Application Type	Original Application
STN	125421/0
CBER Received Date	March 30, 2012
PDUFA Goal Date	April 29, 2013
Division / Office	DH /OBRR
Priority Review	No
Reviewer Name(s)	L. Ross Pierce
Review Completion Date / Stamped Date	
Supervisory Concurrence	
Applicant	CSL Behring GmbH
Established Name	Prothrombin Complex Concentrate (Human)
(Proposed) Trade Name	Kcentra, Beriplex
Pharmacologic Class	Clotting Factors
Formulation(s), including Adjuvants, etc.	Kcentra contains a mixture of Coagulation Factors II, VII, IX, and X, Proteins C and S as a lyophilized concentrate. Kcentra potency is nominally defined by Factor IX content. Dosing instructions are based on actual Factor IX units. The range of Factor IX units per vial is 400 – 620 IU. When reconstituted using its diluent (20 mL of Sterile for Injection, USP), the final concentration of Factor IX in this product will be in a range of 20 – 31 IU/mL
Dosage Form(s) and Route(s) of Administration	Lyophilized powder. For intravenously use only.

Dosing Regimen	Dosing is individualized based on the patient's pre-dose International Normalized Ratio (INR) value, and body weight. Dosing (in FIX IU using actual potency as stated on the carton) is 25, 35, or 50 IU/kg for baseline INR values of 2 - <4, 4 - 6, and >6, respectively.
Indication(s) and Intended Population(s)	Kcentra, (Prothrombin Complex Concentrate (Human)), is indicated for the urgent reversal of acquired coagulation factor deficiency induced by Vitamin K antagonist (VKA, e.g., warfarin) therapy in adult patients with acute major bleeding. Kcentra is not indicated for urgent reversal of VKA anticoagulation in patients without acute major bleeding.

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GLOSSARY

AE	adverse even
AR	adverse reaction
BLA	biologics license application
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CR	complete response
DIS	Division of Inspections and Surveillance
eCTD	electronic Common Technical Document
ELISA	Enzyme-Linked Immunosorbent Assay
ES	Executive Summary
FDAAA	Food and Drug Administration Amendments Act of 2007
ICH	International Conference on Harmonisation (of Technical Requirements for Registration of Pharmaceuticals for Human Use)
ISE	integrated summary of efficacy
ITT	intent-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
NME	new molecular entity
OBE	Office of Biostatistics and Epidemiology
OCOD	Office of Communication Outreach and Development (CBER)
OSE	Office of Surveillance and Epidemiology
PD	pharmacodynamics
PI	package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PREA	Pediatric Research Equity Act
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event

1. EXECUTIVE SUMMARY

Kcentra is a sterile, heat-treated, non-activated, nano-filtered, and lyophilized protein product made from pooled human U.S. Source Plasma. It is manufactured in the CSL Behring facility in Marburg, Germany. This product has been marketed in Germany since 1996 and subsequently licensed in other countries outside the United States.

Kcentra is the first four-factor Prothrombin Complex Concentrate (PCC) in the U.S. for which the applicant is seeking an indication for the urgent reversal of VKA (e.g., warfarin) therapy in patients with acute major bleeding. Other PCCs have been licensed in the U.S. for treatment of hemophilia B. The standard of care in the U.S. for reversal of VKA therapy in patients with acute major bleeding includes withdrawal of VKA therapy, vitamin K administration, and administration of plasma.

The sponsor negotiated with FDA to design a single randomized, open-label plasma-controlled non-inferiority phase three clinical trial in 216 subjects receiving VKA therapy with major acute bleeding and whose baseline International Normalized Ratio (INR) was > 2.0, which was conducted under U.S. IND 13398. No randomized controlled trials (RCTs) using plasma for this indication were available to inform the selection of the non-inferiority margin, which was set at 10% (absolute, not relative percentage) for the primary hemostatic efficacy endpoint (excellent or good = effective vs. poor or none = not effective). FDA required a trial design that included hemostatic efficacy rather than solely relying on INR correction as the primary endpoint because animal data (Dickneite G., *Thrombosis Research* 119:643-51 (2007)) had indicated that abnormal hemostasis could persist despite INR correction and human data to show that INR could be relied upon to predict hemostasis in the context of VKA anticoagulation reversal using PCC were lacking (Kessler CM, *J. Thrombosis and Haemostasis* 4:963-966 (2006)). The clinical trial was designed so that, if non-inferiority were demonstrated for the primary hemostatic endpoint and the co-primary INR correction endpoint, superiority testing would also be performed. Non-inferiority was demonstrated in the primary hemostatic endpoint and the co-primary INR correction endpoint, however, superiority was not demonstrated for the primary hemostatic endpoint despite more rapid INR correction having been demonstrated with Kcentra than with plasma.

Kcentra presents certain practical and theoretical advantages over plasma: (1) no need to thaw the product, (2) no need to check the patient's blood group to administer group-compatible product, (3) administration of the therapeutic dose in a smaller volume in a shorter period of time, (4) viral safety due to the presence of dedicated viral removal and inactivation procedures employed in the manufacturing process, (5) no documented risk of TRALI, (6) potential for reduced allergic reactions, and (7) standardized dose of clotting factors indexed to factor IX content of the product. The advantages seen in the phase 3 randomized controlled trial (RCT) were a trend for a lower incidence of volume overload events and a trend toward fewer (mild) transfusion reactions than observed with plasma.

An identified safety risk of Prothrombin Complex Concentrate (Human), including Kcentra, is arterial and venous thrombosis and thromboembolism (TE) (Dentali F. *Thrombosis and Haemostasis* 106:429-438 (2011); Lusher JM, *Seminars in Hematology* 28:3-5 (1991)). TE events (both total and possibly related to test product administration) were numerically but not statistically significantly more frequent in the Kcentra arm than in the plasma arm of the single pivotal phase three RCT in acute major bleeding (9 vs. 6 total events, and 6 vs. 3 possibly related, probably related, or related events according to the investigator's or masked SAB's causality assessments, respectively; this total excludes a Kcentra subject with an upper extremity venous thrombosis in association with an in-dwelling venous catheter and includes a subject who had a cerebrovascular accident on day 42 considered possibly related to Kcentra by the investigator but unrelated to Kcentra by the masked Safety Adjudication Board). The excess TE events following Kcentra vs. plasma was more striking in the subgroup of subjects with a history of prior TE event or of coronary, cerebrovascular, or peripheral vascular disease, but was not statistically significant. Nonetheless, FDA considers that the data from the RCT in acute major bleeding, taken together with the two TE events seen among 17 (12%) subjects in uncontrolled phase three study BE1116_3001 (including one fatal PE considered by the investigator to be related to Kcentra), and data from the literature on the class of PCC products collectively constitute a safety signal for possible increased risk of TE event following treatment with

Kcentra. The design of the pivotal RCT in VKA reversal in subjects with acute major bleeding precluded a determination of whether plasma also carries a thrombogenic risk in this setting.

The key review issue is whether sufficient data have been presented to conclude that an appropriate benefit:risk balance exists for the requested target population. Using the sponsor's analysis datasets, the FDA biostatistician confirmed the sponsor's primary hemostatic endpoint result showing non-inferiority of Kcentra versus plasma, and confirmed the sponsor's co-primary (INR reduction at 30 min after end of infusion) and secondary efficacy endpoint analysis results, but there were GCP deficiencies related to the process of recording Endpoint Adjudication Board primary endpoint hemostatic efficacy ratings, including a number of missing EAB source documents (22 missing EAB Worksheets by sponsor count, 50 missing EAB worksheets for 35 subjects and 3 missing EAB CRFs for one subject by FDA count). Two robustness analyses conducted by the FDA biostatistician imputing "Poor/None" ratings to subjects with missing EAB worksheets pages 2 or missing EAB CRFs failed to confirm non-inferiority of Kcentra in relation to plasma. *Post-hoc* analysis of hemoglobin and hematocrit changes in subjects with GI bleeding (the most common bleeding site comprising 55-56% of subjects) suggested that plasma might be more effective than Kcentra in this subgroup. A slightly greater than two-fold excess in the incidence of all deaths through day 46 or day 90 in the Kcentra group (not statistically significant at the two-sided 0.05 level) was observed in the bleeding RCT, but the excess deaths occurred beyond day 30, which suggests the excess deaths may not be related to Kcentra administration. No deaths in either group were attributed to the test product by the investigator and the SAB concluded that only one death (sudden death on day 7) was possibly related to Kcentra and none were related to plasma. The primary medical reviewer conducted a blinded review of sponsor- and EAB-prepared narratives for all deaths and TE events reported in both bleeding and surgery RCTs. This analysis suggested that three Kcentra subject deaths and one plasma subject death may have been possibly or probably related to test product administration. Pooling of safety data from bleeding and surgery RCTs did not appear to be scientifically justified, in part because more than twice as many bleeding RCT subjects were in middle and high planned dose cohorts compared to the surgery RCT subjects, due to the higher INR values seen in the bleeding study. In the sponsor's preliminary analysis of the surgery RCT, 3/88 (3.4%) Kcentra and 8/88 (9.1%) plasma subjects died on study. The between-group difference (Kcentra minus Plasma) in the incidence of death was -5.7% (95% CI -14.6 to 2.7%). This reviewer's masked causality analysis of deaths in the surgery RCT concluded that zero Kcentra subject's deaths and one plasma subject's death were possibly or probably related to test product administration.

As noted above, more TE events were seen in the Kcentra arm in the bleeding study, and twice as many possibly or probably related TE events were seen in the Kcentra arm than in the plasma arm, using jointly either the investigator's or the SAB's causality assessments. A finding of particular interest in both bleeding and surgery studies among Kcentra arm subjects was that, treatment-emergent TE events were much more frequent in subjects with a history of prior TE (or of coronary, cerebrovascular, or peripheral vascular disease) than in those without such history. All nine possibly or probably related TE events in the bleeding study (joint investigator's and SAB's assessments) were in subjects with a prior history of TE or vascular disease. A statistical test for treatment group interaction with prior history of TE event in predicting treatment-emergent TE in the study in acute major bleeding gave a p value of 0.05 according to the CBER biostatisticians (email communication). The primary medical reviewer

concluded that the submitted data are marginal in demonstrating substantial evidence of effectiveness and safety for the entire target population enrolled in the pivotal RCT in acute major bleeding. However, the primary medical reviewer and the Clinical Review Branch Chief concluded that sufficient data have been submitted to conclude that there is substantial evidence of effectiveness and safety for patients without a prior history of thromboembolic event or coronary, cerebrovascular, or peripheral vascular disease and an appropriate risk:benefit balance could be established. A preponderance of the available evidence, taking all primary, co-primary, and secondary endpoints into account allows this reviewer to conclude that the efficacy of Kcentra and plasma are comparable in the target population studied. Note that prospective subjects with a history of TE event, myocardial infarction, cerebral vascular accident, transient ischemic attack, unstable angina pectoris, severe peripheral vascular disease, or disseminated intravascular coagulation, within the previous 3 months were excluded from participating in the plasma-controlled RCT. The safety and efficacy of Kcentra in this group of patients has not been established.

It is recommended that Kcentra be licensed with a boxed warning for arterial and venous thromboembolic complications and a statement that the product had not been studied in patients who had a thromboembolic event, myocardial infarction, disseminated intravascular coagulation, cerebral vascular accident, transient ischemic attack, unstable angina pectoris, or severe peripheral vascular disease within the prior 3 months. The sponsor has agreed to amend the package insert to include a boxed warning regarding the risk of thromboembolic complications and the requested statement that the product had not been studied in patients who had a thromboembolic event, myocardial infarction, disseminated intravascular coagulation, cerebral vascular accident, transient ischemic attack, unstable angina pectoris, or severe peripheral vascular disease within the prior 3 months. The sponsor was also asked to introduce a contraindication into the package insert at currently recommended doses for patients with a history of TE event or coronary, cerebrovascular, or peripheral vascular disease. After the sponsor objected to such a contraindication, maintaining that the submitted data did not support it, CBER management concluded that such a contraindication might impede the ability of the sponsor to conduct the post marketing commitment study that FDA had requested the sponsor perform to evaluate the safety and efficacy of a lower dose regimen of Kcentra vs. plasma for the requested indication. Thus it was decided, in lieu of having a contraindication to the use of Kcentra at currently recommended doses in patients with a prior history of TE event, to include a statement in the boxed warning and in Warnings and Precautions stating that "Potential benefits of reversing VKA should be weighed against the potential risks of thromboembolic events (TE), especially in patients with the history of a thromboembolic event." An additional statement was added to the boxed warning and to the Warnings and Precautions statement stating "Kcentra may not be suitable in patients with thromboembolic events in the prior 3 months."

The primary medical reviewer and the Clinical Review Branch Chief concur with the recommendations of the Division of Biostatistics and Epidemiology to have a post marketing requirement (PMR) epidemiologic study to obtain more precise estimates of the risks of death and TE events in patients with and without a prior history of TE event. The primary medical reviewer and the Clinical Review Branch Chief further recommend that the sponsor conduct a post marketing commitment RCT to determine whether a lower dosage regimen of Kcentra is non-inferior to plasma in efficacy and whether such a lower dose regimen may have an improved safety profile, particularly as regard TE events. The sponsor has counter-proposed a 2 arm PMC

safety and efficacy RCT using the currently recommended dose and a to-be-determined lower dose based on body weight and baseline INR stratum. This reviewer recommended that the design be modified to include a plasma randomized arm for the subset of subjects with a history of TE event in the previous 90 days because the safety of the product has not been evaluated in such patients. The Clinical Review Branch Chief did not agree with adding a plasma control arm for such subjects, arguing that this would add complexity to the trial design.

2. CLINICAL AND REGULATORY BACKGROUND

Kcentra is a sterile, heat-treated, non-activated, nanofiltered, and lyophilized plasma protein product made from pooled human US Source Plasma. It is manufactured in the CSL Behring facility in Marburg, Germany. This product has been marketed in Germany since 1996 and subsequently licensed in other countries outside U.S. The isolation and purification process of prothrombin complex factors was established in 1978. Pasteurization was introduced as a virus inactivation step in 1985. To enhance viral safety profile of the product, 35 nm nanofiltration was introduced in the manufacturing process in 1996.

Kcentra is the first member of this class of Prothrombin Complex Concentrates (PCCs) for which the sponsor is seeking an indication in the U.S. for the urgent reversal of VKA (e.g., warfarin, acenocoumarol, etc.) therapy in patients with acute major bleeding. Other PCCs have been licensed in the U.S. for treatment of hemophilia A and B with inhibitors. The standard of care in the U.S. for reversal of VKA (e.g., warfarin) therapy in patients with acute major bleeding includes withdrawal of VKA therapy, vitamin K administration, and administration of plasma. FDA recognizes the indications for Fresh Frozen Plasma (FFP) and for 24 hour plasma listed in the AABB (formerly the American Association of Blood Banks) circular as equivalent to FDA-approved indications. The AABB circular recognizes urgent reversal of VKA anticoagulation for patients with bleeding and patients who require urgent surgery as indications for plasma despite the fact that the efficacy for these indications has not been demonstrated in adequate and well-controlled clinical trials.

Kcentra presents certain practical and theoretical advantages over plasma, (1) no need to thaw the product, (2) no need to check the patient's blood group to administer group-compatible product, (3) administration of the therapeutic dose in a smaller volume in a shorter period of time, (4) viral safety due to the presence of dedicated viral removal and inactivation procedures employed in the manufacturing process, (5) no documented risk of TRALI, (6) potential for reduced allergic reactions, and (7) standardized dose.

A previously identified safety risk of Prothrombin Complex Concentrate (Human), including Kcentra, is arterial and venous thrombosis and thromboembolism (Refs: Dentali F et al. Safety of Prothrombin complex concentrates for rapid anticoagulation reversal of vitamin K antagonists – A meta-analysis. Thrombosis and Haemostasis 106:429-438 (2011); Lusher JM. Thrombogenicity Associated with Factor IX Complex Concentrates. Seminars in Hematology 28:3-5 (1991)).

Prothrombin Complex Concentrate (Human) (PCC) products have been marketed in Europe and other foreign countries for decades for the urgent reversal of VKA anticoagulation for bleeding and also in VKA anticoagulated patients who require urgent surgery. Kcentra (foreign trade

name Beriplex P/N) is currently authorized for marketing in 24 countries outside the U.S., including Canada and the U.K.

During the IND phase, the sponsor negotiated with FDA to design a single randomized, open-label plasma-controlled non-inferiority phase 3 clinical trial in subjects receiving VKA anticoagulation with major acute bleeding and whose baseline INR was > 2.0. No randomized controlled trials (RCTs) using plasma for this indication were available to inform the selection of the non-inferiority margin, which was set at 10% (absolute, not relative percentage) for the primary hemostatic efficacy endpoint (excellent or good = effective vs. poor or none = not effective). FDA required a trial design that included hemostatic efficacy rather than solely relying on INR correction as the primary endpoint because animal data (Dickneite G. Prothrombin complex concentrate versus recombinant factor VIIa for reversal of coumarin anticoagulation. Thrombosis Research 119:643-51 (2007)) had indicated that abnormal hemostasis could persist despite INR correction and human data to show that INR could be relied upon to predict hemostasis in the context of VKA anticoagulation reversal using PCC were lacking (Ref: Kessler CM Urgent Reversal of Warfarin with Prothrombin Complex Concentrate: where are the evidence-based data? J. Thrombosis and Haemostasis 4:963-966 (2006)).

2.1 Disease or Health-Related Condition(s) Studied

Approximately 30 million prescriptions for the vitamin K antagonist (VKA) anticoagulant warfarin are written annually in the U.S. for conditions such as atrial fibrillation, deep venous thrombosis (DVT), pulmonary embolus (PE), artificial heart valve replacement, and others to reduce the risk of arterial and/or venous thromboembolism. Indications such as atrial fibrillation and artificial heart valves require lifelong anticoagulation to reduce the risk of arterial thromboembolism. It has been estimated that approximately one percent of patients on chronic VKA anticoagulation will experience acute major bleeding over a one year period. The mortality rate of acute major bleeding in association with warfarin anticoagulation is very low, except in patients with intracerebral hemorrhage (ICH), where it is roughly 50%. Mild bleeding in patients receiving VKA therapy can often be managed by temporary withdrawal of VKA therapy alone. Moderate bleeding is managed by temporary withdrawal of VKA therapy and administration of vitamin K. As noted above, the standard of care in the U.S. for reversal of VKA (e.g., warfarin) therapy in patients with acute major bleeding includes withdrawal of VKA therapy, vitamin K administration, and administration of plasma. Studies in the literature generally support prompt resumption of anticoagulation (except in ICH) once acute major bleeding is controlled in order to lessen the incidence of arterial and venous thromboembolism due to the underlying disorder for which VKA therapy was originally prescribed.

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

Withdrawal of VKA therapy, fresh frozen plasma (FFP), P24 plasma.

2.3 Safety and Efficacy of Pharmacologically Related Products

A previously identified safety risk of Prothrombin Complex Concentrate (Human), including Kcentra, is arterial and venous thrombosis and thromboembolism (Refs: Dentali F et al. Safety of Prothrombin complex concentrates for rapid anticoagulation reversal of vitamin K antagonists – A meta-analysis. Thrombosis and Haemostasis 106:429-438 (2011); Lusher JM.

Thrombogenicity Associated with Factor IX Complex Concentrates. Seminars in Hematology 28:3-5 (1991)).

Preliminary data from a randomized, plasma-controlled clinical trial of another PCC product (--(b)(4)---) administered for urgent reversal of VKA anticoagulation in patients requiring urgent surgery or invasive procedure indicated a trend in increased mortality in the PCC group compared to the plasma group.

While numerous international and domestic practice guidelines recommend PCCs (or plasma) in conjunction with vitamin K and VKA withdrawal to treat acute major bleeding in patients requiring urgent reversal of VKA anticoagulation, these recommendations are not evidence-based, and rely on the surrogate endpoint of INR correction, which has not been validated in animals or humans to reflect the actual status of hemostasis in the setting of PCC administration after anticoagulation with VKAs.

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

Kcentra, under the foreign trade name Beriplex P/N, was first approved on February 16, 1996 in Germany. It is currently licensed for use in 24 countries. See Pharmacovigilance review memo from the FDA Division of Biostatistics and Epidemiology.

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

The sponsor had originally approached FDA during a "pre-BLA" (actually a pre-IND) meeting during which it asked FDA to accept a BLA application relying on uncontrolled European clinical studies in which the primary efficacy endpoint was reduction in International Normalized Ratio (INR) to or below a pre-specified value indicative of reversal of VKA anticoagulation in the setting of VKA withdrawal. FDA noted during these meetings that data from animal studies suggested that INR did not correlate well with reversal of bleeding tendency during reversal of VKA anticoagulation following PCC administration. Furthermore, it was apparent from literature review that the INR had never been validated in humans as an adequate measure of bleeding tendency during reversal of VKA anticoagulation following PCC administration. For these reasons FDA recommended the sponsor undertake a randomized, fresh-frozen plasma (FFP)-controlled clinical trial to provide substantial evidence of effectiveness and safety in support of BLA for the indication being sought (as well as a separate trial in urgent reversal of VKA anticoagulation in patients requiring urgent surgery or invasive procedure). FFP was recommended as the comparator because of its use as standard of care in the U.S. for these indications and because FDA considers FFP to carry these indications for urgent reversal of VKA anticoagulation via its listing in the AABB circular, notwithstanding the lack of prior randomized controlled trials (RCTs) of FFP/plasma for this indication.

Early during the IND phase the FDA requested the sponsor to revise the definitions for the primary hemostatic efficacy endpoint for RCT BE1116_3002 in acute major bleeding to require a "poor/none" rating for subjects who received whole blood, non investigational plasma, or other blood/coagulation products (but not PRBCs [or platelets]). The sponsor did not comply. FDA made the same request again at the pre-BLA meeting and requested the SAP be revised

accordingly and, if necessary, subjects readjudicated for the primary endpoint by the EAB using the revised definitions. Instead, the sponsor stated in an amendment that it had used a computer program to modify the masked EAB primary endpoint ratings to comply with FDA's request.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission was adequately organized and integrated to accommodate the conduct of a complete clinical review without unreasonable difficulty.

3.2 Compliance with Good Clinical Practices And Submission Integrity

The BiMo inspection of the sponsor included a directive to verify the sponsor's data listings for the pivotal RCT in acute major bleeding (RCT BE1116_3002) against the Endpoint Adjudication Board (EAB) source documents for the primary hemostatic endpoint for all subjects. The inspection revealed that the EAB Worksheets Pages 2 source documents were missing for a number of subjects and all three EAB CRFs were missing for one subject. The FDA biostatistician conducted sensitivity analyses of the data imputing "poor/none" ratings for subjects with missing EAB worksheets pages 2/CRFs. These analyses failed to confirm the non-inferiority of Kcentra in relation to plasma for the primary hemostatic efficacy endpoint.
FDA directed the sponsor-monitor BiMo inspection to investigate why the protocol was not followed in that some assignments of subjects to the various study populations were not done in a blinded manner. FDA was satisfied that those assignments not made in a blinded manner were made in a consistent manner through computer programming.

The results from bioresearch monitoring inspections of five clinical study sites did not reveal problems that impact the data submitted in the application. Inspections were conducted at the following study sites of bleeding randomized controlled trial (RCT) BE1116_3002:

Study site #s	Location	# subjects	FDA 483?	Classification
046	Staten Island, NY	5	No	NAI
030	Rochester, NY	35	Yes	VAI
002	Boston, MA	17	Yes	VAI
013, 051, 052, 053	Austin, TX	44	Yes	VAI
018	Minneapolis, MN	10	Yes	VAI

3.3 Financial Disclosures

The information submitted regarding potential financial conflicts of interest was reviewed. FDA concluded the submitted information did not, in the aggregate, indicate significant financial conflict of interest among investigators of the pivotal clinical trial in patients with acute major bleeding (BE1116_3002).

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

The Pharmacology/Toxicology reviewer noted that there was minimal information submitted regarding the use of INR values to select the doses of Kcentra which were used in the animal efficacy model studies. Deficiencies of the submitted animal efficacy model studies included:

- INR was neither standardized nor validated in the submitted nonclinical studies with PCC.

- Corroborating findings indicate that assay reagents, human error, and the devices employed (analytical methods) can alter the results of the INR values obtained in any given assay (Horsti, et.al Clinical Chemistry 2005 Mar; 51(3): 53-560).

- The pre- and post-dose coagulation parameters did not correlate proportionally to the PCC dose or treatment regimen tested in the submitted nonclinical studies.

The Epidemiology Reviewer noted that 20 cases of suspected viral transmission of hepatitis A, B, C, and HIV were identified during international postmarketing surveillance. Review of these reports by the Epidemiology Reviewer and Medical Officer indicated that these reports were generally confounded by concomitant administration of blood/blood components and/or other plasma-derived products. No causal relationship to Kcentra administration was established for any of these reports.

4.1 Chemistry, Manufacturing, and Controls

Kcentra undergoes heat treatment and nanofiltration during manufacturing to inactivate and reduce viral burden. Kccentra is the only PCC available in the U.S. to contain added anti-thrombin III. The formulation contains heparin, so heparin induced thrombocytopenia is a safety concern and the product is contraindicated in patients with a history of this condition. The product contains a high concentration of FII in relation to several other PCCs. Lot testing of the product includes ----------(b)(4)----------. Kcentra is a non-activated four-factor PCC.

4.3 Nonclinical Pharmacology/Toxicology

The pharmacology/toxicology reviewer concluded that data from the sponsor's completed non-clinical studies program that Kcentra is not expected to pose any greater safety risks than similar PCC products that are currently marketed. "The completed nonclinical program consisted of a series of studies to demonstrate the safety and effectiveness of Kcentra included safety pharmacology (rats and dogs), efficacy (rats, minipigs, and beagles), local tolerance (rabbits), thrombogenicity (rabbits) antigenicity (guinea pigs), and acute toxicity studies (rat, mice, and dogs). There were no repeat dose toxicity studies done using Kcentra in animal studies. Based on

the intended use, no animal reproductive or developmental toxicity studies were required. Long-term animal studies to evaluate the carcinogenic potential of Kcentra or studies to determine the genotoxicity or effects of Kcentra on fertility were not performed, but are not required according to current ICH guidance."

There was no repeat dose testing conducted with PCC in either animal studies or in clinical trials. The pharmacology/toxicology reviewer indicated that there is a potential theoretical safety concern regarding immunogenic responses that may occur in patients following repeated product administration due to the presence of allogeneic human proteins in Kcentra™. The label states that repeated dosing with the product is not supported by clinical data and is not recommended.

As noted above, the Pharmacology/Toxicology reviewer noted that there was minimal information submitted regarding the use of INR values to select the doses of Prothrombin Complex Concentrate which were used in the animal efficacy model studies. Deficiencies of the submitted animal efficacy model studies included:

- INR was neither standardized nor validated in the submitted nonclinical studies with PCC.

- Corroborating findings indicate that assay reagents, human error, and the devices employed (analytical methods) can alter the results of the INR values obtained in any given assay. (Horsti et. al .Clinical Chemistry 2005 Mar; 51(3): 53-560)

- The pre- and post-dose coagulation parameters did not correlate proportionally to the PCC dose or treatment regimen tested in the submitted nonclinical studies.

4.4 Clinical Pharmacology

The sponsor submitted pharmacokinetic (PK) data from a single was a prospective, open-label, phase I pharmacokinetic study in healthy volunteers (15 subjects: 8 males and 7 females, age ranging from 18 to 62 years). The subjects, who had not received VKAs and who were not bleeding, received Kcentra intravenously at a dose of 50 IU/kg body weight. The Clinical Pharmacology Reviewer concluded that the pharmacokinetics of Kcentra in healthy subjects is of limited practical value. No information can be obtained from this study about the dosing of Kcentra in the proposed patient population of bleeding patients who have elevated INR values due to recent treatment with VKA anticoagulants, if the PK were different between healthy subjects and the target patient population. While the time course of plasma levels of vitamin-K dependent clotting factors and of proteins C and S were obtained during the pivotal RCT in acute major bleeding, no pharmacokinetic parameters were calculated, due to the confounding effect of co-administration of vitamin K, which augments hepatic synthesis of Factors II, VII, IX, and X.

4.4.1 Mechanism of Action

Kcentra contains the Vitamin K-dependent coagulation factors II, VII, IX, and X (FX), together known as the Prothrombin Complex, and the antithrombotic Protein C and Protein S. If the patient has an acquired coagulation factor deficiency where one or more of the Vitamin-K-dependent coagulation factors are deficient, bleeding may occur. A dose-dependent acquired deficiency of the Vitamin K-dependent coagulation factors occurs during Vitamin K antagonist treatment. Vitamin K antagonists exert anticoagulant effects by blocking carboxylation of

glutamic acid residues of the Vitamin K-dependent coagulation factors during hepatic synthesis, lowering both factor synthesis and function. The administration of Kcentra increases plasma levels of the Vitamin K-dependent coagulation Factors II, VII, IX, and X as well as the anti-thrombotic Proteins C and S.

4.4.2 Human Pharmacodynamics (PD)

While the International Normalized Ratio (INR) was shown to drop to $\leq$ 1.3 at 30 minutes following administration of Kcentra in the pivotal RCT in acute major bleeding as well as in the earlier uncontrolled CSL Behring-sponsored European study in bleeding (N = 17) and surgery, the correlation between achieving this or any other target INR threshold and clinical hemostasis in the setting of PCC administration has not been established (Kessler et. al, J. Thrombosis and Haemostasis 4:963-966 (2006) and data from RCT BE116_3002).

4.4.3 Human Pharmacokinetics (PK)

See Clinical Pharmacology Review memo.

4.5 Statistical

The statistical reviewer verified that the primary endpoint analysis result for the ITT-E population in the pivotal RCT in acute major bleeding BE1116_3002 cited by the applicant were supported by the sponsor-supplied analysis dataset. Using the sponsor's analysis datasets, the FDA biostatistician verified the results of the sponsor's analyses of the co-primary (INR reduction) endpoint and of the secondary efficacy endpoints. Safety endpoints including deaths and thrombotic/thromboembolic (TE) events were also reviewed. Deaths through day 90 (the last death occurred on day 46) were statistically significantly more frequent using a one-sided, but not a two-sided test at an alpha level of 0.05.

4.6 Pharmacovigilance

The Office of Biostatistics and Epidemiology (OBE) Medical Officer agreed to sponsor's plan for routine pharmacovigilance, but did not agree to the sponsor's initial and subsequent plan for a claims-based epidemiologic cohort study comparing mortality and thromboembolic events following Kcentra vs. plasma as significant design flaws were identified. OBE recommended the sponsor conduct a Post Marketing Requirement (PMR) prospective clinical study and the Clinical Review Branch (CRB) of the Division of Hematology (DH) concurred. The sponsor counter-proposed a retrospective study using data from ----------(b)(4)---------- OBE recommended changes to the PMR study which were conveyed to the sponsor.

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

The clinical efficacy data in this application are obtained from a single phase 3 pivotal trial (study BE1116_3002) conducted under IND 13398 in subjects anticoagulated with vitamin K antagonists (VKA) presenting with acute major bleeding requiring urgent reversal of anticoagulation to help arrest bleeding. Supporting safety and surrogate endpoint (INR) data are submitted from six uncontrolled single arm non-IND studies. Additional safety data are provided from a completed safety analysis of preliminary data (pre-database lock) from pivotal phase 3 surgery study BE1116_3003, a retrospective epidemiology study recently completed in

the U.K (study BE1116_5001), and foreign pharmacovigilance data. The FDA medical review focused on the two RCTs conducted under IND: safety and efficacy data from completed bleeding patient study BE1116_3002 and preliminary safety data from ongoing surgery/invasive procedure patient study BE1116_3003. Additional mortality data from an interim safety analysis of a randomized, plasma-controlled, open label study in patients requiring urgent VKA anticoagulation reversal for urgent surgery or invasive procedure which tested another investigational PCC was also considered. See the OBE epidemiology review memo for summary review information on the uncontrolled studies with Kcentra which were investigator-initiated (not sponsored by CSL Behring).

5.1 Review Strategy

Key data reviewed include the final study report for pivotal RCT BE1116_3002 in acute major bleeding, interim study reports for RCT BE1116_3003 in patients requiring urgent VKA anticoagulation reversal due to the need for urgent surgery/invasive procedure, the sponsor's responses to clinical questions posed by FDA from among 25 amendments, summaries of postmarketing surveillance cases of suspected viral transmission following Kcentra administration prepared by OBE, and the medical literature relating to the safety and Thrombogenicity of PCCs.

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

See section 5.1. The sponsor's revised tables of thrombotic/thromboembolic (TE) events for RCT BE1116_3002 are contained in amendment 23 received 19 March 2013.

5.3 Table of Studies/Clinical Trials

The Pivotal Study for the Requested bleeding Indication was BE1116_3002, a study conducted under the US IND.

Study No./ Phase/ IND?	**Randomized?/Double-Blind?/Control**	**No. (ITT-E)/Type of Subjects**	**(Co-) Primary endpoint(s)**
BE1116_3002/ Phase 3 (IND)	Yes/No/Plasma	212/bleeding, receiving VKA, elevated INR (103 Beriplex, 109 Plasma)	INR correction, Hemostatic Efficacy
BE1116_1001/ Phase 1/ (non-IND)	No/No/None (PK study, single dose 50 IU FIX/kg)	15/ healthy subjects aged 18-62 years	PK
BE1116_3001/ Phase 3 (non-IND)	No/No/None	43/ 26 VKA reversal prior to surgery; 17 VKA	INR correction

Study No./ Phase/ IND?	**Randomized?/Double-Blind?/Control**	**No. (ITT-E)/Type of Subjects**	**(Co-) Primary endpoint(s)**
		reversal for bleeding	
BE1116/7D-202KO/ Phase 2 (non-IND)	No/No/None (single 2K IU FIX dose)	2/ Hemophilia B	
BE1116/7D-201KO/ Phase 2 (non-IND)	No/No/None	30/ 22 Liver disease; 8 VKA reversal	Quick value, Factor levels, In-vivo Recovery (IVR)
Preston 2002 (non-IND, investigator - sponsored)	No/No/None	42/Receiving VKA and Surgery or invasive procedure (5), Bleeding (37)	Rate of correction of INR
Evans 2001 (non-IND, investigator - sponsored)	No/No/None	10/ Receiving VKA and INR $\geq$ 8 and urgent need for reversal	Clinical Response, INR, factor levels

Study No./Phase	**Randomized?/Double-Blind?/IND?/Control**	**No./Type of Subjects**	**(Co-) Primary endpoint(s)**
BE1116_3003	Yes/No/Yes/Plasma	176 (88 Kcentra and 88 plasma)	INR correction, Hemostatic Efficacy

5.4.1 Advisory Committee Meeting (if applicable)

This reviewer and the Clinical Review Branch Chief recommended the product/indication be presented to BPAC. Presentation of this original BLA to the Blood Products Advisory Committee (BPAC) was scheduled and then cancelled on two different occasions for logistical considerations.

5.5 Literature Reviewed

Literature reviewed included:

- Kessler CM Urgent Reversal of Warfarin with Prothrombin Complex Concentrate: where are the evidence-based data? J. Thrombosis and Haemostasis 4:963-966 (2006)
- (Dickneite G. Prothrombin complex concentrate versus recombinant factor VIIa for reversal of coumarin anticoagulation. Thrombosis Research 119:643-51 (2007)
- Dentali F et al. Safety of Prothrombin complex concentrates for rapid anticoagulation reversal of vitamin K antagonists – A meta-analysis. Thrombosis and Haemostasis 106:429-438 (2011)
- Lusher JM. Thrombogenicity Associated with Factor IX Complex Concentrates. Seminars in Hematology 28:3-5 (1991)

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Trial #1

VKA Anticoagulation Reversal in Acute Major Bleeding:

Protocol BE1116_ 3002

Study Title:

"An open-label, randomized, multicenter Phase IIIb study to assess the efficacy, safety and tolerance of Beriplex® P/N [Kcentra] compared with plasma for rapid reversal of coagulopathy induced by coumarin derivatives in subjects with acute major bleeding"

6.1.1 Objectives (Primary, Secondary)

Study Objectives:
Primary:
To compare the hemostatic efficacy of Kcentra and plasma in ceasing spontaneous or traumatically-induced major bleeding in subjects who have a deficiency of vitamin K-dependent coagulation factors II, VII, IX, and X, as well as the proteins C and S, acquired from oral anticoagulation therapy.

Co-Primary:

To compare the efficacy of Kcentra and plasma in rapidly reducing the international normalized ratio (INR $\leq$ 1.3) values between the 2 treatment groups at 30 minutes after end of infusion.

6.1.2 Design Overview

Planned Number of Subjects: 88 per group (176 total)

The study was a prospective, randomized, plasma-controlled, multinational, multicenter study which enrolled patients at least 18 years of age with an INR value > 2.0 who had been on vitamin K antagonist therapy and who had an acute major bleed requiring urgent reversal of VKA anticoagulation. Subjects received one of three single intravenous doses of Kcentra or plasma (including FFP and 24-hour plasma), depending on the magnitude of the baseline INR. The doses of Kcentra used in the trial provided up to ~ 3 -5 times the amount of vitamin-K dependent clotting factors compared with the amounts contained in the standard dosed of plasma used for a particular INR range. Complete blood count (CBC), laboratory markers of coagulation, and clinical assessments of were assessed frequently over a 24 hour period, then clinical and/or laboratory examinations were conducted on days, 10, 20, 45, and 90. Adverse events were collected through day 45 or later if considered at least possibly related to investigational treatment by the investigator.

6.1.3 Population

Inclusion Criteria:

- Male and female subjects > 18 years,
- Subjects who have received anticoagulation therapy (warfarin, acenocoumarol or phenprocoumon)
- Subjects who have acute major bleeding, defined as one of the following:
    - Life-threatening or potentially life-threatening,
    - Acute bleeding associated with a fall in Hb level > 2g/dL,
    - Bleeding requiring blood product transfusion (blood products include plasma, red blood cells and other coagulation factor products),
- INR > 2 within 3 hours before start of study treatment,
- Informed consent has been obtained.

Exclusion Criteria:

- Expected survival of less than 3 days, or expected surgery in less than 1 day
- Pre-existing progressive fatal disease with a life expectancy of less than 2 months,
- Acute trauma for which reversal of vitamin K antagonists alone would not be expected to control the acute bleeding event
- Large blood vessel rupture (e.g. in advanced cancer patient)
- History of thrombotic event, myocardial infarction, disseminated intravascular coagulation, cerebral vascular accident, transient ischemic attack, unstable angina pectoris, or severe peripheral vascular disease within 3 months of enrollment

- Suspected or confirmed sepsis at time of enrollment

- For patients with ICH:

  Glasgow coma score <7
  Intracerebral hematoma volume> 30cc as assessed by ABC/21
  For subdural hematomas: maximum thickness > 10 mm, midline shift > 5 mm,
  For subarachnoid hemorrhage: any evidence of hydrocephalus,
  Infratentorial ICH location,
  Epidural hematomas,
  Intraventricular extension of hemorrhage,
  Modified Rankin score of >3 prior to ICH

- Administration of whole blood, plasma, plasma fractions or platelets within 2 weeks prior to inclusion into the study
  - Note: Administration of packed red blood cells is not an exclusion criterion

- Known history of anti-phospholipid antibody syndrome or lupus anticoagulant antibodies

- Known inhibitors to coagulation factors II, VII, IX, or X; or hereditary protein C or protein S deficiency; or heparin induced, type II thrombocytopenia,

- Prior inclusion in this study or any other CSL Behring sponsored Beriplex study.

Note: Subjects with acute major bleeding requiring minimal invasive procedures (e.g. endoscopy, bronchoscopy, central lines) that are indicated for diagnostic or therapeutic reasons were not excluded per protocol, as long as plasma is intended to be given for treatment of major bleeding.

6.1.4 Study Treatments or Agents Mandated by the Protocol

Subjects were randomized (1:1) to single doses of Kcentra or plasma by IV infusion according to their baseline INR value (see next section).

The protocol required all subjects to receive slow IV vitamin K. The dose of vitamin K was based on local clinical practice (e.g., 2-10 mg as recommended by the American College of Chest Physicians guidelines).

6.1.5 Directions for Use

Dosage Scheme:

Baseline INR	**Kcentra (FIX IU per kg)**	**Plasma (mL per kg)**
2 - < 4	25	10
4 – 6	35	12
>6	50	15

For subjects weighing > 100 kg, the dose was based on a body weight of 100 kg.

The maximum rate of administration of Kcentra was 3 IU/kg/min (based on Factor IX content). No minimum or maximum rate of administration of plasma was specified in the protocol.

6.1.6 Sites and Centers

Thirty-six, multinational, including U.S. and European sites.

6.1.7 Surveillance/Monitoring

Selected Scheduled Assessments

Note: Vitamin K dependent clotting factors are measured at the same time points as INR.

Day 1 Pre-infusion	INR Viral Assessment	DD, TAT, F1+2
30 minutes after start of infusion	INR	
1 hour after start of infusion	INR	DD, TAT, F1+2
30 minutes after end of infusion	INR	
3 hours after start of infusion	INR	
6 hours after start of infusion	INR	
24 hours after start of infusion (include post-procedure)	INR	DD, TAT, F1+2
Day 10 (7-11 days after start of infusion)	Viral Assessment (B19 only)	
Day 45 (43-51 days after start of infusion)	Viral Assessment (HAV, HBV, HCV, HIV-1)	
Day 90 (86–96 days after start of infusion)	Viral Assessment (HC V and HIV 1&2 only)	

The protocol had a DSMB and an independent Safety Adjudication Board (SAB). The DSMB referred deaths and possible thrombotic/thromboembolic (TE) events to the SAB masked to treatment group for confirmation and causality assessment. An Endpoint Adjudication Board (EAB) made masked ratings of the primary hemostatic efficacy endpoint based on data and tentative ratings of key data elements prepared by an unmasked EAB monitor.

6.1.8 Endpoints and Criteria for Study Success

Primary Efficacy Endpoint:

The primary efficacy variable was the hemostatic efficacy as assessed from either the start of end of the test product infusion (depending on the type of bleeding) through 24 hours. The primary efficacy endpoint was assessed by the blinded Independent Endpoint Adjudication Board (EAB) implemented by the data and safety monitoring board (DSMB). Hemostatic efficacy ratings were made in accord with the EAB Charter as excellent, good, or poor/none, based on pre-specified definitions listed in the Appendix. For statistical analysis, these were collapsed into effective (excellent or good) and non-effective (poor/none). EAB members were masked to the

treatment assignment, investigator's assessment, post-baseline INR values, and infusion times. A blinded physician expert, serving as an adjunct member of the EAB, reviewed whether each subject had acute major bleeding as required by the protocol to help determine eligibility of each subject for inclusion/exclusion from the Intent to treat evaluable-for-efficacy (ITT-E) analysis. Subjects who did not have major bleeding, did not receive study medication, or had baseline INR < 1.3 were excluded from the ITT-E and per-protocol (PP) analyses (but not from the ITT analysis, provided they were randomized).

The primary endpoint assessment by the EAB included the clinical signs and symptoms of the subject, laboratory values such as hematocrit, hemoglobin, and whether any additional hemostatic treatments besides the test product were administered up to 24 hours. The EAB also had access to AE data and a "description of the clinical picture," prepared by the unblinded EAB monitor, including any additional testing such as CT scans or endoscopies. FDA noted that a deficiency in the generation of blinded EAB ratings was that the unblinded EAB monitor pre-circled key data elements on an "EAB Worksheet – page 2," deciding whether to place such circles in columns corresponding to ratings of "excellent," "good," or "poor/none." It was then up to the blinded EAB members to concur or not that with the placement of circles of key data by the EAB Monitor in the appropriate column(s) andto record their primary hemostatic efficacy ratings on a separate EAB Worksheet. FDA noted instances in which 2 different, conflicting data element values had been circled in different efficacy columns for the same variable on the EAB Worksheet page 2 source documents without any indication of which had been circled by the presumably unblinded EAB monitor and which had been circled by the blinded EAB member. FDA also noted that "Yes or N/A" was typically circled in lieu of either "Yes," or "N/A," in the "poor/none" column in response to the variable, "For GI only: Need for emergent therapeutic endoscopy." This created an ambiguity in the appropriateness of the location of the circle in the "poor/none" column. In addition, the design of the "EAB Worksheet Page 2" appeared to be flawed in that it included "PRBC transfusion after initial resuscitation as determined by EAB member within 24 h of start of infusion." The protocol made it clear that transfusion with PRBCs during the first 24 hours would not result in a "poor/none" rating, yet a "Yes" answer to this question was printed in the "Poor/None" column on the EAB Worksheet, raising the potential for mis-classification of primary hemostatic efficacy ratings by EAB members.

If the initial blinded EAB ratings for the primary hemostatic efficacy endpoint by each of the 3 primary adjudicators were not in agreement for a given subject, as per the EAB Charter, a teleconference was held and the EAB members attempted to reach consensus. Failing consensus at this teleconference resulted in the final EAB rating being given by the EAB Chair. Fewer than 10% of subjects required a teleconference to resolve lack of consensus in primary EAB adjudicator ratings.

See below for tables defining excellent, good, and poor/none ratings for the primary hemostatic efficacy variable. To FDA's knowledge, the definitions of hemostatic efficacy used in bleeding RCT BE1116_3002 have not been used previously in clinical trials. Specific criteria were established *a priori*, depending on whether bleeding was visible or fell into one of the following 3 non-visible bleeding categories:

- Muscular/skeletal bleeding
- Intra-cerebral hemorrhage (ICH)

- Non-visible bleeding not listed above (such as GI or retroperitonal bleeding)

The site of bleeding determined the specific reference times for evaluation of pre-specified clinical features of hemostasis. For example, subjects with visible bleeding and non-visible muscular/skeletal bleeding, key clinical assessments were made in relation to the time when the test product infusion was completed. In contrast, for ICH and GI/other non-visible bleeding key clinical assessments were performed in relation to the time of initiation of administration of the test product.

The primary endpoint assessment covers the entire period from the start of the test article infusion until 24 hours after the start of infusion and includes the clinical signs and symptoms of the subject, laboratory values such as hematocrit, hemoglobin, and INR, and any additional hemostatic treatments. The efficacy of only the planned study treatment was to be assessed. As noted above, the EAB also had access to AE data and a "description of the clinical picture," including any additional testing such as CT scans or endoscopies. The amended protocol stated "The EAB is masked to treatment assignment,[to the investigator's assessment,] and to post-baseline INR values. It shall adjudicate hemostatic efficacy in accordance with the EAB Charter and the specification of the rating of hemostatic efficacy contained therein (Appendix III of Attachment I of submission). A blinded physician expert, serving as an adjunct member of the EAB, will review the acute major bleeding eligibility of each subject for inclusion/exclusion in/from the ITT-E [analysis. Subjects who did not receive study medication or had baseline INR < 1.3 are excluded from the ["evaluable-for-efficacy"] ITT-E analysis (but not from the ITT analysis, provided they were randomized)."

For analysis purposes, the primary efficacy variable is binary: effective (excellent or good hemostatic rating) or non-effective (poor/none).

Sponsor's Table 4 from Final Protocol - Primary Rating of Hemostatic Efficacy

Rating system	Definition

Rating system	**Definition**
Excellent (Effective)	Visible Bleeding: Cessation of bleeding < 1 hour after end of infusion and no additional coagulation intervention required. Non-visible Bleeding: 1) Muscular/skeletal bleeding: Pain relief or no increase in swelling or unequivocal improvement in objective signs of bleeding : 1 hour after the end of infusion, and the condition has not deteriorated during the 24-hour period. 2) ICH: < 20% increase in hematoma volume compared to baseline on repeat CT scan performed at the 3 and 24-hour time point. 3) Non-visible bleeding that is not listed above (e.g. GI bleeding): < 10% decrease in both hemoglobin/hematocrit (Hb/Hct)* at 24 hours** compared to baseline [initial correction of decrease in Hb with packed red blood cells (PRBCs), with a transfusion trigger of a Hb < 8 ± 1 g/dL (i.e. transfuse PRBCs if the Hb < 8 ± 1 g/dL)]. *For all types of bleeding: no additional plasma, blood products, and/or coagulation factor products required after initial treatment with study drug.**** Notes: Any additional diagnostic data for a particular bleeding site, e.g. nasogastric tube, ultrasound, GI endoscope, or CT scans, will also be taken into account for the overall assessment. Pain, swelling, and signs of bleeding are considered to be typical symptoms in case of muscular/skeletal bleeding and are expected to be present at baseline. * The smallest % decrease in Hb or Hct should be used to determine the efficacy rating of excellent, good, or poor/none. ** For 24 hours adjusted Hb/Hct calculation: for each unit of packed RBC transfusion there is generally an increase of 1 g/dL in Hb or 3% increase in Hct. ***Blood products refers to whole blood products and not PRBCs. For each unit of PRBC transfusion, there is generally an increase of 1 g/dL in Hb or 3% in Hct. The net change is defined as the difference between the corrected Hb/Hct value at baseline and 24 hours after infusion (see Table 5 below).

Rating system	**Definition**
Good (Effective)	Visible Bleeding: Cessation of bleeding between > 1 and < 4 hours after end of infusion and no additional coagulation intervention required. Non-visible Bleeding: 1) Muscular/skeletal bleeding: Pain relief or no increase in swelling or unequivocal improvement in objective signs of bleeding between > 1 and :S 4 hours after the end of infusion; and the condition has not deteriorated during the 24-hour period. 2) ICH: > 20%, but < 35% increase in hematoma volume compared to baseline on repeat CT scan performed at the 24-hour time point. 3) Non-visible bleeding that is not listed above (e.g. GI bleeding): > 10 to :S 20% decrease in both Hb/Hct* at 24 hours** compared to baseline [initial correction of decrease in hemoglobin Hb with PRBCs, with a transfusion trigger of a Hb < 8 ± 1 g/dL (i.e. transfuse PRBCs if the Hb < 8 ± 1 g/dL)]. *For all types of bleeding: no more than 2 additional units of plasma or blood products, and/or coagulation factor products required after initial treatment with study drug.**** Notes: Any additional diagnostic data for a particular bleeding site, e.g., nasogastric tube, ultrasound, GI endoscope, or CT scans, will also be taken into account for the overall assessment. Pain, swelling and signs of bleeding are considered to be typical symptoms in case of muscular/skeletal bleeding and are expected to be present at baseline. * The smallest % decrease in Hb or Hct should be used to determine the efficacy rating of excellent, good, or poor/none. ** For 24 hours adjusted Hb/Hct calculation: for each unit of PRBC transfusion there is generally an increase of 1 g/dL in Hb or 3% increase in Hct. ***Blood products refers to whole blood products and not PRBCs For each unit of PRBC transfusion, there is generally an increase of 1 g/dL in Hb or 3% in Hct. The net change is defined as the difference between the corrected Hb/Hct value at baseline and 24 hours after infusion (see Table 5 below).

Rating system	Definition
Poor/None (Non effective)	Visible Bleeding: Cessation of bleeding > 4 hours after end of infusion, and/or additional coagulation intervention required (e.g. plasma, whole blood cell pack, or coagulation factor products). Non-visible Bleeding: 1) Muscular/skeletal bleeding: No improvement by 4 hours after the end of infusion and/or the condition has deteriorated during the 24 hour period. 2) ICH: > 35% increase in hematoma volume compared to baseline on repeat CT scan performed at the 24-hour time point. 3) Non-visible bleeding that is not listed above: >20% decrease in both Hb/Hct at 24 hours* compared to baseline [initial correction of decrease in Hb with PRBCs, with a transfusion trigger of a Hb < 8 ± 1 g/dL (i.e. transfuse PRBCs if the Hb < 8 ± 1 g/dL]. *For all types of bleeding: more than 2 additional units of plasma, blood products and/or coagulation factor products required after initial treatment with study drug. ***[1].* Notes: Any additional diagnostic data for a particular bleeding site, e.g. nasogastric tube, ultrasound, GI endoscope, or CT scans, will also be taken into account for the overall assessment. Uncontrolled bleeding that did not respond to Beriplex® P/N or plasma and is related to the underling disease will be taken into account for the overall assessment. Pain, swelling and signs of bleeding are considered to be typical symptoms in case of muscular/skeletal bleeding and are expected to be present at baseline. * For 24 hours adjusted Hb/Hct calculation: for each unit of PRBC transfusion there is generally an increase of 1 g/dL in Hb or 3% increase in Hct. **Blood products refers [sic] to whole blood products and not PRBCs. For each unit of PRBC transfusion, there is generally an increase of 1 g/dL in Hb or 3% in Hct. The net change is defined as the difference between the corrected Hb/Hct value at baseline and 24 hours after infusion (see Table 5 below).

[1]FDA required that all subjects for all bleeding types who received any additional units of whole blood, non-investigational product plasma, or other coagulation factor products (not PRBCs or platelets) be assigned "Poor/None" primary hemostatic efficacy endpoint ratings. Because the sponsor had not implemented this change to the protocol as FDA had requested, the sponsor adjusted the EAB ratings of affected subjects by computer programming.

Sponsor's Table 5 from Final Protocol –
Example table of hemoglobin and hematocrit changes

Parameter	**Hemoglobin**	**Hematocrit**
Baseline	7.3 g/dL	20.8%
24 hour	10.6 g/dL	31.3%
24 hour$_{corr}$ after 2 units RBC (24 hour -2g/dLl Hb or 6% Hct)	8.6 g/dL	25.3%
Difference between 24 hour$_{corr}$ and baseline	1.3 g/dL	4.5%
Difference between 24 hour$_{corr}$ and baseline (%)	17.8%	21.6%

Subjects with "poor/none" hemostatic ratings were coded into 2 sub-categories: non-effective rating and missing primary endpoint. Missing data leading to the latter classification are:

Bleeding Type	**Key Missing Variable**
Non-visible GI/other	24 hr Hb/Hct values
Non-visible ICH	Baseline or 24 hr CT scan
Non-visible Musculoskeletal	1 & 4 hr swelling, pain relief and signs of bleeding
Visible	1 & 4 hr cessation of bleeding

Subjects with "poor/none" ratings due to insufficient information available to adjudicate the primary endpoint were excluded from the per-protocol (PP) analysis.

For visible and non-visible non-ICH bleeding, the definitions involve assessments at 1 and 4 hours after the end of a product infusion (changed by amendment 3 from 3 and 6 hours after the start of the test product infusion).

Co-Primary Efficacy Endpoint

The co-primary efficacy variable was the proportion of subjects who had a decrease of the INR ($\leq$ 1.3) at 30 minutes after end of infusion

Secondary Efficacy Variables

• 45-day all-cause mortality in both treatment groups

• Use of other blood products and/or hemostatic agents from randomization through 24 hours after start of infusion (except PRBCs),

• Transfusion of red blood cells.

• Secondary rating of hemostatic efficacy covering the period from start of investigational medicinal product (IMP) infusion until 24 hours after start of infusion.. This rating has definitions of "excellent," "good," and "poor/none" which are in some cases different from the primary hemostatic efficacy endpoint. For example, for visible bleeding:

Contrast in Primary and Secondary EAB-adjudicated Hemostatic Efficacy Endpoint Criteria for Subjects with Visible Bleeding

Analysis	Excellent (Effective)	Good (Effective)	Poor/None (Non-Effective)
Primary Hemostatic Endpoint Criteria for Visible Bleeding	Cessation of bleeding ≤ 1 hr after end of infusion and no additional coagulation intervention[1]	Cessation of bleeding > 1 and ≤ 4 hrs after end of infusion and no additional coagulation intervention[1]	Cessation of bleeding > 4 hrs after end of infusion and no additional coagulation intervention[1]
Secondary Rating of Hemostatic Efficacy	Cessation of bleeding ≤ 3 hrs after start of infusion and no additional coagulation intervention[1]	Cessation of bleeding > 3 and ≤ 6 hrs after start of infusion and no additional coagulation intervention[1]	Cessation of bleeding > 6 hrs after start of infusion and/or additional coagulation intervention[1]

[1] e.g., plasma, whole blood (WB), coagulation factor products.

• Response and in vivo recovery (IVR) of coagulation factors II, VII, IX, and X, protein C, and protein S (at 0.5, 1, 3, 6, 12, and 24 hours)

• Time to INR correction (INR < 1.3) from start of infusion

• Time to INR correction (INR< 1.3) from randomization

Exploratory Efficacy Variables

• Proportion of subjects who have a decreased INR (i.e. INR < 1.3) at 30 minutes from the start of infusion

• Investigator's assessment of hemostatic efficacy

• Neurological outcome assessed by Modified Rankin Scale (mRS) for ICH subjects at day 45

6.1.9 Statistical Considerations & Statistical Analysis Plan

The primary endpoint was hemostatic efficacy, assessed for the time from start or end (depending on bleeding location) of infusion of Kcentra or plasma until 24 hours after the start of the infusion. The primary efficacy analysis in this study was a test for the non-inferiority of the effect of Kcentra compared to that of plasma on the binary hemostatic efficacy variable (a score of "excellent" or "good" versus a score of "poor/none", assessment by the DSMB.

The primary analysis used the method of Farrington and Manning of the 95% confidence interval (C.I.) for the difference in the proportions of subjects with a rating of effective hemostasis (excellent or good) in the two treatment groups, where p_1 is that proportion in the Kcentra group and p_2 is that proportion in the FFP group.

Null Hypothesis: $p_1 - p_2 < \text{delta}$

Alternative Hypothesis: $p_1 - p_2 > \text{delta}$

Where delta = -0.10 (the non-inferiority margin). Thus, the non-inferiority margin was a 10% absolute difference between test and control groups in the proportion of effective hemostasis.

According to the protocol and statistical analysis plan (SAP), Kcentra would be successfully claimed non-inferior to plasma if non-inferiority was shown for both the primary and co-primary endpoints in the ITT population.

If non-inferiority was shown, an additional test will be performed for the superiority of the effect of Kcentra PIN compared to that of plasma on each of the two primary endpoints. FDA informed the sponsor during the IND phase that a claim of superiority would require superiority be shown both for the primary hemostatic efficacy and co-primary (INR correction) endpoints.

For sample size estimation it was assumed that 85% of the hemostatic efficacy assessments of plasma ($p_2 = 0.85$) and 90% of the hemostatic efficacy assessments of Beriplex ($p_1 = 0.90$) would have a score of good or excellent. The acceptable delta was 0.10 (10%). The power to show non-inferiority with the above assumptions was be greater than 80% for two treatment groups of 80 subjects. The primary analysis was originally to be performed for the ITT population, however in the final SAP this was changed to include the ITT, ITT-E, and per-protocol populations. The sample size was be chosen for the per protocol population in order to have enough power to show non-inferiority also in this analysis. With an assumed rate of 10% drop-outs the total number of subjects in the ITT population was anticipated to be about 2 x 88 (176).

6.1.10 Study Population and Disposition

A total of 216 subjects were enrolled of which 212 were randomized and treated.

6.1.10.1 Populations Enrolled/Analyzed

Sponsor's Table 10 – Subject disposition by study population

Population	**No. (%) of subjects**		
	Kcentra	**Plasma**	**Overall**

	(N = 107)	**(N = 109)**	**(N = 216)**
ITT (as randomized)	107 (100)	109 (100)	216 (100)
ITT-S (as treated)	103 (96.3)	109 (100)	212 (98)
ITT-E (as randomized)	98 (91.6)	104 (95.4)	202 (94)
PP population	93 (86.9)	97 (89.0)	190 (88)

ITT = intention-to-treat; ITT-E = evaluable for efficacy; ITT-S = safety population; N = total number of subject; PP = per-protocol.

6.1.10.1.1 Demographics and Important Baseline Characteristics

Baseline demographics were comparable between Kcentra and plasma groups, except that there were more non-whites in the plasma group. Subjects with a medical history of CHF were 5% higher in the Kcentra arm compared to the plasma arm (45 vs. 40%). Subjects with a prior history of TE (or of coronary artery or cerebrovascular disease) were 5% lower in the Kcentra arm compared to the plasma arm (67 vs. 72%). Because prior history of TE event increases the risk of a subsequent TE event, this difference suggests that the Kcentra arm subjects were as a group at a slightly lower risk of experiencing a TE event compared to the plasma group going into the study.

From Sponsor's Table 11 – Demographics (ITT-E population)

Parameter	Kcentra, n = 98	Plasma, n = 104
Males	50	51
Females	48	53
Mean Age (years)	69.8	69.8
Age < 65	33 (34%)	31 (30%)
Age 65 to < 75	24 (25%)	29 (28%)
Age >=	41 (42%)	44 (42%)
White	93	88
Non-White	5 (5%)	16 (15%)
European Site	30	32
U.S. Site	68	72
Weight kg (Mean, Range)	78.7 (45 - 200)	78.4 (46 - 142)
BMI Mean (SD)	27.7 (9)	27.6 (7)

Baseline INR for Dose Group and for Randomization Group (ITT-E)

	Kcentra	Plasma

	Kcentra	Plasma
Low (2 - < 4)	2.9 ± 0.7 (N = 46)	2.8 ± 0.6 (N = 53)
Mid (4 – 6)	4.6 ± 0.7 (N = 24)	4.8 ± 0.6 (N = 20)
High (>6)	10.6 ± 3.9 (N = 27)	10.9 ± 6.9 (N = 31)

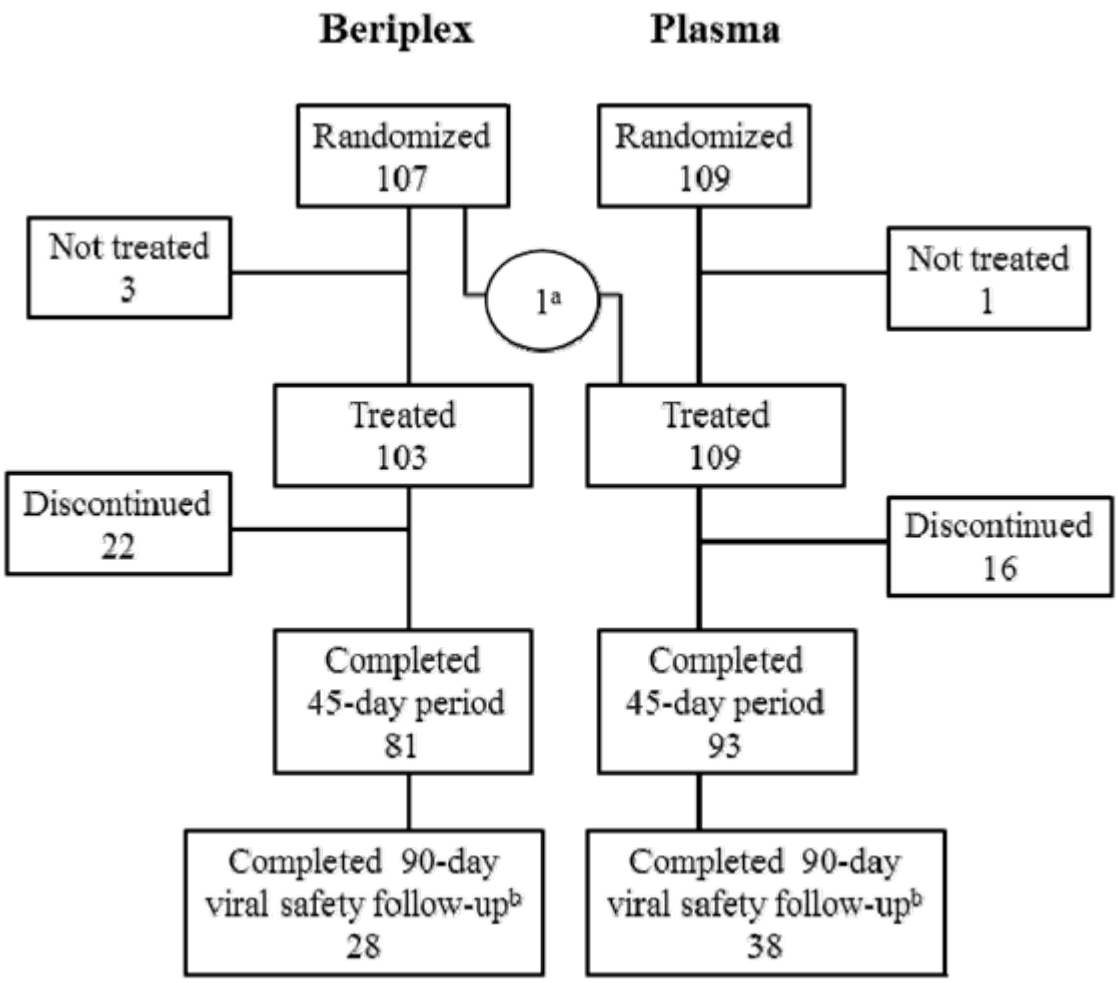
Medical History and Clinical Features at Baseline

Parameter	Kcentra	Plasma
Medical History of CHF	45%	40%
Medical History of Prior TE event, vascular disease, etc.	67%	72%
Baseline INR (Median)	4.1	3.6

Important Baseline Characteristics (ITT-E population)

Parameter	No. of Subjects (%)	
	Kcentra N = 98 (%)	Plasma N = 104 (%)
Type of Acute Bleeding		
Non-visible GI	55 (56.)	58 (55)
Visible	16 (16)	21 (20)
Intracranial Hemorrhage	12 (12)	12 (11)
Other Non-Visible	8 (8)	6 (6)
Non-visible Musc./Skeletal	7 (7)	7 (7)
Reason for VKA therapy		
Arrhythmia	56 (57)	53 (51)
Thromboembolic Event	18 (18)	21 (20)
Artificial valve or joint	13 (13)	13 (12)
Vascular Disease	10 (10)	13 (12)
Other	1 (1.0)	4 (4)

6.1.10.1.3 Subject Disposition



6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

ITT Population

Sponsor's Table 37: Primary endpoint: Proportion of subjects with hemostasis rated effective (ITT population)

Rated Effective[a] n/N (%)		Difference (%): Kcentra– Plasma (95% CI for difference)[b]
Kcentra	Plasma	
74/107 (69.2)	72/109 (66.1)	3.1 (–9.4, 15.6)

[a] Note: Effective = 'excellent' or 'good' (as rated by Endpoint Adjudication Board).
[b] Kcentra non-inferior to plasma: lower limit of the 95% CI exceeds –10%;
Kcentra would have been judged superior to plasma had the lower limit of 95% CI exceeded 0.0.
CI = confidence interval; ITT = Intent-to-Treat; n/N = number of subjects/total number of subjects.
Source: Module 5, Table 14.2.1-1.1a

ITT-E Population

Sponsor's Table 6: Primary endpoint: Proportion of subjects with hemostasis rated effective in the ITT-E population

Rated Effective[a] n/N (%)		Difference (%): Kcentra – Plasma (95% CI for difference)[b]
Kcentra	Plasma	
71/98 (72.4)	68/104 (65.4)	7.1 (–5.8, 19.9)

[a] Note: Effective = 'excellent' or 'good' (as rated by Endpoint Adjudication Board).
[b] Kcentra non-inferior to plasma: lower limit of the 95% CI exceeds –10%;
Kcentra would have been judged superior to plasma had the lower limit of 95% CI exceeded 0.0.
CI = confidence interval; ITT-E = evaluable for efficacy; n/N = number of subjects/total.

The non-inferiority of Kcentra in relation to plasma was consistently observed in the ITT, ITT-E, and the PP analysis populations.

Sensitivity Analyses

One of 4 sensitivity analyses of the primary hemostatic efficacy endpoint conducted by the sponsor failed to demonstrate non-inferiority of Kcentra in comparison to FFP; however, the point estimates for the proportion of subjects for which the treatment was rated effective were numerically slightly greater for Kcentra than for FFP in each of the 4 sensitivity analyses.

FDA conducted two additional sensitivity analyses in which subjects who had one or more Endpoint Adjudication Board (EAB) CRFs or EAB Worksheets Pages 2 missing were imputed with "Poor/None" hemostatic efficacy ratings. Both of these analyses did not confirm non-inferiority of Kcentra, however the point estimates for the proportion of subjects with effective ratings differed in each case by < 10%. There were 25 missing EAB Worksheets (Pages 2) for 22 subjects by sponsor count and up to 39 missing EAB worksheets for 28 subjects and 3 missing EAB CRFs for one subject by FDA count. Among the ten Kcentra subjects for whom EAB worksheets were missing by sponsor count, seven had excellent or good hemostatic endpoint ratings. Among the twelve plasma subjects for whom EAB worksheets were missing by sponsor count, 6 had excellent or good primary hemostatic endpoint efficacy ratings. While the sponsor maintained that EAB Worksheets were not source documents because they lacked a signature block and were created to facilitate masked EAB member adjudications, which were then recorded on the EAB CRFs and signed and dated, FDA disagrees and considers the EAB Worksheets important source documents to inform FDA's understanding of EAB efficacy ratings. The sponsor noted that the 3 primary EAB ratings for each subjects required only 11% of cases to be resolved by consensus meeting and only 3% requiring EAB chair resolution. Among the subjects with missing EAB Worksheets (Pages 2), the EAB agreed on 91% of final ratings (source: BLA Amendment 18 submitted 28 February 2013). FDA notes that several EAB Worksheets contained handwritten comments by the investigators that are germane to an understanding of the quality of primary hemostatic endpoint ratings. For example:

Selected Comments on EAB Worksheets (Pages 2) made by Masked EAB Adjudicators

Subject ID	Comment
013008	Adjudication based on volume measurement, however clinical comment at 24

Subject ID	Comment
	h states '24 h CT essentially unchanged though blood has settled in lateral ventricle. Primary contusion smaller.' To me this is a contradiction.
030028	But this is not really correct [>20% decreased in adjusted Hb/Hct at 24 h]. Yes, there was a >20% fall in adjusted hemoglobin from infusion start, but blood was not given until after the 6-h assessment point. When blood was started, hemoglobin was 7.0 g/dL and after 2 units of red cells was 7.7 g/dL."
101007	Note this patient's platelet count was only 7!!! Thus GI bleeding could have been due to the low platelet count. Should this patient be in the study? According to study entry criteria---Yes. Personally, I have concerns."
314012	Time not reported for emergent endoscopy. This is not the first but one of many. Not sure how this is acceptable.
314015	Another case of LIFE-THREATENING bleeding from hematuria. Sad.
314017	'Life-threatening bleeding' ticked' for bleeding from tooth socket? Guess you can actually see bleeding. Better than Hematuria I guess.
314002	Macrohematuria does not equal 'major bleeding: life-threatening.' This is embarrassing. If there is even a concern, where's the CT scan, the cysto? Hopefully this will be through [sic, assume "thrown' was intended] out, unless I misread the charter and this is an INR reversal study, not a bleeding study.
402001	This assessment is made on the basis of lack of information, rather than on efficacy of the medication. [EAB adjudicator #1] INR > 2 checked on page 115/122, but again, no INR provided. The HS [sic, assume Hb intended] increased by 2.5g without any transfusions? Really? Not sure how I felt like I could grade before [sic]. I do not believe the site. In addition to the amount of data missing for this patient, this patient (and the site) should be tossed. [EAB adjudicator# 2] 'Missing information' [with respect to determination of overall rating]. 'Not possible' [with respect to change in adjusted Hb/Hct at 24 h and no need for plasma, coagulation factors or while blood administered within 24 h. [EAB adjudicator #3]

Only when the totality of the data relating to various analyses of the primary efficacy endpoint and the additional efficacy endpoints were examined, was it concluded by a preponderance of the evidence that the efficacy of Kcentra was comparable to that of plasma for the indication being sought.

Co-Primary (INR Reduction) Efficacy Endpoint (A Surrogate Measure)

ITT-E Analysis
Sponsor's Table 9: Co-primary endpoint: Decrease in INR to <1.3 at 30 min after end of infusion (ITT-E population)

Decrease[a] n/N (%)	Difference (%): Kcentra – Plasma (95% CI for difference)[b]

Kcentra	Plasma	
61/98 (62.2)	10/104 (9.6)	52.6 (39.4, 65.9)

[a]Note: Rapid decrease = INR ≤ 1.3 at 30 minutes after end of infusion.
[b]Kcentra non-inferior to plasma: lower limit of the 95% CI exceeds –10%;
Kcentra superior to plasma: lower limit of 95% CI exceeds 0.0.
CI = confidence interval; INR = international normalized ratio; ITT-E = evaluable for efficacy; n/N = number of subjects/total.
Source: BLA Module 5.3.5.1.1.2, Table 14.2.2-1.1b

ITT Analysis

Similar results were obtained in the ITT analysis of the co-primary endpoint, in which 60% of Kcentra and 9% of plasma subjects had a rapid decrease in INR to ≤ 1.3 at 30 min after the end of test product infusion.

PP Analysis

Similar results were obtained in the ITT analysis of the co-primary endpoint, in which 62% of Kcentra and 10% of plasma subjects had a rapid decrease in INR to ≤ 1.3 at 30 min after the end of test product infusion.

Sensitivity Analyses

The sponsor performed a sensitivity analysis at the request of the FDA in which subjects who received any additional units of plasma, blood products, and/or coagulation factor products (other than Red Blood Cells and platelets) during the 24 hours after the start of the CTM infusion were scored as having no rapid decrease in INR. The results of this sensitivity analysis were similar to that of the co-primary endpoint, with 61% of subjects in the Kcentra group and 10% of subjects in the FFP group showing rapid decrease in INR at 30 min post end of infusion.

FDA Comments on the Primary Hemostatic Efficacy and Co-Primary (Surrogate) Endpoint Analyses

The non-inferiority of Kcentra in relation to plasma was consistently observed in the sponsor's analyses for the ITT, ITT-E, and the PP analysis populations. The FDA biostatistician verified the sponsor's analysis for the ITT-E population, using the sponsor's analysis datasets. Non-inferiority of Kcentra was confirmed in three of four sensitivity analyses of the primary hemostatic efficacy endpoint, but not confirmed in 2 robustness analyses conducted because a substantial number of subjects' source document EAB worksheets and a single subject's EAB CRF were missing during the sponsor-monitor BioResearch Monitoring inspection.

Because Kcentra was not found to be superior to plasma for *both* the primary and co-primary endpoints in the ITT-E population, no conclusion of superiority of Kcentra over plasma can be drawn. Only when the totality of the data relating to various analyses of the primary efficacy endpoint and the additional efficacy endpoints were examined, was it concluded by a

preponderance of the evidence that the efficacy of Kcentra was comparable to that of plasma for the indication being sought.

6.1.11.2 Analyses of Secondary Endpoints

Secondary Endpoint Efficacy Analyses

45-Day Mortality from All Causes

Mortality (through day 45), a pre-specified efficacy endpoint, was examined in ITT-E and ITT-S populations. Mortality through day 45 as well as through the entire 90 day study follow-up period was examined in the ITT-S population as a safety endpoint.

ITT-E population:

All-cause mortality through day 45 showed a risk ratio 1.91 in favor of plasma, but this difference was not statistically significant (95% CI for Kcentra /Plasma 0.66 to 5.50). There were 9 deaths among 98 Kcentra subjects and 5 deaths among 104 plasma subjects in the ITT-E population, giving 45 day mortality rates of 9.2% and 4.8% respectively. (*Two additional deaths in the Kcentra group were observed in the ITT-S population over the entire study follow-up period.)*

ITT-S population:

[Although not a pre-specified efficacy endpoint, through day 90 (or day 46, an observation interval of 45 days), there were 11 deaths (10.7%, 95% CI 6.1, 18.1) in the Kcentra group and 5 (4.6%, 95% CI 2.0, 10.3) in the plasma group, for an absolute difference of 5.1% excess deaths in the Kcentra group. The 95% confidence interval for the between-group difference in 45 day all-cause mortality ranged from -2.7% to 13.5%. Thus, although not statistically significant at the two-sided alpha 0.05 level, the result represents a trend of increased mortality following Kcentra administration, which is of concern, particularly since the study was not designed or powered to detect meaningful differences in mortality. The findings suggest a trend for increased mortality against Kcentra.] [One death occurred 45 days after Kcentra administration, on day 46, the day after the patient was discharged from the hospital and transferred to another facility on comfort care. This subject had sustained a CVA three days prior to death which was confirmed by the investigator as possibly related to prior Kcentra administration. While the masked safety adjudication board (SAB) did not agree with this assessment, the SAB did conclude that the death was likely related to the CVA. Although AEs were routinely collected through the day 45 visit, the protocol specified that AEs deemed by the investigator to be [at least possibly] related to study product were to be reported if they occurred anytime up to day 90.]

Red Blood Cell Transfusions

The mean +/- SD number of transfused units of PRBCs was 1.4 +/- 1.8 and 1.2 +/- 1.57 units in Kcentra and Plasma groups, respectively, and did not differ by the Wilcoxon Rank Sum test (p = 0.45). Volumes of transfused units of PRBCs were available for 21 subjects in the Kcentra group and 23 subjects in the plasma group. The mean volume of all transfused units was 308 mL. Normalization of transfusion volumes to this standard volume per unit also revealed no statistically significant difference between randomization groups (p = 0.50 by Wilcoxon Rank Sum test). [Note that the more appropriate test is to look at confidence intervals for the between-group difference, given that the trial's primary objective is to determine whether Kcentra is non-inferior to plasma.]

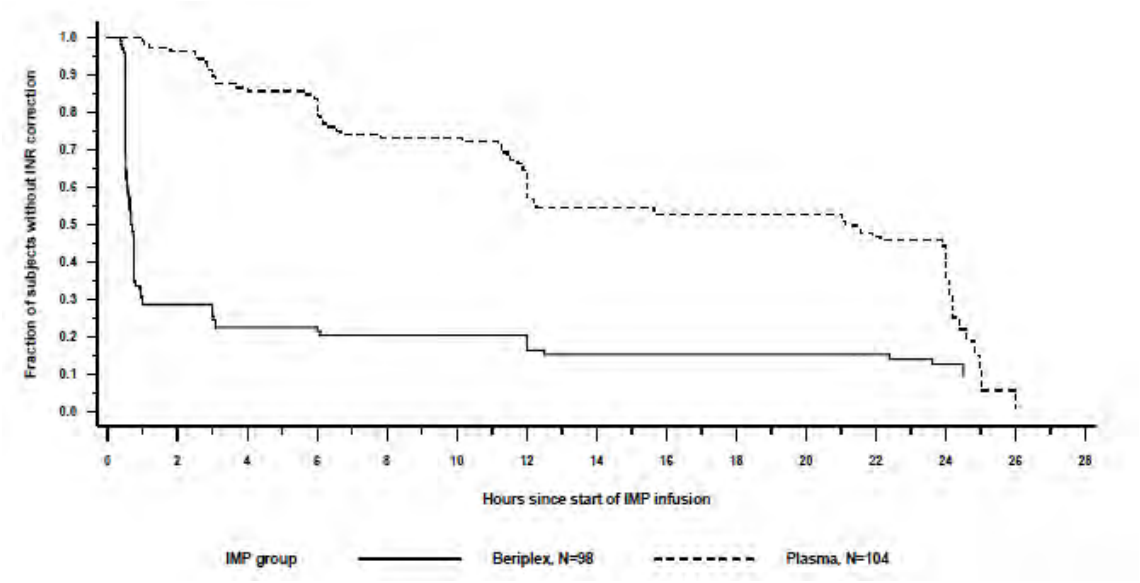
Use of Other Blood Products (besides PRBCs)

The numbers of units of other blood products used by subjects in Kcentra (mean 0.3 +/- 1.36) and plasma (mean 0.3 +/- 0.87) groups up to 24 hours after start of test product infusion were similar and not statistically different (2-sided Wilcoxon test p = 0.3714). FDA noted that albumin was included among the "other blood products" tested, but only a single subject received albumin.

Secondary Hemostatic Efficacy Assessment by Efficacy Adjudication Board (EAB)

The proportions of subjects in each treatment group with effective hemostasis under the secondary EAB rating were similar to that of the primary efficacy endpoint analysis.

Time to INR Correction to ≤ 1.3 from Start of Infusion



In Vivo Recovery of Vitamin K-Dependent Clotting Factors and of Proteins C and S

Sponsor's Table 27: Comparison of incremental IVR (response) and classical IVR for Beriplex [Kcentra] for each component (ITT-E population) Study BE1116_3002

Parameter	N	Mean (SD)	Min/Max
Factor II			
Incremental IVR [(IU/dL)/(IU/kg b.w.)][a]	97	2.00 (0.879)	−0.3/4.8
Classical IVR [%][a]	91	85.83 (37.208)	−13.9/224.8
Factor VII			
Incremental IVR [(IU/dL)/(IU/kg b.w.)][a]	97	2.15 (2.958)	−1.8/20.9
Classical IVR [%][a]	91	96.09 (139.192)	−74.5/987.6
Factor IX			
Incremental IVR [(IU/dL)/(IU/kg b.w.)][a]	97	1.29 (0.711)	−0.7/4.0
Classical IVR [%][a]	91	55.98 (32.422)	−31.4/174.6
Factor X			
Incremental IVR [(IU/dL)/(IU/kg b.w.)][a]	97	1.96 (0.871)	−0.2/4.7
Classical IVR [%][a]	91	84.72 (36.622)	−8.0/221.8
Protein C			
Incremental IVR [(IU/dL)/(IU/kg b.w.)][a]	97	2.04 (0.958)	−0.5/5.0
Classical IVR [%][a]	91	88.59 (41.848)	−22.6/235.1
Protein S			
Incremental IVR [(IU/dL)/(IU/kg b.w.)][a]	97	2.17 (1.661)	−2.2/9.7
Classical IVR [%][a]	91	92.91 (76.539)	−99.1/504.7

[a] Incremental IVR [(IU/dL)/(IU/kg)] = (IU/dL activity rise in plasma)/(IU/kg b.w. infused) and
Classical IVR (%) = 100 × (actual increase)/(expected increase).
b.w. = body weight; ITT-E = evaluable for efficacy; IVR = in vivo recovery; N = total number of subjects; SD = standard deviation.

Selected Pre-Specified Exploratory Efficacy Endpoint

Investigator (Unblinded Rating of Hemostatic Efficacy

Investigator unblinded ratings of hemostatic efficacy were considered comparable for the 2 subgroups of subjects enrolled before and after protocol amendment 3.0.

Sponsor's Table 33 - Investigator unblinded rating of hemostatic efficacy (ITT-E population)

Hemostatic efficacy rating	**No. (%) of subjects**	
	Kcentra	Plasma
Before Amendment 3.0	**n = 64**	**n = 63**
Excellent	38 (59.4)	29 (46.0)
Good	14 (21.9)	16 (25.4)
Poor/none	12 (18.8)	18 (28.6)
After Amendment 3.0	**n = 34**	**n = 41[a]**
Excellent	21 (61.8)	22 (56.4)
Good	4 (11.8)	9 (23.1)
Poor/none	9 (26.5)	8 (20.5)

[a] Two subjects in the plasma group had no rating.
ITT-E = evaluable for efficacy; n = number of subjects.

Combining results from before and after protocol amendment 3, 77 (78.6%) Beriplex group and 76 (73.1) plasma group subjects had effective (excellent or good) hemostatic efficacy investigator ratings. These overall results for unblinded investigator ratings of hemostatic efficacy are consistent with the results of the blinded EAB primary efficacy endpoint ratings, but showed a numerically smaller difference between the treatment groups (5.5% vs. 7.0% difference, absolute).

Section 11.3.1.3.5 of the study report states in part "There were 27 (13.4%) subjects (14 in the Beriplex group and 13 in the plasma group) with a blinded EAB primary assessment which was different from that of the unblinded investigator assessment and that difference resulted in a change in effectiveness (between excellent/good and poor/none)."

Neurological outcome for ICH subjects – Modified Rankin Score (mRS)

Twelve subjects in each treatment group had intracranial hemorrhage (ICH) in the ITT-E population. Data to permit calculation of the mRS were available for only one subject in the Kcentra group and two in the plasma group subjects at 24 hours after start of test product infusion. At day 45 data to compute mRS were available for 9 ICH subjects in each treatment group.

Mean Modified Rankin Scores[1]

Treatment Group	**Baseline mRS**	**Day 45 mRS**	**Difference (D45- Baseline)**
Kcentra	1.2	2.1	+0.9
Plasma	2.0	1.7	- 0.3
Difference (B-P)	- 0.8	+0.4	+1.2

[1]Higher mRS indicates greater neurological dysfunction.

Among the 9 subjects in each treatment group with mRS data at day 45, eight subjects achieved good mRS scores (pre-defined as <5). Using a mRS value of <4 to define a good response, 6 of 9 Kcentra and 7 of 9 plasma group subjects had a good response. The differences in changes from baseline in mRS between treatment groups were not considered clinically relevant by FDA.

6.1.11.3 Subpopulation Analyses

Post-Hoc Analyses of Primary Hemostatic Efficacy Endpoint in the ICH Population

(Total N = 24, 12 each treatment group)

	Effective N (%)	Not Effective N	Not Effective %	LL 95% C.I. % Eff.	UL 95% C.I. % Eff.
Kcentra	5 (42)	7(58)		14	70
Plasma	7(58)	5 (42)		30	86
Difference Kcentra – Plasma			-17 %	-56	23

The percentage of subjects with ICH who had effective primary hemostatic efficacy ratings was 16% higher in the plasma group than in the Kcentra group, but the number of ICH subjects (n = 22) precluded meaningful statistical analysis. FDA concluded that there was no trend to suggest that Kcentra may be superior to plasma in hemostatic efficacy among patients with ICH, despite more rapid correction of INR.

The table below, taken from the FDA biostatistical review memo, shows the percentage of subjects in the pivotal RCT in acute major bleeding with effective hemostasis according to whether the bleeding location was non-visible gastrointestinal or visible.

Type of major bleeding	Kcentra	Plasma	Difference (Kcentra minus Plasma) (95% CI)
Non-visible gastrointestinal	74.5 (41/55)	75.9 (44/58)	*-1.3 (-17.2, 14.6)*
Visible	75.0 (12/16)	57.1 (12/21)	*17.9 (-12.1, 47.9)*

One of the key data elements used by the masked Endpoint Adjudication Board (EAB) in adjudicating primary hemostatic endpoint ratings of subjects with non-visible GI bleeding in RCT BE11126_3002 was the change in hemoglobin and hematocrit from baseline to 24 hours after correcting for any red blood cell transfusions. The results of this analysis suggested that Kcentra may be less effective than plasma in patients with GI bleeding as shown in the table below:

Number (%) of Subjects with Non-Visible GI Bleeding with Effective Hemostasis[1] in RCT BE1116_3002 with Acute Major Bleeding Based Solely on Change in Corrected Hemoglobin or Hematocrit over 24 hours

	Kcentra (n = 55)	Plasma (n = 58)	Difference Kcentra minus Plasma [95% C.I.]
Number (%) with Effective Hemostasis Based on Corrected Hemoglobin Change	38 (69%)	48 (83%)	-14% [-29.3, 2.0]
Number (%) with Effective Hemostasis Based on Corrected Hemoglobin Change	36 (65%)	48 (83%)	-17% [-33.2, 1.4]

[1]Source: Analysis performed by Dr. Jiang (Jessica) Hu, CBER Biostatistician as conveyed by email to L. Ross Pierce, M.D. on 08 April 2013 and confirmed by email on 16 April 2013.

The above table shows strong trends that favor plasma in the subpopulation of patients with non-visible GI bleeding when hemostatic efficacy is determined solely by the magnitude of drop in Hb and Hct over the first 24 hours, but the Kcentra minus plasma differences are not statistically significant, given that the 95% CI crosses zero.

Results of a *post-hoc* analysis of primary rating of hemostatic efficacy stratified by actual dose of Kcentra or plasma administered are presented in the following Table.

Primary Rating of Hemostatic Efficacy Stratified by Actual Dose of Kcentra or Plasma (Number and % of Subjects rated "Effective" in Acute Major Bleeding RCT

	Low Dose	**Mid Dose**	**High Dose**
	N = 49 (K)	N = 22 (K)	N = 26
	N = 55 (P)	N = 18 (P)	N = 31
Kcentra	36 (74.5%)	16 (72.7%)	18 (69.2%)
Plasma	38 (69.1%)	11 (61.1%)	19 (61.3%)
Difference*	(4.4%)	(11.6%)	(7.9%)
95% CI K– P	-13.2 – 21.9	-17.4 – 40.6	-17.0 – 32.9

* Kcentra (K) minus Plasma (P)

FDA requested the sponsor perform *post-hoc* subgroup efficacy analyses of study BE1116_3002 subjects who had (1) a medical history of Congestive Heart Failure (CHF) and (2) a medical history of TE event including TIA or angina pectoris.

Dose Response of INR Response

The table below, adapted from Sponsor Table 14.2.2, depicts INR response by Planned Dosage Group. As previously noted, both Kcentra and Plasma were dosed according to cut points of baseline INR.

Time Since Start of Infusion to Achieve Mean INR ≤ 1.30 (ITT-E)

Dosage Group	Kcentra	Plasma
Low	24 hr	Not Achieved
Mid	3 hr	Not Achieved
High	Not Achieved	Not Achieved

Time Since Start of Infusion to Achieve Median INR ≤ 1.30 (ITT-E)

Dosage Group	Kcentra	Plasma
Low	0.5 hr	24 hr
Mid	0.5 hr	24 hr
High	0.5 hr	24 hr

The sponsor agreed with FDA in its response to an information request that the selection of the threshold of ≤ 1.30 for IND used for the co-primary endpoint was somewhat arbitrary. The clinical significance of this INR threshold is unclear.

Subgroup Efficacy Analyses of Subjects with a History of CHF

Method:

This subgroup was defined as subjects with any medical history term in the MedDRA 12.0 System Organ Class (SOC) "cardiac disorders" including as part of the preferred term either "congestive" or "failure." These included cardiac failure congestive, cardiac failure chronic, cardiac failure, congestive cardiomyopathy, and cardiac failure acute.

Results:

There were 50 subjects out of 107 Beriplex subjects and 50 subjects out of 109 Plasma subjects who had a medical history of CHF (ITT population).

In the ITT-S population there were 50/103 Beriplex subjects and 50/109 Plasma subjects who had a medical history of CHF.

In the ITT-E population there were 46/98 Beriplex subjects and 48/104 Plasma subjects who had a medical history of CHF.

In the PP population there were 44/93 Beriplex subjects and 46/97 Plasma subjects who had a medical history of CHF.

Number and % of Subjects with Effective Primary Hemostatic Efficacy Ratings by History of CHF (ITT-E, bleeding RCT BE1116_3002)

	Kcentra		Plasma	
	N	%		
With Hx CHF	33/42	78.6%	27/42	64.3%
No Hx CHF	38/56	67.9%	41/62	66.1%

Subgroup Efficacy Analyses of Subjects with a History of Thrombotic or Thromboembolic (TE) events or Angina Pectoris

Method:

This subgroup was defined as subjects with any medical history term in the MedDRA 12.0 Standardized MedDRA Queries (SMQs) Embolic and thrombotic events, arterial", "Embolic and thrombotic events, venous" and "Embolic and thrombotic events, vessel type unspecified and mixed arterial and venous" (including transient ischemic attack) or (2) by a PT including the term "angina." In the sponsor's analysis, this included some categories of subjects who presumably had a history of angina or TIA or otherwise would be assumed to be at increased risk of a TE event but who may not necessarily have experienced TE events, such as subjects who had undergone coronary artery bypass grafting, coronary stent insertion, carotid endarterectomy, coronary angioplasty, arterial bypass operation, vascular stent insertion, vascular graft, arterial stent insertion, aortic bypass, endarterectomy, angioplasty, peripheral artery angioplasty, portal shunt, percutaneous coronary intervention, and venous operation.

Results:

In the ITT-S population there were 69/103 Beriplex subjects and 79/109 Plasma subjects who had a medical history of TE events (as defined by the sponsor).

In the ITT-E population there were 65/98 Beriplex subjects and 74/104 Plasma subjects who had a medical history of TE events (as defined by the sponsor).

Number and % of Subjects with Effective Primary Hemostatic Efficacy Ratings by History of Prior TE Event[1] (or vascular disease) (ITT-E, bleeding RCT BE1116_3002)

	Kcentra		**Plasma**	
	N	%		
With Hx TEE	48/65	73.8%	49/74	66.2%
No Hx TEE	23/33	69.7%	19/30	63.3%

[1]TEE = arterial or venous thromboembolic event

Subgroup Efficacy Analyses of Subjects with a History of Congestive Heart Failure (CHF) but without a History of Thrombotic or Thromboembolic (TE) events or Angina Pectoris

Method:

The sponsor used the same methodology for identification of subjects who had a history of CHF or TE event (or angina pectoris or conditions indicative of a prior history of angina pectoris or clinically significant coronary artery disease, such as history of angioplasty, coronary stent placement, or CABG) as noted above, except that history of use of a central venous catheter as a criterion required that the catheter be present on the date of enrollment.

Results:

In the ITT population there were 14/107 Beriplex subjects and 11/109 Plasma subjects who had a history of CHF but no medical history of TE events (or angina, etc.).

Sponsor's Table 1a (amendment 0.9): Primary rating of hemostatic efficacy by medical history ITT population, N=216
Subjects with medical history of congestive heart failure and without medical history of thromboembolic events, N=25

	Beriplex, N = 14		Plasma, N = 11	
	N	%	N	%
Excellent or good	**10**	**71**	**7**	**64**
Poor/None	**4**	**29**	**4**	**36**

The one-sided 97.5 CI for the difference (B – P) in the proportion of subjects who had effective primary hemostatic efficacy ratings was -28.7%. Thus, Beriplex was non-inferior, but not superior to plasma in this combined subgroup of subjects with a history of CHF but without a history of TE event or angina, etc.

6.1.11.4 Dropouts and/or Discontinuations

Three subjects in the plasma group and none in the Kcentra group did not receive all of the planned dose of test product due to AEs. In two cases this was due to symptoms consistent with volume overload and in the third case it was due to symptoms considered to represent a mild transfusion reaction.

Many subjects did not undergo the required viral safety blood draw on day 90.

6.1.11.5 Exploratory and Post Hoc Analyses

Sponsor's Table 32 - Post-hoc Descriptive Analysis of Mean INR at Various Times after Start of Randomized Test Product Infusion (ITT-E Population – Study BE1116_3002)

Time after	Kcentra Bip (N = 98)	Plasma (N = 104)	p-value[a]

Start Infusion	n	Mean INR	n	Mean INR	
Pre-infusion	98	5.44	104	5.62	0.7146
30 min	87	1.49	93	2.85	< 0.0001
1 hour	93	1.39	97	2.42	< 0.0001
3 hours	92	1.34	94	1.81	< 0.0001
6 hours	87	1.35	97	1.63	< 0.0001
12 hours	92	1.32	97	1.45	0.0002
24 hour s	90	1.38	99	1.36	0.0782

[a] 2-sided p-value (Wilcoxon-test).
INR = international normalized ratio; ITT-E = evaluable for efficacy; N = total number of subjects; n = number of subjects.

6.1.12 Safety Analyses

6.1.12.1 Methods

FDA focused its review of safety on the two plasma-controlled RCTs:

- BE1116:3002 – Urgent VKA Reversal in Patients with Acute Major Bleeding
- BE1116:3003 – Urgent VKA Reversal in Patients Requiring Urgent Surgery or Invasive Procedure

RCT BE1116_3003 was an open-label, randomized, multicenter, active (plasma) controlled clinical trial to assess the efficacy, safety and tolerance of Kcentra compared with plasma for rapid reversal of coagulopathy induced by vitamin K antagonists in subjects requiring an urgent surgical or urgent invasive procedure. The RCT randomized 176 subjects (88 to Kcentra and 88 to plasma) and was conducted in the US and overseas. Subjects were randomized 1:1 to receive either Kcentra, containing on average 25 IU FIX per mL) or plasma. The dose of both products depended on the baseline INR using the same dosing scheme as had been used in the bleeding _3002 RCT.

An important issue in the analysis of safety data with Kcentra was whether it was scientifically justified to pool safety data from the RCT in acute major bleeding and the RCT in surgery/invasive procedure. FDA concluded that pooling safety data from these two trials was problematic for the following reasons:

- Subjects in the bleeding RCT had higher INR values on average than in the surgery study.
- The higher INR values in the bleeding study resulted in substantially more subjects being assigned to receive higher (mid and high) doses of Kcentra and Plasma than in the surgery study.

- Because the planned Kcentra dose varied over a 2-fold range, whereas the planned plasma dose varied over a 1.5-fold range in both bleeding and surgery studies, the higher average INR values in the bleeding study had a disproportionate effect in the bleeding study in raising planned Kcentra doses compared to the effect on the planned plasma doses.
- Differences exist between bleeding and surgery RCTs in the proportion of subjects at baseline with a history of
    - prior TE event/coronary/cerebrovascular/peripheral vascular disease.
    - congestive heart failure.
- Differences exist between bleeding and surgery RCTs in the proportion of
    - female subjects. There was a higher percentage of female subjects in the bleeding RCT and in that study the majority of deaths occurred in females (11 of 16 = 69%)
    - non-caucasian subjects
- Differences exist in the pattern of use of concomitant medications between surgery and bleeding RCTs.
- More subjects in the bleeding RCT received blood transfusions.
- A published meta-analysis of 1032 patients treated with PCCs for urgent reversal of VKA anticoagulation found that the TE event rate was more than double in patients being treated for bleeding compared to those undergoing surgery or an invasive procedure.

However, the overall age distribution of subjects between bleeding and surgery RCTs was quite similar,

FDA concluded that pooling safety data from the bleeding and surgery RCTs was not scientifically justified for the reasons noted above. Nevertheless, pooled results for death and TE events are provided below for informational purposes.

As noted, the mean and median INR values at baseline were lower in the surgery study BE1116_3003 vis-à-vis the bleeding study BE1116_3002. The table below shows that, in the surgery RCT median INR values at baseline were 2.9 and 3.0 in Kcentra and plasma groups, respectively). In the bleeding RCT, median INR values in Kcentra and plasma arms were 4.1 and 3.6, respectively.

The percentage of subjects in the Kcentra arm who had a medical history of CHF in the BE1116 _3003 surgery pivotal trial was 12% (absolute) lower than that in the plasma arm, as shown in the table below. A medical history of prior TE (or of coronary, cerebrovascular, or peripheral vascular disease) was 6% lower in the Kcentra arm compared to the plasma arm in the pivotal surgery study.

A medical history of CHF was 5% lower in the Kcentra arm compared to the plasma arm in the pivotal bleeding study (45 vs. 40%). A prior history of TE (or of coronary artery, cerebrovascular disease, or peripheral vascular disease) was 5% lower in the Kcentra arm compared to the plasma arm in the pivotal bleeding RCT (67% vs. 72%).

Comparison of Medical History and Clinical Features at Baseline between Bleeding BE1116_3002 and Surgery BE1116_3003 RCTs

Parameter	Bleeding Study BE1116_3002 Kcentra/Plasma	Surgery Study BE1116_3003 Kcentra/Plasma
Medical History of CHF	45% / 40%	28% / 40%
Medical History of prior TE event, etc.	67% / 72%	64% / 70 %
Baseline INR (Median)	4.1/3.6	2.88 / 2.96 (n = 155 interim anal.)

Planned Doses of Kcentra and Plasma in Bleeding (BE1116_3002) and Surgery (BE1116_3003) RCTs (ITT-S, N = 176)

	Bleeding RCT		Surgery RCT	
	Kcentra	Plasma	Kcentra	Plasma
N	N = 107	N = 109	N = 88	N = 88
Mean	33.8	11.6	28.1	10.6
Std. Dev.	10.4	2.2	7.6	1.8
Median	28.5	10.0	25.0	10.0

Planned dose based on INR: Kcentra (IU/kg), Plasma mL/kg

In the Kcentra arm of the surgery RCT there were 69, 10, and 9 subjects in low, mid, and high planned dosage groups, respectively. By contrast, in the bleeding RCT there were 48, 26, and 29 subjects in the low, mid, and high planned dosage groups respectively. Thus, in the surgery RCT, 21.6% of subjects were in mid and high planned Kcentra dosage cohorts, while in the bleeding RCT, 52.9% of subjects were in the mid and high planned Kcentra dosage cohorts.

All analyses performed with the complete final dataset for the surgery study BE1116_3003 were performed with draft cleaned data prior to database lock, and are therefore termed preliminary.

6.1.12.2 Overview of Adverse Events

Adverse Reactions* Following Kcentra or Plasma Administration in Acute Major Bleeding RCT

	No. (%) of subjects	
	Kcentra (N = 103)	**Plasma (N = 109)**
General disorders and administration site conditions		
Chest pain	1 (1.0%)	3 (2.8%)
Nervous system disorders		
Headache	8 (7.8%)	2 (1.8%)
Hemorrhage intracranial	3 (2.9%)	0
Respiratory, thoracic, and mediastinal disorders		
Respiratory distress/dyspnea/hypoxia	2 (1.9%)	4 (3.7%)
Breath sounds abnormal/rates	1 (1.0%)	3 (2.8%)
Pulmonary edema	0	4 (3.7%)
Gastrointestinal disorders		
Nausea/vomiting	4 (3.9%)	1 (0.9%)
Constipation	2 (1.9%)	6 (5.5%)
Diarrhea	0	3 (2.8%)
Cardiac disorders		
Tachycardia	3 (2.9%)	1 (0.9%)
Investigations		
International normalized ratio increased†	3 (2.9%)	0
Metabolism and nutrition disorders		
Hypokalemia	2 (1.9%)	5 (4.6%)
Fluid overload‡	1 (1.0%)	6 (5.5%)
Hypomagnesemia	0	3 (2.8%)
Psychiatric disorders		
Mental status changes	3 (2.9%)	0
Insomnia	1 (1.0%)	3 (2.8%)
Musculoskeletal and connective tissue disorders		
Arthralgia	4 (3.9%)	0
Vascular disorders		
Hypotension§	5 (4.9%)	3 (2.8%)
Blood pressure increased/hypertension	3 (2.9%)	0
Injury, poisoning, and procedural complications		
Skin laceration/contusion/subcutaneous hematoma	3 (2.9%)	1 (0.9%)
Transfusion reaction‖	0	4 (3.7%)
Blood and lymphatic disorders		
Anemia¶	0	4 (3.7%)

* Adverse Reactions defined as adverse events that began during or within 72 hours of the end of test product infusion plus adverse events where the relationship to study treatment was possibly related, probably related, or related in the opinion of the investigator, sponsor, or the blinded safety adjudication board (SAB), occurring in ≥ 2.8% (≥ 3 Subjects) and with at least a 1.3-fold difference between treatments.

† Two subjects experienced an INR correction that was not sustained past 3 hours; One subject received a lower than protocol specified Kcentra dose.

‡ Includes fluid overload and cardiac failure congestive

§ Includes orthostatic hypotension, hypotension, and hemorrhagic shock

‖ Includes transfusion reaction, allergic transfusion reaction

¶ Includes anemia, hemoglobin decreased, and hemocrit decreased

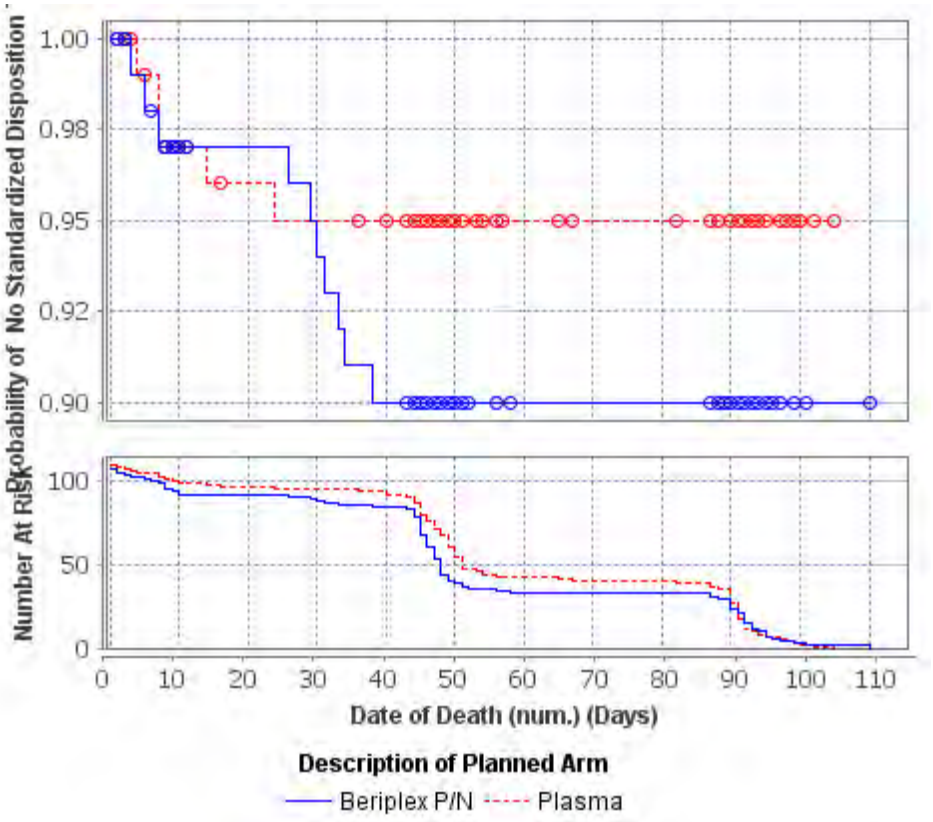
6.1.12.3 Deaths

Forty-five day mortality was a pre-specified secondary efficacy endpoint (see above).

There were 11 deaths (10.7%, 95% CI 6.1, 18.1) among 103 Kcentra subjects compared to 5 deaths (4.6%, 95% CI 2.0, 10.3) among 109 plasma subjects in the ITT-S population throughout the entire study follow-up period. [One death occurred 45 days after Kcentra administration, on day 46, the day after the patient was discharged from the hospital and transferred to another facility on comfort care. This subject had sustained a CVA three days prior to death which was confirmed by the investigator as possibly related to prior Kcentra administration. While the masked safety adjudication board (SAB) did not agree with this assessment, the SAB did conclude that the death was likely related to the CVA. Although AEs were routinely collected through the day 45 visit, the protocol specified that AEs deemed by the investigator to be [at least possibly] related to study product were to be reported if they occurred anytime up to day 90.] The 95% confidence interval for the between-group difference (Kcentra minus Plasma) in deaths through day 90 and through day 46 ranged from -1.9% to 14.6% (ITT-S population). The ratio of the excess deaths among subjects randomized to Kcentra to those randomized to control plasma treatment was 2.2 in the FDA analysis. In a subsequent trial to reverse VKA effects on INR prior to urgent surgery or invasive procedures, Kcentra associated mortality was numerically but not statistically significantly less than in the plasma arm (see below).

From the Kaplan-Meier plots below it can be seen that deaths during the first 30 days following administration of study product were similar in the two groups, but that an excess of deaths was seen in the Kcentra group between days 30 and 45. The deaths occurring after day 30 may be less likely to be causally related to prior administration of the test product, compared to deaths occurring prior to day 30.

Kaplan-Meier Plots of All subjects by Randomized Treatment Group – Study _3002



Pooling the two treatment groups, a preponderance of deaths occurred among women (11 vs. 5 for men).

Deaths in both treatment groups were more common among subjects > 75 years of age, but the excess in deaths among subjects in the Kcentra treatment group was more pronounced among subjects younger than age 75.

While 28% of subjects in the bleeding RCT were in the high planned dosage cohort, seven of eleven deaths among subjects who received Kcentra received actual doses > 35 IU/kg (the planned middle dose). [Actual doses were often ~ 10% higher than planned doses, probably because dosing was done on the basis of nominal potency rather than actual potency.] Five of 11 deaths (45%) occurred in subjects who had received actual doses > 45 IU/kg. By comparison, 26/97 (27%) of Kcentra subjects in the ITT-E population had actual doses > 45 IU/kg. Among deaths considered by FDA possibly or probably related to prior administration of Kcentra three of five (60%) occurred in subjects who received > 35 IU/kg and two of five (40%) occurred in subjects who received > 45 IU/kg (actual dose, based on potency of the particular lot used).

The masked (blinded) safety adjudication board concluded that only one death (in the Kcentra group) was at least possibly treatment-related in the RCT in acute major bleeding. FDA undertook two masked and two unmasked assessments of the possible causal relationship between administration of test product and subsequent deaths. Unmasked analyses examined death incidence by treatment group after sequentially eliminating deaths attributed to (a) malignancy and (b) sepsis. The results all masked and unmasked FDA analyses had numerical imbalances in death incidence in favor of plasma. The initial masked FDA assessment took into account the relative timing of administration of study test product and of the nature and time of onset of the adverse event listed as a contributing to death. In this analysis, eight subjects in the Kcentra group and two subjects in the plasma group were considered to have a possible causal relationship with the respective product. As shown in the table below, the subsequent masked FDA assessment, which examined masked narratives prepared by the sponsor and the Safety Adjudication Board (SAB), found that three Kcentra and one plasma group death were possibly or probably related to prior test product administration.

This reviewer conducted a masked (blinded) causality assessment based on sponsor- and masked-SAB-prepared full narratives of all deaths reported in the RCT in acute major bleeding, since there was a discrepancy because the causality assessment for one subject whose death was considered possibly related to Kcentra by the SAB but not by the investigator, and because the number of reported deaths was 16-fold greater than the number of deaths considered by the SAB to be related to either test product.. Results are shown in the tables below.

FDA's Masked Assessment of Death – Number of Subjects with Death Judged Possibly or Probably Related to Prior Administration of Test Product (Based on Masked Review of Sponsor- and Safety Adjudication Board- Generated Narratives – Bleeding Study BE1116_3002)

Randomization Group:	Kcentra	Plasma
Number of Deaths Possibly or Probably Related to Test Product[a]:	3	1

[a]FDA causality rating of 2 (possibly or probably related to administration of test product).

Reviewer's Blinded Assessment of Causality of Deaths Based on Review of Sponsor Narratives (Study BE1116_3002)

Subject ID / Treatment	Reviewer's Blinded Causality Rating	Comment
--(b)(6)-- B 38.6 IU/kg	0	CVA day 43, death day 45
--(b)(6)-- P	1	Death day 7, worsening metastatic lung cancer, few clinical details or immediate cause of death
--(b)(6)--	2	Death day 4, possible volume overload,

Subject ID / Treatment	Reviewer's Blinded Causality Rating	Comment
P		reviewer cannot rule out PE with slight RV strain on echocardiogram, Acute renal injury, hepatic insufficiency; although death was attributed to systemic infection, blood cultures were neg x 2
--(b)(6)-- B 38.8 IU/kg	0	Respiratory failure day 28, Abnormal CKMB and troponin afterwards, History COPD, cardiomyopathy, CAD
--(b)(6)-- B 47 IU/kg	2	Therapeutic Failure, Death on day 3 from increased size of ICH
--(b)(6)-- B 56 IU/kg	2	Death on day 4 from gradual worsening CHF, possible volume overload
--(b)(6)-- B 28 IU/kg	0	Death day 34 due to respiratory failure and stage IV lung cancer; No workup for PE
--(b)(6)-- B 57.5 IU/kg	0	Death day 26 from sepsis, positive anaerobic blood cultures
--(b)(6)-- P	1	Death on day 14 from E. coli septic shock with "pneumonia" but CXR clear on day of death, hx COPD and pulmonary hyper-tension, probable liver metastases; D dimers abnormal at 3504 on day 5 and > 5K on day 6 with lateral ischemia on ECG, respiratory failure with wheezing and clear CXR, severe pulmonary hypertension, dilated dysfunctional R sided heart with normal LV function, abnormal CKMB and troponin T at 0.03. Cannot rule out PE as possible contributory cause, although DD and RV/RA dysfunction and dilatation could be due to sepsis and chronic pulmonary hypertension, respectively.
--(b)(6)-- B 27 IU/kg	0	Death day 38, cause unknown and unconfirmed by SAB, although attributed by investigator to undocumented MI as listed on death certif..
--(b)(6)-- B 54.4 IU/kg	0	Sudden death day 31 attributed to "Cardiopulmonary arrest"
--(b)(6)-- P	0	Death due to acute cholestatic hepatic injury, cause unknown, on day 22. Viral serologies and ANA negative.
--(b)(6)-- B 53.5 IU/kg	0	Death day 33 from pancreatic cancer

Subject ID / Treatment	Reviewer's Blinded Causality Rating	Comment
--(b)(6)-- B 27 IU/kg	0	Death day 29 from hepato-renal syndrome
--(b)(6)-- B 28 IU/kg	2	Sudden death day 7. Pt presented had a history of Wegner's granulomatosis and recurrent DVT and was being treated with methotrexate and had thrombocytopenia, anemia, and GI bleeding on presentation. Pt discharged on day 3 with Hb of 8.7 g/L and platelets of 29 x 10^9/L.
--(b)(6)-- P	0	Death from respiratory insufficiency on day 7 attributed to progression of post hemorrhagic anemia by investigator (even though anemia improved). Autopsy also showed chronic pneumonia, adhesions in L pleural cavity, and malignant lymphoma of mediastinal, para-aortic, and mesenteric lymph glands.

[a]FDA's Masked Causality Rating Definitions:
0 = Remote to no evidence of causal link between Test Product and Death
1 = Cannot reasonably rule out possible causal link between Test Product and Death
2 = More substantial possible or probable causal link between Test Product and Death
[b]B = Beriplex (Kcentra); P = Plasma randomization treatment group

6.1.12.4 Nonfatal Serious Adverse Events

Serious Adverse Events (SAEs) were numerically more frequent among Kcentra group subjects than among plasma group subjects. Given that the trial was open-label, the possibility of bias in reporting and classification of AEs and ARs cannot be excluded.

Sponsor'sTable 3.2.1 Summary of number of subjects with TEAEs in 3002

	Beriplex, N=103(%)	Plasma, (N=109)(%)
All TEAE	66(64.1)	71(65.1)
Serious TEAEs	21(20.4)	15(13.8)
Moderate TEAEs	35(34.0)	21(19.3)
Mild TEAEs	55(53.4)	62(56.9)
At least possibly treatment-related TEAEs[1]	10(9.7)	23(21.1)
TEAEs leading to treatment discontinuation	0	3(2.8)
Serious TEAEs	33(32.0)	26(23.9)
At least possibly treatment-related SAEs[1]	2(1.9)	4(3.7)
SAEs leading to treatment discontinuation	0	0

[1]As per investigator causality assessment.

6.1.12.5 Adverse Events of Special Interest (AESI)

More arterial and venous thrombotic/thromboembolic events were seen in the Kcentra arm than in the plasma arm of the RCT in Acute Major Bleeding, as seen in the table below.

Incidence of TE Events in Acute Major Bleeding Study (ITT-S)

Type of TE Events	Kcentra	Plasma	Difference Kcentra – Plasma (95% CI)
All TE Events[a]	10 (9.7%) (95% CI 4.5 – 16.0)	6 (5.5%) (95% CI 2.3 – 11.7)	4.2% (-3.9 to 12.7)
TE Events Excluding Upper Extremity Venous Thrombosis[b]	9 (8.7%)	6 (5.5%) (95% CI 2.3 – 11.7)	3.2% (-4.7 to 11.5%)[c] (-3.7 to 10.2%)[d]
TE Events Excluding UE Venous and Fistula Clot Cases[b,e]	8 (7.7%) (95% CI 3.8 – 14.8)	6 (5.5%) (95% CI 2.3 – 11.7)	2.2% (-4.4 to 9.0)

[a]Includes one Kcentra subject who had a basilica vein upper extremity thrombosis in conjunction with an indwelling venous catheter.
[b]Excludes one Kcentra subject who had a basilica vein upper extremity thrombosis in conjunction with an indwelling venous catheter. These values are used for the package insert.
[c]Confidence interval calculated by the sponsor.
[d]Confidence interval calculated by the FDA biostatistician.
[e]Excluded one Kcentra subject who had a fistula clot.

This reviewer conducted a masked (blinded) causality assessment of all possible TE events reported by the sponsor, based on sponsor- and SAB-generated full narratives, and also reviewed all AEs from the sponsor's data listings to identify TE events that might have been missed by the sponsor. This review identified two additional possible TE events in the Kcentra group that were not reported in the original submission:

> Subject 46002 – Cardiopulmonary arrest day 29 considered not related to treatment by the investigator and SAB. The SAB noted that the etiology of sudden death in this patient included PE, MI, and central nervous system event. This subject had no prior history of TE event. In amendment 23 the sponsor agreed to include this possible TE event in the tables and analyses of TE events.
>
> Subject 101007 – Sudden death day 6. This event was considered not related by the investigator, but the SAB considered the death possibly related to the test product and cited PE, CVA, and MI as possible etiologies. In amendment 23 the sponsor agreed

to include this possible TE event in the tables and analyses of TE events as a (possibly related) thrombotic adverse reaction.

This review also identified one case of "old blood in NG tube," which was originally classified as a TE event by the sponsor. In amendment 23, in response to an information request, the sponsor agreed that this event was not an intravascular TE event.

Adverse Reactions* (TEEs only) Following Kcentra or Plasma Administration in the Acute Major Bleeding RCT

System Organ Class	**No. (%) of subjects**	
	Kcentra (N = 103)	**Plasma (N = 109)**
Any possible TEE	**9 (8.7%)**	**6 (5.5%)**
TEE Adverse reactions*	**6 (5.5%)‡**	**4 (3.7%)**
Cardiac disorders		
Myocardial infarction†	0	1 (0.9%)
Myocardial ischemia	0	2 (1.8%)
Nervous system disorders		
Ischemic cerebrovascular accident (stroke)‡	2 (1.9%)	0
Cerebrovascular disorder§	0	1 (0.9%)
Vascular disorders		
Venous thrombosis calf	1 (1.0%)	0
Deep vein thrombosis (DVT)‖	1 (1.0%)	0
Fistula Clot	1 (1.0%)	0
Unknown Cause of Death (not confirmed TEE)		
Sudden death	1 (1.0%)	0

* Adverse Reactions defined as adverse events which began during or within 72 hours of the end of test product infusion plus adverse events where the relationship to study treatment was possibly related, probably related, or related in the opinion of the investigator, sponsor, or the blinded safety adjudication board (SAB). Only deaths and possible thrombotic serious events were reviewed by the SAB for confirmation and causality assessment. The tabulation of possible TEEs includes subjects with confirmed TEEs as well as 3 subjects in the Kcentra group that died of unknown causes on days 7, 31, and 42. The death on day 7 was considered possibly related to study product by the SAB and is tabulated as an adverse reaction. One additional subject who had received Kcentra, not listed in the table, had an upper extremity venous thrombosis in association with an indwelling catheter.

† One subject who had received plasma had an acute myocardial infarction (d1) rated moderate in severity, not considered serious.

‡ One subject, included in the tabulation, had an ischemic cerebrovascular accident on day 43 that was considered unrelated by the SAB.

§ One subject who had received plasma had a cerebrovascular disorder (d1) not considered serious, and

‖ One Kcentra subject had two DVTs, both considered related by SAB.

This reviewer conducted a masked (blinded) causality assessment of all TE events reported in the RCT in acute major bleeding. Results are shown in the tow tables below.

FDA Reviewer's Blinded Assessment of Numbers of Subjects with TE SAEs and Non-Serious TE Events Based on Review of Sponsor- and Safety Adjudication Board-Generated Narratives
Bleeding RCT BE1116_3002

Test Product:	Kcentra	Plasma

Test Product:	Kcentra	Plasma
Subjects with Possibly or Probably Related TE Events	5	2

FDA's Blinded Assessment of TE SAEs Based on Review of Sponsor- and Safety Adjudication Board-Generated Narratives
Bleeding Study BE1116_3002

Subject ID/ Treatment Group/ Actual Dose/ Age/Sex	Reviewer's Blinded Causality Assessment	SAB Causality Assessment	Event & Comment
002003 B 38.6 IU/kg 89 / M	0	Not Related	CVA, confirmed as TEE by SAB, considered possibly related by investigator, day 43 with death day 46
002005 B 39.2 IU/kg 82 / F	2	Possibly Related	CVA (R MCA), confirmed as TEE by SAB, day 9
002010 P 77 / F	1	Possibly Contributory along with severe anemia [and hypotension]	Demand-related myocardial ischemia 6 hr 40 min after administration of IMP, asymptomatic, evidenced by Troponin T values of 0.04m 0.05, and 0.07 ng/mL (normal < 0.03 ng/mL). ECGs: paced rhythm. Serious because "other medically important condition." Recovered.
002011 P 70 / F	2	Possibly Contributory, along with hypotension	Demand-related myocardial ischemia day 2 (no ECG from that day available, but no ST elevation on others), asymptomatic, evidenced by Troponin I 0.10 and 0.08 ng/mL (normal < 0.03 ng/mL) rise from normal at baseline, CK isoenzymes index 2.7, 2.9 (normal). Serious because "medical significance." Recovered.
013008 B 28 IU/kg 80 / M	2	Possibly Related (both events)	DVT bilateral legs day 13 confirmed by Doppler US and on day 30 on other side
013016 P	1	Not Related	Perioperative MI day 13 (surgery on spine day 12)

Subject ID/ Treatment Group/ Actual Dose/ Age/Sex	Reviewer's Blinded Causality Assessment	SAB Causality Assessment	Event & Comment
68 / M			evidenced by CK 2823 with CK_MB 71, Troponin 10, ECG: paced rhythm, age indeterminate inferior infarct, R/O anterior infarct. Echo: periapical wall motion abnormality consistent with recent MI.
030032 P 78 / M	1	Not Related	CVA day 22
30034 B 57.5 IU/kg 66 / F	2	Not Evaluated by SAB	"Fistula clot" at 4.3 hours, considered moderate and related to IMP by investigator (also "not moving right hand or fingers" at 2.3 days, duration unknown, not resolved.
035001 B 28 IU/kg 85 / F	2	Not Related	CVA day 10
046002 B 54.4 IU/kg 54 / F	0	Not Related	Sudden Death day 31
101007 B 28 IU/kg 56 M	2	Possibly Related	Sudden Death day 7, SAB cited PE, CVA, and MI as possible etiologies and noted history of ilio-femoral DVT increased risk of TE event.
43004 B 27 IU/kg 88 / F	0	Not Related	Death Day 38, cause unknown (MI on death cert.)
30022 P 79 / M	Not Rated	Not Evaluated by SAB	Old blood clot in naso-gastric tube – not counted as TE event in FDA analysis. Non-serious
30003 B 56 IU/kg 54 / F	Not Rated Because lesion was superficial in upper extremity and attributed to	Not Evaluated by SAB	Venous Thrombosis Limb (clot in basilic vein due to PICC line on day 9. Non-serious.

Subject ID/ Treatment Group/ Actual Dose/ Age/Sex	Reviewer's Blinded Causality Assessment	SAB Causality Assessment	Event & Comment
	PICC line		
51005 B 29.3 IU/kg 73 F	2	Not Evaluated by SAB	R calf vein thrombosis 13.4 hours after infusion, considered possibly related by investigator. Non-serious
30029 P 64 / F	2	Not Evaluated by SAB	Acute non-STEMI diagnosed 16.5 hours after start of infusion. Also SAE of respiratory failure onset 9 hours post start of infusion considered serious and probably related by investigator. MI considered moderate and non-serious.
15001 P 75 / M	1	Not Evaluated by SAB	Cerebrovascular disorder coded as cerebrovascular disease the same day as test product infusion. Event rated mild and non-serious.

[a]FDA's Masked Causality Rating Definitions:
0 = Remote to no evidence of causal link between Test Product and Event
1 = Cannot reasonably rule out possible causal link between Test Product and Event
2 = More substantial possible or probable causal link between Test Product and Event
[b]B = Beriplex (Kcentra); P = Plasma randomization treatment group

Volume Overload Events

Volume overload events were more than twice as frequent in the plasma group compared to the Kcentra group. Half of the Volume Overload events were rated by the investigator as serious.

Volume Overload (VO) Events (Study _3002 - ITT-S)

Event Type	Kcentra N = N (%) [95% CI}	Plasma, N = N (%) [95% CI}	Difference (B-P) % [95% CI]
V.O.	6 (5.8%) [2.7 – 12.1]	14 (12.8%) [7.8 – 20.4]	-7.0 [-15.8 – 1.8]

Post-Hoc Subgroup Analyses of Key Safety Endpoints

Post-hoc Subgroup Analyses Of Deaths, Thrombotic/Thromboembolic (TE) Events and Volume Overload Events by

- Presence or Absence of History of CHF. This subgroup was defined by the sponsor as subjects with any medical history term in the MedDRA 12.0 System Organ Class (SOC) "cardiac disorders" including as part of the preferred term either "congestive" or "failure." These included cardiac failure congestive, cardiac failure chronic, cardiac failure, congestive cardiomyopathy, and cardiac failure acute.

- Presence or Absence of History of TE or Angina Pectoris. This subgroup was defined by the sponsor as subjects with any medical history term in the MedDRA 12.0 Standardized MedDRA Queries (SMQs) Embolic and thrombotic events, arterial", "Embolic and thrombotic events, venous" and "Embolic and thrombotic events, vessel type unspecified and mixed arterial and venous" (including transient ischemic attack) or (2) by a PT including the term "angina." In the sponsor's analysis, this included some categories of subjects who presumably had a history of angina or TIA or otherwise would be assumed to be at increased risk of a TE event but who may not necessarily have experienced TE events, such as subjects who had undergone coronary artery bypass grafting, coronary stent insertion, carotid endarterectomy, coronary angioplasty, arterial bypass operation, vascular stent insertion, vascular graft, arterial stent insertion, aortic bypass, endarterectomy, angioplasty, peripheral artery angioplasty, portal shunt, percutaneous coronary intervention, and venous operation. Thus, this condition is referred to as "history of thrombotic event or of coronary, cerebrovascular, or peripheral vascular disease" throughout this document.

As can be seen in the first two tables and below, thrombotic and thromboembolic (TE) events were 7.8% less frequent among Kcentra than plasma subjects in the subgroup without a history of TE event (or evidence of coronary, cerebrovascular, or peripheral vascular disease). In contrast, 7.1% more Kcentra than plasma subjects reported a TE event in the subgroup of subjects with a history of TE event. In both subgroups death through day 45 was more frequent in the Kcentra group compared to the plasma group; this excess mortality was 5.5% in the subgroup without a history of TE event and 5.1% in the subgroup with a history of TE event, etc. (Sponsor's analysis done at FDA request. This reviewer verified the sponsor's analysis of TE events in subgroups with and without a history of prior TE event or coronary, cerebrovascular, or peripheral vascular disease).

Subjects with Thromboembolic Events by Prior History of TE Event in Plasma-Controlled RCT in Acute Major Bleeding

	Acute Major Bleeding Study			
	Kcentra		Plasma	
	N	TE Events† N (%)	N	TE Events N (%)
All subjects	103	9 (8.7)	109	6 (5.5)
With history of TE event*	69	8 (11.6)	79	3 (3.8)
Without history of TE event	34	1 (2.9)	30	3 (10.0)

* History of prior TE event.

† One additional subject who had received Kcentra, not listed in the table, had an upper extremity venous thrombosis in association with an indwelling catheter.

Sponsor's Table 14.3.1 - 49: Incidence of possibly thromboembolic events [TE], volume overload events and deaths by medical history in bleeding study BE1116_3002 ITT-S population, N=212

Subjects *with* medical history of TE (or vascular disease) events only, N=148

Event Type	Beriplex, N = 69 N (%) [95% CI}	Plasma, N = 79 N (%) [95% CI}	Difference (B-P) % [95% CI]
TE[b]	9 (13.0) [7.0 – 23.0]	3 (3.8) [1.3 – 10.6]	9.2% [-0.8 – 20.4]
V.O.	3 (4.3) [1.5 – 12.0]	11 (13.9)) [8.0 – 23.2]	-9.6 [-20.1 – 1.2]
Deaths thru d 45	7 (10.1) [5.0 – 19.5]	4 (5.1) [2.0 – 12.3]	5.1 [-4.8 – 15.9]
Deaths (all)	8 (11.6) 6.0 – 21.2]	4 (5.1) [2.0 – 12.3]	6.5 [-3.6 – 17.5]

Source: BLA Amendment 23 dated 19 Mar 2013

See bullet at the top of this section for definition of CHF and TE events or angina, etc.

[b]Includes one subject who had received Kcentra who had an upper extremity venous thrombosis in association with an indwelling catheter.

Sponsor's Table 14.3.1 - 49: Incidence of possibly thromboembolic events [TE], volume overload events and deaths by medical history in bleeding study BE1116_3002 ITT-S population, N=212

Subjects *without* medical history of TE (or vascular disease) events only, N=64

Event Type	Beriplex, N = 34 N (%) [95% CI}	Plasma, N = 30 N (%) [95% CI}	Difference (B-P) % [95% CI]

Event Type	Beriplex, N = 34 N (%) [95% CI}	Plasma, N = 30 N (%) [95% CI}	Difference (B-P) % [95% CI]
TE	1 (2.9) [0.5 – 14.9)	3 (10.0) [3.5 – 25.6]	-7.1 [-25.0 – 8.9]
V.O.	3 (8.8) [3.0 – 23.0]	3 (10.0) [3.5 – 25.6]	-1.2 [-20.0 – 16.4]
Deaths thru d 45	3 (8.8) [3.0 – 23.0]	1 (3.3) [0.6 – 16.7]	5.5 [-11.5 – 21.8]
Deaths (all)	3 (8.8) [3.0 – 23.0]	1 (3.3) [0.6 – 16.7]	5.5 [-11.5 – 21.8]

Source: BLA Amendment 23 dated 19 Mar 2013

Excluding the Kcentra subject who had a upper extremity venous thrombosis in the basilica vein in association with a PICC line gives the following results, reproduced from the draft package insert:

Sponsor's Table 6: **Subjects with Thromboembolic Events by Prior History of TE Event in Plasma-Controlled RCT in Acute Major Bleeding**

	Acute Major Bleeding Study			
	Kcentra		Plasma	
	N	TE Events† N (%)	N	TE Events N (%)
All subjects	103	9 (8.7)	109	6 (5.5)
With history of TE event*	69	8 (11.6)	79	3 (3.8)
Without history of TE event	34	1 (2.9)	30	3 (10.0)

* History of prior TE event [or coronary, cerebrovascular, or peripheral vascular disease].

† One additional subject who had received Kcentra, not listed in the table, had an upper extremity venous thrombosis in association with an indwelling catheter.

Subjects with Fluid Overload Events by Prior History of Congestive Heart Failure in Plasma-Controlled Trial in Subjects with Acute Major Bleeding

Subgroup	Major Bleeding Study	
	Kcentra	Plasma

	N	Fluid Overload N (%)	N	Fluid Overload N (%)
All subjects	103	6 (5.8)	109	14 (12.8)
With history of CHF	46	4 (8.7)	44	11 (25.0)
Without history of CHF	57	2 (3.5)	65	3 (4.6)

Sponsor's Tables 14a and 14b: Incidence of possibly thromboembolic events, volume overload events and deaths by medical history of CHF

Table 14a: Subjects *with* medical history of congestive heart failure only, Study _3002 ITT-S subpopulation, N=90

Event Type	Beriplex, N = 46 N (%) [95% CI]	Plasma, N = 44 N (%) [95% CI}	Difference (B-P) % [95% CI]
TE	3 (6.5) [2.2 - 17.5]	5 (11.4) [5.0-24.0]	-4.8 [-19.6 - 9.5]
V.O.	4 (8.7) [3.4 - 20.3]	11 (25.0) [14.6 - 39.4]	-16.3 [-33.0 – 0.9]
Deaths thru d 45	3 (6.5) [2.2 – 17.5]	2 (4.5) [1.3 – 15.1]	2.0 [-11.1 – 14.9]
Deaths (all)	4 (8.7) [3.4 – 20.3]	2 (4.5) [1.3 – 15.1]	4.2 [-9.4 – 17.7]

See "Method" under efficacy subgroup analyses section for definition of CHF and TE events or angina, etc.
Source: BLA Amendment 7. Note, the numbers of TE events shown in this sponsor analysis table do not reflect the corrections to the number of TE events overall agreed to by the sponsor in subsequent amendment 23. This table includes "thrombosis in device" (clotted blood in NG tube) in Plasma subject 30022 which was removed in the other tables of TE events in this memo. This table does not include the possible TE events (death possibly attributable to MI, CVA, or PE according to the SAB) in Kcentra subjects 46002 and 101007.

Table 14b: Subjects *without* medical history of congestive heart failure only, Study _3002 ITT-S subpopulation, N=122

Event Type	Beriplex, N = 57 N (%) [95% CI]	Plasma, N = 65 N (%) [95% CI]	Difference (B-P) % [95% CI]
TE	5 (8.8) [3.8 - 18.9]	2 (3.1) [0.8 - 10.5]	5.7 [-4.5 – 17.2]
V.O.	2 (3.5) [1.0 - 11.9]	3 (4.6) [1.6 - 12.7]	-1.1 [-10.7 – 9.1]
Deaths thru d45	7 (12.3) [6.1 - 23.2]	3 (4.6) [1.6 - 12.7]	7.7 [-3.7 – 20.2]
Deaths (all)	7 (12.3) [6.1 - 23.2]	3 (4.6) [1.6 - 12.7]	7.7 [-3.7 – 20.2]

See "Method" under efficacy subgroup analyses section for definition of CHF and TE events or angina, etc.

Source: BLA Amendment 7 Note, the numbers of TE events shown in this sponsor analysis table do not reflect the corrections to the number of TE events overall agreed to by the sponsor in subsequent amendment 23. This table does not include the possible TE events (death possibly attributable to MI, CVA, or PE according to the SAB) in Kcentra subjects 46002 and 101007.

The sponsor and FDA also examined the subgroup of subjects who met the dual criteria of a history of CHF and no history of prior TE event, etc. The confidence intervals for all event types in this subgroup are wide given the limited number of subjects meeting these dual criteria (data not shown).

6.1.12.6 Clinical Test Results

Hb and Hct changes at 3 and 24 hours were consistent with the study population experiencing major bleeding.

Sponsor's Table 54: Hemoglobin, hematocrit and platelets over time (ITT-S population) – Study BE1116_3002

Analyte	Beriplex (N = 103)			Plasma (N = 109)		
	Baseline	Change from baseline		Baseline	Change from baseline	
		3 hours	24 hours		3 hours	24 hours
Hb (g/dL)						
Mean	9.33	0.02	0.54	9.86	–0.73	0.31
SD	2.526	1.088	1.602	2.817	1.369	1.984
Range	4.1-16.0	–2.7-3.7	–3.3-4.7	4.1-16.0	–3.3-9.4	–4.3-6.5
Hct (%)						
Mean	28.69	0.16	1.58	30.37	–2.16	0.97
SD	7.654	3.190	4.822	8.340	4.157	5.696
Range	11.7-47.1	–8.2-10.0	–9.1-13.0	13.3-47.0	–9.2-27.5	–13.6-18.4
Platelets ($x10^9$/L)						
Mean	228.0	–18.3	–25.4	218.3	–23.1	–25.6
SD	95.37	45.08	57.74	81.19	40.07	52.84
Range	7-537	–211-115	–314-122	68-639	–191-96	–234-141

Hb = hemoglobin; Hct = hematocrit; ITT-S = safety population; N = total number of subjects; SD = standard deviation.

Laboratory Markers of Activation of Coagulation

Prothrombin fragments 1 and 2 (F1+2), Thrombin anti-thrombin complex (TAT), and D-Dimers (DD) were measured at 1 and 24 hours after the start of test product infusion. The sponsor also performed analyses of these analytes measured at "any time after start of infusion." At FDA request, analyses were further broken down according to whether subjects did or did not have a history of congestive heart failure (CHF) and according to whether subjects did or did not have a prior history of thromboembolic (TE) event. These latter analyses were performed for the pooled final ITT-S databases from the BE1116_3002 bleeding study (final dataset), as well as from the interim dataset for the BE1116_3003 surgery study as submitted in the amendment dated 14 Dec 2012 (total N = 385).

The table below shows that, among subjects with a history of CHF, Kcentra/Beriplex was associated with an incidence of treatment-emergent abnormal F1+2 values approximately 4 times greater than that seen in subjects who received plasma as of one hour after the start of infusion (65/70 = 93% vs. 16/79 = 20%). At 24 hours after the infusion, the percentage of subjects with treatment-emergent abnormal F1+2 values among Kcentra/Beriplex subjects was only modestly higher than those of plasma subjects (46 vs. 32%).

Sponsor's Table 1.1a – F1+2 (pmol/L) in subjects with Medical History of CHF, ITT-S, Combined _3002 and _3003 (interim) databases, N = 385

Time point	Beriplex, N=70 N (%) [95%-CI]				Plasma, N=79 N (%) [95%-CI]						
Time Point	N	%	95% CI		N	%	95% CI		Delta^	95% CI	
1 hour after start of infusion	65	(92.9)	[84.3;	96.9]*	16	(20.3)	[12.9;	30.4]*	72.6	[58.2;	81.7]**
24 hours after start of infusion	32	(45.7)	[34.6;	57.3]*	25	(31.6)	[22.4;	42.5]*	14.1	[-2.5;	29.7]**
Any time after start of infusion	65	(92.9)	[84.3;	96.9]*	34	(43.0)	[32.7;	54.0]*	49.8	[34.9;	61.6]**

Note: Abnormal values are defined as values above normal range (69 – 229 [pmol/L]).
*Wilson confidence intervals are displayed for single rates
**Newcombe-Wilson confidence intervals with continuity correction are displayed for the difference of rates Congestive heart failure is defined as any medical history term in the SOC 'Cardiac disorders' including as part of the preferred term either 'congestive' or 'failure'.
^Delta refers to Difference Beriplex minus Plasma (%, followed by 95% CI).

A similar pattern was seen among subjects without a history of CHF (delta = 61.8, 95% CI 49.9 – 70.9, N = 236 subjects), with a history of TE events (delta 66.2%, 95% CI 55.3 – 74.3, N = 264), and without a prior history of TE events (delta = 63.7%, 95% CI 46.6 – 75.6, N = 121). The pattern was also similar among the dual criteria defined subgroups: without history of CHF or with a history of TE events (N = 340), and those with medical history of CHF and without history of TE events (N = 45). The pattern was also similar among subjects with baseline INR $\geq$ 2 and $\leq$ 3 (delta = 70.4%) and those with baseline INR > 3 (delta = 62.9%).

Among subjects in the combined trial dataset with a history of CHF, the percentage of Beriplex subjects with treatment-emergent abnormal elevations in TAT was 94.3% compared to 68.4% for plasma (delta 25.9%, 95% CI 12.6% - 38.1%) at 1 hour after the start of the infusion. At 24 hours, this difference fell to 7.2%. A similar difference between treatment subgroups (22/4%, 95% CI 11.2% - 33.1%) was seen at 1 hour post start of infusion among subjects without a history of CHF. Again about a quarter more subjects in the Beriplex subgroups compared to plasma subjects had treatment emergent abnormal TAT values among the subgroups with and without a history of TE events and in the dual criteria subgroups noted above. The difference between Beriplex and Plasma subgroups in the proportion developing treatment-emergent abnormal TAT levels among subjects with baseline INR $\geq$ 2 and $\leq$ 3 was delta = 18.4%, 95% CI 4.3% - 31.4%) and those with baseline INR > 3 the delta was 27.5% (95% CI 16.56% - 37.8%). All the above differences at 1 hour post start of infusion diminished markedly by 24 hours post infusion.

Among subjects in the combined trial dataset without a history of CHF, the percentage of Beriplex subjects with treatment emergent abnormal D-Dimer elevations was numerically lower but not statistically significantly lower than among plasma subjects at both 1 hour and 24 hours after the start of infusion. However, when measured "any time after start of infusion," the difference became statistically significant (delta = -13.0, 95% CI -24.9% - -0.7%). The percentage of subjects with treatment-emergent abnormal D-Dimer values among subsets of subjects both with and without a history of prior TE event was similar between Beriplex and plasma subgoups. However, among subjects with a history of CHF but without a history of prior TE event the percentages of subjects at all 3 time points/categories having treatment-emergent abnormal D-dimer values was numerically but not statistically significantly higher among Beriplex as compared to plasma subjects (delta = 20.0% at 1 hour and 14.6% at 24 hours post start of infusion). The delta went slightly in the opposite direction for the subgroup of subjects not meeting the last dual criteria. However, among subjects with baseline INR $\geq$ 2 and $\leq$ 3, the percentages of subjects at 1 hour post start of infusion having treatment-emergent abnormal D-dimer values was statistically significantly lower among Beriplex as compared to plasma subjects (delta a 1 hour = -18.1, 95% CI -33.5 - -1.5). However at 24 hours this difference was less and no longer significant (delta = -6.0, 95% CI -21.0 – 9.1)

6.1.12.7 Dropouts and/or Discontinuations

Three subjects did not receive the entire planned dose of plasma because of adverse events (2 subjects had symptoms consistent with volume overload and one was considered to have had a mild transfusion reaction).

A large percentage of subjects did not undergo the required day 90 viral serology assessment.

6.2 Trial #2

Surgery IND Study BE1116_3003

Study Title:

An open-label, randomized, multicenter Phase IIIb study to assess the efficacy, safety and tolerance of Beriplex compared with plasma for rapid reversal of coagulopathy induced by vitamin K antagonists in subjects requiring an urgent surgical or urgent invasive procedure.

6.2.2 Design Overview

RCT BE1116_3003 was an open-label, randomized, multicenter, active (plasma) controlled clinical trial to assess the efficacy, safety and tolerance of Kcentra compared with plasma for rapid reversal of coagulopathy induced by vitamin K antagonists in subjects requiring an urgent surgical or urgent invasive procedure. The RCT randomized 176 subjects (88 to Kcentra and 88 to plasma) and was conducted in the US and overseas. Subjects were randomized 1:1 to receive either Kcentra, containing on average 25 IU FIX per mL) or plasma. The dose of both products depended on the baseline INR using the same dosing scheme as had been used in the bleeding _3002 RCT. [Because baseline INRs tended to be lower in this surgery study, proportionally fewer subjects were treated with 35 and 50 IU/kg nominal doses of Kcentra (and 12 and 15 mL/kg doses of plasma) than in the RCT in acute major bleeding.]

6.2.3 Population

Inclusion Criteria

- Males and F $\geq$ 18 years old
- Have received VKA therapy (e.g., warfarin, acenocoumarol or phenprocoumon) and in whom either an emergency surgical or invasive intervention is indicated.

- An urgent surgical or urgent invasive procedure is required within 24 hours of the start of IMP.

  Subjects undergoing non-surgical invasive procedures will no longer be enrolled into the study (protocol amendment).

- Due to the nature of the emergency procedure, withdrawal of oral VKA therapy and infusion of plasma are also indicated to reverse the VKA effect.

- INR > 2 within 3 hours before start of IMP. study treatment

- Informed consent.

Exclusion Criteria

- Subjects requiring emergency urgent surgical procedures where, according to the surgeon's clinical judgment, an accurate estimate of blood loss is not possible (e.g., ruptured aneurysm).
- Subjects for whom administration of intravenous vitamin K and vitamin K antagonist withdrawal, alone, can adequately correct the subject's coagulopathy before initiation of the urgent surgical procedure.
- Subjects who despite medical management that includes close monitoring and diuretics may not, by Investigator assessment, tolerate the total volume of IMP required by the protocol.
- Administration of intravenous vitamin K more than 3 hours or administration of oral vitamin K more than 6 hours prior to infusion of IMP.
- Acute trauma for which reversal of vitamin K antagonists alone would not be expected to control or resolve an acute bleeding complication and/or control the acute bleeding event.
- Unfractionated or low molecular weight heparin use within 24 hours before randomization or potential need before completion of the procedure.
- History of thromboembolic event, MI, unstable angina pectoris, critical aortic stenosis, CVA, TIA, severe PVD, DIC within 3 months.
- Subjects in whom lowering INR within normal range may present an unacceptable risk for a thromboembolic complication (e.g, an electrophysiology procedure where the INR goal is to lower but not normalize the INR because of risk of a procedure-associated stroke).
- Expected need for additional non-study blood products before infusion of IMP *(Note: administration of packed red blood cells is not an exclusion criterion)*.
- Expected need for platelet transfusions or desmopressin before Day 10.

- Unfractionated or low molecular weight heparin use within 24 hours before randomization or potential need before completion of the procedure.
- Reversal of VKA therapy alone may not resolve the coagulopathy (e.g., receiving a potent anti-platelet agent, i.e, clopidogrel or prasugrel, or advanced liver disease.
- Known history antiphospholipid Antibody syndrome or lupus anticoagulant antibodies.
- Suspected or confirmed serious viral or bacterial infection, e.g., meningitis or sepsis at time of enrollment.
- Administration of whole blood, plasma, plasma fractions, or platelets within 2 weeks prior to inclusion. Note: PRBCs are OK.
- Life expectancy < 3 months from pre-existing progressive fatal disease.
- Known inhibitors to coagulation factors II, VII, IX, or X, or hereditary protein C or protein S deficiency, or heparin-induced type II thrombocytopenia.
- Use of other investigational products within 30 days.
- Presence of history to hypersensitivity to components of study medication.
- Pregnant, breast feeding.
- Prior inclusion in this study or any CSLB-sponsored Beriplex study.
- For subjects with ICH with:
    - GCS < 10
    - Modified Rankin score > 3 prior to ICH
    - Inracerebral hemorrhage
    - Epidural hematomas
    - Infratentorial hemorrhage
    - Subarachnoid hemorrhage (SAH) subjects with a Hunt and Hess Scale > 2
    - Subdural hematomas that either are judged to be an acute subdural hematoma (based on neurosurgeon review) or that have a concurrent SAH or parenchymal contusion.

6.2.4 Study Treatments or Agents Mandated by the Protocol

Subjects were randomized 1:1 to a receive single IV infusion of either Kcentra or plasma (FFP or P24) according to baseline INR using the same dosage scheme based on body weight as in RCT BE1116_3002.

All subjects received vitamin K (usually 2-10 mg) prior to receiving the test product.

6.2.5 Directions for Use

The dosage algorithm for Kcentra and plasma was the same as in the RCT in acute major bleeding.

6.2.6 Sites and Centers

Multinational U.S. and Europe

6.2.7 Surveillance/Monitoring

Selected Scheduled Assessments

Note: Vitamin K dependent clotting factors are measured at the same time points as INR.

Day 1 Pre-infusion	INR	Viral Assessment	DD, TAT, F1+2
30 minutes after start of infusion	INR		
1 hour after start of infusion	INR		DD, TAT, F1+2
30 minutes after end of infusion	INR		
3 hours after start of infusion	INR		
6 hours after start of infusion	INR		
Pre-surgery/procedure		INR	
Immediately post-procedure			
24 hours after start of infusion (include post-procedure)		INR	DD, TAT, F1+2
Day 10 (7-11 days after start of infusion)		Viral Assessment	
Day 45 (43-51 days after start of infusion)		Viral Assessment	

AEs were collected through day 45. The last visit was on day 90 at which time only a blood sample for vital serology was collected.

Like in the RCT in acute major bleeding, deaths and possible TE events were referred to a SAB for confirmation and causality assessment.

6.2.8 Safety Endpoints

- AEs
- Vital signs
- Physical exam
- Hb, Hct, platelets
- ALT, AST, alkaline phosphatase, and total bilirubin at baseline and on days 10 and 90.
- Serum creatinine and BUN at baseline and at 24 hours after IMP infusion.
- Markers of activation of coagulation (lab markers, including F1+2, TAT, D—Dimers) and clinical signs and symptoms of thrombosis)
- Viral safety (viral Abs before and after tx). HBaAg, antibodies to HIV-1&2, HCV, HAV (IgG and IgM), parvovirus B19 by IgM. PCR for B19V, HACV, HBV, HCV, and HIV-1. A day 90 assessment for viral serology f/u was added in the 01 Nov 2010 amendment.
- For ICH subjects: Modified Rankin Score, GSC
- For SAH subjects: Hunt and Hess grade

Occurrences of possible thromboembolic events and events related to fluid overload, e.g., pulmonary edema and exacerbation of COPD were listed by subject and the incidence summarized by treatment group.

Mortality through 45 days was a secondary efficacy criterion.

6.2.10 Study Population and Disposition

6.2.10.1 Populations Enrolled/Analyzed

Eighty-eight subjects were randomized and treated with Kcentra and 88 were randomized and treated with plasma.

6.2.10.1.1 Demographics and Baseline Characteristics
Demographics were similar in Kcentra and Plasma arms of the surgery RCT.

Mean and Median Baseline INR values were similar in corresponding INR strata for Kcentra and plasma groups, except that the baseline mean and median INR in the high dose (15 mL/kg) plasma group (n = 8) was higher than the corresponding value in the Kcentra group (n = 9, mean values of 13.9 and 8.5, respectively).

6.2.10.1.3 Subject Disposition

6.2.11.3 Subpopulation Analyses

Subgroup Analyses of Subjects from Surgery Study BE1116_3003 Interim Analysis (BLA Amendment 11) who had a medical history of Thrombotic or Thrombo-embolic (TE) events.

Methodology: The sponsor used the same methodology to identify subjects with a medical history of TE events as was used above for the bleeding study BE1116_3002.

Results:

In the ITT-S population interim analysis of study _3003, there were 55/86 (64%) subjects with a medical history of TE events (or coronary artery, cerebrovascular, or peripheral vascular disease) in the Kcentra group and 61/87 (70%) subjects with a medical history of TE events, etc. in the plasma group.

As seen in the table 14g below, among subjects with a history of prior TE event(s), the incidence of TE events during the trial was just slightly greater in the Kcentra subgroup compared to the plasma subgroup, but *in subjects without a history of prior TE event, Kcentra had numerically (-8.3%) fewer TE events than Plasma*, although this difference

was not statistically significant. Deaths were numerically lower in the Kcentra treatment arm in both subgroups with and without a history of prior TE event with the larger difference seen in the subgroup with a history of prior TE event (a difference of -6.2%.. Overall volume overload events were numerically more frequent in the plasma group in both subgroups, however one more serious volume overload event was seen with Kcentra in the subgroup without a history of prior TE event.

Sponsor's Tables 14g and 14h - Incidence of possibly thromboembolic events, volume overload events and deaths by medical history of Prior TE Event (or coronary artery or cerebrovascular disease) in Surgery Study BE1116_3003 (Dec 2012 Interim Analysis), N=173

Table 14g: Events in Subjects with medical history of thromboembolic events, Study _3003 ITT-S Subpopulation, N=116 (*post-hoc* analysis)

Event Type	Beriplex, N = 55 N (%) [95% CI]	Plasma, N = 61 N (%) [95% CI]	Difference (B-P) % [95% CI]
TE (all)	4 (7.3) [2.9 – 17.3]	4 (6.6) [2.6 – 15.7]	0.7 [-10.6 – 12.7]
TE (serious)	1 (1.8) [0.3 – 9.6]	4 (6.6) [2.6 – 15.7]	-4.7 [-15.1 – 5.5]
V.O. (all)	1 (1.8) [0.3 – 9.6	6 (9.8) [4.6 – 19.8]	-8.0 [-19.2 – 2.8]
V.O. (serious)	0 (0.0)	1 (1.6) [0.3 – 8.7]	-1.6 [-10.0 – 6.6]
Death thru d 45	2 (3.6) [1.0 – 12.3]	6 (9.8) [4.6 – 19.8]	-6.2 [-17.6 – 5.3]

See "Method" under efficacy subgroup analyses section for definition of CHF and TE events or angina, etc.
Source: BLA Amendment 11. Note that this sponsor table does not reflect reclassification by FDA and the sponsor of certain listed TE events as not TE events (see amendment 23 submitted 19 March 2013).

Table 14h: Events in Subjects without medical history of thromboembolic events, Study _3003 ITT-S Subpopulation, N=57 (post-hoc analysis)

Event Type	Beriplex, N = 31 N (%) [95% CI]	Plasma, N = 26 N (%) [95% CI]	Difference (B-P) % [95% CI]
TE (all)	1 (3.2) [0.6 – 16.2]	3 (11.5) [4.0 – 29.0]	-8.3 [-28.3 – 9.2]
TE (serious)	1 (3.2) [0.6 – 16.2]	2 (7.7) [2.1 – 24.1]	-4.5 [-23.6 – 12.1]
V.O. (all)	2 (6.5) [1.8 – 20.7]	3 (11.5) [4.0 – 29.0]	-5.1 [-25.5 – 13.4]
V.O. (serious)	1 (3.2) [0.6 – 16.2]	0 (0.0)	3.2 [-13.2 – 18.5]
Death thru d 45	1 (3.2) [0.6 – 16.2]	2 (7.7) [2.1 – 24.1]	-4.5 [-23.6 – 12.1]

See "Method" under efficacy subgroup analyses section for definition of CHF and TE events or angina, etc.
Source: BLA Amendment 11. Note that this sponsor table does not reflect reclassification by FDA and the sponsor of certain listed TE events as not TE events (see amendment 23 submitted 19 March 2013).

6.2.11.4 Dropouts and/or Discontinuations

6.2.11.5 Exploratory and Post Hoc Analyses

Analyses of TE events, V.O. events, and death as a function of medical history or absence of history of TE event, etc. presented above were *post-hoc* analyses performed at FDA request.

6.2.12 Safety Analyses of RCT in Urgent VKA Reversal for Surgery/Invasive Procedure

6.2.12.1 Methods

Safety analyses are performed on the ITT-S population (88 subjects in each treatment group).

6.2.12.2 Overview of Adverse Events

6.2.12.3 Deaths

In the sponsor's preliminary analysis, 3/88 (3.4%) Kcentra and 8/88 (9.1%) Plasma subjects died on study. The between-group difference (Kcentra minus Plasma) in the incidence of death was -5.7% (95% CI -14.6 to 2.7%). FDA's masked causality analysis based on sponsor- and SAB-generated full narratives of subjects who died concluded that zero Kcentra subjects' deaths and one plasma subject's death were possibly related to test product administration.

6.2.12.4 Nonfatal Serious Adverse Events

6.2.12.5 Adverse Events of Special Interest (AESI)

Thrombotic and Thromboembolic Events – Surgery Study

In the sponsor's preliminary analysis, 5/88 (5.7%) Kcentra and 7/88 (8.0%) plasma subjects reported possible TE events. The between-group difference (Kcentra minus Plasma) in the incidence of possible TE events was -2.3% (95% CI -11.3 to 6.6%).

The sponsor's analysis of possible TE events included the following events which FDA did not count as TE events in its analysis:

Subject No.	**Event**
52312	Poor flow in R internal Jugular permacath requiring exchanging catheter
053303	Vena cava filter insertion "due to an increased risk of bleeding.

Volume Overload Events

In the sponsor's preliminary analysis, 3/88 3.4(%) Kcentra and 10/88 (11.4%) Plasma subjects reported possible Volume Overload events. The between-group difference (Kcentra minus Plasma) in the incidence of possible TE events was -7.5% (95% CI -13.6 to -1.5%).

6.2.12.6 Clinical Test Results

Clinical test data from the final dataset for the surgery RCT were not submitted.

6.2.12.7 Dropouts and/or Discontinuations

7. INTEGRATED OVERVIEW OF EFFICACY

This section is not applicable as regards hemostatic efficacy because only the single BE1116_3002 clinical study was adequate and well-controlled and measured hemostatic efficacy. The results of INR correction in this study were similar to that seen among subjects in the uncontrolled phase three European study, BE1116_3002 which enrolled 17 subjects for acute major bleeding and additional subjects undergoing surgery/invasive procedure.

7.1.8 Persistence of Efficacy

The primary efficacy endpoint was defined by key clinical elements which varied by bleeding location over the 24 hour period from start of infusion of the test product. FDA did not evaluate efficacy endpoints beyond this time frame because of the confounding effect of concomitant vitamin K administration.

7.1.9 Product-Product Interactions

In retrospective U.K. epidemiologic study BE1116_5001 there were deaths and TE events among patients who received Kcentra alone, Kcentra plus plasma, but not with plasma alone. The number of patients who received plasma alone was smaller than number of Kcentra- and Kcentra plus plasma- treated patients. The sponsor stated in an amendment received April 2013 that the study was a "usage study" and was not designed to capture safety events. This seemed puzzling, given that such deaths are TE were reported.

No safety analyses were conducted of subjects in the RCT in acute major bleeding who received both Kcentra and plasma.

7.1.11 Efficacy Conclusions

This reviewer concludes that the submitted data were marginal to conclude that there is substantial evidence of effectiveness and safety for the entire target population enrolled in the pivotal RCT in acute major bleeding. The true net efficacy of Kcentra is indeterminate because of the non-inferiority design of the plasma-controlled RCT in acute major bleeding and the fact that no data are available by which to quantify the efficacy of plasma against placebo using the hemostatic efficacy methodology employed in RCT BE1116_3002 (or any other methodology). Kcentra corrected INR to $\leq$ 1.3 by 30 min after the end of the infusion in a much greater proportion of subjects than was the case with plasma, yet Kcentra and plasma hemostatic efficacy were comparable in the sponsor's analysis. Data quality problems in the form of suboptimally designed EAB worksheets and a substantial number of missing EAB worksheets reduced somewhat FDA's confidence in the sponsor's results. Although two sensitivity analyses conducted by the CBER biostatistician in which subjects with missing EAB Worksheets Pages two or missing EAB CRFs were imputed to have poor/none hemostatic efficacy ratings failed to confirm the non-inferiority of Kcentra vis-à-vis plasma for the primary endpoint, the point estimates for the proportion of subjects with effective hemostasis were within 10% of each other. An subgroup analysis of subjects with non-visible GI bleeding, which was the most common site of bleeding comprising 55-56% of subjects showed a strong but not statistically significant trend favoring plasma when the change in Hb and Hct, adjusted for transfusions, from baseline to 24 hours were used as the sole criterion to evaluate hemostatic efficacy. Taking the results of all of the analyses of the primary endpoint and of the secondary and exploratory endpoints into account, this reviewer concludes that a preponderance of evidence indicates that Kcentra and plasma have comparable efficacy for the indication being sought.

8. INTEGRATED OVERVIEW OF SAFETY

8.1 Safety Assessment Methods

As noted in section 6.1.12.1, FDA concluded it was not scientifically valid to pool safety data from the RCTs in acute major bleeding and surgery. Nevertheless, for informational purposes, selected pooled analyses are presented.

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

Selected safety endpoints are presented from pooled final data from RCT BE1116_3002 and preliminary final data (database not locked at time of submission) from surgery RCT BE1116_3003. In addition, TE events in uncontrolled sponsor study BE1116_3001 are considered separately.

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

See section 6.1.12.1

8.2.3 Categorization of Adverse Events

Initially, the sponsor included as TE events in its tables, listings and analyses for both RCTs, events that were not true intravascular TE events. Examples include old blood in nasogastric tube and prophylactic insertion of an umbrella device in the inferior vena cava. In amendment 23 submitted 19 March 2013 the sponsor agreed to correct their tables and analyses to reflect corrections to these mis-classifications of TE events.

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

FDA concludes that pooling of safety data from RCTs in acute major bleeding and surgery is not scientifically justified. See section 6.1.123.1.

8.4 Safety Results

Pooled RCT Analyses

As noted earlier in this section, pooling of the safety data from the pivotal phase 3 bleeding and surgery RCTs may not be scientifically justified. Pooled safety analyses for key safety endpoints are presented for informational purposes.

Incidence of Deaths – Pooled RCT Analysis[1]
(RCTs _3002 + _3003, ITT-S, N = 388)

	Kcentra N (%) N = 191	Plasma N (%) N = 197	Difference (Kcentra minus Plasma) (95% CI)
Deaths N (%):	15 (7.9%)	13 (6.6%)	1.3 % (95% CI -4.4 to 7.0%)

[1]Final data for bleeding RCT BE1116_3002 combined with preliminary final data for surgery RCT BE11126_3003, as amended in amendment 23 dated 19 Mar 2013.

Given the size of the target population of the indication being sought, an excess mortality of even a few percent with Kcentra this could potentially translate into hundreds to over a thousand excess deaths per year in the U.S., depending on the extent to which Kcentra replaces plasma for the intended use.

Pooled RCT Analyses of TE Events

Incidence of TE Events – Pooled RCT Analysis[1]
(RCTs _3002 + _3003, ITT-S)

Types of TE Events	Kcentra N (%) N = 191	Plasma N (%) N = 197	Difference (Kcentra minus Plasma) (95% CI)
All TE Events	14 (7.3%)	13 (6.6%)	-0.7% (-4.9 to 6.4%)
Possibly and Probably Related TE Events[2]	8 (4.2%)	8 (4.1%)	0.1% (-3.8 to 4.1%)

[1]Final data for bleeding RCT BE1116_3002 combined with preliminary final data for surgery RCT BE11126_3003, as amended in amendment 23 dated 19 Mar 2013.
[2]Masked FDA causality analysis

The 95% confidence interval for the Kcentra group minus plasma group difference in the incidence of thromboembolic events combined bleeding and surgery VKA reversal populations ranged from -4.9 to 6.4%. Given the size of the target population of the indication being sought, an excess incidence of thromboembolic events following Kcentra usage could translate into hundreds to a few thousand excess TE events per year in the U.S., depending on the extent to which Kcentra replaces plasma for the intended use.

Subgroup Analyses of Death, TE Events, and Volume Overload Events by Baseline History of Prior TE Event or Vascular Disease

As can be seen by comparing the two tables below, a history of prior thrombo-embolic event appeared to have a disproportionate effect in raising the incidence of TE events in the Kcentra subgroup compared to the plasma subgroup. With a medical history of TE event, the incidence of TE events in the Kcentra subgroup was 9.7% of 124 subjects, with an upper 95% CI boundary of 16.2%; without a history of TE event, the incidence of TE events in the Kcentra subgroup was only 3.0% of 67 subjects, with an upper 95% CI boundary of 10.2%. The incidence of TE events in the Kcentra subgroup was more than 3 fold-reduced by eliminating subjects with a history of prior TE events. The opposite trend was seen for the plasma subjects, in which the incidence of TE events was 5.0% among 140 subjects with a prior history of TE event vs. 10.5% among 57 subjects without a prior history of TE event. The statistical test for the interaction between treatment group and TE prior history on TE incidence was statistically significant at $p < 0.05$.

In addition, in the subgroup of subjects with no prior history of TE event (or coronary, cerebrovascular, or peripheral vascular disease), the incidence of deaths through day 45 were 0.7% higher (absolute) in the Kcentra group, compared to 0.1% higher in the subgroup with a history of prior TE event. The upper bound of the 95% C.I. for the Kcentra minus Plasma group difference in incidence of death among subjects without a medical history of prior TE event or vascular disease through day 45 was 11.9%.

Sponsor's Tables: Incidence of possibly thromboembolic events, volume overload events and deaths by medical history of prior TE Event - Pooled RCT data (19 Mar 2013

Amendment 23 Final Dataset Preliminary Sponsor Analysis, Entire ITT-S population N=385)

Subjects with medical history of thromboembolic events, Pooled RCTs _Subpopulation, N=264

Event Type	Beriplex, N=124 N (%) [95% CI}	Plasma, N= 140 N (%) [95% CI}	Difference (B-P) % [95% CI]
TE (all)	12 (9.7) [5.6 – 16.2]	7 (5.0) [2.4 – 10.0]	4.7 [-2.3 – 12.2]
TE (serious)	8 (46.5) [3.3 – 12.2]	6 (4.3) [2.0 – 9.0]	2.2 [-4.1 – 8.9]
V.O. (all)	4 (3.2) [1.3 – 8.0]	17 (12.1) [7.7 – 18.6]	-8.9 [-16.1 – -1.8]
V.O. (serious)	3 (2.4) [0.8 – 6.9]	7 (5.0) [2.4 – 10.0]	-2.6 [-8.3 – 3.2]
Death thru d 45	9 (7.3) [3.9 – 13.2]	10 (7.1) [3.9 – 12.6]	0.1 [-6.9 – 7.4]

See "Method" under efficacy subgroup analyses section for definition of CHF and TE events or angina, etc.
Source: BLA Amendment 11

Subjects without medical history of thromboembolic events, Pooled RCTs _ N=121

Event Type	Beriplex, N = 67 N (%) [95% CI}	Plasma, N = 57 N (%) [95% CI}	Difference (B-P) % [95% CI]
TE (all)	2 (3.0) [0.8 – 10.2]	6 (10.7) [5.0 – 21.5]	-7.5 [-19.5 – 2.9]
TE (serious)	2 (3.0) [0.3 – 8.2]	4 (7.0) [2.8 – 16.7]	-4.0 [-15.1 – 5.6]
V.O. (all)	5 (7.5) [3.2 – 16.3]	7 (12.3) [6.1 – 23.2]	-4.8 [-17.7 – 7.1]
V.O. (serious)	1 (1.5) [0.3 – 8.0]	1 (1.8) [0.3 – 9.3]	-0.3 [-9.3 – 7.6]
Death through day 45	4 (6.0) [2.3 – 14.4]	3 (5.3) [1.8 – 14.4]	0.7 [-10.3 – 10.9]

See "Method" under efficacy subgroup analyses section for definition of CHF and TE events or angina, etc.

Additional TE Event Data from Uncontrolled Study BE1116_30012.

This uncontrolled CSLB-sponsored study in urgent VKA anticoagulation reversal was conducted in Europe and enrolled 17 subjects with acute major bleeding and additional subjects who ----------(b)(4)----------. The primary efficacy endpoint was INR reduction. Among the 17 subjects with acute major bleeding, 2 TE events (12%) were reported, including one fatal pulmonary embolus considered related to Kcentra administration and one non-fatal TE event.

8.5.8 Immunogenicity (Safety)

The sponsor did not assay antibodies to any of the components of the product during the clinical trials. The preclinical pharmacology-toxicology reviewer recommended the sponsor examine potential immunogenicity and look for development of neutralizing antibodies against VKA-dependent clotting factors and protein C and S during postmarketing. The sponsor will be asked to report any cases of immunogenicity observed during postmarketing surveillance as expedited reports.

8.6 Safety Conclusions

The medical literature associates PCC use with increased arterial and venous thromboembolic risk (Dentali F. *Thrombosis and Haemostasis* 106:429-438 (2011); Lusher JM, *Seminars in Hematology* 28:3-5 (1991)). There were numerically more TE events in the Kcentra group of the pivotal RCT in subjects with acute major bleeding than in the plasma group (10 vs. 6 respectively; 9 vs. 6 if one excludes a Kecentra subject's upper extremity venous thrombosis that occurred in conjunction with an in-dwelling venous catheter). While this difference in TE event incidence between treatment groups was not statistically significant, it, together with data from the class and from TE events observed in uncontrolled study BE1116_3001, represents a safety signal. The interaction between treatment group and prior history of TE event, or of coronary, cerebrovascular, or peripheral vascular disease in predicting a treatment-emergent TE event had a p value of 0.05. Among subjects in the RCT in acute major bleeding with a prior history of TE event, or of coronary, cerebrovascular, or peripheral vascular disease, the incidence of treatment emergent TE event was 11.6% in the Kcentra arm and 3.8% in the plasma arm, a difference of 7.8% in favor of plasma. It is well known that subjects with a prior history of arterial or venous TE events are at increased risk of recurrent TE events. More data are needed to determine conclusively whether Kcentra confers greater risk of TE events than plasma. PMR and PMC studies are recommended, and have been agreed to by the sponsor. These studies will provide additional data on this important issue.

Deaths through day 90 (as well as through day 46 and through day 45) were more frequent in the Kcentra group than in the plasma group. The difference, including all deaths not significant at the $p = 0.05$ level using a two-sided test. Inspection of the Kaplan-Meier plot reveals that the excess deaths with Kcentra occurred beyond day 30 and are thus less likely to be product-related. This reviewer's masked causality assessment concluded that only 4 of 16 deaths in the RCT in acute major bleeding were possibly related to the test products (3 in the Kcentra arm and 1 in the plasma arm). The sponsor's masked SAB concluded that a single death in the Kcentra arm and none in the plasma arm may possibly have been related to the test treatment.

FDA concluded that for a variety of reasons it is not scientifically justified to pool the safety data from the RCTs in acute major bleeding and surgery. In retrospect, it was wise for FDA to have requested separate trials in VKA reversal in bleeding and surgery. A peer-reviewed published meta-analysis of over 1000 patients treated with a variety of PCC products and followed over varying time periods suggested that the incidence of TE

events may be greater in patients with acute major bleeding than in surgery patients undergoing urgent VKA anticoagulation reversal (Dentali F. *Thrombosis and Haemostasis* 106:429-438 (2011)). The trends for both mortality and TE events with Kcentra vs. plasma went in the opposite direction in the bleeding RCT compared to their directions in the RCT in acute major bleeding. The significant of this finding is unclear. Data with another four-factor PCC product used in a randomized, plasma-controlled trial indicate a trend toward excess deaths in the PCC group in all time frames of follow-up examined by the sponsor (BLA). More data are needed to better characterize the relative TE event and death risk of PCC products when used for urgent reversal of VKA anticoagulation.

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data

None.

9.1.2 Use During Lactation

No data are available.

9.1.3 Pediatric Use and PREA Considerations

Given that the product has orphan status for this indication, FDA cannot require pediatric studies for this product/indication. The prevalence of acute major bleeding among the few pediatric patients in the U.S. receiving VKAs is expected to be so low as to make clinical studies in pediatrics for this product/indication impractical.

9.1.5 Geriatric Use

Of the total number of subjects (229) with acute major bleeding treated to reverse VKA anticoagulation in two clinical studies (BE1116)3002 and BE1116_3001), 71% were 65 years old or greater and 43% were 75 years old or greater.

Geriatric patients were well represented in the RCTs. Most on-study deaths occurred among very elderly subjects. To the extent that very elderly subjects have a higher prevalence of prior TE event and that patients with a history of prior arterial or venous TE event are more at risk of a subsequent TE event compared to patients without such history, the elderly are an at-risk population. Complications from acute major bleeding also may be more frequent and severe among the elderly. The data so not demonstrate conclusively a different benefit:risk among the elderly.

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

10. CONCLUSIONS

This reviewer concludes that the submitted data were somewhat marginal to conclude that there is substantial evidence of effectiveness and safety for the entire target population enrolled in the pivotal RCT in acute major bleeding. The true net efficacy of Kcentra is indeterminate because of the non-inferiority design of the plasma-controlled RCT in acute major bleeding and the fact that no data are available by which to quantify the efficacy of plasma against placebo using the hemostatic efficacy methodology employed in RCT BE1116_3002 (or any other methodology). Kcentra corrected INR to $\leq$ 1.3 by 30 min after the end of the infusion in a much greater proportion of subjects than was the case with plasma, yet Kcentra and plasma hemostatic efficacy were comparable in the sponsor's analysis of non-inferiority. Data quality problems in the form of suboptimally designed EAB worksheets and a substantial number of missing EAB worksheets reduced somewhat FDA's confidence in the sponsor's results. Although two sensitivity analyses conducted by the CBER biostatistician in which subjects with missing EAB Worksheets Pages two or missing EAB CRFs were imputed to have poor/none hemostatic efficacy ratings failed to confirm the non-inferiority of Kcentra vis-à-vis plasma for the primary endpoint, the point estimates for the proportion of subjects with effective hemostasis were within 10% of each other. An subgroup analysis of subjects with non-visible GI bleeding, which was the most common site of bleeding comprising 55-56% of subjects showed a strong but not statistically significant trend favoring plasma when the change in Hb and Hct, adjusted for transfusions, from baseline to 24 hours were used as the sole criterion to evaluate hemostatic efficacy. Taking the results of all of the analyses of the primary endpoint and of the secondary and exploratory endpoints into account, this reviewer concludes that a preponderance of evidence indicates that Kcentra and plasma have comparable efficacy for the indication being sought. Given that FDA considers FFP and P24 plasma to carry the indication being sought in this BLA, licensure of Kcentra with a boxed warning regarding TE event risk and a statement that Kcentra at currently recommended doses may not be suitable for patients with history of TE event is reasonable. This reviewer also notes that Kcentra does have certain practical advantages over plasma in terms of the much shorter period of time needed for administration, no need to thaw the product or obtain type-specific plasma, and there were a few mild transfusion reactions diagnosed in the plasma group but none in the Kcentra group in the RCT in acute major bleeding. Concerns regarding possible excess TE event and/or death incidence with Kcentra will be addressed in the PMR epidemiologic study and additional safety data regarding these events will become available from the PMC study the sponsor has agreed to conduct.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

The key review issue is whether sufficient data have been presented to conclude that an appropriate benefit:risk balance exists for the requested target population. The FDA

biostatistician confirmed the sponsor's primary hemostatic endpoint result showing non-inferiority of Kcentra versus plasma, but there were GCP deficiencies related to the process of recording Endpoint Adjudication Board primary endpoint hemostatic efficacy ratings, including a number of missing EAB source documents. Two robustness analyses conducted by the FDA biostatistician imputing "Poor/None" ratings to subjects with missing EAB worksheets pages 2 or missing EAB CRFs failed to confirm non-inferiority of Kcentra in relation to plasma. Analysis of hemoglobin and hematocrit changes in subjects with GI bleeding (the most common bleeding site comprising over 55-56% of subjects) suggested that plasma might be more effective than Kcentra in this subgroup. A greater than two-fold excess in the incidence of all deaths in the Kcentra group (not statistically significant) was observed in the bleeding RCT, but the excess deaths occurred beyond day 30, which suggests they may not be related to Kcentra administration. No deaths in either group were attributed to the test product by the investigator and the SAB concluded that only one death (sudden death on day 7) was possibly related to Kcentra and none were related to plasma. This medical reviewer conducted a blinded review of sponsor- and EAB-prepared narratives for all deaths and TE events reported in both bleeding and surgery RCTs. That analysis suggested that 3 deaths in the Kcentra group and one in the plasma group may possibly or probably have been related to test product administration. Pooling of safety data from bleeding and surgery RCTs does not appear to be scientifically justified, in part because more than twice as many bleeding RCT subjects were in middle and high planned dose cohorts compared to the surgery RCT subjects, due to the higher INR values seen in the bleeding study. There was a trend toward more TE events in the Kcentra arm in the bleeding study, and twice as many possibly or probably related TE events were seen in the Kcentra arm than in the plasma arm, using jointly either the investigator's or the SAB's causality assessments. A finding of particular interest in both bleeding and surgery studies among Kcentra arm subjects was that treatment-emergent TE events were much more frequent in subjects with a history of prior TE. All nine possibly or probably related TE events in the bleeding study (joint investigator's and SAB's assessments) were in subjects with a prior history of TE or vascular disease. A statistical test for treatment group interaction with prior history of TE event in predicting treatment-emergent TE gave a p value of 0.05. The primary medical reviewer concluded that the submitted data are somewhat marginal in demonstrating substantial evidence of effectiveness and safety for the entire target population enrolled in the pivotal RCT in acute major bleeding. However, the primary medical reviewer and the Clinical Review Branch Chief concluded that sufficient data have been submitted to conclude that there is substantial evidence of effectiveness and safety and an appropriate risk:benefit balance for patients without a prior history of thromboembolic event or coronary, cerebrovascular, or peripheral vascular disease.

The medical reviewer recommended Kcentra be licensed with a boxed warning for arterial and venous thromboembolic complications and a statement that the product had not been studied in patients who had a thromboembolic event, myocardial infarction, disseminated intravascular coagulation, cerebral vascular accident, transient ischemic attack, unstable angina pectoris, or severe peripheral vascular disease within the prior 3 months. The sponsor has agreed to amend the package insert to include a boxed warning regarding the risk of thromboembolic complications and the requested statement that the

product had not been studied in patients who had a thromboembolic event, myocardial infarction, disseminated intravascular coagulation, cerebral vascular accident, transient ischemic attack, unstable angina pectoris, or severe peripheral vascular disease within the prior 3 months. The sponsor was also asked to introduce a contraindication into the package insert at currently recommended doses for patients with a history of TE event or coronary, cerebrovascular, or peripheral vascular disease. After the sponsor objected to such a contraindication, maintaining that the submitted data did not support it, CBER management concluded that such a contraindication might impede the ability of the sponsor to conduct the post marketing commitment study that FDA had requested the sponsor perform to evaluate the safety and efficacy of a lower dose regimen of Kcentra vs. plasma for the requested indication. Thus it was decided, in lieu of having a contraindication to the use of Kcentra at currently recommended doses in patients with a prior history of TE event, to include a statement in the boxed warning and in Warnings and Precautions stating that "Potential benefits of reversing VKA should be weighed against the potential risks of thromboembolic events (TE), especially in patients with the history of a thromboembolic event." In addition, the statement, "At recommended doses, Kcentra may not be suitable in patients with thromboembolic events in the prior 3 months," has been added to the boxed warning and to the Warnings and Precautions section.

The primary medical reviewer and the Clinical Review Branch Chief concur with the recommendations of the Division of Biostatistics and Epidemiology to have a post marketing requirement (PMR epidemiologic study to obtain more precise estimates of the risks of death and TE events in patients with and without a prior history of TE event). The primary medical reviewer and the Clinical Review Branch Chief further recommend that the sponsor conduct a post marketing commitment RCT to determine whether a lower dosage regimen of Kcentra is non-inferior to plasma in efficacy and whether such a lower dose regimen may have an improved safety profile, particularly as regard TE events. The sponsor instead agreed to a PMC RCT comparing the currently recommended dosage regimen of Kcentra to a to-be-determined dosage regimen. Should the lower dosage regimen prove to be non-inferior to the currently-recommended dosage regimen, and depending on the safety findings in that trial, which is anticipated to be approximately twice the size of BE1116_3002, FDA will re-examine whether the benefits and risks of the currently-recommended dosage regimen of Kcentra would still pertain.

11.2 Risk-Benefit Summary and Assessment

This reviewer concludes that a preponderance of the evidence indicates that the efficacy of Kcentra and plasma for the requested indication are comparable. There is judged to be substantial evidence of efficacy and safety for the subpopulation of patients without a history of prior arterial or venous thromboembolic event, coronary, cerebrovascular, or peripheral vascular disease. The safety in subjects with a history of prior TE event, MI, DIC, CVA, TIA, unstable angina pectoris, or severe peripheral vascular disease within the prior 3 months has not been established because these subjects were excluded from the RCTs.

11.3 Discussion of Regulatory Options

Regulatory options include:

- Licensure with a boxed warning for arterial and venous thromboembolic complications which includes the a statement regarding to weigh the risks of VLA reversal using Kcentra with the risks of TE event, particularly in patients with a history of TE event, as well as a statement that in subjects with a history of prior TE event, MI, DIC, CVA, TIA, unstable angina pectoris, or severe peripheral vascular disease within the prior 3 months has not been established because these subjects were not studied. PMR to better define risks of death and TE events compared to plasma in patients with and without a history of TE event. PMC RCT to determine if a lower dose of Kcentra has a lower risk of TE event and death but equivalent efficacy to the recommended dose.
- The above option plus a contraindication in patients with a history of prior TE event or coronary, cerebrovascular, or peripheral vascular disease.
- The first bullet plus a contraindication in patients with a history of prior TE.
- The first bullet plus a contraindication in patients with a history of prior TE within the previous 3 months.
- CR letter requesting an additional RCT of Kcentra vs. plasma in patients requiring urgent reversal of VKA anticoagulation in acute major bleeding, preferable including an arm with a lower dosage regimen of Kcentra to determine if a lower dosage regimen has improved safety, especially in terms of TE event risk, with comparable efficacy.

This reviewer favors any of the first 4 options, which highlight the risk of TE events and the need for balancing the risk of TE against the risk of continued bleeding. Should the PMC or PMR studies suggest the need, the contraindications section of the PI can be updated to include a contraindication for use in patients with a [recent] history of TE event. If the product were not licensed at this time, but is licensed ----------
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----------(b)(4)----------

----------, this reviewer anticipates substantial off-label use of Kcentra for urgent VKA anticoagulation reversal in patients with acute major

bleeding. It will be useful for clinicians to have ready access to the information in the draft package insert negotiated with the sponsor under the present BLA to better inform them of the risks and benefits of using Kcentra vs. plasma for the VKA anticoagulation reversal in acute major bleeding. This consideration tends to support licensure of the current BLA.

11.4 Recommendations on Regulatory Actions

Kcentra, Prothrombin Complex Concentrate (Human), is recommended for licensure. The risk of thromboembolism will be further evaluated in a post marketing requirement (PMR) prospective epidemiologic cohort study using a concurrent plasma comparison group in patients who have been receiving VKA anticoagulation therapy and who have acute major bleeding requiring urgent reversal of the acquired VKA-dependent clotting factor deficiency. In addition, the sponsor has been requested to conduct a post marketing commitment (PMC) study to evaluate the clinical benefit and risks against a concurrent plasma control group in a randomized clinical trial evaluating a lower dose scheme of the product, conventional doses of plasma, and, optionally, the currently recommended dosage scheme of the product. The sponsor elected to conduct a two-arm blinded RCT of Kcentra at the currently recommended dosage regimen and at a to-be-determined lower dosage regimen. The PMC RCT will be stratified according to whether subjects have a history of prior TE event and whether they have had a TE event within the last 90 days, and also by baseline INR. Stopping rules will be included for subjects with a history of TE event, MI, DIC, CVA, TIA, unstable angina pectoris, or severe peripheral vascular disease within the 3 months prior to enrollment. The study will be powered for efficacy (non-inferiority with a non-inferiority margin of 10% absolute in the percentage of subjects achieving hemostatic efficacy) with an n of at least ~ 415 subjects and the primary safety endpoint will be the incidence of TE events by randomization group. The incidence of deaths will be evaluated separately.

11.5 Labeling Review and Recommendations

This reviewer recommended and FDA management accepted to ask the sponsor to add a boxed warning to the draft PI for Kcentra and also to implement a boxed warning for arterial and venous thrombotic complications for the class of PCC products for all currently marketed indications. This reviewer supported the initial recommendation of the Clinical Review Branch Chief to add a contraindication in patients with a history of TE event, or coronary, cerebrovascular, or peripheral vascular disease and this request was conveyed to the sponsor. FDA had noted that the Sponsor's Core Data Sheet submitted with the original BLA included a contraindication in patients judged at increased risk of TE event and for patients with angina pectoris and recent MI. After asking the sponsor to add the less restrictive contraindication for patients with a history TE event, the sponsor submitted an updated Core Data Sheet approved by the EMA in January 2013 which lacked the aforementioned contraindication. ----------
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----------. FDA reconsidered its position and allowed the sponsor to submit a

revised draft PI without the requested contraindication, but with language in the Warnings and Precautions section regarding increased risk of TE events in patients with a history of TE event. This was done in return for the sponsor agreeing to conduct a PMC RCT to evaluate safety and efficacy of a lower dosage regimen vs. the currently recommended dosage regimen (based on body weight and INR stratum), which the sponsor agreed to do in their amendment dated 11 April 2013. A statement that "At recommended doses, Kcentra may not be suitable in patients with thromboembolic events in the prior 3 months" was also added to the boxed warning and the Warnings and Precautions section.

11.6 Recommendations on Postmarketing Actions

POST MARKETING REQUIREMENTS

The risk of thromboembolism will be further evaluated in a post marketing requirement (PMR) prospective epidemiologic cohort study using a concurrent plasma comparison group in patients who have been receiving VKA anticoagulation therapy and who have acute major bleeding requiring urgent reversal of the acquired VKA-dependent clotting factor deficiency. The sponsor had originally proposed a claims-based matched cohort study using the Premier Database with medical chart review on a subset of the patients from selected hospitals. FDA determined that the sponsor's original PMR study proposal was unacceptable because it would not be possible to adequately identify patients receiving Kcentra and plasma for urgent reversal of VKA anticoagulation therapy and it also would not be possible to identify whether the patients had a history of prior TE event, which is a key eligibility criterion of the study being required by FDA. FDA accepted the sponsor's revised proposal to perform a retrospective case control study using the database of ----------(b)(4)----------.

POST MARKETING COMMITMENTS

The sponsor has been requested to conduct a post marketing commitment (PMC) study to evaluate the clinical benefit and risks against a concurrent plasma control group in a randomized clinical trial evaluating a lower dose scheme of Kcentra, conventional doses of plasma, and, optionally, the currently recommended dosage scheme of the product. The sponsor counter-proposed a two-arm blinded RCT comparing safety and efficacy of the current Kcentra dosage regimen against a to-be-determined lower dosage regimen with a secondary composite endpoint of pooled deaths plus TE events. The PMC study will be stratified according to whether subjects have a history of prior TE event and by baseline INR. This reviewer initially recommended that the design of the two-arm RCT that the sponsor counter-proposed be modified to include a plasma randomized arm for the subset of subjects with a history of TE event in the previous 90 days because the safety of the product has not been evaluated in such patients. After internal discussion with the CRB Chief and the Biostatistician review team, it was agreed to instead required stopping rules for TE events in subjects with a history of TE event, MI, DIC, CVA, TIA, unstable angina pectoris, or severe peripheral vascular disease within the 3 months prior to enrollment and to not require a concurrent plasma control for this subset. The stopping

rule boundary would adapt to the sample size of enrolled subjects as the trial progresses. Should the stopping rule be triggered, this will likely have implications for the package insert of the product.

INR – International Normalized Ratio
VKA – Vitamin K Antagonist
TE – thrombotic/thromboembolic [event]
VO – volume overload [event]