Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research

MEMORANDUM

From:	Sukhminder K. Sandhu, PhD, MPH, MS Analytic Epidemiology Branch Division of Epidemiology Office of Biostatistics and Epidemiology, CBER, FDA
To:	Ze Peng, PhD Chair, Review Committee Office of Blood Research and Review
Through:	Wei Hua, MD, PhD, MS, MHS Acting Chief, Analytic Epidemiology Branch Division of Epidemiology Office of Biostatistics and Epidemiology, CBER, FDA Michael D. Nguyen, MD Deputy Director, Division of Epidemiology Office of Biostatistics and Epidemiology, CBER, FDA
Subject:	Pharmacovigilance Plan Review
Applicant:	CSL Behring LLC
Product:	Kcentra®, Prothrombin Complex Concentrate (Human)
Proposed Indication:	Kcentra is indicated for the urgent reversal of Vitamin K antagonist (e.g., warfarin) therapy in patients with acute major bleeding
Current Indication:	Not applicable in US
Submission type	Original BLA
BLA number/Submission Date:	STN 125421/0.0, Submitted March 30, 2012
PVP Submission Date	Original- March 30, 2012 Amendment 1 (Sequence 0001)-May 31, 2012 Amendment 2(Sequence 0002)-June 28, 2012 Amendment 5(Sequence 0006)-September 28, 2012 Amendment 17(Sequence 0018)-February 28, 2013 Amendment 28(Sequence 0032)-April 09, 2013 Amendment 35(Sequence 0038)-April 18, 2013 (PMR) Amendment 37(Sequence 0040)-April 19, 2013 (Update to PMR)
Action Due Date:	Original-January 28, 2013 Major Amendment-April 28, 2013

INTRODUCTION

1.1 Product description:

Kcentra, Prothrombin Complex Concentrate (Human) is a heat-treated, non-activated, virus filtered and lyophilized Plasma protein concentrate made from pooled human Plasma. Please note that Beriplex and Kcentra may be interchangeably throughout this review memo. It is comprised of blood coagulation Factors II, VII, IX, and X and Proteins C and S. Factor IX is the lead factor for potency of the preparation as stated by the manufacturer and in the label. Excipients include Antithrombin III, heparin, human albumin, sodium chloride and sodium citrate. According to the manufacturer, the preparation is sterile, pyrogen free and does not contain any antimicrobial preservative. In addition, ----------(b)(4)----------.

1.2 Pertinent regulatory history:

Kcentra® is a proposed Tradename for the US. The current Tradenames in countries with a license are Beriplex® P/N and Confidex®. Worldwide, Beriplex® P/N was first granted license in Germany in February 1996. The product is currently licensed in a total of 24 countries.

1.3 Indications and usage

BeriplexP/N (Confidex) contains the human Plasmatic coagulation factors II, VII, IX and X (prothrombin complex) in concentrated form (prothrombin complex concentrate), and considerable amounts of protein C and protein S. The product is available in two presentations, with nominal content of 250 IU F IX (Beriplex P/N 250), and 500 IU F IX (Beriplex P/N/ 500). Beriplex P/N (Confidex) is prepared exclusively from Plasma donations which have been tested negative for antibodies to HIV-1, HIV-2, and HCV, and for HBs antigen. The amount and the frequency of administration should be calculated on an individual basis. The estimated standard daily dose of Beriplex P/N (Confidex) is 2500 IU. After reconstitution with water for injections, Beriplex P/N is to be administered slowly intravenously.

Approved usage in the EU (and most other countries): 1) Treatment and perioperative prophylaxis of bleedings in acquired deficiency of the prothrombin complex coagulation factors, such as deficiency caused by treatment with vitamin K antagonists, or in case of overdose of vitamin K antagonists, when rapid correction of the deficiency is required. 2) Treatment and perioperative prophylaxis of bleedings in congenital deficiency of any of the vitamin K dependent coagulation factors when purified specific coagulation factor products are not available.

Approved usage in Australia: 1) Treatment and perioperative prophylaxis of bleedings in acquired deficiency of the prothrombin complex coagulation factors, such as deficiency caused by treatment with vitamin K antagonists, or in case of overdose of vitamin K antagonists, when rapid correction of the deficiency is required.

Approved usage in Canada: 1) Treatment of bleeding and perioperative prophylaxis of bleeding in acquired deficiency of the prothrombin complex coagulation factors, such as deficiency caused by treatment with vitamin K antagonists, when rapid correction of the deficiency is required in adults. 2) No adequate study in subjects with congenital deficiency is available. Beriplex P/N can be used of the treatment of bleeding or perioperative prophylaxis of bleeding in congenital deficiency of any of the vitamin K dependent coagulation factors only if purified specific coagulation product is not available.

1.4 Contraindications, Warnings, and Precautions

The Company Core Data Sheet for Beriplex P/N dated 17-Jan-2013 submitted on April 10, 2013 states the following contraindications, special warnings and precautions for use:

Contraindications:

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 of the CCDS.
- In the case of disseminated intravascular coagulation, prothrombin complex-preparations may only be applied after termination of the consumptive state,
- Known history of heparin-induced thrombocytopenia.

Special warnings and precautions for use:

- The advice of a specialist experienced in the management of coagulation disorders should be sought.
- In patients with acquired deficiency of the vitamin K-dependent coagulation factors (e.g., as induced by treatment of vitamin K antagonists), Beriplex should only be used when rapid correction of the prothrombin complex levels is necessary, such as major bleedings or emergency surgery. In other cases, reduction of the dose of the vitamin K antagonist and/or administration of vitamin K is usually sufficient,
- Patients receiving a vitamin K antagonist may have an underlying hypercoagulable state and infusion of human prothrombin complex may exacerbate this.
- In congenital deficiency of any of the vitamin K-dependent factors, specific coagulation factors should be used when available.
- If allergic or anaphylactic-type reactions occur, the administration of Beriplex has to be stopped immediately (e.g., discontinue injection) and an appropriate treatment has to be initiated. Therapeutic measures depend on the kind and severity of the undesirable effect. The current medical standards for shock treatment are to be observed.
- There is a risk of thrombosis or disseminated intravascular coagulation when patients, with either congenital or acquired deficiency, are treated with human prothrombin complex particularly with repeated dosing. The risk may be higher in treatment of isolated factor VII deficiency, since the other vitamin K-dependent factors, with longer half-lives, may accumulate to levels considerably higher than normal. Patients given human prothrombin complex should be observed closely for signs or symptoms of disseminated intravascular coagulation or thrombosis.
- Because of risk of thromboembolic complications, close monitoring should be exercised when administering Beriplex to patients with a history of coronary heart disease or myocardial infarction, to patients with liver disease, to patients per- or postoperatively, to neonates or to patients at risk of thromboembolic phenomena or disseminated intravascular coagulation or simultaneous inhibitor deficiency. In each of these situations, the potential benefit of treatment with Beriplex should be weighed against the potential risk of such complications. In patients with DIC and sepsis antithrombin III substitutions should be considered prior to treatment with Beriplex.
- In patients with disseminated intravascular coagulation, it may, under certain circumstances, be necessary to substitute the coagulation factors of the prothrombin complex. This substitution may, however, only be carried out after termination of the consumptive state (e.g., by treatment of the underlying cause, persistent normalization of the antithrombin III level).

- When Beriplex is used to normalize impaired coagulation, prophylactic administration of heparin should be considered.
- No data are available regarding the use of Beriplex in case of perinatal bleeding due to vitamin K deficiency in neonates.
- Beriplex contains up to ----------(b)(4)----------. To be taken into consideration by patients on a controlled sodium diet.

Virus safety:

- Standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma include selection of donors, screening of individual donations and plasma pools for specific markers of infection and the inclusion of effective manufacturing steps for the inactivation/removal of viruses. Despite this, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown emerging viruses and other pathogens.
- The measures taken are considered effective for enveloped viruses such as human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV), and for the non-enveloped virus hepatitis A virus.
- The measures taken may be of limited value against non-enveloped viruses such as parvovirus B19.
- Parvovirus B19 infection may be serious for pregnant women (fetal infection) and for individuals with immunodeficiency or increased erythropoiesis (e.g., haemolytic anaemia).
- Appropriate vaccination (hepatitis A and B) should be considered for patients in regular/repeated receipt of human plasma-derived prothrombin complex products.
- It is strongly recommended that every time that Beriplex is administered to a patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the product.

1.5 Worldwide distribution data and post-marketing (non-study) exposure:

Kcentra is not currently licensed for use in the US. Beriplex was first approved on February 16, 1996 in Germany. It is currently licensed for use in 24 countries. According to the sponsor, as of February 14, 2012, an approximately --------(b)(4)--------- were distributed worldwide. This corresponds to --(b)(4)-- estimated single standard doses based on the current average single standard dose of 2500 IUs. During the period from 16-Feb-1996 to 15-Feb-2012, 58 spontaneous AE case reports were received; however one report was actually a duplicate of a clinical study case and in fact there were only 57 spontaneous reports. According to the sponsor, this reflects an overall reporting rate of 1 report of every (b)(4) estimated current single standard doses. Exposure of patients from the non-interventional clinical study BE1116_5001 is included in the calculation of the marketed product above since for this study the sponsor does not supply the study drug. According to FDA, including the cases from this post marketing study BE1116_5001 as well as the unsponsored studies, there are a total of 78 post-marketing cases reported to FDA with an overall reporting rate of 1 report of every (b)(4) estimated current single standard doses.

Postmarketing use of Beriplex outside of the US has identified and reported the following important adverse reactions:

a) Thromboembolic complications
b) Hypersensitivity or Allergic reactions including

Important potential risks identified through postmarketing include Viral Transmission and Medication/Dosing Errors.

1.6 Objectives/Scope of the review:

The purpose of this review is to identify potential safety issues that may need to be addressed through postmarketing safety surveillance or studies should the product be licensed, and to evaluate the pharmacovigilance plan submitted by CSL Behring for the Kcentra Biologics License Application (BLA).

2 MATERIALS REVIEWED

2.1 Sequence 0000, 3/30/2012, STN 125421/0.0, Module 1.16 Risk Management Plans/Beriplex Pharmacovigilance Plans Version 1.0

2.2 Sequence 0000, 3/30/2012, STN 125421/0.0, Module 2.5 Clinical Overview

2.3 Sequence 0000, 3/30/2012, STN 125421/0.0, Module 2.7.4 Clinical Summary/Summary of Clinical Safety

2.4 Sequence 0002, 6/28/2012, STN 125421/0.2, Module 1.11.3 Efficacy Information Update

2.5 Sequence 0040, 4/19/2013, STN 125421/0.37, Module 1.11.3 Efficacy Information Update

2.6 Sequence 0024, 3/19/2013, STN 125421/0.23, Module 5.3.5 Reports of Efficacy and Safety Studies

2.7 Sequence 0001, 5/31/2012, STN 125421/0.1, Module 1.16 Risk Management Plans/Beriplex Pharmacovigilance Plan Version 2.0

2.8 Sequence 0002, 6/28/2012, STN 125421/0.2, Module 1.16 Risk Management Plans/Beriplex Pharmacovigilance Plan Version 3.0

2.9 Sequence 0006, 9/28/2012, STN 125421/0.5, Module 1.16 Risk Management Plans/Beriplex Pharmacovigilance Plan Version 4.0

2.10 Sequence 0018, 2/28/2013, STN 125421/0.17, Module 1.16 Risk Management Plans/Beriplex Pharmacovigilance Plan Version 5.0 (Referred to as Version 4 by Sponsor)

2.11 Sequence 0032, 4/09/2013, STN 125421/0.28, Module 1.16 Risk Management Plans/Pharmacovigilance Plan Version 6.0/CSL Behring Proposed BLA 125421 PMR Study Concept (received 04/10/2013)

2.12 Sequence 0038, 4/18/2013, STN 125421/0.35, Module 1.16 Risk Management Plans/Pharmacovigilance Plan Version 6.0/CSL Behring Proposed BLA 125421 PMR Study Concept

2.13 Sequence 0000, 3/30/2012, STN 125421/0.0, Module 5.3.6 Reports of Postmarketing Experience. Periodic Safety Update Reports (PSURs) for the following time periods:

- PSUR 1: 02/16/1996 – 09/30/2000
- PSUR 2: 10/01/2000 – 09/30/2005
- PSUR 3: 10/01/2005 – 09/30/2008
- PSUR 4: 10/01/2008 – 09/30/2009
- PSUR 5: 10/01/2009 – 09/30/2010
- PSUR 6: 10/01/2010 – 09/30/2011

2.14 Sequence 0001, 5/31/2012, STN 125421/0.1, Module 5.3.6 Reports of Postmarketing Experience. Periodic Safety Update Reports (PSURs) and Safety Bridging Reports (SBR) for the following time periods:

- PSUR 6: 10/01/2011 – 02/15/2012
- SBR: 10/01/2005 – 02/15/2012

2.15 Sequence 0006, 9/28/2012, STN 125421/0.5, Module 5.3.6 Reports of Postmarketing Experience.

The following line listings and case summary reports:

- PSUR Cases E2C LL
- PSUR Case Sum Rep
- PSUR TEE Cases E2C LL
- PSUR TEE Cases Sum Rep
- PSUR EbP Final List
- Indications
- PSUR EbP Final List (Excel)
- Indications (Excel)

2.16 Sequence 0018, 02/28/2013, STN 125421/0.17, Module 5.3.6 Reports of Postmarketing Experience. The following line listings and case summary reports:

- PSUR Beriplex Cases E2C LL
- PSUR Beriplex Cases Summary Report
- PSUR Beriplex EbP Final (Excel Format)
- PSUR Beriplex Unrelated Cases E2C LL
- PSUR Beriplex Unrelated Case Summary Report

2.17 Sequence 0023, 3/18/2013, STN 125421/0.22, Module 5.3.6 Reports of Postmarketing Experience. Safety Bridging Reports (SBR) for the following time period:

- SBR: 02/16/1996 – 02/15/2012

2.18 Sequence 0000, 3/30/2012, STN 125421/0.0, Module 5.4 Literature References. Manufacturer provided published study reports for review for Study Preston_2002 and Evans_2001.

- Preston, et al. Rapid Reversal of Oral Anticoagulation with Warfarin by a Prothrombin Complex Concentrate (Beriplex): Efficacy and Safety in 42 patients. BJH. 2002, 116, 619-624.
- Evans, et al., Beriplex P/N reverses severe warfarin-induced over anticoagulation immediately and completely in patients presenting with major bleeding. BJM. 2001, 115, 998-1001.

2.19 Sequence 0000, 3/30/2012, STN 125421/0.0, Module 5.4 Literature References as 1.8.1 Pharmacovigilance System-DDPS. Description of the CSL Global Pharmacovigilance System-DDPS. This section documents CSL's routine practices for conducting pharmacovigilance for any medicinal products.

2.20 Sequence 0033, 4/10/2013, STN 125421/0.30, Module 5.4 Literature References/CCDS

2.21 CBER/EDR, STN 125421/0, CBER documents\CBER Review Memo, Statistical Review and Evaluation BLA (Midcycle). Note: Final determination of the safety profile of the product used in the studies submitted to this BLA is pending final clinical, statistical and/or product review(s).

2.22 Input from CBER Clinical Reviewer

- A draft memo dated May 02, 2012 from the OBRR Clinical Reviewer that was distributed at the First Committee meeting on April 12, 2012.
- An updated mid-cycle review memo sent by the Clinical Reviewer on September 06, 2012
- Input from CBER Clinical Reviewer presented on September 11, 2012 at the CBER Blood Meeting.
- Input of key data sent by CBER Clinical Reviewer on April 01, 2013.

Note: Final determination of the safety profile of the product used in the studies submitted to this BLA is pending final clinical, statistical and/or product review(s).

3 PHARMACOVIGILANCE PLAN REVIEW

3.1 Clinical Safety Database

The Sponsor presented safety data analyses for two IND studies, Study BE1116_3002 and Study BE1116_3003 and for four non-controlled and/or non-IND studies. All of the clinical studies included in this submission used the Beriplex P/N product and "Beriplex" is used to refer to the Beriplex formulation.

Due to disagreement in assessment of certain cases, the FDA Clinical Reviewer requested the Sponsor to reanalyze their data of TEE cases and classification, as well as conduct stratified analyses by medical history of TEE. The data below is a summary of the safety data provided as part of the Pharmacovigilance Plan Version 3.0 submitted on June 18, 2012 and the Sponsor's updated analyses provided as part of Amendment 23 submitted on March 19, 2013.

3.1.1 Sponsor Analysis

3.1.1.1 IND Studies

3.1.1.1.1 Study BE1116_3002

Phase IIIb/Efficacy and Safety Pivotal IND study in subjects anticoagulated with vitamin K antagonists (VKA) presenting with acute major bleeding requiring urgent reversal of anticoagulation. There are a total of 212 subjects: 103 Kcentra group and 109 Plasma group. The primary objective of this study is to compare the hemostatic efficacy of Beriplex® P/N and Plasma in ceasing spontaneous or traumatically-induced major bleeding in subjects who have been on oral coagulation therapy and have acquired a deficiency of vitamin K-dependent Factors II, VII, IX, and X as well as proteins C and S. This endpoint was assessed for the time period from start of infusion until 24 hours after the start of infusion with Beriplex® P/N or Plasma. The co-primary objective of this study is to compare the efficacy of Beriplex® P/N and Plasma in rapidly reducing the international normalized ratio (INR) values at 30 minutes post infusion. The endpoint for this co-primary endpoint was the proportion of subjects who achieve an INR of 1.3 or lower within the 30 minutes post infusion. There are also a number of secondary objectives including assessing the safety and tolerability and all-cause mortality at 45 days post-treatment.

Please see the Clinical and Statistical Review Memos for results of the efficacy data. According to the results in the Pharmacovigilance Plan Version 3.0, overall Treatment-emergent adverse events (TEAEs) were similar among the Kcentra (64.1%) and Plasma (65.1%) groups (for TEAEs in at least 3 subjects in one subgroup by age). Stratified by age, TEAEs were more frequent among the Kcentra group (78.6%) in comparison to the Plasma group (70.8%) in the elderly aged 76 years and older; however the TEAEs were lower among the Kcentra group in comparison to the Plasma among those younger than 75 years old (<65 years: 48.5% Kcentra group vs. 56.3% Plasma group; ≥65-<75 years: 60.7% Kcentra group vs. 65.5% Plasma group). The frequency of Serious TEAEs was higher for the Kcentra group (31.1%) in comparison to Plasma group (23.9%) overall (Serious TEAEs in at least 2 subjects in one subgroup by age). By age, the frequency was also higher among those less than 65 years old and those aged 75 years and older (<65 years: 27.3% Kcentra group vs. 15.6% Plasma group; ≥75 years: 40.5% Kcentra group vs. 27.1% Plasma group) but not among those aged 65 to 75 years old(21.4% Kcentra group vs. 27.6% Plasma group). The frequency of treatment-related TEAEs (as assessed by investigator) were lower in the Kcentra group (9.7%) in comparison to the Plasma group (21.1%).

The Sponsor submitted analyses for TEE and subgroup analyses stratified by medical history of TEE on March 19, 2013 as part of Amendment 23 in response to a request by FDA for both Study BE1116_3002 and BE1116_3003 separately and pooled. The Sponsor analysis for study BE1116_3002 indicated that overall the frequency of TEE was higher among the Kcentra group (10 subjects, 9.7%) vs. the Plasma

group (6 subjects, 5.5%) with a difference of 4.2% (95% CI: -3.9%-12.7%). It should be noted that of the 10 TEE cases among the Kcentra group, one subject had an upper extremity venous thrombosis in association with an indwelling catheter. The frequency of serious TEE was also higher among the Kcentra group (7 subjects, 6.8%) vs. Plasma group (4 subjects, 3.7%) with a difference of 3.1% (95% CI: -4.0%-10.7%). There were 6 subjects (5.8%) with volume overload among the Kcentra group and 14 subjects (12.8%) among the Plasma group with a difference of -7.0% (-15.8%-1.8%). There were 10 deaths (9.7%) among the Kcentra group and 5 deaths (4.6%) among the Plasma group for a difference of 5.1% (95% CI: -2.7%-13.5%) within 45 days of treatment and 11 deaths (10.7%) in the Kcentra group and 5 deaths (4.6%) in the Plasma group overall with a difference of 6.1% (95% CI: -1.9%-14.6%).

Among those with a history of TEE, 9 (13.0%) Kcentra subjects and 3 (3.8%) Plasma subjects had a TEE with a difference of 9.2% (95% CI: -0.8%-20.4%). It should be noted that of the 9 TEE cases among the Kcentra group with a history of TE, one subject had an upper extremity venous thrombosis in association with an indwelling catheter. The frequency of serious TEE was also higher among the Kcentra group (6 subjects, 8.7%) vs. Plasma group (2 subjects, 2.5%) with a difference of 6.2 % (95% CI: -2.6%-16.3%). There were 3 subjects (4.3%) with volume overload among the Kcentra group and 11 subjects (13.9%) among the Plasma group with a difference of -9.6% (-20.1%-1.2%). There were 7 deaths (10.1%) among the Kcentra group and 4 deaths (5.1%) among the Plasma group for a difference of 5.1% (95% CI: -4.8%-15.9%) within 45 days of treatment and 8 deaths (11.6%) in the Kcentra group and 4 deaths (5.1) in the Plasma group overall with a difference of 6.5% (95% CI: -3.6%-17.6%).

Among those without a history of TEE, the incidence of TEE is 1 (2.9%) among the Kcentra group and 3 (10.0%) among the Plasma group for a difference of -7.1% (95% CI: -25.0%-8.9%). There was 1 (2.9%) serious TEE in the Kcentra group and 2 (6.7%) serious TEEs in the Plasma group with a difference of -3.7% (95% CI: -20.8%-11.4%). The frequency of volume overload was 3 (8.8%) for the Kcentra group and 3 for the Plasma group (10.0%) with a difference of -1.2% (95% CI: -20.0%-16.4%). The frequency of death was higher among the Kcentra group (3, 8.8%) in comparison to the Plasma group (1, 3.3%) for a difference of 5.5% (-11.5%-21.8%) within 45 days of treatment and also overall.

3.1.1.1.2 Study BE1116_3003

Interim Phase IIIb/Safety IND study in subjects requiring urgent VKA reversal (VKAR) for emergency surgery or invasive intervention. For the interim analysis as of November 16, 2011 provided as part of the Pharmacovigilance Plan 3.0 on June 18, 2013, there were a total 155 subjects: 77 Kcentra and 78 Plasma group. A total of 176 subjects were expected in total.

According to the results in the Pharmacovigilance Plan Version 3.0, the overall incidence of treatment-emergent adverse events (TEAEs) was 57.1% in the Kcentra group and 60.3% in the Plasma group (for TEAEs in at least 3 subjects in one subgroup by age). Serious TEAEs were reported in 23.4% in the Kcentra group and 24.4% in the Plasma group (Serious TEAEs in at least 2 subjects in one subgroup by age group). There were 7 subjects in the Kcentra group and 15 subjects in the Plasma group that had TEAEs at least possibly related to study product as assessed by the investigator. There were 3 subjects in the Kcentra group that had a SAE considered possibly related to treatment by the investigator and 3 in the Plasma group.

The Sponsor analysis for TEE for study BE1116_3003 on March 19, 2013 as part of Amendment 23 with final complete data indicated that overall the frequency of TEE was lower among the Kcentra group (4 subjects, 4.5%) vs. the Plasma group (7 subjects, 8.0%) with a difference of -3.4% (95% CI: -12.2%-5.1%). The frequency of serious TEE was also lower among the Kcentra group (3 subjects, 3.4%) vs. the Plasma

group (6 subjects, 6.8%) with a difference of -3.4% (95% CI: -11.8%-4.6%). There were 3 subjects (3.4%) with volume overload among the Kcentra group and 10 subjects (11.4%) among the Plasma group with a difference of -8.0% (-17.3%-0.9%). There were 3 deaths (3.4%) among the Kcentra group and 8 deaths (9.1%) among the Plasma group for a difference of -5.7% (95% CI: -14.6%-2.7%) within 45 days of treatment and 4 deaths (4.5%) in the Kcentra group and 8 deaths (9.1%) in the Plasma group overall with a difference of -4.5% (95% CI: -13.6%-4.2%).

Among those with a history of TEE, 3 (5.5%) Kcentra subjects and 4 (6.6%) Plasma subjects had a TEE with a difference of -1.1% (95% CI: -12.1%-10.4%). The frequency of serious TEE was lower among the Kcentra group (2 subjects, 3.6%) vs. the Plasma group (4 subjects, 6.6%) with a difference of -2.9 % (95% CI: -13.5%-8.0%). There was 1 subject (1.8%) with volume overload among the Kcentra group and 6 subjects (9.8%) among the Plasma group with a difference of -8.0% (-19.2%-2.8%). There were 2 deaths (3.6%) among the Kcentra group and 6 deaths (9.8%) among the Plasma group for a difference of -6.2% (95% CI: -17.6%-5.3%) within 45 days of treatment and also overall.

Among those without a history of TEE, the incidence of TEE is 1 (3.0%) among the Kcentra group and 3 (11.1%) among the Plasma group for a difference of -8.1% (95% CI: -27.5%-8.6%). There was 1 (3.0%) serious TEE in the Kcentra group and 2 (7.4%) serious TEEs in the Plasma group with a difference of -4.4% (95% CI: -22.9%-11.3%). The frequency of volume overload was 2 (6.1%) for the Kcentra group and 4 for the Plasma group (14.8%) with a difference of -8.8% (95% CI: -29.2%-9.7%). There was 1 death (3.0%) among the Kcentra group in comparison to 2 deaths (7.4%) in the Plasma group for a difference of -4.4% (-22.9%-11.3%) within 45 days of treatment and 2 deaths (6.1%) in the Kcentra group and 2 deaths (7.4%) in the Plasma group overall with a difference of -1.3% (95% CI: -20.4%-15.4%).

3.1.1.2 Non-controlled/non-IND Studies

3.1.1.2.1 Study BE 1116_3001

Phase III/Efficacy and Safety Non-IND study in subjects requiring urgent VKAR for acute bleeding or prior to surgery. There are a total of 43 subjects. There is no control arm for this study and data was not presented separately but only as part of a secondary pool that includes data from the bleeding Study BE1116_3002 and the surgery BE1116_3003 study in the pharmacovigilance plan. Data below is from the clinical safety summary.

Of the 43 subjects, 58% subjects experienced at least 1 AE. Six subjects had a SAE including-2 possible thromboembolic event, 1 subject with pulmonary embolism following a second dose of Beriplex outside of the protocol and 1 subject with a cerebral artery embolism and peripheral embolism. There were a total of 5 deaths during the follow-up period, with deaths occurring during the observation period for TEAEs (defined as the time from giving the informed consent until the first viral safety follow-up visit on Day 7-10 post-infusion) and 2 subjects died in the follow-up period (Day 34 and Day 79). One death was considered to be possibly related to the study product by the investigator. This event of suspected pulmonary embolism occurred following a second dose of 1500 IU of marketed Beriplex product which was not permitted per protocol.

3.1.1.2.2 Study BE1116/7D-201KO

Phase II/Efficacy and Safety Non-IND study in subjects with severe liver disease or treatment with oral anticoagulation. There are a total of 30 subjects: 22 severe liver disease and 8 VKAR.

Safety data was presented for a total of 30 subjects (21 men, 9 women) of which 23 had received a single infusion and 7 subjects had received multiple infusions of Beriplex. A total of 7 AEs were reported

among the 22 subjects with severe liver disease including hepatitis A in 3 subjects, hepatic failure, septic shock, laboratory test abnormal and vomiting. Two subjects had a SAE of hepatic failure and septic shock and both died. Causality to treatment could not be established as the subjects had AEs that may have been caused by their underlying disease. There were no AEs among subject on VKAR.

3.1.1.2.3 Study BE1116/7D-202KO

Phase II/Efficacy and Safety Non-IND study in subjects with congenital deficiency of Factor IX (hemophilia B). There are a total of 2 subjects.

No safety data was presented separately for this study as part of the pharmacovigilance plan. The clinical safety summary indicated there were no AEs reported in this study.

3.1.1.2.4 Study BE1116_1001

Phase I/Pharmacokinetic (PK) Non-IND study among healthy subjects. There are a total of 15 subjects.

No safety data was presented for this study as part of the pharmacovigilance plan. The clinical safety summary indicated that there was a single AE of nasopharyngitis reported on Day 7 considered not to be related to the product by the investigator.

3.1.1.2.5 Study Preston_2002

Investigator-initiated study in subjects requiring immediate VKAR. There are a total of 42 subjects.

A total of 8 subjects died within 7 days of being treated with Beriplex. Many subjects had comorbidities upon admission and were elderly. In 1 of the 8 subjects that died, there was a thromboembolic event and died of a thrombotic stroke following leg amputation and 48 hours after receiving Beriplex. The possible association as a contributing factor cannot be excluded, but subject also had severe arterial thrombovascular disease necessitating emergency amputation of leg, severe sepsis, and both renal and cardiac failure. No other thromboembolic events occurred within 7 days of treatment. There was no evidence of either venous or arterial thromboembolism in 3 of the 7 subjects that died and had autopsies.

3.1.1.2.6 Study Evans_2001

Investigator-initiated study in subjects with INR>8 due to warfarin treatment and with major bleeding or requiring urgent surgery. There are a total of 10 subjects.

There were 2 subjects with thrombocytopenia but no evidence of disseminated intravascular coagulation. There were also 2 subjects that had abnormal alanine transaminase levels on admission of which one was found to have rectal carcinoma with liver mestases. There were no other adverse events.

3.1.1.3 Sponsor Pooled Analyses (Pharmacovigilance Plan Version 3.0 Submitted June 18, 2012)

The Sponsor also provided pooled analyses for clinical safety in the Pharmacovigilance Plan Version 3.0 submitted on June 18, 2012. The pooled analyses included a Primary Pool of Studies 3002 and 3003 and a Secondary Pool for studies 3002, 3003 and 3001 from above. The Primary Pool is data integrated across two controlled IND clinical studies (3002 and interim analysis of 3003) whereas the Secondary Pool includes subjects in the Primary Pool and subjects from Study 3001 which had no Plasma control group but did administer the same dose as the two IND studies.

The overall incidence of TEAEs for the Primary Pool was 61.1% for Kcentra subjects and 63.1% for Plasma subjects and for the Secondary Pool the incidence was 61.0% among the Kcentra group (TEAEs by SOC with at least 2% of subjects in one population). The frequency of serious TEAEs was slightly higher among the Kcentra group (27.2%) in the Primary Pool in comparison to the Plasma group (24.1%); the incidence of serious TEAEs was 25.1% among the Secondary Pool Kcentra group (Serious TEAEs including deaths in at least 2 subjects in any group).

Serious Adverse Events (SAEs) considered at least possibly related to treatment was reported among 9.4% of the Kcentra group in the Primary Pool and 20.3% of the Plasma group; the incidence was 8.5% among the Secondary Pool Kcentra group (TEAEs at least possibly related to treatment in at least 2 subjects in any group).

3.1.1.4 Pooled Analysis of Study BE1116_3002 and Study BE1116_3003 (Amendment 23 Submitted March 19, 2013)

As part of Amendment 23 submitted on March 19, 2013 the Sponsor submitted a pooled analysis of data from both IND 3002 and 3003 and data are presented below. However, the Clinical Reviewer notes with which the Epidemiology Reviewer agrees that pooling data from the two clinical studies may not be scientifically justified for a number of reasons including:

- Subjects in 3002 study (acute bleeding patients) had higher INR values on average than the 3003 study (surgery patients) resulting in subjects receiving higher doses of Kcentra and Plasma
- Difference in the proportion of subjects
    - With baseline history of prior TE/coronary/cerebrovascular/peripheral vascular disease
    - With baseline history of congestive failure
    - Who were female. The 3002 study had a higher percentage of females and the majority of deaths (11 of 16, 69%) occurred in females
    - Who were non-Caucasian
    - That underwent surgery or had invasive procedure was seldom in the 3002 subjects but 100% in study 3003
    - Receiving blood transfusions
- Difference in pattern of concomitant medication use
- Meta-analysis of 1,032 subjects treated with PCCs for acute reversal of VKA anticoagulation found that the TEE rate was more than double in patients being treated for bleeding in comparison to patients undergoing surgery or invasive procedures

It should be noted that at the time of this pooled analysis, the data collection for IND 3003 was complete and included 176 patients total with 88 Kcentra subjects and 88 Plasma subjects. In the pooled analyses there were 13 deaths (6.8%) in the Kcentra group and 13 deaths (6.6%) in the Plasma group with a difference of 0.2% (95% CI: -5.3%-5.8%) within 45 days and 15 deaths (7.9%) in the Kcentra group and 13 deaths (6.6%) in the Plasma group overall with a difference of 1.3% (95% CI: -4.4%-7.0%). Overall, there were 14 TEE events (7.3%) in the Kcentra group and 13 TEE events (6.6%) in the Plasma group for a difference of 0.7% (95% CI: -4.9%-6.4%). It should be noted that of the 14 TEE cases among the Kcentra group, one subject had an upper extremity venous thrombosis in association with an indwelling catheter. The frequency of serious TEE was similar among the Kcentra group (10 subjects, 5.2%) vs. the Plasma group (10 subjects, 5.1%) with a difference of 0.2% (95% CI: -4.9%-5.3%). There were 9 subjects (4.7%) with volume overload among the Kcentra group and 24 subjects (12.2%) among the Plasma group with a difference of -7.5% (-13.6%-(-1.5%)).

Among those with a history of TEE, 12 (9.7%) Kcentra subjects and 7 (5.0%) Plasma subjects had a TEE with a difference of 4.7% (95% CI: -2.3%-12.2%). It should be noted that of the 12 TEE cases among the Kcentra group with a history of TEE, one subject had an upper extremity venous thrombosis in association with an indwelling catheter. The frequency of serious TEE was slightly higher among the Kcentra group (8 subjects, 6.5%) vs. the Plasma group (6 subjects, 4.3%) with a difference of 2.2% (95% CI: -4.1%-8.9%). There were 4 subjects (3.2%) with volume overload among the Kcentra group and 17 subjects (12.1%) among the Plasma group with a difference of -8.9% (-16.1%-(-1.8%)). There were 9 deaths (7.3%) among the Kcentra group and 10 deaths (7.1%) among the Plasma group for a difference of 0.1% (95% CI: -6.9%-7.4%) within 45 days of treatment and 10 deaths (8.1%) in the Kcentra group and 10 deaths (7.1%) in the Plasma group overall with a difference of 0.9% (95% CI: -6.2%-8.4%).

Among those without a history of TEE, the incidence of TEE is 2 (3.0%) among the Kcentra group and 6 (10.5%) among the Plasma group for a difference of -7.5% (95% CI: -19.5%-2.8%). The frequency of serious TEE was also lower among the Kcentra group (2 subjects, 3.0%) vs. the Plasma group (4 subjects, 7.0%) with a difference of -4.0% (95% CI: -15.1%-5.6%). The frequency of volume overload was 5 (7.5%) for the Kcentra group and 7 for the Plasma group (12.3%) with a difference of -4.8% (95%CI: -17.7%-7.1%). The frequency of death was slightly higher among the Kcentra group (4, 6.0%) in comparison to the Plasma group (3, 5.3%) for a difference of 0.7% (-10.3%-10.9%) within 45 days of treatment and also overall (Kcentra group-5 deaths (7.5%) vs. Plasma group 3 deaths (5.3%) for difference of 2.2% (95% CI: -9.1%-12.7%)).

3.1.2 FDA Analysis

The FDA Clinical Reviewer conducted two masked (blinded) and 2 unmasked analyses of data from both controlled IND clinical studies 3002 and 3003. The key data from the analysis and review confirmed the analyses provided by CSLB in Amendment 23 submitted on March 19, 2013. The following briefly summarizes the key results, in addition to the results above from the Sponsor analysis.

3.1.2.1 Study BE1116_3002

There were 11 deaths (10.7%, 95% CI: 6.1%-18.1%) among 103 Kcentra subjects and 5 deaths (4.6%, 95% CI: 2.0%-10.3%) among the 109 Plasma subjects in the ITT-S population for a RR 2.33 of excess death among the Kcentra group. The masked adjudication board concluded that only 1 death in the Kcentra group was at least possibly treatment related. Please note that one of these deaths is outside the 45 day observation period.

The initial FDA masked analysis took into account relative timing of administration of study test product and the nature and time of onset of the adverse event listed as contributing to death. In the FDA masked analysis, eight of the Kcentra subjects and 2 of the Plasma subjects were considered to have a possible causal relationship with the respective product administered.

In the second FDA masked analysis, the Sponsor- and Safety Adjudication Board-prepared subject narratives were reviewed to assess causality based on clinical judgment, including plausibility that a thrombotic event with appropriate symptom onset in a reasonable timeframe with respect to when the product was administered contributed to subject's death. The FDA analyses showed that 3 Kcentra subjects and 1 Plasma subject with deaths judged possibly or probably related to treatment administered based on masked review of the Sponsor- and Safety Adjudication Board generated narratives.

As seen in the Sponsor analysis submitted on March 19, 2013 as part of Amendment 23, the incidence of thromboembolic events (TEE) was 10 (9.7%) among the Kcentra subjects and 6 (5.5%) among the Plasma subjects with a difference of 4.2% (95% CI: -3.9%-12.7%). The frequency of Possibly, Probably, or Definitely Related TEE was higher among the Kcentra group (6 subjects, 5.8%) in comparison to the Plasma group (3 subjects, 2.8%). The FDA Reviewer's blinded assessment based on Sponsor- and Safety Adjudication Board-Generated narratives found 3 Kcentra subjects and 2 Plasma subjects with Possibility or Probably related TEE events.

3.2 Safety concerns within the BLA and/or Clinical Mid-Cycle Review Memos:

3.2.1 Important Identified Safety Issues:

A number of numerical imbalances were identified among Kcentra subjects in comparison to Plasma subjects; the differences were not statistically significant, possibly due to the small sample size of the trials.

3.2.1.1 Study BE1116_3002 (Pivotal Study)

- TEE events more frequent among the Kcentra group (10 subjects, 9.7%) compared to the Plasma group (6 subjects, 5.5%). It should be noted that of the 10 TEE cases among the Kcentra group, one subject had an upper extremity venous thrombosis in association with an indwelling catheter.
- Serious TEE events more frequent among the Kcentra group (7 subjects, 6.8%) compared to the Plasma group (4 subjects, 3.7%)
- Possibly, Probably, Definitely Related TEE events more frequent among the Kcentra group (6 subjects, 5.8%) compared to the Plasma group (3 subjects, 2.8%)
- Deaths within 45 days more frequent among the Kcentra group (10 subjects, 9.7%) compared to the Plasma group (subjects 5, 4.6%)
- Overall deaths more frequent among the Kcentra group (11 subjects, 10.7%) compared to the Plasma group (5 subjects, 4.6%)
- Among patients with a history of TEE:
    - TEE events more frequent among the Kcentra group (9 subjects, 13.0%) compared to the Plasma group (3 subjects, 3.8%). It should be noted that of the 9 TEE cases among the Kcentra group with a history of TE, one subject had an upper extremity venous thrombosis in association with an indwelling catheter.
    - Death within 45 days more frequent among the Kcentra group (7 subjects, 10.1%) compared to the Plasma group (4 subjects, 5.1%)
    - Overall death more frequent among the Kcentra group (8 subjects, 11.6%) compared to the Plasma group (4 subjects, 5.1%)
- Among patients without a history of TEE:
    - Death within 45 days and overall more frequent among the Kcentra group (3 subjects, 8.8%) compared to the Plasma group (1 subject, 3.3%)
    - Potential risk of TEE among the Kcentra group (1 subject, 2.9%) compared to the Plasma group (3 subjects, 10.0%)

It should be noted that the population of those without prior history of TEE was too small to evaluate adequately as there were only 64 patients in total without prior history of TEE (34 Kcentra subjects and 30 Plasma subjects).

3.2.1.2 Pooled Analysis of Study BE1116_3002 (Pivotal Study) and Study BE1116_3003 (Surgery Study):

- TEE events marginally more frequent among the Kcentra group (14 subjects, 7.3%) compared to the Plasma group (13 subjects, 6.6%). It should be noted that of the 14 TEE cases among the Kcentra group, one subject had an upper extremity venous thrombosis in association with an indwelling catheter.
- Overall deaths slightly more frequent among the Kcentra group (15 subjects, 7.9%) compared to the Plasma group (13 subjects, 6.6%)
- Among patients with a history of TEE
    - TEE events more frequent among the Kcentra group (12 subject, 9.7%) compared to the Plasma group (7 subjects, 5.5%). It should be noted that of the 12 TEE cases among the Kcentra group with a history of TEE, one subject had an upper extremity venous thrombosis in association with an indwelling catheter.
    - Serious TEE more frequent among the Kcentra group (8 subjects, 6.5%) compared to the Plasma group (6 subjects, 4.3%)
- Among patients without a history of TEE
    - Death within 45 days was similar among the Kcentra group (4 subjects, 6.0%) compared to the Plasma group (3 subjects, 5.3%)
    - Death overall more frequent among the Kcentra group (5 subjects, 7.5%) compared to the Plasma group (3 subjects, 5.3%)

The Sponsor included hypersensitivity as an important identified risk. Although there have been no case reports in the clinical studies, in the postmarketing experience 5 cases of hypersensitivity were identified of which 3 were considered serious.

3.2.2 Important potential safety issues

Other potential safety issues include possible volume overload, viral transmission as related to administration of blood products, hypersensitivity reactions, and medication error.

3.3 Sponsor's Proposed Risk Management Plan

3.3.1 Routine Pharmacovigilance

The Sponsor will adhere to routine pharmacovigilance practices which are part of the Sponsor's Global Pharmacovigilance organization. The Sponsor has provided a literature reference of this organization. The Sponsor has also indicated that they will comply with standards set by regional and local authorities, and specifically will adhere to 21 CFR 600.80 and per CSLB requirements, will conduct routine pharmacovigilance activities of adverse events reported as part of routine surveillance including spontaneous reports as well as those assessed from the literature. Reports will be priorities according to seriousness (i.e., fatal/life-threatening, serious, non-serious). The Sponsor will collect AEs and SAEs in a validated global electronic database for centralized collection, permanent retention and retrieval. The Sponsor will conduct real time medical review of all AEs and follow-up with appropriate cases for additional information if needed. Case reports will also be prepared and submitted to Competent Authorities in accordance with 21 CFR 600.80 and CSLB requirements with expedited reporting of unexpected serious adverse events and expected serious adverse events reported as part of aggregate periodic adverse experience reports. The Sponsor also provides a plan for signal detection where aggregate signal detection review will be conducted monthly if there are ≥ 50 adverse event reports per year and 3-monthly if there are ≤ 50 adverse event reports per year. Signal analysis will consist of 3 key steps: Signal substantiation and prioritization, Signal investigation planning and Signal Evaluation.

3.3.2 Active Surveillance

The sponsor proposes conducting a study entitled "Post-marketing Surveillance Program – Risk of thromboembolic and all-cause mortality among users of Kcentra and Plasma" using the ---(b)(4)--- database to estimate the risk of thromboembolic events (TEE) among patients treated with Kcentra for acute reversal of VKA. The sponsor originally in the previous four versions of the PVP proposed conducting a study with two phases; however in version five of the PVP the Sponsor now proposes an extensively revised study with three phases. The first phase of the study is a feasibility study pre-licensure to determine feasibility of conducting larger postmarketing surveillance Program in the proposed ---(b)(4)-- database, the second phase is a pilot study to determine feasibility of post-discharge monitoring, and conduct descriptive analyses and phase three is the main study to estimate the risk of TEE and all-cause mortality in patients treated with Kcentra™ and patients treated with Plasma for acute reversal of oral anticoagulation.

All three phases propose use of the ---(b)(4)-- database from ----------(b)(4)---------- The ---(b)(4)--- database is repository of hospital administrative data from across the US and represent mostly small to middle sized nonteaching facilities serving largely urban populations. Age, gender, length of stay, mortality, primary discharge diagnosis, and primary procedure groups appear to be representative of US hospitalized patients. All billing and administrative coding information can be cross-linked to hospital pharmacy billing records. Service level data recorded include charges for medications, procedures, and laboratory tests but no lab results are available. ---(b)(4)--- had access to hospital charts for additional clinical data in patient medical records. All hospitalizations are entered for all payors, not just Medicare. A patient with repeated hospital episodes can only be linked if the patient visited the same hospital.

3.3.3 First Phase-Feasibility Study Pre-licensure

Objective: To learn about adequacy of the ---(b)(4)--- data for the Post Marketing Surveillance program, and to refine criteria to define VKA reversal and TEEs if necessary, before Kcentra is introduced to the market.

Data source: ---(b)(4)-- database.

Study population: 30 patients treated with Plasma for VKA reversal in up to five hospitals. IRB approval will be needed from each participating hospital. Eligible patients will be those with diagnosis codes in the ---(b)(4)-- database indicating acute major bleeding and a history of anticoagulant use, who were treated with Plasma during their admission. Patients will need to only meet the first criteria for eligibility.

1) a recording of "long term current use of anticoagulants" identified by International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code V58.61 at the index hospitalization,
2) use of oral or intravenous vitamin K,
3) a previous hospitalization for deep vein thrombosis (DVT) or pulmonary embolism (PE) in the preceding 180 days,
4) a history atrial fibrillation or a prosthetic valve implant recorded any time prior to the administration of Kcentra or Plasma, or
5) major orthopedic surgery of a lower limb in the preceding 8 weeks.

Study design: The retrospective study cohort will include 30 patients in the U.S. --(b)(4)-- database using Plasma for reversal of VKAs. Patient's medical charts will be abstracted. Medical chart abstraction will be reviewed to validate definitions of VKA reversal, TEEs and death based on ---(b)(4)--- codes. The Sponsor also proposes to obtain further information about the patient's underlying risk of developing TEEs.

Analysis: Based on clinical trial data, expect 4 or fewer subjects with TEE or death. Only descriptive analyses will be conducted, although possible to include these subjects in subsequent analyses unless there are major changes to protocol. If further information is desired from chart reviews, possibility to expand the number of patients from the participating hospitals for relatively modest added unit cost.

Additional analysis based entirely on --(b)(4)-- data will be conducted to provide early experience to FDA. This analysis will include all patients in ---(b)(4)--- database who meet initial criteria for VKA reversal with Plasma from January 2010 through June 2012. Data will cover index admission and any subsequent admission within 45 days of VKA reversal at the same hospital to help explore feasibility of monitoring readmissions for TEEs. This analysis will also provide more stable numbers for TEEs and deaths for sample size calculations for the main study (Phase 3), insights into changing patterns of VKA reversal therapy and role of covariates for which information is available in the database. However, these estimates will be based on data without chart confirmed validation.

3.3.4 Second Phase-Pilot Study Post-licensure

Objectives: Feasibility of post-discharge monitoring and pilot comparative study of Kcentra and Plasma patients for TEE and mortality

Data source: ---(b)(4)-- database.

Study population: The pilot study will be conducted in 5 hospitals selected to include some where Kcentra is the preferred treatment and somewhere it is not yet used. The patient population will be those meeting the eligibility criteria as described above for the Phase 1 study with possible modifications depending on the results of the feasibility study. The study population will include 30 Kcentra patients and 30 Plasma patients from non-Kcentra hospitals matched for age, sex and treatment data. Matching on the specific indication for VKA reversal will also be considered.

Study design: Prospective cohort study. The observational period will start with the date of administration of Kcentra or Plasma (index day) and end 45 days after that, or at the occurrence of a study outcome or at the patient leaving the healthcare provider, whichever comes first. Medical records will be abstracted for all patients and submitted for expert review for validation of treatments and events and assessment of underlying risk of TEEs.

The Sponsor proposes to conduct a post-discharge survey for monitoring for TEEs within 45 days of VKA reversal and identifying out-of-hospital deaths through the Social Security Administration's Death Master File (SSA DMF). Both would require hospital participation and individual IRB approval. The post-discharge survey would be an "opt-out" approach in which hospitals send a letter to patients asking about their willingness to participate. If they do not "opt-out", the hospital would forward contact information to the Sloane Epidemiology Center (SEC).

If hospitals are unwilling to contact patients for the survey, the second option the Sponsor proposes to explore is evaluating readmissions via ---(b)(4)-- to the same hospital and out-of-hospital deaths via SSA DMF. For the SSA DMF, it would still require hospitals to forward information to the SSA for vital status determination, but there would be no direct contact with the patients. In this approach, retrospective data may also be used which may minimize treatment bias once Kcentra is available.

If the patient survey can be conducted, the Sponsor is proposing to do both so results can be compared to determine which is more informative.

Analysis: Descriptive Analyses-simple comparisons of subject characteristics and any events in the two groups. The Plasma patients will also be compared with the 30 patients from the feasibility study to assess potential treatment bias and inter-hospital variation in VKA practices.

A ---(b)(4)---only comparative analysis of TEEs and deaths in all Kcentra patients from the database who meet eligibility criteria and a matched series of Plasma patients. Readmission within 45-days to the same hospital will also be evaluated.

The Sponsor also proposes the possibility of using data from the Pilot Study as part of the final analyses of the main study.

3.3.5 Third Phase-Main Study

Objective: To estimate the risk of TEE and all-cause mortality in patients treated with Kcentra and patients treated with Plasma for acute reversal of oral anticoagulation

Data source: ---(b)(4)--- database.

Study population: The patient population will be those meeting the eligibility criteria as described above for the Phase 1 study with possible modifications depending on the results of the feasibility and pilot studies. The Sponsor provided a table of patients meeting the eligibility criteria described above under the Phase 1 study in a recent 6-month period and the numbers in the 10 hospitals with highest subject that meet criteria 1. According to this table, there are 2,696 patients meeting the criteria in the six months.

Sample Size: The Sponsor's initial plan is to include 500 patients per cohort based on the incidence of TEE and mortality within 45 days seen among Plasma patients in the pivotal bleeding study. The rates however do not take into account varying lengths of follow-up and the infeasibility to conduct post-discharge monitoring.

Study design: Prospective cohort study. The observational period will start with the date of administration of Kcentra or Plasma (index day) and end 45 days after that, or at the occurrence of a study outcome or at the patient leaving the healthcare provider, whichever comes first.

Exposure: Administration of Kcentra or Plasma. Data on the dose of Kcentra and number of Plasma administered will also be collected if available.

Outcome of interest: Study outcomes are required to occur after the index date. The primary study outcome is TEE which is comprised of DVT, PE, acute myocardial infarction, ischemic stroke and mesenteric artery thrombosis. Depending on the feasibility study, expansion of TEE definition to include other related entities such a distal limb thrombosis, transient ischemic stroke, acute coronary syndrome without MI, and sagittal sinus thrombosis will be considered. Death after exposure will also be evaluated. ICD-9-CM codes will be used to define outcome except for death which is coded as a discharge status. Of note, since records in the ---(b)(4)--- database are coded at discharge, there is no corresponding date of diagnosis. It will be assumed that all outcome events that occurred during the hospitalization with

Kcentra or Plasma was administered (index hospitalization) occurred after the start of Kcentra or Plasma treatment and within the 30 days and thus were study outcomes.

Case validation: A chart review is planned for all potential TEE cases from selected hospitals (at least 50% of these outcomes, is possible), and for a sample of patients without outcomes, as well as subjects in the feasibility and pilot studies. A Medical expert will receive all information available in the ---(b)(4)-- database, chart abstracted information and anonymized copies of hospital discharge summaries. Draft abstraction forms were provided by the Sponsor. The medical expert will confirm VKA reversal as ---(b)(4)-- do not specify that VKAs were used and assess likelihood of TEE.

Covariates: Covariates for analysis will include age, gender, ethnicity, the recording of the presence or absence of known medical conditions (ischemic heart disease, congestive heart failure, cerebrovascular disease, hypertension, renal insufficiency, diabetes, hyperlipidemia, liver disease, disseminated intravascular coagulation, atrial fibrillation, and non-skin cancer), and any hospital stays in the preceding 90 days with corresponding procedures and discharge diagnoses (with particular focus on total hip replacement, total knee replacement, lower limb fractures, and other factors known to be associated with an increased risk of DVT and PE). Acute bleeding events before the index date will also be recorded. For each surgical patient, the type of surgery, whether admission was elective or emergency, and the hospital at which the operation took place will be recorded. Adequacy of ---(b)(4)-- for covariates will be assessed in the feasibility and pilot studies.

Post-discharge monitoring: The Sponsor proposes using the feasibility and pilot studies to resolve issues of post-discharge monitoring. Median length of hospital stay after VKA reversal with Plasma is 5 days and with 75% having stays of less than 10 days. The Sponsor proposes exploring options in the pilot study which includes both post-discharge monitoring by survey and readmissions at the same hospital for TEEs and for out-of-hospital deaths via the SSA DMF. The Sponsor states that if post-discharge monitoring is determined not to be feasible at all, most reported TEEs have occurred within a few days of VKA reversal so data using the index admission will still be informative even if it does not provide a comprehensive picture of risk.

Analysis: The Sponsor provides a summary description of the planned analyses but states a more detailed statistical analysis plan will be provided with the final protocol of the main study that will be prepared after the feasibility and pilot studies are completed.

1) Descriptive analysis: Descriptive analysis of the two cohorts will be performed for the following variables extracted from the database: age, gender, ethnicity, Kcentra dose/amount charged, number of Plasma units charged, in-hospital use of Vitamin K, presence of the medical conditions known to be risk factors described above as potential covariates, and any hospital stay in the preceding 90 days with corresponding procedures and discharge diagnoses (in particular total hip replacement, total knee replacement, lower limb fractured and other factors known to be associated with an increased risk of DVT and PE). Surgical interventions and diagnostic medical procedures performed after the administration of Plasma and Kcentra will be recorded.

For each outcome, separate analyses will be conducted to estimate crude overall and age- and sex-specific incidence rates (including rate differences and 95% confidence intervals) of TEE and all-cause mortality within 45 days following administration of Kcentra and Plasma. If information is available, rates will be estimated according to Kcentra dose/number of vials charged and number of Plasma units charged.

2) Multivariate Cox model: Cox proportional hazard models will be used to evaluate the association between exposure to Kcentra or Plasma and outcome in separate models for each outcome of interest (e.g., TEE, all cause mortality). The models will account for age, gender, ethnicity, Kcentra dose, number of bags of Plasma administered, and underlying condition for use of oral anticoagulants. The models will also include the medical conditions known to be risk factors as well as any hospital stay in the preceding 90 days.

Limitations:

1) This study is intended to study patients receiving Kcentra or Plasma for the acute reversal of oral anticoagulation. One of the concerns of using the ---(b)(4)-- database is that use of anticoagulants in the community is not recorded as a part of this database. The Sponsor proposes using ICD-9-CM Diagnosis Codes for recording of "long term current use of anticoagulants". However the codes are unable to identify codes for VKA therapy, the population of interest for the post marketing study. In addition, the time period of VKA therapy needs to better defined.

2) The current study assumes that all events that occurred during the index hospitalization occurred after the start of Kcentra or Plasma treatment and within the following 30 days and are counted as study outcomes. A medical chart review is proposed by the sponsor for all potential TEE and all-cause mortality cases from selected hospitals (at least 50% of all cases). However, since only a subset of the population will be chart confirmed, this assumption may lead to an overestimation of the number of events after exposure.

Especially given the imbalance of TEE death seen in the clinical studies and the potential risk of TEE observed in Postmarketing Study 5001, it is important that a medical record review is conducted to confirm the date of the outcomes, as well as confirm exposure and potential confounders.

3) Currently Plasma is the only approved treatment choice. Upon Kcentra approval, it will be the first 4 factor prothrombin complex concentrate in the US. Thus, physicians may intend to use Kcentra in more severe patients. It is important that the profile of the patients and the urgent reversal of oral anticoagulation are well documented and if there is a bias, potential confounders can be adequately adjusted for in the analysis. To minimize the bias due to selected treatment for severe patients, the Sponsor proposes using either different hospitals for Kcentra patients and Plasma patients recruited contemporaneously or using a retrospective Plasma cohort. While a retrospective cohort may minimize treatment bias, changes in treatment of acute bleeding over time may be of concern. Furthermore, since the ---(b)(4)-- database may not have data on potential confounders, the ability to control for underlying risk factors and to identify prior history of TEE is limited.

3.4 FDA's comments on Sponsor's proposed postmarketing study

The Sponsor has proposed that a "postmarketing observational database study which is served as a surveillance project will be conducted to actively monitor thromboembolic events and mortality in patients treated with Kcentra". "The Company believes this project may contribute to the understanding of this identified risk in this population."

Since the original BLA submission on March 30, 2012, the Sponsor had provided a more detailed protocol in response to our requests for information. Originally the Sponsor was proposing a two-phase study, but as of Version 5 of the Post Marketing Surveillance Program, the current proposed study is a 3 Phase Study.

The Phase 1 Study is a feasibility study of using the proposed --(b)(4)-- database. The Phase 2 Study is a Pilot Study that proposes to evaluate the ability to conduct post-discharge monitoring using cases identified in the --(b)(4)-- database. The Phase 3 Study is the main study to be conducted to evaluate the risk of TEE and Mortality within 45 days post treatment among Kcentra subjects in comparison Plasma subjects. FDA still has a number of concerns with the current proposed protocol. The following are the major concerns discussed with the Sponsor on a telecom on April 05, 2013 as well as FDA proposed PMR Study Concept:

1) The new protocol is referred to as Version 4; however a Version 4 dated 28 September, 2012 was submitted earlier. Please clarify the version of the current protocol dated 20 February, 2013 to version 5.

2) The study population should accurately address the proposed indication for treatment. The inability to identify patients on VKA therapy vs. other anticoagulants is concerning. Although the feasibility study would evaluate the usefulness of the ICD-9 codes to identify this population, it is unclear what the alternative plan will be if Phase 1 of the study proposed demonstrates that --(b)(4)-- is unable to adequately identify the study population of interest. In addition, the prior version of the protocol, patient needed to meet the first criteria and one or more other criteria for entry into the study. However; in the current version only criteria 1 is required. This is concerning as the additional criteria may better indicate the study population of interest.

3) The proposed database should accurately identify potential confounders for matching/adjustment during analysis. The proposed database is unable to identify important baseline characteristics of the study population that may be necessary for matching and/or adjustments during analysis. This includes potential confounders such as history of TEE and other underlying medical conditions. Since the proposed database is unable to link across hospitals or other databases, it is unclear how this information will be collected. Although the Sponsor proposes conducting medical chart review, it will only be on a limited subset of the population from select hospitals. Furthermore in the previous protocols, the Sponsor indicated that prescription medications can be made available for a subset of 3% to 8% of the patients in --(b)(4)-- by linking data with ----------(b)(4)----------. However in the current protocol this is not indicated. Also, in the earlier Version 4 protocol, the Sponsor indicated that characteristics of surgeons and hospitals are also available; but is unclear in the current version whether that is the case.

4) Kcentra and Plasma patients should be enrolled contemporaneously to minimize potential biases in changes in practices for acute bleeding, as well as hospital matched if possible to minimize intra-hospital variability. If contemporaneous hospital matching of Plasma controls is not possible, information on potential confounders should be available for proper adjustment during analysis. The Sponsor proposes evaluating usefulness of both a retrospective Plasma cohort and a contemporaneous cohort from different hospitals. There may be difference in practice over time for the management of acute bleeding patients and therefore a retrospective cohort is concerning. A contemporaneous Plasma control from different hospitals although may minimize treatment bias; there would be concern of intra-hospital variability in practices and or study populations. Since --(b)(4)-- is unable to assess potential confounders in the existing database, use of different hospitals would not be desirable due to the inability to control for potential confounders during analysis.

5) The dose of Kcentra and Plasma should be measured. It is unclear from the proposed protocol whether this will be feasible. In addition the Sponsor indicates that one of the issues is “to

determine the ability to characterize dose of exposure or a suitable proxy for purposes of performing "dose-specific" analyses." It is not clear what a "suitable proxy" would be.

6) Follow-up is required for all patients for a minimum of 45 days following treatment. In the current protocol you have provide data on length of stay among patients in --(b)(4)-- and indicate that the median time is 5 days with 75% of patients with less than 9 days. Since the clinical study data indicate that possible TEE may occur beyond 10 days and an imbalance in death was observed for days 30-45, FDA requires that patients are followed for a minimum of 45 days to ensure full capture of all TEE events potentially related to product exposure.

7) Medical chart review of all cases of TEE and death is required to confirm exposures, outcomes and potential confounders. The current study assumes that all events that occurred during the index hospitalization occurred after the start of Kcentra or Plasma treatment and within the following 45days and are counted as study outcomes. A medical chart review is proposed by the Sponsor for all potential TEE cases to confirm from selected hospitals (at least 50% of all TEE and mortality cases) to confirm this assumption, but this assumption will not be verified for the remaining patients and is concerning. In addition, it is not clear in the current protocol whether medical experts reviewing the abstracted information will be blinded to Plasma or Kcentra administration.
8) The Sponsor provides a sample size calculation for simple event rates for the 45 day follow-up. In the analysis section however the Sponsor also indicates that as a last resort that data may need to be censored after discharge if post-discharge monitoring is not feasible. Given this possibility, additional sample size calculations should take into account varying lengths of shorter follow-ups either due to loss to follow-up or infeasibility of post-discharge monitoring.

9) In the new protocol the Sponsor indicates that "Interim results will not be used as a basis for stopping the study before the full sample is enrolled and analyzed". This was not indicated in the earlier study protocols. This would need to be discussed with FDA.

4 REVIEW OF OTHER INFORMATION FROM THE MANAGED REVIEW PROCESS

4.1 Clinical review memo

In the draft clinical mid-cycle review memo, the Clinical Reviewer noted an imbalance of deaths between those receiving Kcentra vs. Plasma for the indication being sought. There is also concern of thromboembolic events after Kcentra in addition to other potential safety issues. An increased risk of TEE among those with a history of TEE was seen in the clinical study data and a potential increase among those without a history of TEE; however the size of the cohort without prior history of TEE was limited and could not be adequately evaluated. See section 3.1.2 for Clinical Reviewer's reanalysis of clinical study death and TEE cases. Final clinical review memo is pending.

4.2 Statistical review memo

The statistical mid-cycle review memo confirmed that although Kcentra met the non-inferiority primary goal in comparison to Plasma, it did not meet the criteria for superiority. Also, although it was assumed that volume overload would be less of a concern with Kcentra in comparison to Plasma, there was not statistically significant improvement. No statistically significantly increased risk of safety outcomes was identified in the pre-licensure clinical studies. Final statistical review memo is pending.

5 POSTLICENSURE SAFETY REVEIW

Kcentra is not currently licensed for use in the US. Beriplex was first approved on February 16, 1996 in Germany. It is currently licensed for use in 24 countries. The manufacturer provided 7 PSURs, a Safety Bridging Report and a line listing of their safety database with a cutoff date of February 15, 2012. As of the most current line listing submitted on February 28, 2013 for the time period from 16-FEB-1996 to 15-FEB-2012, there 85 cases total in the Sponsor safety database, of which 78 are Post Marketing Cases and 6 Sponsor Clinical Study Cases. There are actually 79 postmarketing cases in the Sponsor database; however one is a clinical study case that was reported inadvertently as a spontaneous case report. This duplicate spontaneous report is not included in the numbers for spontaneous reports or clinical study reports above and only the original clinical study report is included. Of the 78 Post Marketing Cases, 57 were Spontaneous cases, 13 were Postmarketing study cases and 8 were from Unsponsored studies.

	Postmarketing Cases (N=78)					**Clinical Study Cases (N=6*)**
	Spontaneous Cases (n=57*)			**Non-spontaneous Cases (n=21)**		
	Spontaneous reports	**Health Authority reports**	**Literature reports**	**Sponsored Postmarketing Study reports (BE1116_5001)**	**Unsponsored Study reports**	
Total Cases	**51**	**3**	**3**	**13**	**8**	**6**
Serious Cases	**42**	**3**	**3**	**13**	**8**	**6**
Fatal Cases	**13**	**0**	**1**	**2**	**8**	**2**

*There are actually 79 postmarketing cases in the Sponsor database; however one is a clinical study case that was reported inadvertently as a spontaneous case report. This duplicate spontaneous report is not included in the numbers for spontaneous reports or clinical study reports above and only the original clinical study report is included.

The 78 postmarketing adverse event reports include the following according to FDA's classification:

	Spontaneous Cases (Spontaneous/Health Authority/Literature reports) (N=57)	**Postmarketing Study BE116_5001 (N=13)**	**Unsponsored Studies (N=8)**
Thromboembolic events	**17 cases, 8 deaths**	**8 cases, 2 deaths**	**1 cases, 1 death**
Hypersensitivity or allergic reactions	**5 cases, 0 deaths**	**0 cases**	**0 cases**

Viral Transmission	**20 cases, 2 deaths** • **2 HAV** • **6 HBV** • **1 HBV & HIV** • **11 HCV**	**0 cases**	**0 cases**
Lack of effect/insufficient dose	**6 cases, 1 death**	**5 cases, 0 deaths**	**0 cases**
Other	**9 cases, 3 deaths**	**0 cases**	**7 cases, 7 deaths**

Of the 57 spontaneous reports, according to the Sponsor 19 events were at least possibly related to Beriplex administration (16 possibly related, 2 probably related, 1 related) as assessed by the sponsor. For the remaining events, there was insufficient evidence for 6 events, unlikely for 17 events, and unrelated for 15 events as assessed by the sponsor.

Postmarketing use of Beriplex outside of the US has identified and reported the following important adverse reactions:

1) Thromboembolic complications
    a) Arterial thromboembolic events including
        i) acute myocardial infarction
        ii) arterial thrombosis
    b) Venous thromboembolic events including
        i) pulmonary embolism
        ii) venous thrombosis
    c) Disseminated intravascular coagulation

2) Hypersensitivity or Allergic reactions including
    a) Angioedema
    b) Anxiety
    c) Bronchospasm
    d) Dyspnea
    e) Flushing
    f) Hypotension
    g) Nausea
    h) Pulmonary edema
    i) Tachycardia
    j) Tachypnea
    k) Urticaria
    l) Vomiting
    m) Wheezing

Important potential risks identified through postmarketing include
1) Viral Transmission
2) Medication/Dosing Errors

Important missing information includes data on

1) Efficacy and Safety in Pregnancy
2) Efficacy and Safety in Labor and Delivery
3) Efficacy and Safety in Breastfeeding Mothers
4) Efficacy and Safety in the Pediatric Population
5) Safety in in combination with other coagulation factor products (such as Novoseven®) in bleeding patients.

Of the 78 post marketing cases, there were a total of 26 TEE cases, 17 as spontaneous reports, 8 from Postmarketing study BE1116_5001 and 1 from a unsponsored study. Of the 26 TEE cases, there were 11 fatal cases of which 8 were reported as a spontaneous report, 2 from Postmarketing study BE1116_5001 and 1 from an unsponsored study.

Since licensure on 16-FEB-1996, there have been 20 potential viral transmission post marketing cases reported after Beriplex. Of the 20 cases reported, 2 cases were for HAV transmission 7 cases of HBV transmission of which 1 also included HIV transmission, and 11 cases of HCV transmission. There were two fatal cases, one with potential HAV transmission and 1 with HBV transmission. Among 17 of the 20 cases, potential viral transmission was excluded as the Beriplex batch administered was tested to be negative or the batch was manufactured from source material tested to be negative with no issues in safety, purity and/or potency. The three cases that did not reference batch and/or source material testing are described further below:

1. Fatal HAV Case-A 73 year old female with a history of mitral valve replacement for which she received oral anticoagulation therapy. In September 1997 she underwent surgery and received Beriplex, RBCs FFP and Kybernin P. Eight weeks later she developed icterus and symptoms of sub-acute liver failure. She was hospitalized in Nov 1997 and hepatitis serology was negative for Hep B and Hep C, IgG positive but IgM negative for Hep A. The patient died 4 weeks later of liver failure and no autopsy performed. According to the report there was no hint of acute Hep A, B, C--suspect preexisting affection of bile duct with consecutive malfunction of liver and exclude causal relationship to Beriplex. There was no information on batch testing.
2. HBV Case- A 73 year old male underwent heart surgery and had received Beriplex and other blood- and Plasma products including virus inactivated human Plasma. Eight days after surgery the patient tested positive for Hep B antibodies (anti-HBs and anti-HBc). Causal relationship excluded as patient had never been Hep B-Ag positive. According to the report, the incubation period for Hep B is 30 days minimum and the observed incubation period of only 8 days is almost impossible. Hep-serology indicates that this was a passive transfusion of antibodies most likely caused by virus inactivated human Plasma according to the report. There was no reference to Beriplex testing.
3. HBV Case-A 24 year old male had a liver transplantation in July 2006. Intraoperatively he received Beriplex and other blood products. In August 2006 a hepatitis serology showed a terminated Hep B infection. According to the report, a causal relationship excluded to Beriplex because the time interval was too short. In Jan 2008 the patient was hospitalized again due to relapse of hemolytic uremic syndrome. During hospitalization, acute highly replicative Hep B diagnosed. According to the reporting physician, this demonstrates a reactivation of preexisting terminated Hep B infection evoked by recent therapies with steroids for treatment of hemolytic uremic syndrome. There was no reference to Beriplex testing.

6 INTEGRATED RISK ASSESSMENT

Important safety issues identified in the clinical studies by either the Sponsor or the FDA include the following comparing Kcentra subjects to Plasma subjects, which will be monitored in a required postmarketing observational study:

1) Increased frequency of TEE overall and among those with a history of TEE

2) Potential increased frequency of TEE among those without a history of TEE

The IND studies, non-controlled/non-IND studies and the post-market surveillance data also indicate the following are potential safety concerns: (Note: Incidence rate or between-group comparison is not available.)

1) Death- The IND studies, non-controlled/non-IND studies and post-marketing data have identified fatalities after administration of Beriplex. There have been a total of 24 deaths reported after Beriplex in the postmarketing data, with 14 as spontaneous reports, 2 from the Postmarketing Study BE1116_5001 and 8 from unsponsored studies. There were at least 3 cases in the PSURs that were possibly related to the product, in addition to 1 case in the pivotal bleeding trial and an additional due to medication error in study BE1116_3001. Kcentra is indicated in high risk populations and deaths will inevitably be reported by chance alone, natural causes, or pre-existing disease in single arms studies, as they do in passive surveillance. Individual case causality assessments are challenging and the ability to infer whether a death is product related is limited. Population level surveillance to assess for differences in all-cause mortality, as proposed in the PMR, should enhance our abilities to detect safety concerns related to fatal outcomes. Moreover, the PMR will allow FDA to assess for patterns in the organ systems affected, the timing, and/or risk factors in deaths observed after licensure through detailed case review.

2) Hypersensitivity- The PSURs indicate there are at least 5 AEs of hypersensitivity/allergic reactions. This concern is already listed in the sponsor's PVP and will be addressed by routine pharmacovigilance.

3) TEE-The addition clinical studies and post marketing data indicate that thrombotic and thromboembolic events are a potential SAE reported after Beriplex administration. There are a total of 26 TEE cases reported as postmarketing adverse events, with 17 cases as spontaneous reports, 8 cases from Postmarketing Study BE1116_5001 and 1 case from an unsponsored study. This concern is already listed in the sponsor's PVP and will be addressed by routine pharmacovigilance and the proposed PMR.

4) Viral Transmission- There were 20 potential viral transmission spontaneous reports of which 1 was fatal. However causality cannot be established as for 17 cases there was some evidence of Beriplex testing showing negative results either for the lot and/or manufactured batch, other blood products were concomitantly administered and/or there is insufficient data. This concern is already listed in the sponsor's PVP and will be addressed by routine pharmacovigilance.

5) Medication/dosing error- In the postmarketing data there are 11 cases of lack of effect/insufficient dose. Of the 11 cases, 6 cases were spontaneous reports and 5 were reported in Postmarketing Study BE1116_5001. Among the 6 spontaneous reports, there was 1 fatal case among a patient that

did not receive a sufficient dose of Beriplex. In the clinical studies data there is at least one SAE of medication error which was fatal and possibly causally related to Beriplex. The subject was given a second dose of the product which deviated from the protocol. This concern is already listed in the sponsor's PVP and will be addressed by routine pharmacovigilance.

6) There have been 3 cases of suspicion of TRALI AEs reported in the PSURs. Although this event is not listed in the sponsor's PVP, FDA believes that the risk can be monitored by routine pharmacovigilance.

OBE/DE believes the numerical imbalances observed in the Clinical Study 3002 are adequate to indicate signals of serious risks of TEE related to the use of Kcentra. Specifically, the numerical imbalances represent signals of serious risks of TEE in patients with a history of TEE, but potential signals in patients without a history of TEE because no increased frequency of TEE was observed in this sub-population, possibly due to the small sample size (64 subjects in total) which is insufficient to identify cases even if a risk exists. OBE/DE therefore requests a required post-marketing safety study (PMR) under section 901 of FDAAA 2007 Title IX to further evaluate the risk of TEE after Kcentra administration. Please refer to the PMR justification document for the full rationale for a required study to assess thromboembolic events.

Although the sponsor argues that these numerical imbalance decrease with pooling of the safety data from both studies 3002 and 3003, OBE/DE agrees with OBRR that pooling data from two clinical studies may not be scientifically justified due to the fundamental differences in the baseline characteristics (including INR values, medical history, concomitant medication use, demographics, etc.) between the acute bleeding patients (Study 3002) and surgery patients (Study 3003).

In summary, FDA's risk assessment has not identified any new safety concerns from the sponsor's safety specification. However, OBE believes that monitoring for the known risk of thromboembolic events should enhanced through a targeted safety study of this outcome of interest and has required an observational study to enhance the pharmacovigilance plan.

7 RECOMMENDATIONS

Based on the review of the pre-licensure safety data, the sponsor's proposed pharmacovigilance plan, and the post-marketing safety reports from outside the US, OBE/DE recommends the following actions for post-licensure safety surveillance activities:

1) Routine pharmacovigilance: Adverse event reporting in accordance with 21 CFR 600.80.

2) Enhanced surveillance: All serious and non-serious adverse experience reports for thromboembolic events (TEE) should be reported as 15-day expedited reports under 21 CFR 600.80 (c)(1)(i), in the first five years after licensure.

3) Active surveillance: OBE/DE and OBRR agree that a phase IV observational study should be conducted as a post-marketing requirement (PMR) under section 901 of FDAAA 2007 Title IX.

3.1) OBE/DE proposed a PMR study concept to the Sponsor during a telecom on April 05, 2013. The Sponsor has agreed to conduct a PMR. On April 10, 2013, FDA received a CSLB PMR Study Concept dated

April 09, 2013. FDA reviewed the Sponsor proposed PMR study concept and provided comments. CSLB provided a revised PMR Study Concept on April 18, 2013 and after a telecom with FDA, the Sponsor provided updates to the proposed PMR study Concept on April 19, 2013.

FDA agrees with the overall CSL Behring proposed PMR Study Concept of a Retrospective observational, cohort study among patients treated with Kcentra or plasma for urgent reversal of VKA therapy in the setting of major acute bleeding submitted April 18, 2013 with changes that were agreed to on April 19, 2013 between CSLB and FDA.

CSL Behring
Prothrombin Complex Concentrate (Human), Kcentra™
BLA 125421/0
Post-Marketing Requirement (PMR) Study Concept Submitted April 18, 2013 and Updated April 19,2013

Primary Objectives	To estimate among patients without a recent (within the prior 90 days) history of thromboembolic events (TEE), treated with Kcentra or plasma for urgent reversal of VKA therapy in the setting of acute major bleeding: 1) The risk of TEE within 45 days following VKA reversal with Kcentra vs. plasma 2) The risk of all-cause mortality within 45 days following VKA reversal with Kcentra vs. plasma
Secondary objectives	To estimate among all patients treated with Kcentra or plasma for urgent reversal of VKA therapy in the setting of acute major bleeding: 1) The risk of TEE within 45 days following VKA reversal with Kcentra vs. plasma 2) The risk of all-cause mortality within 45 days following VKA reversal with Kcentra vs. plasma 3) The risk of TEE within 14 days following VKA reversal with Kcentra vs. plasma 4) The risk of all-cause mortality within 14 days following VKA reversal with Kcentra vs. plasma To estimate among patients without a recent (within the prior 90 days)history of thromboembolic events (TEE), treated with Kcentra or plasma for urgent reversal of VKA therapy in the setting of acute major bleeding: 1) The risk of TEE within 14 days following VKA reversal with Kcentra vs. plasma 2) The risk of all-cause mortality within 14 days following VKA reversal with Kcentra vs. plasma
Exploratory objective	To estimate among patients without a recent history of TEE treated with Kcentra or plasma for urgent reversal of VKA therapy in the setting of acute major bleeding: 1) The risk of fatal TEE within 45 days following VKA reversal with Kcentra vs. plasma 2) The risk of fatal TEE within 14 days following VKA reversal with Kcentra vs. plasma

Study design	Retrospective observational, cohort study among patients treated with Kcentra or plasma for urgent reversal of VKA therapy in the setting of major acute bleeding. The Kcentra treated group will be identified following inclusion of Kcentra on the (b)(4) formulary Two control groups of plasma-treated patients will be included: • Contemporaneously treated with plasma • Historically treated with plasma (identified from the (b)(4) database in the 5-10 years prior to the inclusion of Kcentra on the (b)(4) formulary) The rationale for the two plasma groups is to: • Assess characteristics of the patient population treated with plasma over time • Assess changes in plasma treatment patterns over time • Provide a control group that is not subject to channeling bias in the comparison of Kcentra with plasma
Data Source	----------(b)(4)---------- database prior to and during the period when Kcentra is included on the (b)(4) formulary. The (b)(4) health care plan serves a total population of approximately 3.3 million members. Under a mutual exclusivity arrangement, physicians of ----------(b)(4)----------, care for ----------(b)(4)---------- members at facilities owned by ----------(b)(4)----------. All 17 ----------(b)(4)---------- hospitals and 44 outpatient clinics use the same information systems with a common medical record number and can track care covered by the plan but delivered elsewhere The (b)(4) databases / data sources include: • Inpatient diagnoses and procedures and in-hospital mortality from a database that contains data for ---------(b)(4)---------- hospitalizations. • Inpatient diagnosis and procedures for members treated on an emergent basis at non --------(b)(4)--------- facilities, determined from a --------(b)(4)--------- billing claims database. • Outpatient diagnoses from a database of assigned diagnoses for all ambulatory encounters (outpatient clinics, urgent care, and emergency department). • Medication data from a pharmacy database. • Laboratory data from a laboratory results database • Death outside of hospital can be determined by linkage to the Social Security Master Death File or the National Death Index (NDI). The former does not include cause of death, whereas the latter can provide death certificate data as well. We propose to use the NDI as the primary means to identify death in patients in whom vital status is not known. However there is a 12-15 month lag before death data is available in the NDI while there is only a 1-2 month lag for the SSA DMF. CSL Behring will use the SSA DMF as back-up to the NDI to identify possible death in the event that vital status information is not available in the NDI database.

Study Population	The primary objective of the study and the study sample size will be based on the subset of adult patients without a recent history of TEE, defined as above in the Primary Objectives. However, all adult patients with acute major bleeding treated with Kcentra or plasma for urgent reversal of VKA therapy meeting entry criteria will be included until the Kcentra cohort is fully enrolled. Therefore, patients with a history of recent TEE will also be included for purposes of the secondary study objectives. The primary analysis will be based on the comparison of outcomes in patients treated with Kcentra compared with the historical plasma-treated controls. The number of contemporaneous plasma-treated controls that will be included in the study is not known. It is proposed to include all contemporaneous plasma controls that qualify until the Kcentra group is fully enrolled then stop the study enrollment regardless of the number of contemporaneous plasma controls at that point in time, rather than delay completion of the study to accrue more contemporaneous plasma-treated controls. Analyses comparing Kcentra-treated patients with contemporaneous plasma-treated controls will be matched on history of TEE.
Entry criteria	Inclusion criteria • Aged 18 years and older • A minimum of 365 (or 180 days, feasibility to be determined) days of enrollment in the --(b)(4)-- prior to index VKA reversal treatment date* • Treatment with Kcentra or plasma for urgent reversal of VKA therapy in the setting of acute major bleeding Exclusion criteria • Patients requiring urgent reversal of VKA therapy in the setting of bleeding due to major trauma (e.g., motor vehicle accidents) • Patients requiring urgent reversal of VKA therapy for surgical reasons * CSL Behring will ask ----------(b)(4)---------- to assess the feasibility of identifying sufficient numbers of historical plasma controls using the criterion that all patients have a minimum of 365 days of enrollment in the health care plan prior to index treatment for VKA. If it is not possible to enroll the projected number of historical plasma controls needed, we will assess whether the event rates observed in the historical plasma controls justifies a smaller sample size. The results of these feasibility assessments will be discussed with the FDA (before finalizing the protocol if possible).
Exposure	Administration of Kcentra or plasma as prescribed in routine care for urgent reversal of VKA therapy in patients with major acute bleeding.

Outcomes	Fatal# and non-fatal TEE including • Venous events (e.g., DVT, PE, saggital sinus thrombosis etc.) • Arterial events (e.g., acute MI, ischemic stroke, acute coronary syndrome without MI, mesenteric artery thrombosis, acute distal limb thrombosis etc.) Fatal TEE# All-cause death# # If cause of death is not available in the (b)(4) database CSL Behring will explore the feasibility of using the National Death Index to identify subjects who died and the cause of death per death certificates.
Follow-up	Each patient will be followed until the earliest of • Lost to follow-up* • Disenrollment from (b)(4) • Death • The end of the study period, 45 days after Kcentra or plasma administration * Patients without complete follow-up (i.e., who are lost to follow-up or who disenroll prior to the end of the 45 day follow-up period will be replaced until the final sample size for analysis, based on patients with complete follow-up, is achieved.
Validation of Exposure/ Outcome	Exposures will be determined from the e-medical record. Detailed treatment data are available. TEE and death will be adjudicated by reviewers blinded to treatment (feasibility to be determined). TEE diagnoses will be confirmed using pre-specified criteria and death will be adjudicated as TEE-related or not.

Covariates	• Age • Gender • Hospital • Ethnicity • Social economic status if available • Indication or warfarin treatment • Type of bleeding event • Date of treatment with Kcentra or plasma • Last INR value prior to VKA reversal • Dose of Kcentra • Total volume of plasma • Dose of vitamin K • History of TEE and date(s) of prior diagnosis(-es) • CV risk factors (prior diagnosis of hypertension, hyperlipidemia, and current tobacco use, obesity and family history of premature MI [if available]) • Major comorbidities (e.g., prior diagnosis of ischemic heart disease, congestive heart failure, cerebrovascular disease, renal insufficiency, diabetes, , liver disease, disseminated intravascular coagulation, atrial fibrillation, and non-skin cancer, etc.) • Hospital admissions in the preceding 90 days for total hip replacement, total knee replacement, lower limb fractures, or other conditions known to be associated with an increased risk of DVT and PE) • History of acute bleeding events requiring treatment or transfusion • Post-exposure (after index VKA reversal treatment date) variables collected for purposes of descriptive analysis of patients with events: resumption of warfarin or other anticoagulation and date, hospitalizations, surgical procedures and/or other invasive treatments.
Sample size	With a 4:1 ratio of plasma- to Kcentra-treated subjects by design, two-sided alpha=0.05 and power = 80%, a sample size of 575 Kcentra patients and 2300 historical plasma-treated control patients without a history of recent TEE will rule out a risk with Kcentra that is 2-fold greater than plasma (i.e., the 95% upper confidence bound of the relative risk will be less than 2.0). It is CSL Behring's intention to perform a feasibility assessment by analyzing the rates of outcomes in the historical plasma control group (before finalizing the protocol if possible) to verify the outcome event rates and, if justified, reconsider the sample size.

Analysis Plan	• Analyses to address the primary study objectives will be done in patients without a recent history (with 90 days prior to VKA reversal) history of TEE • Analyses to address the secondary analyses study objectives will be done in the overall population, and also stratified by history of TEE: 1) TE ≤90 days prior to VKA reversal 2) TE >90 days prior to VKA reversal 3) No history of TE in the prior 365 days prior to VKA reversal • An analysis of TEE, all cause death, and fatal TEE will be conducted at both the 14-day and 45-day post VKA reversal time points. • Descriptive analysis of study cohorts • Descriptive analysis of the two plasma control groups for changes over time in the characteristics of patients treated with plasma and changes over time in the use of plasma for VKA reversal • Crude overall and crude age-, gender-specific incidence rates (95% CIs) for outcomes, in each study group; crude rates will also be estimated by history of TEE as indicated above • Cox proportional hazards models with adjustment for potential confounders to evaluate the association between treatment with Kcentra vs. plasma and the first event for each outcome of interest (TEE, fatal TEE, and all deaths, respectively); these models will be done for the primary and secondary objectives as specified. Post-hoc analyses by other subgroups may be performed based on review of the data • An interim analysis will be conducted after first 180 Kcentra patients have been enrolled, compared with historical plasma control patients. The study sample size will be reconsidered based on the incidence rates observed in this analysis. • A final analysis will be conducted when enrollment for the Kcentra group is completed
Timelines	• First protocol for FDA review 31 Oct 2013 • FDA approved protocol 28 Feb 2014 • Study start within 3 months following FDA approval of protocol • Study completion when enrollment for the Kcentra group is completed. The estimated time needed 6 years. Target 1 June 2020 • Draft study report 8 months following completion of study. Target 28 Feb 2021. • Final study report submitted 31 May 2021.