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Application Type	Original Application
STN	125506/0
CBER Received Date	April 27, 2015 (resubmission)
PDUFA Goal Date	October 27, 2015
Division / Office	DHRR /OBRR
Priority Review	Yes
Reviewer Name(s)	Lisa M. Faulcon
Review Completion Date / Stamped Date	
Supervisory Concurrence	
Applicant	Bio Products Laboratory
Established Name	Coagulation Factor X (Human)
(Proposed) Trade Name	COAGADEx
Pharmacologic Class	
Formulation(s), including Adjuvants, etc	Intravenous Injection
Dosage Form(s) and Route(s) of Administration	Lyophilized powder in single-use vials of 250 or 500 international units per vial
Dosing Regimen	On-demand treatment of bleeds: 25 IU/kg every 24 hours until resolution of bleed. Perioperative management: Dosage required determined using the following formula: required dose (IU) = Body weight (kg) x Desired factor (IU/dL) X rise x 0.5
Indication(s) and Intended Population(s)	Indicated in adults and children (>12 years of age) with hereditary factor X deficiency for: <ul style="list-style-type: none"> • On-demand treatment and control of bleeding episodes • Peri-operative management of bleeding in patients with mild hereditary Factor X deficiency Perioperative management of bleeding in major surgery in patients with moderate and severe hereditary Factor X deficiency has not been studied.
Orphan Designated (Yes/No)	Yes

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GLOSSARY

AE	Adverse Events
AUC	Area Under The Concentration Versus Time Curve
BLA	Biologics License Application
BPL	Bio Products Laboratory Ltd
CABG	Coronary Artery Bypass Graft
CR	Complete Response
DRC	Data Review Committee
ED	Exposure Day
EMA	European Medicines Agency
FFP	Fresh-Frozen Plasma
FX	Factor X
ICH	Intracranial Hemorrhage
IR	Incremental Recovery
IU	International Units
MedDRA	Medical Dictionary for Regulatory Activities
NOEL	No-Observed-Effect-Level
PCC	Prothrombin Complex Concentrate
PK	Pharmacokinetics
PMC	Postmarketing Commitment Study
SAE	Serious Adverse Events
TRALI	Transfusion Related Acute Lung Injury

1. EXECUTIVE SUMMARY

Bio Products Laboratory Ltd (BPL) submitted an original biologics license application (BLA) to seek U.S. licensure for FACTOR X (FX), a human plasma-derived, purified factor X concentrate. The proprietary name of the U.S. marketed product is Coagadex. Coagadex is indicated in adults and children (> 12 years of age) for on-demand treatment, control of bleeding with hereditary FX deficiency and perioperative management of bleeding with mild hereditary FX deficiency.

This BLA was originally submitted on 10 July 2013. During the first review cycle, the Chemistry, Manufacturing and Controls team identified multiple deficiencies in the validations of the manufacturing process including those for cleaning and analytical methods. These deficiencies were also confirmed at the pre-license inspection. As a result, FDA also issued a complete response (CR) letter on 10 March 2014 delineating these deficiencies and the information required to address them. No clinical deficiencies were noted by the clinical reviewer of the original submission. On 27 April 2015, FDA received BPL's resubmission to BLA STN 125506/0, which constituted a complete, class 2 response to the CR letter.

Clinical trials that provided the evidence for safety and efficacy of Coagadex were conducted under IND 14235. To support licensure for the proposed indication, the clinical development program included: (1) a pivotal phase 3 open label, multicenter study to investigate the pharmacokinetics (PK), safety and efficacy of Coagadex in the

treatment of 16 adults and children (greater than 12 years of age) with severe and moderate hereditary FX deficiency (trial Ten01), and (2) a phase 3 open-label, multicenter study to investigate the safety and efficacy of Coagadex in the treatment of 2 individual subjects with hereditary FX deficiency undergoing surgery (Ten03). Trial Ten03 was curtailed after two subjects underwent two surgical procedures each because BPL received feedback from the European Medicines Agency that data from three major surgical procedures would be appropriate to demonstrate the safety and efficacy.

A total of 18 individual subjects (greater than 12 years of age) were enrolled and received at least one dose of Coagadex for PK assessment, to treat an acute bleeding episode, or for perioperative management. This includes 16 subjects that were enrolled in pivotal trial Ten01 and two individual subjects enrolled in trial Ten03.

A total of 208 spontaneous, menorrhagic or traumatic bleeding episodes were treated with Coagadex, of which 88 (42%) bleeds were spontaneous and 66 (32%) were menorrhagic. Most of the bleeds were major (n=108; 52%) and covert (n=117; 56%). A total of 65 (31%) were joint bleeds. The number of bleeds per subject ranged from 1 to 59 bleeds, with an average of 13 bleeds per subject. The mean number of bleeds per subject per month was 0.85. All subjects received an initial dose of 25 international units (IU) per kg of Coagadex; the dose and frequency of additional doses were based on clinical judgment. Efficacy was determined using a four-point rating scale of 'excellent', 'good', 'poor', or 'unassessable' and each category was based on the number of infusions required to control bleeding. Coagadex would be deemed effective if 80% of treated new and assessable bleeds were found to have an 'excellent' or 'good' response. A treatment failure was defined as the need for more than two doses of Coagadex to treat an overt or menorrhagia bleed, or more than three doses to treat a covert bleed.

Based on subject assessments, 194 (93%) of the 208 bleeds received an 'excellent' or 'good response' and 6 (2.9%) were failures. Of the 208 bleeds treated with Coagadex, 187 were reviewed by the Data Review Committee (DRC) and considered suitable for safety and efficacy evaluation. Twenty bleeds were not considered suitable for evaluation by the DRC because of questions about the qualifying bleed or the regimen used to treat the bleed. An additional bleed was considered 'unassessable' by the subject and the DRC. Of the bleeds reviewed by the DRC, 184 (98.9%) were treated successfully and 2 (2.1%) were treated unsuccessfully.

Seven surgical procedures in five individual subjects were also reviewed by the DRC and included for evaluation; all were considered successfully treated. These included four major surgeries (teeth extractions, coronary artery bypass graft and two total knee arthroplasties) in two subjects with mild FX deficiency and three minor surgeries of tooth extraction in three subjects with moderate and severe disease. A review of the case narrative revealed that one subject with moderate disease underwent a minor surgical procedure of tooth extraction that was complicated by postoperative bleeding (blood-stained saliva) that required hospitalization and was therefore considered a failure by this reviewer. The data submitted were insufficient to support a broad indication for

perioperative management; additional data in subjects undergoing major surgery with moderate to severe FX deficiency is needed.

The safety of Coagadex was assessed using the following endpoints: frequency of adverse events, vital signs, clinical laboratory tests, and immunogenicity testing. Adverse events (AEs) were coded using Medical Dictionary for Regulatory Activities, Version 13 and were analyzed based on the principle of treatment emergence during study treatment. All safety analyses were based on the safety population, which included all subjects who received at least one dose of Coagadex (n=18). There was one unrelated death: a 58 year-old female with severe FX deficiency and hepatitis C died from bilateral pneumonia and multi-organ failure. There were no reports of anaphylaxis, thromboembolic events or FX inhibitor development in any subject. Three of the 18 subjects (17%) experienced significant elevations in at least one of the thrombogenic markers measured (thrombin-antithrombin complex, d-dimer, prothrombin fragments 1+2) following a dose of 25 IU/kg. These findings were not associated with clinical signs or symptoms of thrombosis.

A total of 202 adverse events were reported in 18 subjects, including 176 in trial Ten01 and 26 in Ten03. Most were mild or moderate in severity. Six (3%) AEs of infusion site erythema (n=2), fatigue (n=2), back pain (n=1) and infusion site pain (n=1) were considered related to Coagadex. The most frequently reported AEs ($\geq 25\%$) were: headache (reported by 8 subjects; 6.7% of all AEs), nasopharyngitis (reported by 7 subjects; 5.4% of all AEs), back pain (reported by 6 subjects; 5.0% of all AEs), and pain in extremity (reported by 6 subjects; 4.0% of all AEs). Adverse reactions were those categorized by the investigator as very likely, possibly or probably related causally to Coagadex. Two subjects (12.5%) who were enrolled in trial Ten01 experienced a total of six events that were considered by the investigator and this reviewer to be adverse reactions.

This product received orphan designation for treatment of hereditary factor X deficiency on 08 November 2007; therefore STN 125506/0 is exempt from the Pediatric Research Equity Act.

Efficacy and safety clinical data for Coagadex support a favorable risk/benefit determination for the proposed indication of on-demand treatment and control of bleeding episodes and for perioperative management in subjects with mild disease. Additional data to evaluate major surgery in patients with moderate/severe disease is needed, and should be obtained through a postmarketing commitment study (PMC) for a registry study.

Recommendation:

Based on my review of the submitted data, Coagadex appears safe and efficacious in patients with hereditary FX deficiency. No post-marketing requirement study or Risk Evaluation and Mitigation Strategy are recommended for this product; however, a PMC for a registry study to obtain additional data on major surgeries in subjects with moderate to severe disease is needed to confirm the safety and efficacy of Coagadex for perioperative management in this patient population. An approval is recommended for

the proposed indication of on-demand treatment and control of bleeding and for perioperative management in patients with mild disease.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

Table 1. Subject Demographics

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

Source: Section 14.1. Table A.1.2.1.

Of the 16 subjects treated in pivotal trial Ten01, 14 (87.5%) had severe FX deficiency (FX:C level <1 IU/dL) and two subjects had moderate disease (FX:C level in the range of 1 to <5 IU/dL). The majority of subjects were female (n=10; 62.5%) and Caucasian (n=12; 75%). The enrolled population was an adequate representation of the broader population targeted by the proposed indication. There is no racial or ethnic predilection reported in hereditary FX deficiency; therefore there is no expectation of different efficacy based on gender or ethnicity.

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied

Factor X, or Stuart-Prower factor, is a vitamin K–dependent, liver-produced serine protease that serves as the first enzyme in the common pathway of thrombus formation. The gene for factor X is on the long arm of chromosome 13. Inherited factor X (FX) deficiency is a rare autosomal recessive bleeding disorder that affects an estimated one individual per 1,000,000 population worldwide¹. It is reportedly more common in populations in which consanguinity is common, such as Iran, where the frequency is

¹ Uprichard J, Perry DJ. Factor X deficiency. *Blood Reviews*. 2002;16:97-110

reported to be 1:200,000². FX deficiency varies in its severity and is classified as mild, moderate, or severe according to the endogenous level of factor X in the plasma (FX:C activity measurements): 'severe' is defined as endogenous FX activity that is <1 IU/dL (1%); 'moderate' as activity of 1-5 IU/dL (1-5%) and 'mild' as 6-<20 IU/dL (6 to <20%), as compared to activity in the general population of 65-120 IU/dL³.

Approximately 95 variants of the FX gene have been identified. Type I deficiency, in which a mutation in the FX gene leads to the production of truncated proteins, results in reduced FX activity (FX:C) and FX antigen (FX:Ag) levels and results in more severe clinical manifestation. With type II deficiency, FX:C is reduced but FX:Ag levels are near normal; this qualitative defect of the FX protein often results in milder symptoms.

The bleeding pattern of FX deficiency includes mucosal hemorrhages (e.g. recurrent epistaxis, hematuria, gastrointestinal bleeding), hemarthroses, intracranial and soft tissue hemorrhages, and menorrhagia. Males and females are affected equally. Mucocutaneous bleeding symptoms, such as epistaxis and menorrhagia, occur in the majority of subjects. Patients with severe FX deficiency may present in the neonatal period with bleeding with circumcision, umbilical stump bleeding (usually when the stump falls off at 7–14 days), intracranial hemorrhage (ICH) or gastrointestinal bleeding. Moderately affected patients may be recognized only after hemostatic challenge, such as surgery, trauma or menses. Mild FX deficiency may be diagnosed during routine screening or because of a positive family history. The spectrum of the clinical manifestations does not always correlate well with endogenous levels of FX; however, based on registry data, patients with severe FX deficiency tend to have the most severe symptoms^{4,5,6,7}. Severe clinical symptoms, such as ICH, gastrointestinal bleeding and hemarthrosis, are uncommon in patients with FX:C levels >2%. FX levels above 20% are infrequently associated with bleeding and heterozygotes are usually asymptomatic. Targeted levels for treatment and surgery are not well established. In the Greifswald Factor X Deficiency Registry, the median level of FX:C in symptomatic patients was 13.3%.⁴

2 Brown DL, Kouides A. Diagnosis and treatment of inherited factor X deficiency. *Hemophilia*. 2008; 14:1176-1182.

3 Peyvandi F, Mannucci PM, Lak M, et al. Congenital factor X deficiency: spectrum of bleeding symptoms in 32 Iranian patients. *British Journal of Haematology*. 1998;102:626-628.

4 Karimi M, Yarmohammadi H, Ardeshiri R, Yarmohammadi H. Inherited coagulation disorders in southern Iran. *Haemophilia*. 2002; 8: 740–4.

5 Acharya SS, Coughlin A, DiMichele DM, T.N.A.R. B.D.S. Group. Rare Bleeding Disorder Registry: deficiencies of factors II, V, VII, X, XIII, fibrinogen and dysfibrinogenemias. *J Thromb Haemost*. 2003; 2: 248–56.

6 Bolton-Maggs PHB, Perry DJ, Chalmers EA et al. The rare coagulation disorders – review with guidelines for management from the United Kingdom Haemophilia Centre Doctors Organisation. *Haemophilia*. 2004; 10:593–628.

7 Herrmann FH, Auerswald G, Ruiz-Saez A et al. Factor X deficiency: clinical manifestation of 102 subjects from Europe and Latin America with mutations in the factor 10 gene. *Haemophilia*. 2006; 12: 479–89.

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

To date, no purified FX concentrate is available in the U.S. FX deficiency is currently treated using either fresh-frozen plasma (FFP) or a prothrombin complex concentrate (PCC), both of which contain variable and, generally, unspecified amounts of factor X. For minor bleeding symptoms, topical therapies and antifibrinolytic agents may be sufficient treatment.

Three types of PCC products are available: 3-factor complex containing factors II, IV, and X; 4-factor complex containing factor VII in addition to the above; and a complex combining factor IX and X. PCC products have the advantage over FFP as the coagulation factors in PCC are concentrated, thus requiring smaller infusion volumes. FFP has been associated with allergic reactions and transfusion-associated lung injury. The use of PCC in high doses has been associated with thrombosis in hemophilia patients, but the precise frequency is unknown. For patients treated with FFP or PCC, there have been no reported cases of inhibitory antibodies to FX in patients with inherited FX deficiency.

Table 2. Commercial Clotting Factor Products Containing Factor X

Product Manufacturer		Factor units/100 U of factor IX			
		II	VII	IX	X
Factor X	CSL Behring	0	0	100	100-200 ¹
Factor IX	CSL Behring	100	20	100	140
Profilnine SD	Grifols	148	11	100	64
Proplex T	Baxter	50	400	100	50
Bebulin VH	Baxter	120	13	100	140
KCentra	CSL Behring	Variable amounts of activated factors ¹			
FEIBA	Baxter	Variable amounts of activated factors ¹			

¹Actual FX content is included in the product label

Source: *Hemophilia* (2008), 14, 1176-1182 (revised).

2.3 Safety and Efficacy of Pharmacologically Related Products

The development of activity-neutralizing antibodies (inhibitors), allergic reactions and pathogen transmission are the main safety concerns of treatment in subjects receiving plasma-derived factor replacement products. The risk of viral transmission has been mitigated by viral inactivation procedures.

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

Coagadex is not currently licensed in any other country.

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

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

Surgery Study (Ten03) Protocol Revision

To support an indication for perioperative management, trial Ten03, an open label, multicenter, non-randomized, prospective study, was conducted to investigate the safety and efficacy of Coagadex in preventing bleeding and achieving hemostasis in FX deficient subjects undergoing surgery. Based on FDA feedback, EMA's scientific advice and requests by the German regulatory authority, the primary efficacy endpoint was revised from "presence or absence of excessive blood loss during surgery" to "blood loss during and after surgery" as assessed by a number of factors (clinical estimation of blood loss, requirement for blood transfusion) that would be used to provide an overall assessment of efficacy using a four point scale of 'excellent,' 'good,' 'poor,' or 'unassessable' (IND 14235/20). A target of a minimum of five and a maximum of ten subjects were to be enrolled in order to achieve ten evaluable surgical procedures. However, the trial was curtailed after two subjects underwent two surgical procedures each because Bio Products Laboratory Ltd (BPL) received feedback from the EMA that data from three major surgical procedures would be appropriate to demonstrate the safety and efficacy.

Pre-Biologics License Application (BLA) Meeting

A Type B meeting was held on 23 October 2012 to gain agency feedback on the data that would be included in the biologics license application (BLA) submission. BPL advised that the clinical program was based on FDA's previous recommendations for licensure in the U.S. (a minimum of pharmacokinetic data from 8 patients, individual bleeding episode data in 12 patients and data from one major surgery) and as such would include PK data at baseline and after 6 month for a minimum of eight subjects, data on at least 12 bleeding episodes from 12 subjects, and data from three surgical procedures (two tooth extractions and one knee replacement). FDA agreed that these data would be acceptable for review of a BLA, but did not specify whether the data from at least one major surgery needed to be from a patient with moderate or severe disease.

Original Submission

This BLA was originally submitted on 10 July 2013. FDA granted this product Orphan Drug status (No. 07-2469) on 8 November 2007, Fast Track designation on 12 April 2012, and Priority Review for this BLA on 6 September 2013.

During the first review cycle, the Chemistry, Manufacturing and Controls team identified multiple deficiencies in the validations of the manufacturing process including those for cleaning and analytical methods. These deficiencies were also confirmed at the pre-license inspection of the BPL facility conducted on 21-25 October of 2013, which were conveyed to BPL as observations in Form FDA 483. As a result, FDA also issued a complete response (CR) letter on 10 March 2014 delineating these deficiencies and the

information required to address them. No clinical deficiencies were noted by the clinical reviewer of the original submission. On 27 April 2015, FDA received BPL's resubmission to BLA STN 125506/0, which constituted a complete, class 2 response to the CR letter. This review memo is based on the data submitted in the resubmission.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The resubmission was adequately organized and integrated to accommodate the conduct of a complete clinical review without unreasonable difficulty. This submission consisted of the five modules in the Common Technical Document structure.

3.2 Compliance With Good Clinical Practices And Submission Integrity

In order to assess compliance with good clinical practices and to verify the key submitted safety and efficacy data against source documents, a sampling of trial sites of the pivotal trial (Ten01) was done. CBER Bioresearch Monitoring issued high-priority inspection assignments for one domestic site and four international sites. The five sites selected represent 63% of the clinical study sites that enrolled subjects and 77% of the total subjects in the study.

Table 3. Inspection Results

Site Number	Study Site	# Subjects	FDA Form 483	Final Classification
3	St. George's Haemophilia Centre, UK (Site 03)	2	Yes	VAI
4	Leicester Haemophilia Comprehensive Care Centre, UK (Site 04)	1	Yes	VAI
11	Unidad de Coagulopatias Congenitas y Adquiridas, Spain (Site 11)	3	Yes	VAI
21	New York Presbyterian Hospital, USA	1	No	NAI
32	Yuzuncu Yil Universitesi Kampusu, Turkey	3	No	NAI

VAI = Voluntary Action Indicated NAI = No Action Indicated

Protocol Deviations

Reported deviations included procedural deviations related to assessments or samples not taken, dose noncompliance, the use of prohibited concomitant medications and FX treatment for routine prophylaxis in two subjects (b) (6) and (b) (6)

Treatment Noncompliance

Dosage noncompliance was reported in seven subjects. Five subjects (b) (6) each received single doses of less than standard dosing to treat a bleeding episode. Three subjects received higher doses ((b) (6)), including subject (b) (6) who received 75 IU/kg instead of 25 IU/kg with no sequelae. Eight covert bleeds were considered to have potentially been undertreated (i.e. a second infusion of Coagadex could have been justified but was not administered) by the Sponsor and this reviewer (see Section 6.1.11.2 Analyses of Secondary Endpoints).

Prohibited Concomitant Medications

Deviations in concomitant medications were reported for the following subjects:

- Subject (b) (6) reported a change in hormonal contraception for the treatment of menorrhagia in the three months before the Screening Visit.
- Subject (b) (6) was administered a transfusion of red blood cells for management of anemia during the Baseline Visit PK assessment.
- Subject (b) (6) received several infusions of PCC and FFP during hospitalization for bilateral pneumonia.

Missing Diary Cards

Diary cards were routinely not completed by five Subjects: (b) (6). For Subjects (b) (6), all infusions were administered at the study site so all bleeds and infusions were recorded in the hospital records. Subject (b) (6) experienced just one bleed requiring treatment with FX during the study.

Reviewer Comment: Although the protocol deviations undermine the quality of the trial data, the overall trial conclusions are not invalidated.

3.3 Financial Disclosures

Covered clinical study (name and/or number): Ten01 and Ten03		
Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from applicant)
Total number of investigators identified: <u>12</u>		
Number of investigators who are sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):		
Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____		
Significant payments of other sorts: _____		
Proprietary interest in the product tested held by investigator: _____		

Significant equity interest held by investigator in sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request explanation from applicant)

Financial certification and disclosure information (Form 3454) have been submitted for both US and Non-US sites. No questions about the integrity of the data were raised.

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

4.1 Chemistry, Manufacturing, and Controls

Coagadex is a sterile, (b) (4) freeze-dried concentrate of human coagulation FX and is presented in two dose sizes of 250 International Units (IU) and 500 IU (nominal). After reconstitution with sterilized Water for Injection, Coagadex forms a clear, colorless solution. It is produced from human plasma, which is collected at FDA licensed centers in the U.S. The manufacturing process includes three dedicated virus inactivation steps: solvent-detergent treatment, virus-filtration, and terminal dry heat treatment. The two dose sizes contain the same concentration of FX active ingredient (about 100 IU/mL) and formulation chemicals upon reconstitution. The FX concentration in Coagadex is approximately 100-fold greater than that in normal plasma.

The composition of Coagadex includes human FX (active ingredient), citric acid (b) (4) phosphate ((b) (4) sodium chloride ((b) (4) sucrose (stabilizer), and water for injections (solvent).

4.2 Assay Validation

Factor X activity (FX:C) assays were performed by the Hematology Department, (b) (4) and by each center's local laboratory. Factor X activity was measured using both the one-stage clotting and chromogenic assays at (b) (4), which was used as the central laboratory. Local laboratory results were used for subject monitoring and Coagadex dose adjustment, as determined by the investigator. Central laboratory results were used in the efficacy analysis. FX:Ag assays were performed by the Hematology Department, (b) (4).

Neutralizing antibodies against human FX (anti-human FX inhibitors) were measured in a central lab using a Nijmegen-Bethesda assay.

4.3 Nonclinical Pharmacology/Toxicology

Please see Michael Wyatt's review memo for complete details. Per his review, the submitted nonclinical studies and resulting data are adequate to establish the desired pharmacologic and pro-coagulant activity of Coagadex.

Single dose toxicity studies in rats established a no-observed-effect-level (NOEL) of >2400 IU/kg body weight, a greater than 40 fold safety margin. Repeat dose toxicity studies in rats, with repeated administration every 2 days, established a NOEL at 30 IU/kg body weight, a greater than 6 fold safety margin.

Thrombogenicity testing in rabbits demonstrated that thrombogenicity at doses of 100-400 IU/kg body weight was not significantly different to that of the physiological saline negative control.

4.4 Clinical Pharmacology

Coagadex is a low clearance drug with a half-life of approximately 30 hours. See Dr. Iftekhar Mahmood's Clinical Pharmacology review memo for complete details.

4.4.1 Mechanism of Action

Factor X is an inactive zymogen that is converted from its inactive form to the active form (factor Xa) by the cleavage of a 52-residue activation peptide from the heavy chain. Activation can occur through the intrinsic or extrinsic pathways. Activation through the extrinsic pathway occurs via tissue factor:FVIIa complex with calcium ions on a phospholipid surface to form the prothrombinase complex, which activates prothrombin to thrombin. Thrombin then acts upon soluble fibrinogen and factor XIII to generate a cross-linked fibrin clot. Intrinsic pathway activation occurs most efficiently in the 'tenase' complex, which contains the serine protease FIXa and its cofactor FVIIIa in the presence of calcium ions on a phospholipid surface.

4.4.2 Human Pharmacodynamics (PD)

The active ingredient in Coagadex, FX, is derived from human plasma and used as replacement therapy in patients with hereditary FX deficiency.

4.4.3 Human Pharmacokinetics (PK)

The PK of Coagadex was similar following single and repeat doses and are summarized in the table below:

Table 4. Pharmacokinetic parameters of Coagadex

	Baseline Visit (n=13)	Repeat PK Assessment (n=8)	Repeat PK Assessment (n=8)
	mean (CV)	mean (CV)	(% Baseline Visit)
T _{max} (hr)	0.367 (0.233, 1.20)*	0.417 (0.250, 3.00)*	ND
C _{max} (IU/mL)	0.508 (19.1)	0.465 (23.7)	96.4
Half-life (hr)	30.9 (24.8)	29.2 (17.8)	93.2
AUC _{0-144h} (IU.hr /mL)	17.6 (21.9)	16.0 (27.2)	96.6
AUC _(0-∞) (IU.hr /mL)	18.5 (21.5)	16.8 (28.7)	ND
C ₀	0.488 (20.1)	0.453 (43.0)	102
V _{ss} (mL/kg)	53.3 (28.7)	58.2 (14.8)	102
CL (mL/kg/hr)	1.23 (24.1)	1.43 (23.8)	110
MRT _(0-∞) (hr)	43.2 (21.0)	40.7 (20.0)	ND
Incremental recovery (IU/dL per IU/kg) [§]	2.22 (22.1)	1.93 (22.3)	91.1

* Presented as median and range

[§] Using peak increment within 1 hour post-dose

ND Not done

4.5 Statistical

Please see Dr. Boris Zaslavsky's memo for a complete review.

The statistical reviewer verified that the primary study endpoint analyses cited by the applicant were supported by the submitted data.

4.6 Pharmacovigilance

Additional data are required to support an indication for perioperative management in adults and children with moderate to severe hereditary factor X deficiency. These data will be obtained as a postmarketing commitment from a registry study.

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

5.1 Review Strategy

This review focuses on the multicenter, open-label, prospective safety, efficacy and PK trial in adolescents and adults with moderate or severe hereditary FX deficiency (trial Ten01). In addition, supportive efficacy and safety data from a completed surgery trial (Ten03) was reviewed and included in the integrated analysis of efficacy (Section 7) and safety (Section 8).

Table 5: Review Responsibilities

Discipline Review	
Chemistry, Manufacturing and Controls Review; BLA Chairperson	Mikhail Ovanesov
Clinical Review	Lisa Faulcon
Clinical Pharmacology Review	Iftekhar Mahmood
Statistical Review	Boris Zaslavsky
Pharmacology / Toxicology Review	Michael Wyatt; Yolanda Branch
Bioresearch Monitoring Review	Carla Jordan
Pharmacovigilance Review	Faith Barash
Labeling Review	Loan Nguyen

Discipline Review	
Regulatory Project Manager	Pratibha Rana

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

<u>Volume(s)</u>	<u>Information</u>
2.5	Clinical Overview
2.7	Clinical Summary
5.2	Tabular listing of all clinical studies
5.3.3	Reports of human PK studies
5.3.5	Reports of efficacy and safety studies

5.3 Table of Studies/Clinical Trials

Table 6: Listing of Clinical Studies

Dosage Regimen	Trial	Objectives	Dosage Regimen	Subjects (n)	Diagnosis	duration	Study status
Efficacy, safety , PK	Ten01	PK profiles, safety and efficacy in on-demand treatment of bleeds	On demand: 25 IU/kg Surgery: Dose calculated from a nominal recovery of 1.5 IU/kg per IU/dL to raise FX level to 70 to 90 IU/dL before surgery; maintain FX level at 50 IU/dL after	16	Moderate to severe hereditary FX deficiency	6 months to 2 years for on-demand; up to 14 days for surgery	Completed
Efficacy, safety , PK	Ten03	Safety and efficacy In control of bleeding during surgery	Same surgery dose as in Ten01	2 (4 surgical procedures)	Mild to severe hereditary FX deficiency	21 days maximum	Completed

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Trial #1

Ten01

6.1.1 Objectives (Primary, Secondary, etc)

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

Secondary objectives included:

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

6.1.2 Design Overview

This was an open-label, multicenter, nonrandomized, prospective study in 16 adolescents and adults (aged ≥ 12 years) with severe and moderate FX deficiency to assess the PK, safety and efficacy of Coagadex. The subjects were recruited at 11 sites in 5 countries. All subjects were in a non-bleeding state. Subjects received Coagadex for on-demand treatment and control of bleeding or for perioperative management for any surgical or invasive procedure during the course of the trial, whether planned or emergency. An objective assessment of the severity of the surgical procedures (major or minor) and suitability of each bleed for efficacy evaluation was made by an independent Data Review Committee (DRC). The duration of the study for each subject was at least 27 weeks: at least 1 week between the Screening Visit and the Baseline Visit to allow for analyses, at least 25 weeks through the 6-Month Visit, and an End-of-Study Visit at least 1 week after the 6-Month Visit.

Reviewer Comment: The design of the pivotal trial is sufficient to support the indication of treatment of bleeding in patients with hereditary FX deficiency. As this is an orphaned population, randomized clinical trials in a larger cohort were not feasible.

6.1.3 Population

Important Eligibility Criteria

Inclusion Criteria

- Aged ≥ 12 years of age.
- Hereditary severe or moderate FX deficiency with $< 5\%$ (< 5 IU/dL) basal FX:C at diagnosis.
- Currently treated with FFP, a PCC, or a factor IX/X concentrate.
- History of a minimum of one spontaneous or menorrhagic bleed that required treatment with FFP, PCC, or a factor IX/X concentrate.

Exclusion Criteria

- History of inhibitor development to FX or a positive result at the Screening Visit (quantitative result of ≥ 0.6 Bethesda units [BU]).

- Thrombocytopenia (platelets <50 X 10⁹/L).
- Clinically significant renal disease (serum creatinine >200µmol/L) or liver disease (serum alanine aminotransferase [ALT] levels >3× upper normal limit).
- History of other coagulopathy or thrombophilia.
- Female subjects who were pregnant or lactating.

Reviewer Comment: The inclusion and exclusion criteria are appropriate for developing a population that is representative of the target population.

6.1.4 Study Treatments or Agents Mandated by the Protocol

After an initial dose and PK assessment at the Baseline Visit, subjects received Coagadex for on-demand treatment and control of spontaneous or traumatic bleeds or for specific short-term preventative use.

On-demand Treatment and Control

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

Perioperative Management

Doses were calculated based on the subject's FX level and body weight and a nominal recovery of 1.5 IU/dL per IU/Kg. The loading dose was calculated to raise the subject's factor X level to 70 to 90 IU/dL. The post-surgery maintenance dose was calculated to maintain the subject's factor X level at least 50 IU/dL.

6.1.5 Directions for Use

Coagadex is supplied as a powder for administration by intravenous injection after reconstitution. The reconstituted solution was given through intravenous infusion at a suggested rate of 10 mL/min but no more than 20 mL/minute.

6.1.6 Sites and Centers

The subjects were recruited at 11 sites in 5 countries: Germany (1 site), Spain (2 sites), Turkey (4 sites), United Kingdom (2 sites), and the United States (2 sites).

6.1.7 Surveillance/Monitoring

In addition to an Institutional Review Boards/Independent Ethics Committee, the DRC was responsible for the review and analysis of individual subject data on an ongoing basis throughout the study and on collated subject data (study data review) at specific time points throughout the study. The DRC was composed of three clinicians (specialists in hemophilia) independent of the clinical trial and Sponsor. Each set of data was analyzed by a minimum of two of the DRC members. Activities of the DRC were described in a DRC Charter, which was finalized prior to the first subject's enrollment in the trial.

Safety monitoring was considered adequate by this reviewer and included: physical examinations, and assessments of AEs, vital signs, and laboratory testing (viral serology, hematology, biochemistry, coagulation factors and parameters). Viral serology was assessed by the central safety laboratory at the Baseline Visit (Day 1), at the End-of-Study Visit and, if applicable, at the 9-Month Visit. If a subject changed Coagadex batch, a blood sample for an additional viral serology assessment was taken immediately before dosing with the new batch. Inhibitors were measured at these specified time points: baseline, one month and every three months thereafter. The Nijmegen-Bethesda assay was used to monitor for inhibitors. The DRC reviewed each subject's Baseline and Repeat PK data to assess the possible development of covert inhibitors. To address theoretical concerns about the potential development of non-inhibitory antibodies to Factor X, BPL agreed to the post-market development of methods to detect binding antibodies to COAGADEX in available, retained patient samples.

6.1.8 Endpoints and Criteria for Study Success

Primary Efficacy Endpoints

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

Secondary Efficacy Endpoints

On-demand Treatment and Control

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

Note: In cases where a discrepancy existed between the subject and investigator ratings, the DRC would review the data and make the final decision, which would be considered the primary efficacy rating for analysis. All ratings would be presented.

- Investigator's overall assessment of efficacy as 'excellent', 'good', 'poor' or 'unassessable'.
- Total dose of Coagadex (IU and IU/kg FX:C), total number of infusions and average dose per infusion to treat a new bleed and ongoing bleeds, for any additional preventative use and overall use per subject.
- Total dose of Coagadex (IU/kg FX:C) to treat a bleed (including initial dose for new bleeds and any repeated doses for ongoing bleeds), number of infusions and dose per infusion on a per bleed and a per subject basis.
- Dose of Coagadex per infusion for all infusions, all infusions to treat bleeds, all first infusions to treat bleeds, all subsequent infusions to treat bleeds and all infusions taken as a preventative measure.

- Average monthly and yearly dose of Coagadex (IU/kg FX:C) and average monthly and yearly number of infusions to treat a bleed, for any additional preventative use and overall use per subject.
- Number of exposure days (EDs) overall and per subject.
- Average number of bleeds per subject per month.
- Number of bleeds including severity, duration, location and cause.

Perioperative Management:

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

1. Clinical estimation of volume of blood loss during surgery;
2. Requirement for blood transfusion (units of packed red blood cells or units of whole blood) or infusion of autologous red cells during and after surgery;
3. Number and duration of post-operative bleeding episodes;
4. Measurements of hemoglobin pre-operatively, post-operatively and at discharge.

Secondary Efficacy Endpoints for Surgery:

The following parameters were assessed:

1. Assessment of IR of FX:C and FX:Ag at 30 minutes after the pre-surgery bolus infusion.
2. Assessment of FX:C and FX:Ag levels on each day post-surgery.
3. Assessment of the cumulative weight-adjusted Coagadex (IU/kg body weight FX:C) administered to each subject to maintain hemostasis.
4. Assessment of the cumulative doses of Coagadex (IU FX:C) administered to each subject to maintain hemostasis.
5. Amount of weight-adjusted FX:C (IU/kg body weight FX:C) administered daily (day of surgery and each post-operative day) to maintain hemostasis.

Safety Endpoints

The following parameters were measured to assess the safety of Coagadex:

- Adverse events (AEs)
- Thrombogenicity markers
- Hematology
- Biochemistry
- Prothrombin time (PT) and activated partial thromboplastin time (aPTT)
- Viral serology
- FX inhibitor screen and Nijmegen-Bethesda assay
- Vital signs
- Physical examination
- Infusion site observations
- Genotype analysis (optional)
- Pregnancy test (for females of childbearing potential)

Safety Assessments for Surgery:

- AEs
- Hemoglobin and hematocrit
- Serum ferritin
- PT and aPTT
- FX inhibitor screen and Nijmegen-Bethesda assay
- Vital signs
- Physical examination
- Infusion site observations

Assessment Criteria for Efficacy in Treating a Bleed

Efficacy was assessed by the subject for all bleeds and by the investigator or a trained clinician for bleeds requiring assessment at the hospital/clinic using a bleed-type specific four-point rating scales (see Tables 7 through 13). For menorrhagic bleeds (Table 8), efficacy was based on the number of doses of Coagadex required in the peri-menstrual period (the first dose being not more than 1 day before commencement of bleeding) to maintain bleeding at a manageable level (i.e. with no significant limitation to normal activities). Examples of covert bleeds were provided in the protocol and included melena, intraperitoneal bleed, joint bleeds, muscle bleeds, intracranial hemorrhage, hematoma/bruising and internal bleeding due to injury.

Table 7. Criteria for Assessment of Coagadex in Treating an Overt bleed (investigator’s assessment)

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

Table 8. Criteria for Assessment of Coagadex in Treating an Overt bleed (subject’s assessment)

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

Table 9. Criteria for Assessment of Coagadex in Treating a Menorrhagic Bleed (investigator's assessment)

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

Table 10. Criteria for Assessment of Coagadex in Treating a Menorrhagic Bleed (subject's assessment)

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

Table 11. Criteria for Assessment of Coagadex in Treating a Covert Bleed (investigator's assessment)

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

Table 12. Criteria for Assessment of Coagadex in Treating a Covert Bleed (subject's assessment)

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

Table 13. Criteria for Investigator’s Overall Assessment of Efficacy

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

Reviewer Comment: The rating scale categories are defined based on the number of infusions only; the applicant could have included more subjective measures (e.g. reduction in pain or swelling, increased range of motion), where appropriate, to provide a more comprehensive assessment. The lack of subjective measures may lead to a discrepancy in the number of bleeds receiving a ‘poor’ rating and the number of actual failures based on the number of infusions administered. In this reviewer’s opinion, the rating scale used for the investigator’s overall assessment of efficacy is not informative and does not contain enough objectives measures to make an adequate or meaningful assessment. For the ‘excellent’ category, it is unclear what is meant by “regularly met...expectations.” The protocol does not provide sufficient guidance (e.g. require that a percentage of total infusions that were rated excellent/good be used to assign each rating category) to allow for consistent evaluation across investigators. For this reason, the efficacy assessment was based on the assessment of efficacy that were reviewed by the DRC.

Study Success Criteria

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

6.1.9 Statistical Considerations & Statistical Analysis Plan

The hypothesis for the PK parameters was that, over at least eight PK assessments of $t_{1/2}$ at the Baseline Visit, the lower 95% confidence interval (CI) of the $t_{1/2}$ estimate was greater than 20 hours. Pharmacokinetic parameters were calculated by non-compartmental analysis.

The evaluation of data was based on descriptive statistics. The primary population for the purposes of analysis was the safety population, which included all subjects who received at least one dose of Coagadex. Categorical variables were presented using counts and percentages, and continuous variables were presented using the mean, 95% CI for the mean, standard deviation (SD), median, minimum, maximum, and number of subjects (or number of surgeries for the surgery population). The efficacy analysis was to be performed on the intent-to-treat population, and the safety population was used to report all safety data, in accordance with the statistical analysis plan. Demographic data were to be reported for the safety population.

6.1.10 Study Population and Disposition

A total of 17 patients were screened, of which 16 (94%) were treated with at least one dose of Coagadex during the study. Subject (b) (6) was withdrawn at the Screening Visit due to the subject's history of unreliability or non-cooperation (exclusion criteria). A total of 15 subjects (88%) completed the study. One subject ((b) (6)) discontinued because of an unrelated death (see section 6.1.12.3 Deaths).

Analysis Populations

- *Safety*: all subjects who received at least part of one dose of study medication
- *Per Protocol*: all treated subjects who had sufficient FX:C data to characterize the time course of Coagadex in plasma at the Baseline Visit and the Repeat PK assessment (usually at the 6-Month Visit).
- *Surgery*: all treated subjects requiring any surgical or invasive procedure during the course of the trial, regardless whether the surgeries were planned or emergency, who received at least one part of one dose of the study medication as prophylaxis against excessive bleeding during or after the procedure.
- *Per-protocol Surgery*: all treated subject in the surgery population who underwent surgical procedures in which the pre-surgery FX:C level was ≥ 70 IU/dL and were dosed in accordance with the protocol.

6.1.10.1 Populations Enrolled/Analyzed

Subjects included in the analyzed populations are as follows:

- *Safety analysis*: 16 subjects received at least 1 dose of Coagadex.
- *PK analysis*: 15 subjects had sufficient FX:C data to characterize the time course of Coagadex in plasma at the Baseline and the Repeat PK assessments.
- *Efficacy for on-demand treatment and control of bleeds*: 15 subjects had at least 1 bleed selected by the DRC for analysis.
- *Efficacy for perioperative management*: three subjects were included in the surgery population, two of whom were included in the per-protocol surgery primary analysis and per-protocol surgery secondary analysis. One subject was included in the surgery population but excluded from the per-protocol primary and secondary analyses populations because the subject's FX:C levels pre-dose at the pre-surgery visit was ≥ 20 IU/dL, as measured by the central laboratory, due to a recent dose of factor X-containing product.

6.1.10.1.1 Demographics

Of the 16 subjects treated, 14 (87.5%) had severe FX deficiency (FX:C level <1 IU/dL) and two subjects had moderate disease (FX:C level in the range of 1 to <5 IU/dL). The majority of subjects were female (n=10; 62.5%) and Caucasian (n=12; 75%).

Reviewer Comment: The enrolled population is an adequate representation of the broader population targeted by the proposed indication. There is no racial or ethnic predilection reported in hereditary FX deficiency; therefore there is no expectation of different efficacy based on gender or ethnicity.

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Fourteen subjects (87.5%) experienced a spontaneous bleed. A total of 15 (94%) subjects were previously treated with replacement factor, 14 (87.5%) with FFP and 12 (75%) with other blood products.

Table 14. Bleed History of Subjects Enrolled in Ten01

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

Source: Section 14.1, Table A.1.3.4.2.

^a Within 12 months before the Screening Visit or, for significant bleeds, within the subject's lifetime.

6.1.10.1.3 Subject Disposition

A total of 17 patients were screened, of which 16 (94%) were treated with at least one dose of Coagadex during the study. Subject (b) (6) was withdrawn at the Screening Visit due to the subject’s history of unreliability or non-cooperation (exclusion criteria). A total of 15 subjects (88%) completed the study. One subject ((b) (6)) discontinued because of an unrelated death (see Section 6.1.12.3 Deaths). Three subjects received Coagadex before surgical procedures to control bleeding.

6.1.11 Efficacy Analyses

The criterion for treatment success for the primary endpoint was met: the 95% CI lower limit of the $t_{1/2}$ for FX:C at the Baseline Visit, using the clotting assay, was 26.9 and 26.8 hours using the geometric and arithmetic means, respectively, and therefore greater than 20 hours.

6.1.11.1 Analyses of Primary Endpoint(s)

See Dr. Iftekhar Mahmood’s memo for complete review of the PK data.

For the PK assessment, blood samples were taken at 0.25, 0.5, 1, 3, 6, 24, 48, 72, 96, 120, 144, and 168 hours post dose. Factor X concentrations were measured by both the one-stage clotting and chromogenic assays. The concentrations of FX:C and FX:Ag at pre-dose were subtracted from all subsequent post-dose concentrations. Pharmacokinetic parameters were calculated by non-compartmental analysis and are shown in Table 15. Plasma concentration-time profiles of Factor X are shown in Figures 1-2.

Table 15. Pharmacokinetic parameters of Coagadex

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

Source: Appendix 16.5, Pharmacokinetic Report Amendment 1.

Abbreviations: CV, coefficient of variation; IR, incremental recovery.

^a Calculated from factor X levels at 30 minutes post-dose per protocol.

^b Calculated from peak factor X level in the first hour post-dose per EMA guidelines.

^c Presented as median and range, as t_{max} is not a continuous variable.

^d Range.

Figure 1: Mean pre-dose-adjusted plasma concentrations of FX:C (clotting) following a single IV bolus dose of 25 IU/kg of Coagadex

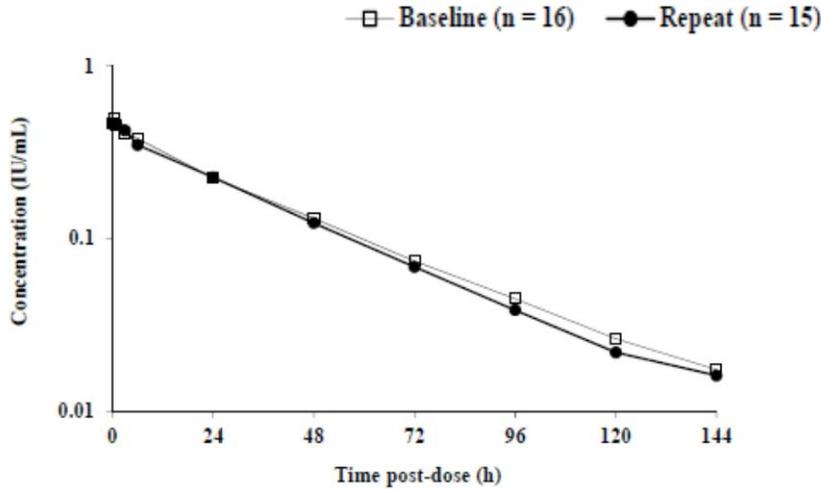
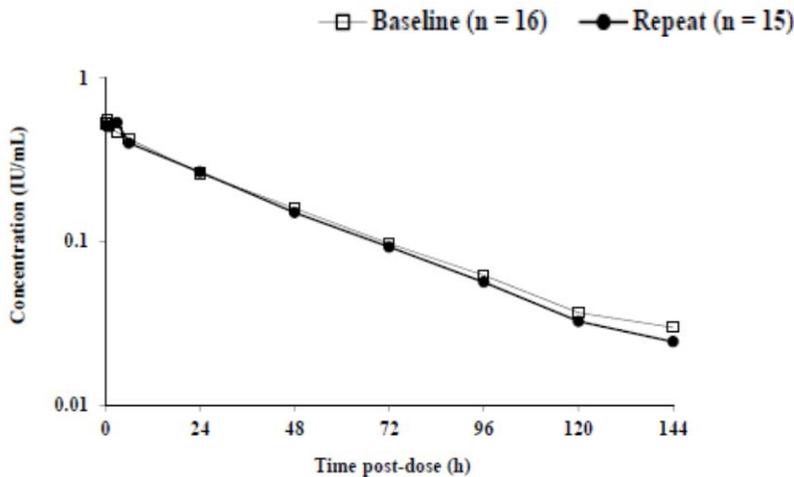


Figure 2: Mean pre-dose-adjusted plasma concentrations of FX:C (chromogenic) following a single IV bolus dose of 25 IU/kg of Coagadex



6.1.11.2 Analyses of Secondary Endpoints

On-Demand Control and Treatment of Bleeds

A total of 208 spontaneous, menorrhagic or traumatic bleeding episodes were treated with Coagadex, of which 117 (56%) were covert, 25 (12%) were overt. A total of 88 (42%) bleeds were spontaneous and 66 (32%) were menorrhagic. As expected, most of the reported bleeds were mucosal bleeds (n=80; 38.5%); 65 (31%) were joint bleeds. A total of 108 (52%) were considered major bleeds. Seven of the 208 bleeds were considered unassessable. Total bleeds per subject ranged from 1 to 59 bleeds, with an average of 13 bleeds per subject. The mean number of bleeds per subject per month was 0.85.

Narrative of Subjects with Greater than Fifteen bleeds on Study

- Subject (b) (6) was a 15 year-old Caucasian female with a history of moderate FX deficiency (diagnosed 10 years prior to enrollment on study) who experienced 59

bleeds while on study (listing 12.5). Most (n=42; 71%) were considered major bleeds; 12 (20%) were menorrhagic, and 20 (34%) were due to injury. The subject had an extensive history of spontaneous and traumatic bleeds, including joint bleeds (resulting in synovitis and arthrosis in her left knee, as well as arthrosis in both ankles), for which she routinely received 600 units Factor XP Behring. She also suffered from menorrhagia, which was routinely treated with antifibrinolytics. The subject's bleeding history in the previous year included at least eight bleeds (listing 7.6) that were treated with PCCs; five of these were joint bleeds and one was a menorrhagic bleed. Three of these bleeds were due to injury. This subject was enrolled into study Ten01 on 20th September 2011 and completed the first PK assessment in the following week. She completed the study on January 17, 2013 (listing 3.1).

- Subject (b) (6) was a 20 year-old Caucasian male with a history of severe FX deficiency who experienced 20 bleeds while on study. Most (70%) were minor bleeds and were either mucosal (45%), muscle (30%) or joint (25%) bleeds. The patient had an extensive history of spontaneous and traumatic bleeds, including muscle and nose bleeds, which were treated with on-demand therapy with low doses of prothrombin complex concentrate.
- (b) (6) was a 12 year-old Caucasian male with a history of moderate FX deficiency who experienced 19 bleeds while on study. Most (88%) were major bleeds; 7 (37%) were joint bleeds; 5 (26%) were muscle bleeds. The subject had a history of gastrointestinal and muscle bleeds and had received >150 exposure days (EDs) to replacement factor concentrates, >20 EDs to FFP and >10 EDs to other blood products.
- (b) (6) was a 17 year-old Caucasian female with a history of severe FX deficiency who experienced 18 bleeds while on study. The majority of bleeds were mucosal (72%); 44% were major bleeds. The subject's history was significant for numerous menorrhagic bleeds, requiring blood transfusions. She had >150 EDs to replacement factor concentrates, >100 EDs to FFP and >20 EDs to other blood products.

A total of 207 bleeds were reviewed by the DRC (Appendix 16.4). One bleed for subject (b) (6) (bleed #15) was not reviewed before datalock. The DRC selected 187 bleeds for review, and 186 of these bleeds in 15 subjects were considered assessable. Of these 187 bleeding episodes, 79 (42%) occurred spontaneously, 47 (25%) were traumatic and 61 (33%) were menorrhagic. Seventy three (39%) were mucosal in origin, 63 (34%) were joint bleeding episodes, 26 (14%) were muscle bleeding episodes, and 25 (13%) were located elsewhere. Ninety eight (53%) were major bleeding episodes, as assessed by an independent data review committee, and 88 (47%) were minor bleeds (one bleed not assessed).

Case narratives for the 20 on-demand bleeds in eight subjects that were not reviewed by the DRC are summarized by subject below:

- Subject (b) (6) (n=1 bleed): the DRC could not determine if the bleed was really a menorrhagic bleed or a routine menses.

- *Subject (b) (6) (n=1 bleed)*: the DRC considered the dose administered to have been given prophylactically following a previous menorrhagic bleed.
- *Subject (b) (6) (n=8 bleeds)*: Eight bleeds (rectal bleeding x 5 episodes, hematuria x 2 episodes, stomach ulcer), were reported during a hospitalization for bilateral pneumonia. During the course of 19 days, the subject received factor X-containing products including a total of 4000 IU of PCC and 10 doses (each approximately 250 mL) of FFP.
- *Subject (b) (6) (n=1 bleed)*: The DRC was confused by the description of the trauma-induced muscle bleed and its treatment.
- *Subject (b) (6) (n=1 bleed)*: The subject was treated simultaneously for a menorrhagic bleed and an injury-related joint bleed; it was not clear to the DRC that the outcome of the joint bleed could be determined.
- *Subject (b) (6) (n=3 bleeds)*: Three bleeds were not chosen, including a gastrointestinal (GI) bleed with insufficient information to assess the nature and extent of the bleeding, a second GI bleed that was considered unassessable by the subject and investigator as the subject completed the study before the treatment for the bleed had been completed, and a traumatic wound bleeding that was treated with two separate infusions, each of 16 IU/kg (protocol deviation), instead of 25 IU/kg.
- *Subject (b) (6) (n=2 bleeds)*: The subject received over three times the dose prescribed in the protocol for one menorrhagic bleed, and a second menorrhagic bleed was considered unassessable by the subject and investigator as the subject completed the study before the treatment for the bleed had been completed.
- *Subject (b) (6) (n=3 bleeds)*: A menorrhagic and a traumatic joint bleed occurring simultaneously and were not selected for assessment of outcome because it was difficult to distinguish which doses of Coagadex were administered for the treatment of each bleed. A third bleed was not selected because it was unclear from the information provided whether the bleed was a joint bleed or soft tissue hematoma.

Reviewer Comment: Based on a review of the case narratives, this reviewer agrees that these 20 bleeding episodes should be excluded from the efficacy analysis.

Treatment Successes

Of the 187 bleeds reviewed by the DRC, 184 (98.9%) were considered a treatment success (i.e. excellent or good response; Appendix 16.2, Listing 12.5 and Listing 13.1). The 95% CI for treatment success rate was 96.2 to 99.9%. Two bleeds (1%) received a poor response.

On average, 1.2 (0.5) infusions were needed to treat a bleed. A total of 170 bleeds (82%) were treated with one infusion, 32 bleeds (15%) with two infusions, 3 bleeds (1%) with three infusions, 1 bleed (0.5%) with four infusions and 2 bleeds (1%) required six infusions. The mean dose per infusion of Coagadex was 25.4 IU/kg, which confirms that the recommended dose of 25 IU/kg is appropriate. The mean (SD) total dose of Coagadex given to treat a bleed was 30 (12) IU/kg.

Treatment success based on the subject's assessment, showed similar results: 194 (96.5%) of the 201 assessable bleeds and 93% of all 208 bleeds received an excellent or good response. Three subjects (1.4%) received a poor response.

Investigators' assessments of bleeds were made for 55 bleeds in 10 subjects, including seven that were unassessable. A total of 46 bleeds were treated successfully and two bleeds were treated unsuccessfully. The DRC reviewed 42 of these bleeds and rated 41 bleeds successfully; one bleed was considered unsuccessfully treated.

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

Treatment Failures

The treatment failure rate was 2.1% based on the bleeds reviewed by the DRC. Narratives for the four treatment failures are as follows:

- *Subject (b) (6)* The subject received four doses of Coagadex to treat a covert muscle bleed. The subject did not seek medical attention until three days after the bleed started, at which time it was considered severe. As a result of the delay in treatment, the initial dose of 25 IU/kg of Coagadex was considered insufficient, and an additional dose of 8 IU/kg was given on the same day. The site considered these two infusions as a single treatment. As per the definition of treatment failure, because four infusions were administered, the assessments of efficacy by the investigator and subject were recorded as 'poor'.
- *Subject (b) (6)* On three separate occasions, the subject required more than two doses of Coagadex to treat a menorrhagic bleed, which met the definition of treatment failure.

Of the 208 bleeds with subject assessments, 6 (2.9%) were failures, including the four discussed above and two additional bleeds in a single subject who was amongst the 20 bleeding episodes that were not reviewed by the DRC:

- *Subject (b) (6)* The subject required six infusions to treat simultaneous major traumatic joint and menorrhagic bleeding.

In addition, data from the following ten bleeds could have potentially affected efficacy assessments:

- The standard dose of Coagadex was increased for two subjects in an attempt to resolve future bleeding episodes with a single infusion: subject (b) (6) received a dose of 33 IU/kg following a serious covert muscle bleed and subject (b) (6) received a dose of 30 IU/kg following a bleed to the left forearm.
- Eight covert bleeds were reported to have lasted longer than 48 hours but did not receive a second or third treatment dose. These bleeds were considered potentially undertreated by the sponsor and this reviewer. Assessment of efficacy was based on the number and timing of infusions of Coagadex required to achieve hemostasis, and per protocol all ongoing covert bleeds were to be assessed 48 hours after the first infusion of Coagadex to determine whether

further doses were required (no subjective criteria were considered in the assessment). For seven of the eight bleeds, the subject was treated with only one infusion so a second infusion would have still qualified the bleed as a successful treatment. However, it is unclear if more than two doses should have been used to treat these bleeding episodes so for the purpose of this review these bleeds are being discussed under treatment failures. Of the eight bleeds that were potentially undertreated, the DRC excluded one of these bleeds (from (b) (6)) from the efficacy analysis.

Reviewer Comment: In this reviewer's opinion, these 10 bleeds should either be considered treatment failures or excluded from the analysis. If counted as failures, the treatment failure rate for the DRC-reviewed bleeds would be 6.9% (13/187); 175 bleeds (93.5%) would be considered as successfully treated, instead of the 184 reported successes. The failure rate for the 208 treated bleeds would be 7.7% (16/208); 88% (184/208) would be considered treatment successes. Either approach does not alter the conclusions drawn about the trial's clinical efficacy results in that greater than 80% of treated new and assessable bleeds would still have an excellent or good response. It is important to note that dosing for on-demand therapy is not modified based on the type of bleed; an initial dose of 25 IU/kg is recommended for minor, moderate and major bleeds and dosing is not based on targeting a specific Factor X level. This has important implications for dosing recommendations in the label.

Perioperative Management

In three subjects undergoing tooth extraction procedures, hemostasis was maintained during and after the surgical procedures:

- Subject (b) (6) was a 35 year-old male with severe FX deficiency who underwent a planned tooth extraction due to persistent pain. Expected blood loss for a patient without a bleeding disorder was estimated as 10 mL. The subject received one pre-surgical dose on the day of the procedure. Actual blood loss for this procedure was considered 'as expected.' No bleeding complications or blood transfusion were reported. The subject's post-procedural management included five days of treatment with tranexamic acid that began the day of surgery.
- Subject (b) (6) was a 16 year-old male with a history of severe FX deficiency who underwent a tooth extraction. Expected blood loss for a patient without a bleeding disorder was estimated as 10 mL. Actual blood loss for this procedure was considered 'as expected.' No bleeding complications or blood transfusions were reported. The subject received an additional dose of Coagadex on post-operative days 2 and 3.
- Subject (b) (6) was a 15 year-old female with a history of moderate FX deficiency who underwent a planned tooth extraction of her right mandibular first molar (46) and left mandibular second molar (37). Expected blood loss for a patient without a bleeding disorder was estimated as 300 mL based on the invasive dental technique used in Germany. The subject received one pre-operative dose of Coagadex and received tranexamic acid for three days post-operatively. The actual blood loss of 100 mL was 'less than expected.' BPL stated that no bleeding complications or

blood transfusion were reported; however, a review of the case narrative revealed that there was an unplanned delay to the procedure, several swabs were used and the subject needed to be hospitalized overnight because of persistent blood-stained saliva. This subject also had a decrease in hemoglobin and hematocrit that did not trigger a blood transfusion. This surgical procedure was excluded from the per-protocol analysis as this subject's plasma FX:C levels were ≥ 20 IU/dL at the pre-surgery visit, which reflected her use of Coagadex the day prior to the procedure.

Table 16. Assessment of Hemoglobin for Subject (b) (6)

Time point	Local Laboratory		Central Laboratory	
	Haemoglobin (g/dL)	Haematocrit (%)	Haemoglobin (g/L)	Haematocrit (L/L)
Pre-surgery pre-dose	12.1	37.4	127	0.40
Post-surgery pre-dose, Day 1	10.9	32	111	0.34
Day 2, Discharge	10.9	33.6	115	0.37

Source: Appendix 16.2, Listing 19.2.

The investigators assessed the overall efficacy of all three procedures as 'excellent.' All surgical procedures were judged as minor by the DRC. For the two surgical procedures in the per-protocol analysis, the pre-surgical doses were 49 and 51.4 IU/kg, which resulted in increments of 90 and 120 IU/dL, respectively. One subject did not require additional doses and the other received three post-operative doses of 26 IU/kg each. The mean cumulative dose of Coagadex administered to maintain hemostasis was 89.2 IU/kg.

Reviewer Comment: These data alone are insufficient to support a perioperative management indication as no major surgeries were conducted. As stated during the pre-BLA meeting, data from at least one major surgery is required to support licensure. Additional data to support this indication was provided from Trial Ten03 and will be reviewed in Section 7 below. Overall, only one of these procedures (subject (b) (6)) clearly supports a perioperative management indication. The postoperative use of antifibrinolytic agents in subject (b) (6) may have confounded the efficacy assessment. The fact that subject (b) (6) did not receive a blood transfusion for the drop in hemoglobin is not surprising, as different centers have different thresholds for transfusion and a transfusion in a subject who was not symptomatic (i.e. tachycardic, dyspneic) would not be appropriate. However, because the subject was hospitalized due to complications from minor surgery (blood-stained saliva) and this event was considered a serious adverse event (due to hospitalization) this reviewer considers this procedure as a failure.

6.1.11.3 Subpopulation Analyses

The sample size was too small to allow for any meaningful subgroup analyses.

6.1.11.4 Dropouts and/or Discontinuations

Subject (b) (6) was withdrawn at the Screening Visit due to the subject's history of unreliability/noncooperation (exclusion criteria), and another subject ((b) (6)) discontinued because of an unrelated death (see section 6.1.12.3 Deaths).

6.1.11.5 Exploratory and Post Hoc Analyses

Routine Prophylaxis

As this study was not designed to evaluate the effectiveness of the prophylaxis regimen, presentation of this data is only for exploratory purposes.

Two subjects ((b) (6)) received Coagadex for routine prophylaxis:

- *Subject (b) (6)* a 60 year-old female with severe disease, was started on once-weekly routine prophylaxis therapy at a dose of approximately 28 IU/kg after nearly 12 months on the study. At the request from the Sponsor, the investigator ceased routine prophylaxis for this subject for a period; however, shortly before completing the study, the subject received routine prophylaxis once every 2 weeks at a dose of approximately 25 IU/kg. During the total period of 7.2 months on routine prophylaxis, the subject did not report any bleeds. In the non-prophylaxis periods (a total of 21.7 months), the subject reported a total of six bleeds. In the year prior to study entry the subject was treated for one spontaneous bleed in the psoas muscle.
- *Subject (b) (6)* a 22 year-old male with severe disease, was started on once-weekly routine prophylaxis at a dose of 25 IU/kg per infusion of Coagadex. In the year prior to study entry, the subject was treated for four separate bleeding episodes: three muscle bleeds (right ankle, foot and knee) and one joint bleed in the right elbow. During the 8.5 months on routine prophylaxis, the subject reported no bleeds. During the 8.5 months prior to routine prophylaxis therapy, the subject had seven bleeds.

6.1.12 Safety Analyses

6.1.12.1 Methods

Adverse events (AEs) were coded by using Medical Dictionary for Regulatory Activities (MedDRA), Version 13 and are analyzed based on the principle of treatment emergence on or after first infusion with the trial drug. All safety analyses are based on the safety population, which constitutes of all subjects who received at least one dose of Coagadex at the study site, at home, and/or at a local clinic (n=16). Causality (unrelated, unlikely, possible, probable, very likely/certain) was assessed by the investigator.

6.1.12.2 Overview of Adverse Events

Exposure to Coagadex

For the 16 subjects treated with Coagadex, the median cumulative dose used was 36,194 IU (503.0 IU/kg) with a range of 7,818 IU (123.7 IU/kg) to 221,229 IU (2,942.0 IU/kg). The number of EDs to Coagadex for on-demand use ranged from 3 to 111, with a median of 17 days. The total number of infusions given to any subject for overall use ranged from 5 to 115 infusions, with a median of 20 per subject.

Treatment Emergent Adverse Events

Treatment-emergent AEs, herein after referred to as AEs, occurred in all 16 subjects treated with Coagadex. A total of 176 AEs, including 13 serious adverse events (SAEs), were reported.

Most of these AEs were mild (137; 80%) or moderate (28, 16%) in severity, and six (3.4%) were considered by the investigator and this clinical reviewer to be possibly related to the study drug:

- Subject (b) (6) experienced two events of infusion site erythema, two events of fatigue, and one event of back pain.
- Subject (b) (6) experienced one event of infusion site pain

The most common AEs were headache (eight subjects [50.0%]), nasopharyngitis (seven subjects [43.8%]), back pain (six subjects [37.5%]), pain in extremity (six subjects [37.5%]) and arthralgia (five subjects [31.3%]). Adverse events that occurred in four subjects (25.0%) were anemia, upper respiratory infection and hypotension.

The most common infusion-associated AEs, defined as all AEs, irrespective of causality, with onset within 24 hours after the start of a Coagadex infusion, reported in at least 10% of subjects were: headache (4 subjects [25.0%]), nasopharyngitis (3 subjects [18.8%]), upper respiratory infection (3 subjects [18.8%]), arthralgia (3 subjects [18.8%]), nausea (2 subjects [12.5%]), ulcer (2 subjects [12.5%]), joint injury (2 subjects [12.5%]), back pain (2 subjects [12.5%]) and hypotension (2 subjects [12.5%]).

Two subjects (12.5%), Subjects (b) (6), experienced a total of six adverse drug reactions, defined as AEs categorized by the investigator as very likely, possibly or probably related to Coagadex: fatigue (two events in one subject), infusion site erythema (two events in one subject), infusion site pain (one event in one subject) and back pain (one event in one subject).

6.1.12.3 Deaths

Subject (b) (6) a 58 year-old female with severe FX deficiency and hepatitis C, died from bilateral pneumonia and multi-organ failure after presenting to the hospital with six days of nausea, diarrhea, shortness of breath, productive cough, fever, and chest pain. A chest X-ray showed right lower lobe pneumonia associated with bilateral pleural effusion and she was admitted to the intensive care unit in respiratory distress. Seventy-two hours after being hospitalized, the subject developed acute respiratory distress syndrome, requiring intubation for artificial ventilation. She also developed shock and acute renal failure with urine retention. The subject was treated with wide-spectrum antibiotics and vasopressor medications. Despite treatment with Coagadex, the subject developed hematuria and upper gastrointestinal bleeding. An endoscopy was performed, which revealed esophageal varices II/IV, erosive gastritis and gastric ulcer, requiring endoscopic sclerotherapy. On the day of endoscopy, PCC was required to stop bleeding, as the subject's factor II level was low (26.4%). The frequency of Coagadex administration was increased to daily instead of every 48 hours. Despite all treatment efforts, the subject died

on (b) (6) because of multi-organ failure. After the subject’s death, urine cultures were positive for Klebsiella.

6.1.12.4 Nonfatal Serious Adverse Events

A total of 11 nonfatal SAEs, were reported in 5 subjects (31%) during the study. None of the SAEs were considered related to study treatment by the investigator, applicant or this clinical reviewer.

Table 17. Serious Adverse Events from Clinical Trials

Subject	Preferred Term	Severity	Outcome	Relationship to Coagadex
(b) (6)	Muscle hemorrhage	Moderate	Recovered	Unrelated
	Dysmenorrhea	Moderate	Recovered	Unrelated
	Menorrhagia	Moderate	Recovered	Unrelated
(b) (6)	Tooth abscess	Moderate	Recovered	Unrelated
(b) (6)	Gastritis	Moderate	Recovered	Unrelated
	Anemia	Moderate	Recovered	Unrelated
	Anemia	Moderate	Not Recovered	Unrelated
(b) (6)	Anemia	Severe	Recovered	Unrelated
	Gastric ulcer Helicobacter	Severe	Recovered	Unrelated
(b) (6)	Syncope	Mild	Recovered with sequelae	Unrelated
	Post procedural hemorrhage	Mild	Recovered	Unrelated

Selected Narratives for SAEs:

- *Subject (b) (6)* a 32 year-old female with severe FX deficiency was hospitalized for a right forearm hemorrhage after presenting with pain and swelling in the right forearm associated with tingling and numbness in the right forearm. She was treated with Coagadex and tranexamic acid and discharge home without incident. She was hospitalized on a separate occasion for dysmenorrhea and menorrhagia after presenting with pain and was treated with Coagadex and tranexamic acid. All three events were classified as serious due to hospitalization.
- *Subject (b) (6)* a 14 year-old female was hospitalized for observation after fainting while showering. The unwitnessed fall and resultant head trauma and concussion warranted in a CT scan, which did not show any evidence of an intracranial bleed. A clinical investigation showed a peri-occipital hematoma of the head. The fainting was not associated with anemia. The subject was not on any concomitant medications. The incident occurred three days after her last dose of COAGADEX. The subject continued to experience intermittent headaches and dizziness. A MRI scan of the brain done to evaluate the recurring symptoms was unremarkable.

- Subject (b) (6) a 14 year-old male was hospitalized with gastric bleeding and a hemoglobin of 5.4 g/dL for which he received a Red Blood Cell transfusion and was treated with COAGADEX. Endoscopy confirmed gastric ulcer and *Helicobacter pylori* infection.

6.1.12.5 Adverse Events of Special Interest (AESI)

Thromboembolic events:

No confirmed thromboembolic events were reported; however, three of the 16 subjects (19%) experienced significant elevations in at least one of the thrombogenic markers measured (thrombin-antithrombin complex, d-dimer, prothrombin fragments 1+2) following a dose of 25 IU/kg (see below).

Immunogenicity

Blood samples for FX inhibitor screens and quantitative assays were collected at the Screening Visit, pre-dose at the Baseline Visit (Day 1), at the 1-Month Visit, the 3-Month Visit, pre-dose at the 6-Month Visit, at Study Extension Visits, the End-of-Study Visit and at any Unscheduled Visit for a bleed. If a subject changed Coagadex batch, a blood sample for a FX inhibitor screen and Nijmegen-Bethesda assay was taken immediately before dosing with the new batch. All study subjects were negative for FX inhibitors at Baseline and remained negative during the study period. The potential development of non-inhibitory antibodies to Factor X was not evaluated; however, BPL committed to evaluating this post-market.

Hypersensitivity/Allergic Reactions

Subject (b) (6) was a 35 year-old who experienced infusion site swelling, back and hip pain and hypotension after receiving a dose of FX as preventative treatment prior to undergoing physiotherapy. On the day of the first dose (August 14, 2012) the subject noted mild left arm swelling, for which was treated with ibuprofen. On the following day mild lumbar swelling and tenderness with severe back pain and severe right hip pain developed and the subject received a CT scan of the abdomen and pelvis. That evening he was found to have a blood pressure of 97/57 mm Hg, which resolved without intervention. All other symptoms (infusion site swelling, back and hip pain) were resolved on August 17, 2012 after treatment with dihydrocodeine and paracetamol. These events were all considered unrelated by the investigator. The subject's second preventative dose was associated with left foot swelling and the second PK assessment dose was associated with discomfort in the right calf. However, no adverse events were reported with other doses of FX that were received during the trial (n=3).

Reviewer Comment: The subject narrative was provided by BPL on request, and after review, this reviewer finds that these events may be related and is therefore considered an adverse reaction; hypersensitivity reaction cannot be ruled out.

6.1.12.6 Clinical Test Results

Clinically significantly abnormal laboratory values were observed in all subjects and were consistent with the subjects' underlying diseases. Hypotension was reported as an

AE following Coagadex infusion for subjects (b) (6) (discussed above), (b) (6) (in the setting of worsening anemia) and (b) (6) (no associated signs or symptoms).

Although no thromboembolic events were reported during clinical trials, substantial elevations in one or more thrombogenicity markers D-dimer, thrombin-antithrombin complex (TAT), and prothrombin fragments 1+2 (F1+2) were observed in 3 of the 16 subjects following administration of Coagadex at the Baseline Visit and the Repeat PK assessment visit:

Subject number	Parameter	Visit
(b) (6)	D-dimer	Baseline Visit only
	TAT	Baseline and Repeat ^a PK visits
	F1+2	Baseline and Repeat ^a PK visits
	TAT	Repeat PK visit only
	F1+2	Repeat PK visit only
	TAT	Baseline Visit only ^b
	F1+2	Baseline Visit only ^b

Source: Section 14.3.5, Table 14.1 to Table 14.6.

^a The subject was reported to be bleeding (normal menstrual bleed) throughout this visit (Appendix 16.2, Listing 4.2).

^b Elevations at the Repeat PK assessment could not be assessed due to haemolysis of samples

These markers were measured at intervals of up to 72 hours post-dose after the baseline visit (16 subjects) and at the repeat PK visit (15 subjects).

Review Comment: All thrombogenicity profiles in which any one result exceeded the upper limit of the normal range were reviewed by the DRC. The applicant reported that in the absence of any clinical signs or symptoms of thrombosis in any subject in the safety population, the DRC did not consider any subject's thrombogenicity results to be indicative of a possible thrombogenic effect. Although this reviewer agrees with that assessment it is important to note that the protocol did not have a specific plan, such as structured history and physical exams, to clinically monitor for thromboembolic events. Theoretically, a thrombogenic response could become apparent following repeated dosing; however, this was not assessed during this study. Furthermore, data for two subjects ((b) (6)) were inconclusive as thrombogenicity markers were elevated at baseline (in both) or could not be evaluated on repeat analysis due to hemolysis of the sample ((b) (6))

6.1.12.7 Dropouts and/or Discontinuations

No subjects were discontinued due to adverse events.

7. INTEGRATED OVERVIEW OF EFFICACY

7.1 Indication #1

On-demand treatment and control of bleeding

The data to support this indication is discussed in Section 6.

7.1.8 Persistence of Efficacy

No tolerance effects were observed during the study. The hemostatic effect was unrelated to the number of months that the subjects were treated.

7.1.11 Efficacy Conclusions

The data to support the use of Coagadex for on-demand treatment and control of bleeding episodes in patients with hereditary FX deficiency was obtained from Trial Ten01 and discussed in section 6. The efficacy of Coagadex for the proposed indication has been demonstrated. The recommended dose in the label is appropriate.

7.2 Indication #2

Perioperative Management of Bleeding

7.2.1 Methods of Integration

The data to support the use of Coagadex for perioperative management was obtained from trials Ten03 and Ten01. The primary efficacy endpoints, dosing regimens, and key inclusion/exclusion criteria were sufficiently similar between the two trials to allow for an integrated analysis of efficacy for this indication.

Trial Ten03 was an open-label, multicenter study to investigate the safety and efficacy of Coagadex in the treatment of FX deficient subjects undergoing surgery. Similar to Ten01, Coagadex was given by intravenous infusion and subjects were administered a loading dose before surgery. The loading dose was calculated to raise the subject's FX level to 70% to 90% of normal. The post-surgery maintenance dose was calculated to maintain the subject's FX level at least 50% of normal.

7.2.2 Demographics and Baseline Characteristics

A total of five individual subjects underwent seven surgical procedures during clinical trials of Coagadex, including three subjects in Ten01 and two individual subjects in Ten03. Subjects had severe (n=2), moderate (n=1) or mild disease (n=2) and ranged in age from 14 to 59 years (14-36 years in Ten01 and 55-59 in Ten03). A total of 80% were male, 60% were Caucasian, and the remaining 40% were Asian.

Reviewer Comment: Subjects were consented and enrolled for each surgical procedure; as a result, a total of four subjects are reported as being enrolled in Ten03 when in fact only two unique/individual subjects were enrolled. This review focuses on the unique number of subjects.

Note: the narrative for subject (b) (6) states that he had moderate FX deficiency; however, the lowest recorded FX:C was 6 IU/dL, which suggests mild disease. In response to an information request, BPL confirmed that this subject had mild disease.

7.2.3 Subject Disposition

All subjects who underwent surgical procedures completed the surgical hemostasis assessment. No subjects were withdrawn from the study.

7.2.4 Analysis of Primary Endpoint(s)

A total of four major surgeries were performed in two subjects with mild disease (Ten03) and an additional three minor procedures of tooth extractions were performed in three subjects (Ten01). One minor surgical procedure was excluded from the per-protocol analysis as this subject's plasma FX:C levels were ≥ 20 IU/dL at the pre-surgery visit, which reflected her use of Coagadex the day prior to the procedure.

The major surgeries included six teeth extractions (molar and premolar) and coronary artery bypass graft (CABG) in one subject, and two total knee arthroplasties in the other subject:

- Subject (b) (6) was a 59 year-old Asian male with mild FX deficiency who was diagnosed following routine pre-surgical screening coagulation tests for a CABG were reported as abnormal. The subject was never treated with PCC or FFP for his previous three surgical procedures; however, two of those (minor) procedures (coronary angiography and dental extraction) were complicated by bleeding and required further surgical intervention. He underwent surgery for a CABG. The estimated and actual blood loss was 750 and 402 mL, respectively. The subject re-enrolled in the study as Subject (b) (6) and underwent oral surgery for a dental extraction of molar and pre-molar teeth (four teeth in the upper jaw and two teeth in the lower jaw). The expected and actual blood loss was 40 mL, respectively.

Subject (b) (6) was a 55 year-old Caucasian male with mild FX deficiency, who was diagnosed after presenting with a spontaneous bleed in his right foot. Other than reports of easy bruising, the subject did not experience any additional bleeding complications but did receive PCC on three occasions for perioperative management. He underwent a left knee total arthroplasty (lateral). The estimated and actual blood loss was 150 mL, respectively. The subject re-enrolled in the study as Subject (b) (6) and underwent surgery for a right knee total replacement. The estimated and actual blood loss was 50 mL, respectively. The minor surgeries are discussed above in Section 6.1.11.2.

Clinical Estimation of Volume of Blood Loss During Surgery

For all surgeries, the estimated blood loss was 'as expected' for five of the seven surgeries, and 'less than expected' for two surgeries, including the CABG (Ten03) and the tooth extraction that was excluded from analysis (Ten01).

Requirement for Blood Transfusions

None of the subjects required any blood transfusions during the study.

Number and Duration of Postoperative Bleeding Episodes

No postoperative bleeding episodes were reported by the applicant. However, as noted in Section 6.1.11.2, subject (b) (6) experienced persistent blood-stained saliva that required overnight hospitalization for observation.

Measurement of Hemoglobin

In four surgeries (three major and one minor), hemoglobin and hematocrit levels decreased significantly after the surgery; however, no subjects received a blood transfusion:

- Subject (b) (6) (Ten01) was a 15 year-old female with a history of moderate FX deficiency who underwent a planned tooth extraction of her right mandibular first molar and left mandibular second molar. The local lab reported a pre-surgery hemoglobin of 12.1 g/dL and a post-surgery level of 10.9 on postoperative day 1 and 2.
- Subject (b) (6) (Ten03) underwent CABG procedure and experienced a decrease in hemoglobin from 16.2 g/dL to 11.4 g/dL at the end of therapy.
- Subject (b) (6) experienced a drop in hemoglobin after both arthroplasty procedures. After left knee total arthroplasty the hemoglobin decreased from 16.5 g/dL to 10.2 g/dL. After the right total knee replacement the hemoglobin decreased from 15.4 g/dL to 12.3 g/dL.

All seven surgical procedures were assessed by the investigator and the DRC as 'excellent' in the control of bleeding during and after surgery.

Review Comment: The pre-BLA meeting minutes do not specify if the required surgery needed to support licensure should have been completed in a specific category of disease (e.g. moderate or severe disease). Although caution has been raised about categorizing subjects according to their endogenous levels of FX as the clinical phenotype does not correlate well with the laboratory phenotype, the subjects undergoing major surgery did not have a robust bleeding history. Still, the limited bleeding history for subject (b) (6) is most relevant because they occurred in the surgical setting and resulted in the need for additional surgical intervention, which suggests that this subject was at a high risk for postoperative bleeding despite his mild disease. However, these data are not sufficient to support a general indication for perioperative management; additional data in subjects with moderate to severe disease is need to further characterize the safety and efficacy of this product.

7.2.5 Analysis of Secondary Endpoint(s)

The pre-surgery dose for all surgeries ranged from 30.6 – 51.4 IU/kg and resulted in increments of 70 – 120 IU/dL. In Ten03, the pre-surgery dose ranged from 30.6 to 54.4 IU/kg and resulted in increments of 70-120 IU/dL.

Table 18. Summary of Surgical Procedures

Surgery Type & Description	N	Number of Infusions of Coagadex to Maintain Hemostasis			Cumulative Dose of Coagadex to Maintain Hemostasis (IU/kg)		
		mean	median	range	mean	median	range
Major <ul style="list-style-type: none"> • Left total knee arthroplasty • Right total knee arthroplasty • Coronary artery bypass graft • Molar and premolar tooth extractions 	4	10.8	13.0	2-15	154.0	180.7	44.6-210.1
Minor <ul style="list-style-type: none"> • Tooth extraction • Tooth extraction 	2*	2.5	2.5	1-4	89.2	89.2	51.4-127.0

Reviewer Comment: The doses and regimens used for all surgeries were sufficiently similar to support the recommended dosing regimen.

7.2.6 Other Endpoints

Not applicable.

7.2.7 Subpopulations

The sample size was too small to allow for any meaningful subgroup analyses.

7.2.8 Persistence of Efficacy

No tolerance effects were observed during the study. The hemostatic effect was unrelated to the number of months that the subjects were treated.

7.2.9 Product-Product Interactions

Not applicable.

7.2.10 Additional Efficacy Issues/Analyses

Not applicable.

7.2.11 Efficacy Conclusions

The efficacy of Coagadex for a limited indication has been demonstrated by data from four major surgeries conducted in subjects with mild disease and from one minor surgery in a subject with severe disease.

8. INTEGRATED OVERVIEW OF SAFETY

8.1 Safety Assessment Methods

The safety concerns for this product are hypersensitivity and allergic reactions, thromboembolic events, and inhibitor development. The safety profile of Coagadex is based on the analysis of safety data from clinical trials Ten01 and Ten03. Both trials were designed as phase 3, open label, multicenter studies. The safety evaluation plans were similar across the clinical studies and included assessments of medical history and concomitant medications, physical examinations, clinical observations, clinical laboratory measurements, vital signs, blood coagulation tests, inhibitor testing, and evaluations of bleeding and AEs. In both studies, all AEs were considered associated with the product if the onset was within 24 hours of the start of the infusion of Coagadex, if the AE was classified as related/possibly related to Coagadex or if causality was missing or indeterminate.

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

An integrated analysis of safety was conducted using data from the 18 subjects who were enrolled in clinical trials between 05 May 2010 and 30 October 2013 and received Coagadex to treat a bleeding event, for perioperative management, or for PK assessment:

- **Ten01:** 16 subjects with moderate or severe hereditary FX deficiency who received Coagadex for PK assessment, on-demand treatment of bleeding episodes or for controlling bleeding in surgical procedures.
- **Ten03:** 2 individual subjects with mild FX deficiency underwent four major surgical procedures and received Coagadex for perioperative management.

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

Subjects in Ten01 ranged from 12 to 58 years old, with a mean age of 27.1 years. Six were male and 10 were female. Twelve (75.0%) were white/Caucasian, 2 (12.5%) were black/African American, and 2 (12.5%) were Asian. Four subjects (25.0%) were Hispanic or Latino. Fourteen subjects (87.5%) had severe FX deficiency and the other two subjects had moderate deficiency.

In Ten03 there were two patients, both male, who underwent four surgical procedures. The median age was 57 years (range 55 to 59 years). One patient was Asian and the other was Caucasian. Both had mild FX deficiency with endogenous levels of FX of 6 and 8 IU/dL, respectively.

8.2.3 Categorization of Adverse Events

AEs are coded by using MedDRA. All observed or volunteered AEs, regardless of treatment group or suspected causal relationship to Coagadex, were recorded in the AE fields of the case report form.

8.3 Caveats Introduced by Pooling of Data Across Studies/Clinical Trials

Trial objectives were not identical in that Ten03 only enrolled subjects receiving Coagadex for perioperative management. Although the target population was the same, the demographics of the subjects enrolled were different:

- Ten01 enrolled subjects with moderate and severe disease while Ten03 enrolled subjects with mild disease.
- Subjects in Ten03 were older.
- Subjects Ten01 had more exposure to Coagadex since they received intermittent doses for the treatment of acute bleeding episodes.

In addition, the surgeries in Ten01 were minor, as compared to the major surgeries of Ten03 so the AE profiles may be different.

Reviewer Comment: Despite these differences, safety results from these trials can be combined to allow for an integrated analysis of safety.

8.4 Safety Results

8.4.1 Deaths

One death was reported in trial Ten01 and is discussed in section 6.1.12.3.

8.4.2 Nonfatal Serious Adverse Events

All SAEs were reported in trial Ten01 (see Section 6.1.12.4 *Nonfatal Serious Adverse Events*); no SAEs were reported in Ten03.

8.4.3 Study Dropouts/Discontinuations

No subjects were discontinued due to AEs. See Section 6.1.11.4 *Dropouts and/or Discontinuations*.

8.4.4 Common Adverse Events

All 18 individual subjects experienced at least one AE. In total, there were 202 AEs, including 176 from trial Ten01 and 26 from Ten03.

The most common, which were reported by at least 25 % of the combined study population, were: headache (reported by 8 subjects; 6.7% of all AEs), nasopharyngitis (reported by 7 subjects; 5.4% of all AEs), back pain (reported by 6 subjects; 5.0% of all AEs), and pain in extremity (reported by 6 subjects; 4.0% of all AEs).

Reviewer Comment: A review of AEs that occurred in a lower percentage of the population (e.g. >10% (n=2 or more subjects), >20% (n=4 or more subjects) did not capture additional clinically relevant AEs.

Adverse reactions were those categorized by the investigator as very likely, possibly or probably related causally to Coagadex. Two subjects (12.5%) who were enrolled in trial Ten01 experienced a total of six events that were considered by the investigator to be adverse reactions (see Section 16.1.12.2 *Overview of Adverse Events*). No subject in

Ten03 experienced an AE which the investigator regarded as very likely, possibly or probably related to Coagadex.

8.4.5 Clinical Test Results

There were no obvious trends of abnormality that were observed for any clinical laboratory indicators. There were no clinically significant changes in viral serology that suggested seroconversion in either study. Elevations of thrombogenicity markers D dimer, TAT, and/or F 1+2 were observed in several subjects in trial Ten01 but were not associated with clinical thromboembolic events.

8.4.8 Adverse Events of Special Interest

No thromboembolic events, inhibitors, viral seroconversion or hypersensitivity reactions were reported for any subject during the clinical development program of Coagadex.

8.5 Additional Safety Evaluations

8.5.7 Overdose, Drug Abuse Potential, Withdrawal, and Rebound

One subject ((b) (6)) received 80 IU/kg instead of 25 IU/kg to treat a bleed, which was higher than the maximum recommended dose of 60 IU/kg. No AE were reported relating to this overdose.

8.5.8 Immunogenicity (Safety)

In both studies, all subjects tested negative for FX inhibitors.

8.6 Safety Conclusions

The results of the integrated analysis of safety demonstrate the safety and tolerability of Coagadex for the proposed indication of on-demand treatment and control and perioperative management of bleeding in patients with hereditary FX deficiency.

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

There is no information regarding the presence of COAGADEX in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for COAGADEX and any potential adverse effects on the breast-fed infant from COAGADEX or from the underlying maternal condition. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when COAGADEX is administered to a nursing woman.

9.1.1 Human Reproduction and Pregnancy Data

One report of miscarriage in a patient receiving Coagadex on a compassionate use basis was reported (BPL incident number QR 81002) in a subject receiving once-weekly FX

1500 IU. The subject became concerned she might be pregnant and sought medical advice. β -HCG levels, measured on the day after vaginal bleeding commenced, were low and indicated that the pregnancy was not intact prior to the abortion. The bleeding was a consequence, and not a cause, of the abortion. A diagnosis of spontaneous abortion at 6 weeks + 3 days was made.

9.1.3 Pediatric Use and PREA Considerations

This product received orphan designation for treatment of hereditary factor X deficiency on 08 November 2007. A total of six pediatric subjects aged 12 to 17 years were studied in Ten01.

10. CONCLUSIONS

Coagadex appears reasonably safe and likely to provide therapeutic benefit to patients with hereditary FX deficiency. No confirmed thromboembolic events or inhibitors to FX were reported in any clinical trial. The initial dose of 25 U/kg, expected to raise the factor X level by approximately 35-40 IU/dL, was sufficient to successfully achieve hemostasis in the treatment of initial acute bleeding episodes. The recommended dosing for surgery was sufficient to raise the subject's FX level to 70-90 IU/dL, and proved to be sufficient for the management of perioperative bleeding for subjects with mild disease.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

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Table 19. Risk-Benefit Considerations for Coagadex

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	<ul style="list-style-type: none"> Hereditary FX deficiency is a rare, but potentially life-threatening, bleeding disorder caused by inherited lack of coagulation factor X. The clinical manifestations include hemorrhage into the skin, muscles, or soft tissues and mucous membranes, menorrhagia, excessive bleeding following surgery or trauma, and occasionally cerebral hemorrhage. The objectives of treatment are to effectively control bleeding during acute bleeding episodes (on-demand treatment) and in the surgical setting (perioperative management). 	<ul style="list-style-type: none"> Hereditary FX deficiency is a rare, but potentially life-threatening disease.
Unmet Medical Need	<ul style="list-style-type: none"> Currently, there are no approved purified FX concentrate replacement therapies. Current treatment regimens include FFP and PCC; neither is labeled with the specific FX content. PCCs are associated with a risk of thrombotic adverse events and FFP requires large volumes because of the low FX content, which increases the risk of transfusion related acute lung injury (TRALI). 	<ul style="list-style-type: none"> This product treats a serious condition and, if approved, would provide significant improvement in safety and effectiveness over current treatment options.
Clinical Benefit	<ul style="list-style-type: none"> Of the 208 bleeds treated with Coagadex, greater than 90% were treated effectively (i.e. received an excellent or good rating by the subject, investigator and/or DRC). Coagadex was used for perioperative management for seven surgical procedures, including four major surgeries that were performed in two subjects with mild FX deficiency and three minor surgeries in three subjects with moderate or severe disease. One minor surgery was considered a failure by this reviewer as a result of postsurgical bleeding that required hospitalization. 	<ul style="list-style-type: none"> Results of trial Ten01 demonstrate that Coagadex is effective in treating acute bleeds. Data from Ten01 and Ten03 demonstrate that Coagadex is effective for perioperative management of bleeding.
Risk	<ul style="list-style-type: none"> The risks of treatment with Coagadex are allergic reactions, FX inhibitor development, and thrombogenicity. There were no reports of FX inhibitors or confirmed thromboembolic events. 	<ul style="list-style-type: none"> All the evidence indicates that Coagadex was well tolerated.
Risk Management	<ul style="list-style-type: none"> The potential risks are outlined in the package insert under <i>Contraindications and Warnings and Precautions</i> sections. No other safety signals were apparent. 	<ul style="list-style-type: none"> The package insert and the current pharmacovigilance plan are adequate to manage the risks.

11.2 Risk-Benefit Summary and Assessment

Hereditary FX deficiency is a rare type of bleeding disorder with an estimated prevalence of 1 in 1 million people⁸. Currently there is no approved pure FX factor treatment; FX-deficient patients are generally treated with FFP or PCC products, which contain numerous other plasma proteins and are not labeled with the specific FX content. PCCs are associated with a risk of thrombotic adverse events. FFP requires large volumes because of the low FX content, which increases the risk of TRALI. The availability of a purified FX concentrate would increase treatment options by providing a more accurate dosing regimen and less exposure to other plasma proteins.

Risks

The safety concerns for this product are hypersensitivity reactions, thromboembolic events, and the development of FX inhibitors. The ability to clearly define these risks in this patient population and for this product is limited by the study size. However, of the 18 subjects treated with Coagadex, no subjects were positive for FX inhibitors or had a reported thromboembolic event. Minor elevation of thrombogenicity markers was observed in some subjects, but no clinical signs or symptoms of thrombosis were observed in any subject. There were no reports of anaphylaxis. The potential for these risks is discussed in the Warnings and Precautions section of the Package Insert. No serious AEs were found to be attributable to Coagadex.

Benefits

The lower limit of 95% CI for the half-life of FX:C in 16 subjects, measured using the clotting assay, was 26.9 hours (geometric mean) and 26.8 hours (arithmetic mean). Therefore, the criterion for treatment success (the lower limit of 95% CI of half-life was greater than 20 hours in at least 8 PK assessments at baseline) was met. The clinical response to Coagadex for on-demand treatment and control of bleeds was good or excellent for 99% of 187 bleeds in 15 subjects that were reviewed by the DRC. Coagadex was considered effective in controlling bleeding in four subjects who underwent six surgical procedures; one minor surgery was considered not effective by the clinical reviewer because of the complication of postoperative bleeding that required hospitalization. Data from Ten01 and Ten03 demonstrate that the proposed dosing for the treatment of acute bleeds and dosing for perioperative management of major surgical procedures in subjects with mild disease are appropriate.

The safety data of Coagadex was demonstrated in the 18 subjects in that were enrolled in phase 3 trials Ten01 and Ten03. No SAE was considered related to Coagadex. There were no reports of FX inhibitor development or reports of thrombosis in the Ten01 and Ten03 studies. No safety signals were identified. The accidental overdosing of one subject had no apparent sequelae. If approved, Coagadex would be the first purified plasma-derived FX product approved in the U.S. Approval of this product would fulfill an unmet medical need.

11.3 Discussion of Regulatory Options

The regulatory options considered included:

1. Approve for the proposed indications with routine surveillance.
2. Approve for the proposed indication of on-demand treatment and control but limit the indication for perioperative management to adults and children >12 years with mild disease and request a PMC to obtain additional data on surgical procedures.
3. Approve for on-demand treatment and control only and request additional data on surgical procedures pre-licensure.
4. Approve for the proposed indication of on-demand treatment and control but limit the indication for perioperative management to adults and children >12 years with mild disease, request a PMC to obtain additional data on surgical procedures, and consider a registry study to evaluate use for routine prophylaxis, use in pregnancy and use in children <12 years.

As a result of insufficient data in subjects with the highest risk for postoperative bleeding (i.e. subjects with moderate or severe FX deficiency), a broad postoperative indication was not approvable. In order to support a perioperative indication in patients with moderate to severe disease, FDA advised BPL that additional data on major surgeries conducted in subjects with moderate to severe FX deficiency is needed. FDA initially recommended obtaining these data from an observational study similar in design to Ten03. However, BPL asserted that such a study would not be feasible, stating that the “number of those patients undergoing a major surgical procedure would be a very small percentage of an already small number. Attempting to identify sites where those patients might exist would be difficult at best, and would require opening many sites and keeping those sites open for an indefinite period of time.” FDA advised that these data could be obtained from a registry study. Prophylactic treatment will be evaluated in a separate pediatric study.

11.4 Recommendations on Regulatory Actions

This clinical reviewer recommends approval of this BLA for the proposed indication of on-demand treatment of control of bleeding episodes and a narrow indication of perioperative management in adults and children >12 years of age with mild hereditary FX deficiency. The manufacturing process for Coagadex is validated and adequately controlled. Efficacy and safety clinical data for Coagadex supported a favorable benefit/risk determination for the proposed indication.

11.5 Labeling Review and Recommendations

The proposed proprietary name, Coagadex, was reviewed by the Advertising and Promotional Labeling Branch (APLB) from a promotional and comprehension perspective and determined to be acceptable. The package insert, carton and container labels submitted to BL STN 125506/0 are currently being reviewed.

11.6 Recommendations on Postmarketing Actions

The safety data reviewed do not substantiate a need for a post-marketing requirement or risk evaluation and mitigation strategy. Additional data to evaluate major surgery patients with moderate/severe disease should be obtained through a PMC for a registry study.

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