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# BLA Clinical Review Memorandum

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| Application Type | BLS-Efficacy |
| STN | 125506.46 |
| CBER Received Date | March 23, 2018 |
| PDUFA Goal Date | September 21, 2018 |
| Division / Office | DCEPT/OTAT |
| Priority Review (Yes/No) | Yes |
| Reviewer Name(s) | Jay Lozier, M.D., Ph.D. |
| Review Completion Date / Stamped Date | |
| Supervisory Concurrence | |
| Applicant | Bio Products Laboratory, Limited |
| Established Name | Coagulation Factor X (Human) |
| (Proposed) Trade Name | Coagadex |
| Pharmacologic Class | Plasma derived coagulation factor |
| Formulation(s), including Adjuvants, etc. | When reconstituted with Sterile Water for Injection, COAGADEX contains nominally (approximately) 100 IU/mL of coagulation Factor X and the following inactive ingredients: chloride, phosphate, citrate, sucrose, and sodium. |
| Dosage Form(s) and Route(s) of Administration | COAGADEX is available as lyophilized powder for reconstitution in single-use vials containing nominally (approximately) 250 IU or 500 IU of Factor X activity. To be given intravenously. |
| Dosing Regimen | <u>For prophylaxis of bleeding episodes</u><br>**Children:** Less than 12 years of age<br>40 IU/kg twice weekly<br>**Adults and Adolescents**: 12 years of age or older:<br>25 IU/kg twice weekly<br>Due to inter-and intra-patient variability, it is recommended that trough blood levels of Factor X should be monitored at intervals, especially in the first weeks of therapy or after dosages changes. Adjust dosage |

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| | regimen to clinical response and trough levels of Factor X of at least 5 IU/dL. Do not exceed a peak level of 120 IU/dL.<br><br><u>For on-demand treatment and control of bleeding episodes</u><br>**Children:** Less than 12 years of age<br>30 IU/kg<br>**Adults and Adolescents**: 12 years of age or older:<br>25 IU/kg<br>Infuse COAGADEX when the first sign of bleeding occurs *[see Clinical Trial Experience (6.1)].* Repeat at intervals of 24 hours until the bleed stops.<br><br>For perioperative management of bleeding<br>**Children:** Less than 12 years of age<br>Calculate dose (IU) using 0.6 as shown in the 'Dose' formula (2.1). The increment of Factor X can be estimated using *in vivo* recovery value of 1.7 (see formula [below])*<br><br>***Estimated Increment of Factor X (IU/dL or % of normal) = [Total Dose (IU)/Body Weight (kg)] x 1.7**<br><br>**Adults and Adolescents**: 12 years of age or older:<br>Calculate dose (IU) using 0.5 as shown in the 'Dose' formula (2.1). The increment of Factor X can be estimated using *in vivo* recovery value of 2.0 (see formula [below])**<br><br>****Estimated Increment of Factor X (IU/dL or % of normal) = [Total Dose (IU)/Body Weight (kg)] x 2**<br><br>Measure post-infusion plasma Factor X levels for each patient before and after surgery to ensure that hemostatic levels are obtained and maintained.<br><br>**Pre-surgery:** calculate the dose of COAGADEX to raise plasma Factor X levels to 70-90 IU/dL |

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| Indication(s) and Intended Population(s) | Routine prophylaxis to reduce the frequency of bleeding episodes<br>On-demand treatment and control of bleeding episodes<br>Perioperative management of bleeding in patients with mild and moderate hereditary Factor X deficiency |
| Orphan Designated (Yes/No) | Yes |

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## GLOSSARY

| | |
|---|---|
| ADR | adverse drug reaction |
| AE | adverse event |
| BLA | biologics license application |
| BPCA | Best Pharmaceuticals for Children Act |
| CFR | Code of Federal Regulations |
| CMC | chemistry, manufacturing, and controls |
| DIC | disseminated intravascular coagulation |
| eCTD | electronic Common Technical Document |
| ELISA | Enzyme-Linked Immunosorbent Assay |
| FDAAA | Food and Drug Administration Amendments Act of 2007 |
| FX | Factor X |
| GRMP | good review management principles |
| ICH | International Conference on Harmonisation (of Technical Requirements for Registration of Pharmaceuticals for Human Use) |
| ISE | integrated summary of efficacy |
| ITT | intent-to-treat |
| MedDRA | Medical Dictionary for Regulatory Activities |
| OBE | Office of Biostatistics and Epidemiology |
| OSE | Office of Surveillance and Epidemiology |
| PCCs | prothrombin complex concentrates |
| PD | pharmacodynamics |
| PeRC | Pediatric Review Committee (CDER) |
| PI | package insert |
| PK | pharmacokinetics |
| PMC | postmarketing commitment |
| PMR | postmarketing requirement |
| PREA | Pediatric Research Equity Act |
| REMS | risk evaluation and mitigation strategy |
| RMS/BLA | regulatory management system for the biologics license application |
| SAE | serious adverse event |

## 1. EXECUTIVE SUMMARY

Factor X deficiency is a bleeding disorder caused by the complete or partial absence deficiency of coagulation factor X activity in the blood stream. The degree of bleeding is inversely proportional to the level of factor X coagulation activity present in the plasma. Severe disease is defined by plasma factor X activity levels of <2% of normal. Moderate disease is defined by plasma factor X activity levels of 2-5%, and mild disease is defined by plasma factor X activity levels of between 5% and 20%.

COAGADEX, coagulation factor X (human), is a plasma-derived human blood coagulation factor X concentrate produced by Bio Products Laboratory, Limited (BPL) and licensed in the United States since 2016 for use in adults and children > 12 years of age with hereditary factor X deficiency for:

- On-demand treatment and control of bleeding episodes, and
- Perioperative management of bleeding in patients with mild hereditary Factor X deficiency.

On-demand and perioperative management of factor X deficiency was studied in BPL's clinical trials Ten01 and Ten03, in support of licensure for these indications. Routine

prophylaxis and perioperative management of bleeding in major surgery in patients with moderate and severe hereditary Factor X deficiency was not studied in these trials and those limitations are stated in the current approved package insert (October 2016). A post marketing commitment to study perioperative management of bleeding in factor X deficiency with COAGADEX in major surgery, negotiated during the initial product approval, remains in effect; however, the study has not enrolled any subjects (Study Ten06).

In this efficacy supplement, BPL now submits results of two additional studies of COAGADEX in support of an indication for routine prophylaxis for patients with severe or moderate factor X deficiency in all ages and peri-operative management and on-demand treatment of children under age 12 with severe or moderate factor X deficiency.

Study Ten02 is the primary study that evaluates efficacy and safety during routine prophylaxis and on-demand treatment for severe and moderate factor X deficiency in subjects under the age of 12 years.

Study Ten05 is a retrospective survey of COAGADEX use under compassionate use provisions in patients of all ages (including children), and is the primary study in support of an indication for routine prophylaxis in adults with factor X deficiency, on-demand treatment, and perioperative management in children 12 years and older with factor X deficiency. Study Ten 05 also provides supportive data with Study Ten 02 as the primary study for routine prophylaxis and on-demand treatment in children < 12 years of age.

Ten02 is a prospective, multicenter, uncontrolled study of COAGADEX in children under age 12 years for routine prophylaxis and on-demand treatment of bleeding for congenital factor X deficiency. Prophylaxis was tested for at least 50 exposure days and 26 weeks' treatment duration. Subjects received a starting dose of 40-50 IU/kg of COAGADEX, twice weekly. Investigators were advised to maintain a trough factor X activity level of at least 5% of normal and a peak level of no more than 120% of normal, however, no adjustments to the initial dose were required to maintain these target levels. The starting dose was based on the empiric observation that two children on routine prophylaxis in an earlier study of compassionate use (study Ten05) were successfully treated with 50 IU/kg of COAGADEX. On-demand treatment for breakthrough bleeds were treated with 25 IU/kg COAGADEX (minor bleeds) or 50 IU/kg COAGADEX (major bleeds). Subjects were monitored for the development of inhibitors and pharmacokinetic assessments were performed prior to and at the end of the study. Primary efficacy assessment for routine prophylaxis was based on the number of annualized breakthrough bleeding episodes assessed by the investigator with input from subject's recording of the bleeding episodes through electronic diaries. Primary efficacy assessment for on-demand treatment was assessed based on a four-point rating scale as assessed by the investigator and reported by the subject. Descriptive analyses were used to assess efficacy.

Ten05 was a multicenter, international, uncontrolled, open-label, retrospective survey of the use of COAGADEX in treatment of congenital factor X deficiency, including surgery. It was conducted before Ten02, and the results of prophylaxis in the two children in Ten05 likely informed the empiric recommendations for starting doses for children in Study Ten02. Data collection was completed in 2016 on use of COAGADEX in the period from March 2011 to December 2015 (prior to licensure). Subjects receiving routine prophylaxis received COAGADEX at a dose determined by their provider.

Routine prophylaxis was tested for at least 50 exposure days and 12.5 months' treatment duration (range 12.5-48.8 months). Four adult subjects received an average routine prophylaxis dose of 27 IU/kg of COAGADEX, once weekly (range 0.32-1.47 times per week). Two adolescents received an average routine prophylaxis dose of 24.8 IU/kg, once weekly (range 1-1.2). Two children <12 years of age received an average of 51.1 IU/kg, twice weekly. Notably, both children had ABRs of 0, while the ABRs for adolescents and adults ranged from 0 to 4.45.

Overall, adults and adolescents received an average dose of 26.4 IU/kg, once or twice weekly, and children <12 years of age received an average dose of 51.1 IU/kg, twice weekly (Table 1). Bleeds that occurred during routine prophylaxis, or during on-demand therapy were treated with 25 IU/kg COAGADEX until the bleeding stopped. Surgical procedures were covered with treatment plans at the discretion of the Investigator. Safety and efficacy parameters similar to those in the Ten02 trial were assessed, though retrospectively, except for adverse drug reactions that were reported to BPL in real time as part of the compassionate use agreement.

The recommended dose of 40 IU/kg twice weekly in children under 12 years of age is based on the results of the prospective study of prophylaxis in nine children < 12 years of age, for whom this dose was safe and effective.

**Table 1.**

**Empiric Dosing Results of Ten05 Routine Prophylaxis, by Age Group**

| **Children 0-5 yrs (n = 1)** | **Children 6-11 yrs (n = 1)** | **All Children < 12 yrs (n = 2)** | **Adolescents 12-17 yrs (n = 2)** | **Adults ≥18 yrs (n = 4)** | **Adults and Adolescents (n = 6)** |
|---|---|---|---|---|---|
| 48.5 IU/kg | 53.6 IU/kg | 51.1 IU/kg | 24.8 IU/kg | 27.1 IU/kg | 26.4 IU/kg |

The combined efficacy results of Ten 02 and Ten 05 study are provided below (Table 2):

**Table 2.**

| **Treatment type** | **0-5 years (Study, n)** | **6-11 years (Study, n)** | **12-17 years (Study, n)** | **≥ 18 years (Study, n)** |
|---|---|---|---|---|
| *Routine Prophylaxis, Mean ABR* | 0.5 (Ten02, 4)<br>0 (Ten05,1) | 3.6 (Ten02, 5)<br>0 (Ten05, 1) | 1.1 (Ten05, 2) | 1.6 (Ten05, 4) |
| *On-demand therapy, % Excellent/good* | 100% (Ten02, 4) | 100% (Ten02, 5) | 100% (Ten05, 5) | 100% (Ten05, 6) |
| *Perioperative management,* % Excellent/good* | 100% (Ten05, 1) | NA | 100% (Ten05, 1) | 100% (Ten05, 1) |

*No major surgical procedures were evaluated.

The Ten 02 study demonstrates the efficacy of Coagadex for the on-demand treatment and routine prophylaxis of children < 12 years of age with severe to moderate factor X deficiency. The results of Study Ten 05 demonstrate the efficacy of Coagadex for routine prophylaxis in adults, adolescents, and children, and in the perioperative management of

children <12 years, adolescents and adults. The limitations of this study include a) the small sample sizes in all age groups receiving prophylaxis b) the small sample sizes notably in children receiving perioperative treatment c) the type of surgery evaluated in that no subjects were evaluated for perioperative management of major surgical procedures. These limitations are addressed through extrapolation of data from pharmacokinetic studies particularly for routine prophylaxis in adults and adolescents and the data from the target factor X levels that were achieved pre-operatively which were consistent with the historical data and standard of care guidelines that support the use of target factor levels to reduce or prevent bleeding in the perioperative management of major surgical procedures and target levels for on-demand treatment of bleeding (which is consistent with target levels for major surgical procedures) in patients with severe factor X deficiency. The retrospective nature of Ten 05 is unlikely to have had a substantial negative impact on the outcomes as collection of data to support the efficacy assessment was considered adequate. The regulatory flexibility provided in assessment of efficacy is consistent with FDA's approach to BLA review of study data for products used in the treatment of rare diseases.

Primary safety endpoints were adverse drug reactions and serious adverse reactions, as well as incremental recovery measurements, and tolerability. COAGADEX usage ranged from 0.3 to 4.0 years, with an average of 91 exposure days (EDs) in the non-surgical EDs, for a total of 1359 EDs in that group (1366 EDs for all cases combined). No adverse drug reactions, inhibitors, infusion site reactions or serious adverse reactions were reported in this cohort.

The only surgery that occurred in a child under age 12 was insertion of a Portacath access device in subject (b) (6) (a 1 year old). Other surgeries in subjects > 12 years of age were dental procedures on Subjects (b) (6) (age 17), and (b) (6) (age 32). No excessive post-operative bleeding was observed in the three subjects, and hemostasis was judged to be satisfactory in all. The two dental procedures were performed with single doses of COAGADEX (27 IU/kg and 29 IU/kg) and concomitant amicar (typical peri-operative management strategy for factor replacement therapy for dental procedures in hemophilia). The Portacath insertion was performed with COAGADEX alone, given as an initial dose of 73 IU/kg and 49 IU/kg per day, times four days thereafter.

There is no evidence for efficacy in the setting of pregnancy/delivery, despite treatment of a pregnant patient in labor and post-partum, but not at the time of delivery. No meaningful statement on pregnancy and lactation can be made in the label.

Clinical safety and efficacy data support a favorable risk/benefit determination for the proposed indication of prophylaxis of bleeding in children less than 12 years of age.

**Recommendation:**
COAGADEX appears to be safe and effective for prophylaxis of bleeding in children less than 12 years of age, when used in accordance with the proposed label instructions. No additional post-marketing requirement or risk evaluation and mitigation study for this product is recommended. The existing post-marketing commitment to study COAGADEX for perioperative management of bleeding in moderate to severe factor X deficiency should be modified to study major surgery in severe factor X deficiency. Approval for routine prophylaxis and on-demand treatment in children < 12 years of age, adolescents, and adults, is recommended. Approval for perioperative management in

children < 12 years of age with moderate deficiency is recommended. Extrapolation of data from the adult subjects who underwent major surgery and the adequate target level observed in the pediatric subject for whom perioperative levels were available forms the basis for including major and minor surgery in the indication. Limitations of the data from Ten 02 and Ten 05 studies relate to the small size, the absence of target levels in the on-demand group to provide robust support to the peri-operative indication particularly for the major surgeries and paucity of perioperative data in patients with severe deficiency. Recommendations in the package insert for calculating the dose for the perioperative management in children <12 years of age differ from the empiric dosing of the Ten 05 surgery subjects. However, analysis of factor X levels recovered post COAGADEX administration in the patient with moderate deficiency were consistent with the IR30 and showed that dosing based on the IR30 will achieve the desired target level for perioperative management of patients with mild-moderate deficiency.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

Study Ten02

Study Ten 02 is the primary study intended to support both the routine prophylaxis and on-demand indication in children < 12 years of age. The demographic data are provided in Table 3:

**Table 3.**

**Demographics of the Ten02 Study Population Subjects Treated Per Protocol**

| **Subject Characteristic** | **0-5-year-old group (N = 4)** | **6-11-year-old group (N = 5)** | **Overall (N = 9)** |
|---|---|---|---|
| **Age (years)** | | | |
| Average (± STD) | 3.0 (± 0.5) | 10.7 (± 1.4) | 7.3 (± 4.2) |
| Range | 2.6 -3.6 | 8.5 – 11.9 | 2.6 – 11.9 |
| **Sex** | | | |
| Female | 2 (50%) | 3 (60%) | 5 (55.6%) |
| Male | 2 (50%) | 3 (40%) | 4 (44.4%) |
| **Race** | | | |
| Asian | 4 (100%) | 3 (60%) | 7 (77.8%) |
| Caucasian | - | 2 (40%) | 2 (22.2%) |
| **Weight (kg)** | | | |
| Average (± STD) | 13.5 (±1.4) | 13.5 (±1.4) | 13.5 (±1.4) |
| Range | 12.4 – 15.4 | 18.7 - 46.7 | 12.4 – 46.2 |
| **Severity of Factor X Deficiency** | | | |
| Severe | 3 (75%) | 5 (100%) | 8 |
| Moderate | 1 (25%) | - | 1 |

***Reviewer comment**: Factor X deficiency is a rare disorder, the sample sizes in the pediatric age group (< 12 years) are acceptable in this context. The racial distribution, particularly the lack of Caucasian subjects 0-5 years is noted. With our current understanding of FX deficiency, there is no reason to believe that racial differences have an impact on the efficacy or safety outcomes for factor replacement. Thus, the results observed in this age group (0-5 years) may be extrapolated to all races and does not limit the assessment of efficacy.*

Study Ten05

The data from Ten 05 is from a compassionate use study with treatments from March 2011 to December 2015 (prior to licensure in the United States). This study is the primary study that supports the indication for perioperative management in children <12 years of age, and routine prophylaxis and on-demand treatment in adults and adolescents and is supportive of the indication as with Ten 02 (routine prophylaxis and on-demand treatment in children < 12 years). Ten 05 provides supportive data for the perioperative and on-demand treatment of adolescent and adult subjects which is an approved indication.

**Table 4.**

**Demographics of the Ten05 Study Population, Intention to Treat Subjects**

| Subject Characteristic | 0-5-year-old group (N = 1) | 6-11-year-old group (N = 1) | ≥12-year-old group (N = 13) | Overall (N = 15) |
|---|---|---|---|---|
| **Age (years)** | | | | |
| Average (± STD) | 1 | 6 | 22.8 | 20.3 |
| Range | 1 - 1 | 6-6 | 13 – 43 | 1 – 43 |
| **Sex** | | | | |
| Female | 0 (0%) | 1 (100%) | 7 (54%) | 8 (53%) |
| Male | 1 (100%) | 0 (0%) | 6 (46%) | 7 (47%) |
| **Race** | | | | |
| Asian | 1 (100%) | 0 (0%) | 2 (15%) | 3 (20%) |
| Caucasian | 0 (0%) | 1 (100%) | 11 (85%) | 12 (80%) |
| **Severity of Factor X Deficiency** | | | | |
| Severe | 0 (0%) | 1 (100%) | 11 (85%) | 12 (80%) |
| Moderate | 1 (100%) | 0 (0%) | 2 (15%) | 3 (20%) |

***Reviewer comment:*** *The sample size in the pediatric age group is small and limits the ability to understand the impact of demographic distribution on the efficacy results. To support the efficacy conclusions for perioperative management in children given the limited sample size of two subjects, extrapolation of efficacy and dosing from the adult population and the target level achieved in the single pediatric patient is the basis for extending the indication to the perioperative management. Therefore, the small sample size in itself is not considered a substantial impediment in assessing the efficacy of the product in the perioperative management of pediatric subjects, especially given the rarity of the disease.*

1.2 Patient Experience Data

Patient Experience Data Relevant to this Application:

**Table 5.**

| | | | | |
|---|---|---|---|---|
| ☒ | The patient experience data that was submitted as part of the application include: | | | |
| | ☒ | Clinical outcome assessment (COA) data, such as | | |
| | | ☐ | Patient reported outcome (PRO) | |
| | | ☒ | Observer reported outcome (ObsRO) | 3.2, 6.1.7, 6.1.8, 6.1.11, 6.2.3, 6.2.11 |

| | | | | |
|---|---|---|---|---|
| | | ☒ | Clinician reported outcome (ClinRO) | 6.1.11.1, 6.2.11.1, 7.1.4, 7.2.4, 7.3.4 |
| | | ☐ | Performance outcome (PerfO) | |
| | ☐ | Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.) | | |
| | ☐ | Patient-focused drug development or other stakeholder meeting summary reports | | |
| | ☐ | Observational survey studies designed to capture patient experience data | | |
| | ☐ | Natural history studies | | |
| | ☐ | Patient preference studies (e.g., submitted studies or scientific publications) | | |
| | ☐ | Other: (Please specify) | | |
| ☐ | Patient experience data that were not submitted in the application, but were considered in this review | | | |
| | | ☐ | Input informed from participation in meetings with patient stakeholders | |
| | | ☐ | Patient-focused drug development or other stakeholder meeting summary reports | [e.g., Current Treatment Options] |
| | | ☐ | Observational survey studies designed to capture patient experience data | |
| | | ☐ | Other: (Please specify) | |
| ☐ | Patient experience data was not submitted as part of this application. | | | |

## 2. Clinical and Regulatory Background

### 2.1 Disease or Health-Related Condition(s) Studied

Factor X is a vitamin K-dependent clotting factor that is central to the series of enzymatic reactions that activates prothrombin and generates fibrin clot as part of the process of blood coagulation. Factor X deficiency is a bleeding disorder caused by the complete absence or deficiency of coagulation factor X in the blood stream. The degree of bleeding is inversely proportional to the level of factor X coagulation activity present in the plasma. Severe disease is defined by plasma factor X activity levels of <2% of normal. Moderate disease is defined by plasma factor X activity levels of 2-5%, and mild disease is defined by plasma factor X activity levels of between 5% and 20%. The gene for factor X is on chromosome 13. Since 50% of normal factor X is sufficient for normal blood clotting, a single gene defect is not associated with a bleeding disorder. Since it requires two defective factor X genes to have a bleeding disorder, factor X deficiency is a very rare disease; severe factor X deficiency is found in approximately one in one million people. Bleeding from deficiency of factor X manifests as hemarthrosis (joint bleeding), soft tissue hemorrhage (e.g., into muscle or brain), and mucosal bleeding (epistaxis, gastrointestinal bleeding, and menorrhagia in females). Umbilical stump bleeding is a common finding in infants with severe factor X deficiency. As expected, patients who are deficient in factor X will bleed excessively with surgery, dental extractions, and trauma. Literature suggests that factor X levels of 10-20% provide sufficient hemostasis for hemarthroses and soft tissue hemorrhage (Gailani and Neff, 2009), and levels of 35-50% are sufficient for major surgery (Brown and Kouides, 2008).

In the era of treatment with prothrombin complex concentrates (PCCs) it was inadvisable to exceed 50% factor X levels due to the risk for thrombosis or disseminated intravascular coagulation (DIC) that was common (Gailani and Neff, 2009).

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

Prior to development of the purified factor X concentrate COAGADEX, factor X deficiency was treated with fresh frozen plasma or prothrombin complex concentrates, neither of which have specified amounts of coagulation factor X.

Fresh frozen plasma (FFP). One IU of coagulation factor X is defined as the amount of factor X found in 1 ml of plasma, but there may be considerable variability in the factor X content between individual donors of plasma. FFP is usually not subject to viral inactivation (except solvent-detergent treated products) and due to the low factor X content, limitation on the volumes that can be administered without causing heart failure have limited factor X replacement to ~20% of normal, as a practical matter. Due to the presence of ABO antibodies, FFP must be cross matched to the recipient to prevent potentially fatal hemolysis.

Prothrombin complex concentrates (PCCs). PCCs are coagulation factor concentrates purified from plasma by ion exchange chromatography and contain variable amounts of vitamin K dependent clotting factors and inhibitors, namely factors IX, X, VII, and II, as well as anticoagulant proteins C and S. Prothrombin complex concentrates were developed in the 1960s for treatment of hemophilia B (factor IX deficiency) and have been labeled per their factor IX content. The amount of coagulation factors X and II are assumed to be approximately the same as factor IX; factor VII content is usually found in much lower quantity, except in so-called “four factor” PCCs, such as Kcentra, where the factor VII content is approximately equivalent to the factor IX content, and its content is specified on the label. PCCs have the advantage of minimal volume required to deliver high quantities of factor X, as well as extensive viral inactivation steps, making the risk of virus transmission negligible as a practical matter.

Factor IX/Factor X concentrate. A factor IX/factor X concentrate, known as Factor X P Behring is manufactured by CSL Behring and licensed for use in Europe (but not the United States).

***Reviewer Comment:*** *Notably, the Factor X P concentrate licensed in Europe does not provide a specific recommendation for prophylaxis/treatment of bleeding in factor X deficiency based on its demonstrated efficacy in clinical trials. The manufacturer (CSL Behring) suggests “Prophylactic treatment in infants and young children has been described in the literature, with up to 40 IU/kg of Prothrombin Complex Concentrates every 3 to 10 days (3) or 20 to 40 IU of Factor X per kg body weight once to twice a week (Auerswald 1998 and Auerswald 2006). Further, the factor X recovery is stated to be 1.5 IU/kl/IU/kg administered, resulting in the dosing formula:*

*Required units = body weight [kg] x desired factor X rise [% or IU/dl] x 0.7*

*This advice and empiric observation of the incremental recovery is similar to that seen for COAGADEX.*

## 2.3 Safety and Efficacy of Pharmacologically Related Products

Fresh frozen plasma may cause various adverse events, including acute infusion reactions, ranging in severity from mild febrile reactions, allergic reactions, or rarely anaphylaxis. Transfusion related acute lung injury (TRALI) may occur after FFP administration and its occurrence is not predictable or preventable. If large volumes of FFP are administered, transfusion associated cardiac overload (TACO) may ensue. Minor transfusion reactions can often be treated with acetaminophen or anti-histamines. More serious reactions may require use of high doses of systemic corticosteroids. Transfusion associated cardiac overload may be managed with diuretics.

There is risk for thromboembolic events with the use of PCCs, and some products of this class carry a black box warning of this possibility. With prolonged administration of PCCs (especially for perioperative management) prothrombin levels may accumulate to levels several times normal, due to its longer half-life than other vitamin K dependent clotting factors, and this may contribute to the thromboembolic risk.

***Reviewer comment:*** *Unlike FFP and PCCs, Coagadex is a factor X concentrate and it is anticipated that the some of the risks (for example, volume overload, thromboembolic events) associated with FFP and PCC are unlikely to occur.*

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

COAGADEX was licensed for use in the United States in 2015 based on data from Study Ten01, in which 16 subjects aged 12 to 58 years with moderate or severe factor X deficiency received a total of 468 infusions of COAGADEX for pharmacokinetic studies, on demand treatment of bleeding, and perioperative management for surgical procedures. Additional data on use of COAGADEX in humans for perioperative management of bleeding in two subjects with factor X deficiency from Study Ten03 were also reviewed.

BPL Study Ten05 was a retrospective survey of the use of COAGADEX in 15 patients, in clinical centers in Europe, the United Kingdom, the United States, and Turkey, from March 2011 to December 2015 (prior to licensure in the United States).

The data from BPL studies Ten01 and Ten05 describe all known use of COAGADEX in 31 humans prior to licensure and during licensure studies.

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

BPL commenced investigational studies of Coagadex on January 6, 2010 under IND 14235, submitted on December 7, 2009.

BPL Limited filed a Biologics License Application on July 10, 2013 to market Coagadex for a) Control and prevention of bleeding episodes in adults and children with hereditary factor X deficiency; and b) Peri-operative management in adults and children (aged 12 years and above) with hereditary factor X deficiency. This was approved on October 20, 2015.

BPL Limited made CMC post-marketing commitments to do the following:

1. Develop and qualify test methods to (b) (4) , and to provide the final study report to the FDA by October 31, 2016 (submitted October 26, 2016).

1. Conduct a study to implement (b) (4) (October 20, 2015). Study report was submitted April 4, 2017.

Coagadex was granted Orphan Designation by FDA on November 8, 2007 (07-2469) and has orphan drug exclusivity for treatment of adults and children 12 years of age and older through October 20, 2022. The current study (Ten 02) under consideration was done outside the United States, under a European Union Pediatric Investigational Plan and the Applicant represents that it meets the requirements for acceptance of a foreign clinical study not done under IND, as described in 21 CFR 312.120 (a) (1). The Applicant seeks priority review for this PAS efficacy supplement because Coagadex would be a significant improvement in the safety and effectiveness in a new subpopulation (pediatric) for treatment of hereditary factor X deficiency, a rare and serious condition (in accordance with FDA Guidance "Expedited Programs for Serious Conditions-Drugs and Biologics, May 2014").

Notably, FDA advised BPL Limited during a teleconference held on March 27, 2012 that it should conduct a pharmacokinetics study using factor X measurements at multiple time points after administration of COAGADEX, as part of its pediatric studies of the product. BPL submitted study Ten02 with a single time point measurement of factor X activity after administration of COAGADEX, with the explanation that multiple blood samples for a formal study of pharmacokinetics would be impractical to obtain, particularly in younger pediatric subjects.

BPL Limited made Clinical Post-Marketing commitments to do the following:

At the time of licensure BPL committed to evaluate the safety and efficacy of COAGADEX for perioperative management in patients with moderate to severe hereditary Factor X deficiency undergoing major surgical procedures in Study Ten06 (*A post-marketing registry study of perioperative management of moderate to severe hereditary factor X deficient patients receiving Coagadex (human factor X concentrate) for major surgical procedures)*.

A pre-submission meeting was not held for this efficacy supplement.

### 2.6 Other Relevant Background Information

Not applicable.

## 3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

### 3.1 Submission Quality and Completeness

For the most part, the submission was adequately organized and a complete clinical review could be conducted without unreasonable difficulty. The datasets were not submitted in CDISC format but accepted for filing as these were considered legacy data. Two tables of data describing bleeding events and bleeding history were found to be devoid of data and revised by the Applicant during the review cycle to provide the required information to complete the review.

3.2 Compliance With Good Clinical Practices And Submission Integrity

Study Ten02 was done under IND 14235. Applicant, through authorized US representative, declares on FDA from 3674 that "the requirements of 42 U.S.C. § 282(j), section 402(j) of the Public Health Service Act, apply to one or more of the clinical trials referenced in the application/submission which this certification accompanies and that the requirements of 42 U.S.C. 282(j), including any applicable provisions of 42 CFR part 11, have been met. Submitted in amendment 125506.46.1, received April 18, 2018. In addition, the clinical study reports of Ten 02 and Ten 05, document in Section 5.1 and 5.2 the details of how the researched conformed to GCP (in case of Ten 02) and General Epidemiological Practices (GEP) as with Ten 05.

An inspection conducted July 9, 2018 to July 13, 2018 of Great Ormand Street Children's Hospital (which accrued 6 of the 9 subjects) showed protocol deviations pertaining to entry of the actual versus nominal doses of COAGADEX in case report forms and missing vital signs at one visit. These discrepancies were judged not to have affected the safety of the study or its efficacy, and no action was indicated. Sheffield Children's Hospital (which accrued 2 of the 9 subjects) underwent inspection from July 16, 2018 to July 17, 2018 with no objectionable observations and no action was indicated.

**Protocol Deviations**
Two subjects at Great Ormand Street Children's Hospital in London were enrolled and treated for at least 50 exposure days, but they did not complete 26 weeks of observation as required by the protocol. These two subjects were re-enrolled and treated for an additional 26-week period with at least 50 exposure days of COAGADEX treatment.

***Review comment:*** *The re-enrollment of the two subjects is acceptable as the study treatment was re-initiated and completed per protocol without compliance issues in these two subjects. Therefore, inclusion of the efficacy data resulting from the re-enrollment in the primary analysis is acceptable.*

Protocol deviations were seen in three subjects who had lower doses of COAGADEX for the baseline factor X recovery study than prescribed in the protocol. Two were the subjects who each repeated 50 exposure days and completed 26 weeks of observation, per protocol. The third was a subject who had been on COAGADEX prophylaxis at a dose of 750 IU every 3 days on compassionate use basis prior to enrolling in the Ten02 study (Subject (b) (6). He was given his "usual" dose of 750 IU, which is 16.2 IU/kg, with approval of the Applicant, and continued that dose for prophylaxis for the entire 26-week observation period, without bleeding. At the end of study visit, he received the prescribed 50 IU/kg dose for determination of an incremental recovery. This subject was an outlier in the tabulated mean dose administered for prophylaxis (18.8 IU/kg, versus 33.3 to 47.4 IU/kg for the other eight unique subjects on the per protocol analysis set), however this was due to following an empiric practice that had led to successful prevention of bleeding prior to the Ten02 study, and was done with the Applicant's approval. This individual's experience should not change the recommended prophylactic dose calculated for the group (39.05 IU/kg, rounded to 40 IU/kg for the label/package insert).

Diary cards for Subject (b) (6) did not contain the actual number of vials administered. The Investigators entered the prescribed number of vials on the case report forms,

however, a later audit determined that two more unused vials were returned than expected (151 rather than 149 vials). This was deemed by the Applicant not to affect the conclusions of the study, as there was no breakthrough bleeding and the subject received more than 50 exposure days, as required by the protocol.

Inspection of sites 1 and 3 for Study Ten02 revealed no observations that affect the validity of the data, and no observations requiring action.

***Review comment:*** *The Applicant's inference that the two vial discrepancy (likely due to the subject not taking all prescribed doses) does not affect the conclusion of the study, is reasonable.*

3.3 Financial Disclosures

**Table 6.**

<table>
<tr><td colspan="3">Covered clinical study (name and/or number): StudiesTen02 and Ten05</td></tr>
<tr><td>Was a list of clinical investigators provided:</td><td>Yes X</td><td>No ☐ (Request list from applicant)</td></tr>
<tr><td colspan="3">Total number of investigators identified: 13<br><br>StudyTen02 Investigators:<br>Dr Ri Liesner<br>Dr Michael Gattens<br>Dr Jeanette Payne<br><br>Study Ten05 Investigators:<br>Dr Maria Teresa Alvarez<br>Dr Steven Austin<br>Dr Nuria Bermejo<br>Dr Martina Buhrlen<br>Dr Tulin Celkan<br>Dr James Huang<br>Dr Kaan Kavakli<br>Dr Karaman Kamuran<br>Dr Ri Liesner<br>Dr Patrick Mensah<br>Dr Jeanette Payne<br>Dr Cetin Timur<br>Dr Karaman Kamuran</td></tr>
<tr><td colspan="3">Number of investigators who are sponsor employees (including both full-time and part-time employees): 0</td></tr>
<tr><td colspan="3">Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0</td></tr>
<tr><td colspan="3">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)):<br><br>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____<br><br>Significant payments of other sorts: _____<br><br>Proprietary interest in the product tested held by investigator: _____</td></tr>
</table>

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

No Investigators were declared to have disclosable financial interests or arrangements with BPL, Limited, and none were employed by BPL, Limited.

## 4. Significant Efficacy/Safety Issues Related to Other Review Disciplines

### 4.1 Chemistry, Manufacturing, and Controls

BPL produces Coagadex in Elstree, UK, from source plasma obtained in the United States at FDA-licensed facilities. The bulk drug substance is subjected to viral inactivation by solvent/detergent extraction, nanofiltration, and dry heat treatment. The final drug product consists of a sterile, freeze-dried concentrate packaged in two nominal dose size vials (250 IU and 500 IU), to be reconstituted immediately prior to use with sterile water for injection, using a 510(k)-cleared device (Mix2Vial, K031861) to transfer the sterile water into the lyophilized COAGADEX product for reconstitution, and to transfer the reconstituted product into a syringe for administration. The reconstituted product contains factor IX and factor II as impurities in amounts not to exceed 1 IU/mL. Factor Xa content is controlled in the final product with a non-activated partial thromboplastin time release specification.

### 4.2 Assay Validation

Coagadex potency for manufacture is measured by a chromogenic substrate-based factor X activity assay, using a WHO 3rd International Standard for Factors II and X Concentrates as the reference standard.

Factor X activity for incremental recovery and trough levels for clinical trials Ten02 and Ten 03 were performed at a central laboratory operated by the Haematology Department at (b) (4) , using a one-stage clotting assay, and at local laboratories at each Investigator's site. Assay results from the central laboratory were used in the efficacy analysis and activity assay results from the local laboratories were used to adjust the dose based on peak and trough levels. There was good agreement between the central and local laboratory factor X levels (R2 = 0.98).

### 4.3 Nonclinical Pharmacology/Toxicology

FDA approved COAGADEX in December of 2015. The BLA review at the time of approval indicated the Pharmacology/Toxicology reviewer found the data submitted at that time adequate to characterize the pharmacology and pro-thrombotic activity of COAGADEX. Specific reference was made to single dose toxicity studies in rats in which a no-observed-effect-level (NOEL) of >2400 IU/kg body weight was established (>40-

fold safety margin), and 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, not significantly different to that of the physiological saline negative control.

### 4.4 Clinical Pharmacology

COAGADEX is a slow clearance protein/drug with a half-life of approximately 30 hours. See Dr. Iftekhar Mahmood's Clinical Pharmacology memorandum for detailed review.

#### 4.4.1 Mechanism of Action

Coagulation factor X is a vitamin K-dependent serine protease produced by hepatocytes in the liver, and secreted into the circulation as a zymogen precursor to its activated form, factor Xa. Factor X is activated by either activated factor IX (with factor VIII and phosphatidylserine as cofactors) or by activated factor VIIa (with tissue factor, its cofactor). Regardless of how factor X is activated, factor Xa (with factor V and phosphatidylserine) catalyzes the conversion of prothrombin to thrombin, the critical enzyme for generation of fibrin clot, activation of platelets, and simultaneous activation of other clotting factors and activation of inhibitors of coagulation such as proteins C and S. Accordingly, factor X has a central role in blood coagulation.

#### 4.4.2 Human Pharmacodynamics (PD)

Replacement of missing coagulation factor X activity is the basis for the therapeutic effect of COAGADEX. Factor activity levels is a PD measure of treatment with COAGADEX.

#### 4.4.3 Human Pharmacokinetics (PK)

*See Dr. Iftekhar Mahmood's review memo for complete Clinical Pharmacology review details.* The Applicant was advised by FDA during a teleconference in March 2015 to conduct a pharmacokinetics study in children that employed multiple time points to guide dosing in children. Instead, the Applicant conducted a study in which the incremental recovery of factor X activity at 30 minutes (IR30) was measured after an intravenous bolus of 50 IU/kg of COAGADEX was administered, and a trough level was obtained 72 hours later. The IR30 was compared for children in the age groups 0-5 years of age and 6-11 years of age. Though the Applicant modeled an elaborate set of pharmacokinetic parameters to describe the elimination of COAGADEX, including area under the curve 0-144 hours, clearance, volume of distribution at steady state, and maximum concentration, we rejected these since they were not based on multiple data points. In studies to support routine prophylaxis and treatment of breakthrough bleeding, the dosing proposed in the package insert is based on the starting dose in the study. The IR30 from the study, provides for estimated incremental recoveries in children, adolescent and adults to calculate doses based on desired (target) levels for major and minor surgeries..

The IR30 for children for the initial, baseline dose was found to be lower for both age groups (0-5 years and 6-11 years of age) compared to adolescent pediatric and adult

subjects studied in the original Ten01 licensing trial, but not significantly different between pediatric age groups, as below:

**Table 7.**
**Incremental Recovery 30 minutes after Standardized COAGADEX Dose**

| Age Group | 0-5 years Mean (n = 4) | 6-11 years Mean (n = 5) | 0-11 years Mean (n = 9) | Adults/ Adolescents Mean (n = 16) |
|---|---|---|---|---|
| IR30, IU/dl per IU/kg | 1.45 | 1.83 | 1.66 | 2.0 (Ten01 study) |

Similar IR30 values were seen, whether the two subjects who underwent repeat treatment cycles were included in the analysis, or not (ITT vs PP groups). The IR30 was repeated for each subject at the End-of-Study Visit 5, to look for evidence of inhibitor development to factor X, or any other cause for impaired recovery. The values for the End-of-Study measurement were the same or better than at the baseline, indicating there was no inhibitor development during the trial. One subject had been on compassionate use of COAGADEX prior to entry into Ten02, and had no bleeds when using 16.2 IU/kg doses for routine prophylaxis (7.5 ml of 500 IU nominal dose vial). He was allowed to use a dose of 18 IU/kg (7.0 ml of 600 IU nominal dose vial) for Study Ten02. His experience with routine prophylaxis prior to Study Ten02 is reported in Study Ten05.

***Reviewer Comment:*** *The chief utility of the IR30 determination was to examine the inhibitor issue, and additionally to serve as the basis for the coefficient to use in the formula to calculate the COAGADEX dose required to attain a desired factor activity level in children. The Ten02 study investigators were allowed to use the IR30 data (with peak and trough factor activity levels) to modify dosing of the subjects in the study. However, all routine prophylaxis dosing of the subjects (with one exception) was done using the suggested starting dose and not deviating from this value for the duration of the study. The IR30 was an experimentally determined measurement that indicates the recovery of factor X activity in children <12 years of age is less than that of adolescents and adults, and is consistent with the higher dose of COAGADEX that was given to these children in Study Ten02.*

4.5 Statistical

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

The analysis of these studies was limited to descriptive statistics; there was no *a priori* hypothesis proposed or tested.

4.6 Pharmacovigilance

A detailed formal pharmacovigilance plan was submitted as amendment 125506.46.2 (Effective date February 27, 2018, submitted to FDA April 19, 2018) to the BLA supplement. In that amendment, BPL Limited committed to routine pharmacovigilance activities, to include (from the amendment):

- Maintain systems and processes that ensure that information about all suspected adverse reactions that are reported to the personnel of the company is collected and collated in an accessible manner.
- Prepare reports for regulatory authorities:
    - Expedited Adverse Drug Reaction (ADR) reports
    - Periodic Safety Update Reports (PSURs)
- Conduct continuous monitoring of the safety profile of approved products including signal detection, issue evaluation, updating of labelling and liaison with regulatory authorities.

Pharmacovigilance activities will be conducted through the main pharmacovigilance site at Elstree, in the UK. At that site, individual case safety report forms from UK and overseas distributors, periodic safety update reports, trend analysis, and global safety-related inquiries from EMA, FDA, and other regulatory authorities will be processed.

Areas of concern to be monitored include hypersensitivity/infusion reactions, inhibitor antibody development, viral transmission, TSE transmission, and use in special populations (geriatrics, and pregnant/lactating females). There is empiric evidence of no infusion reactions or inhibitor development with the clinical data at hand, and the manufacturing process excludes human source plasma from regions where BSE has occurred, and incorporates screening and robust viral inactivation procedures against likely important blood borne pathogens (HIV, hepatitis A/B/C, parvovirus).

The pharmacovigilance measures described in amendment 125506.46.2 should be sufficient to address outstanding concerns.

## 5. Sources of Clinical Data and Other Information Considered in the Review

### 5.1 Review Strategy

This review focuses primarily on the multicenter, open-label, prospective safety, efficacy and PK trial in children <12 years of age with hereditary FX deficiency (trial Ten02). In addition, data from a retrospective data collection trial (Ten05) that included data on use of COAGADEX in some children (including perioperative management) was reviewed and included in the integrated analysis of efficacy (Section 7) and safety (Section 8).

**Table 8.**

| **Review Discipline** | **Reviewer** |
|---|---|
| Regulatory Product Manager | Yu Do |
| Clinical Review; BLA Chairman | Jay Lozier |
| Clinical Pharmacology | Iftekhar Mahmood |
| Labeling Review | Kristine Khuc |
| Statistical Review | Boris Zaslavsky |
| Pharmacovigilance/Epidemiology | Faith Barash |
| BIMO Review | Carla Jordan |
| Chemistry, Manufacturing, Controls | Mikhail Ovanesov |

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

One prospective clinical trial of COAGADEX was the principal study that served as the basis for review of the efficacy in children (Ten02). A second retrospective study of the use of COAGADEX prior to licensure (Ten05) provides additional evidence for safety

and efficacy of COAGADEX in children <12 years of age (Ten05), as well as in adults and adolescents with severe or moderate FX deficiency with severe bleeding phenotype. Three surgical procedures are described in Study Ten05 as well. The review of Ten02 will focus on prophylaxis in children, and the review of Ten05 will focus on supporting evidence for safety and prophylaxis in all age groups, as well as for on-demand therapy and perioperative management in adult and pediatric subjects with severe/moderate FX deficiency.

5.3 Table of Studies/Clinical Trials

**Table 9.**

**Studies Utilized in Clinical Review of COAGADEX**

| BPL Study | Title | Population/Indication sought | Reference |
|---|---|---|---|
| Ten02 | A Phase III Open-Label Multicentre Study to Confirm the Safety, Pharmacokinetics and Efficacy of BPL's High Purity Factor X in the Prophylaxis of Bleeding in Factor X Deficient Children Under the Age of 12 Years | Children < 12 years of age to evaluate the efficacy of routine prophylaxis and on-demand treatment.<br><br>Multi-center study in UK. | BLA Efficacy Supplement 125506.46.0 eCTD 5.3.4.2 Ten02 Study Reports of Uncontrolled Clinical Studies, Received March 23, 2018. |
| Ten05 | A Multicenter, Retrospective Data Collection Study on the Use of BPL's High Purity Factor X (COAGADEX®) in the Treatment of Patients with Hereditary Factor X Deficiency | Retrospective study of efficacy of routine prophylaxis in adults and perioperative management in children < 12 years. Provides safety of COAGADEX in patients of all ages. Multi-center study in UK, Spain, USA, Turkey, and Germany. | BLA Efficacy Supplement 125506.46.0 eCTD 5.3.4.4 Ten05 Other Study Reports. Received March 23, 2018. |

5.4 Consultations

The review of safety and efficacy of COAGADEX in children < 12 years of age did not require consultation outside the Review Team. Evaluation by PeRC was not required due to Orphan Designation conferred by FDA on November 8, 2007 (07-2469).

5.4.1 Advisory Committee Meeting (if applicable)

No Advisory Committee Meeting was deemed necessary for the review of this efficacy supplement, as no novel issues were presented by its use for in patients with congenital factor X deficiency, in particular, prophylaxis in children <12 years of age in the Ten 02 study, for perioperative management in children < 12 years of age in the Ten 05 study and in adolescents and adults in the Ten 05 study.

5.4.2 External Consults/Collaborations

No outside consultation was required for the review of this submission.

5.5 Literature Reviewed (if applicable)

Literature reviewed during the evaluation of this efficacy supplement included the following:

Auerswald G, Auberger K, Kurnik P, Heilmeier T, Münchow N. Therapy in eight children withcongenital Factor X deficiency. Blood 92 (10) Supplement 1: 358a; 1998.
*[Abstract on use of PCCs in factor X deficiency.]*

Auerswald D. Prophylaxis in Rare Coagulation Disorders – Factor X Deficiency. Thromb Res,118 (Suppl. 1): S29S31; 2006
*[Abstract on use of PCCs in factor X deficiency.]*

Brown DL, Kouides PA. Diagnosis and treatment of inherited factor X deficiency. *Haemophilia* 2008; 14: 1176–82.
*[Effective perioperative hemostasis may be achieved with factor X levels of 35-50%.]*

Factor X P Behring package insert, July 2010 revision.
*[Factor X P instructions for use, licensed in European Union.]*

Gailani D, Neff AT. Rare Coagulation Factor Deficiencies, chapter 137 in, *Hematology Principles and Practice*, Hoffman R, editor, 2009.
*[Describes effective hemostatic levels of 10-15% for hemarthroses and soft tissue bleeding. Advises against exceeding levels of 50% when using PCCs due to risk for thrombosis and DIC.]*

Khair K, Kumar P, Mathias M, Efford J, Liesner R. Sussessful use of BPL factor X concentrate in a child with severe factor X deficiency. *J Haemophilia Practice* 2014; 1: 8-10.
*[Case report of prolonged (>3 year) safe and effective routine prophylaxis with COAGADEX at 50 IU/kg dose given twice weekly. No bleeding or thrombosis under prophylaxis, with trough levels >13 IU/dL. Describes compassionate use experience of subject* (b) (6)*, prior to enrollment on study Ten02.]*

Lechler E. Use of Prothrombin Complex Concentrates for Prophylaxis and Treatment of BleedingEpisodes in Patients with Heriditary Deficiency of Prothrombin, Factor VII, Factor X, Protein C, Protein S, or Protein Z. Thrombosis Research 95: S39S50; 1999
*[Abstract on use of PCCs in factor X deficiency.]*

Roberts HR & White GC. Inherited Disorders of Prothrombin Conversion. In: Colman RW Hirsh J, Marder VJ, Clowes AW, George JN (eds): Hemostasis and Thrombosis – Basic Principles and Clinical Practice. 4th Ed., pp 839853, JB Lippincott Company, Philadelphia, 2001.
*[Advises against exceeding levels of 50% when using PCCs due to risk for thrombosis and DIC.]*

## 6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

### 6.1 Trial #1

Ten02: A Phase III Open-Label Multi-centre Study to Confirm the Safety, Pharmacokinetics and Efficacy of BPL's High Purity Factor X in the Prophylaxis of Bleeding in Factor X Deficient Children Under the Age of 12 Years

#### 6.1.1 Objectives (Primary, Secondary, etc)

Primary Analysis
The primary efficacy analysis is the Investigator's assessment of COAGADEX in reducing bleeding during routine prophylactic treatment over 6 months

#### 6.1.2 Design Overview

This was an open-label, multicenter, single-arm trial of prophylaxis of bleeding in children < 12 years of age with congenital factor X deficiency, over 26 weeks. Pharmacokinetics (immediate recovery at 30 minutes, IR30) is performed at study entry and at the end of the study (26 weeks) after at least 50 exposure days of treatment.

***Reviewer comment:*** *The single arm study design is consistent with efficacy studies of rare disease. The limitations of the design are addressed through pharmacokinetic information, use of target factor levels and success at achieving these levels during the study treatments.*

#### 6.1.3 Population

The Study Ten02 population was chosen according to the following parameters:

Inclusion Criteria
1. Subjects who had hereditary severe or moderate FX deficiency (FX:C <5 IU/dL, based on their lowest reliable FX:C recorded).
2. Subjects under 12 years old, whose parent/guardian gave written informed consent.
3. Subjects who had a history of severe bleeding (a minimum of one bleed with a bleed score of 3 or 4 [on the Vicenza Bleeding Score], Appendix VI of the study protocol) **or** a mutation in the F10 gene causing a documented severe bleeding phenotype

Exclusion Criteria
1. Subjects who had a history or suspicion of inhibitor development to FX.
2. Subjects who had thrombocytopenia (platelets <50 x $10^9$/L).
3. Subjects who had clinically significant renal disease (serum creatinine >200μmol/L).
4. Subjects who had clinically significant liver disease (serum ALT levels greater than three times the upper normal limit).

#### 6.1.4 Study Treatments or Agents Mandated by the Protocol

All Ten02 research subjects underwent a baseline pharmacokinetic study that consisted of intravenous injection of COAGADEX at a dose of 50 IU/kg body weight, followed by a plasma factor X activity level 30 minutes after administration to determine the immediate recovery at 30 minutes (IR30). The investigators were then instructed to administer COAGADEX two or three times weekly, by intravenous injection, and to adjust the dose to maintain a trough factor X activity level that was > 5% of normal, and to maintain a

peak factor X activity level of no more than 120% of normal. After 26 weeks and at least 50 treatments (exposure-days) to COAGADEX, the determination of the IR30 factor X level was repeated after a 50 IU/kg dose of COAGADEX injected intravenously to evaluate for neutralizing antibodies (IR30 would be expected to be reduced in the presence of neutralizing antibodies to FX).

The protocol recommended dose was 40-50 IU/kg twice weekly. The basis for this dosing recommendation was from the limited compassionate use experience in two subjects (aged 1 and 6 years). Additional changes to IU/kg dosing were to be made based on the IR assessments performed at the beginning of the study and factor X trough levels, measured locally.

6.1.5 Directions for Use

Investigators were instructed to administer COAGADEX at a dose of 40-50 IU/kg two or three times weekly, by intravenous injection, and to adjust the dose to maintain a trough factor X activity level that was > 5% of normal, and to maintain a peak factor X activity level of no more than 120% of normal, as determined by the local clinical laboratory. In the previous studies with FACTOR X in adults and adolescents aged 12 years and above, FACTOR X was administered at a suggested rate of 10 mL/min but no more than 20 mL/min. In this study, it was considered appropriate to use a lower infusion rate of up to 3 mL/min, as a precautionary measure in these subjects aged <12 years.

***Reviewer comment:*** *The lack of infusion reactions observed in the Ten02 study suggests that there is no need to modify the current label with respect to recommended infusion rates.*

6.1.6 Sites and Centers

The subjects were recruited and treated at one of three sites that participated in the study (all in the UK):

Site 01 Great Ormond Street Hospital, London
Site 02 Addenbrooke's Hospital, Cambridge
Site 03 Sheffield Children's Hospital, Sheffield

6.1.7 Surveillance/Monitoring

After screening and eligibility determination, subjects were treated on Visit 1 with the IR30 determination, then seen again at Visit 2, 72 hours later for the trough determination. Visit 3 for evaluation and trough determination occurred at week 2-4, and visit 4 for evaluation and trough determination occurred at weeks 5-6. A repeat weight assessment was done at week 16, for the purpose of adjusting the COAGADEX dose at the visit 5 assessment and IR30 and trough determination (End of Study Visit), which occurred at 6 months/26 weeks. Safety follow-up was conducted 28 days after the End of Study Visit, at which time severe adverse events were checked. Investigators recorded clinical study data and their evaluations in electronic Case Report Forms. Between visits, research subjects' parents or guardians completed diary cards to record information on bleeding or adverse events.

6.1.8 Endpoints and Criteria for Study Success

Primary Efficacy Endpoint

The primary endpoint used to meet the primary objective of Study Ten02 (assessment of efficacy of COAGADEX in reduction of bleeding compared to on-demand treatment when given as routine prophylaxis) was the Investigator's overall assessment of hemostatic efficacy.

Table 10, from Section 9.5.1.1 of the Ten02 Clinical Study Report describes the four-point hemostatic efficacy assessment scale used to evaluate study subjects' experience during the 26-week study period.

**Table 10.**
**Section 9.5.1.1 Criteria for Investigator's overall assessment of efficacy**

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

The efficacy endpoint analysis was applied to the Per-Protocol dataset (experience of 9 unique subjects treated with at least 50 exposure days of COAGADEX, evaluated for a full 26-week period).

The four-point hemostatic efficacy is limited by its subjectivity, however, there is no alternative method that has been validated for use in clinical research, and the FDA has accepted its use for licensure of many hemostatic products, including factor VIII and factor IX concentrates. The Applicant adapted the global 4-point hemostatic efficacy scale for use in assessment of various types of bleeding events for multiple secondary efficacy endpoints, as described below.

There were multiple secondary efficacy endpoints used to measure efficacy of COAGADEX for prophylaxis in Study Ten02. These included: number of bleeds per month (including severity, duration, location, and cause); factor X activity at trough levels; the factor X activity incremental recovery 30 minutes post-dose at baseline (Visit 1) and at the end of study visit (Visit 5); dose of COAGADEX used to treat bleeds; number of infusions to treat bleeding events; average monthly dose of COAGADEX for prophylaxis, treatment of bleeding, or management of surgery; the Investigator's assessment of hemostatic efficacy for individual bleeds (as for the primary efficacy assessment endpoint); and Parent/Guardians' assessment of efficacy of treatment of

bleeds, using the same four-point hemostatic efficacy scale as for the primary efficacy assessment endpoint).

The four-point hemostatic efficacy scale was adapted (prior to the study) for evaluation of overt bleeds, which included epistaxis, tongue/gum bleeds, hematemesis, hematuria, rectal bleeding and external wound bleeding due to injury. Overt bleeds were observed and rated at 12 and 24 hours. This is described in Table 11from Section 9.5.1.2.1 of the Ten02 Clinical Study Report, below:

**Table 11.**
**Section 9.5.1.2.1**
**Criteria for assessment of efficacy of FACTOR X* in treating an overt bleed.**

| **Category** | **Criterion** |
|---|---|
| Excellent | Bleeding stopped within 12 hours after dosing with FACTOR X only, with only 1 dose of FACTOR X required. |
| Good | Bleeding stopped within 24 hours after first dose of FACTOR X, and no more than 2 doses of FACTOR X were needed to stop bleeding. |
| Poor | Bleeding stopped after 24 hours after first dose of FACTOR X or more than 2 doses of FACTOR X were needed to stop bleeding, or there was no response to therapy. |
| Unassessable | FACTOR X was given but another replacement therapy given before a response to FACTOR X could be assessed. |
| Not Done | Efficacy was not assessed. |

*Applicant refers to COAGADEX as FACTOR X at various times in Study Report Ten02

The four-point hemostatic efficacy scale was adapted (prior to the study) for evaluation of menorrhagia as described in Table 12 from Section 9.5.1.2.1 of the Ten02 Clinical Study Report, below:

**Table 12**.
**Section 9.5.1.2.1**
**Criteria for assessment of efficacy of FACTOR X* in treating a menorrhagic bleed.**

| **Category** | **Criterion** |
|---|---|
| Excellent | No additional doses of FACTOR X required to maintain bleeding at a manageable level. |
| Good | 1 or 2 additional doses of FACTOR X required to maintain bleeding at a manageable level. |
| Poor | More than 2 doses of FACTOR X required to maintain bleeding at a manageable level or bleeding could not be maintained at a manageable level. |
| Unassessable | FACTOR X was given but before a response to FACTOR X could be assessed another replacement therapy given. |
| Not Done | Efficacy was not assessed. |

*Applicant refers to COAGADEX as FACTOR X at various times in Study Report Ten02

Covert bleeds were defined by the Applicant as melena, intra-peritoneal bleed, joint bleeds, muscle bleeds, intracranial hemorrhage, hematoma/bruising and internal

bleeding due to injury. Covert bleeds were assessed by various diagnostic/imaging methods, including CT/MRI, and clinical signs (for intracranial hemorrhage); pain, swelling, mobility and range of motion (for joint and muscle bleeds); and CBC parameters and occult blood testing (for gastrointestinal bleeds).

The modified 4-point hemostatic efficacy rating scale for treatment of covert bleeding event is shown in Table 13 from Section 9.5.1.2.1 of the Ten02 Clinical Study Report, below:

**Table 13.**
**Section 9.5.1.2.1**
**Criteria for assessment of efficacy of FACTOR X* in treating a covert bleed**

| **Category** | **Criterion** |
|---|---|
| Excellent | Bleeding resolved following 1 or 2 doses of FACTOR X. |
| Good | Bleeding resolved following 3 doses of FACTOR X. |
| Poor | Bleeding resolved following >3 doses of FACTOR X<br>OR<br>Bleeding did not resolve. |
| Unassessable-(FACTOR X dose given ) | FACTOR X was given but another replacement therapy given before a response to FACTOR X could be assessed. |
| Unassessable-(FACTOR X dose not given ) | FACTOR X was not given. Other replacement therapy was given. |
| Not Done | Efficacy was not assessed. |

*Applicant refers to COAGADEX as FACTOR X in Study Report Ten02

***Reviewer comment:*** *The Applicant's adaptation of the four-point hemostatic rating for assessment of various individual types of bleeding events is reasonable.*

Secondary Efficacy Endpoints
Secondary efficacy endpoints included the following:

- Number of bleeds per month, including severity, duration, location and cause.
- FX:C trough levels at all scheduled study visits and at all Bleed Assessment and Trough Measurement unscheduled visits.
- FX:C incremental recovery 30 minute post-dose at the Visit 1 (Baseline) and the End of Study Visit based on central laboratory results.
  The investigational medicinal product used in the study contains biologically active compounds which are also present endogenously, therefore the FX:C trough levels and incremental recovery are a surrogate for efficacy.
  Incremental recovery was defined as the rise in FX:C level recorded at 30 min (± 5 min)30 after the infusion divided by the actual dose administered.
- FX:C incremental recovery and trough levels following any change in dose regimen required for clinical reasons/insufficient trough levels.
- Dose of FACTOR X to treat a bleed (IU/kg) (including initial dose for new bleeds and any repeated doses for ongoing bleeds), number of infusions to treat a bleed anddose per infusion; all analysed on a per-bleed and a per-subject basis. For each value, summary tables were produced on a per bleed and a per subject basis.

- Total dose of FACTOR X in IU/kg, total number of infusions and average dose per infusion for: prophylactic use, to treat a bleed, any additional preventative use and overall use; all analysed on a per subject basis.
- Average monthly dose in IU/kg of FACTOR X, and average monthly number of infusions for: prophylactic use, to treat a bleed, any additional preventative use, any surgical use and overall use; all analysed on a per-subject basis.
- Investigators' assessment of efficacy as 'excellent', 'good', 'poor' or 'unassessable' in treating major bleeds or life-threatening break-through bleeds and excessive bleeding following injury . The bleed assessment criteria are detailed in Section 9.5.1.2.1 [of Ten02 Study Report].
- Parents'/Guardians' assessment of efficacy in treating all bleeds as 'excellent', 'good', 'poor' or 'unassessable'. All bleeds were assessed by the subject's parent(s)/ guardian(s) as detailed in Section 9.5.1.2.1.

6.1.9 Statistical Considerations & Statistical Analysis Plan

All statistical analysis of Study Ten02 was descriptive; no hypothesis testing was conducted. See Dr. Boris Zaslavsky's Biostatistics review memorandum for details. Safety was assessed in the intention to treat data set (11 treatment cycles in 9 unique subjects) and efficacy was assessed in the per protocol data set (9 treatment cycles in 9 unique subjects).

6.1.10 Study Population and Disposition

At the outset it was planned that a minimum of 8 and a maximum of 12 children less than 12 years of age would be enrolled in COAGADEX Study Ten02. Nine unique study subjects were enrolled in the study. Two subjects at the Great Ormand Street Children's Hospital (site 01) completed 50 exposure days of treatment but were not followed for the full 26-week observation period specified in the protocol, and therefore were re-enrolled in the trial for a second round of treatment with 50 exposure days and 26 weeks of follow-up, as indicated in the table below. The safety data was collected on all treatment given to all subjects (intention to treat group, N = 11) and the safety data was collected on all subjects who were treated (per protocol group, N = 9). All subjects screened were enrolled and treated, for Study Ten02. There were no withdrawals due to death or adverse event.

**Table 14.**

**Disposition of Ten02 Study Subjects**

| Subject Identifier | Age Group (years) | Intention to Treat (safety) Group? n = 11 | Per Protocol (efficacy) Group? n = 9 |
|---|---|---|---|
| (b) (6) | 0-5 | + | - |
| | 6-11 | + | + |
| | 0-5 | + | - |
| | 0-5 | + | + |
| | 6-11 | + | + |
| | 6-11 | + | + |
| | 0-5 | + | + |
| | 0-5 | + | + |
| | 6-11 | + | + |
| | 0-5 | + | + |
| | 6-11 | + | + |

** Subjects* (b) (6) *and* (b) (6) *were the same person.*
*** Subjects* (b) (6) *and* (b) (6) *were the same person*.
Source: FDA Clinical Reviewer

**Ten02:**
Prospective Study of COAGADEX for routine prophylaxis in children < 12 years of age.

Nine pediatric subjects > 12 years of age.

(b) (6)

6.1.10.1 Populations Enrolled/Analyzed

The nine unique subjects enrolled in Study Ten02 are likely representative of children with severe or moderate factor X deficiency. Due to the scarcity of the disease they are probably all such children known to live in England, where the study was conducted.

6.1.10.1.1 Demographics

Although all but two subjects in Study Ten02 were Asian, all had unique factor X mutations, which indicates that they were not related. In any event, there is no reason to believe that this should affect the results of the safety and efficacy of the product in children, given the pathophysiology of disease.

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

All but one of the nine subjects enrolled in this study had severe factor X deficiency (<2% factor X activity in plasma). The one moderate factor X deficiency subject (b) (6) had 2% factor X levels. All subjects enrolled in Study Ten02 had been exposed to coagulation factor X by prior treatment with factor X containing products, such as fresh frozen plasma or prothrombin complex concentrates. Subject (b) (6) had been on COAGADEX for prophylaxis of bleeding prior to enrolling in the Ten02 study. As such, all study subjects would be characterized as previously treated patients (PTPs), and at low risk for factor X inhibitor antibody development. Two subjects had documented mild iron deficiency anemia prior to entry into the study. One study subject (b) (6) had a prior, unrelated medical history of muscular dystrophy, and scoliosis and musculoskeletal abnormalities on the basis of that disorder. Another subject (b) (6) had an atrial septal defect at baseline that was documented by echocardiography. Six of the nine unique subjects had Portacath central venous access in place at the time of enrollment.

Lifetime bleeding history prior to entry into Study Ten02 is shown below (adapted from Ten02 Study Report listing 08.1):

**Table 15.**

**Summary of Lifetime Bleeding History Prior to Enrollment in Study Ten02**

| | | Location | | | | | | Cause | |
|---|---|---|---|---|---|---|---|---|---|
| ID | # | cut | joint | muscle | mucosa | other | menorrhagia | spontaneous | surgery/ injury |
| (b) (6) | 2 | 1 | | | | 1 | | 1 | |
| | 2 | | | | | 2 | | 2 | |
| | 1 | | | | | 1 | | 1 | |
| | 2 | | | | | 2 | | 2 | |
| | 1 | 1 | | | | | | 1 | |
| | 1 | | | | | 1 | | 1 | |
| | 3 | | | | 2 | 1 | 2 | 1 | |
| | 7 | 2 | 2 | 2 | | 1 | | 5 | 1 |
| | 2 | | | | | 2 | | 2 | |

**Bleeding events for* (b) (6) *occurred prior to participation in Ten05 or Ten02 studies.*

***Reviewer Comment:*** *The inclusion of the one moderate factor X deficiency subject* (b) (6) *in this study is unlikely to influence the results obtained, or their interpretation. In fact, that subject had a prior history of 7 bleeds (the highest of all nine subjects), of which 5 were spontaneous in character (also the highest of all nine subjects). Therefore, for the purpose of this study, the bleeding phenotype of this subject was equally severe as the other subjects' phenotype.*

6.1.10.1.3 Subject Disposition

Subject disposition in Study Ten02 is shown below. Note: two subjects enrolled in Study Ten02 were treated twice. The first six month treatment cycle did not count for per-protocol analysis because they were not followed for the entire six month period prescribed in the protocol. Note, the analysis of COAGADEX efficacy in these two subjects that is not part of the per-protocol treatment group is reported in Study Ten02 is reported in retrospective study Ten05.

6.1.11 Efficacy Analyses

In the Per-Protocol population (N = 9), prophylactic use with COAGADEX was rated as excellent by the Investigators for all subjects. The incremental recovery of factor X activity was successfully measured for all subjects. Other pharmacokinetic parameters were modeled on the basis of the measured recovery of factor X activity 30 minutes after administration of COAGADEX. Please see Dr. Iftekhar Mahmood's review memorandum for a detailed critique of the pharmacokinetic parameters that were modeled by the Applicant.

6.1.11.1 Analyses of Primary Endpoint(s)

The primary efficacy analysis on the Investigator's assessment of COAGADEX in reducing/preventing bleeding during routine prophylactic treatment over 6 months (26 weeks) in children < 12 years of age is detailed in Section 11.4.1 of the Ten02 Study Report. All subjects in the Per-Protocol group (n = 9) were judged to have an overall assessment of "Excellent" by the Investigators. The rating of Excellent was defined as 'no major or minor bleeds occurred or lower frequency of bleeds than expected, given the subjects medical/treatment history'.

For routine prophylaxis the efficacy assessment also includes measurement of the annual bleed rate (ABR) and the dose of COAGADEX administered, as in Table 16:

**Table 16.**

**Trial 1 Annualized Bleed Rates in children < 12 years old on Routine Prophylaxis**

| | 0-5 years (n = 4) | 6-11 years (n = 5) | Combined (n = 9) |
|---|---|---|---|
| # of bleeding events | 1 | 9 | 10 |
| Mean ABR | 0.5 | 3.6 | 2.2 |
| (Range) | (0 – 2) | (0-10) | (0-10) |
| Median ABR | 0 | 0 | 0 |
| Median dose (IU/kg) | 44 | 38 | 38 |

*No COAGADEX was administered for four of nine bleeds in 6 – 11 year age group

Source: Compiled from narratives in Section 16.4.1 of Study Ten02 (pp 1967-1979).

***Reviewer Comment:*** *The Applicant calculated bleeds per subject per month. We extrapolated this to bleeds per subject per year to be comparable to annual bleed rates for subjects with hemophilia, which is the benchmark we have used to judge efficacy. We asked the Applicant to place the ABR rate in the label rather than the per month bleed rate, to which they agreed. Two bleeds occurred due to trauma on the day of prophylaxis, which was given as scheduled.*

For on-demand therapy, in addition to the Investigator's global assessment of hemostatic efficacy, other assessments include the number of events, characterization as major or minor, and the dose of COAGADEX given to control bleeding, as below:

**Table 17.**

**Trial 1 Outcomes for on-demand treatment in children < 12 years**

| | 0-5 years (n = 4) | 6-11 years (n = 5) | Combined (n = 9) |
|---|---|---|---|
| # of bleeding events | 1 | 9 | 10 |
| Major bleeding events (n) | 0 | 5 | 5 |
| Spontaneous (%) | 0 (0%) | 3 (33%) | 3 (30%) |
| Traumatic (%) | 1 (100%) | 2 (22%) | 3 (30%) |
| Menorrhagia (%) | 0 (0%) | 4 (44%) | 4 (40%) |
| Excellent Outcome (%) | 0 (0%) | 3 (33%) | |
| FX not given (%) | 1 (100%) | 6 (67%) | |
| Median dose in IU/kg per bleeding episode(Range) | NA | 38 (24.6-40.5) | 38 (24.6-40.5) |
| Number of infusions required to achieve excellent/good hemostasis | | | |
| 1 infusion | 0 | 3 | 3 |

Treatment of Bleeds: Three subjects had a total of ten bleeds during the six month study period. Only four bleeds in two subjects were deemed to require treatment separate from scheduled prophylaxis) and each was treated successfully with one dose of COAGADEX. Parents or guardians rated the hemostatic efficacy of COAGADEX as "Excellent" for three bleeds; the remaining bleed(menorrhagia) was not assessed for hemostatic efficacy.

6.1.11.2 Analyses of Secondary Endpoints

Secondary Efficacy Analysis (page 57 of Ten02 study report):
The secondary efficacy endpoints were parameters as described in Section 9.5.1.2 and summarized below:

- Number of bleeds per month, were summarized on a per subject basis. Severity, duration, location, and cause of bleeds were to be summarized on a per bleed basis. In the final analysis, all the summaries were not generated; see Section 9.8.2 for more details.
- FX:C trough levels at all scheduled and unscheduled visits. (detailed in Section 9.7.4).
- Factor X incremental recovery at scheduled and unscheduled visits (detailed in Section 9.7.4)
- Dose of FACTOR X to treat a bleed (IU/kg), including for new bleeds and ongoing bleeds, the number of infusions to treat a bleed and dose per infusion. For each value, summary tables were produced on a per bleed and a per subject basis.
- The total dose of FACTOR X (IU/kg), number of infusions and average dose per infusion for: prophylactic use, to treat a bleed, any additional preventative use and overall use. For each value and for each cause and overall, summary tables were produced.
- Average monthly dose in IU/kg of FACTOR X, and average monthly number of infusions for: prophylactic use, to treat a bleed, any additional preventative use, any surgical use and overall use. For each value and for each cause and overall, summary tables were produced.
- Bleed assessments conducted by the subject's parents/guardians and the Investigators were presented on a per bleed and per subject basis.

Bleeding Events: Ten bleeds were reported in 3 of the 9 subjects in the Per-Protocol group. Three were major, six were minor, and one was not assessed. Four of the ten bleeds were controlled with a single dose of COAGADEX. These included spontaneous mucosal bleeding, traumatic bleeding from a cut, and menorrhagic bleeding.

Bleeding Episodes per Year (ABR): Bleeding episodes per month were calculated by the Applicant from the data (10 bleeds in 9 subjects in Per-Protocol group over 6 month observation period). See Table 18 below, adapted from Study Ten02 Study Report Table 25 in Section 11.4.2.5.

**Table 18.**

**Trial 1 Annual Bleed Rate (ABR)**

| Total # Bleeds | Total # Subjects | Bleeds/Subject/Year (ABR) |
|---|---|---|
| 10 | 9 | 2.1 |

Trough levels: Factor X trough activity measurements were done on 45 occasions throughout the Ten02 study period (Baseline/Visit 1, Visits 2, 3, 4, and End of Study/Visit 5). Trough levels remained above the 5% target inn 91% of all determinations for the Per-Protocol group, overall. See Table 19 below, adapted from Table 5.1.3 in Ten02 Study Report:

**Table 19.**

**Trial 1 Trough Factor X Activity Levels**

| | Age Group | | |
|---|---|---|---|
| | 0-5 (n =4) | 6-11 years (n = 5) | Overall (n = 9) |
| FX Activity ≥5% | 18 (90) | 23 (92) | 41 (91.1) |
| FX Activity <5% | 2 (10) | 2 (8) | 4 (8.9) |

***Reviewer's comment:*** *The dosing regimen used for prophylaxis achieved the target trough levels in the overwhelming majority of subjects.*

Factor X Activity Incremental Recovery: The incremental recovery of factor X activity was determined by measuring factor X activity 30 minutes after administration of 50 IU/kg of COAGADEX (IR30) at baseline (Visit 1) and at the End of Study visit (Visit 5). Similar values were obtained for each age group and for Baseline and End of Study determinations.

**Table 20.**

Trial 1 Incremental Recovery 30 minutes after 50 IU/kg COAGADEX

| Age Group, years | Baseline | End of Study | Mean |
|---|---|---|---|
| 0-5 (n = 4) | 1.61 | 1.70 | 1.65 |
| 6-11 (n = 5) | 1.83 | 1.99 | 1.91 |
| Overall (n = 9) | 1.71 | 1.83 | 1.77 |

Source: Data presented in Applicant's Ten02 study report for actual COAGADEX dose, subject weight, and pre- and post-dose factor X activity level measured in plasma.

***Reviewer's comment:*** *The Applicant calculated IR30 values on the subjects treated per-protocol. The values shown in Table 5 were calculated by the reviewer from the intention to treat subjects, meaning all measurements of the IR30 were included, since the IR30 is an experimentally measured value that is not a measure of efficacy nor a pivotal endpoint. This was done for this review to improve the reliability since the population is very small for this rare disease. Nearly identical values were obtained whether the intention to treat or per protocol subject data set was used. The Applicant calculated a highly significant difference in IR30 for the 0-5 year age group compared to the 6-11 year age group, and the overall group of children age <12 years had a significantly lower IR30 than the adult and adolescent subjects reported in Study Ten01 (the licensure trial). The coefficient for the formula to achieve a desired target factor X activity level in the package insert is the reciprocal of the IR However, the difference in coefficients between the age 0-5 year group and the 6-11 year group is significant only if the per protocol 0-5 year age group is considered. The coefficient for the 0-5 year group is the same as that for the 6-11 year age group if the intention to treat group is considered. Since including repeat measurements on these two subjects (of four unique subjects) causes the coefficient to no longer be different, it indicates that any analysis of the four per protocol subjects is not robust enough to justify a different coefficient than for the 6-11 year old group. Therefore, the Applicant's proposal to use a dosing coefficient of 0.6 (based on data from all children <12 years of age) is reasonable.*

Number of Infusions and Dose Per Subject. A total of 559 infusions of COAGADEX were administered to 9 subjects in the Per-Protocol population, of which 537 were for routine prophylaxis, 4 were for treating bleeds, and 18 were bolus doses at Visit 1 (Baseline) and End of Study.

Starting Dose, Infusions per Week, and Changes to Dose. Table 21 shows the starting dose, infusions per week, changes to dose, and deviations from target range of 5-120% specified in protocol, during 26 weeks of prophylaxis.

**Table 21.**

**Starting Dose, Infusions per Week, Changes, and Deviations from FX Target**

| Subject | Starting Dose | Dose Change? | Infusions per Week | Trough FX <5% | Peak FX > 120% |
|---|---|---|---|---|---|
| (b) (6) | 45 | none | 2.4 | 0 | 0 |
| | 40 | increase to 50 | 2.3 | 0 | 2 (136%, v1, 144%, v5) |
| | 40 | none | 2.4 | 0 | 0 |
| | 45 | none | 2.4 | 0 | 1 (125%, v1) |
| | 40 | none | 2.6 | 0 | 0 |
| | 42 | none | 2.4 | 0 | 1 (136%, v1) |
| | 40 | none | 2.4 | 0 | 0 |
| | 40 | none | 2.3 | 0 | 0 |
| | 43 | none | 1.8 | 0 | 0 |
| | 48 | decrease to 45 | 2.2 | 1 (4%, v4) | 0 |
| | 18 | none | 2.3 | 0 | 0 |

* Denotes same individual. Factor X activity levels are from local laboratory.
v = visit

Table 21 indicates that the nine subjects (two treated twice) had remarkably stable dosing of COAGADEX during the course of their 26 weeks of prophylaxis. One subject (b) (6) increased from 40 IU/kg for no clear reason during the study (no bleeding), and notably had peak factor X activities >120% at the PK analyses done at the beginning and end of the study. Another (b) (6) had a decrease from 48 to 45 IU/kg solely due to a change in weight measured mid-study; the absolute dose of COAGADEX remained unchanged; the marginally low trough value of 4% was not associated with bleeding. Subject (b) (6) had been on prophylaxis at a dose of 16 IU/kg prior to enrolling, and was permitted to continue this dose during the study (adjusted up to 18 IU/kg, due to larger vial size).

***Reviewer Comments:*** *The dosing for prophylaxis remained essentially unchanged for almost all subjects, and the frequency of treatment was 2.3 times per week, on average, with little deviation. The deviations from the target were modest and not associated with bleeding or thrombosis. A weight adjusted prophylactic dose of 40 IU/kg, twice weekly for children < 12 years of age, as requested by Applicant should ensure adequate prophylaxis and low risk for being outside the target factor X levels.*

6.1.11.3 Subpopulation Analyses

The sample size for Study Ten02 was too small to allow for any meaningful subgroup analyses. The numbers for the 0-5 year, and 6-11 year age groups are so small (n = 4 and n = 5, respectively) that even the differences found between age groups are not likely meaningful.

6.1.11.4 Dropouts and/or Discontinuations

Dropouts and Discontinuations: There were no subjects who dropped out, for any reason.

Missing Data:
With regard to missing data, one subject who received COAGADEX for menorrhagia did not have an assessment of hemostatic efficacy. One subject (b) (6) who had the greatest number of bleeds (both spontaneous and traumatic) had two bleeds of unknown duration, however, these both were minor in severity and not treated with COAGDEX in any event. Overall, these missing data do not prevent assessment of efficacy of COAGADEX.

***Reviewer Comment:*** *All 4 treatments for breakthrough menorrhagia were accomplished with single doses of COAGADEX. The fact that this patient didn't receive a second dose or concomitant hemostatic treatment is an indirect indicator that hemostasis was successful with COAGADEX.*

6.1.11.5 Exploratory and Post Hoc Analyses

Exploratory analyses were not performed.

6.1.12 Safety Analyses

6.1.12.1 Methods

In Study Ten02, adverse events (AEs) were coded by using Medical Dictionary for Regulatory Activities (MedDRA), Version 19 and are analyzed based emergence during the 26 week treatment period with COAGADEX. All safety analyses are based on the safety (intention to treat) population, consisting of all eleven treatment periods for the nine unique subjects enrolled in Study Ten02 (two subjects were treated for two cycles). Causality (unrelated, unlikely, possible, probable, very likely/certain) was assessed by the investigator. In retrospective Study Ten05, adverse events possibly, probably, or very likely/certainly related to COAGADEX treatment that occurred prior to enrollment were included in the medical history listing, and listed as separate adverse events.

6.1.12.2 Overview of Adverse Events

Among the nine unique subjects, evaluated over 11 treatment cycles (intention to treat data set) eight subjects experienced 28 treatment emergent adverse events, none of which were related to the study product, COAGADEX. Two serious adverse events were seen in one subject (b) (6) in which there was a lower respiratory tract infection (moderate severity), and a later episode of influenza (mild severity); these were deemed serious because they required hospitalization. Both resolved completely and were not related to administration of COAGADEX. The majority of adverse events were mild (93%) or moderate (7%) in severity. There were no severe adverse events. The most common adverse events were pyrexia, bacterial or viral infections, rhinitis, nasopharyngitis or coughs, and adverse events skewed toward the younger (0-6 years) age group (20 of 28 events) compared to the older (6-11 years) age group.

***Reviewer's Comment:*** *The adverse events were unremarkable for children of this age group and do not suggest any safety issues for the product, COAGADEX.*

**Table 22.**

**Summary of treatment-emergent adverse events by MedDRA system organ class and preferred term**

| System Organ Class<br>Preferred Term | Number (%) of subjects<br>N=9 | Number (%) of AEs<br>n=28 |
|---|---|---|
| Any AE | 8 (88.9) | 28 (100%) |
| **Blood and lymphatic system disorder** | **1 (11.1%)** | **1 (3.6%)** |
| Anemia | 1 (11.1%) | 1 (3.6%) |
| **General disorders and administration site conditions** | **3 (33.3%)** | **4 (14.3%)** |
| Pyrexia | 3 (33.3%) | 4 (14.3%) |
| **Infections and infestations** | **5 (55.6%)** | **10 (35.7)** |
| Bacterial Disease Carrier | 1 (11.1%) | 1 (3.6%) |
| Lower Respiratory Tract Infection | 1 (11.1%) | 1 (3.6%) |
| Nasopharyngitis | 3 (33.3%) | 4 (14.3%) |
| Rhinitis | 1 (11.1%) | 1 (3.6%) |
| Influenza | 1 (11.1%) | 1 (3.6%) |
| Viral Infection | 2 (22.2%) | 2 (7.1%) |
| **Investigations** | **1 (11.1%)** | **1 (3.6%)** |
| Temperature Elevation | 1 (11.1%) | 1 (3.6%) |
| **Metabolism and nutrition disorders** | **1 (11.1%)** | **2 (7.1%)** |
| Decreased Appetite | 1 (11.1%) | 2 (7.1%) |
| **Musculoskeletal and Connective Tissue Disorders** | **2 (22.2%)** | **3 (10.7%)** |
| Pain in Extremity | 2 (22.2%) | 3 (10.7%) |
| **Nervous System Disorders** | **2 (22.2%)** | **2 (7.1%)** |
| Headache | 1 (11.1%) | 1 (3.6%) |
| Lethargy | 1 (11.1%) | 1 (3.6%) |
| **Reproductive System and Breast Disorders** | **1 (11.1%)** | **1 (3.6%)** |
| Dysmenorrhea | 1 (11.1%) | 1 (3.6%) |
| **Respiratory, Thoracic, and Mediastinal Disorders** | **3 (33.3%)** | **3 (10.7%)** |
| Cough | 3 (33.3%) | 3 (10.7%) |
| **Skin and Subcutaneous Tissue Disorders** | **1 (11.1%)** | **1 (3.6%)** |
| Vitiligo | 1 (11.1%) | 1 (3.6%) |

6.1.12.3 Deaths

There were no deaths in subjects studied on COAGADEX clinical studies Ten02.

6.1.12.4 Nonfatal Serious Adverse Events

There were no serious adverse events encountered during the study of COAGADEX for congenital factor X deficiency in children < 12 years of age (Ten02

6.1.12.5 Adverse Events of Special Interest (AESI)

There were no infusion reactions or thrombotic events during the 26-week observation period, nor was there diminished recovery of factor X after 50 exposure days of treatment and 26 weeks of observation to suggest neutralizing antibodies (inhibitors) to factor X in study Ten02. No factor X inhibitors were detected in the clinical laboratory by formal assay using a (Nijmegen-modification of the Bethesda inhibitor assay) before or after 50 exposure days of treatment and 26 weeks of observation in study Ten02.

6.1.12.6 Clinical Test Results

There was mild, iron deficiency anemia noted in two subjects, not related to COAGADEX treatment, likely due to underlying factor X deficiency and prior bleeding history in two subjects. There were trivial, transient elevations of total bilirubin and trivial, depressions of serum alkaline phosphatase, creatinine, urea, potassium, and eosinophil counts in several subjects; none were thought to be clinically significant or related to COAGADEX treatment. No laboratory markers of thrombosis (i.e., D-dimer, fibrin split products) were performed in this pediatric study.

6.1.12.7 Dropouts and/or Discontinuations

There were no discontinuations or dropouts due to adverse events on Study Ten02. However, due to administrative error, two subjects who each had 50 exposure days to COAGADEX but fell short of the minimum 26 weeks of observation were re-enrolled in this study, and each underwent an additional 50 exposure days of treatment with COAGADEX and completed the required 26 weeks of observation to complete the study, per protocol. Thus, there were nine unique subjects, with eleven treatment cycles. This had no impact on our ability to interpret the data, nor did it call into question any results obtained from Study Ten02.

6.1.13 Study Summary and Conclusions

Study Ten02 provides data on safety and efficacy of COAGADEX as routine prophylaxis of bleeding in children < 12 years of age. Overall efficacy was judged to be Excellent by Investigators who evaluated 9 unique subjects treated with adjusted dose prophylaxis to keep factor X activity levels between 5% and 120% of normal. Annual bleeding rates were approximately 2 per subject per year, which compares favorably with annual bleeding rates observed in prophylaxis of bleeding with factor VIII and factor IX concentrates in hemophilia A and B. Incremental recovery data obtained in this study indicates that the recovery of factor X activity was less than that for adults taking COAGADEX, which guides dosing instructions for pediatric subjects. No adverse events attributable to use of COAGADEX were observed, particularly infusion reactions, thromboembolic events, and development of inhibitors of factor X.

6.2 Trial #2

Ten05: A Multicenter, Retrospective Data Collection Study on the Use of BPL's High Purity Factor X (COAGADEX®) in the Treatment of Patients with Hereditary Factor X Deficiency

6.2.1 Objectives (Primary, Secondary, etc)

Primary Objectives. The primary objectives are to collect retrospective data on the compassionate use of FACTOR X in adult and pediatric subject for the treatment of the following:

- bleeding episodes.
- routine prophylaxis.
- peri-operative management.
- other short-term preventative use.

Secondary Objective. The secondary objective was to collect data on any adverse drug reactions and serious adverse drug reactions.

6.2.2 Design Overview

This was a retrospective, multicenter, effort to collect data on the safety and efficacy of COAGADEX administered under provisions of compassionate use prior to licensure in December of 2015.

6.2.3 Population

In Study 2, subjects of any age were eligible for inclusion if they had hereditary factor X deficiency and administered at least one dose of COAGADEX prior to its licensure in December 2015. It was intended to enroll 16 subjects, and 15 subjects were eventually enrolled with informed consent from themselves, or a parent or guardian, as applicable.

6.2.4 Study Treatments or Agents Mandated by the Protocol

Subjects on routine prophylaxis received a starting dose of 25 IU/kg of COAGADEX, once or twice weekly, adjusted at the discretion of the Investigator. Bleeds that occurred during routine prophylaxis, or during on-demand therapy were treated with 25 IU/kg COAGADEX until the bleeding stopped. Surgical procedures were covered with treatment plans at the discretion of the Investigator.

***Reviewer Comment on Dose Interval**: Adult and adolescent subjects received median dose of 26.4 IU/kg, with most subjects receiving a once weekly dose. The recommended dose of 25 IU/kg twice weekly for adults and adolescents is adequate based on the median dose administered in the study and the half-life of the product.*

6.2.5 Directions for Use

The reconstituted solution was given through intravenous infusion at a suggested rate of 10 mL/min but no more than 20 mL/minute. Treatment included on-demand, short-term preventative, and routine prophylactic treatment regimens, at the discretion of the Investigator. Peri-surgical hemostatic cover was also permitted.

6.2.6 Sites and Centers

Twelve sites participated in Study 2. These include the following centers and Co-ordinating Investigators:

Spain:

Investigator Site 51: Dr Maria Teresa Alvarez, Hospital Universitario La Paz, Madrid.
Investigator Site 52: Dr Nuria Bermejo, Hospital San Pedro de Alcantara, Caceres.

USA:

Investigator Site 56: Dr. James Huang, UCSF Pediatric Hematology/Oncology, San Francisco.

Turkey:

Investigator Site 57: Dr Kaan Kavakli, Ege Universitesi Tip Fakultesi, Bornova, Izmir.
Investigator Site 58: Dr Karaman Kamuran, Yizuncu Yil University Kampusu, Van.
Investigator Site 59: Dr Tulin, Celkan Istanbul University Cerrahpasa School of Medicine, Istanbul
Investigator Site 60: Dr Cetin Timur, Istanbul Göztepe Training & Research Hospital, Istanbul.

Germany:

Investigator Site 61: Dr Martina Buhrlen, Klinikum Bremen-Mitte, Bremen.

UK:

Investigator Site 53: Dr Steven Austin, St George's NHS Healthcare Trust, London.
Investigator Site 54: Dr Patrick Mensah, Leicester Royal Infirmary Leicester.
Investigator Site 62: Dr. Ri Liesner, Great Ormond Street Hospital NHS Foundation Trust, London
Investigator Site 63: Dr Jeanette Payne, Sheffield Children's Hospital, Sheffield.

6.2.7 Surveillance/Monitoring

For Study 2, the Applicant received reports of adverse drug reactions in real time under the provisions of compassionate use. Charts were reviewed and electronic case report forms were generated retrospectively for safety and efficacy endpoints by the investigators.

6.2.8 Endpoints and Criteria for Study Success

Efficacy Endpoints:

Primary:

• *For routine prophylaxis with FACTOR X*: number of bleeds per year and per month, per subject (including severity, location and cause) and total dose (IU and IU/kg) per year and per month, per subject.
• *For on–demand treatment with FACTOR X*: the Investigator's retrospective assessment of FACTOR X efficacy in treating each bleed (assessment criteria were 'effective', 'not effective', or 'unknown') and the dose of FACTOR X, IU and IU/kg, to treat a bleed.
• *For both treatment regimens*, the Investigator's retrospective assessment of the overall efficacy of FACTOR X throughout the compassionate use period (assessment criteria were 'excellent', 'good', 'poor' or 'unassessable').

Other:

• *For routine prophylactic use:*
  - dose of FACTOR X, IU and IU/kg, per year and per month, per subject.
  - number of infusions per year and per month, per subject.
  - average dose of FACTOR X, IU and IU/kg FX:C, per infusion.
  - number of exposure days (EDs) per year and per month, per subject.
• *For short-term preventative use*
  - dose of FACTOR X (IU and IU/kg) per year and per month, per subject.
  - number of infusions per year and per month, per subject.
  - average dose of FACTOR X (IU and IU/kg) per infusion.
  - number of exposure days overall per year and per month, per subject.

- *For bleeding episodes*
  - dose of FACTOR X, IU and IU/kg, to treat a bleed per year and per month, per subject and per bleed.
  - number of infusions per year and per month (analyzed on a per subject and per bleed basis).
  - dose of FACTOR X, IU and IU/kg per infusion.
  - number of exposure days overall per year, per month and per subject.
- *For peri-surgical hemostatic cover usage*
  - pre-surgery dose and total dose of FACTOR X, IU and IU/kg, to prevent peri-surgical bleeding per subject and per procedure.
  - total number of infusions per procedure, per subject.
  - dose of FACTOR X, IU and IU/kg, per infusion.
  - investigator's assessment of peri-operative wound bleeding.
- *For total FACTOR X usage*
  - dose of FACTOR X, IU and IU/kg, for all subjects; and per year and per month, per subject.
  - number of infusions for all subjects; and per year and per month, per subject.
  - dose per infusion when FACTOR X is used for routine prophylaxis, preventatively, perisurgically and on-demand.
  - number of exposure days for all subjects; and per year and per month, per subject for subjects who did not undergo surgery.
  - in the event the subject has a positive result on an inhibitor test, the number of exposure days to this point.

Safety Endpoints:

Primary:

Adverse drug reactions (ADR) and Serious adverse reactions (SAR).
Depending on the extent of retrospective data collected, the following analyses were considered:

- FX:C trough levels.
- Incremental recovery

6.2.9 Statistical Considerations & Statistical Analysis Plan

All statistical analysis of Study Ten05 was descriptive; no hypothesis testing was conducted. See Dr. Boris Zaslavsky's Biostatistics review memorandum for details. All 15 subjects were included in an intention to treat (ITT) study population for safety and efficacy analyses.

6.2.10 Study Population and Disposition

At the outset it was planned that about 16 subjects of any age with factor X deficiency who had administered at least one dose of COAGADEX would be enrolled in COAGADEX Study Ten05. Fifteen subjects were enrolled in the study. Two subjects were enrolled in Study Ten05 and subsequently participated in Study Ten02. This includes Ten05 study subject (b) (6) who later enrolled in Ten02 as study subjects (b) (6), respectively. The safety data was collected on all treatment given to all subjects (intention to treat group, N = 15). All subjects screened were enrolled and treated, for Study Ten05. There were no withdrawals due to death or adverse event.

**Table 23.**

| Disposition of Ten05 Study Subjects (all Intention to Treat Group) | | | | |
|---|---|---|---|---|
| **Subject Identifier** | **Age Group (years)** | **Routine Prophylaxis n = 8** | **On-Demand* n = 11** | **Surgery n = 3** |
| (b) (6) | ≥ 18 | + | | |
| | ≥ 18 | + | | |
| | ≥ 18 | + | + | + |
| | ≥ 18 | | + | |
| | ≥ 18 | | + | |
| | 12 - 17 | + | + | + |
| | ≥ 18 | + | + | |
| | ≥ 18 | | + | |
| | 12 - 17 | | + | |
| | ≥ 18 | | + | |
| | 12 - 17 | | + | |
| | 12 - 17 | | + | |
| | 12 - 17 | + | + | |
| | 6 – 11 | + | | |
| | 0 – 5 | + | | + |

* *Some subjects were treated on-demand, only, or on-demand during routine prophylaxis, or alternated between on-demand and routine prophylaxis.*
** *Subject* (b) (6) *participated in Study Ten02 as subject* (b) (6)
*** *Subject* (b) (6) *participated in Study Ten02 as subject* (b) (6)

Source: FDA Clinical Reviewer, compiled from Ten05 study report narratives and listing 02.3: Demographics (page 804 of Ten05 study report).

6.2.10.1 Populations Enrolled/Analyzed

The Applicant planned to enroll 16 subjects of any age with factor X deficiency who they knew to have administered at least one dose of COAGADEX in Study Ten05. Fifteen of subjects who had received COAGADEX under compassionate use were enrolled, and one pediatric subject who had received COAGADEX under compassionate use refused to participate in Study Ten05. and 15 subjects were enrolled in the study. This includes two pediatric subjects who later participated in Study Ten02. The pediatric subject in Ten02 had received COAGADEX on a compassionate use basis, but declined to be enrolled in retrospective study Ten05 did provide data on COAGADEX use on compassionate use basis as part of the baseline assessment for Study Ten02.

***Reviewer Comment:*** *Study Ten05 appears to capture all but one subject who used COAGADEX on compassionate use basis prior to licensure, and the subject missing from Study Ten05 provided that data on COAGADEX use and bleeding during Study Ten02, so the Applicant's dataset is representative of the compassionate use of COAGADEX prior to licensure.*

6.2.10.1.1 Demographics

**Table 24.**

| **Demographics of the Ten05 Study Population, Intention to Treat Subjects** | | | | |
|---|---|---|---|---|
| **Subject Characteristic** | **0-5-year-old group (N = 1)** | **6-11-year-old group (N = 1)** | **≥12-year-old group (N = 13)** | **Overall (N = 15)** |
| **Age (years)** | | | | |
| Average (± STD)<br>Range | 1<br>1 - 1 | 6<br>6-6 | 22.8<br>13 – 43 | 20.3<br>1 – 43 |
| **Sex** | | | | |
| Female | 0 (0%) | 1 (100%) | 7 (54%) | 8 (53%) |
| Male | 1 (100%) | 0 (0%) | 6 (46%) | 7 (47%) |
| **Race** | | | | |
| Asian | 1 (100%) | 0 (0%) | 2 (15%) | 3 (20%) |
| Caucasian | 0 (0%) | 1 (100%) | 11 (85%) | 12 (80%) |
| **Severity of Factor X Deficiency** | | | | |
| Severe | 0 (0%) | 1 (100%) | 11 (85%) | 12 (80%) |
| Moderate | 1 (100%) | 0 (0%) | 2 (15%) | 3 (20%) |

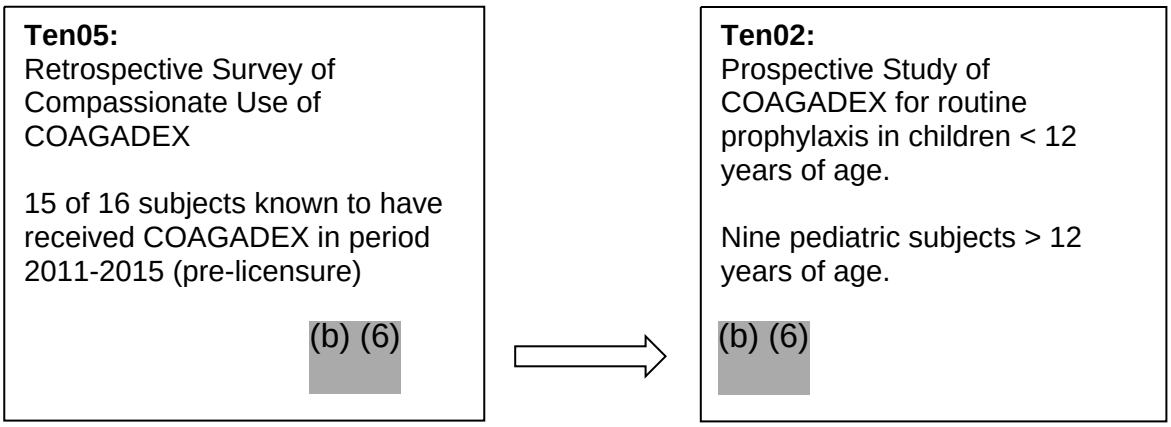
6.2.10.1.2 Medical/Behavioral Characterization of the Enrolled Population
All but three of the fifteen subjects enrolled in this study had severe factor X deficiency (<2% factor X activity in plasma). Subject (b) (6) had a factor X activity level of <5% and could not be characterized as severe or moderate factor X deficiency on the basis of laboratory measurements, but had clinically severe bleeding phenotype. Of the three subjects described as having moderate factor X deficiency, two had at least 10 bleeds in the year prior to starting Ten05, and the other had between 6 and 10 bleeds the prior year.

All subjects enrolled in Study Ten05 had been exposed to coagulation factor X by prior treatment with factor X containing products, such as fresh frozen plasma, prothrombin complex concentrates, or a combined factor X/factor IX product. As such, all study subjects would be characterized as previously treated patients (PTPs), and at low risk for factor X inhibitor antibody development.

Subject (b) (6) a 32 year old female, was on estrogen-containing oral contraceptives during the course of the study.

***Reviewer Comment:*** *The inclusion of the three moderate factor X deficiency subjects in this study is unlikely to influence the results obtained, or their interpretation. Those subjects had a prior history of several bleeds in the year prior to the study, and appear to have a bleeding phenotype comparable to the other subjects with severe factor X deficiency. Therefore, for the purpose of this study, the bleeding phenotype of this subject was equally severe as the other subjects' phenotype.*

6.2.10.1.3 Subject Disposition
Subject disposition in Study Ten05 is shown below. two subjects enrolled in Study Ten05 were later enrolled in Study Ten02.




Note: two subjects were enrolled in Study Ten05 and subsequently participated in Study Ten02. This includes Ten05 study subject (b) (6) and (b) (6) who later enrolled in Ten02 as study subjects (b) (6) and (b) (6), respectively.

6.2.11 Efficacy Analyses

In the intention to treat population (n = 15), COAGADEX efficacy was rated as Excellent by the Investigators for 14 subjects, and Good for one (b) (6)

6.2.11.1 Analyses of Primary Endpoint(s)

Routine Prophylaxis Primary Endpoints:

- number of bleeds per year and per month, per subject (including severity, location and cause) and
- total dose (IU and IU/kg) per year and per month, per subject.

The primary efficacy analysis on the Investigator's assessment of COAGADEX in reducing/preventing bleeding during routine prophylactic treatment over 6 months (26 weeks) in children < 12 years of age is detailed in Section 11.4.1 of the Ten02 Study Report. All subjects in the Per-Protocol group (n = 9) were judged to have an overall assessment of "Excellent" by the Investigators. The rating of Excellent was defined as 'no major or minor bleeds occurred or lower frequency of bleeds than expected, given the subjects medical/treatment history'.

For routine prophylaxis the efficacy assessment also includes measurement of the annual bleed rate (ABR) and the dose of COAGADEX administered, as shown below, in Table 24:

**Table 25.**

| **Annualized Bleed Rates by Age Group, Study Ten05** | | | | |
|---|---|---|---|---|
| | **0-5-year-old group (n = 1)** | **6-11-year-old group (n = 1)** | **12 - 17year-old group (n = 2)** | **≥ 18 yr-old (adult) group (n = 4)** |
| # of bleeding events | 0 | 0 | 5 | 12 |
| Mean ABR (Range) | 0 (0) | 0 (0) | 1.1 (1.0-1.2) | 1.6 (0 – 4.5) |

| | | | | |
|---|---|---|---|---|
| Median ABR | 0 | 0 | 0 | 1 |
| Mean Dose, IU/kg (Range) | 48.5 (48.5) | 53.6 (53.6) | 24.8 (21.9 – 27.7) | 27.12 (23.4 – 29.8) |
| Median Dose, IU/kg | 48.5 | 53.6 | 24.8 | 27.6 |

Compiled from Study Ten05 Listing 17.3.2. Duration of prophylaxis ranged from 12.9 to 48.8 months.

***Reviewer Comment:*** *The Applicant calculated bleeds per subject per month. We extrapolated this to bleeds per subject per year to be comparable to annual bleed rates for subjects with hemophilia, which is the benchmark we have used to judge efficacy. We asked the Applicant to place the ABR rate in the label rather than the per month bleed rate, to which they agreed.*

On-Demand Primary Endpoints:

For on-demand therapy, in addition to the Investigator's global assessment of hemostatic efficacy, other assessments include the number of events, characterization as major or minor, and the dose of COAGADEX given to control bleeding, as below. There were 88 such bleeds, of which 79 were treated with COAGADEX, all with effective hemostasis ratings, per the Investigators. All bleeding events (for on-demand only in 8 subjects, or breakthrough bleeding during routine prophylaxis for 3 subjects) occurred in adolescents or adults.

**Table 26.**

| **Outcomes for On-Demand Treatment by Age Group, Study Ten05** | | | | |
|---|---|---|---|---|
| | **0-5-year-old group (n = 0)** | **6-11-year-old group (n = 0)** | **12 - 17year-old group (n = 5 )** | **≥ 18 yr-old (adult) group (n = 8)** |
| Bleeding events treated | - | - | 44 | 35 |
| Major bleeding events (n) | - | - | 3 | 2 |
| Spontaneous (%)<br>Traumatic (%)<br>Menorrhagia (%)<br>Unknown (% | -<br>-<br>- | -<br>-<br>- | 6 (13.6%)<br>10 (22.7%)<br>28 (63.6%)<br>0 (0%) | 7 (20.0%)<br>18 (51.4%)<br>9 (25.7%)<br>1 (2.9%) |
| Effective Outcome(%) | - | - | 100% | 100% |
| Mean, Median dose in IU/kg per bleeding episode (Range) | - | - | 26.0, 23.8 (10 – 87) | 31.2, 23.1 (7.9 – 338) |
| Number of infusions required to achieve excellent/good hemostasis | | | | |
| 1 infusion | - | - | 91% | 89% |

Source: Compiled by reviewer from Ten05 Study report Listing 10.1.1.a/b

***Reviewer Comment:*** *The results of treatment of on-demand bleeding episodes and breakthrough bleeding on routine prophylaxis in this study shows that ~90% of episodes can be treated with one infusion of COAGADEX, and all treatment was judged to be effective by the Investigators. The recommendation for dosing patients > 12 years of age with 25 IU/kg for bleeding episodes is in agreement with the empiric experience for*

*adults and adolescents, if the effect of high dose outlier is taken into account (see discrepancy between mean and median dose per bleeding episode for ≥ 18 year age group. Note that relatively few bleeds were major in severity.*

Efficacy Analysis of Peri-operative management

Surgery Subjects (Study 2). Three subjects who underwent surgery on Study 2 had the following demographic characteristics:

**Table 27.**

**COAGADEX Perioperative Subjects (Study 2, Only)**

| Subject Characteristic | 0-5-year-old group (n = 1) | 6-11-year-old group (n = 0) | 12 - 17year-old group (n = 1) | ≥ 18 yr-old (adult) group (n = 1) |
|---|---|---|---|---|
| **Age (years)** | 1 | - | 17 | 32 |
| **Sex** | | | | |
| Female | 0 (0%) | - | 0 (0%) | 0 (0%) |
| Male | 1 (100%) | - | 1 (100%) | 1 (100%) |
| **Race** | | | | |
| Asian | 1 (100%) | - | 0 (0%) | 0 (0%) |
| Caucasian | 0 (0%) | - | 1 (100%) | 1 (100%) |
| **Severity of FX Deficiency** | | | | |
| Severe | 0 (0%) | - | 1 (100%) | 1 (100%) |
| Moderate | 1 (100%) | - | 0 (0%) | 0 (0%) |

Notably, two had severe factor X deficiency, one had moderate factor X deficiency. All procedures were considered to be minor.

All three subjects completed the observation period for perioperative management. Subject (b) (6) had a dental extraction under coverage of tranexamic acid and COAGADEX (28.5 IU/kg). Subject (b) (6) had multiple teeth extracted under coverage of aminocaproic acid and COAGADEX (55.4 IU/kg). Both bleeding episodes resolved with combined therapy with no reported problems, and the surgical procedures were characterized by investigators as having Excellent hemostasis, and no reported problems. The third subject had a Portacath placement done without concomitant fibrinolytics and provides the only evidence of efficacy of COAGADEX treatment alone in children < 12 years of age. Though his lowest measured factor X level was 2% (lower end of moderate factor X deficiency level), the subject had a bleeding phenotype that was severe, with several bleeds prior to starting on COAGADEX. This subject achieved a pre-operative factor X level of 61% with administration of 48.5 IU/kg COAGADEX the day of surgery.

The factor X recovery was 1.21 IU/dL per IU/kg COAGADEX administered, which approximates the IR30 values measured later when participating in Study 1 (IR30 1.56 and 1.26 at beginning and end of study), indicating the IR30 predicts levels that will be obtained with a given dose of factor X.

***Reviewer comment:*** *The data from the third subject (Portacath placement) forms the basis for the dosing recommendation in children less than 12 years of age and for the recommendation to include an indication for perioperative management of patients with*

*moderate deficiency. Although the data from Ten 05 did not include perioperative management of subjects <12 years who underwent major surgery, supportive data from the adult subjects with major surgery and the published data to support target levels of >50% factor activity level for perioperative management of major surgery is used to extend the indication to include major surgery in children. In addition, the factor X incremental recovery studies done in nine pediatric subjects provide important information indicating a lower recovery of administered factor X compared to adults and the need for higher doses of factor X to be administered to achieve a desired level. There is no reason to believe that children require a different hemostatic level for successful surgery than adults, and it is reasonable to conclude the IR30 will predict levels that will be achieved prior to surgery. The target factor X level specified for the surgical studies described in the original licensure application was 70-90%. It is not clear how that target level was chosen, since expert opinion historically recommended that levels of 35-50% were acceptable for major surgery (Brown and Kouides, 2008) and further, that levels of greater than 50% were to be avoided (Roberts and White, 2008, and Gailani and Neff, 2009). The former observation comes from the fact that carriers of factor X deficiency do not bleed excessively with ~50% of normal factor X levels. Further, before PCCs were available, all surgery in factor X deficient patients had to be performed using plasma, and volume constraints make it hard to achieve 50% levels in any event. The injunction against exceeding 50% comes from thromboses that occurred during use of PCCs to get to higher factor X levels. A recommended target level of 70-90% provides a generous margin above the traditional 50% target, and with pure single-factor concentrates like COAGADEX, there does not appear to be the problem with thromboembolic events that are seen with PCCs.*

*The target level achieved (61%) following the first dose of Coagadex is supportive that IR30 based dosing is adequate to achieve target factor levels necessary in subjects <12 years of age with moderate deficiency who undergo major surgery.*

*Despite the uncertainties that remain for perioperative management of factor X deficiency, I believe that the safety benefits of a pure factor X product such as COAGADEX (compared to plasma or PCCs) warrant approval for perioperative management in the group < 12 years of age with mild or moderate disease, based on the available data. For instance, at least one of the pediatric subjects in Study 1 had a prior history of thrombosis on a PCC product prior to entry on the study, but had no such events on COAGADEX administered as routine prophylaxis for more than 4 years at relatively high doses (~50 IU/kg, twice weekly).*

6.2.11.2 Analyses of Secondary Endpoints

No secondary endpoints were analysed in this study.

6.2.11.3 Subpopulation Analyses

The number of subjects was too small for any analysis of subpopulations.

6.2.11.4 Dropouts and/or Discontinuations

There were no dropouts or discontinuations for any reason.

6.2.11.5 Exploratory and Post Hoc Analyses

No exploratory analysis was undertaken.

6.2.12 Safety Analyses

6.2.12.1 Methods

In Study Ten05, adverse drug reactions (ADRs) were compiled from a retrospective survey of medical records during compassionate use of COAGADEX for prophylaxis, on-demand treatment, and perioperative management of bleeding. All safety analyses are based on the intention to treat population, consisting of all fifteen subjects enrolled in Study Ten05.

6.2.12.2 Overview of Adverse Events

There were no adverse drug reactions reported for use of COAGADEX in the compassionate use population enrolled in Study Ten05.

6.2.12.3 Deaths

There were no deaths in this study.

6.2.12.4 Nonfatal Serious Adverse Events

There were no SAEs during this trial.

6.2.12.5 Adverse Events of Special Interest (AESI)

There were no infusion reactions, anaphylaxis, or thromboembolic events reported in Study Ten05.

6.2.12.6 Clinical Test Results

No inhibitor antibodies to factor X were reported in this study.

6.2.12.7 Dropouts and/or Discontinuations

There were no dropouts or discontinuations for any reason in this study.

6.2.13 Study Summary and Conclusions

Study Ten05 captured nearly all data on the compassionate use of COAGADEX for routine prophylaxis, on-demand treatment of bleeding, and perioperative management of factor X deficiency during surgery. The product appears to be safe in the population studied, with no serious adverse events reported or any adverse events of special interest in this study population. Hemostasis was judged by Investigators to be Effective ("Excellent" or "Good") in all 15 subjects ("Excellent" in 14 of the 15 subjects). Investigators judged hemostasis to be effective for all of 79 bleeds treated with COAGADEX in this study. The ABR for subjects on routine prophylaxis in this study (1.1) was much lower than that for subjects treated on-demand (9.5) and comparable to the ABR results for Ten02 (2.2). Three surgical procedures (two dental extractions and one Portacath placement were conducted under COAGADEX coverage with no abnormal bleeding reported.

***Reviewer Comment:*** *The lack of prospective plan for surveillance makes it likely that adverse events were under-reported as compared to Study Ten02. Nevertheless, the results of this study are consistent with those of Study Ten02, and provide additional important information regarding on-demand treatment and perioperative management that are not available from Study Ten02*

## 7. INTEGRATED OVERVIEW OF EFFICACY

### 7.1 Indication #1

Routine Prophylaxis to Reduce the Frequency of Bleeding Episodes.

#### 7.1.1 Methods of Integration

Data from Study 1 (Ten02) and Study 2 (Ten05) for prophylaxis are combined to form the integrated summary of efficacy. Note, Subject (b) (6) in Study 2 (age 11.6 years) was the same as Subject (b) (6) in Study 1, and Subject (b) (6) in Study 2 was the same as Subject (b) (6) in Study 1 (listing 04: Patient Overview, in Ten05 Study Report). Prophylaxis efficacy is described for age groups 0-5 years, 6-11 years, 12-7 years (adolescents), and adults 18 years and older.

#### 7.1.2 Demographics and Baseline Characteristics

Integrated demographic results should be discussed with use of tables if not already discussed in Section 6, Discussion of Individual Studies/Clinical Trials.

**Table 28.**

| **Demographics of Combined Study 1 & 2 Prophylaxis Populations** | | | | |
|---|---|---|---|---|
| **Subject Characteristic** | **0-5-year-old group (n = 5)** | **6-11-year-old group (n = 6)** | **12 - 17year-old group (n = 2)** | **≥ 18 yr-old (adult) group (n = 4)** |
| **Age (years)** | | | | |
| Average (± STD)<br>Range | 2.6<br>1 – 3.6 | 10<br>6-11.9 | 16<br>15 – 17 | 24.5<br>21 – 32 |
| **Sex** | | | | |
| Female | 2 (40%) | 4 (67%) | 1 (50%) | 1 (25%) |
| Male | 3 (60%) | 2 (33%) | 1 (50%) | 3 (75%) |
| **Race** | | | | |
| Asian | 5 (100%) | 3 (50%) | 0 (0%) | 0 (0%) |
| Caucasian | 0 (0%) | 3 (50%) | 2 (100%) | 4 (100%) |
| **Severity of FX Deficiency** | | | | |
| Severe | 2 (40%) | 6 (100%) | 1 (50%) | 4 (100%) |
| Moderate | 3 (60%) | 0 (0%) | 1 (50%) | 0 (0%) |

#### 7.1.3 Subject Disposition

All but one subject who received COAGADEX before licensure was enrolled in Study 2. That subject participated in Study 1 as subject (b) (6) (age 11.8 years). Information in Listing 11.2: Previous FACTOR X [COAGADEX] Infusions-Compassionate Use (page 1741 in Ten02 Study report) indicates that this subject received 158 infusions over approximately 15 months (June 2014-September 2015), given every 3 days.

There were no screening failures, withdrawals, or deaths in Study 1 or Study 2.

Subject (b) (6) (age 10.2 years when enrolled) had received COAGADEX under compassionate use for prophylaxis in Study 2 (age 6 when enrolled). The duration of prophylaxis for that subject in Study 2 was 48.8 months, and in Study 1 was 6 months,

for a total of 54.8 months, the longest period of time in which prophylaxis was studied, for any age subject.

Subject (b) (6) (age 2.6 years when enrolled) had received COAGADEX under compassionate use for prophylaxis in Study 2 (age 1 when enrolled). The duration of prophylaxis for that subject in Study 2 was 12.9 months, and in Study 1 was 6 months, for a total of 18.9 months.

As stated previously, for Study 1 there were two subjects (b) (6) whose first prophylactic treatment period included 50 exposure days, but did not make 6 months, as per protocol, so they were excluded from the efficacy analysis but included in the safety analysis. The applicant provides Investigator assessments for those two intention to treat cycles, and both were judged to have Excellent hemostatic efficacy during those treatment cycles.

There is poor documentation of bleeding events and/or hemostatic efficacy, as in the case of Study 2 subject (b) (6) who is listed as having had 3 years of menorrhagia; however, this is to be expected with a retrospective survey.

***Reviewer Comments:*** *The combined data from Study 1 and Study 2 provide a reasonable dataset for assessing efficacy of COAGADEX for routine prophylaxis in children and adults, given the rarity of the disease. The combined data for one subject captures over 4.5 years of continuous prophylaxis with Excellent overall hemostatic efficacy assessment for the entire period. Despite the fact that Subject* (b) (6) *from Study 1 did not enroll in Study 2 (retrospective survey), the previous COAGADEX use listing for Study 1 captures that information. The combined data set therefore appears to capture all data for compassionate use of the product.*

7.1.4 Analysis of Primary Endpoint(s)

The Applicant's primary goal of this BLA supplement is to gain the indication of routine prophylaxis of bleeding in factor X deficiency, for patients of all ages, as studied prospectively in children < 12 years of age in Study 1, and in subjects of all ages under compassionate use in (retrospective) Study 2.

The primary efficacy endpoint for both Study 1 and Study 2 were the Investigators' global assessment of hemostatic efficacy for routine prophylaxis, using a four point rating scale. In both studies, for all subjects, of all ages, for both male and female, and severe and moderate factor X deficiency, the Investigators' assessment was uniformly "Excellent".

***Reviewer Comments:*** *Studies 1 and 2 are not directly comparable, since Study 1 was a prospectively designed trial with pre-specified dose and dosing intervals, as well as studies of factor X recovery with standardized doses. Also, the four point rating scale for Study 1 defined "Excellent" hemostasis as "No minor or major bleeds occurred during the study period or lower frequency of bleeds than expected, given subject's medical/treatment history" while Study 2 defined "Excellent" hemostasis as "efficacy regularly met or exceeded expectations". Nevertheless, Study 2 provides complementary "real world" data on routine prophylaxis in patients of all ages including one child 1-5 years of age, one child 6-11 years of age, two adolescents, and four adults. Further, subjects on Study 2 had prophylaxis over a much longer period of time*

*(average 24 months, range 12.5-48.8 months), than the six month Study 1. Subject* (b) (6) *(age 6 years) underwent prophylaxis for 48.8 months on Study 2, then continued with prophylaxis on Study 1 for 6 more months. The longer periods of successful prophylaxis in Study 2 increase confidence in the results in children < 12 years of age in Study1, and lend credence to the Applicant's assertion that routine prophylaxis should also be extended to adolescents and adults.*

7.1.5 Analysis of Secondary Endpoint(s)

The important secondary efficacy endpoints that were common to Study 1 and Study 2 included number of bleeds per subject per month *[converted in this review to annual bleed rate for comparability to other hemostatic agents used for routine prophylaxis];* routine prophylaxis dose of COAGADEX in IU/kg. Although factor X activity levels were measured occasionally, including some pre-dose, and some post-dose levels, there was no calculation of incremental recovery in Study 2 since pre- and post-dose activity levels were not done on the same day. Therefore, IR30 values are not evaluated as part of the combined efficacy analysis.

Annual Bleed Rate. Annual bleed rates were consistently lower in the 0-5 year age group than for other age groups. The annual bleed rate for the 6-11 year age group was skewed by five nosebleeds in Subject (b) (6), an 8.5 year old male, and Subject (b) (6) an 11.8 year old female, who had 4 menstrual bleeds associated with onset of menarche; otherwise, there were no bleeds in subjects in Studies 1 and 2 from that age group. Two of the nosebleeds were minor and not treated with COAGADEX, and one was traumatic. Only 1 of the menstrual bleeds was treated with COAGADEX outside the routine prophylaxis schedule.

The overall ABR for Study 1 was 2.2, and the overall ABR for Study 2 was 1.1.

**Table 29.**
**Annual Bleed Rate, Combined Routine Prophylaxis, Studies 1* and 2****

| Age Group | 0 – 5 years | 6 – 11 years | 12 – 17 years | ≥ 18 years |
|---|---|---|---|---|
| Study 1 ABR Mean (Median) | 0.5 (0) n = 4 | 3.6 (0) n = 5 | - | - |
| Study 2 ABR Mean (Median | 0 (0) n = 1 | 0 (0) n = 1 | 1.1 (1.1) n = 2 | 1.6 (1) n = 4 |
| Overall ABR Mean (Median) | 0.4 (0) n = 5 | 3 (0) n = 6 | 1.1 (1.1) n = 2 | 1.6 (1) n = 4 |

**Study 1 per-protocol group, n = 9*
***Study 2 intention to treat group, n = 8*

Source: FDA Reviewer, from Ten02 and Ten05 study reports.

Routine Prophylaxis Dose of COAGADEX. The overall average routine prophylactic dose for the combined Study 1 and Study 2 population was 35.83 IU/kg. The average routine prophylaxis dose for Study 1 was 38.76 IU/kg, and the average routine prophylaxis dose for Study 2 was lower, at 32.53 IU/kg.

The average routine prophylaxis dose by age group and study is shown below:

**Table 30.**
**Average Routine Prophylaxis Dose, Combined Studies 1* and 2****

| Age Group | 0 – 5 years | 6 – 11 years | 12 – 17 years | ≥ 18 years |
|---|---|---|---|---|
| Study 1 Dose, IU/kg Mean (Median) | 40.14 (40.8) n= 4 | 37.66 (39.60) n = 5 | - | - |
| Study 2 Dose IU/kg Mean (Median) | 48.54 (48.54) n = 1 | 53.57 (53.57) n = 1 | 24.83 (24.83) n = 2 | 27.12 (27.12) n = 4 |
| Overall Dose IU/kg Mean (Median) | 41.82 (43.23) n = 5 | 40.32 (41.77) n = 6 | 24.83 (24.83) n = 2 | 27.12 (27.12) n = 4 |

**Study 1 per-protocol group, n = 9*
***Study 2 intention to treat group, n = 8*

Source: FDA reviewer, calculated from data presented in Ten02 Study Report Listing 36.2.3.2.1, and Ten05 study report Listing 17.3.2

***Reviewer Comments:*** *There is a clear trend for higher average prophylaxis doses in younger subjects, especially in Study 2, though the number of subjects is small. It is likely that the higher prophylactic doses in the two subjects <12 years of age in Study 2 (average dose 51.06 IU/kg) informed the Applicant's design of Study 1, in which a starting dose of 40-50 IU/kg was recommended for routine prophylaxis in children < 12 years. The dose recommendation in the package insert is primarily based on the findings from Study 1 given the large sample size. Note, two subjects who were less than 12 years of age in Ten 05 (Study 2) study who were subsequently included in the Ten 02 (Study 1) study.*

7.1.6 Other Endpoints

No other endpoints were analysed.

7.1.7 Subpopulations

Studies 1 and 2 were too small to permit subpopulation analysis.

7.1.8 Persistence of Efficacy

Study 2 describes 8 subjects with average duration of COAGADEX prophylaxis of 24.1 months (range 12.9 to 48.8 months), prior to licensure, and prior to the formal prophylaxis study Ten02. The fact that patients elected to remain on prophylaxis for these substantially longer periods of time, with no apparent decline in hemostatic efficacy is indirect evidence that long term prophylaxis with COAGADEX is feasible.

7.1.9 Product-Product Interactions

Concomitant Antifibrinolytic Therapy. Antifibrinolytic agents are commonly used in conjunction with factor replacement therapy (hemophilia A, hemophilia B, factor XI deficiency, factor X deficiency) to treat bleeding or for perioperative management. Some

subjects in Studies 1 and 2 were treated for bleeding or surgery with antifibrinolytic drugs (tranexamic acid or aminocaproic acid) concurrently with COAGADEX.

In Study 1, Subject (b) (6) (an 11.9 year old Asian female) entered into menarche at approximately the time she enrolled onto the study. She experienced four menorrhagic bleeds while taking COAGADEX (days 17, 72, 117, and 143) for which she also took tranexamic acid, an antifibrinolytic agent.

In Study 2, Subject (b) (6) had traumatic joint bleeding on day 18 of the study that was treated with tranexamic acid and COAGADEX. The same subject later (day 632) had a dental extraction under coverage of tranexamic acid and COAGADEX. Subject (b) (6) had multiple teeth extracted under coverage of aminocaproic acid and COAGADEX. All bleeding episodes resolved with combined therapy with no reported problems, and the surgical procedures were characterized by Investigators as having Excellent hemostasis, and no reported problems.

7.1.10 Additional Efficacy Issues/Analyses

No other efficacy analyses were undertaken.

7.1.11 Efficacy Conclusions

The prospective efficacy data for children under 12 years of age described in Study 1, with the primary efficacy data retrospectively assessed in children under 12 year of age, adolescents, and adults in Study 2, support the claim that COAGADEX is effective for routine prophylaxis of bleeding in children and adults with factor X deficiency.

7.2 Indication #2

On-Demand Treatment and Control of Bleeding Episodes.

7.2.1 Methods of Integration

On-demand treatment COAGADEX is assessed by review of data in Study 1 (treatment of breakthrough bleeds in children < 12 years of age on routine prophylaxis) and data in Study 2 (patients receiving COAGADEX for on-demand treatment and breakthrough bleeding in patients on routine prophylaxis). Study 1 provides data on children < 12 years of age and Study 2 provides data on factor X deficient subjects of all ages, including two children <12 years of age.

7.2.2 Demographics and Baseline Characteristics

Demographics for two Study 1 subjects who underwent on-demand treatment for breakthrough bleeding and Study 2 subjects who underwent on-demand therapy aloneor for breakthrough bleeding while on prophylaxis with COAGADEX are shown below, compiled from Study Report narratives and line listings.

**Table 31.**
**COAGADEX Combined Study 1* and Study 2 On-Demand Subjects**

| **Subject Characteristic** | | | | |
|---|---|---|---|---|
| **Age (years)** | **0 – 5 years n = 0** | **6 – 11 years n = 2** | **12 – 17 years n = 5** | **≥ 18 years n = 6** |

| | | | | |
|---|---|---|---|---|
| Average, ± STD<br>(Range) | - | 10.2 ± 2.4<br>(8.5-11.9) | 15.2 ± 1.8<br>(13 - 17) | 29.5 ± 9.3<br>(21-43) |
| **Sex** | | | | |
| Female | - | 1 (50%) | 3 (60%) | 4 (67%) |
| Male | - | 1(50%) | 2 (40%) | 2 (33%) |
| **Race** | | | | |
| Asian | - | 1 (50%) | 0 (0%) | 2 (33%) |
| Caucasian | - | 1(50%) | 5 (100%) | 4 (67%) |
| **Severity** | | | | |
| Severe | - | 2 (100%) | 3 (60%) | 6 (100%) |
| Moderate | - | 0 (0%) | 2 (40%) | 0 (0%) |

*Two subjects with breakthrough bleeds during prophylaxis on Study 1, four subjects with breakthrough bleeding during routine prophylaxis on Study 2, and five subjects treated only on-demand in Study 2 are included.

7.2.3 Subject Disposition

There were no screening failures, withdrawals, or deaths in Study 1 or Study 2, for subjects who received on-demand treatment only, or who had breakthrough bleeds while on on prophylactic COAGADEX.

7.2.4 Analysis of Primary Endpoint(s)

All subjects in Study 1 received routine prophylaxis. On-demand only treatment was studied in five subjects in Study 2. For the five subjects who were treated only on-demand with COAGADEX, four were evaluated with a hemostatic efficacy assessment of "Excellent" by the Investigator and one subject (b) (6) was assessed as having a hemostatic efficacy of "Good" by the Investigator.

***Reviewer Comment:*** *It is not clear why Subject* (b) (6) *was given an assessment of "Good" hemostasis for two bleeding events that were a minor traumatic joint bleed and a spontaneous muscle bleed of unknown severity and duration, each treated with only one dose of COAGADEX (22.4 IU/kg, and 23.2 IU/kg, respectively), and no other hemostatic agent.*

7.2.5 Analysis of Secondary Endpoint(s)

The secondary endpoints for Study 1 and Study 2 are not the same. In this section I review the annual bleed rate data, and outcomes of bleeds treated on-demand for both studies.

Annual Bleed Rate. Another important secondary endpoint common to both Study 1 and Study 2 was the annual bleed rate. For the on-demand subjects in Study 2, the annual bleed rate was 9.5, which was more than the annual bleed rate for subjects in that study on routine prophylaxis (2.1) or the annual bleed rate for subjects on routine prophylaxis in Study 1 (2.2).

Outcomes of Bleeds Treated On-Demand. In Study 1 there were two subjects with a total of four breakthrough bleeds treated with COAGADEX outside of scheduled routine prophylaxis. In Study 2 there were 79 bleeds treated with COAGADEX (including

breakthrough bleeding while on routine prophylaxis and bleeding on-demand), for a combined total of 83 bleeds treated “on-demand”.

**Table 32.**

| **Combined Study 1 and Study 2 Bleeds and Outcomes of On-Demand Treatment** | | | | |
|---|---|---|---|---|
| **Age Group** | **0-5 years** | **6-11 years** | **12-17 years** | **≥ 18 years** |
| (# subjects treated on-demand) | (0) | (2) | (5) | (6) |
| **# BleedsTreated** | 0 | 4 | 44 | 35 |
| **Excellent Outcome (%)** | NA | 4 (100%) | 44 (100%) | 33 (94.3%) |
| **Mean Dose Per Bleed** (Median) | NA | 35.28 (38.0) | 23.18 (23.8) | 31.19 (23.1) |
| **Infusions required to achieve effective hemostasis (%)** | | | | |
| 1 infusion | - | 4 (100%) | 40 (91%) | 31 (88.6%) |
| 2 infusions | - | | 1 (2%) | 2 (5.7%) |
| ≥ 3 infusions | - | | 2 (7%) | 2 (5.7%) |

Source: Abstracted from Ten02 Study Report and Ten05 Study Report Listing 10.1.1.b (page 820).

***Reviewer Comment:*** *The pooled data shows that ~90% of bleeding episodes can be treated with a single COAGADEX dose of ~25 IU/kg for subjects > 12 years of age. A higher dose seems to be required for children < 12 years of age.*

7.2.6 Other Endpoints

No other endpoints were analysed.

7.2.7 Subpopulations

The population of subjects treated on-demand in Study 1 and Study 2 was too small for meaningful analysis.

7.2.8 Persistence of Efficacy

Not applicable to these studies.

7.2.9 Product-Product Interactions

Tranexamic acid was administered concomitant with a dose of COAGADEX (28.3 IU/kg) to treat a minor traumatic joint bleed in one subject with no apparent problem noted.

7.2.10 Additional Efficacy Issues/Analyses

No other analyses of efficacy were conducted.

7.2.11 Efficacy Conclusions

On-demand treatment of bleeding with COAGADEX was highly effective in both Study 1 and Study 2. For Study 2, as judged by the “Excellent” hemostatic efficacy rating in both subjects treated for breakthrough bleeding and the overall “Excellent” rating for four of the five subjects who were treated with on-demand therapy, only.

The lower ABR with routine prophylaxis in both Study 1 and Study 2 compared to the on-demand group ABR rate in Study 2 serves as an indirect indicator of the efficacy of routine prophylaxis with COAGADEX.

### 7.3 Indication #3

Since Study Ten 02 did not include perioperative data, the discussion of the efficacy analysis is included in Section 6.2 of this memo.

## 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 Study 1 and Study 2. 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 safety analysis was done with data from 24 subjects who were enrolled in Study 1 and Study 2 and treated with COAGADEX between March 2011 and October 2016 for routine prophylaxis of bleeding, on-demand treatment of bleeding, and perioperative management of factor X deficiency.

Study 1 (Ten02): 9 subjects (all < 12 years of age) with moderate or severe factor X deficiency who received COAGADEX for routine prophylaxis (and breakthrough bleeding, on demand) for six months/≥ 50 exposure days.

Study 2 (Ten05): 15 subjects (adults and children) with moderate or severe factor X deficiency who received COAGADEX under provisions of compassionate use, prior to licensure for routine prophylaxis, on-demand therapy, and perioperative management of factor X deficiency.

#### 8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

Subjects in Study 1 ranged from 1 to 11.8 years of age (mean 7.3 years). Four were male, five were female. Seven were Asian (77%), and two were Caucasian (23%). Eight had severe factor X deficiency, one had moderate disease.

Subjects in Study 2 ranged from 1 to 43 (mean 20.3 years). Six were male, nine were female. Thirteen were Caucasian (87%) and two were Asian (13%). Thirteen had severe disease, two had moderate disease.

8.2.3 Categorization of Adverse Events

AEs were categorized with 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, whether followed prospectively (Study 1) or entered from medical records retrospectively (Study 2). In Study 1, nine unique subjects underwent 11 treatment cycles with COAGADEX, since two subjects were treated with 50 exposure days but not the complete 6 month period of follow-up, and therefore were both re-enrolled and treated again, per protocol. The safety analysis of this study includes data from all 11 treatment cycles (intention to treat population). All adverse events that occurred subsequent to the first dose of COAGADEX were considered to be treatment emergent adverse events.

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

Study 1 and Study 2 enrolled complementary groups of patients. Study 1 was limited to children < 12 years of age (9 subjects), and studied routine prophylaxis with COAGADEX. Study 2 enrolled predominantly adults (9 subjects), and some adolescents (4) and two children < 12 years of age, and studied routine prophylaxis, on-demand treatment, and perioperative management of bleeding with COAGADEX. Study 1 was a prospective study, while Study 2 was a retrospective survey. Although Study 2 was retrospective, the Applicant received safety data in real time from Investigators under terms of compassionate use of their product, and captured data for all but one user of the product. Study 1 collected data on all adverse events, regardless of relationship to COAGADEX use, however Study 2 only collected adverse drug reactions.

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

8.4 Safety Results

8.4.1 Deaths

There were no deaths on either Study 1 or Study 2

8.4.2 Nonfatal Serious Adverse Events

There were 28 treatment-emergent adverse events (TEAEs) reported in 8 (89%) of the unique subjects in the ITT population of Study 1. TEAEs were considered to be mild in 93% of cases, and serious in 7% of cases and unrelated to the treatment. The only two adverse events that occurred during of Study 1 were in the same subject. These included a lower respiratory tract infection 88 days after baseline visit, and a case of influenza A 159 days after baseline, both of which required hospitalization. Both resolved completely, and were not considered to be due to COAGADEX use. For Study 2, the Applicant only collected adverse drug reactions, and none were reported in that study.

See 6.1.12.2 Overview of Adverse Events for details of all TEAEs in Study 1.

***Reviewer Comment:*** *The two serious adverse events encountered in Study 1 are likely to be experienced in normal daily life of children in this age group. It is not plausible that*

*influenza A or pneumonia would be caused by COAGADEX. These findings do not raise any concern about their relationship with use of COAGADEX.*

8.4.3 Study Dropouts/Discontinuations

No subjects dropped out of Study 1 or Study 2 due to adverse events or any reason.

8.4.4 Common Adverse Events

Review of safety data in Study 1 and Study 2 shows no pattern of adverse events that are associated with use of COAGADEX.

8.4.5 Clinical Test Results

In Study 1 routine, prospective laboratory testing was conducted, per protocol. There was mild, iron deficiency anemia noted in two subjects, not related to COAGADEX treatment, likely due to underlying factor X deficiency and their prior bleeding history. There were trivial, transient elevations of total bilirubin and trivial, depressions of serum alkaline phosphatase, creatinine, urea, potassium, and eosinophil counts in several subjects; none were thought to be clinically significant or related to COAGADEX treatment. No laboratory markers of thrombosis (i.e., D-dimer, fibrin split products) were performed in this study.

There was no routine, prospective laboratory testing done on subjects in Study 2, and no laboratory abnormalities were noted in any study participants based on the AE reports.

8.4.6 Systemic Adverse Events

There were no systemic adverse events encountered in Study 1 or Study 2.

8.4.7 Local Reactogenicity

No local reactions to infusion of COAGADEX were encountered in Study 1 or Study 2.

8.4.8 Adverse Events of Special Interest

No factor X inhibitors, thromboembolic events, or hypersensitivity reactions were reported in subjects treated with COAGADEX in either Study 1 or Study 2. Surveillance for HIV1, HIV2, hepatitis A, hepatitis B, hepatitis C, and parvovirus B19 seroconversion was conducted as part of Study 1 and there were no seroconversions observed for any virus among the nine subjects who participated in 11 treatment cycles with at least 50 exposure days (intention to treat data set).

8.5 Additional Safety Evaluations

8.5.1 Dose Dependency for Adverse Events

Not analysed.

8.5.2 Time Dependency for Adverse Events

Not analysed.

8.5.3 Product-Demographic Interactions

Not analysed.

### 8.5.4 Product-Disease Interactions

Not analysed.

### 8.5.5 Product-Product Interactions

One female subject in Study 1 took tranexamic acid concomitant with COAGADEX during four menorrhagic bleeds, without apparent ill effect. On Study 2 one subject took tranexamic acid concomitant with COAGADEX for a traumatic joint bleed, and two dental procedures were performed with single doses of COAGADEX and concomitant amicar (a typical peri-operative management strategy for factor replacement therapy for dental procedures in hemophilia).

### 8.5.6 Human Carcinogenicity

Not analysed.

### 8.5.7 Overdose, Drug Abuse Potential, Withdrawal, and Rebound

No overdoses of COAGADEX were observed in Study 1 or Study 2.

### 8.5.8 Immunogenicity (Safety)

In Study 1 and Study 2 all subjects tested negative for inhibitor antibodies to factor X. In Study 1 there was measurement of incremental recovery of factor X activity after a standardized dose at baseline, and again after 50 exposure days and six months of observation that showed no deterioration following extensive treatment, which would be an indirect indicator of an inhibitor antibody.

### 8.5.9 Person-to-Person Transmission, Shedding

Not analysed.

## 8.6 Safety Conclusions

COAGADEX does not appear to cause any serious or important adverse events, and there is no safety signal that emerges from review of Study 1 and Study 2.

# 9. ADDITIONAL CLINICAL ISSUES

## 9.1 Special Populations

As a rare disease, factor X deficiency would be difficult or impossible to study in a meaningful number of patients in special populations other than pediatric patients. Pediatric subjects were the focus of Study 1.

### 9.1.1 Human Reproduction and Pregnancy Data

Pregnancy was not studied in either Study 1 (pediatric subjects < 12 years of age) or adolescents and adults in Study 2.

### 9.1.2 Use During Lactation

Use of COAGADEX was not studied in either Study 1 (pediatric subjects < 12 years of age) or Study2.

### 9.1.3 Pediatric Use and PREA Considerations

PREA does not apply to this product and the indications that are sought due to the Orphan Designated Status.

### 9.1.4 Immunocompromised Patients

Use of COAGADEX in immunocompromised patients was not studied.

### 9.1.5 Geriatric Use

Geriatric use was not studied for this product.

### 9.2 Aspect(s) of the Clinical Evaluation Not Previously Covered

Not analysed.

## 10. CONCLUSIONS

Valuable information was obtained on the safety and efficacy of routine prophylaxis and on-demand therapy with COAGADEX in children and adults with severe or moderate factor X deficiency, from both Studies 1 and 2. Information suggesting decreased recovery of factor X activity in children < 12 years of age, compared to adults, was obtained in Study 1, and may guide dosing of COAGADEX to attain a desired target factor X activity level. Modest additional support for perioperative management of factor X deficiency in minor surgery was obtained from Study 2.

## 11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

### 11.1 Risk-Benefit Considerations

Risk-Benefit considerations are tabulated below.

| Decision Factor | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| **Analysis of Condition** | • Congenital factor X deficiency results in a bleeding condition similar to that of hemophilia A (factor VIII deficiency) or hemophilia B (factor IX deficiency), with spontaneous hemorrhage of joints, soft tissue, and mucosal surfaces, including menorrhagia in females. Intracranial hemorrhage can occur and can be fatal (even with treatment after the event).<br>• Factor X activity levels of < 2% are associated with severe disease, and frequent spontaneous bleeding, moderate disease (excessive bleeding with trauma and occasional spontaneous bleeding) is associated with factor X activity levels of >5%.<br>• The gene for factor X is found on chromosome 13, so the deficiency is autosomal recessive, and therefore much more rare that hemophilia A or hemophilia B (annual incidence is on the order of one case per 1-2 million births per year). | • Factor X deficiency is a rare, life-threatening disease that can be ameliorated by replacement therapy with factor X.<br>• Replacement of missing factor X to levels of > 5% should make severe factor X deficiency a bleeding condition with much less frequent and less serious bleeding.<br>• Prophylaxis to prevent major hemorrhage would be preferable to treatment after a bleeding event has occurred.<br>• Bleeding events should be treated with factor X replacement.<br>• Perioperative replacement of factor X should permit surgical procedures to be done safely in factor X deficiency. |
| **Unmet Medical Need** | • Factor X replacement therapy is the standard treatment of bleeding with factor X deficiency.<br>• Prophylaxis to reduce the rate of bleeding is a useful goal for patients with factor X deficiency.<br>• Replacement of factor X currently is accomplished with intravenous infusions of fresh-frozen plasma or prothrombin complex concentrates.<br>• Unwanted features of replacement therapy with plasma include volume overload, transfusion related acute lung injury, and allergic reactions, occasionally including anaphylaxis.<br>• Unwanted features of replacement therapy with prothrombin complex concentrates include thromboembolic events, likely due to infusion of multiple vitamin K-dependent coagulation factors like factor II (prothrombin) and factor IX, that may accumulate to high levels with replacement therapy. | • A pure factor X concentrate with high potency and specific activity would be advantageous over fresh-frozen plasma or prothrombin complex concentrates, especially in children who have less tolerance for volume overload with intravenous infusions.<br>• A pure factor X concentrate with less predisposition to causing DIC or thromboembolic events than PCCs would offer a safety advantage, especially in the setting of surgery. |

| | | |
|---|---|---|
| **Clinical Benefit** | • One clinical trial of routine prophylaxis of bleeding in children under 12 years of age with severe or moderate factor X deficiency with at least 50 exposure days over 26 weeks was characterized by a finding of excellent hemostasis for all nine subjects by study Investigators. COAGADEX was administered two or three times weekly, with a goal of trough levels of no less than 5% and no more than 120% of normal factor X activity. The annual bleeding rate was 2.1, extrapolated from six months of observation.<br>• Incremental recovery at 30 minutes for the nine pediatric subjects that were studied in the trial showed a lower recovery than for adults studied in previous trials of COAGADEX.<br>• Another retrospective survey of use of COAGADEX under provisions of compassionate use for routine prophylaxis in two children < 12 years of age, two adolescents, and four adults with severe or moderate factor X deficiency, likewise showed excellent hemostasis for routine prophylaxis, on demand treatment, and surgery in three subjects who were 1, 17, and 32 years of age. The annual bleed rate for eight subjects was 1.1, measured over 12.5 to 48.8 months of routine prophylaxis.<br>• In both studies, on-demand treatment of bleeding, and treatment of breakthrough bleeding on routine prophylaxis, was characterized by successful treatement with single doses of COAGADEX, and hemostasis was judged to be excellent in all cases. | • The ABR for routine prophylaxis is much lower than for on-demand therapy in factor X deficiency, indicating efficacy of COAGADEX.<br>• Most treatment of breakthrough bleeding on prophylaxis or on-demand treatment of bleeding is successful with a single dose of COAGADEX, and there were no treatment failures reported.<br>• The data for routine prophylaxis is limited since only 17 unique subjects were studied. Similarly, only three subjects underwent surgery under COAGADEX coverage under compassionate use; of these only two were children.<br>• Larger studies of COAGADEX in children with factor X deficiency are not feasible to conduct, due to the rarity of the disease. |
| **Risk** | • There were no adverse events attributable to COAGADEX in the nine pediatric subjects studied prospectively, or the 15 subjects of all ages studied retrospectively under compassionate use.<br>• No inhibitors or thromboembolic events occurred in the course of the six month routine prophylaxis study in children less than 12 years of age, studied prospectively. No inhibitors or thromboembolic events were observed in the 17 subjects of all ages who were treated for 12.5 to 48.8 months under provisions for compassionate use of COAGADEX. | • All the evidence indicates that the risk for treatment of congenital factor X deficiency with COAGADEX is minimal, and it may have a safety advantage over PCCs for perioperative management during surgical procedures. |
| **Risk Management** | • No safety signal has been observed for use of COAGADEX in children less than 12 years of age, adolescents, or adults. | • If COAGADEX were to be approved for routine prophylaxis and on-demand treatment of bleeding in patients with congenital factor X deficiency, the guidance for treatment in the package insert, as well as the current pharmacovigilance plan, would be adequate to manage the risks.<br>• If COAGADEX were to be approved for perioperative managment in all ages, the |

| | | |
|---|---|---|
| | | guidance for treatment in the package insert, as well as the current pharmacovigilance plan, would be adequate to manage the risks. |

**Table 33.**

11.2 Risk-Benefit Summary and Assessment

COAGADEX is a highly purified factor X concentrate derived from (b) (4) plasma. It is manufactured with robust viral inactivation procedures against the most important blood-borne pathogens. There has been no evidence of inhibitory antibodies to factor X, no evidence of thromboembolic complications of its use, and no hypersensitivity to the product manifested by anaphylaxis or local infusion reactions. Subjects on prophylaxis have ABRs of 1-2 events per year, which is a clear improvement over the ABR rate of 9.5 seen in patients treated on-demand only. Effective control of breakthrough bleeding or on-demand bleeding is achieved with one dose of the product in 91.5% of the time. Surgical procedures have been completed under coverage with COAGADEX with no excessive bleeding and favorable assessments of hemostasis.

The risk-benefit relationship suggests a high degree of benefit with no discernable risk and is quite favorable.

11.3 Discussion of Regulatory Options

The available regulatory options are

- To approve routine prophylaxis in all age groups and to remove the age restrictions on the use of COAGADEX for on-demand treatment of bleeding and perioperative management of factor X deficiency, as requested by the Applicant; or
- To approve routine prophylaxis and to remove the age restrictions on the use of COAGADEX for on-demand treatment of bleeding and perioperative management of factor X deficiency, as requested by the Applicant, with a requirement for additional information to be collected as part of a post-marketing commitment; or
- To approve routine prophylaxis and on-demand treatment in all age groups, but not lift the age restriction on perioperative management; or
- To approve routine prophylaxis in all age groups and to remove the age restrictions on the use of COAGADEX for on-demand treatment of bleeding and perioperative management of factor X deficiency, and to extend the perioperative management indication to include moderate as well as mild factor X deficiency; or

- To approve none of the provisions requested by the Applicant.

11.4 Recommendations on Regulatory Actions

This clinical reviewer recommends approval of this BLA for the proposed indication of routine prophylaxis, and removal of the age restriction for on-demand and perioperative management of factor X deficiency, and extending the perioperative management indication to moderate as well as mild factor X deficiency. Efficacy and safety clinical data for Coagadex supported a favorable benefit/risk determination for the proposed indication. No post-marketing commitment or risk mitigation strategy is recommended.

### 11.5 Labeling Review and Recommendations

The Advertising and Promotional Labeling Branch (APLB) has reviewed the proposed label and found it to be acceptable, with changes negotiated during the review cycle with the Applicant. See APLB review memorandum for details.

### 11.6 Recommendations on Postmarketing Actions

The safety data do not indicate a need for additional post-marketing requirement or risk evaluation and mitigation strategy. The existing post-marketing study should be maintained to focus on major surgery in severe factor X deficiency.