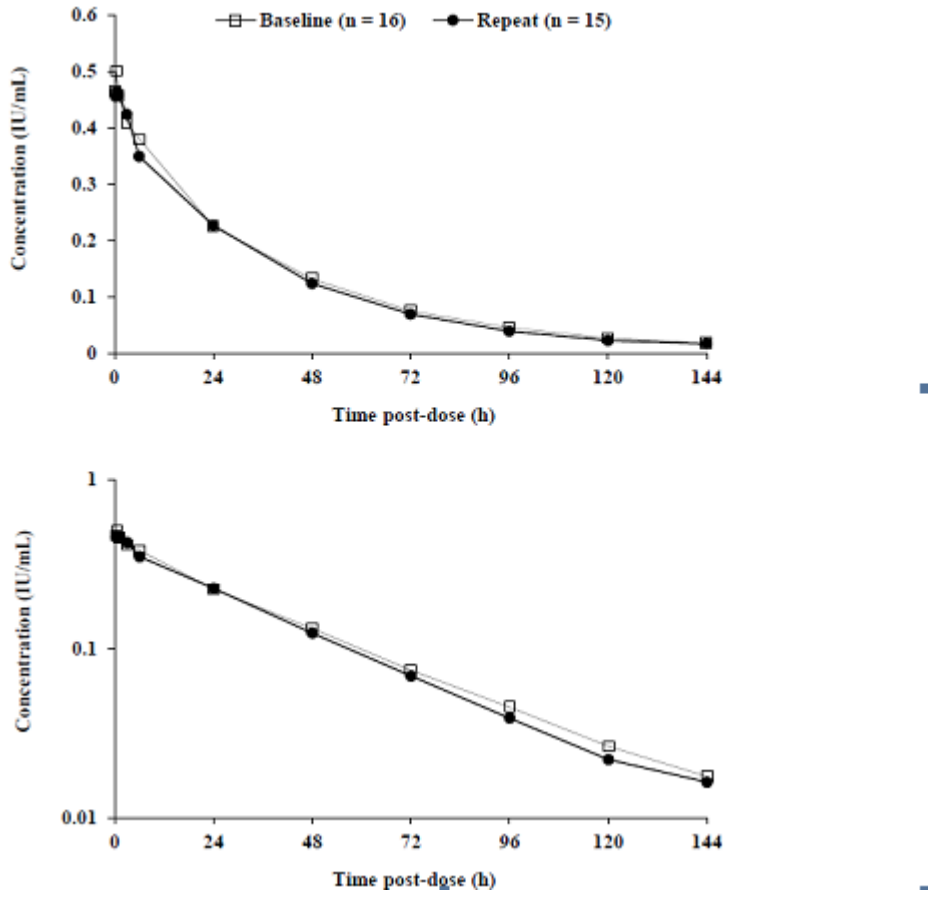
Clotting Assay

Table 7: Pharmacokinetic parameters of FX:C (clotting) at Baseline and Repeat PK assessment visits

	IR_{30min} (IU/dL per IU/kg)[a]	IR_{1h} (IU/dL per IU/kg)[b]	C_0 (IU/mL)	C_{max} (IU/mL)	t_{max} (h)	AUC_{0-144h} (IU·h/mL)	$AUC_{0-\infty}$ (IU·h/mL)	λz (/h)	$t_{1/2}$ (h)	CL (mL/h/kg)	V_{ss} (mL/kg)	V_d (mL/kg)	MRT (h)
Baseline PK assessment (N=16)													
Geometric mean	2.04	2.08	0.481	0.504	NA[c]	17.1	18.0	0.0229	30.3	1.35	56.3	58.9	41.8
CV (%)	19.5	18.1	19.0	17.2	0.233, 1.20[d]	21.0	20.9	22.8	22.8	21.7	24.0	24.6	21.7
Median	2.12	2.12	0.476	0.500	0.434	16.7	17.2	0.0237	29.2	1.40	54.5	56.6	40.9
Repeat PK assessment (N=15)													
Geometric mean	1.90	2.06	0.461	0.495	NA[c]	16.3	17.0	0.0244	28.4	1.41	55.2	57.8	39.2
CV (%)	23.2	24.1	33.5	21.8	0.200, 3.00[d]	24.3	25.6	17.2	17.2	27.2	21.7	18.7	19.0
Median	1.91	2.02	0.454	0.500	0.500	15.4	15.8	0.0263	26.3	1.50	57.8	58.0	37.3

Source: Appendix 16.5, Pharmacokinetic Report Amendment 1.
Abbreviations: CV, coefficient of variation; IR, incremental recovery.
[a] Calculated from factor X levels at 30 minutes post-dose per protocol.
[b] Calculated from peak factor X level in the first hour post-dose per EMA guidelines.
[c] Presented as median and range, as t_{max} is not a continuous variable.
[d] Range.

Figure 3: Mean pre-dose-adjusted plasma concentrations of FX:C (clotting) following a single intravenous bolus dose of 25 IU/kg FACTOR X: Baseline and Repeat PK assessment



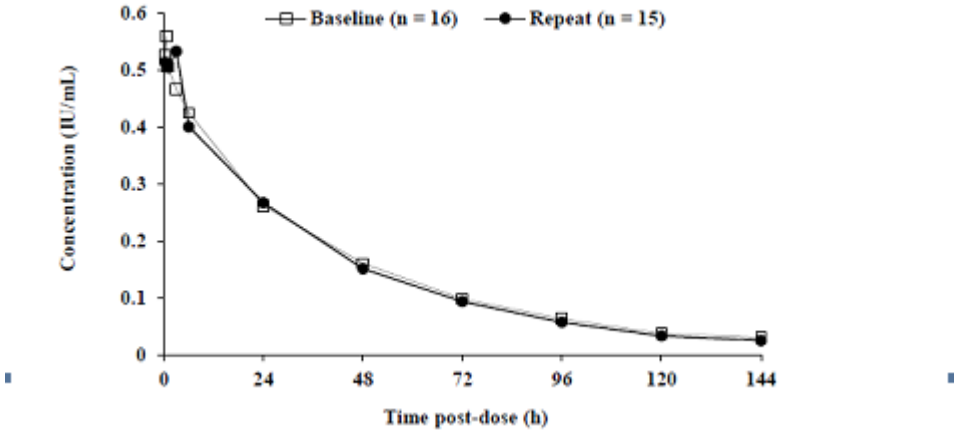
Chromogenic Assay

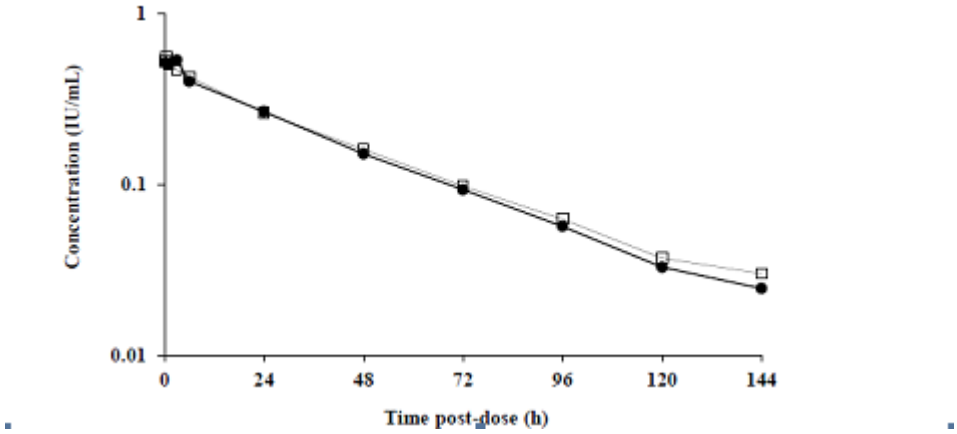
Table 8: Pharmacokinetic parameters of FX:C (chromogenic) at Baseline and Repeat PK assessment visits

	IR_{30m} (IU/dL per IU/kg)[a]	IR_{1h} (IU/dL per IU/kg)[b]	C_0 (IU/mL)	C_{max} (IU/mL)	t_{max} (h)	AUC_{0-144h} (IU·h/mL)	$AUC_{0-\infty}$ (IU·h/mL)	λz (/h)	$t_{1/2}$ (h)	CL (mL/h/kg)	V_{ss} (mL/kg)	V_d (mL/kg)	MRT (h)
Baseline PK assessment (N=16)													
Geometric mean	2.16	2.21	0.542	0.563	NA[c]	20.5	21.8	0.0205	33.8	1.17	54.5	56.9	46.7
CV (%)	18.9	16.1	20.2	15.7	0.217, 0.817[d]	24.1	25.6	25.7	25.7	23.9	22.5	21.9	22.2
Median	2.21	2.22	0.530	0.560	0.409	21.0	22.1	0.0193	35.9	1.16	53.9	57.5	48.5
Repeat PK assessment (N=15)													
Geometric mean	2.00	2.14	0.531	0.577	NA[c]	20.0	20.9	0.0223	31.1	1.20	51.2	53.8	42.7
CV (%)	19.0	18.6	22.0	30.7	0.250, 3.25[d]	24.8	27.4	23.7	23.8	27.5	17.2	17.6	21.2
Median	2.04	2.07	0.547	0.550	0.500	20.1	21.0	0.0223	31.1	1.27	50.8	55.6	44.5

Source: Appendix 16.5, Pharmacokinetic Report Amendment 1.
Abbreviations: CV, coefficient of variation; IR, incremental recovery; NA, not applicable.
[a] Calculated from factor X levels at 30 minutes post-dose per protocol.
[b] Calculated from peak factor X level in the first hour post-dose per EMA guidelines.
[c] Presented as median and range, as t_{max} is not a continuous variable.
[d] Range.

Figure 4: Mean pre-dose-adjusted plasma concentrations of FX:C (chromogenic) following a single intravenous bolus dose of 25 IU/kg FACTOR X: Baseline and Repeat PK assessment visits





In study Ten01, all 16 subjects underwent the initial PK evaluation at baseline, and 15 subjects were available for the repeat PK profile after 6 months.

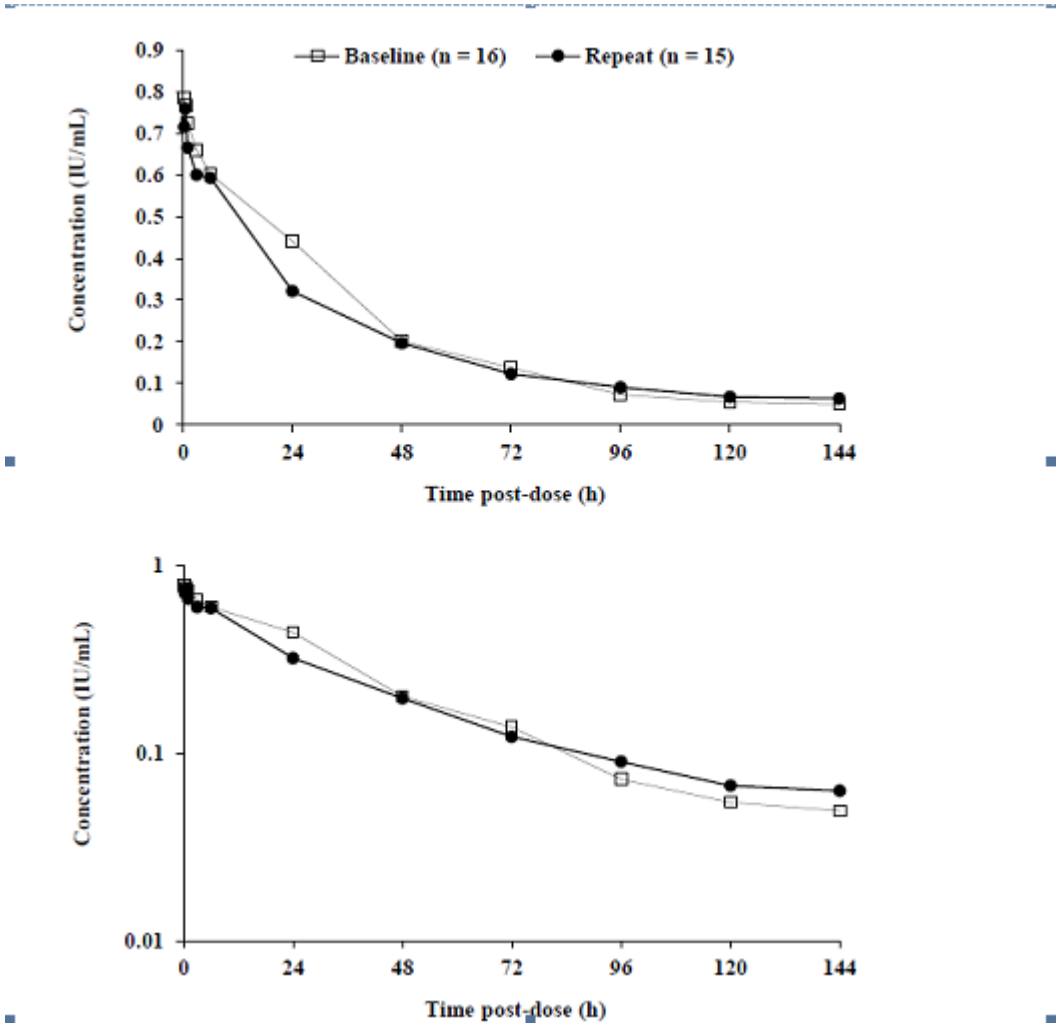
Secondary PK Endpoints

Table 9: Pharmacokinetic parameters of FX:Ag at Baseline and Repeat PK assessment visits

	IR_{30min} (IU/dL per IU/kg)[a]	IR_{1h} (IU/dL per IU/kg)[b]	C_0 (IU/mL)	C_{max} (IU/mL)	t_{max} (h)	AUC_{0-144h} (IU·h/mL)	$AUC_{0-\infty}$ (IU·h/mL)	λz (/h)	$t_{1/2}$ (h)	CL (mL/h/kg)	V_{ss} (mL/kg)	V_d (mL/kg)	MRT (h)
Baseline (N=16)													
Geometric mean	2.63	3.02	0.863	0.848	NA[c]	29.1	31.1	0.022	31.5	0.904	40.9	41.0	45.2
CV (%)	29.9	25.2	40.8	27.2	0.217, 3.37[d]	31.8	32.0	27.9	27.9	31.4	37.3	38.2	28.6
Median	2.77	3.27	0.849	0.885	0.434	28.4	31.0	0.0225	31.0	0.901	40.8	39.2	43.9
Repeat (N=15)													
Geometric mean	2.58	2.67	0.722	0.777	NA[c]	26.1	28.6	0.0199	34.8	0.996	48.8	50.1	49.0
CV (%)	27.1	25.7	28.3	29.8	0.250, 0.617[d]	34.9	38.4	33.2	33.2	37.9	30.6	23.5	36.4
Median	2.55	2.81	0.770	0.780	0.533	24.5	27.7	0.0195	35.6	0.949	45.0	48.6	49.3

Source: Appendix 16.5, Pharmacokinetic Report Amendment 1.
Abbreviations: CV, coefficient of variation; IR, incremental recovery; NA, not applicable.
[a] Calculated from factor X levels at 30 minutes post-dose per protocol.
[b] Calculated from peak factor X level in the first hour post-dose per EMA guidelines.
[c] Presented as median and range, as t_{max} is not a continuous variable.
[d] Range.

Figure 5: Mean pre-dose-adjusted plasma concentrations of FX:Ag following a single intravenous bolus dose of 25 IU/kg FACTOR X: Baseline and Repeat PK assessment visits



IR in surgery

The pre-surgery IR30min results in the three subjects who underwent surgery, calculated using doses measured using the results from BPL's chromogenic batch-release assay (First Subject: 2.34 IU/dL per IU/kg; Second Subject: 1.84 IU/dL per IU/kg; Third Subject 41001: 1.67 IU/dL per IU/kg), were similar to those in subjects undergoing PK assessments. However, the doses used were larger than those used in the formal PK studies (First Subject: 51.4 IU/kg; Second Subject :49.0 IU/kg; Third Subject : 45.0 IU/kg) because of the requirement to increase the pre-surgical FX:C to 70-90IU/dL.

Study Ten03

Ten03 was an open, multi-center, non-randomised prospective study in subjects with mild to severe factor X deficiency (<20% basal levels of FX:C) to assess the safety and efficacy of FACTOR X in preventing bleeding and achieving hemostasis during planned surgery. Assessment of incremental recovery of FX:C and FX:Ag after the pre-surgery bolus infusion was foreseen.

The IR30 min values of FX:C (clotting and chromogenic assays) and FX:Ag after the presurgery bolus infusion were calculated, for the first loading dose in two male subjects undergoing 2 surgical procedures each.

Pharmacokinetic Endpoints

The IR30 min values of FX:C (clotting and chromogenic assays) and FX:Ag after the presurgery bolus infusion were calculated, for the first loading dose.

Table 10: Summary Statistics for Incremental Recovery of FX:C and FX:Ag

	IR_{30min} FX:C Clotting (IU/dL per IU/kg)	IR_{30min} FX:C Chromogenic (IU/dL per IU/kg)	IR_{30min} FX:Ag (IU/dL per IU/kg)
Number	4	4	4
Mean	2.14	1.98	2.50
Standard deviation	0.224	0.124	1.194
Minimum	1.80	1.82	1.71
Median	2.24	2.00	2.02
Maximum	2.27	2.10	4.24

Source: Module 5.3.5, Ten03 CSR, Table 14.
Abbreviation: IR_{30min}, incremental recovery based on the concentration 30 min after infusion of FACTOR X.

During study Ten03, incremental recovery was investigated during four surgical procedures in 2 subjects. Both subjects have mild congenital factor X deficiency, with values of 7 and 8 IU/dl at inclusion, respectively. Observed values are compatible with those from the formal PK evaluations of study Ten01.

Incremental Recovery across studies

Table 11: Incremental recovery (IR_{30min}) values of FX:C (clotting) in subjects across Ten01 and Ten03 studies

Parameter	Ten01			Ten03
	Full PK – Baseline (N = 16)	Full PK - Repeat PK (N = 15)	Surgical procedures (N = 3)	Surgical procedures (N = 4) (2 subjects)
Median (IU/dL per IU/kg)	2.12	1.91	1.84	2.24
Individual values (IU/dL per IU/kg)	N/A	N/A	1.67 1.84 2.34	1.80 2.21 2.27 2.27
Range (IU/dL per IU/kg)	1.40 – 2.93	1.32 – 2.93	1.67 – 2.34	1.80 – 2.27

Special populations

Impaired renal function

No PK data were provided in patients with impaired renal function (see discussion on clinical pharmacology).

Impaired hepatic function

No PK data were provided in patients with impaired hepatic function (see discussion on clinical pharmacology).

Gender

In the PK study Ten01, 10 subjects (62.5%) were female and 6 were male. In addition, two male patients were included in study Ten03 (see discussion on clinical pharmacology).

Race

In study Ten01, 12 patients (75.0%) were white/Caucasian, 2 (12.5%) were black/African American, and 2 (12.5%) were Asian. Four subjects (25.0%) regarded themselves as Hispanic or Latino and the others as of other ethnicity. There were 1 white/Caucasian patient and 1 Asian patient in study Ten03 (see discussion on clinical pharmacology).

Weight

Subjects with a body weight from 41 to 119 kg) were included in study Ten01. In study Ten03 two patients were investigated with a body weight of 76 kg and 88 kg (see discussion on clinical pharmacology).

Elderly

No elderly patients were studied. The age range of enrolled patients was 12 to 58 years (see discussion on clinical pharmacology).

Children

The ongoing study (Ten02) in children with mild to severe hereditary factor X deficiency has been granted a deferral for completion by October 2017 [EMA/PDC0/209107/2014 Corr].

Six adolescent patients from 12 to 17 years of age were included. Full baseline and repeat PK data were measured (see discussion on clinical pharmacology).

Pharmacokinetics results

Per the study protocol, all subjects in Ten02 were to receive FACTOR X prophylactic doses at 40 – 50 IU/kg twice weekly to maintain trough FX:C concentrations of at least 5 IU/dL; the bolus dose used for incremental recovery (IR) evaluation was 50 IU/kg.

Three subjects have completed the study (note 2 subjects completed the study 4 weeks early and will be re-entered into the trial). Thus far approximately 280 exposure days have been reported.

The mean baseline IR30min = 1.77 IU/dL per IU/kg [range 1.41 to 2.20], and the mean Visit 5 IR30min = 1.93 IU/dL per IU/kg [range 1.77 to 2.06]. The combined mean baseline and Visit 5 IR30min = 1.81 IU/dL per IU/kg [range 1.41 to 2.20].

In subjects in the Ten01 study ≥ age 12, the mean IR30min, calculated using the factor X levels at 30 minutes post-dose, was 2.04 IU/dL per IU/kg administered at the baseline Visit and 1.90 IU/kg per IU/kg at the repeat PK assessment visit. The IR at the repeat PK visit was statistically equivalent to that at the baseline visit. The range of IR30min in the population studied in Ten01 was from 1.40 to 2.93 (IU/dL per IU/kg). The IR values currently demonstrated in study Ten02 are consistent with values reported in subjects ≥ 12 years of age in study Ten01.

Pharmacokinetic interaction studies

Not provided (see discussion on clinical pharmacology).

Pharmacokinetics using human biomaterials

N/A

2.4.3. Pharmacodynamics

Mechanism of action

Studies on the mechanism of action were not submitted (see discussion on clinical pharmacology).

Primary and Secondary pharmacology

Clinical pharmacodynamic studies were not submitted (see discussion on clinical pharmacology).

Genetic differences in PD response

In the Ten01 study, 16 subjects provided genetic samples for genotyping analysis on the specific F10 gene mutation resulting in factor X deficiency. 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.

The subjects' genotype was compared with the frequency of bleeds and selected PK parameters and no associations can be drawn between factor X genetic variants and clinical symptoms or the PK parameters.

2.4.4. Discussion on clinical pharmacology

Pharmacokinetic profiles after a bolus infusion of 25 IU/kg BW are available from 16 subjects for the initial evaluation and 15 patients for the repeat PK assessment at least 6 months later with severe or moderate congenital FX deficiency in study Ten01. The timing of blood samplings is adequate and covers about 5 half-lives of FX. Each subject's set of plasma samples was assayed in a single run for both baseline and repeat PK assessment at the central laboratory which is acceptable. 14 subjects had severe Factor X deficiency (endogenous FX:C <1 IU/dL) and 2 subjects had moderate Factor X deficiency (FX:C >1 to <5 IU/dL). The inclusion of patients with moderate disease can be accepted with regard to the rarity of the disease.

The PK profile of Coagadex was assessed by the clotting assay and the chromogenic assay measuring Factor X activity and the Factor X antigen assay. Choice and description of the applied PK parameters follow the current standards and are considered sufficient.

Individual PK data of four patients show baseline FX:C levels (pre-dose) of at least 6 IU/dl. As there might be an impact of baseline FX:C levels >5 IU/dl on the PK results, a stratified re-analysis of PK according to FX baseline levels was performed and the effects of the raised pre-PK baseline were appropriately evaluated. In fact, AUC0-144h, Cmax, IR1h and t1/2 were significantly higher in subjects classed as baseline FX:C levels >5 IU/dL by the FX:C assay as compared to Factor X FX:C <1 IU/dL subjects. A reduction of these effects could be shown after accounting for covariates as weight, BMI, $Ln_{dose?}$, gender and age. Since there were only four of 16 patients with moderate elevation above baseline the effect on the overall PK data is regarded minimal. Nevertheless, the recommendation (see section 4.2. of the SmPC) to monitor blood levels after FACTOR X dosing is important and will also account for individual variability as well as weight or other demographic variables.

The PK data obtained in study Ten01 result in a mean IR of approximately 2.0 IU/dL per IU/kg and a half-life of 29.4 hours. Therefore, the criterion of treatment success that the half-life of FACTOR X (clotting assay) would be at least 20 hours (lower bound for the 95%CI) was achieved. The PK parameters for FX:C did not substantially differ between the clotting and the chromogenic assays. The FX:C PK data were quite similar between Baseline and Repeat PK visit and the 90% CIs of the mean Repeat PK/Baseline ratios ranged within the prescribed limits. Results are reflected in the SmPC section 5.2.

The mean (CV%) for incremental recovery as 2.08 (18.1). The mean (CV%) maximun plasma concentration (C_{max}) was 0.504 (17.2) IU/mL. The mean (CV%) for area under the curve (AUC_{0-144h}) was 17.1 (21.0) IU.hr/mL. As the human coagulation factor X is largely retained within the vascular compartment: mean apparent volume of distribution (V_{ss}) was 56.3 (24.0) mL/kg. The mean (CV%) half-life of human coagulation factor X was 30.3 (22.8) hr and clearance was 1.35 (21.7) mL/kg/hr. The PK parameters for FX:Ag followed similar trends but an apparent disparity between the Baseline and Repeat PK results was observed. In addition, the CVs were almost universally larger than for FX:C (clotting and chromogenic) and were accounted for the difference between Baseline/Repeat PK. However, the FX:Ag assay was performed manually by ELISA which explains the greater CV in comparison to the clotting and chromogenic assays which was performed automatically.

In study Ten01, additionally 3 patients underwent minor surgical procedures and incremental recovery of FX was available for the loading dose pre-surgery.

PK parameters were also regarded as surrogates for efficacy by the applicant, which is considered acceptable for a plasma derived coagulation factor. PK parameters have been thoroughly characterised for plasma derived FX. The outcomes of this PK exercise provide the basis for dose level recommendations (IR ~2 IU/dl/IU/kg) and dose interval ($t_{1/2}$ ~30h). Results achieved with the chromogenic and one-stage clotting assay are generally comparable. The repeat PK evaluation provided results very similar to those of the initial assessment.

No pharmacokinetic studies have been conducted in patients with renal or hepatic impairment or in the elderly but there is no anticipated effect of age, gender, renal function or hepatic function on the pharmacokinetic profile of Coagadex.

There are limited data on long-term use.

Pharmacokinetic studies have not been performed in children under the age of 12 years. Data on incremental recovery is limited but appears similar to that seen in the patient population of 12 years of age or older. PK data in children < 12 years will be collected in the ongoing study (Ten02), which has been granted a deferral for completion by the PDCO. Until submission of this study report, missing data in children < 12 years are reflected in the summary of product characteristics. (See SmPC section 5.2).

Body weight/body mass index may have an impact on PK parameter and consequences on dosing. Further evaluation is needed. In addition, possible differences in PK characteristics between male and female subjects as well as adult and adolescent subjects have not been analysed. (See RMP).
Study Ten03 was conducted in two patients with mild factor X deficiency who underwent two surgical procedures each. This trial is regarded only supportive for PK since solely IR30min values were calculated. In study Ten03 the median IR30min values were relatively close to the median values of the same parameter measured in study Ten01.

Overall, the PK data presented support the efficacy of FACTOR X in providing hemostasis in patients with factor X deficiency.

2.4.5. Conclusions on clinical pharmacology

PK parameters of Coagadex have been thoroughly characterized for both FX:C (using the one stage clotting assay and the chromogenic assay) as well as for FX:Ag..The results have adequately been reflected in the SmPC.

As the role of human plasma derived FX in the coagulation cascade is clear, the absence of pharmacodynamic studies is justified.

2.5. Clinical efficacy

2.5.1. Dose response studies

No specific dose response studies have been conducted.

2.5.2. Main study

Study Ten01

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.

Methods

Study Participants

Inclusion criteria were:

1. Subjects who had given written informed consent or, for subjects aged 12-17 years, who had given written assent and whose parent/guardian had given written informed consent.
2. Subjects who were at least 12 years of age at date of written informed consent/assent.

3. Subjects with hereditary severe or moderate factor X deficiency (<5% basal FX:C at diagnosis).

4. Subjects currently treated with FFP, a PCC, or a factor IX/X concentrate.

5. Subjects must have had a minimum of one spontaneous or menorrhagic bleed in the past 12 months which required treatment with FFP, PCC, or factor IX/X concentrate. Newly diagnosed subjects who presented at the hospital with a bleed could be included in the study (such subjects would not be included in PK analysis).

6. Subjects must have had at least 7 days, and ideally 10-14 days, since an infusion of FFP, PCC, or factor IX/X concentrate at the Baseline Visit*.

7. Female subjects of childbearing potential must have had a negative result on a human chorionic gonadotrophin-based pregnancy test. If a female subject was or became sexually active, she must practice contraception by using a method of proven reliability for the duration of the study*.

*Re-assessed before the PK assessment at the Baseline Visit.

Exclusion criteria were:

1. Subjects with a history of inhibitor development to factor X or a positive result at the Screening Visit (quantitative result of ≤0.6 Bethesda units [BU])*.

2. Subjects who were bleeding at the appointment for the PK assessment*. However, the subject could enter the study after the bleed was controlled.

3. Subjects who had thrombocytopenia (platelets <50 X 109/L)*.

4. Subjects who had clinically significant renal disease (serum creatinine >200µmol/L)*.

5. Subjects who had clinically significant liver disease (serum alanine aminotransferase [ALT] levels >3× upper normal limit)*.

6. Subjects who were known to have other coagulopathy or thrombophilia.

7. Subjects known or suspected to have hypersensitivity to the investigational medicinal product or its excipients.

8. Subjects known to have abused chemicals or drugs within the past 12 months.

9. Subjects with a history of unreliability or non-cooperation.

10. Subjects who were participating or who had taken part in another trial within the last 30 days, with the exception of BPL's FACTOR X surgery study (protocol code Ten03). In such cases, subjects should have completed their End-of-Study Visit in the other trial before or on the day of the Screening Visit for this study.

11. Female subjects who were pregnant or lactating.

12. Subjects who were planning more than 4 weeks' absence from the locality of the investigational site between the Screening Visit and the PK assessment.

*Re-assessed before the PK assessment at the Baseline Visit.

Treatments

Patients received their first dose of FACTOR X at the investigational site and underwent assessments during the Baseline/Day 1 visit. Subsequently, patients could be provided with FACTOR X for home administration or administration at their local clinics as agreed by the investigator. It was

recommended that the first bleeding episode be treated under the supervision of a physician. Alternatively, patients could return to the investigational site for treatment.

Selection of Doses in the Study

The standard dosage for the bolus administration, to treat a bleed, and preventative therapy was 25 IU/kg, which was based on the empirical finding that 1 IU/kg of factor X administered can raise a patient's factor X level by 1.5 IU/dL. Any unused portion of reconstituted FACTOR X solution was discarded.

Dose to Treat a Bleed

Spontaneous bleeds were initially treated with a single dose of 25 IU/kg FACTOR X, which was expected to raise the factor X level by approximately 35-40 IU/dL. Additional doses could be given as necessary until haemostasis was restored.

If more than two doses of FACTOR X were required to treat an overt bleed or menorrhagia, or if more than three doses of FACTOR X were required to treat a covert bleed, the treatment for that specific bleed would be considered a treatment failure. If a dose of 25 IU/kg of FACTOR X was insufficient to treat a bleed in a subject, the dose for subsequent bleeds in that subject could be increased, but justification for the change in standard dose had to be recorded in the subject's CRF.

Preventative Therapy

Some subjects might need to administer FACTOR X prophylactically for a short period for reasons such as in anticipation of increased physical activity or during rehabilitation of a joint following a bleed. This use was documented as preventative therapy. A dose of 25 IU/kg should be administered, with the calculated total dose rounded to the nearest 1 mL. Unlike treatment for bleeds, the dose for preventative therapy was fixed throughout the study for any subject. If a female subject was treated in anticipation of a menorrhagic bleed, the response to FACTOR X was assessed as treatment of a bleed, not as preventative treatment.

Surgery

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 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 all PK assessments to 144 hours post-dose.

Surgical procedures requiring day case or overnight stay, such as laparoscopic or arthroscopic procedures, were defined as *minor procedures*. Procedures typically requiring full anaesthesia and involving opening of the major cavities, such as thoracic, abdominal, orthopaedic or open heart surgery, were defined as *major procedures*.

Pre-surgery Loading Dose

A dose of FACTOR X required to raise the subject's factor X level to 70-90 IU/dL was calculated by the investigator, according to the following equation:

dose required (IU) = weight (kg) X rise required (IU/dL) X 0.7

The above equation was based on the empirical finding that 1 IU factor X/kg bodyweight raises the factor X level by 1.5 IU/dL. However, if the subject's observed recovery at the Baseline Visit was

significantly different to this value, the equation above could be adjusted to ensure that a factor X level of 70-90 IU/dL was reached. The initial dose was not to exceed 60 IU/kg.

The bolus loading dose of FACTOR X was given between 1 and 4 hours before surgery. The subject could receive an additional dose of FACTOR X after the pre-surgery loading dose. This might be required if the surgery was delayed to more than 8 hours after the loading dose, or if local laboratory tests indicated that the required level of FX:C was not reached. The assessment of IR was performed on a blood sample taken 30 minutes (± 5 minutes) after the first pre-surgery dose of FACTOR X.

Post-surgery Maintenance Doses

During the first few days after the surgical procedure, FX:C was monitored at least once daily while the subject was in hospital and further doses of FACTOR X were given as required targeting the FX:C level to be at least 50 IU/dL, calculated by the investigator according to the equation above, or adjusted to account for the subject's observed recovery at the Baseline Visit. Treatment with FACTOR X continued until the subject was considered to no longer be at risk due to post-operative bleeding and returned to the on-demand treatment regimen. The duration of post-surgery maintenance dosing was anticipated to be 5 to 10 days.

Objectives

The primary objective of this study 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:

1. To assess the efficacy of FACTOR X in the treatment of spontaneous bleeds over at least 6 months.
2. To assess the safety of FACTOR X in the treatment of spontaneous bleeds over at least 6 months.
3. For factor X-deficient subjects enrolled in the study who needed a surgical procedure, an additional objective was to prospectively investigate the safety and efficacy of FACTOR X, administered by bolus infusion, to control bleeding and achieve haemostasis.

Outcomes/endpoints

Because the investigational medicinal product in this study contained biologically active, endogenous compounds, the PK variables below were used as a surrogate for efficacy variables. The main PK parameters of FX were defined as the primary efficacy endpoints and additional ones as secondary (See PK section of this AR). Clinical efficacy endpoints included the following assessments:

- 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 given 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'.

Assessment Criteria for Efficacy in Treating a Bleed

The clinical manifestation of factor X deficiency includes covert (hidden) as well as overt (obvious) bleeds. The assessment of efficacy of FACTOR X in treating a bleed depended on the type of bleed to be assessed. Efficacy was assessed by the subject for all bleeds and by the investigator or a trained clinician for bleeds requiring assessment at the hospital/clinic.

Overt bleeds

Examples of overt bleeds were epistaxis, tongue/gum bleeds, haematemesis, haematuria, rectal bleeding and external wound bleeding due to injury. Overt bleeding was assessed at 12 hours and, if necessary, at 24 hours after the first dose of FACTOR X. Efficacy was assessed by the investigator and subject according to the guidelines shown in Table 24 and Table 25 below.

Table 12: Criteria for assessment of efficacy of FACTOR X in treating an overt bleed: investigator's assessment

Category	Criterion
Excellent	Bleeding stopped within 12 hours, with 1 dose of FACTOR X
Good	Bleeding stopped within 24 hours, with or without a second dose of FACTOR X
Poor	Bleeding stopped after 24 hours, or >2 doses of FACTOR X were needed to stop bleeding, or there was no response to therapy.
Unassessable	Other replacement therapy given before response to FACTOR X (if given) could be assessed.

Table 13: Criteria for assessment of efficacy of FACTOR X in treating an overt bleed: subject's assessment

Category	Criterion
Excellent	Bleeding stopped within 12 hours after dosing with FACTOR X, with only 1 dose required.
Good	Bleeding stopped within 24 hours after the first dose of FACTOR X, with 1 or 2 doses required.
Poor	Bleeding stopped later than 24 hours after the first dose of FACTOR X; or More than 2 doses of FACTOR X were needed to stop bleeding; or FACTOR X did not work at all.
Unassessable	I did not take any FACTOR X for this bleed; or I was given a dose of fresh-frozen plasma, prothrombin complex concentrate, or factor IX/X concentrate, before the FACTOR X I took for this bleed had time to work.

Bleeding should have been assessed as close to the 12-hour and 24-hour time points as possible.

Menorrhagia

Menorrhagia, although an overt bleed, may vary significantly within individuals from one menses to the next. Efficacy was based on the number of doses of FACTOR X required in the peri-menstrual period (the first dose being not more than 1 day before commencement of bleeding) to maintain bleeding at a manageable level (i.e. with no significant limitation to normal activities), as shown in Table 26 and Table 27 below.

Table 14: Criteria for assessment of efficacy of FACTOR X in treating a menorrhagic bleed: investigator's assessment

Category	Criterion
Excellent	1 or 2 doses of FACTOR X required within 48 hours
Good	2 doses of FACTOR X required over >48 hours
Poor	>2 doses of FACTOR X required; or Bleeding could not be maintained at a manageable level.
Unassessable	Other replacement therapy given before response to FACTOR X (if given) could be assessed.

Table 15: Criteria for assessment of efficacy of FACTOR X in treating a menorrhagic bleed: subject's assessment

Category	Criterion
Excellent	1 dose of FACTOR X was required; or 2 doses of FACTOR X were required, less than 48 hours apart.
Good	2 doses of FACTOR X were required, with more than 48 hours between the first and the last dose.
Poor	More than 2 doses of FACTOR X were required; or Bleeding could not be kept at a manageable level.
Unassessable	I did not take any FACTOR X for this bleed; or I was given a dose of fresh-frozen plasma, prothrombin complex concentrate, or factor IX/X concentrate, before the FACTOR X I took for this bleed had time to work.

Covert bleeds

Examples of covert bleeds were melena, intraperitoneal bleed, joint bleeds, muscle bleeds, intracranial haemorrhage, haematoma/bruising and internal bleeding due to injury. Assessment of covert bleeds, which might not have associated pain, was difficult, since it was not always possible to ascertain the start and stop time of bleeding, the severity and timescale of response to therapy.

Efficacy was assessed by the investigator and subject, based on the number of doses of FACTOR X required to achieve haemostasis within 48 hours after the first dose, according to the guidelines shown in Table 28 and Table 29 below. The bolus infusion of 25 IU/kg FACTOR X could be repeated to achieve haemostasis. For gastrointestinal ulcers, failure to achieve haemostasis did not equate failure of the efficacy of FACTOR X, since even patients without factor deficiencies would continue to bleed with these lesions.

Table 16: Criteria for assessment of efficacy of FACTOR X in treating a covert bleed: investigator's assessment

Category	Criterion
Excellent	1 or 2 doses of FACTOR X required within 48 hours.
Good	3 doses of FACTOR X required within 48 hours.
Poor	>3 doses of FACTOR X required within any timeframe; or No response to therapy.
Unassessable	Other replacement therapy was given before response to FACTOR X (if given) could be assessed.

Table 17: Criteria for assessment of efficacy of FACTOR X in treating a covert bleed: subject's assessment

Category	Criterion
Excellent	1 dose of FACTOR X was required; or 2 doses of FACTOR X were required, less than 48 hours apart.
Good	3 doses of FACTOR X were required, with less than 48 hours between the first and last doses.
Poor	More than 3 doses of FACTOR X required within any timeframe; or FACTOR X did not work at all.
Unassessable	I did not take any FACTOR X for this bleed; or I was given a dose of fresh-frozen plasma, prothrombin complex concentrate, or factor IX/X concentrate, before the FACTOR X I took for this bleed had time to work.

Investigator's Overall Assessment of Efficacy

At the End-of-Study Visit, the investigator made an assessment of the overall efficacy of FACTOR X throughout the study, taking into account its use in all bleeds, preventative doses and surgical procedures. For any subject who withdrew from the study but did not attend an End-of-Study Visit, efficacy would be assessed by the investigator if the subject had received at least one infusion of FACTOR X for treatment of a bleed, for preventative use, or for surgery. Efficacy was assessed according to the criteria in Table 30.

Table 18: Criteria for investigator's overall assessment of efficacy

Category	Criterion
Excellent	Efficacy of FACTOR X regularly met or exceeded expectations.
Good	Efficacy of FACTOR X was less than expected, but still adequate.
Poor	In general, FACTOR X did not provide satisfactory haemostasis.
Unassessable	Efficacy of FACTOR X was not possible to assess during the study, e.g. no bleeds requiring treatment with FACTOR X, or other replacement, therapy given for all bleeds during the study.

Sample size

No formal sample size calculation was performed, as no formal hypothesis testing was planned. The sample size is based on formal scientific advice received from the EMA and FDA. A minimum of 12, and a maximum of 16 subjects were planned to be enrolled to receive FACTOR X on demand in order to achieve at least 12 evaluable pharmacokinetic profiles at the Baseline Visit and the 6 Month Visit and, separately, at least 12 bleeding episodes treated with FACTOR X in 12 subjects.

Randomisation

This was a single-arm trial.

Blinding (masking)

This study was not blinded.

Statistical methods

The following analysis populations were planned for this study:

Safety Population (Safety): The safety population will be defined as all treated subjects (i.e. all subjects who receive at least part of one dose of study medication). Safety data will be analysed up to the point of withdrawal for subjects who withdraw if the number of data points is adequate to allow a scientific analysis.

Per-Protocol Population (PP): The PP population will be defined as all treated subjects who have sufficient FX:C data to characterise the time course of FACTOR X in plasma (i.e. a PK profile evaluable by WinNonlin) at the Baseline Visit and the repeat PK assessment (usually at the 6 Month Visit).

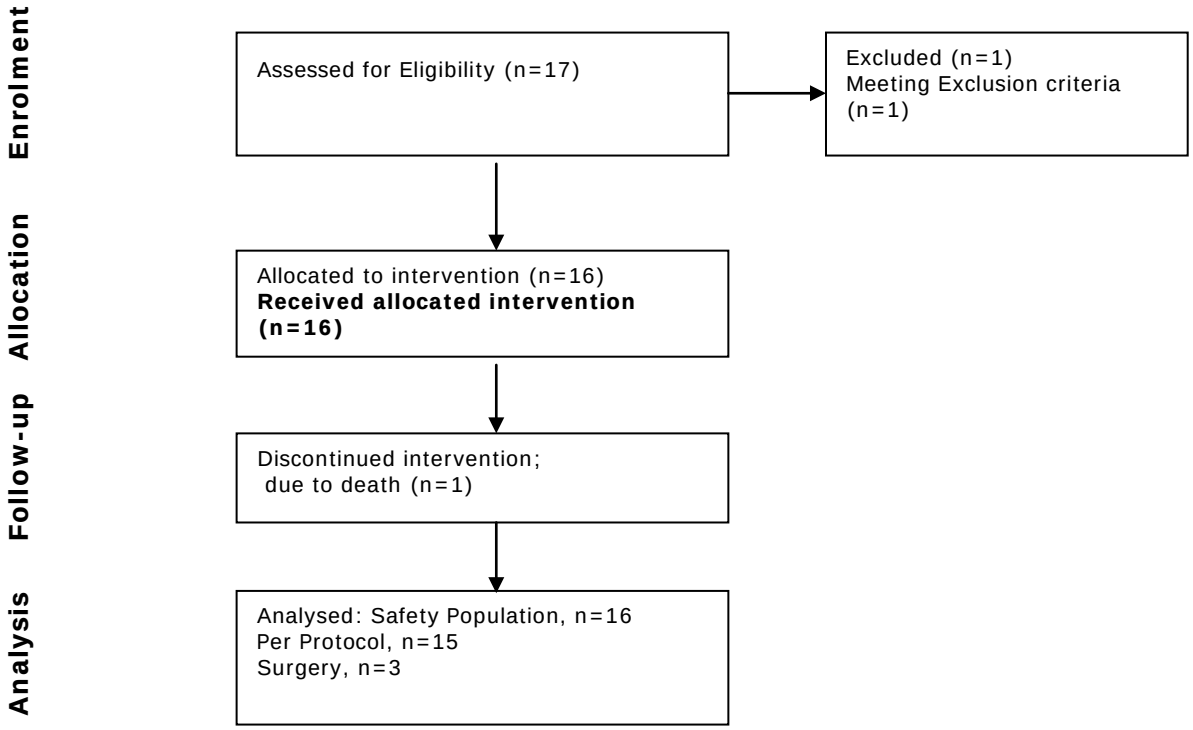
Surgery Population (Surgery): The surgery population will be defined as all treated subjects requiring any surgical or invasive procedure during the course of the trial, whether planned or emergency, who receive at least one part of one dose of study medication as prophylaxis against excessive bleeding during or after the procedure.

Per-Protocol Surgery Population (PP Surgery): The PP surgery population is a subgroup of the surgery population, which includes subjects undergoing surgical procedures in which the pre-surgery FX:C level is ≥70 IU/dL and in which subjects were dosed in accordance with the protocol.

The most important evaluation of efficacy of FACTOR X was based on the subject's assessment of each new bleed. FACTOR X was planned to be deemed effective if at least 80% of a subject's treated new assessable bleeds for on demand treatment are assessed as having an 'excellent' or 'good' response. All other efficacy endpoints (as listed above) have been analysed descriptively.

Results

Participant flow



Recruitment

Date first patient enrolled: 05 May 2010

Date last patient completed: 30 Oct 2013

Conduct of the study

Protocol Amendments

The Ten01 protocol version 2 (incorporating protocol amendments [PA] 01-02), dated 02 Nov 2009, was used at the start of the study. Ten amendments were made during the study, most noteworthy: the 2nd was to add definition of treatment failure, as recommended by FDA; 3rd was an update in definitions of efficacy criteria, as recommended by FDA; the 5th was the addition of success criteria, as recommended by FDA; the 7th was an update in efficacy assessment criteria for menorrhagic bleeds.

Amendment (PA05) dated 22 Sep 2010 incorporated the following changes: Addition of blood sample collections for thrombogenicity marker assays at 24, 48 and 72 hours post-dose time points; Change to the infusion rate from a maximum of 3 mL/min to a suggested rate of 10 mL/min but no more than 20 mL/min (The initial infusion rate ceiling was based on administration instructions of BPL's other coagulation factors. Because of the low amount of protein in FACTOR X, the low infusion volume and the lack of evidence that faster infusion rates were associated with AEs, the infusion rate was increased.); Clarification on the efficacy assessment of FACTOR X in treating a bleed if the investigator's and the subject's assessments differed.

Three subjects enrolled at sites in Spain were enrolled before this amendment and therefore did not undergo the revised procedures related to the thrombogenicity marker assays at the Baseline Visit or the infusion rate requirement.

Amendment (PA06) incorporated the following changes: Addition of a table listing the number of bleeds required to meet the criteria for treatment success. The maximum number of bleeds, defined up to 20 in the previous protocol version, was increased due to the number of bleeds reported at the time; Addition of the PK parameter AUC0-t in the analysis. This parameter was identified as necessary during a review of the statistical analysis plan.

An amendment (PA08) dated 09 Aug 2012 incorporated a change to the primary efficacy endpoint for the surgery component of the protocol (as per the request by the PEI) and to ensure that the surgery data analysis in Ten01 was consistent with the surgery data analysis in the Ten03 study and a change to the secondary efficacy endpoints for the surgery component of the protocol as a consequence of above change to the primary endpoint as requested by PEI. Two subjects underwent surgical procedures during the study before this amendment and therefore efficacy assessments reflect the previous version of the protocol.

Protocol Deviations

Only minor deviations occurred, none of them was considered a protocol violation or a serious breach; thus, no subject was excluded from planned PK analysis. Two subjects received FACTOR X as routine prophylaxis, even though this use was not specified in the protocol.

Baseline data

Table 19: Subject demographics

Subject Characteristic	Safety Population (N=16)
	Mean (± SD)
Age (yr)	27.1 (± 15.10)
Weight (kg)	67.91 (± 18.230)
	Number (%)
Sex	
Male	6 (37.5)
Female	10 (62.5)
Race	
American Indian or Alaska Native	0
Asian	2 (12.5)
Black or African American	2 (12.5%)
Native Hawaiian or other Pacific Islander	0
White or Caucasian	12 (75.0)
Other	0
Ethnicity	
Hispanic or Latino	4 (25.0)
Not Hispanic or Latino	12 (75.0)

Source: Section 14.1, Table A.1.2.1

Baseline Clinical Characteristics and Disease History

Of the 16 subjects in the safety population, 14 had severe factor X deficiency with endogenous FX:C level <1 IU/dL and 2 subjects had moderate disease with endogenous FX:C level in the range of 1 to <5 IU/dL.

The subjects had been diagnosed with factor X deficiency for a mean duration of 20.7 years. Before entering this study, 15 subjects had been treated with replacement factor concentrates, 14 had been treated with FFP and 12 had been treated with other blood products. Fourteen subjects (87.5%) had experienced spontaneous bleeding in the past.

A bleeding score (modified Vicenza score) based on that developed for von Willebrand disease was used to grade the severity of bleeds in the subject's disease history.

Table 20: Bleed history

Parameter	N = 16 n (%)
Type of bleed experienced[a]	
Overt bleed	8 (50.0)
Covert bleed	14 (87.5)
Menorrhagic bleed	7 (43.8)
Unknown	1 (6.3)
Highest bleed score (modified Vicenza score)[a]	
1	0
2	1 (6.3)
3	5 (31.3)
4	10 (62.5)
Location of past bleeds[a]	
Joint	8 (50.0)
Mucosal	10 (62.5)
Cut/Wound	2 (12.5)
Muscle	9 (56.3)
Other	8 (50.0)
Unknown	1 (6.3)
Cause of past bleeds [a]	
Spontaneous bleeding	14 (87.5)
Injury	6 (37.5)
Menorrhagia	7 (43.8)
Unknown	4 (25.0)

Source: Section 14.1, Table A.1.3.4.2.
[a] Within 12 months before the Screening Visit or, for significant bleeds, within the subject's lifetime.

Of the 16 subjects in the safety population, 14 had severe factor X deficiency with endogenous FX:C level <1 IU/dL and 2 subjects had moderate disease with endogenous FX:C level in the range of 1 to <5 IU/dL.

The subjects had been diagnosed with factor X deficiency for a mean duration of 20.7 years. Before entering this study, 15 subjects had been treated with replacement factor concentrates, 14 had been treated with FFP and 12 had been treated with other blood products. Fourteen subjects (87.5%) had experienced spontaneous bleeding in the past.

Numbers analysed

16 patients were enrolled into the trial.

The per-protocol population included 15 subjects who 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 Visit

and the Repeat PK assessment (typically at the 6-Month Visit). One subject was excluded from the per-protocol population because the subject discontinued the study (death) before the Repeat PK assessment.

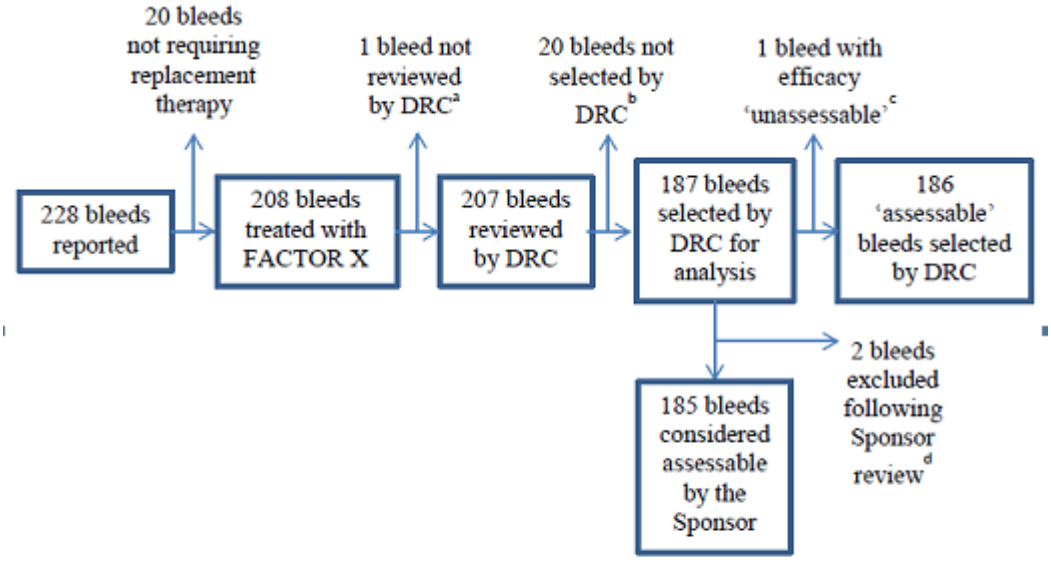
The surgery population included 3 subjects who received FACTOR X as prophylaxis against excessive bleeding during or after their surgical procedure. Two of the subjects were included in the per-protocol surgery primary analysis population and secondary analysis population. One subject was included in the surgery population but excluded from the per-protocol surgery primary analysis and per-protocol surgery secondary analysis because the pre-dose FX:C level was ≥20 IU/dL. The safety population included 16 subjects who received at least one dose of FACTOR X during the study.

Outcomes and estimation

Treatment of Bleeding Events

A total of 228 bleeds were documented, 208 of which were treated with FACTOR X. Figure 9 shows the number of bleeds included in the analyses.

Figure 6: Numbers of bleeding episodes reported and included in the analyses



Source: Section 14.2, Table A.2.1.2 and Table A.2.1.3.
Abbreviations: DRC, Data Review Committee.
[a] Subject 32002, bleed ID 15 was not reviewed by the DRC before database lock.
[b] Described in Section 11.5.1.1.2.
[c] Subject 41001 bleed ID30 FACTOR X efficacy was considered unassessable by the subject.
[d] See Section 11.5.1.2.1 and Section 11.5.1.2.4.

A total of 207 on-demand bleeds in 16 subjects were reviewed by the DRC, for which a bleed severity (major/minor/not known) has been assigned. Of these, 187 bleeds were selected by the DRC. The treatment success rate in these 187 bleeds is presented in Table 33 below. Nearly all (98.4%) of the bleeds treated with FACTOR X were considered a treatment success (i.e. excellent or good response). The 95% CI for treatment success rate is 96.2 to 99.9%. When the one bleed considered unassessable by the subject was excluded, 98.9% of the assessable bleeds treated with FACTOR X were considered a treatment success.

Table 21: Treatment success rate in bleeds selected by the DRC

Treatment Response per Subject	Number (%) Bleeds N=187	Number (%) Assessable Bleeds[a] N=186
Excellent response	170 (90.9)	170 (91.4)
Good response	14 (7.5)	14 (7.5)
Treatment success (excellent or good response)	184 (98.4)	184 (98.9)
Poor response	2 (1.1)	2 (1.1)
Unassessable	1 (0.5)	0

Source: Section 14.2, Table A.2.1.1.
[a] Calculated by Sponsor.

Among the 208 on-demand bleeds treated with FACTOR X, there were 6 treatment failures in 2 subjects (one with a covert muscle bleed that required 4 infusions and as a consequence treatment of future bleeds for this subject was increased to 33 IU/kg FACTOR X per dose; a subject with a menorrhagic bleed requiring 3 infusions; a major traumatic joint bleed with a delay in treatment not accounted for and a menorrhagic bleed). Among the 187 bleeds that were selected by the DRC to be included in the assessment of outcome, 4 treatment failures (2.1%) are included.

Assessments of bleeds were made by investigators for 42 bleeds in 10 of the 16 subjects. Of these, 37 (88.1%) responses were categorised as excellent, 4 (9.5%) as good and 1 (2.4%) as poor.

Preventative Dosing

Nine subjects received a total of 184 infusions of FACTOR X for preventative use during the study period; however, one subject for whom the doses administered in the 2 infusions given for preventative use were not recorded is excluded from the summary statistics of dose. The mean dose per infusion was 25.24 IU/kg per subject, similar to the standard dose of FACTOR X of 25 IU/kg. The total number of infusions of FACTOR X for preventative use during the study period ranged from 1 to 70 infusions per subject, with a mean of 20.4 infusions per subject, equivalent to a monthly average ranging from 0.1 to 4.8 infusions per subject per month, and a mean of 1.62 infusions per subject per month.

Of the 184 preventative doses, 56 (30.4%) were given as secondary prophylaxis to prevent re-bleeding and 45 (24.5%) were given as a short-term preventative measure (e.g. before increased physical activity). Routine prophylaxis in two subjects discussed below accounted for 57 (31.0%) of preventative infusions. This was a deviation from the treatment regimen prescribed in the protocol. Prophylactic infusions for both subjects were administered at the investigational site. The remaining 26 (14%) of preventative infusions were administered for a variety of reasons, such as dental/orthodontic visits and prophylaxis for a rectal bleeding.

Routine prophylaxis

One Subject received a total of 20 infusions as routine prophylaxis for a duration of 878 days or 28.9 months. During the total period of 7.2 months on routine prophylaxis, the subject did not report any bleeds. In the non-prophylaxis periods the subject reported a total of six bleeds. Thus, it appeared that the once-weekly routine prophylaxis reduced the bleeding frequency in this subject from 0.23 bleeds per month to 0 bleeds per month. Another subject received a total of 37 infusions as routine and secondary prophylaxis (discussed below).

Secondary prophylaxis

One subject received a total of 37 infusions as routine prophylaxis. This subject commenced once-weekly routine prophylaxis at a FACTOR X dose of 24.6 IU/kg per infusion of FACTOR X, with the sponsor's approval, on 17 Jan 2011 following a series of serious joint bleeds. Secondary prophylactic dosing to prevent re-bleeding in this patient was given to this subject in 3 cases of a spontaneous joint bleed. In the first cased the subject received 14 infusions of 25 IU/kg FACTOR X at the investigational site 0, of which 10 were on consecutive days. The first infusion was given to treat the bleed and the remaining 13 infusions were given as secondary prophylaxis, to prevent re-bleeding. The second time the subject received nine infusions (first one to treat the bleed and the remaining eight as secondary prophylaxis) of 25 IU/kg FACTOR X at the investigational site all on consecutive days. The third time the subject received eight infusions of 25 IU/kg FACTOR X at the investigational site all on consecutive days; the first 2 were to treat the bleed and the remaining six infusions were given as secondary prophylaxis to prevent re-bleeding. During the 8.5 months the subject had seven bleeds. Thus, it appeared that the once-weekly routine prophylaxis reduced the bleeding frequency in this subject from 0.82 bleeds per month to 0 bleeds per month.

Investigator's Overall Assessment of Efficacy

In the 16 subjects in the safety population, the investigator assessed the overall efficacy of FACTOR X in 15 subjects (efficacy was not assessed for a subject who did not attend an End-of Study Visit). Of these 15 subjects, the investigator assessed the overall efficacy of FACTOR X during the study as excellent in 12 subjects (80%) and good in 3 subjects (20%).

Number of Bleeds per Subject

For the 16 subjects in the safety population, there was a mean of 13.1 bleeds per subject, and a mean of 13.0 bleeds treated with FACTOR X per subject, ranging from 1 to 59 bleeds. The median number of bleeds per subject per month was 0.85.

Consumption

Total dose of FACTOR X on a per bleed and per subject basis

For treatment of a bleed, including initial and repeat doses, the mean total dose of FACTOR X was 31.75 IU/kg per bleed and the mean number of infusions was 1.2 per bleed. A total of 170 bleeds (81.7%) were treated with one infusion, 32 bleeds (15.4%) needed two infusions, 3 bleeds (1.4%) needed three infusions, 1 bleed (0.5%) needed four infusions and 2 bleeds (1.0%) needed six infusions. The mean dose per infusion of FACTOR X on a per bleed basis was 25.43 IU/kg for overall use.

The average mean dose per infusion of FACTOR X per subject was 25.44 IU/kg for overall use, 25.37 IU/kg for treating bleeds, 25.50 IU/kg for treating new bleeds, 25.25 IU/kg for treating ongoing bleeds and 25.24 IU/kg for any preventative use.

Average monthly dose of FACTOR X

The mean average monthly dose of FACTOR X for overall use was 63.07 IU/kg/month. The average monthly dose of FACTOR X per subject was 57.99 IU/kg/month for on demand use treatment of bleeds and preventative use, 33.40 IU/kg/month for treating bleeds, 25.88 IU/kg/month for treating new bleeds, 13.95 IU/kg/month for ongoing bleeds and 46.10 IU/kg/month for additional preventative use.

Perioperative Management

Three subjects received FACTOR X before undergoing surgical procedures to prevent excessive blood loss. The surgical procedures for two of them (both tooth extractions and considered minor) were included in the per-protocol analysis, whereas the surgical procedure for a third subject who underwent a multiple-tooth extraction (also minor) was excluded from the per-protocol analysis as this subject's plasma FX:C levels were ≥20 IU/dL at the pre-surgery visit. The investigators assessed the overall efficacy of FACTOR X to be excellent in both subjects by the following parameters:

Clinical estimation of volume of blood loss during surgery: Blood loss was rated as 'as expected' for 2 Subjects and 'less than expected' for a third Subject on Day 1 (as soon as possible after wound closure) and at subsequent time points.

Requirement of blood transfusion: No blood transfusion was required or given for any of the three subjects.

Number and duration of post-operative bleeding episodes: None of the subjects experienced any post-operative bleeding complication or bleeding episodes at a location other than the site of surgery.

Measurement of haemoglobin pre-operatively, post-operatively and at discharge: There was no apparent change in haematocrit or haemoglobin levels before and after the surgical procedure for 2 Subjects, for a third Subject, both haematocrit and haemoglobin levels decreased following surgery and remained lower than the normal range at discharge.

Analysis of Clinical Information Relevant to Dosing Recommendations

In the Ten01 study up to and including the cut-off date, the nominal dose of 25 IU/kg appeared to be effective in the on-demand treatment of most bleeds (treatment success rate: 98.4%; 95% CI 96.2 to 99.9%). The doses given were generally around this level (mean 25.25; SD ± 2.449 IU/kg). Therefore, an initial dose of 25 IU/kg would seem to be appropriate for the first dose to treat a bleed whether overt, covert or menorrhagic and irrespective of the site. The majority of the bleeds responded to a single dose with the mean (± SD) number of doses per bleed being 1.2 (0.47). Because the mean (± SD) overall dosage to treat a bleed was 30.37 ± 12.467 IU/kg per bleed this indicates that the subsequent doses were of a similar magnitude (25.3 IU/kg; i.e. 30.37/1.2).

Ancillary analyses

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 22: Summary of Efficacy for trial Ten01

Title: Ten01		
Study identifier	Ten01	
Design	phase III open, multicenter study to investigate the pharmacokinetics, safety and efficacy of FACTOR X in the treatment of severe and moderate factor X deficiency (basal FX:C level <5%).	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	At least 27 weeks per subject; not applicable could be extended to a maximum of 2 years
Hypothesis	Exploratory: PK, efficacy, safety	

Treatments groups	All enrolled patients treated with Factor X per protocol, non-comparative, non-randomised		
Endpoints and definitions	Primary endpoint	Main PK parameters	IR at 30 minutes post-dose (IR30min), apparent terminal t1/2 (non-compartmental), area under the concentration versus time curve (AUC) from time zero to 144 hours (AUC0-144h), AUC estimated from time zero to infinity (AUC0-∞), AUC from time zero to sampling time at the last quantifiable concentration (AUC0-t), systemic clearance (CL), mean residence time (MRT) estimated from time zero to infinity (MRT0-∞), volume of distribution (Vd), concentration at time zero (C0), maximum observed concentration (Cmax), time at which Cmax was apparent (tmax) and terminal elimination rate constant (λz) for FX:C (clotting and chromogenic) - at the Baseline Visit and the Repeat PK assessment (usually at the 6-Month Visit).
	Secondary Efficacy	Subject's assessment of efficacy	(all bleeds) Assessed by the patient as 'excellent', 'good', 'poor' or 'unassessable';
	Secondary Efficacy	Investigator's assessment of efficacy	(if bleeds required assessment at the hospital) to be assessed as 'excellent', 'good', 'poor' or 'unassessable'.
	Secondary Efficacy	Consumption	Total dose of factor X on a per bleed and per subject basis as mean total dose per bleed
Database lock	<date>		

Results and Analysis

Analysis description	**Primary Analysis**	
Analysis population and time point description	Per protocol Baseline PK assessment of FX:C (clotting assay)	
Descriptive statistics and estimate variability	Treatment group	
	Number of subject	(N=15)
	IR_{30min} Geometric	2.04 (IU/dL per IU/kg)[a]
	CV (%)	19.5
	Median	2.12

<table>
<tr><td></td><td colspan="3">mean (CV%) for incremental recovery as 2.08 (18.1).
mean (CV%) maximun plasma concentration (C_{max}) was 0.504 (17.2) IU/mL.
mean (CV%) for area under the curve (AUC $_{0\text{-}144h}$) was 17.1 (21.0) IU.hr/mL.

mean apparent volume of distribution (V_{ss}) was 56.3 (24.0) mL/kg.
mean (CV%) half-life of human coagulation Factor X was 30.3 (22.8) hr and clearance was 1.35 (21.7) mL/kg/hr.</td></tr>
<tr><td></td><td>Treatment success rate (assessed by the patient)</td><td colspan="2">16 patients
208 bleeds
207 bleeds reviewed by the DRC
187 (90.3%) selected by the DRC</td></tr>
<tr><td></td><td></td><td>Number (%) bleeds N=187</td><td>Number (%) assessable bleeds N= 186</td></tr>
<tr><td></td><td></td><td>excellent 170 (90.9%)</td><td>excellent 170 (91.4%)</td></tr>
<tr><td></td><td></td><td>Good 14 (7.5 %)</td><td>Good 14 (7.5 %)</td></tr>
<tr><td></td><td></td><td>Success 184 (98.4)</td><td>Success 184 (98.9)</td></tr>
<tr><td></td><td></td><td>95% CI for success rate</td><td>96.2 – 99.9 %</td></tr>
<tr><td></td><td>Treatment success rate (assessed by the investigator)</td><td colspan="2">42 bleeds were assessed by the investigator in 10 of the 16 subjects.</td></tr>
<tr><td></td><td></td><td>excellent</td><td>37 (88.1%)</td></tr>
<tr><td></td><td></td><td>good</td><td>4 (9.5%)</td></tr>
<tr><td></td><td></td><td>poor</td><td>1 (2.4%)</td></tr>
<tr><td></td><td>Consumption</td><td>Mean total dose</td><td>31.75 IU/ kg/ bleed</td></tr>
<tr><td></td><td></td><td>Mean number of infusions</td><td>1.2 per bleed</td></tr>
<tr><td></td><td></td><td>Bleeds treated with 1 infusion</td><td>170 bleeds
81.7% of total</td></tr>
<tr><td></td><td></td><td>Bleeds needed 2 infusions
Bleeds needed 3 infusions</td><td>32 bleeds (15.4%)

3 bleeds (1.4%)</td></tr>
<tr><td>Notes</td><td colspan="3"></td></tr>
</table>

Analysis performed across trials

Table 23: Summary of surgical results for Ten01, Ten03 and combined

Variable	Ten01	Ten03	Combined studies
Procedures	3	4	7
Major (n)	0	4	4
Minor (n)	3	0	3
Tooth extractions (n)	3	1	4
CABG (n)	0	1	1
Total knee arthroplasty (n)	0	2	2
Pre-surgery dose			
Range (IU/kg)	45.0 - 51.4	30.9 - 54.4	30.9 - 54.4
Increment (IU/dL)	75 - 120	70 - 120	70-120
Post-op doses			
Range (IU/kg)	26.2-26.3	6.5-22.8	6.5-26.3
Post-op range FX:C (IU/dL)	66 – 114	29 - 115	29 – 115
No. of doses			
Range (n)	1-3	1-15	1-15
Blood loss			
'as expected' (n)	2	3	5
'less than expected' (n)	1	1	2
Blood transfusions (n)	0	0	0
Post-op bleeds (n)	0	0	0
Haemoglobin			
Minimal change (n)	2	1	3
Decrease (n)	1	3	4
Clinically significant (n)	0	0	0
Haematocrit			
Minimal change (n)	2	1	3
Decrease (n)	1	3	4
Clinically significant (n)	0	0	0
Overall assessment of efficacy			
Excellent (n)	3	4	7

Clinical studies in special populations

- **Children**

The ongoing study (Ten02) in children with mild to severe hereditary factor X deficiency has been granted a deferral for completion by October 2017 [EMA/PDC0/209107/2014 Corr]. The Applicant has provided an update on the status of Study Ten02 in paediatric patients including preliminary data.

Study Ten02 is an open-label, multi-centre trial evaluating the safety, pharmacokinetics, and efficacy of BPL's FACTOR X concentrate, in the prophylaxis of bleeding in subjects < 12 years of age. The study

is being conducted at three sites in the UK, and is currently ongoing. The clinical study report with final data from study Ten02 is expected in Q3 2017.

Although the planned recruitment was completed, two subjects were discontinued early in error by the site. The two subjects met the 50 exposure days criterion but were released from the study four weeks early. Due to the rarity of paediatric factor X deficient patients, these two patients are expected to be re-screened and re-consented and repeat the entire study. The current recruitment status is presented in Table 36 below:

Table 24: Ten02 Recruitment status (cut off Nov 30, 2015)

Planned screened	Actual screened	Planned enrolled	Actual enrolled	Completed	Discontinued	Withdrawn
9**	9	9	9	3*	0	0

*Two patients completed the study 4 weeks early i.e. less than 6 months but had 50EDs.

** Two patients need to be re-screened again and repeat study.

Reported Bleeds

Eight bleeds reported in four subjects were presented. Four of these bleeds were from injury, one spontaneous and three were menorrhagic. All were considered minor bleeds except one menorrhagic bleed which was considered major. No other bleed information is available at this time.

Supportive study

Ten03

Ten03 was an open, multi-centre, non-randomised prospective study in subjects with mild to severe factor X deficiency (<20% basal levels of FX:C) to assess the safety and efficacy of FACTOR X in preventing bleeding and achieving hemostasis during planned surgery conducted from 29 June 2012 to 03 April 2013.

Subjects were enrolled at two study sites in two countries: USA (Study site 22) and UK (Study site 05).

A target of a minimum of five and a maximum of ten subjects were intended to 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, efficacy and safety study (Protocol Ten01) could be combined with the data collected in this Ten03 surgery study. 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).

On Day 1, subjects received a pre surgery bolus dose of FACTOR X between 1 and 4 hours before the surgical procedure that was anticipated to raise the FX:C level to 70-90 IU/dL. 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. 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 after an early discharge from hospital. Subjects who were discharged early were given a subject diary to complete at home. The duration of treatment for most subjects was anticipated to be 5 to 10 days (maximum up to 21 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 primary efficacy endpoint was blood loss during and after surgery 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. This assessment was made by the investigator and by the DRC after all other factors which might affect the blood loss had been taken into account.

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

Results

Four surgical procedures in two male subjects have been studied, all of which were classified by the DRC as major, namely, coronary artery bypass graft (CABG) and, 3 months later, molar and premolar teeth extractions (6); total knee arthroplasty (TKA) and 4 months later a TKA on the other knee. The ages at the time of the procedures ranged from 55 to 59 years, one subject was Asian and the other Caucasian. Both subjects had mild factor X deficiency with lowest recorded FX:C of 6 and 8 IU/dL; one had a history of post-operative bleeds only and the other had a life-time history of two spontaneous bleeds, one mild and the other major.

Doses for adjusted FX:C (clotting) ranged from 30.88 to 54.41 IU/kg, for FX:C (chromogenic) from 32.97 to 52.40 IU/kg and for FX:Ag from 39.85 to 65.60.

Approximately 30 minutes after an infusion of FACTOR X, the incremental recovery (IR 30min) for FX:C (clotting) ranged from 1.80 to 2.27 IU/dL per IU/kg and that for FX:C (chromogenic) had a similar range (1.82 to 2.10 IU/dL per IU/kg). For FX:Ag, the range was appreciably wider (1.71 to 4.24 IU/dL per IU/kg). However, the median values were similar (2.24, 2.00 and 2.02 IU/dL per IU/kg respectively).

The pre-surgical doses (from 30.88 to 54.41 IU/kg) raised the subjects' FX:C (clotting) levels by 70 to 120 IU/dL. The median levels over the post-operative period from Day 2 onwards ranged from 0.36 to 0.48 IU/mL (36 to 48 IU/dL) with an absolute range across subjects of 0.23 to 0.69 IU/mL (23 to 69 IU/dL) on Days 8 and 6 respectively. The median total dose of FACTOR X infused pre-surgery was 38.65 IU/kg. The median number of infusions was 13 per subject. The median total dose of FACTOR X

to maintain hemostasis was 180.65 IU/kg. The estimated volume of blood loss at wound closure was 'as expected' for three of the four surgical procedures (75.0%) and 'less than expected' for the CABG. None of the subjects had any bleeds during the study. None of the subjects required any blood transfusions during the study.

All subjects' haemoglobin and haematocrit levels were within normal range before surgery. In one procedure (teeth extractions), haemoglobin and haematocrit levels remained within the normal range throughout but, in the other three procedures, haemoglobin and haematocrit levels decreased below the lower limit of the normal range at either the 2 hour post-surgery time point or discharge/early discharge or both. The mean value of haemoglobin was 157.8 g/L pre-surgery, which was 145.8 g/L at 2 hours post-op and 121.8 g/L at end of treatment period. The respective values of haematocrit were 47.43 %, 44.10 % and 38.25 %. However, none of the levels were considered clinically significant by the investigators.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The open-label, unblinded design of the submitted pivotal clinical trial Ten01 investigating the efficacy of Coagadex in 16 patients with hereditary FX deficiency is considered adequate in light of the orphan setting and the given design and objectives of the trial, where it is evident that feasibility issues drive the number of patients enrolled. The targeted patient/bleeding numbers were achieved. The focus of data analysis is on the thorough description of the PK/efficacy/safety data observed in the patient set investigated. For most important outcome measures, point estimates were planned to be reported together with confidence intervals, which is acceptable.

The investigated patient population was multi-national and included 6 adolescents (between 12 and 17 years of age) and 10 adults. Fourteen subjects (87.5%) had severe Factor X deficiency (endogenous FX:C <1 IU/dL) and the other two subjects had moderate deficiency (FX:C >1 to <5 IU/dL). The included population is considered to be adequately representative of patients with hereditary FX deficiency.

Apart from the thorough characterisation of the PK parameters of this plasma derived FX, the efficacy in the treatment of bleeding events and for surgical procedures was investigated. The use as a secondary prophylaxis to avoid rebleeding e.g. after joint bleeds and as a short-term prevention before anticipated physical activity was also foreseen in the protocol.

Study Ten03 enrolled two male patients with mild factor X deficiency (endogenous levels of FX being 7 and 8 IU/dL, respectively), who underwent four major surgical procedures (2 each). This study was curtailed after advice received from CHMP indicated that surgical data from Ten03 together with surgical data from Ten01 could be sufficient to support assessment of the effects of FX in invasive procedures.

After advice received at a Follow-up Protocol Assistance procedure indicated that the already collected data on 6 surgical procedures in 4 patients might be sufficient to show evidence of the safety and efficacy of FACTOR X in surgery, Ten03 was curtailed after two subjects, with two surgical procedures each, completed the study, since at that point 2 of the 3 surgical procedures in Ten01 had taken place. As subjects were consented for each surgery separately, the total enrolment in Ten03 is considered equivalent to four study subjects.

Mild congenital FX deficiency is usually defined as plasma levels below 10 IU/dl. The inclusion criteria allowed enrolment subjects with FX activity up to 20 IU/dl. As the two enrolled subjects had baseline values of 7 and 8 IU, respectively, this criticism is considered not relevant.

The two subjects underwent 4 major surgeries without any bleeding complications. In fact blood loss was 'as expected' in 3 patients and 'less than expected' in one patient, which, taken together with the other outcomes available, is considered adequate proof of the efficacy of FX substitution for surgical interventions.

The most important evaluation of efficacy of FX was based on the subject's assessment of each new bleed. FX was planned to be deemed effective if at least 80% of a subject's treated new assessable bleeds for on demand treatment were assessed as having an 'excellent' or 'good' response. This criterion is defined on a 'per-patient' level and can hence only be assessed per patient. The SAP, however, foresees in addition a 95% CI for the proportion of excellent/good response in all bleeds over all patients, assuming independence between bleeds within patient.

Efficacy data and additional analyses

In study Ten01, all sixteen (16) patients received FACTOR X for on-demand treatment of 208 spontaneous, menorrhagic or traumatic bleeds of which 187 bleeds in 15 subjects were selected for the analysis by the DRC who categorised the majority as major (98; 52.4%). The majority were covert (110; 58.8%) with 16 (8.6%) overt (79 were spontaneous and 47 traumatic) and 61 (32.6%) menorrhagic. These bleeds occurred in various locations: mucosal 73 (39.0%); joint 63 (33.7%); muscle 26 (13.9%), cuts/wounds 4 (2.1%) and other 21 (11.2%). Additionally, three minor surgical procedures (tooth extractions) were performed during study Ten01, with satisfactory outcomes.

Two patients with recurring bleeding events even used routine FX infusions as a long-term prophylactic treatment although this constituted a protocol deviation. For the use as long-term prophylaxis, available data indicate that it was effective in both patients and reduced the bleeding rate meaningfully (to 0 for both subjects). Other preventative doses accounted for 56 (30.4%) infusions which were given as secondary prophylaxis to prevent re-bleeding and 45 (24.5%) infusions which were given as a short-term preventative measure (e.g. before increased physical activity). In only three cases new bleeding event started within 24 hours of the preventative infusion, of which two were menorrhagic bleeds. This supports the usefulness of FX for short-term prophylaxis.

Of the 208 captured spontaneous, traumatic or menorrhagic bleeds, 187 were selected for evaluation by the DRC. 90.7% of those bleeding events were assessed as having an excellent response to FX and 7.5% as having a good response. Thus, a satisfactory effect in the treatment of bleeding events was shown for Coagadex. The observed number of bleeds was heavily dominated by one subject, who experienced the most bleeding events during the study, i.e. 59. Nearly all of those bleeding events (BEs)(56 out of 59) were selected by the DRC for evaluation. Therefore the assessment of efficacy of FX was heavily influenced by the assessment of one specific subject. The applicant has provided a sensitivity analysis of the treatment of bleeding events that excluded bleeds experienced by this subject. It was shown that the proportion of bleeding events assessed as having an excellent or good response stays consistently high. The efficacy of FX treatment was also shown to be similarly satisfactory for minor and major bleeds.

With regard to preventative treatment with FX, 56 (30.4%) infusions were given as secondary prophylaxis to prevent re-bleeding and 45 (24.5%) infusions were given as a short-term preventative measure (e.g. before increased physical activity). Only in three instances a new bleeding event was reported during the next 24 hours, of which 2 were menorrhagic bleeds. This supports the usefulness of short term preventative use. Investigators' overall assessment of efficacy was good (20%) or

excellent (80%) for all evaluated subjects (15 out of 16), illustrating that the observed efficacy is regarded as beneficial also from the clinicians view.

The efficacy in surgery is supported by the three minor surgeries undertaken during study Ten01, where FX substitution was shown to be adequate to prevent excessive bleeding. In addition, in study Ten03, two patients underwent 4 major surgeries without any bleeding complications. The efficacy assessment was excellent in all seven surgical procedures performed in five patients. Blood loss was as expected or reduced. No post-operative transfusions were needed. There was no clinically significant drop of haemoglobin levels and haematocrit. Due to the high target levels of 70-90% Factor X the pre-surgery doses ranged from 30.9 to 54.4 IU/kg. However, all four major surgical procedures were performed in patients with only mild factor X deficiency. Surgical data in patients with severe factor X deficiency were only available in two minor interventions of tooth extraction. However, it is agreed that there is no data to suggest that dosing or monitoring should be different in patients with severe factor X deficiency undergoing major surgical procedures. The inclusion of dosing recommendations for all severity grades and major procedures in the SmPC was considered appropriate to provide relevant guidance to clinicians caring for these rare patients (see SmPC section 4.2.). Nevertheless, CHMP recommends the applicant to submit the report of the outcomes of major surgeries undertaken in three additional patients with moderate to severe FX deficiency post marketing.

Safety and efficacy data in both Ten01 and Ten03 studies are based on a maximum recommended dose of 60 IU/kg. Although this dose was exceeded in one subject a maximum daily dose of 60 IU/kg is recommended as a precautionary measure (See SmPC section 4.2.).

The update on the status of Study Ten02 in the prophylaxis of bleeding in paediatric patients (< 12 years of age) was submitted during the assessment and included preliminary data. The fact that the planned recruitment (of 8 patients) was even exceeded as 9 patients are already enrolled provided enough reassurance to the CHMP that an indication of Coagadex across age groups will not have a negative impact on the completion of the PIP.

Study Ten02 is an open-label, multi-centre trial evaluating the safety, pharmacokinetics, and efficacy of FACTOR X concentrate, The study is being conducted at three sites in the UK, and is currently ongoing. The clinical study report with final data from study Ten02 is expected in Q3 2017.

Assessment of paediatric data on clinical efficacy

The Applicant provided an overview over the current status of study Ten02 in children below 12 years of age, and preliminary data were in line with those observed in patients ≥12 in study Ten01. The final clinical study report is expected by end 2016 – See RMP.

2.5.4. Conclusions on the clinical efficacy

Data from trial Ten01 are considered sufficient to demonstrate the efficacy of Coagadex for the treatment of bleeding events in patients with hereditary FX deficiency in surgical procedures as also supported by the results of study Ten03. The efficacy of preventative infusions in relationship to the time to the start of a new bleeding event provides evidence of short-term prophylactic use of FX. Available data from two patients who received long term prophylaxis confirm that these patients experienced no bleeding events for the duration of therapy. Preliminary data from the ongoing paediatric study Ten02 support efficacy across age groups and provide reassurance on the completion of the ongoing PIP. Further efficacy data in children aged less than 12 years with Hereditary Factor X Deficiency will be available from study Teno2 (PIP).

The CHMP considers the following measures necessary to address issues related to efficacy:

- Submission of final clinical study report from study Ten02; Efficacy, safety and pharmacokinetics of Coagadex in subjects aged less than 12 years with Hereditary Factor X Deficiency.

2.6. Clinical safety

The overall safety evaluation of FACTOR X is based on safety data from Ten01 and Ten03 clinical studies.

Patient exposure

	Patients enrolled	Patients exposed	Patients exposed to the proposed dose range	Patients with long term* safety data
Open studies				
Ten01	16	16	16	15
Ten03	2	2	2 pat/ 4 procedures	

* In general this refers to 6 months and 12 months continuous exposure data, or intermittent exposure.

In the study Ten01, 16 subjects received at least one dose of FACTOR X for on-demand treatment for bleeds, for prophylaxis of bleeds and/or for controlling bleeding during surgical procedures. The mean (±SD) duration of study participation was 457.9 (±284.32) days per subject. During this time, there were a total of 468 infusions given of which 242 were for treatment of bleeds, 184 as preventative treatment, 31 for PK assessments, 6 for surgical procedures and 5 at a batch change.

The number of infusions of FACTOR X overall ranged from 5 to 115 per subject with a median of 20.0 per subject. Mean total number of infusions per subject given for overall use was 29.3. Exposure days per subject ranged from 3 to 111, median 17.0 days. The monthly average use, for all uses, ranged from 0.3 to 9.6 (mean 2.33) infusions per subject per month.

The mean dose per infusion overall was 25.47 IU/kg per subject. The recommended dose of 25 IU/kg FACTOR X to treat a bleed was maintained during the study for 14 of the 16 subjects. The other two subjects used doses of up to 30 IU/kg and 33 IU/kg.

In the study Ten03, 2 male subjects, received FACTOR X for controlling haemostasis during two surgical procedures each. Their surgical procedures were all regarded as major by the DRC: one subject had a coronary artery bypass graft and, at a later date, six dental extractions; the other subject had two total knee arthroplasties about 4 months apart.

Total exposure days in Ten03 were 40, a mean of 10 per surgical procedure. The median number of infusions per procedure was 13, mean 10.8 and range 2 to 15. The pre-surgery doses ranged from 30.6 to 49.2 IU/kg with a median of 38.65 IU/kg and mean of 39.28 IU/kg. The total dose of FACTOR X in Ten03 ranged from 44.6 IU/kg to 210.1 IU/kg with a median of 180.65 IU/kg and a mean of 154.00 IU/kg.

Adverse events

Adverse events (AEs) were analysed in several ways:

• All treatment emergent AEs (TEAEs) irrespective of the time of occurrence in relation to any infusion

• Product-associated AEs

- infusion-associated i.e. onset within 24 h of start of infusion of FACTOR X, or

- classed as related/possibly related to FACTOR X, or

- where causality was missing or indeterminate

• Product-related AEs

- classed as related/possibly related to FACTOR X

In both studies, all product-associated AEs had an onset within 24 hours of the start of infusion of FACTOR X so the data for product-associated and infusion-associated are identical; only 'infusion-associated' will be used for further reference. There were no AEs in which causality was missing or indeterminate.

The definition and capture of adverse events is in principle acceptable. However, no adverse events of special interest for coagulation factor replacement have been defined. Allergic reactions, thrombotic events, adverse events related to bleeding, infections and hepatobiliary events are considered of special relevance for a plasma derived coagulation factor and analyses presenting the incidence and severity of all AEs captured by these terms should be submitted by the applicant.

All 18 individual subjects (100%), in Ten01 and Ten03 combined, experienced at least one treatment-emergent AE (TEAE).

A total of 202 treatment-emergent AEs were reported: 176 in study Ten01 and 26 in study Ten03. Most of these AEs were mild or moderate in severity. Of the 202 treatment-emergent AEs, 6 (3.0%) were considered by the investigator to be possibly related to the study drug. There were a total of 84 infusion-associated AEs: 71 in Ten01 and 13 in Ten03.

Ten01 and Ten03 differ because in Ten01 infusions of FACTOR X were given intermittently and when required to stop a bleed or as a preventative measure, so infusions were widely spread and were rarely given on a daily basis; in general, each subject in Ten01 usually received many more infusions that the subjects in Ten03, whose infusions were given daily over a relatively short period.

All 18 individual subjects (100%), in Ten01 and Ten03 combined, experienced at least one treatment-emergent AE (TEAE).

Treatment-emergent adverse events (TEAEs)

A total of 202 treatment-emergent AEs were reported: 176 in study Ten01 and 26 in study Ten03. Most of these AEs were mild or moderate in severity. Of the 202 treatment-emergent AEs, 6 (3.0%) were considered by the investigator to be possibly related to the study drug.

Table 25: All treatment-emergent adverse events (TEAEs) by study and overall according to MedDRA system organ class and preferred term

System Organ Class Preferred Term	Ten01		Ten03		Combined studies	
	Number (%)Subjects N=16	Number (%) AEs N=176	*Number (%) Subjects N=4	Number (%) AEs N=26	Number (%)Subjects N=20	Number (%) AEs N=202
Any AE	16 (100)	176 (100)	3 (75)	26 (100)	19 (95)	202 (100)
Blood and lymphatic system disorder	5 (31.3)	8 (4.5)	1 (25)	1 (3.8)	6 (30)	9 (4.5)
Anaemia	4 (25.0)	7 (4.0)	1 (25)	1 (3.8)	4 (20)	8 (4.0)
Iron deficiency anaemia	1 (6.3)	1 (0.6)	0	0	1 (5)	1 (0.5)
Gastrointestinal disorders	8 (50.0)	20 (11.4)	3 (75)	7 (26.9)	11 (55)	27 (13.4)
Abdominal pain upper	1 (6.3)	1 (0.6)	0	0	1 (5)	1 (0.5)
Constipation	1 (6.3)	2 (1.1)	3 (75)	3 (11.5)	4 (20)	5 (2.5)
Diarrhoea	1 (6.3)	1 (0.6)	0	0	1 (5)	1 (0.5)
Dyspepsia	0	0	3 (75)	3 (11.5)	3 (15)	3 (1.5)
Gastritis	1 (6.3)	1 (0.6)	0	0	1 (5)	1 (0.5)
Gastro-oesophageal reflux disease	2	2 (1.1)	0	0	2 (10)	2 (1.0)
Gingivitis	1 (6.3)	1 (0.6)	0	0	1 (5)	1 (0.5)
Nausea	2 (12.5)	6 (3.4)	1 (25)	1 (3.8)	3 (15)	7 (3.5)
Odynophagia	1 (6.3)	3 (1.7)	0	0	1 (5)	3 (1.5)
Toothache	1 (6.3)	1 (0.6)	0	0	1 (5)	1 (0.5)

Vomiting	2 (12.5)	2 (1.1)	0	0	2 (10)	2 (1.0)
General disorders and administration site conditions	7 (43.8)	16 (9.1)	2 (50)	2 (7.7)	9 (45)	18 (8.9)
Fatigue	1 (6.3)	2 (1.1)	0	0	1 (5)	2 (1.0)
Infusion site erythema	1 (6.3)	2 (1.1)	0	0	1 (5)	2 (1.0)
Infusion site pain	1 (6.3)	1 (0.6)	0	0	1 (5)	1 (0.5)
Malaise	1 (6.3)	2 (1.1)	0	0	1 (5)	2 (1.0)
Non-cardiac chest pain	1 (6.3)	1 (0.6)	0	0	1 (5)	1 (0.5)
Oedema peripheral	1 (6.3)	2 (1.1)	2 (50)	2 (7.7)	3 (15)	4 (2.0)
Pyrexia	1 (6.3)	2 (1.1)	0	0	1 (5)	2 (1.0)
Swelling	1 (6.3)	1 (0.6)	0	0	1 (5)	1 (0.5)
Ulcer	2 (12.5)	2 (1.1)	0	0	2 (10)	2 (1.0)
Vessel puncture site haematoma	1 (6.3)	1 (0.6)	0	0	1 (5)	1 (0.5)
Immune system disorders	1 (6.3)	2 (1.1)	0	0	1 (5)	2 (1.0)
Urticaria	1 (6.3)	2 (1.1)	0	0	1 (5)	2 (1.0)
Infections and infestations	14 (87.5)	36 (20.5)	1 (25)	1 (3.8)	15 (75)	37 (18.3)
Bronchitis	1 (6.3)	1 (0.6)	0	0	1 (5)	1 (0.5)
Cystitis	2 (12.5)	2 (1.1)	0	0	2 (10)	2 (1.0)
Fungal infection	1 (6.3)	1 (0.6)	0	0	1 (5)	1 (0.5)
Gastric ulcer helicobacter	1 (6.3)	1 (0.6)	0	0	1 (5)	1 (0.5)

Herpes zoster	0	0	1 (25)	1 (3.8)	1 (5)	1 (0.5)
Naso-pharyngitis	7 (43.8)	11 (6.3)	0	0	7 (35)	11 (5.4)
Nosocomial infection	1 6.3)	1 (0.6)	0	0	1 (5)	1 (0.5)
Oral infection	1 (6.3)	1 (0.6)	0	0	1 (5)	1 (0.5)
Osteomyelitis	1 (6.3)	1 (0.6)	0	0	1 (5)	1 (0.5)
Otitis media	2 (12.5)	2 (1.1)	0	0	2 (10)	2 (1.0)
Pneumonia	1 (6.3)	1 (0.6)	0	0	1 (5)	1 (0.5)
Respiratory tract infection	1 (6.3)	1 (0.6)	0	0	1 (5)	1 (0.5)
Tooth abscess	1 (6.3)	1 (0.6)	0	0	1 (5)	1 (0.5)
Tooth infection	1 (6.3)	1 (0.6)	0	0	1 (5)	1 (0.5)
Upper respiratory tract infection	4 (25.0)	9 (5.1)	0	0	4 (20)	9 (4.5)
Urinary tract infection	1 (6.3)	1 (0.6)	0	0	1 (5)	1 (0.5)
Injury, poisoning and procedural complications	4 (25.0)	8 (4.5)	1 (25)	1 (3.8)	4 (20)	8 (4.0)
Contusion	1 (6.3)	2 (1.1)	1 (25)	1 (3.8)	2 (10)	3 (1.5)
Fall	1 6.3)	1 (0.6)	0	0	1 (5)	1 (0.5)
Head injury	1 (6.3)	1 (0.6)	0	0	1 (5)	1 (0.5)
Joint injury	2 (12.5)	2 (1.1)	0	0	2 (10)	2 (1.0)
Post procedural haemorrhage	1 (6.3)	1 (0.6)	0	0	1 (5)	1 (0.5)
Post procedural	0	0	1 (25)	2 (7.6)	1	1

discomfort					(5)	(0.5)
Post procedural pain	0	0	2 (50)	2 (7.6)	1 (5)	1 (0.5)
Thermal burn	1 (6.3)	1 (0.6)	0	0	1 (5)	1 (0.5)
I**nvestigations**	0	0	1 (25)	1 (3.8)	1 (5)	1 (0.5)
Haemoglobin decreased	0	0	1 (25)	1 (3.8)	1 (5)	1 (0.5)
Metabolism and nutrition disorders	1 (6.3)	1 (0.6)	0	0	1 (5)	1 (0.5)
Fluid overload	1 (6.3)	1 (0.6)	0	0	1 (5)	1 (0.5)
Metabolism and nutrition disorders	0	0	1 (25)	3 (11.5)	1 (5)	3 (1.5)
Hyper- glycaemia	0	0	1 (25)	1 (3.8)	1 (5)	1 (0.5)
Hypo- kalaemia	0	0	1 (25)	1 (3.8)	1 (50)	1 (0.5)
Hypo-magnesaemia	0	0	1 (25)	1 (3.8)	1 (5)	1 (0.5)
Musculoskeletal and connective tissue disorders	9 (56.3)	48 (27.3)	0	0	9 (45)	48 (23.8)
Arthralgia	5 (31.3)	14 (8.0)	0	0	4 (20)	14 (6.9)
Back pain	6 (37.5)	10 (5.7)	0	0	6 (30)	10 (5.0)
Groin pain	1 (6.3)	1 (0.6)	0	0	1 (5)	1 (0.5)
Joint stiffness	1 (6.3)	1 (0.6)	0	0	1 (5)	1 (0.5)
Muscle haemorrhage	1 (6.3)	1 (0.6)	0	0	1 (5)	1 (0.5)
Muscle spasms	2 (12.5)	2 (1.1)	0	0	2 (10)	2 (1.0)
Musculo-skeletal pain	3 (18.8)	3 (1.7)	0	0	3 (15)	3 (1.5)

Musculo-skeletal stiffness	1	1 (0.6)	0	0	1 (5)	1 (0.5)
Myalgia	2 (12.5)	2 (1.1)	0	0	2 (10)	2 (1.0)
Neck pain	1 (6.3)	4 (2.3)	0	0	1 (5)	4 (2.0)
Osteoarthritis	1 (6.3)	1 (0.6)	0	0	1 (5)	1 (0.5)
Pain in extremity	6 (37.5)	8 (4.5)	0	0	6 (30)	8 (4.0)
Nervous system disorders	8 (50.0)	18 (10.2)	0	0	8 (40)	18 (8.9)
Dizziness	1 (6.3)	1 (0.6)	0	0	1 (5)	1 (0.5)
Headache	8 (50.0)	14 (8.0)	0	0	8 (40)	14 (6.7)
Migraine	1 (6.3)	2 (1.1)	0	0	1 (5)	2 (1.0)
Syncope	1 (6.3)	1 (0.6)	0	0	1 (5)	1 (0.5)
Psychiatric disorders	1 (6.3)	1 (0.6)	1 (25)	1 (3.8)	2 (10)	2 (1.0)
Insomnia	1 (6.3)	1 (0.6)	1 (25)	1 (3.8)	2 (10)	2 (1.0)
Renal and urinary disorders	1 (6.3)	1 (0.6)	0	0	1 (5)	1 (0.5)
Nephrolithiasis	1 (6.3)	1 (0.6)	0	0	1 (5)	1 (0.5)
Reproductive system and breast disorders	1 (6.3)	2 (1.1)	0	0	1 (5)	2 (1.0)
Dysmenorrhoea	1 (6.3)	1 (0.6)	0	0	1 (5)	1 (0.5)
Menorrhagia	1 (6.3)	1 (0.6)	0	0	1 (5)	1 (0.5)
Respiratory, thoracic and mediastinal	4 (25.0)	5 (2.8)	1 (25)	1 (3.8)	5 (25)	6 (3.0)

disorders						
Cough	1 (6.3)	1 (0.6)	0	0	1 (5)	1 (0.5)
Dyspnoea	1 (6.3)	1 (0.6)	0	0	1 (5)	1 (0.5)
Nasal congestion	1 (6.3)	1 (0.6)	0	0	1 (5)	1 (0.5)
Oro-pharyngeal pain	1 (6.3)	1 (0.6)	1 (25)	2 (7.7)	2 (10)	3 (1.5)
Tachypnoea	1 (6.3)	1 (0.6)	0	0	1 (5)	1 (0.5)
Skin and subcutaneous tissue disorders	3 (18.8)	4 (2.3)	1 (25)	2 (7.7)	4 (20)	6 (3.0)
Acne	1 (6.3)	2 (1.1)	0	0	1 (5)	2 (1.0)
Dermatitis allergic	1 (6.3)	1 (0.6)	0	0	1 (5)	1 (0.5)
Ecchymosis	0	0	1 (25)	1 (3.8)	1 (5)	1 (0.5)
Pruritus	1 (6.3)	1 (0.6)	1 (25)	1 (3.8)	2 (10)	2 (1.0)
Vascular disorders	5 (31.3)	6 (3.4)	1 (25)	1 (3.8)	6 (30)	7 (3.5)
Haematoma	1 (6.3)	2 (1.1)	1 (25)	1 (3.8)	2 (10)	3 (1.5)
Hypotension	4 (25.0)	4 (2.3)	0	0	4 (20)	4 (2.0)

*for Ten03, the number of subjects is the number of surgical procedures, not of individual subjects

The most common TEAEs, which were reported by at least 25 % of the combined study population, were as follows:

Headache (reported by 8 subjects; 6.7% of all AEs)

Nasopharyngitis (reported by 7 subjects; 5.4% of all AEs)

Back pain (reported by 6 subjects; 5.0% of all AEs)

Pain in extremity (reported by 6 subjects; 4.0% of all AEs)

Infusion-associated AEs

Of the total of 202 TEAEs, 84 (41.6%) were categorised as infusion-associated (**Table 38**).

Table 26: Infusion-associated adverse events by study and overall according to MedDRA system organ class and preferred term

System Organ Class Preferred Term	Ten01		Ten03		Combined studies	
	Number (%) Subjects N=16	**Number (%) AEs** N=71	***Number (%) Subjects** N=4	**Number (%) AEs** N=13	**Number (%) Subjects** N=20	**Number (%) AEs** N=84
Any product-associated AE	15 (93.8)	71 (100)	3 (75)	13 (100)	18 (90)	84 (100)
Blood and lymphatic system disorder	2 (12.5)	2 (2.8)	0	0	2 (10.0)	2 (2.4)
Anaemia	1 (6.3)	1 (1.4)	0	0	1 (5.0)	1 (1.2)
Iron deficiency anaemia	1 (6.3)	1 (1.4)	0	0	1 (5.0)	1 (1.2)
Gastrointestinal disorders	4 (25.0)	11 (15.5)	3 (75)	5 (26.9)	7 (35.0)	16 (19.0)
Constipation	1 (6.3)	2 (2.8)	1 (25.0)	1 (7.7)	2 (10.0)	3 (3.6)
Diarrhoea	1 (6.3)	1 (1.4)	0	0	1 (5.0)	1 (1.2)
Dyspepsia	0	0	2 (50.0)	2 (15.4)	2 (10.0)	2 (2.4)
Gastro-oesophageal reflux disease	1 (6.3)	1 (1.4)	0	0	1 (5.0)	1 (1.2)
Nausea	2 (12.5)	5 (7.0)	1 (25.0)	2 (7.7)	3 (15.0)	7 (8.3)
Toothache	1 (6.3)	1 (1.4)	0	0	1 (5.0)	1 (1.2)
Vomiting	1 (6.3)	1 (1.4)	0	0	1 (5.0)	1 (1.2)
General disorders and administration site conditions	5 (31.3)	10 (14.1)	0	0	5 (25.0)	10 (11.9)
Fatigue	1 (6.3)	2 (2.8)	0	0	1 (5.0)	2 (2.4)
Infusion site erythema	1 (6.3)	2 (2.8)	0	0	1 (5.0)	2 (2.4)
Infusion site pain	1 (6.3)	1 (1.4)	0	0	1 (5.0)	1 (1.2)
Oedema peripheral	1 (6.3)	1(1.4)	0	0	1 (5.0)	1 (1.2)
Pyrexia	1 (6.3)	1 (1.4)	0	0	1 (5.0)	1 (1.2)
Swelling	1 (6.3)	1 (1.4)	0	0	1 (5.0)	1 (1.2)
Ulcer	2 (12.5)	2 (2.8)	0	0	2 (10.0)	2 (2.4)
Infections and infestations	9 (56.3)	14 (19.7)	0	0	9 (45.0)	14 (16.7)
Cystitis	1 (6.3)	1 (1.4)	0	0	1 (5.0)	1 (1.2)

Naso- pharyngitis	3 (18.8)	4 (5.6)	0	0	3 (15.0)	4 (4.8)
Nosocomial infection	1 (6.3)	1 (1.4)	0	0	1 (5.0)	1 (1.2)
Osteomyelitis	1 (6.3)	1 (1.4)	0	0	1 (5.0)	1 (1.2)
Otitis media	1 (6.3)	1 (1.4)	0	0	1 (5.0)	1 (1.2)
Tooth abscess	1 (6.3)	1 (1.4)	0	0	1 (5.0)	1 (1.2)
Tooth infection	1 (6.3)	1 (1.4)	0	0	1 (5.0)	1 (1.2)
Upper respiratory tract infection	3 (18.8)	5 (7.0)	0	0	3 (15.0)	5 (6.0)
Injury, poisoning and procedural complications	4 (25.0)	6 (8.5)	3(75.0)	3(23.1)	5 (25.0)	7(8.3)
Contusion	1 (6.3)	2(2.8)	0	0	1 (5.0)	2(2.4)
Fall	1 (6.3)	1 (1.4)	0	0	1 (5.0)	1 (1.2)
Joint injury	2 (12.5)	2 (2.8)	0	0	2 (10.0)	2 (2.4)
Post-procedural discomfort	0	0	1 (25.0)	1 (7.7)	1 (5.0)	1 (2.4)
Post-procedural pain	0	0	2 (50.0)	2 (15.4)	2 (10.0)	2 (2.4)
Post procedural haemorrhage	1 (6.3)	1 (1.4)	0	0	1 (5.0)	1 (1.2)
Thermal burn	1 (6.3)	1 (1.4)	0	0	1 (5.0)	1 (1.2)
Metabolism and nutrition disorders	0	0	1 (25.0)	3 (23.1)	1 (5.0)	3 (3.6)
Hyper- glycaemia	0	0	1 (25.0)	1 (7.7)	1 (5.0)	1 (1.2)
Hypo- kalaemia	0	0	1 (25.0)	1 (7.7)	1 (5.0)	1 (.2)
Hypo- magnesaemia	0	0	1 (25.0)	1 (7.7)	1 (5.0)	1 (1.2)
Musculoskeletal and connective tissue disorders	6 (37.5)	12 (16.9)	0	0	6 (30.0)	12 (14.3)
Arthralgia	3 (18.8)	4 (5.6)	0	0	3 (15.0)	4 (4.8)
Back pain	2 (12.5)	2 (2.8)	0	0	2 (10.0)	2 (2.4)
Muscle spasms	1 (6.3)	1 (1.4)	0	0	1 (5.0)	1 (1.2)
Musculo- skeletal pain	2 (12.5)	2(2.8)	0	0	2 (10.0)	2 (2.4)
Musculo-skeletal stiffness	1 (6.3)	1 (1.4)	0	0	1 (5.0)	1 (1.2)
Osteoarthritis	1 (6.3)	1 (1.4)	0	0	1 (5.0)	1 (1.2)
Pain in extremity	1 (6.3)	1 (1.4)	0	0	1 (5.0)	1 (1.2)

Nervous system disorders	4 (25.0)	8 (11.3)	0	0	4 (20.0)	8 (9.5)
Headache	4 (25.0)	7 (9.9)	0	0	4 (20.0)	7 (8.3)
Migraine	1 (6.3)	1 (1.4)	0	0	1 (5.0)	1 (1.2)
Psychiatric disorders	0	0	1 (25.0)	1 (7.7)	1 (5.0)	1 (1.2)
Insomnia	0	0	1 (25.0)	1 (7.7)	1 (5.0)	1 (1.2)
Renal and urinary disorders	1 (6.3)	1 (1.4)	0	0	1 (5.0)	1 (1.2)
Nephrolithiasis	1 (6.3)	1 (1.4)	0	0	1 (5.0)	1 (1.2)
Respiratory, thoracic and mediastinal disorders	1 (6.3)	1 (1.4)	1 (25.0)	1 (7.7)	2 (10.0)	2 (2.4)
Oro- pharyngeal pain	0	0	1 (25.0)	1 (7.7)	1 (5.0)	1 (1.2)
Tachypnoea	1 (6.3)	1 (1.4)	0	0	1 (5.0)	1 (1.2)
Skin and subcutaneous tissue disorders	2 (11.5)	3 (4.2)	0	0	2 (10.0)	3 (3.6)
Acne	1 (6.3)	2 (2.8)	0	0	1 (5.0)	2 (2.4)
Dermatitis allergic	1 (6.3)	1 (1.4)	0	0	1 (5.0)	1 (1.2)
Vascular disorders	3 (18.8)	3 (4.2)	0	0	3 (15.0)	3 (3.6)
Haematoma	1 (6.3)	1 (1.4)	0	0	1 (5.0)	1 (1.2)
Hypotension	2 (12.5)	2 (2.8)	0	0	2 (10.0)	2 (2.4)

*for Ten03, the number of subjects is the number of surgical procedures, not of individual subjects

The most common Infusion-associated AEs were:

Headache 4 subjects (20%) and 7 reports (8.3% of all this category of AEs)

Nausea 3 subjects (15%) and 7 reports (8.3% of all this category of AEs)

URTI 3 subjects (15%) and 5 reports (6.0% of all this category of AEs)

Nasopharyngitis 3 subjects (15%) and 4 reports (4.8% of all this category of AEs)

Arthralgia 3 subjects (15%) and 4 reports (4.8% of all this category of AEs)

Product-related AEs (ADRs)

Product-related AEs (i.e. ADRs) were those categorised by the investigator as very likely, possibly or probably related causally to FACTOR X. Two subjects (12.5%) experienced a total of six events, considered by the investigator to be ADRs. No subject in Ten03 experienced an ADRs.

Of the total of 202 TEAEs, six (3%) were regarded as ADRs, which represented 7.1% of the 84 infusion-associated AEs. None was serious.

Infusion site erythema 1 subject (5%), 2 reports both of mild severity

Infusion site pain 1 subject (5%), 1 report of mild severity

Fatigue 1 subject (5%), 1 report each of moderate and mild severity

Lower back pain 1 subject (5%), 1 report of mild severity

Serious adverse event / deaths / other significant events

One subject in the Ten01 study died of pneumonia and nosocomial infection. This subject developed pneumonia about 3 weeks after the first dose of FACTOR X and was hospitalised until she died about 45 days later after nosocomial infection complicated by multi-organ failure. The events were considered unrelated to FACTOR X treatment. There were no other deaths in either study.

Including the one death (in Ten01), a total of 6 subjects experienced a total of 13 treatment emergent SAEs, all of which occurred in the Ten01 study. There were three bleeds in two subjects, three worsening of anemia in two subjects, one of whom also had acute gastritis and the other one worsening gastric ulcer with H pylori infection, one syncope, one tooth abscess and one dysmenorrhea. All SAEs were deemed unrelated to FACTOR X treatment. There were no treatment-emergent SAEs in Ten03.

Laboratory findings

No clinically significant trends of abnormality were observed in any of the laboratory indicators, haematology, biochemistry, and PT and APTT during the study period of both trials (Ten01, Ten03).

There were no clinically significant changes in viral serology suggesting seroconversion in either study.

In the Ten01 study, the thrombogenicity markers d-dimer, thrombin-antithrombin complex (TAT), and prothrombin fragments 1+2 (F1+2), were measured at intervals up to 72 hours post-dose at the Baseline visit (16 subjects) and at the Repeat PK visit (15 subjects). All thrombogenicity profiles in which any one result exceeded the upper limit of the normal range were reviewed by the Data Review Committee (DRC). The DRC did not consider any subject's thrombogenicity results to be indicative of a possible thrombogenic effect of FACTOR X. A genuine thrombogenic response to FACTOR X would be expected to cause an early, substantial and sustained elevation of all three parameters at the Baseline visit, which would be reproduced at the Repeat PK visit; however, this was not observed in any subject.

Safety in special populations

Intrinsic Factors

The patient sample size was too small to allow for the analyses of FACTOR X safety by demographic and clinical characteristics. All subjects in the Ten01 and Ten03 studies were aged 12 years or older.

Extrinsic Factors

The patient sample size was too small for analyses of FACTOR X on the basis of ethnic factors as defined in ICH E5 guidance. No potential interactions of FACTOR X with other drugs, use of tobacco, use of alcohol, or food habits were observed in the Ten01 and Ten03 studies.

Use in Pregnancy and Lactation

Neither clinical trial investigated the effect of FACTOR X in pregnancy and lactation. As a naturally existing protein derived from human plasma, FACTOR X is not expected to be teratogenic. Factor X is not likely to cross the placenta or to be excreted into milk.

Overdose

One case of overdose was reported in study Ten01. On 01 July 2013 subject 35001 received 80 IU/kg instead of 25 IU/kg to treat a bleed as a result of a dosing error, which was above the maximum recommended dose of 60 IU/kg. Plasma FX:C was not measured, but based on the subject's observed incremental recoveries the factor X level would be expected to rise to 99-150 IU/dL. No adverse events were reported relating to this overdose. An overdose of FACTOR X may present theoretical risks of thrombosis.

Factor X inhibitors

In the Ten01 and Ten03 studies, all study subjects tested negative for factor X inhibitors throughout the study periods. When the PK parameters for FX:C (measured using the one-stage clotting assay) at the Repeat PK visit were compared with those at the Baseline visit (Ten01), the DRC found no indication of development of covert factor X inhibitors.

Infusion Site Observations

Infusion site observations (for discomfort, erythema, induration, tenderness and warmth) in Ten01 were performed immediately before each post-dose sample at the Baseline visit, the Repeat PK assessment and any Batch Change visits. One subject (21001) had a mild reaction 15 and 30 minutes post-dose at both the Baseline and Repeat PK visits. One subject had moderate discomfort, mild erythema and mild warmth pre-dose at the Repeat PK visit. No other symptoms were noted. In Ten03, all infusions were well tolerated without any infusion site reactions.

Immunogenicity

There were 3 reports of infusion site reactions in 2 patients (2 erythema, 1 pain), which were all mild and considered as ADRs.

Safety related to drug-drug interactions and other interactions

Interactions of FACTOR X and other drugs or with certain types of foods have not been studied. Theoretically, FACTOR X should be used with caution in combination with other coagulation factor products, including prothrombin complex concentrates or fresh/frozen plasma.

There are no known theoretical drug interactions, except that the effects of FACTOR X are likely to be counteracted by factor Xa inhibitors.

Discontinuation due to adverse events

Apart from the one death, due to pneumonia and nosocomial infection, no subject discontinued study participation due to AE.

Post marketing experience

FACTOR X has not been marketed in any country. However, FACTOR X has been supplied to 13 patients completing study Ten01, and at least 5 patients in the UK not enrolled in study Ten01, on a compassionate use basis.

One miscarriage (BPL incident number QR 81002) was reported in a subject receiving once weekly FACTOR X 1500 IU (approximately 20 IU/kg). The subject became concerned she might be pregnant and sought medical advice. β-HCG levels, measured on the day after vaginal bleeding commenced, were low, indicating the pregnancy was not intact prior to the abortion, hence the bleeding was a consequence and not a cause of the abortion. A diagnosis of spontaneous abortion at 6 weeks + 3 days was made. This event was classed as serious and unrelated to FACTOR X.

2.6.1. Discussion on clinical safety

Safety data are based on exposure of 18 subjects (> 12 years) with hereditary factor X deficiency to FACTOR X (Coagadex).

Generally, adverse event reports are to be within the expected range of the anticipated safety-profile of coagulation factor products. FACTOR X intravenous infusions were well tolerated. Two patients experienced a total of six events, considered to be ADRs: infusion site erythema (1 subject; 2 reports), Infusion site pain (1 subject), Fatigue (1 subject; 2 reports), lower back pain (1 subject). Including one death, a total of 6 subjects experienced a total of 13 treatment-emergent SAEs, that all were deemed unrelated to FACTOR X treatment. In study Ten01 one patient had two AEs of urticaria and one patient one AE of allergic dermatitis. But these events were not regarded as product-related AEs (ADRs). Since allergic reactions are expected complications of protein-based products, further information and analysis of these cases is required. The adverse event reporting mentioned “headache” as a common reported treatment-emergent and infusion-associated adverse event. There could be a relation to the administration of FACTOR X.

FACTOR X use was not associated with any clinically significant abnormality in clinical laboratory parameters or physical signs. There was no evidence to suggest that FACTOR X induced factor X inhibitor. Shifts of thrombogenicity markers were observed in some subjects, but no clinical signs or symptoms of thrombosis were observed in any subject. No drug-drug or drug-food interactions were reported in the studies. There might be a theoretical interaction or counteraction of Coagadex by factor Xa inhibitors such as novel oral anticoagulant drugs.Due to the limited size of the investigated population no detailed analyses and predictions could be made for special populations and situations. The accidental overdosing of one subject had no apparent sequelae.

During compassionate use of FACTOR X a miscarriage occurred. A relation to FACTOR X treatment appears to be unlikely.

Evaluation in general follows the currently valid clinical guideline. The presented results are considered to be acceptable. No unexpected patterns in the reported adverse events and serious adverse events were observed. No safety data in children < 12 years are available. No patients developed Factor X inhibitors or thromboembolic events. The presented results are considered to be acceptable.
JAR
The overall safety database for Coagadex, 18 individual patients in two clinical trials, is very small but taking into account the rarity of the investigated disease with a prevalence of approximately 1: 1 000 000, considered sufficient to characterize the preauthorisation safety profile.

The 16 patients enrolled in Ten01 achieved 3 to 111 (median 17.0 days) exposure days per subject. A total of 468 infusions were given of which 242 were for treatment of bleeds, 184 as preventative treatment, 31 for PK assessments, 6 for surgical procedures and 5 at a batch change. The number of infusions of FACTOR X overall ranged from 5 to 115 per subject with a median of 20.0 per subject.

In the study Ten03 two male subjects received FX for controlling haemostasis during two surgical procedures each. All procedures were major: A coronary artery bypass graft, six dental extractions and two total knee arthroplasties. Total exposure days in Ten03 were 40, a mean of 10 per surgical procedure. The median number of infusions per procedure was 13, mean 10.8 and range 2 to 15.

The adverse event profile of Coagadex did not reveal any unexpected safety signals. Only a minority of AEs were considered as related by the investigator (6/202: 3%): Two subjects (12.5%) in study Ten01 experienced a total of six events. No SAE was considered related to treatment with FX. From a quality point of view, a high rate of aggregates was observed in the final drug product, which could lead to an

increased immunogenicity of Coagadex. However, no patient developed signs of covert inhibitor activity or a positive inhibitor assay result in the course of the study.

An analysis for adverse events of special interest (allergic reactions, thrombotic events, adverse events related to bleeding, infections and hepatobiliary events) were submitted to complete the overall safety evaluation of Coagadex. No occurences of these AESIs could be identified in the database.

The use of Coagadex was not associated with any clinically significant abnormality in clinical laboratory parameters or physical signs. There was no evidence to suggest that Coagadex induced factor X inhibitor. Shifts of thrombogenicity markers were observed in some subjects, but no clinical signs or symptoms of thrombosis were observed in any subject. No drug-drug or drug-food interactions were reported in the studies. There might be a theoretical interaction or counteraction of Coagadex by factor Xa inhibitors such as novel oral anticoagulant drugs. Due to the limited size of the investigated population no detailed analyses and predictions could be made for special populations and situations. The accidental overdosing of one subject had no apparent sequelae.

Coagadex is likely to be counteracted by factor Xa inhibitors, direct or indirect. It is recommended that these antithrombotic agents should not be used in patients with factor X deficiency. Coagadex should not be used as an antidote to the effects of direct oral anti-coagulants (DOACs) in patients who do not have factor X deficiency.

During compassionate use of FACTOR X a miscarriage occurred. A relation to FACTOR X treatment appears to be unlikely.

From the safety database all the adverse reactions reported in clinical trials (back pain, infusion site erythema, fatigue and infusion site pain) have been included in the Summary of Product Characteristics section 4.8 as common.

Assessment of paediatric data on clinical safety

Only preliminary safety data in children <12 years are available at this point in time, as the paediatric study Ten02 has already started enrolment. An update on the status of the study showed that all 18 treatment emergent adverse events reported in 5 subjects so far were not considered related to study medication.

No patients developed Factor X inhibitors or thromboembolic events.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.6.2. Conclusions on the clinical safety

Clinical safety data reported in studies Ten01 and Ten03 are considered appropriate to elucidate the tolerability and safety of Coagadex for use in hereditary FX deficiency. No unexpected patterns in the reported adverse events and serious adverse events were observed. No patients developed Factor X inhibitors or thromboembolic events. Preliminary safety data in children <12 years do not raise any specific concern for the use of the product. Further safety data in children aged less than 12 years with Hereditary Factor X Deficiency will be available from study Ten02 (PIP). All safety information available has been included in the SmPC.

2.7. Risk Management Plan

Safety concerns

Summary of safety concerns	
Important identified risks	Hypersensitivity or allergic reactions, including anaphylaxis
Important potential risks	Inhibitor development Virus transmission Transmissible infectious agents (TSE) transmission Inadequate product traceability Thrombogenicity (under special consideration for off label use and overdose cases)
Missing information	Very limited clinical experience in pregnancy No experience in lactating females No clinical data in subjects age less than 12 years No clinical data for use in patients older than 60 years Limited clinical data on long term safety

Pharmacovigilance plan

The PRAC, having considered the data submitted, was of the opinion that routine pharmacovigilance is sufficient to identify and characterise the risks of the product.

The MAH is currently investigating the possibility of participation in EUHASS or another rare bleeding disorders registry.

The PRAC also considered that routine PhV is sufficient to monitor the effectiveness of the risk minimisation measures.

Risk minimisation measures

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Hypersensitivity or allergic reactions, including anaphylaxis	Section 4.3 of proposed SmPC contraindicates use in patients with a history of hypersensitivity to the active substance or any of the excipients. Warning in section 4.4 of proposed SmPC regarding risk of hypersensitivity reactions.	None
Inhibitor development	Warning in section 4.4 of proposed SmPC regarding risk of inhibitor development.	None
Virus transmission	Warning in section 4.4 of proposed SmPC regarding risk of transmissible infectious agents.	None
TSE transmission	Warning in section 4.4 of proposed SmPC regarding risk of transmissible infectious agents	None
Inadequate product traceability	Section 4.4 of proposed SmPC recommends that every time product is administered, product name and batch number should be recorded. Contractual requirement for distributors to participate in any product recall and comply with	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	national requirements relating to product storage and transportation.	
Thrombogenicity (under special consideration for off label use and overdose cases)	Off label use Section 4.5 of the proposed SmPC provides warning that Coagadex should not be used as an antidote to the effects of direct oral anticoagulants (DOACs) in patients who do not have Factor X deficiency. Coagadex is indicated for hereditary factor X deficiency and not acquired factor X deficiency. Overdose In addition, section 4.2 of the proposed SmPC recommends that treatment should be initiated under the supervision of a physician experienced in the treatment of rare bleeding disorders and for home therapy, the patient should be given appropriate training and reviewed at intervals. Warning in section 4.9 of proposed SmPC regarding the potential for thromboembolism with overdose.	None
Very limited clinical experience in pregnancy No experience in lactating females	Warning in section 4.6 of proposed SmPC that COAGADEX® should only be used during pregnancy and lactation only if clearly indicated.	None
No clinical data in subjects age less than 12 years	Section 4.2 of the proposed SmPC for COAGADEX® states that “The safety and efficacy of Coagadex in children < 12 years of age have not yet been established”.	None
No clinical data for use in patients older than 60 years	Section 5.2 of the proposed SmPC for COAGADEX® states that no pharmacokinetic studies have been conducted in the elderly but there is no anticipated effect of age on the pharmacokinetic profile of COAGADEX®.	None
Limited clinical data on long term safety	Section 5.2 of the proposed SmPC states that there are limited data on long term use.	None

Conclusion

The CHMP and PRAC considered that the risk management plan version 06 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, COAGADEX (factor X) is included in the additional monitoring list as it is a biological product that is not covered by the previous category and authorised after 1 January 2011.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

Benefits

Beneficial effects

PK profiles covering extensive blood draw time points of nearly 5 half lifes showed that half-life in plasma was found to consistently be about 30 hours and incremental recovery about 2 IU/dl/IU/kg, translating into dosing and dose interval recommendations as set in the SmPC.

In the pivotal study, Ten01, Coagadex was able to satisfactorily treat bleeding events in subjects with severe (14) or moderate (2) hereditary factor X deficiency. Of the 187 bleeds evaluated, nearly all (98.4%) of the bleeds treated with Coagadex were considered a treatment success (i.e. excellent or good response). In addition, the overall efficacy in the three minor surgeries undertaken in this study was rated as excellent by investigators. Four major surgeries (two total knee replacements, a cardiac bypass operation and an exctraction of 6 pre/molars) undertaken in two subjects (2 procedures each) in trial Ten03 demonstrated that blood loss during and after these procedures was less than expected or as expected under FX coverage. These results underline that Coagadex acts as a functional blood coagulation factor X in the blood of the recipient and is able to correct symptoms of FX deficiency.

Two patients with recurring bleeding events used routine FX infusions as a long-te rm prophylactic treatment although this constituted a protocol deviation. For the use as long-term prophylaxis, available data indicate that it was effective in both patients and reduced the bleeding rate meaningfully (from 0.23 and 0.82 bleeds/month to 0 for both subjects). Other preventative doses accounted for 56 (30.4%) infusions which were given as secondary prophylaxis to prevent re-bleeding and 45 (24.5%) infusions which were given as a short-term preventative measure (e.g. before increased physical activity). In only three cases new bleeding event started withing 24 hours of the preventative infusion, of which two were menorrhagic bleeds. This supports the usefulness of FX for short-term prophylaxis.

Uncertainty in the knowledge about the beneficial effects.

The final efficacy assessment in surgery is influenced by missing data in major surgery in patients with severe factor X deficiency. However it is expected that, if FX levels are raised to 70-90 IU/dl according

to dosing recommendations, the coagulant activity of Coagadex will also provide sufficient protection for subjects with severe FX deficiency during major surgical procedures. Furthermore there is no evidence to suggest that dosing or monitoring should be different in subjects with severe factor X deficiency undergoing major surgical procedures. Including dosing recommendations for all severity grades and major procedures will provide appropriate guidance to clinicians caring for these rare patients. The applicant has agreed with the FDA to provide data on three additional patients with moderate to severe factor X deficiency undergoing major surgical procedures.

Although the final study report from study Ten02 on PK and clinical data in paediatric patients younger than 12 years of age -is outstanding at the moment, preliminary data provide adequate expectation that the plasma derived factor X would have comparable effects in children.

Risks

Unfavourable effects

Only a small proportion (6/202: 3%) of observed treatment emergent adverse events were assessed as related to Coagadex. Related AEs (infusion site reactions, fatigue and back pain) were of mild or moderate severity and manageable. The nature and frequency of all AEs reported do not give rise to concern and did not reveal unexpected safety signals.

Uncertainty in the knowledge about the unfavourable effects

The available safety database of 18 unique subjects is very small but taking into account the rarity of the disease it is acceptable. A high and variable percentage of aggregates in the final drug product could potentially cause tolerability problems or the formation of inhibitors that were not captured during these small trials (see RMP). Information will be collected at post – marketing phase.

Effects table

Table 27. Effects Table for Coagadex in the treatment of hereditary FX deficiency

Effect	Short Description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
PK	Half-life (mean) chromogenic	h	33.8	N/A	Full PK profiles from 16 subjects, repeat profile from 15 subjects, extensive blood draw time points	PK in target population
	Half-life (mean) one-stage clotting	h	30.3			
	IR_{1h} (mean) chromogenic	IU/dl per IU/kg	2.21			
	IR_{1h} (mean) One-stage clotting	IU/dl per IU/kg	2.08			
Treatment of bleeding events						
N=187 bleeds	3-point rating scale	Excellent	90.9%		56 bleeds experienced by one subject	Summary of main efficacy results for Ten01
		good	7.5%			

Effect	Short Description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Surgery						
Trial Ten01						Summary of main efficacy results for Ten01
Minor surgery	Investigators assessment	excellent	3			
Trial Ten03						
Major surgery	Volume of blood loss		4			Supportive study
	As expected		3			
	Less than expected		1			
Unfavourable Effects						
Related AEs	From a total of 202 TEAEs in 18 subjects				Very small database	2.4.8 Safety
Infusion site erythema			2 mild			
Infusion site pain			1 mild			
Fatigue			1 mild, 1 moderate			
Lower back paint			1 mild			
AEs of special interest						
Inhibitors		n	0			2.4.8 Safety

Benefit-risk balance

Importance of favourable and unfavourable effects

In view of the lack of specific therapy, bleeding events in Patients with FX deficiency are currently treated with coagulation factor compounds such as FFP or prothrombin complex concentrates. Dosing of FX with these products is difficult and the danger of elevating other coagulation factors into the supraphysiological range with the consequent potential complications of thrombosis and embolism and, due to the large volumes needed, of fluid overload are limiting factors for optimal treatment.

The favourable effects of a targeted factor X substitution with Coagadex are considered to outweigh the observed unfavourable effects, which were generally benign and did not negatively impact the patients' ability and willingness to continue treatment with Coagadex. On the contrary, two patients even initiated regular prophylactic infusions once weekly in order to stave off bleeding events. These

favourable effects are expected to apply also to patients younger than 12 years of age, in patients with severe or moderate FX deficiency undergoing major surgery and for preventative therapy (long and short term prophylaxis of bleeding events).

From a clinical point of view FX was shown to be a safe and efficacious product with a reproducible beneficial effect on the treatment of bleeding events and during surgery. Limited data also support the usefulness of FX for short-term or long-term prophylaxis of bleeding events. Furthermore, Coagadex will represent the only specific therapy available for patients with hereditary FX deficiency.

Benefit-risk balance

Discussion on the benefit-risk balance

The efficacy of Coagadex for the treatment of bleeding episodes and prophylaxis in minor surgery in subjects 12 years of age or older is considered established. Data from two patients initiating long-term prophylaxis and experiencing a reduction of the annualized bleeding rate to zero underline the usefulness of FX for long-term prevention of bleeds. Additionally, the applicant has adequately addressed open issues with regard to short-term preventative treatment and major surgery in patients with severe deficiency. In support of an extrapolation of the beneficial effects of Coagadex to the paediatric population below 12 years of age, the applicant has submitted an update on the paediatric trial Ten02, in which 9 children below 12 years of age 12 are enrolled and receive long-term prophylaxis and treatment of bleeding events with Coagadex. Preliminary data are consistent with those observed in the pivotal trial Ten01, in which 6 adolescents between 12 and 17 years participated.

The safety profile of Coagadex appears to be satisfactory from the data presented so far. Preliminary safety data from the paediatric trial Ten02 are also considered favourable. Due to the extreme rarity of the disease the safety database is very small even compared to other new medicinal products with an orphan designation. Rare events cannot be expected to be captured during the clinical development programme; therefore the measures proposed in the RMP will provide additional insights into the safety and tolerability of Coagadex once it is available on the market.

4. Recommendations

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Coagadex in the treatment and prophylaxis of bleeding episodes and for perioperative management in patients with hereditary factor X deficiency is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Official batch release

In accordance with Article 114 Directive 2001/83/EC, the official batch release will be undertaken by a state laboratory or a laboratory designated for that purpose.

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set

out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Not applicable.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

These conditions fully reflect the advice received from the PRAC.

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0188/2014 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.