26 July 2018
EMA/CHMP/455550/2018
Committee for Medicinal Products for Human Use (CHMP)

CHMP extension of indication variation assessment report

Coagadex

International non-proprietary name: human coagulation factor X

Procedure No. EMEA/H/C/003855/II/0007

Note

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

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List of abbreviations

ADR	Adverse drug reactions
AE	Adverse event
Ag	Antigen
ALT	Alanine aminotransferase
APTT	Activated partial thromboplastin time
AUC	Area under the concentration versus time curve
BD	Twice daily
BPL	Bio Products Laboratory, Ltd. (the Sponsor)
b.p.m	Beats per minute
BU	Bethesda Units
CI	Confidence intervals
C0	Concentration at time zero
CHMP	Committee for Medicinal Products for Human Use
CFR	Code of Federal Regulations
CRA	Clinical Research Associate
CRF	Case Record Form
CSR	Clinical Study Report
ED	Exposure Day (s)
EMA	European Medicines Agency
EOS	End of Study
EU	European Union
F1+2	Prothrombin Fragments F1 and F2
F10	Gene for factor X
FACTOR X	BPL's high purity factor X concentrate (commercial name COAGADEX®)
FDA	US Food and Drug Administration
FFP	Fresh Frozen Plasma
FX	Factor X
FVIII	Factor VIII
FIX	Factor IX
FX:C	Factor X activity
g	Grams
GMP	Good Manufacturing Practice
GCP	Good Clinical Practice
HAV	Hepatitis A virus
Hb	Haemoglobin
HBV	Hepatitis B virus
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HEENT	Head, ear, eye, nose and throat
HIV	Human immunodeficiency virus
hr(s)	hour(s)
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent ethics committee
IMP	Investigational medicinal product
IR	Incremental recovery
IRB	Institutional Review Board
ISTH	International Society of Thrombosis and Haemostasis
ITT	Intention-To-Treat
IU	International units
IV	Intravenous
Kg	Kilogrammes
LCL	Lower Confidence Limit
Ltd	Limited
Max	Maximum
MCV	Mean corpuscular volume
MCHC	Mean corpuscular haemoglobin concentration
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency (regulatory authority for the United Kingdom)
mins	Minute(s)
Min	Minimum

mL	Millilitre(s)
MREC	Multi-Centre Research Ethics Committee
MRI	Magnetic resonance imaging
PCC	Prothrombin complex concentrate
PCR	Polymerase chain reaction
PDCO	EMA Paediatric Committee
PK	Pharmacokinetic
PP	Per-Protocol
PT	Prothrombin time
Q1	Lower Quartile (25%)
Q3	Upper Quartile (75%)
SAE	Serious adverse event
SD	Standard deviation
SOC	System Organ Class
SUSAR	Suspected Unexpected Serious Adverse Reaction
TRALI	Transfusion Related Acute Lung Injury
TEAE	Treatment Emergent Adverse Event
TLF	Tables, Listings and Figures
UK	United Kingdom
unk	Unknown
US	United States (of America)
UCL	Upper Confidence Limit
WFI	Water For Injection
WHO	World Health Organisation
wk(s)	Week(s)
yr(s)	Year(s)

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Bio Products Laboratory Limited submitted to the European Medicines Agency on 14 March 2018 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Update of sections 4.2, 4.8, 5.1 and 5.2 of the SmPC in order to include safety and efficacy data in children aged less than 12 years of age based on final results from the study Ten02, a phase III open-label multicentre study to confirm the safety, pharmacokinetics and efficacy of BPL's high purity factor X in the prophylaxis of bleeding in factor X deficient children under the age of 12 years, provided in accordance with the agreed paediatric investigational plan. The Package Leaflet is updated accordingly. The RMP version 7.0 has also been submitted.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

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

The new indication, which is the subject of this application, falls within the above mentioned orphan designation.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0389/2017 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0389/2017 was completed.

The PDCO issued an opinion on compliance for the PIP P/0389/2017.

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 did not seek Protocol Assistance at the CHMP.

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: N/A

Timetable	Actual dates
Submission date	14 March 2018
Start of procedure:	28 April 2018
CHMP Co-Rapporteur Assessment Report	n/a
CHMP Rapporteur Assessment Report	22 June 2018
PRAC Rapporteur Assessment Report	31 May 2018
PRAC members comments	4 July 2018
Updated PRAC Rapporteur Assessment Report	N/A
PRAC Outcome	12 July 2018
CHMP members comments	16 July 2018
Updated CHMP Rapporteur(s) (Joint) Assessment Report	19 July 2018
CHMP Opinion	26 July 2018

2. Scientific discussion

2.1. Introduction

Hereditary factor X deficiency is a rare type of bleeding disorder caused by the inherited lack of coagulation factor X. Factor X deficiency can result in bleeding patterns similar to, if less frequent than, those seen in males with haemophilia A or B. Unlike haemophilia A and B, however, the gene for factor X is located on the long arm of chromosome 13. Therefore, both genders can be carriers and both can develop factor X deficiency.

The prevalence of severe factor X deficiency in the general population is approximately 1 in 1 million, which puts it between one hundredth and one twentieth of the prevalence of haemophilia A and B, respectively.

Factor X deficiency varies in severity, which is defined according to the endogenous level of factor X in the plasma. Severe factor X deficiency is defined as endogenous concentration of factor X being <1% (< 1 IU/dL); moderate deficiency is when the factor X level is 1-5%; and mild deficiency is when factor X level is >5%. The level of endogenous factor X activity in the general population has been reported at 65 to 120 IU/dL.

Coagadex (Coagulation Factor X [Human]) is a human plasma-derived coagulation factor that is used as a replacement for the naturally existing coagulation factor X in patients with hereditary factor X deficiency.

Currently Coagadex is licensed in the European Union (EU) with the following indication:

“Coagadex is indicated for the treatment and prophylaxis of bleeding episodes and for perioperative management in patients with hereditary factor X deficiency.”

The initial marketing authorisation was based on the results of trials Ten01 and Ten03 in 18 patients >12 years old with hereditary FX deficiency.

In the EU, a post-marketing commitment to study the prophylactic use of Coagadex in a population of young children (<12 years of age) was agreed which resulted in study Ten02. This study has been confirmed as complying with the requirements of the Paediatric Investigational Plan (PIP) and is the focus of this submission. As a result of this study, there are changes to the Summary of Product Characteristics (SmPC) and Patient Information Leaflet (PIL).

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trial 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

Type of Study	Study ID	Location of Study Report	Objectives of the Study	Study Design and Type of Control	Test Product; Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Treatment Duration	Study Status; Type of Report	Countries Involved in Study
Paediatric - Efficacy, Safety, Pharmacokinetic	Ten02	5.3.5.2	To assess the efficacy of FACTOR X in the reduction/prevention of bleeding when given as routine prophylaxis over 6 months (26 weeks) Secondary Objectives: (1) To assess the pharmacokinetics (factor X incremental recovery and trough levels) of FACTOR X after a single dose of 50 IU/kg (2) To assess the safety of FACTOR X when given as routine prophylaxis over 6 months (26 weeks)	A multicentre, open-label trial. Not controlled.	FACTOR X: a high purity, plasma-derived human coagulation factor X concentrate. A dosage regimen of 40-50 IU/kg twice a week was recommended. The maximum dose per infusion was not to exceed 60 IU/kg. Recommended dosage for bleeding episodes was 25 IU/kg for a minor bleed and 50 IU/kg for a major bleed. Intravenous infusion	9	Patients with moderate or severe hereditary factor X deficiency	Subjects were treated for a minimum of 6 months (26 weeks) and for a minimum of 50 exposure days.	Complete; Final study report	UK only

2.3.2. Pharmacokinetics

One of the objectives of trial Ten02 was to assess the pharmacokinetic (FX incremental recovery and trough levels) of FACTOR X after a single dose of 50 IU/kg. The recommended bolus doses at the Visit 1 (Baseline) and the End of Study Visit recovery assessment visit was 50 IU/kg. This was higher than the bolus dose of 25 IU/kg used in the Ten01 clinical trial of FACTOR X in adults and adolescents.

Factor X Activity Measurements (defined as FX:C levels)

FX:C assays for incremental recovery and trough level measurements were performed by the central laboratory (Haematology Department, Addenbrooke's Hospital, Cambridge, UK using the one-stage clotting assays) and the local laboratories at each Investigator Site. Central laboratory results were used in the efficacy analysis.

The pre- and post-dose plasma samples for incremental recovery were assayed together. Local laboratory results were used to check an appropriate trough level was being maintained and for dose adjustment, if necessary. All central and local laboratory results were recorded in the CRF. FX:C assays were performed on a pre-dose sample if the subject has a major bleed.

Blood samples for incremental recovery were taken at 30 minutes post-dose and were ideally drawn from the opposite arm to the arm in which FACTOR X was administered. However, if blood samples were drawn from the same site as the infusion, which includes venous access devices (e.g. Portacath), in these cases the line/device was flushed with saline (equivalent to 2 volumes of the dead space) and a volume of blood equivalent to 2 volumes of the dead space of the infusion line was withdrawn before obtaining the blood samples. If the sample was drawn from the same site as the infusion, this was documented in the CRF in case of spurious results.

Incremental Recovery

Visit 1 (Baseline) and End of Study Visit (V5) recovery data was available for all 9 subjects. Plasma concentrations were obtained for FX:C, using the one-stage clotting assay.

The recommended bolus dose of FACTOR X was 50 IU/kg, the mean dose administered at Visit 1 (Baseline) was 48.7 IU/kg and 50.0 IU/kg at End of Study (V5). The mean incremental recovery at Visit 1 (Baseline) was 1.66 IU/dL per IU/kg and 1.82 IU/dL per IU/kg after 50 exposures and 6 months treatment (End of Study Visit, V5). The high degree of overlap of the 95% confidence intervals (CI) for each visit indicated the appropriateness of combining data from the 2 visits, which gave an overall mean incremental recovery of 1.74 IU/dL per IU/kg, see Table 15a.

Table 15a- Incremental recovery for all subjects in IU/dL per IU/kg- Per-Protocol population			
Parameters	**Visit 1 (Baseline)**	**End of study (V5)**	**Overall**
	Mean	**Mean**	**Mean**
No of subjects (N)	9	9	9
Bolus dose (IU/kg)	48.7	50.0	49.3
30 min post-bolus FX: C Recovery in IU/dL per IU/kg (Min, Max)	1.66 (1.3, 2.2)	1.82 (1.3, 2.2)	1.74 (1.3, 2.2)
95% CI (LCL, UCL)	1.45, 1.88	1.62,2.03	1.60, 1.88

Source: Section 14, Table 2.2 , LCL =lower confidence limit, UCL =upper confidence limit

A statistical analysis to compare IRs between the two age groups was conducted using a linear regression model with terms for an overall intercept and age group. The overall mean IR for the younger age group (0 to 5 years) was statistically lower than that observed for the older subjects: mean IR (IU/dL per IU/kg) of 1.53 (Table 15c) and 1.91 (Table 15b) respectively (p=0.0013). In addition, the minimum and maximum IR values were lower in the younger age group than the older age group.

Table 15b- Incremental recovery for 6 to 11 year age group in IU/dL per IU/kg- Per-Protocol population			
Parameters	**Visit 1 (Baseline)**	**End of study (V5)**	**Overall**
	Mean	**Mean**	**Mean**
No of subjects (N)	5	5	5
Dose (IU/kg)	47.7	50.0	48.9
30 min post-bolus FX: C Recovery in IU/dL per IU/kg (Min, Max)	1.83 (1.6, 2.2	1.99 (1.8, 2.2)	1.91 (1.6, 2.2)
95% CI (LCL, UCL)	1.53, 2.13)	1.80, 2.17	1.76, 2.06

Source: Section 14, Table 2.2, LCL =lower confidence limit, UCL =upper confidence limit

Table 15c- Incremental recovery for 0 to 5 year age group in IU/dL per IU/kg- Population: Per-Protocol			
Parameters	**Visit 1 (Baseline)**	**End of study (V5)**	**Overall**
	Mean	**Mean**	**Mean**
No of subjects (N)	4	4	4
Dose (IU/kg)	49.9	49.9	49.9
30 min post-bolus FX: C Recovery in IU/dL per IU/kg (Min, Max)	1.45 (1.3, 1.6)	1.62 (1.3, 1.8)	1.53 (1.3, 1.8)
95% CI (LCL, UCL)	1.21,1.68	1.23, 2.00	1.36,1.70

Source: Section 14, Table 2.2, LCL =lower confidence limit, UCL =upper confidence limit

The difference in the IR values between the age groups was found to be statistically significant at each visit, Table 15d.

Table 15d- Statistical summary comparing incremental recovery between age groups (p values) Population: Per Protocol			
Difference in IRs between age groups 6- 11 years and 0-5 years	**IR at Visit 1 (Baseline)**	**IR at End of study (V5)**	**Overall IR**
P values	0.0270	0.0251	0.0013

Source: Section 14, Table 2.2

The IR for the two subjects excluded from the Per-Protocol population were slightly higher than those observed in the other subjects in the same age group (0 to 5 years) and that compared to the IRs observed when these subjects re-entered the study for their second treatment cycle (Table 16). This difference was not considered to be clinically significant.

Table 16- Recovery (IU/ dL per IU/kg) data for two subjects excluded from the Per-Protocol population and comparing re-screening data				
Subject number	**Visit 1 (Baseline)**		**End of study (V5)**	
1st treatment cycle	Dose (IU/kg)	IR IU/dL per IU/kg	Dose (IU/kg)	IR IU/dL per IU/kg
	47.9	2.1	50.8	1.8
	47.5	1.8	50.2	2.0
2nd treatment cycle				
	50.2	1.6	49.8	1.8
	50.2	1.3	49.9	1.7

Source: Listing 25

FX:C activity levels

FX:C trough levels were measured at Screening Visit, Visit 1(Baseline) pre-bolus (V1), then 48 to 72 hours post-infusion (V2), 9 to 28 days (V3) and 29 to 42 days (V4) after the first infusion, and after 6 months treatment and 50 EDs (V5/End of Study, EOS).

Table 17a – Central FX:C levels (IU/dL) at each visit for all the subjects in the Per-Protocol population

Subject Numbers	Screening visit	V1 pre-bolus	[e]V1 post-bolus	V2	V3	V4	V5 pre-bolus	V5 (EoS) post-bolus
6 to 11 year group								
	6	9	96	10	7	13	11	114
	11	5	84	15	10	9	14	112
	9	8	118	17	14	17	11	106
	6	2	99	15	8	7	10	120

Table 17a – Central FX:C levels (IU/dL) at each visit for all the subjects in the Per-Protocol population

Subject Numbers	Screening visit	V1 pre-bolus	[e]V1 post-bolus	V2	V3	V4	V5 pre-bolus	V5 (EoS) post-bolus
	8	5	71	10	5	7	9	100
0 to 5 year group								
	6	5	75	12	15	15	12	95
	10	8	87	13	12	11	13	104
	8	8	71	12	7	8	9	94
	7	5	82	7	4	8	11	74
N	**9**	**9**	**9**	**9**	**9**	**9**	**9**	**9**
Mean	**7.9**	**6.1**	**87.0**	**12.3**	**9.1**	**10.6**	**11.1**	**102.1**
Min	**6**	**2**	**71**	**7**	**4**	**7**	**9**	**74**
Max	**11**	**9**	**118**	**17**	**15**	**17**	**14**	**120**

Source: Listing 18b, Section 14, Table 5.1.3, [e]not trough levels, N= number of subjects

Table 17a displays the central laboratory FX:C values for each subject in the PP population. Two subjects had trough levels below 5 IU/dL (dose adjustment stage). It was assumed that subjects would have reached steady state by V4. Table 17b displays the doses taken by each subject in the PP group prior to V4 and the number of days prior to V4 the doses were administered. For all the subjects in the PP group the doses and dosing intervals used in the study were sufficient to maintain trough levels above the target level of 5 IU/dL from visit 4 onwards (steady state).

Table 17b Summary of FACTOR X dose taken prior to V4 in the Per-Protocol population		
Subject Numbers	Dose (IU/kg) prior to V4	Number of days prior to V4 when dose was taken
6 to 11 year group		
	50.8	3
	40.5	2
	41.0	3
	43.4	4
	18.1	3
0 to 5 year group		
	44.0	3
	38.6	3
	33.5	3
	47.6	3

Source: Listing 36.1.1

For the two subjects excluded from the Per-Protocol population, FX:C levels were maintained above 5 IU/dl throughout the study (Table 18a). Summary of doses taken prior to V4 are summarised in Table 18b.

Table 18a – Central FX:C levels (IU/dL) at each visit for the subjects excluded from the Per-Protocol population								
Subject Numbers	Screening visit	V1 pre-bolus	V1 post-bolus[f]	V2	V3	V 4	V5 pre-bolus[f]	V5 post-bolus
	12	11	110	13	11	10	15	105
	10	12	96	10	6	6	8	107

Source: Listing 18b, [f]not trough levels

Table 18b Summary of FACTOR X dose taken prior to V4 for the subjects excluded from the Per-Protocol population		
Subject Numbers	Dose (IU/kg) prior to V4	Number of prior to V4 when dose was taken (days)
	43.6	3
	37.1	3

Source: Listing 36.1.1

2.3.3. Pharmacodynamics

Mechanism of action

Factor X is one of the vitamin-K-dependent serine proteases and plays a crucial role in blood coagulation in both the intrinsic and extrinsic pathways of the clotting cascade. Factor X is an inactive

zymogen, which can be activated by factor IXa (via the intrinsic pathway) or by factor VIIa (via the extrinsic pathway). Factor X is converted from its inactive form to the active form (factor Xa) by the cleavage of a 52-residue peptide from the heavy chain. Factor Xa associates with factor Va on a phospholipid surface to form the prothrombinase complex, which activates prothrombin to thrombin in the presence of calcium ions. Thrombin then acts upon soluble fibrinogen and factor XIII to generate a cross-linked fibrin clot. The replacement of factor X in patients with hereditary deficiency aims to restore clinically relevant levels of FX in order to allow coagulation to occur in a timely manner.

2.3.4. Discussion on clinical pharmacology

Study Ten02 was conducted with nine children below 12 years of age and aimed at characterising incremental recovery at 30 minutes after a dose of 50 IU/kg BW and trough levels at least 4 time points during the prophylactic administration of FX over 26 weeks.

Although all enrolled children were shown to display a genotype consistent with severe FX deficiency, at baseline all subjects were found to have elevated FX levels (mean 7.9 IU/dl, min 6 IU/dl, max 11 IU/dl). These values can be explained by recent (i.e. in the prior 3-4 days) use of FX containing products in all subjects, most often prothrombin complex concentrate.

In all subjects, trough levels were shown to be above the 5 IU/dl minimum defined as acceptable for this trial at all visits, except for one subject at V4, at which time steady state was probably not reached.

Mean incremental recovery was found to be 1.74 (min 1.3, max 2.2) IU/dL per IU/kg for the overall group. However, values for the younger (0-5) and older (6-11) age cohort were shown to differ. The younger subjects had a mean IR of 1.53 (1.3, 1.8) while the older subjects had mean IR values of 1.91 (1.6, 2.2). The difference was shown to be statistically significant. However, the impact on the formula used for calculation of units necessary to achieving a desired level increase using a specific value for each age group is considered to be minimal. In addition, introducing three different calculation formulas (for ≥12, 6-11, 0-5) into the SmPC is unnecessarily complex.

Therefore it is agreed to use the average value for both younger age cohorts in the SmPC (please see section 4.2 of the SmPC).

2.3.5. Conclusions on clinical pharmacology

Full PK profiles from adolescents and adults are available from trial Ten01. In this paediatric trial Ten 3, the clinical pharmacology objective was to elucidate the incremental recovery and the trough levels in children below 12 years of age.

The trough levels during routine prophylaxis were shown to be in a range deemed as protective by available literature. As with most coagulation factors, incremental recovery was demonstrated to be lower in the overall paediatric population of trial Ten02 than in the adolescent and adult population of trial Ten01. The recommendations as given in section 4.2 of the SmPC are considered adequate.

2.4. Clinical efficacy

2.4.1. Main study

Ten02

A phase III open-label multicentre study to confirm the safety, pharmacokinetics and efficacy of Coagadex in the prophylaxis of bleeding in factor X deficient children under the age of 12 years

Methods

Study participants

Inclusion Criteria

All of the criteria below had to be met for a subject to be eligible:

1. Subjects who had hereditary severe or moderate FX deficiency (FX:C <5 IU/dL, based on their lowest reliable FX:C recorded).

2. Subjects under 12 years old, whose parent/guardian gave written informed consent.

3. Subjects who had a history of severe bleeding (a minimum of one bleed with a bleed score of 3 or 4, Appendix VI of the study protocol) or a mutation in the F10 gene causing a documented severe bleeding phenotype.

Exclusion Criteria

The presence of any of the following criteria would make a subject ineligible:

1. Subjects who had a history or suspicion of inhibitor development to FX.

2. Subjects who had thrombocytopenia (platelets $<50 \times 10^9$/L).

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

4. Subjects who had clinically significant liver disease (serum ALT levels greater than three times the upper normal limit).

5. Subjects were known to have other coagulopathy or thrombophilia.

6. Subjects who had known or suspected hypersensitivity to the investigational medicinal product or its excipients.

7. Subjects who had a history of unreliability or non-cooperation.

8. Subjects who had participated or have taken part in another trial within the last 30 days.

9. Subjects who were planning more than 4 weeks continuous absence from the locality of the Investigator Site, between the Screening Visit and the End of Study Visit.

Treatments

Treatments Administered

The subjects received the first dose of FACTOR X at Visit 1 (Baseline) and the second at Visit 2 (48-72 hrs post first dose), both were at the Investigator Site under clinical supervision.

After Visit 2, the subject's parent(s)/guardian(s) were provided with sufficient FACTOR X for routine prophylactic treatment at home between study visits. For the purpose of this study, 'home therapy' included any therapy administered to a subject at a clinic local to their home which was not the Investigator Site. Alternatively, subjects could return to the Investigator Site to be treated.

All major bleeding episodes were to be treated under the supervision of a physician. Each subject was to undergo treatment for a minimum of 6 months (26 weeks) and complete 50 exposure days.

FACTOR X administered at the Visit 1 (Baseline), and at the End of study (Visit 5) were calculated and rounded to the nearest 0.1 mL. FACTOR X administered for routine prophylaxis or to treat a bleed or for preventative use was rounded to the nearest 1 mL. This difference in rounding took into account the likely limit of precision in the volume of reconstituted product self-administered by the subject at home.

Selection of Doses in the Study

Routine prophylaxis therapy in subjects with severe hereditary coagulation factor deficiencies is common to avoid development of target joints. Subjects are usually dosed once weekly or twice a week, but sometimes more frequently, depending on the severity of the symptoms. The standard dose for treating FX deficiency is 10-20 IU FX/kg; or 20-30 IU/kg (based on FX units and adjusted according to trough levels) for 1-4 year olds. However, higher doses have been described, such as 70 IU/kg once weekly for a 15 year old, 40-80 IU/kg on alternate days in a 5-year old, and 70 IU/kg once weekly in a 13 year old.

Plasma FX levels of 10-20 IU/dL are generally accepted to be required for haemostasis in adults. Trough levels as low as 5 IU/dL have been found to effectively prevent bleeding in children. For this study, a minimum trough level of 5 IU/dL was set for all subjects.

However, higher trough levels in subjects with a history or family history of intracranial haemorrhage were acceptable.

The recommended routine prophylaxis dose was 40-50 IU/kg twice a week. There is limited pharmacokinetic data available in children, however it is suggested that in children incremental recovery may be lower and half-life shorter than in adults, thus more frequent dosing in the 0-5 year age group could be considered.

Based on experience from the previous FACTOR X study (Ten01) the recommended dose for a minor bleed was 25 IU/kg and major and life-threatening bleed was 50 IU/kg and preventative therapy (for example in anticipation of increased physical activity or during rehabilitation of a joint following a bleed) was 25 IU/kg. Any unused portion of reconstituted FACTOR X solution was discarded.

Bolus Dose Before Recovery Assessments

The recommended bolus doses at the Visit 1 (Baseline) and the End of Study Visit recovery assessment visit was 50 IU/kg. This was higher than the bolus dose of 25 IU/kg used in the Ten01 clinical trial of FACTOR X in adults and adolescents. A higher bolus dose was considered necessary in this routine prophylaxis study to maintain a minimum trough level of 10 IU/dL, with twice-weekly dosing.

Dose for routine prophylaxis

Initial doses

The initial bolus dose of 50 IU/kg of FACTOR X was given at the Visit 1 (Baseline) during recovery assessment.

The second dose of FACTOR X (40-50 IU/kg) was given 72 hours ± 2 hours (Day 4) after the Visit 1 (Baseline). In the case of subjects in the 0-5 year age group, the second dose of FACTOR X could be given at 48 hours ± 2 hours (Day 3) after the Visit 1 (Baseline), at the Investigator's discretion to maintain the minimum trough level.

Consistent with the Ten01 study and based on pre-clinical toxicology studies, the maximum dose per infusion was not to exceed 60 IU/kg.

Dose adjustment – up to 6 Weeks

Due to the very scarce data available for dosing in subjects under 12 years of age, and the potential for high intra-subject variability in bleeding symptoms, once the second dose had been given and up to 6 weeks post Visit 1 (Baseline), the Investigator could adjust the dosage regimen, with the aim of maintaining trough (pre-infusion) levels of at least 5 IU/dL. The calculated dosage for routine prophylaxis was based on the subject's observed recovery at the Visit 1 (Baseline) and the subsequent trough level measurements. During weeks 2-6, the subject attended a minimum of 2 scheduled visits (Visit 3 occurring between Day 9-28; Visit 4 occurring between Day 29-42) for measurement of trough levels; unscheduled visits for additional trough level measurements were also permitted throughout the study.

To achieve the minimum trough of 5 IU/dL, assuming a half-life of 30 hours and a recovery of 1.5-2.0 IU/dL per IU/kg, a twice-weekly dose of 40-50 IU/kg was recommended, but was not mandatory. Treatment was given no more frequently than every 48 hours, and a maximum peak FX:C of 120 IU/dL was recommended. The maximum dose per infusion was not to exceed 60 IU/kg. The dosage regimen was to be adjusted with the objective of achieving a trough level of at least 5 IU/dL.

Steady State

It was expected that after 6 weeks of treatment the subject would have been on a regular dosage regimen. However, in any subject receiving coagulation factor replacement therapy on a prophylactic regimen, regular monitoring of trough levels and dose adjustment was necessary as bodyweight and FX half-life increase. Plasma FX levels were measured at both the central and local laboratories. The dose could be adjusted if the subject experienced a break-through bleed or excessive bleeding following injury, or the target trough level was not maintained. Any such dose adjustments were documented as a Dose Adjustment Unscheduled Visit and followed by an unscheduled trough measurement visit within 2 weeks combined with a second dose adjustment visit to confirm that adequate trough levels were met and the recovery was as expected.

Dose to Treat a Bleed

All major/life-threatening break-through bleeds or excessive bleeding due to injury were treated at the Investigator Site.

Recommended dosage to treat bleeding episodes was 25 IU/kg for a minor bleed and 50 IU/kg for a major bleed, which was repeated as often as required based on the FX:C recovery levels and clinical need. The dose of 25 IU/kg for minor bleeds was used in another study involving FACTOR X (Ten01) in subjects aged 12 years and above, this dose effectively treated bleeding episodes. The higher dose of 50 IU/kg for major bleeds was introduced in this study to build in flexibility, especially in the case of

very serious bleeds such as intracranial haemorrhage, in which the Investigator might wish to raise plasma FX:C close to 100 IU/dL. The maximum dose per infusion was not to exceed 60 IU/kg. Justification for any changes from the recommended dose were recorded in the CRF. The subject's weight was documented at regular study visits, and at bleed assessment, trough measurement and dose adjustment unscheduled visits, following which the total dose in IU was adjusted accordingly.

Prior to dosing, a blood sample was taken for FX:C assay, to determine whether the minimum trough level of 5 IU/dL was met. While the plasma FX level may have allowed the calculation of an appropriate dose of FACTOR X, in urgent cases dosing was not delayed until the result was made available.

If the subject was discharged while the bleed was ongoing, the Investigator Site staff then contacted the subject's parent/guardian by telephone to re-assess the bleed, at a minimum 24 hours and, if the bleed was still ongoing, at 48 hours following the first dose of FACTOR X.

A single dose was to be given to treat a bleed in the first instance. However, additional doses could be given if required until haemostasis was restored. The decision as to whether or not an additional dose should be given had to be made by the Investigator and not by a parent/guardian. Therefore, if the pain or visible bleeding continued, the subject's parent/guardian had to contact the Investigator Site. The Investigator then assessed if an additional dose was needed and if the subject needed to be brought into the hospital.

Preventative Therapy

In addition to their routine prophylaxis, subjects could have received additional doses of FACTOR X for short periods; for example, in anticipation of increased physical activity, or during rehabilitation of a joint following a bleed. This use of FACTOR X was recorded as 'preventative therapy'. The recommended dose was 40-50 IU/kg.

Objectives

Primary Objective

The primary objective of the study was to assess the efficacy of FACTOR X in the reduction/prevention of bleeding when given as routine prophylaxis over 6 months (26 weeks).

Secondary Objectives

The secondary objectives were:

1. To assess the pharmacokinetic (FX incremental recovery and trough levels) of FACTOR X after a single dose of 50 IU/kg.

2. To assess the safety of FACTOR X when given as routine prophylaxis over 6 months (26 weeks).

Outcomes/endpoints

Primary Efficacy Endpoints

The primary endpoint was the Investigator's assessment of efficacy of FACTOR X in the reduction/prevention of bleeds when given as routine prophylaxis over 6 months (26 weeks).

At the End of Study Visit (conducted after 6 months treatment), the Investigator made an assessment of the overall efficacy of FACTOR X in reduction/prevention of bleeding when given as routine prophylaxis over 6 months (26 weeks). For any subject who withdrew from the study but did not

attend an End of Study Visit, efficacy was assessed by the Investigator if the subject had received at least one infusion of FACTOR X. Efficacy was assessed according to the criteria in Table 5.

Table 5: Criteria for Investigator's overall assessment of efficacy	
Category	**Criterion**
Excellent	No minor or major bleeds occurred during the study period OR Lower frequency of bleeds than expected, given subject's medical/treatment history.
Good	Frequency of bleeds as expected, given subject's medical/treatment history..
Poor	Higher frequency of bleeds than expected, given subject's medical/treatment history. OR FACTOR X did not work at all.
Unassessable	Subject did not complete 6 weeks treatment with FACTOR X OR Subject developed inhibitors to FACTOR X OR Failure to meet the minimum trough level due to non-compliance with the dosing regimen.

Secondary Efficacy Endpoints

The analysis set used was the Per-Protocol population.

For subjects who withdrew from the study, efficacy was assessed if the subject had completed at least 6 weeks of treatment with FACTOR X. For subjects who completed less than 6 weeks of treatment with FACTOR X, efficacy was reported as 'unassessable'.

Secondary efficacy endpoints included the following:

- Number of bleeds per month, including severity, duration, location and cause.
- FX:C trough levels at all scheduled study visits and at all Bleed Assessment and Trough Measurement unscheduled visits.
- FX:C incremental recovery 30 minute post-dose at the Visit 1 (Baseline) and the End of Study Visit based on central laboratory results.

The investigational medicinal product used in the study contains biologically active compounds which are also present endogenously, therefore the FX:C trough levels and incremental recovery are a surrogate for efficacy.

Incremental recovery was defined as the rise in FX:C level recorded at 30 min (± 5 min) after the infusion divided by the actual dose administered.

- FX:C incremental recovery and trough levels following any change in dose regimen required for clinical reasons/insufficient trough levels.

- Dose of FACTOR X to treat a bleed (IU/kg) (including initial dose for new bleeds and any repeated doses for ongoing bleeds), number of infusions to treat a bleed and dose per infusion; all analysed on a per-bleed and a per-subject basis. For each value, summary tables were produced on a per bleed and a per subject basis.
- Total dose of FACTOR X in IU/kg, total number of infusions and average dose per infusion for: prophylactic use, to treat a bleed, any additional preventative use and overall use; all analysed on a per subject basis.
- Average monthly dose in IU/kg of FACTOR X, and average monthly number of infusions for: prophylactic use, to treat a bleed, any additional preventative use, any surgical use and overall use; all analysed on a per-subject basis.
- Investigators' assessment of efficacy as 'excellent', 'good', 'poor' or 'unassessable' in treating major bleeds or life-threatening break-through bleeds and excessive bleeding following injury . The bleed assessment criteria are detailed in Section 9.5.1.2.1.
- Parents'/Guardians' assessment of efficacy in treating all bleeds as 'excellent', 'good', 'poor' or 'unassessable'. All bleeds were assessed by the subject's parent(s)/ guardian(s) as detailed in Section 9.5.1.2.1.

Assessment Criteria for Efficacy in Treating a Bleed

The clinical manifestation of FX 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 subjects' parent(s)/guardian(s) for all bleeds and by the Investigator or a trained clinician for major bleeds and or life-threatening break-through bleeds and excessive bleeding following injury.

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 6.

Table 6:	Criteria for assessment of efficacy of FACTOR X in treating an overt bleed.
Category	**Criterion**
Excellent	Bleeding stopped within 12 hours after dosing with FACTOR X only, with only 1 dose of FACTOR X required.
Good	Bleeding stopped within 24 hours after first dose of FACTOR X, and no more than 2 doses of FACTOR X were needed to stop bleeding
Poor	Bleeding stopped after 24 hours after first dose of FACTOR X or more than 2 doses of FACTOR X were needed to stop bleeding, or there was no response to therapy.
Unassessable (FACTOR X dose given)	FACTOR X was given but another replacement therapy given before a response to FACTOR X could be assessed..
Unassessable (FACTOR X dose not given)	FACTOR X **was not** given. Other replacement therapy was given.
Not done	Efficacy was not assessed.

Bleeding was to be 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 addition to routine prophylactic treatment 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 7 below.

Table 7:	Criteria for assessment of efficacy of FACTOR X in treating a menorrhagic bleed.
Category	**Criterion**
Excellent	No additional doses of FACTOR X required to maintain bleeding at a manageable level
Good	1 or 2 additional doses of FACTOR X required to maintain bleeding at a manageable level
Poor	More than 2 doses of FACTOR X required to maintain bleeding at a manageable level or bleeding could not be maintained at a manageable level.
Unassessable (FACTOR X dose given)	FACTOR X was given but before a response to FACTOR X could be assessed another replacement therapy given
Unassessable (FACTOR X dose given)	FACTOR X **was not** given. Other replacement therapy was given.
Not done	Efficacy was not assessed.

Covert bleeds

Examples of covert bleeds were melena, intra-peritoneal 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. Cessation of bleeding was judged according to clinical symptoms such as pain, swelling, tenderness and mobility, this took into account the fact that some of these symptoms could have continued even after the bleed has stopped.

The following criteria were used to assist the Investigator in making a decision as to when the bleed had stopped (Table 8):

Table 8:	**Criteria for an Investigator to assess if a covert bleed had stopped**
Type of bleed	**Objective Criteria**
Intracranial haemorrhage	CT scan, MRI scan, clinical signs (*e.g.* fitting, vomiting)
Joint bleed	Pain, swelling, mobility, range of movement
Muscle bleed	Pain, swelling, mobility
Gastro-intestinal bleed	Haemoglobin, red cell counts, faecal occult blood test

Where possible, at least one objective measurement was recorded, to enable comparison at different timepoints after treatment.

Efficacy was assessed by the Investigator and subject's parent(s)/guardian(s), based on the number of doses of FACTOR X required to achieve haemostasis, according to the guidelines shown in Table 9 below. The bolus infusion of 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 subjects without factor deficiencies would continue to bleed with these lesions.

Table 9: Criteria for assessment of efficacy of FACTOR X in treating a covert bleed	
Category	**Criterion**
Excellent	Bleeding resolved following 1 or 2 doses of FACTOR X
Good	Bleeding resolved following 3 doses of FACTOR X.
Poor	Bleeding resolved following >3 doses of FACTOR X OR Bleeding did not resolve.
Unassessable-(FACTOR X dose given)	FACTOR X was given but another replacement therapy given before a response to FACTOR X could be assessed.
Unassessable (FACTOR X dose not given)	FACTOR X **was not** given. Other replacement therapy was given.
Not done	Efficacy was not assessed.[#]

[#]Reason for not completing assessment was recorded.

Sample size

No formal sample size calculation was performed, as no formal hypothesis testing was planned. The sample size was requested by the EMA Paediatric Committee (PDCO).

Randomisation

This was a single arm study. All subjects received the same treatment.

Blinding (masking)

Not applicable.

Statistical methods

Version 2.0 of the SAP was signed prior to database lock.

All tables, figures and listings were produced using SAS (v9.3).

Unless otherwise stated, categorical data are presented using counts and percentages, whilst continuous variables are presented using the mean, 95% confidence intervals (CI) for the mean, standard deviation (SD, median, minimum, maximum, number of subjects (N), number of events (n) and number of missing subjects (or number of surgeries for surgery populations) or data points.

Minima and maxima are quoted to the number of decimal places as recorded in the CRF; means, SDs and medians are quoted to one additional decimal place. Percentages are rounded to one decimal place.

The efficacy analyses were performed for the Per-Protocol population, and the Safety/ITT population was to be used to report all safety data, in accordance with the SAP. The definition of Safety/ITT population was later re-defined. As per the SAP, demographic data was planned to be reported only for the Safety/ITT populations, this was later changed.

Any subjects enrolled under previous versions of the protocol were included in the analysis populations (if they were otherwise eligible).

Analysis Populations

In version 2.0 of the SAP the study populations analysed were defined as detailed below:

Safety/ITT Population

The safety/ITT population was defined in the protocol as all treated subjects (i.e. all subjects who received at least part of one dose of study medication). Safety data were analysed up to the point of withdrawal for subjects who withdrew if the number of points were adequate to allow a scientific analysis.

Two subjects had not completed the study as Per-Protocol, these subjects were re-screened and enrolled as subjects into the study, therefore the study populations was later re-defined (see Conduct of the Study).

Per-Protocol Population

The Per-Protocol population was defined as all subjects who had completed a minimum of 6 months (26 weeks) and a minimum of 50 exposure days of routine prophylactic treatment with FACTOR X at a dosing schedule consistent with the protocol.

Results

Participant flow

Table 11: Disposition of all subjects and number of Treatment Cycles			
Number of Subjects/treatment cycles	**0 to 5 years age group**	**6 to 11 years age group**	**Total**
Unique number of subjects (Safety/ITT)[a]	4 (100%)	5 (100%)	9 (100%)
Number of subjects in the PP analysis	4 (66.7)	5 (100%)	9 (81.8)
Treatment Cycles			
In PP analysis	4[b] (66.7)	5 (100%)	9 (81.8)
In Safety/ITT treatment cycle analysis	6 (100%)	5(100%)	11 (100%
Treatment Cycles completed Per-Protocol (50 EDs and 26 weeks treatment)	4[b] (66.7)	5(100%)	9 (81.8%)
Withdrew from study or did not complete PP	2	-	2
[b]Other –left study before completing 26 weeks treatment, but completed 50 EDs (re-screened and re-entered)	2 (33.3%)	-	2 (18.2%)

Source: Section 14, Tables 1.01 to 1.03, [b]subjects treatment cycle not included in the PP, [a] 1st and 2nd treatment cycle data merged for re-screened subjects

A total of 9 unique subjects underwent 11 treatment cycles in the study. Two subjects completed 50 exposure days (EDs), however were withdrawn from the study prior to completing 26 weeks treatment with FACTOR X in error. These subjects were then rescreened and enrolled into the study again under new subject numbers.
All 9 unique subjects received at least one dose of FACTOR X during the study and were included in the Safety/ITT population.

Recruitment

Date first subject enrolled: 20 Apr 2015

Date last subject completed: 19 Oct 2016

Conduct of the study

Protocol Deviations

A total of 44 deviations were recorded in the Safety/ITT treatment cycle group:

- Four deviations were related to FACTOR X dosing, including 3 related to the less than 50 IU/kg bolus doses being administered at incremental recovery assessment due to calculation errors.
- One deviation was related to an error in drug accountability.
- Twenty deviations were categorised as laboratory deviations, including blood samples not being taken. The majority (14) of these deviations were for subjects in the 0 to 5 year group.
- Nine deviations related to visit assessment/schedules not conducted within the timeframe specified in the protocol, including the 2 subjects who terminated the study prior to completing 26 weeks treatment. The majority (7) of these deviations were for subjects in the 0 to 5 year group.
- Ten deviations were categorised as other, of which 9 were due to vital signs or infusion site observations not being conducted. The remaining deviation was related to a temperature excursion in the storage of FACTOR X at the Investigator Site. BPL's quality assurance (QA) department confirmed that the IMP was unaffected and so stock was not replaced.

Below are brief summaries of protocol deviations which BPL considered significant and where appropriate were followed through for further information from the Investigator Site.

This subject was inadvertently withdrawn from the study prior to completing 26 weeks' treatment with FACTOR X (deviation 027) and so did not meet the definition of the Per-Protocol population (see Section 8.1). This subject was re-screened and completed 50 EDs and 26 weeks treatment as subject.

HCV was negative at Visit 1 (Baseline) and recorded as not done for End of Study Visit in the CRF (deviation 023). Subsequent follow-up with site clarified that the test was conducted, but the result was not available at the time of database lock and so 'not done' was recorded in the CRF. The site confirmed the HCV for this subject at the End of Study Visit was negative.

This subject was inadvertently withdrawn from the study prior to completing 26 weeks treatment with FACTOR X (deviation 028) and so did not meet the definition of the Per-Protocol population (see Section 8.1). This subject was re-screened and completed 50 EDs and 26 weeks treatment as subject

HCV testing was not performed at Visit 1 (Baseline), deviation 037. This is subject who was re-screened and the HCV results were negative at both Visit 1 (Baseline) and End of Study Visit during this treatment cycle. The HCV testing for subject HCV was negative at End of Study Visit (V5). Therefore, since the result was negative prior to the first dose of FACTOR X in the first treatment cycle and at the last dose of FACTOR X in the second treatment cycle, the missing result was not considered a significant safety issue.

Changes in Study Conduct

Version 2.0 of the Statistical Analysis Plan was finalised prior to database lock. All data, except for administrative questions in the CRF, were listed.

The study was initiated under **protocol version 3** (including amendment 2). The following amendments were subsequently added:

Protocol version 4 (including amendment 3):

- Name of BPL's medical contact was changed.

- Further clarification on the type of data required for surgical procedures was provided.
- Due to the difficulty of obtaining assent in some children and because this was not a legally required the need to obtain assent was withdrawn from the protocol.
- The requirement for a parvovirus test was withdrawn from the study, as there is no strong scientific rationale or regulatory requirement for children to have this additional test.

Protocol version 5 (including amendment 4):

- Defining severity of factor X deficiency by just using the subject's basal plasma FX:C levels proved to be misleading due to the fact that:
    - the FX:C assays at most hospital laboratories were not sensitive enough to measure very low FX levels.
    - the data on basal levels was scarce for subjects who commenced routine prophylaxis therapy shortly after diagnosis.

Therefore, severity of factor X deficiency was re-defined to allow for all components that contribute to a severe diagnosis to be accurately documented, including genotype.

- Clarification was added to explain that a laboratory result considered by the investigator to be clinically significant or lead to clinically significant pathological changes from baseline should be recorded as an AE.
- Revision of bleed assessment criteria. Previous assessment criteria were applicable for on-demand treatment. These were therefore revised to allow a better efficacy assessment for subjects on prophylactic treatment. Also it was clarified that as covert or menorrhagic bleeds cannot be timed, a re-assessment of the bleed was not applicable.
- Administrative consistency amendments.

Protocol version 6 (including amendment 5):

- Two subjects completed 4 weeks early in error. As these subjects are rare, the protocol was amended to allow the re-enrolment of subjects who had previously taken part in the protocol.
- The definition of the primary efficacy assessment was expanded to include the reduction of bleeds.
- Text expanded to clarify that an inhibitor assessment should be conducted if there was a clinical suspicion of inhibitor development.
- Administrative consistency amendments.

Changes in Planned Analysis

Detailed below are changes to the planned analysis following the finalisation of the SAP (V2.0):

<u>Analysis of retrospective data</u>

In the statistical analysis plan (SAP) it was planned to analyse the retrospective data separately, as well as in combination (where possible) with the data for subjects entering the prospective portion of the trial. In practice, limited data was collected on only 3 subjects who had received FACTOR X on a

compassionate use basis and no bleeds or related AEs were reported. Therefore, the data was presented in a separate Listing and not combined with the prospective data.

Analysis population

Eleven treatments cycles were initiated across 9 subjects. Two subjects completed 50 exposure days, but not 26 weeks treatments with FACTOR X. These two subjects were re-screened and completed a further treatment cycle as subjects, respectively. The data for these subjects' first treatment cycle as subjects were excluded from the Per-Protocol analysis. For the Safety/ITT analysis, the data for the two treatment cycles for these subjects have been merged. As a result of the re-screening of these two subjects, the Safety/ITT group was re-defined and an additional population was included in the analysis to allow comparison between first and second treatment periods for the two subjects (Safety/ITT treatment cycles).

- **Safety/ITT analysis set** – Re-defined as all unique subjects who received at least one dose of study medication. For this analysis the data for subject was merged with data for subject, and data for subject was merged with, as they are the same patients. Therefore, there were 9 unique subjects (i.e. N=9).
- **Safety/ITT Treatment Cycles analysis set** – This was a new analysis set and not detailed in the SAP. For this analysis set, the data for those re-screened subjects was not merged, and was presented separately, therefore N=11. This analysis set was only required for demographic/baseline assessments and all Laboratory and vital signs data.

All the listings generated were for the Safety/ITT treatment cycle population, except in the case of infusion data (all the Listings numbered 36). Listings containing the individual and derived infusion data were generated for the PP and Safety/ITT populations.

Statistical testing of incremental recovery (IR) between age groups

No formal hypothesis testing was planned in the protocol or SAP. A statistical analysis to compare IRs between the two age groups was added. The IR values at each visit and across both visits were analysed using linear regression models with terms for an overall intercept and age group. The null hypothesis was that the age group effect was 0.

Demographic and baseline disease characteristics

In the SAP, it was planned to only generate Safety/ITT demographic and baseline disease characteristics tables. In the final analysis these tables were generated for the PP and Safety/ITT treatment cycle populations instead.

Dose interval

The analysis of dosing interval for each subject was detailed in the SAP. Initially bolus doses were not to be included in the interval calculations, this was later amended as the prophylactic doses were scheduled around the bolus doses, therefore, including the bolus doses in the calculations was a more sensible approach. In addition, descriptive statistics for dosing intervals on a per infusion basis for all subjects and by age group were generated. This was to enable a better overview of prophylactic dosing frequencies across the study and in the two age groups.

Analyses not conducted/Tables not generated

Adverse events

All the AEs were considered not related, therefore product-related tables for AEs and SAEs were not generated. Also none of the AEs led to death or withdrawal, so these listings and tables were not applicable.

Analysis of number of bleeds per month

Ten bleeds were reported by 4 subjects in the Safety/ITT population, therefore the analysis of bleeds per month by severity, duration, location and cause of bleeds was not performed. The data was presented in the Listings, and summary tables for bleeds on a per bleed and per subject basis were generated.

Sub-group analysis by severity

In the SAP, it was planned to analyse data by severity. In practice only 1 subject had moderate FX deficiency; therefore this analysis was not conducted.

Bleed risk category

All the subjects were considered to be at low risk, therefore a sub-analysis by risk category was not applicable.

Physical examination

Only one (1) change between Visit 1 (Baseline) and End of Study Visit was recorded for Physical examination. All the data was presented in the Listing, therefore a summary table was not generated.

Infusion site observations

There were no incidence of infusion site reactions; therefore a summary table was not generated.

FX inhibitor exposure days

As per the SAP, if a FX inhibitor was detected the number of exposure days until development of inhibitors was to be summarised. No inhibitors were detected or suspected during the study, therefore this summary was not required.

Baseline data

The demographics of all subjects in the PP population at Visit 1 (Baseline) are summarised in Table 12 below. The Per-Protocol mean age was 7.3 years with a range of 2.6 to 11.9 years. Four subjects were aged between 0 and 5 years, the remaining 5 subjects were aged between 6 and 11 years. The majority of subjects were Asian (7, 77.8%) and the remainder were Caucasian/White (2, 22.2%).

Table 12: Demographics for the Per-Protocol population			
Subject Characteristic	**0 to 5 years age group (N=4)**	**6 to 11 years age group (N=5)**	**Overall (N=9)**
Age (yrs)			
Mean (± SD) Min, Max	**3.0 (±0.5)** 2.6, 3.6	**10.7 (±1.4)** 8.5, 11.9	**7.3 (±4.2)** 2.6, 11.9
Weight (kg)			
Mean (SD) Min, Max	**13.5 (±1.4)** 12.4, 15.4	**37.2 (±11.2)** 18.7, 46.2	**26.7 (±14.8)** 12.4, 46.2
Sex			
Female	2 (50%)	3 (60%)	5 (55.6%)
Male	2 (50%)	2 (40%)	4 (44.4%)
Race			
Asian	4 (100%)	3 (60%)	7 (77.8%)
White or Caucasian	-	2 (40%)	2 (22.2%)
Ethnicity			
Not Hispanic or Latino	4 (100%)	5 (100%)	9 (100%)

Source: Section 14, Table 1.05.1. SD= standard deviation, Min = minimum, Max=maximum, N=number of subjects

Baseline Clinical Characteristics and Disease History

Of the 9 subjects in the Per-Protocol population, all except one subject (i.e. 88.9%) had severe FX deficiency. The one remaining subject (11.1%) had moderate disease (Table 13a). Genotyping was available for 6 out of the 9 subjects. In the case of subjects, and the lowest FX:C level recorded at the time of diagnosis was greater than 1 IU/dL, however the genotyping data confirmed that they all had severe FX deficiency.

Table 13a: Severity summary of all subjects in the Per-Protocol population					
Subject number	**Severity at time of diagnosis**	**FX Deficiency FX:C <5 IU/dL**	**FX Activity (FX:C) result (IU/dL) at lowest level**	**Genotype (if available)**	**Confirmed FX Severity at study entry**
	Severe	Yes			Severe
	Severe	Yes			Severe
	Severe	Yes			Severe
	Severe	Yes			Severe
	Severe	Yes			Severe
	Severe	Yes			Severe
	Severe	Yes			Severe
	Moderate	Yes			Moderate
	Severe	Yes			Severe

The mean time since diagnosis was 7.2 years and ranged from 2.5 to 11.9 years (Table 13b).

Table 13b: Baseline FX deficiency characteristics for the Per-Protocol population			
Parameter	**0 to 5 years age group (N=4)**	**6 to 11 years age group (N=5)**	**Overall (N=9)**
Time since diagnosis (yrs)			
Mean (±SD) Min, Max	**3.0 (±0.5)** 2.5, 3.6	**10.6 (±1.4)** 8.5, 11.9	**7.2 (±4.2)** 2.5, 11.9
FX:C at diagnosis (IU/dL)			
Mean (±SD) Min, Max	**2.3 (±1.9)** 1[c], 5	**1.9 (±1.2)** 1[c], 4	**2.1 (±1.5)** 1[c], 5
Time since lowest FX:C recorded (yrs)			
Mean (±SD) Min, Max	**2.9 (±0.5)** 2.5, 3.6	**9.2 (±2.1)** 6.2, 11.6	**6.4 (±3.6)** 2.5, 11.6
Lowest FX:C recorded (IU/dL)			
Mean (±SD) Min, Max	**1.5 (±0.6)** 1[c], 2	**1.8 (±1.3)** 1[c], 4	**1.7 (±1.0)** 1[c], 4

Source: Section 14.1, Table 1.06.1, [c]values less than 1 have been recorded as 1 for descriptive statistical analysis, N=number of subjects

Three subjects had administered FACTOR X on a compassionate use basis prior to enrolling in the Ten02 study.

Excluding the previous use of FACTOR X in the PP group all subjects had been exposed to other blood products or other factor concentrates. Before entering this study, 3 (33.3%) subjects had been treated with other replacement factor concentrates, 5 (55.6%) had been treated with FFP and 1 (11.1%) had been treated with other blood products. Listing 20 presents information of the last dose of FX containing product prior to Visit 1 (Baseline).

TEN02: Listing 20: Most Recent Dose of Factor X-Containing Product Prior to Study Entry (Visit 1 (Baseline))

Age Group (Years)	Visit Date	Date	Days Since Screening	Days Since Baseline	Most Recent FX-Containing Treatment	Dose (IU)
0-5			9	-3	Prothrombin Complex Concentrate	375
6-11			30	-3	FACTOR X	750
0-5			15	-3	Factor IX/X Concentrate	500
0-5			9	-3	Prothrombin Complex Concentrate	375
6-11			9	-3	Prothrombin Complex Concentrate	750
6-11			15	-3	Prothrombin Complex Concentrate	1000
0-5			9	-3	Prothrombin Complex Concentrate	375
0-5			27	-3	Factor IX/X Concentrate	500
6-11			2	-4	Prothrombin Complex Concentrate	360 - 600
0-5			15	-4	FACTOR X	500
6-11			4	-3	FACTOR X	750

Table 14: Bleed history PP population			
Parameter	**0 to 5 years age group (N=4)** N[d] (%) /n	**6 to 11 years age group (N=5)** N[d] (%) /n	**Overall (N=9)** N[d] (%) /n
Number of bleeds (n)	4 (66.7) /12	5 (100.0) /9	9 (81.8) /21
Type of bleed experienced			
Overt bleed	4 (66.7) /7	3 (60.0) /3	7 (63.6) /10
Covert bleed	2 (33.3) /5	4 (80.0) /4	6 (55.5) /9
Menorrhagic bleed	-	1 (20.0) /2	1 (9.1) /2
Highest bleed score (modified Vicenza score)			
1	-	-	-
2	1 (16.7) /2	1 (20.0) /2	2 (18.2) /4
3	2 (33.3) /5	2 (40.0) /2	4 (36.4) /7
4	3 (50.0) /4	4 (80.0) /4	7 (63.6) /8
Unknown	1 (16.7) /1	1 (20.0) /1	2 (18.2) /2
Location of past bleeds			
Joint	1 (16.7) /2	-	1 (9.1) /2
Mucosal	-	1 (20.0) /2	1 (9.1) /2
Cut/Wound	2 (33.3) /3	1 (2.0.0) /1	3 (27.3) /4
Muscle	1 (16.7) /2	-	1 (9.1) /2
Other	4 (66.7) /5	4 (80.0) /6	8 (72.7) /11
Cause of past bleeds			
Spontaneous bleeding	4 (66.7) /9	5 (100.0) /7	9 (81.8) /16
Injury	2 (33.3) /2	-	2 (18.2) /2
Menorrhagia	-	1 (20.0) /2	1 (9.1) /2
Surgery	1 (16.7) /1	-	1 (9.1) /1

Source: Section 14, Table 1.09.1, N=number of subjects, n=number of bleeds, [d]The sum of the numbers of subjects or events by category can be higher than the overall number due to some subjects having bleeds in more than 1 category

Table 14 summarises the bleed history data for the PP population. All the subjects in the PP group experienced at least one bleed prior to study entry. Of the 21 bleeds reported the majority were spontaneous bleeds (16, 76.1%).

One subject reported a bleed due to surgery (this was prior to starting compassionate use with FACTOR X). This surgery (circumcision) was conducted under the cover of Beriflex 120 IU and tranexamic acid 300 mg.

A total of 11 bleeds were reported as 'other' which consisted of: blood streaked stool (1), circumcision (1), cord bleed (3), haematoma on back (1), intracranial bleed/haemorrhage (2), vomiting small amounts of blood (1), umbilical and thigh haematoma (1) and umbilical stump bleed (1). Subjects in the 0 to 5 year group reported slightly more bleeding episodes than the older age group.

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. Seven subjects reported 8 bleeds (38.1%) with the highest bleed score of 4, four subjects reported 7 bleeds (33.3%) with a bleed score of 3.

All subjects were considered to be at a low risk of break-through bleeds.

Measurement of Treatment Compliance

The majority of infusions were administered at home (90.7%). The remaining 9.3% were administered at the Investigator Site, these also include all the bolus infusions given at Visit 1 (Baseline) and End of Study (Visit 5).

Significant non-compliances

Lower bolus doses administered than recommended in the protocol Three subjects had less than 50 IU/kg administered at Visit 1 (Baseline) due to calculation errors; two of these subjects were excluded from the Per-Protocol analysis, as they did not complete 26 weeks treatment. The remaining subject, received a lower bolus of 38.8 IU/kg. Prior to the Ten02 study subject was on compassionate use with FACTOR X at a dose of (see Section 12.8).

At the Ten02 Visit 1 (Baseline) the subject weighted 46.4 kg, so a dose of 750 IU equates to 16.2 IU/kg. The Investigator requested for a lower bolus to be administered, due to theoretical concerns of thrombosis. This reduction in dose was approved by the Sponsor. The subject was later administered the full bolus dose of 50 IU/kg at the End of Study Visit.

Diary Cards Missing data

In one subject the diary cards did not always log the actual number of vials administered. The Investigator Site staff therefore made the assumption that the prescribed numbers of vials were administered and entered this information on the CRF. However, IMP accountability checks completed at a later date indicated that 2 extra unused vials were returned than expected. It was concluded that at some point, the subject must have administered 2 fewer prophylactic vials than usual, but it was difficult to assess when this may have occurred. Therefore, the database records the administration of 151 vials of FACTOR X were used, rather than 149 vials which was the actual number of vials used. It was confirmed that the subject had completed at least 50 exposure days and 26 weeks treatment and so was included in the Per-Protocol analysis. The Sponsor did not consider the administration of fewer vials to be clinically significant, as this did not result in break-through bleeding due to failure to reach sufficient FX:C trough levels.

Numbers analysed

The following datasets were analysed:

Per-Protocol (PP) population: Included 9 subjects who had received at least 50 exposures with FACTOR X and had been in the study for at least 6 months. Two subjects' data were excluded from the Per-Protocol (PP) population because the subjects discontinued the study prior to completing 6 months treatment (26 weeks), although they had had at least 50 EDs. These 2 subjects were re-screened into the study. They were reassigned new subject numbers and completed a further 50 exposures days during at least a further 6 months in the study.

Safety / ITT population: This was redefined as all unique subjects who received at least one dose of FACTOR X during the study. So the data for one subject was merged with data for another subject, and data for one subject was merged with another one as they are the same patients. Therefore N was 9 for this population.

Safety / ITT treatment cycle population: This was a new analysis set and was not mentioned in the SAP. For this analysis set the data from the re-screened subjects was not merged, and is presented separately. This analysis set was only conducted for demographic/baseline assessments and all laboratory and vital signs datasets. Therefore N was 11 for this population.

Outcomes and estimation

Primary Efficacy Analysis

Investigator's assessment of efficacy

Nine subjects were included in the PP population.

The primary efficacy endpoint was the Investigator's overall assessment of FACTOR X in reducing or preventing bleeding following 6 months (26 weeks) prophylactic. In the Per-Protocol population (N=9) prophylactic use with FACTOR X was rated as excellent by the Investigators for all the subjects. Excellent was defined as 'no major or minor bleeds occurred or lower frequency of bleeds than expected, given the subjects medical/treatment history'.

TEN02: Table 2.1: Investigator Overall Assessment of FACTOR X Efficacy
Population: Per-Protocol

	Age_Group				
Variable	0-5		6-11		All
	N	%	N	%	N
All	4	100.0	5	100.0	9
Assessment of FX Efficacy					
Excellent	4	100.0	5	100.0	9

A total of 10 bleeds were reported in 3 (33.3%) subjects in the Per-Protocol group. Three bleeds were considered major, 6 were minor and severity was not assessed for the remaining bleed. Of the 10 bleeds 4 (40%) were treated with FACTOR X. Only a single infusion of FACTOR X was required to treat each bleed.

Two subjects were excluded from the Per-Protocol analysis, as they did not complete 26 weeks treatment. The Investigator rated the overall efficacy of FACTOR X as excellent in these subjects. Only subject reported a bleed.

Secondary Efficacy Analysis

Incremental Recovery

FX:C activity levels

Please see the Clinical pharmacology section for the results.

Overall FACTOR X usage

A total of 559 infusions of FACTOR X were administered to 9 subjects in the Per-Protocol population, of which 537 were for routine prophylaxis, 4 were for treating bleeds, and 18 were bolus doses at Visit 1 (Baseline) and End of Study. No infusions were given for short-term preventative use.

In no case was more than one infusion administered per day, therefore the number of infusions is equal to the number of exposure days (EDs). The mean number of infusions per subject was 62.1, ranging from 50 to 70. The mean dose per month per subject was 375.88 IU/kg and the mean number of infusions per subject per month was 9.70. The mean total dose per subject of FACTOR X consumed during the study was 2416.8 IU/kg.

Prophylactic dose data

A total of 537 prophylactic infusions were administered across the 26-week treatment cycle, of which 503 (93.7%) were administered at home, and 34 (6.3%) at the Investigator Site. The mean (SD) number of prophylactic infusions per subject was 59.7 (+5.1), with a median dosing interval per subject of 3.0 days which ranged from 2 to 8 days. The mean (SD) dose per infusion per subject was 38.76 IU/kg (+8.98), this ranged from 18.0 to 47.3 IU/kg, Table 20a.

Table 20a– Prophylactic use of FACTOR X all subjects in the Per-Protocol group

Number of Prophylactic infusions in all subjects: 537

	n	Mean	SD	Median	Min	Max	95% LCL	95% UCL
No. of infusions per subject	9	59.7	5.1	61.0	47	65	55.7	63.6
Dosing interval per infusion (days)	528	3.1	0.5	3.0	2	8	3.0	3.1
No. of infusions per month per subject	9	9.31	1.02	9.65	7.3	10.6	8.53	10.10
Dose per Infusion per subject (IU/kg)	9	38.76	8.98	39.60	18.0	47.3	31.86	45.67
Dose per month per subject (IU/kg)	9	357.95	79.84	389.28	173.2	426.4	296.58	419.32
Total dose per subject (IU/kg)	9	2302.4	542.89	2406.4	1116.2	2982.4	1885.1	2719.7

Source: Tables 2.3.1 and 2.3.2.

Table 20b– Prophylactic use of FACTOR X subjects aged 6 to 11 years in the Per-Protocol group								
Number of Prophylactic infusions in 6 to 11 year age group: 298								
	n	Mean	SD	Median	Min	Max	95% LCL	95% UCL
No. of infusions per subject	5	59.6	7.2	62.0	47	65	50.7	68.5
Dosing interval per infusion (days)	293	3.1	0.7	3.0	2	8	3.1	3.2
No. of infusions per month per subject	5	9.16	1.33	9.62	7.3	10.6	7.51	10.81
Dose per Infusion per subject (IU/kg)	5	37.66	11.47	39.60	18.0	47.3	23.42	51.91
Dose per month per subject (IU/kg)	5	340.24	100.97	389.28	173.2	420.9	214.87	465.60
Total dose per subject (IU/kg)	5	2228.8	704.24	2406.4	1116.2	2982.4	1354.3	3103.2

Source: Section 14, Tables 2.3.1 and 2.3.2

Table 20c– Prophylactic use of FACTOR X subjects aged 0 to 5 years in the Per-Protocol group								
Number of Prophylactic infusions in 0 to 5 year age group: 239								
	n	Mean	SD	Median	Min	Max	95% LCL	95% UCL
No. of infusions per subject	4	59.8	1.3	60.0	58	61	57.7	61.8
Dosing interval per infusion (days)	235	3.0	0.3	3.0	3	7	3.0	3.1
No. of infusions per month per subject	4	9.51	0.58	9.76	8.6	9.9	8.58	10.44
Dose per Infusion per subject (IU/kg)	4	40.13	5.93	40.80	32.7	46.2	30.70	49.57
Dose per month per subject (IU/kg)	4	380.09	47.22	389.19	315.6	426.4	304.95	455.23
Total dose per subject (IU/kg)	4	2394.5	322.97	2467.2	1961.4	2682.3	1880.6	2908.5

Source: Section 14, Tables 2.3.1 and 2.3.2

Slightly higher prophylactic doses were infused by the younger subjects (0-5 years) compared to the older subjects; 40.13 and 37.66 IU/kg respectively, resulting in a slightly higher dose per month of 380.09 IU/kg, compared to 340.24 IU/kg.

Individual subject prophylactic dose data

A summary of dosing frequency, compliance, and doses for each subject in the Per-Protocol population is summarised below (Table 21). Three subjects were also using FACTOR X on compassionate use prior to enrolling in the Ten02 study.

In the protocol the recommended prophylactic dose was 40-50 IU/kg twice a week.

Dosing regimens varied in the study, these were set at the discretion of the Investigator, which was based on each subject's weight, age and investigator's knowledge of the subject.

Table 21– Prophylactic use of FACTOR X for each subject

	Planned schedule	Actual dosing interval (days)	Actual dose per infusion (IU/kg)			No of bleeds
		Mean (Min, Max)	Mean	Min	Max	
6 to 11 year group						
	50.8 IU/kg every 3 days	3.0 (2, 4)	47.34	40.1	50.1	-
	40.5 IU/kg three times a week	2.8 (2, 7)	39.60	38.0	40.5	5
	41.0 IU.kg every 3 days	3.0 (3, 3)	39.45	34.9	41.0	-
	43.4 IU/kg every 4 days	4.1 (4, 8)	43.93	43.4	44.6	4
	18.1 IU/kg every 3 days	3.0 (2, 4)	18.00	16.2	18.1	-

Table 21– Prophylactic use of FACTOR X for each subject

	Planned schedule	Actual dosing interval (days)	Actual dose per infusion (IU/kg)			No of bleeds
		Mean (Min, Max)	Mean	Min	Max	
0 to 5 year group						
	44.0 IU/kg every 3 days	3.0 (3, 3)	43.23	42.1	44.0	1
	38.6 IU/kg every 3 days	3.0 (3,3)	38.37	38.0	38.6	-
	33.5 IU/kg every 3 days	3.1 (3, 4)	32.69	31.3	42.8	-
	47.6 IU/kg twice a week	3.1 (3, 7)	46.25	40.3	48.4	-
All subjects	Mean	3.1	38.8			

Source: Listings 26, 31, 36.2.1, 36.2.3.1, Section 14, Table 2.3.1 and 2.3.2

The dosing schedule for the two subjects excluded from the Per-Protocol analysis is summarised below Table 22.

Table 22– Prophylactic use of FACTOR X for each subject						
	Planned schedule	Actual dosing interval (days)	Actual dose (IU/kg)			No of bleeds
		Mean (Min, Max)	Mean	Min	Max	
	43.6 IU/kg every 3 days	3.0 (3, 3)	42.18	34.9	43.6	0
	37.1 IU/kg every 3 days	3.0 (3, 4)	35.81	35.2	37.1	1

Source: Listings 26 and 36.2.1

Bleeding data

In the Per-Protocol group, a total of 10 bleeds in 3 subjects were reported. One subject was in the 0 to 5 year group, the remaining two were aged between 6 to 11 years. Two subjects reported more than 1 bleed. Data on the bleeds in the Per-Protocol are summarised in Table 23.

For three (75%) of the bleeds treated the subjects' parent(s)/guardian(s) rated FACTOR X treatment as excellent. Efficacy was not assessed by the parents/guardians for the remaining bleed, Table 23. As Per-Protocol, Investigators only assessed efficacy for major bleeds or life-threatening break-through bleeds and excessive bleeding following injury. No life-threatening bleeds or excessive bleeding was reported. Of the 3 major bleeds treated clinicians' assessment of efficacy was excellent for two bleeds; an assessment was not conducted in the third bleed (menorrhagic bleed).

Table 23– Summary of bleeds in the Per-Protocol population							
Minor Bleeds							
Subject Number	Study Day	Duration	Location	Cause	Dose to treat the bleed (IU/kg)	Subject's assessment	Clinician's assessment
	18	unk	Cut/wound	injury	not dosed	Not assessed	Not assessed
	12	unk	Mucosal-nose bleed	Injury	not dosed	Not assessed	Not assessed
	19	unk	Mucosal-nose bleed	Injury	not dosed	Not assessed	Not assessed
	68	Not recorded	Mucosal-nose bleed	Spontaneous	40.5	Excellent	Not assessed
	117	120 hrs	Mucosal	Menorrhagia	not dosed	Unassessable FX Not Given[g]	Unassessable FX Not Given[g]
	143	144.0 hrs	Mucosal	Menorrhagia	not dosed	Unassessable FX Not Given[g]	Unassessable FX Not Given[g]
Major Bleeds							
Subject Number	Study Day	Duration	Location	Cause	Dose (IU/kg)	Subject's assessment	Clinician's assessment
	145	1 hrs 30 mins	Mucosal-nose bleed	Spontaneous	38.0	Excellent	Excellent
	173	10 mins	Mucosal-nose bleed	Spontaneous	38.0	Excellent	Excellent
	17	144 hrs	Mucosal	Menorrhagia	24.6[h]	Not assessed	Unassessable FX Given[g]
Severity not recorded							
	72	144 hrs	Mucosal	Menorrhagia	not dosed	Unassessable FX Not Given[g]	Unassessable FX Not Given[g]

Source: Listing 31, 33[h], 34[h] and 36.3.2, hrs = hours, mins = minutes, unk= unknown, [h]tranexamic acid also administered. [g]the Investigator Site ticked unassessable (FACTOR X given/not given another replacement factor given) in error. The bleeds were treated at home and not assessed by the Investigator Site or subject; no other replacement factor was given.

Table 24a –Treatment of bleeds those subjects who had a bleed in Per-Protocol population						
	Total subjects	Mean	SD	Median	Min	Max
All bleeds						
No. of bleeds per subject	3	3.3	2.1	4.0	1	5
No. of bleeds per month per subject	3	0.533	0.335	0.617	0.16	0.82
Dose per bleed per subject (IU/kg)	2	31.70	10.08	31.70	24.6	38.8
New bleeds						
Dose per bleed per subject (IU/kg)	2	31.70	10.08	31.70	24.6	38.8
Ongoing bleeds						
Dose per bleed per subject (IU/kg)	-	-	-	-	-	-

Source: Section 14, Tables 2.3.5.1, 2.3.7

Across the whole PP group (N=9) the mean number of bleeds per subject was 1.1, which equates to 0.178 bleeds per month per subject and the mean dose to treat a bleed was 31.7 IU/kg, which ranged from 24.6 to 38.8 IU/kg.

Surgical data

There were no surgical interventions in the prospective arm of the study. In the retrospective data collection one surgical procedure was reported.

One subject (0 to 5 age group)

This subject initially commenced FACTOR X to undergo a surgical procedure (insertion of a central venous access device, Portacath). At the time this subject weighted 10.3 kg, so this weight has been used to calculate the IU/kg dose.

During the surgery it is estimated that a total of 2,750 IU (267 IU/kg) of FACTOR X was used across 6 infusions, 2 infusions were administered on the day of surgery therefore this equates to 5 exposure days (EDs). No other concomitant therapy was given and there were no bleeding complication or any safety concerns reported.

After surgery the subject continued using FACTOR X at a prophylactic dose of 500 IU (48.5 IU/kg) twice a week for two weeks, until Visit 1 (Baseline) for Ten02. Overall during compassionate use the subject received an estimated total of 59,650 IU (5,791 IU/kg) of FACTOR X across 119 infusions (118 EDs) over 1.07 years (use during surgery and prophylactic treatment). No bleeds, ADRs or any other safety concerns were reported during compassionate use.

Ancillary analyses

Not applicable.

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 1. Summary of Efficacy for trial Ten02

Title: A phase III open-label multicentre study to confirm the safety, pharmacokinetics and efficacy of BPL's high purity factor X in the prophylaxis of bleeding in factor X deficient children under the age of 12 years				
Study identifier	**Ten02**			
Design	Open-label, multi-centre, non-randomized			
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		26 weeks not applicable not applicable	
Hypothesis	No null hypothesis was specified, only descriptive statistics are given			
Treatments groups	FX prophylaxis		FX was administered prophylactically and for the treatment of bleed over a period of 26 weeks to subjects <12	
	0-5		Younger age group	
	6-11		Older age group	
Endpoints and definitions	Primary endpoint	Investigators take	Investigators assessment of prophylactic efficacy: Excellent, good, poor, un-assessable	
	Secondary	IR	Incremental recovery	
	Secondary	#Bleeds	Number of Bleeds per month	
Database lock	<date>			
Results and Analysis				
Analysis description	**Primary Analysis**			
Analysis population and time point description	Per protocol			
Descriptive statistics and estimate variability	Treatment group	**0-5**	**6-11**	**Overall**
	Number of subject	4	5	9
	Investigators take	excellent	excellent	excellent
	IR Mean (min, max)	1.53 (1.3, 1.8)	1.91 (1.6, 2.2)	1.74 (1.3, 2.2)
	95% CI	1.36; 1.70	1.76; 2.06	1.60; 1.88
	#Bleeds Mean (min, max)	0.041 (0.0; 0.16)	0.287 (0.0; 0.82)	0.178 (0.0; 0.82)
Notes				

2.4.2. Discussion on clinical efficacy

Trial Ten02 in nine paediatric subjects with severe hereditary FX insufficiency investigated the efficacy of routine factor X substitution on bleeding rates. A prophylactic dose of 40-50 IU/kg twice weekly was suggested in the protocol, which could be modified by investigators to fit their patients' needs.

After 26 weeks, the mean dose per infusion per subject was 38.76 IU/kg, ranging from 18.0 to 47.3 IU/kg. Dosing intervals from 2 to 8 days were employed, with a mean of 3.1 days.

The investigator rated the efficacy of prophylactic dosing as excellent in 11 treatment cycles in 9 subjects. 10 bleeds were reported in the study, of which 4 were treated. One infusion of Coagadex was sufficient to control each treated bleeding event. The mean dose to treat a bleed was 31.7 IU/kg, with a range from 24.6 to 38.8 IU/kg. A bleeding rate of 0.178 bleeds per month per subject was observed during the 26 weeks of prophylactic use of Coagadex.

Data on surgical use of Coagadex are available for one subject, who underwent an implantation of a Port-a-Cath and subsequently received Coagadex prophylactically via a compassionate use programme prior to enrolment into Ten02.

2.4.3. Conclusions on the clinical efficacy

The efficacy of Coagadex in the routine prophylaxis of bleeding events as well as the treatment of bleeds in children below 12 years of age has been satisfactorily shown.

The extension of indication can be supported from a clinical efficacy point of view.

2.5. Clinical safety

Introduction

The safety evaluation of Coagadex for the initial marketing authorisation was based on safety data from clinical studies Ten01 and Ten03, which enrolled 18 subjects (> 12 years) with hereditary factor X deficiency.

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 Coagadex 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 Coagadex 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 Coagadex 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.

Coagadex intravenous infusions were well tolerated. 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.

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

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. 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.

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.

Patient exposure

9 subjects were enrolled into study Ten02, 4 in the 0-5 age group and 5 in the 6-11 age group.

Two subjects completed 50 EDs, however inadvertently withdrew from the study prior to completing 26 weeks treatment. These subjects were re-screened and re-entered into the study as subjects. The data for these subjects' first treatment cycle as subjects were excluded from the Per-Protocol analysis. For the Safety/ITT analysis the data for the two treatment cycles for these subjects has been merged to assess overall exposure and safety for each subject. Therefore the data of 9 unique subjects has been assessed for the Safety/ITT analysis.

In the 9 unique subjects a total of 665 EDs were experienced with a mean of 73.9 EDs per subject (Table 26a). The mean dose per infusion was 38.99 IU/kg, which equates to 926.69 IU (Section 14, Table 3.1.1). Therefore, the total amount of FACTOR X used in the prospective study was 25,928.4 IU/kg (616,248.9 IU).

Table 26a–Overall exposure days with FACTOR X for all subjects

Total number of EDs = 665

	n	Mean	SD	Median	Min	Max	95% LCL	95% UCL
No. of EDs per subject	9	73.9	24.2	64.0	50	116	55.3	92.5
Dosing interval per infusion (days)	654	3.1	0.5	3.0	1	8	3.0	3.1
No. of EDs per month per subject	9	9.71	1.09	10.05	7.7	11.4	8.87	10.54

Source: Section 14, Tables 3.1.1and 3.1.2.

Adverse events

Table 27: Overview of treatment-emergent adverse events –Safety/ITT population		
	Number[i] (%) of unique subjects ITT/safety population N=9	**Number (%) of Events**
Any AE	8 (88.9%)	28 (100%)
Any SAE	1 (11.1%)	2 (7.1%)
Death	0	0
Other AE leading to discontinuation	0	0
Study drug-related AE	0	0
Study drug-related SAE	0	0
By relationship to study drug		
Very likely	0	0
Probably	0	0
Possibly	0	0
Unlikely	0	0
Unrelated	8 (88.9%)	28 (100%)
By severity of event		
Severe	0	0
Moderate	1 (11.1%)	2 (7.1%)
Mild	8 (88.9%)	26 (92.9%)

Source: Section 14, Table 4.1.1, 4.1.2. [i]The sum of the numbers of subjects or events by category can be higher than the overall number due to some subjects having AEs in more than 1 category. N=number of unique subjects

Eight unique subjects (88.9%) experienced at least one TEAE. Two TEAEs in one subject were considered serious (SAE). All TEAEs were considered unrelated to FACTOR X. The majority of TEAEs were mild in severity, 92.9% (Table 27).

As mentioned previously, the exposure period data for the re-screened subjects has been combined with their second treatment cycle, respectively. During the first treatment subject reported no AEs, whereas subject reported 2 TEAEs, , both unrelated to FACTOR X, no further action was taken and the TEAEs resolved.

Analysis of Adverse Events

The most common TEAEs were pyrexia and nasopharyngitis, both with 4 events in 3 (33.3%) unique subjects (Table 28). All 4 unique subjects in the 0 to 5 age group reported at least 1 TEAE, they also reported more TEAEs (20 events) compared with the older age group (Listing 32.1). These were mainly pyrexia, bacterial or viral infections, rhinitis, nasopharyngitis or coughs.

Table 28: Summary of treatment-emergent adverse events by MedDRA system organ class and preferred term		
System Organ Class **Preferred Term**	**Number (%) of subjects** **N=9**	**Number (%) of AEs** n=28
Any AE	8 (88.9)	28 (100%)
Blood and lymphatic system disorder	**1 (11.1%)**	**1 (3.6%)**
Anaemia	1 (11.1%)	1 (3.6%)
General disorders and administration site conditions	**3 (33.3%)**	**4 (14.3%)**
Pyrexia	3 (33.3%)	4 (14.3%)
Infections and infestations	**5 (55.6%)**	**10 (35.7)**
Bacterial Disease Carrier	1 (11.1%)	1 (3.6%)
Lower Respiratory Tract Infection	1 (11.1%)	1 (3.6%)
Nasopharyngitis	3 (33.3%)	4 (14.3%)
Rhinitis	1 (11.1%)	1 (3.6%)
Influenza	1 (11.1%)	1 (3.6%)
Viral Infection	2 (22.2%)	2 (7.1%)
Investigations	**1 (11.1%)**	**1 (3.6%)**
Temperature Elevation	1 (11.1%)	1 (3.6%)
Metabolism and nutrition disorders	**1 (11.1%)**	**2 (7.1%)**
Decreased Appetite	1 (11.1%)	2 (7.1%)
Musculoskeletal And Connective Tissue Disorders	**2 (22.2%)**	**3 (10.7%)**
Pain In Extremity	2 (22.2%)	3 (10.7%)
Nervous System Disorders	**2 (22.2%)**	**2 (7.1%)**
Headache	1 (11.1%)	1 (3.6%)
Lethargy	1 (11.1%)	1 (3.6%

Table 28: Summary of treatment-emergent adverse events by MedDRA system organ class and preferred term		
System Organ Class **Preferred Term**	**Number (%) of subjects** **N=9**	**Number (%) of AEs** n=28
Reproductive System And Breast Disorders	**1 (11.1%)**	**1 (3.6%)**
Dysmenorrhoea	1 (11.1%)	1 (3.6%)
Respiratory, Thoracic And Mediastinal Disorders	**3 (33.3%)**	**3 (10.7%)**
Cough	3 (33.3%)	3 (10.7%)
Skin And Subcutaneous Tissue Disorders	**1 (11.1%)**	**1 (3.6%)**
Vitiligo	1 (11.1%)	1 (3.6%)

Source: Section 14, Table 4.1.2. N=number unique of subjects

None of the AEs reported during the study were considered related to FACTOR X.

Infusion Site Observations

Infusion site observations (for discomfort, erythema, induration, tenderness and warmth) were performed by a nurse or site clinician at pre-dose and immediately before each post-dose sample collection at the Visit 1 (Baseline) and at the End of Study Visit assessment.

The majority of unique subjects (6, 66.7%) had FACTOR X administered via a venous access device, Portacath. Subject was administered a total of 63 infusions, site of administration was only provided for 3 infusions (the left arm), for the remaining infusions, the site of administration was unknown. Subject had 50 infusions of which 3 were administered into the right/left arm; for the remaining infusions site of administration was unknown. Subject had 64 infusions all administered into the right arm. No infusion site discomfort, erythema, induration, tenderness or warmth was reported during the study.

Serious adverse event / deaths / other significant events

No deaths were reported during the study.

Laboratory findings

Haematology, Biochemistry

No apparent trends of abnormality were observed in any of the laboratory indicators during the study period. There were no clinically significant trends or changes from Screening Visit in clinical haematology and biochemistry measurements.

Viral Serology

No changes in viral serology from Visit 1(Baseline) to End of Study Visit were observed during the study.

Factor X inhibitor

It was planned to archive all the Visit 1 (Baseline) FX inhibitor samples and only analyse these if an inhibitor was detected. All the End of Study Visit samples were analysed at the central laboratory. In the case of subject the Visit 1 (Baseline) sample was analysed in error. All the samples tested had a negative inhibitor screen and a Nijmegen-Bethesda quantitative value of less than 0.6 BU, thus no signs of inhibitor development.

Discontinuation due to adverse events

There were no withdrawals due to an AE.

Post marketing experience

The first approval for marketing worldwide was granted in the United States on 20 October 2015 (International Birth Date, IBD). Following the first approval, it was further approved in the 28 EU member states via a centralised procedure on 16 March 2016. Overall, Coagadex is currently authorized in 29 countries worldwide. It was launched in the USA on 7 December 2015, in the UK on 7 June 2016 and in Germany on 28 October 2016. Launch was pending in the remaining 25 EU countries at the DLP of the PSUR.

Post-marketing data (and clinical trial data) are provided in the second Periodic Safety Update Report (PSUR) for Coagadex, covering the cumulative data from 20 October 2015 (International Birth Date [IBD]) to 16 September 2017 (data lock point [DLP]) as well as for the reporting interval from 17 March 2016 to 16 September 2017 (PSUR Coagadex dated 13 October 2017).

During the 23 cumulative months of post-marketing experience, a total of were distributed. Based on the mean monthly usage of Coagadex from the clinical trials (Ten01, Ten03) of 2.33 infusions the distribution of almost assuming a mean patient weight of 68 kg and a mean dose of 25 IU/Kg. Alternatively, the post-marketing exposure could be considered as.

Cumulatively, since the IBD (20 October 2015) to 16 September 2017 (DLP of PSUR), there have been no serious adverse reactions reported. A total of nine non-serious adverse reactions (abdominal pain, arthralgia, joint swelling, dizziness, hypoaesthesia, paraesthesia, cough, pruritus generalised and urticaria) have been reported in three spontaneous case reports (PSUR Coagadex dated 13 October 2017). None of these reactions is in the current prescribing information but they were single reports. However, hypersensitivity is included as a warning (e.g. pruritus generalised and urticaria); the currently listed adverse reactions are infusion site erythema, infusion site pain, fatigue and back pain. These three case reports do not require any changes to be made to the safety sections of the current prescribing information.

2.5.1. Discussion on clinical safety

The clinical safety data from trial Ten02 encompass 9 subjects who were enrolled for 11 treatment cycles of twice weekly prophylactic administration of Coagadex for 26 weeks, resulting in a minimum of 50 and a maximum of 116 exposure days.

Coagadex was well tolerated and no treatment emergent adverse events were assessed as related to study treatment and no subject left the study due to an AE.

No local infusion reactions were observed, neither for infusions administered via a venous access device nor given directly into a vein.

The important identified risks for Coagadex are hypersensitivity or allergic reactions, including anaphylaxis, please see RMP.

2.5.2. Conclusions on clinical safety

The observed safety profile is therefore considered to be favourable and to support the use of Coagadex in children.

2.5.3. PSUR cycle

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.

2.6. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 07 is acceptable. The PRAC endorsed PRAC Rapporteur assessment report is attached.

The MAH is reminded that, within 30 calendar days of the receipt of the Opinion, an updated version of Annex I of the RMP template, reflecting the final RMP agreed at the time of the Opinion should be submitted to h-eurmp-evinterface@emea.europa.eu.

The CHMP endorsed the Risk Management Plan version 07 with the following content (new text marked as underlined, deletions marked as strikethrough):

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

Summary of safety concerns	
	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 together with participation in the European Haemophilia Safety Surveillance System (EUHASS registry) is sufficient to identify and characterise the risks of the product.

The PRAC also considered that routine pharmacovigilance 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 national requirements relating to product storage and transportation.	None
Thrombogenicity (under special consideration for off label use and overdose	Off label use Section 4.5 of the proposed SmPC provides	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
cases)	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. <u>Overdose</u> 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.	
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

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2., 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

2.7.1. User consultation

No justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH. However, the changes to the package leaflet are minimal and do not require user consultation with target patient groups.

2.7.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Coagadex (INN) 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

3.1. Therapeutic Context

3.1.1. Disease or condition

Hereditary factor X deficiency is a rare haemophilia caused by the inherited lack of coagulation factor X. Factor X deficiency can result in bleeding patterns similar to, if less frequent than, those seen in males with haemophilia A or B. Unlike haemophilia A and B, however, the gene for factor X is located on the long arm of chromosome 13. Therefore, both genders can be carriers and both can develop factor X deficiency.

The prevalence of severe factor X deficiency in the general population is approximately 1 in 1 million, which puts it between one hundredth and one twentieth of the prevalence of haemophilia A and B, respectively.

Factor X deficiency varies in severity, which is defined according to the endogenous level of factor X in the plasma. Severe factor X deficiency is defined as endogenous concentration of factor X being <1% (< 1 IU/dL); moderate deficiency is when the factor X level is 1-5%; and mild deficiency is when factor X level is >5%. The level of endogenous factor X activity in the general population has been reported a 65 to 120 IU/dL.

3.1.2. Available therapies and unmet medical need

Coagadex is a human plasma-derived coagulation factor X that is used as a replacement therapy in patients with hereditary factor X deficiency. It is the only specific factor replacement option available and was licensed in March 2016 in the EU.

It is possible to treat bleeding events with coagulation factor compounds like FFP or prothrombin complex concentrates. However 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.

Another alternative treatment is an anti-fibrinolytic, such as tranexamic acid. In general, this medication is usually used as an adjunct to one of the above options especially in anatomical sites where endogenous fibrinolytic activity is high. It can be used alone for mild deficiency or for minor bleeding episodes.

3.1.3. Main clinical studies

Trial Ten02 was an open-label, non-randomized study investigating the efficacy, safety and certain PK parameters of Coagadex in 9 paediatric subjects below 12 years of age.

3.2. Favourable effects

A prophylactic dose of 40-50 IU/kg twice weekly was suggested in the protocol, which could be modified by investigators to fit their patients' needs. After 26 weeks, the mean dose per infusion per subject was 38.76 IU/kg, ranging from 18.0 to 47.3 IU/kg. Dosing intervals from 2 to 8 days were employed, with a mean of 3.1 days.

The investigator rated the efficacy of prophylactic dosing as excellent in 11 treatment cycles in 9 subjects.

10 bleeds were reported in the study, of which 4 were treated. One infusion of Coagadex was sufficient to control each treated bleeding event. The mean dose to treat a bleed was 31.7 IU/kg, with a range from 24.6 to 38.8 IU/kg. A bleeding rate of 0.178 bleeds per month per subject in the per protocol analysis set was observed during the 26 weeks of prophylactic use of Coagadex.

The incremental recovery for the two age cohorts was established with a mean of 1.53 for the 0-5 year old subjects and a mean of 1.91 for the 6-11 year old subjects.

3.3. Uncertainties and limitations about favourable effects

None.

3.4. Unfavourable effects

The clinical safety data from trial Ten02 encompass 9 subjects who were enrolled for 11 treatment cycles of twice weekly prophylactic administration of Coagadex for 26 weeks, resulting in a minimum of 50 and a maximum of 116 exposure days.

Coagadex was well tolerated and no treatment emergent adverse events were assessed as related to study treatment and no subject left the study due to an AE.

No local infusion reactions were observed, neither for infusions administered via a venous access device nor given directly into a vein.

3.5. Uncertainties and limitations about unfavourable effects

None.

3.6. Effects Table

Table 2. Effects Table for Coagadex, addition of paediatric data from Ten02

Effect	Short description	Unit	Treatment	References
Prophylactic Efficacy	Investigators assessment of prophylactic efficacy:	Excellent, good, poor, unassessable	Excellent in all 9 subjects for all 11 treatment cycles	Discussion on Efficacy/Pharmacology
# of Bleeds	Number of bleeding events per month	Mean (min, max)	**0-5:** 0.041 (0.0; 0.16)	
			6-11: 0.287 (0.0; 0.82)	
IR	Incremental recovery at 30 min	Mean (min, max)	**0-5:** 1.53 (1.3, 1.8)	
			6-11: 1.91 (1.6, 2.2)	
AE	No related AEs			Discussion on Safety
SAE	No related SAEs			

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Coagadex is able to replace the missing coagulation factor X and to prevent and treat bleeding events in children with congenital factor X deficiency, an extremely rare form of haemophilia. This is considered an important beneficial treatment option for these patients, analogous to prophylactic and therapeutic replacement of factor VIII or factor IX, which is established in haemophilia A or B.

3.7.2. Balance of benefits and risks

The observed favourable effects on bleeding rates and treatment of bleeds were accompanied by a benign safety profile.

3.7.3. Additional considerations on the benefit-risk balance

The benefit-risk balance in children below 12 years enrolled in trial Ten02 of age is comparable to what was established in adolescents and adults in trials Ten01 and Ten03.

3.8. Conclusions

The overall B/R of Coagadex is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Update of sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC in order to include safety and efficacy data in children aged less than 12 years of age based on final results from the study Ten02, a phase III open-label multicentre study to confirm the safety, pharmacokinetics and efficacy of BPL's high purity factor X in the prophylaxis of bleeding in factor X deficient children under the age of 12 years, provided in accordance with the agreed paediatric investigational plan. The Package Leaflet is updated accordingly. The RMP version 7.0 has also been submitted.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

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.

In addition, 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.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0389/2017 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

In accordance with Article 45(3) of Regulation (EC) No 1901/2006, significant studies in the agreed paediatric investigation plan P/0389/2017 have been completed after the entry into force of that Regulation.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Update of section sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC in order to include safety and efficacy data in children aged less than 12 years of age based on final results from the study Ten02, a phase III open-label multicentre study to confirm the safety, pharmacokinetics and efficacy of BPL's high purity factor X in the prophylaxis of bleeding in factor X deficient children under the age of 12 years, provided in accordance with the agreed paediatric investigational plan. The Package Leaflet is updated accordingly. The RMP version 7.0 has also been submitted.

Summary

Please refer to the Scientific Discussion Coagadex EMEA/H/C/003855/II/0007.

Attachments

1. Product information (changes highlighted) as adopted by the CHMP on 26 July 2018.

Reminders to the MAH

1. In accordance with Article 13(3) of Regulation (EC) No 726/2004 the Agency makes available a European Public Assessment Report (EPAR) on the medicinal product assessed by the Committee for Medicinal Products for Human Use. The EPAR is first published after the granting of the initial marketing authorisation (MA) and is continuously updated during the lifecycle of the medicinal product. In particular, following a major change to the MA, the Agency further publishes the assessment report of the CHMP and the reasons for its opinion in favour of granting the change to the authorisation, after deletion of any information of a commercially confidential nature.

   Should you consider that the CHMP assessment report contains commercially confidential

information, **please provide the EMA Procedure Assistant your proposal for deletion of commercially confidential information** (CCI) in "track changes" and with detailed justification by **10 August 2018**. The principles to be applied for the deletion of CCI are published on the EMA website at http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/03/WC500124536.pdf.

2. The MAH is reminded that, within 30 calendar days of the receipt of the Opinion, an updated version of Annex I of the RMP template, reflecting the final RMP agreed at the time of the Opinion should be submitted to h-eurmp-evinterface@emea.europa.eu.

3. The MAH is reminded to submit an eCTD closing sequence with the final documents provided by Eudralink during the procedure (including final PI translations, if applicable) within 15 days after the Commission Decision, or prior to the next regulatory activity, whichever is first. For additional guidance see chapter 4.1 of the *Harmonised Technical Guidance for eCTD Submissions in the EU*.