Clinical Mid-Cycle Review of Original BLA
OBRR/DH

BLA STN# 125421/0

SEE ALSO: IND 13398

PRODUCT: Beriplex P/N, Human Prothrombin Complex Concentrate, Pasteurized and Nanofiltered

Proposed Use (Indication): The urgent reversal of vitamin K antagonist (e.g., warfarin) therapy in patients with acute major bleeding (Formerly: Treatment of major bleeding resulting from an acquired deficiency of Vitamin K dependent coagulation factors and proteins C and S due to vitamin K antagonist (warfarin) therapy

Sponsor: CSL Behring LLC

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Receipt Dates: 30 March 2012

Submission Letter Dates: 30 March 2012

- **Fast Track Application:** N/A. The sponsor requested priority review for the BLA, which was denied because the sponsor has not submitted data demonstrating either superior efficacy or greater safety for Beriplex vis-à-vis plasma (current standard of care in the U.S.).

Orphan Status: Request held in abeyance pending sponsor's response to 3rd deficiency letter issued by Orphan Products.

Product name(s)/Product Type:

Prothrombin Complex, Human, Freeze Dried

Product Type: BLOOD /Sub type: OTHER/UNSPECIFIED

Review Team:
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Through: Nisha Jain, M.D., Chief, CRB, HFM-392

Cross-referenced INDs, IDEs, MFs, BLA: IND 13398 – See esp. amendments 82 and /83

RECOMMENDATION:

- Presentation of the safety and efficacy data to BPAC with the questions:

    - "Given the similar hemostatic efficacy outcomes in the single randomized, open-label, plasma-controlled study to urgently reverse vitamin K antagonist (VKA) anticoagulation in bleeding patients, BE1116_3002 and the available safety findings showing an unfavorable trend for Beriplex Human Prothrombin Complex Concentrate in 45-day mortality in this study and for another Human Prothrombin Complex Concentrate product in an interim analysis of an ongoing surgery study in patients requiring urgent VKA anticoagulation reversal, do you recommend additional safety data, including mortality data, be collected in order to provide substantial evidence of safety for Beriplex for the indication being sought?

    - If not, what additional postmarketing study/studies and/or changes to the pharmacovigilance plan for Beriplex do you

recommend to better characterize the comparative safety profile of Beriplex to plasma/FFP?

- **I recommend granting the sponsor's full waiver request for pediatric studies.**

LETTER READY COMMENTS FOR INFORMATION REQUEST:

1. Please provide blinded narratives for all subjects who (a) died prior to day 46, (b) were suspected of having a thrombotic or thromboembolic TE) event, (c) were suspected of having possible volume overload. Please remove randomization/treatment group, test product infusion volumes, post-baseline INR and Prothrombin time values, infusion times, and time of completion of infusion of test product from the above subject narratives. Please submit the data and safety monitoring board (DSMB) and safety adjudication board (SAB) narratives in the order of subject ID number (i.e, randomly as regards treatment group, not grouped by treatment group as they presently appear in the BLA) and remove information from the unblinded DSMB narratives which would potentially unblind the reader.

2. Please perform and submit the results of the following exploratory efficacy analyses by treatment group for the subset of subjects having intracranial hemorrhage. Include the primary hemostatic efficacy analysis and all other *a priori* secondary and other (exploratory) efficacy analyses in the above subgroup analyses. Although the results are not in Table 39 of the study report in the original BLA for study _3002, we note that Table 14.2.1 - 10a shows that in the Beriplex ITT Group (n = 107), there were 5 ICH subjects with excellent or good primary hemostatic EAB ratings and 7 ICH subjects with poor/none primary hemostatic EAB ratings. For Plasma (n = 109), there were similarly 5 ICH subjects with excellent or good primary hemostatic EAB ratings and 7 ICH subjects with poor/none primary hemostatic EAB ratings. The 2-sided p value for the difference was 0.4241. Please provide the location in the BLA of analogous results for the subgroup of ICH subjects by treatment group for the ICH-E population and the 95% confidence intervals for the difference in the percentage of subjects in each subgroup with excellent or good ratings for all 4 study populations (ITT, ITT-S, ITT-E, and PP). Please provide results of ICH subgroup analyses for each study population for the following endpoints:

- use of non-study-prescribed blood products and/or hemostatic agents (other than PRBCs) in both treatment groups
- number of RBC units transfused
- Proportion of subjects with 1 or more RBC units transfused.
- the 4 elements of Healthcare Utilization
- Re-hospitalization due to study drug related complications within 45/90 days.

3. Please perform and submit exploratory analyses looking at the within-subject correlation/relationship between INR correction and the primary hemostatic efficacy endpoint rating using various alternative thresholds of INR correction in addition to the protocol-specified INR correction to a value < 1.3 (for example, INR reduction to values < 1.5, < 1.7, < 1.9, < 2.1 at 30 min post end of IMP infusion).

4. You state in the study report for study _3002 that the procedure required by the protocol for blinded assignment of subjects to the various analysis populations (ITT, ITT-E, PP, and ITT-S) was not followed. The protocol stated that "The determination of each subject's membership (yes/no) in each of the study populations will be accomplished during the Blinded Data Review Meeting (BDRM), before database lock and before the unblinding of the primary/secondary efficacy ratings. The assignments will be documented in the BDRM meeting minutes." Instead, as documented on p 74 of 4514 of the study report (section 9.8.2.6), "The determination of the subject's membership in the ITT-E population was partially done after the unblinding of the primary/secondary efficacy ratings since the corresponding information (eligibility of subjects, efficacy rating of 'poor/none' due to missing information for subjects with visible or non-visible muscular/skeletal bleeding enrolled before Amendment 3) was not available until the Clinical Research Organization managing the adjudication data provided the unblinded assessments to the Clinical Research Organization managing the clinical database." Please submit a detailed explanation of why the protocol was not followed regarding the determination of each subject's membership in each of the study populations. Which subjects, if any, did not have determination of study analysis populations may during the BDRM as required by the protocol? Which subjects, if any, had their determination of study analysis populations made during the BDRM but then subsequently changed with knowledge of randomization treatment group assignments? If any subjects had their membership in any of the 4 analysis populations changed after an initial assignment made during the

BDRM, please provide the details of why such changes were made in apparent violation of the protocol.

5. Please clarify the time window permitted in the analysis of the co-primary endpoint. You state in item 7 of section 9.8.2.6 of the final study report for study _3002 "INR ≤ 1.3 at 30 minutes after start of infusion:

   Change: **In the calculation of INR ≤ 1.3 at the 30-minute time point after start of infusion, if** a subject's INR value was missing, or **the assessment time was more than 45 minutes prior to start of infusion** or if the assessment time was more than 15 minutes after the scheduled 30 minutes post infusion, **the subject was counted as having "no rapid decrease" of INR. [emphasis added]"** The bolded portion of your statement suggests that INR values obtained up to and including 45 minutes prior to the start of the infusion of investigational product were used in your analysis of whether subjects achieved an INR ≤ 1.3 at the 30-minute time point after start of infusion. Please clarify.

EXECUTIVE SUMMARY

CSL's Prothrombin Complex, Human, Freeze Dried (proposed trade name Beriplex) is the first member of this class of prothrombin complex concentrates (PCCs) to seek an indication for the urgent reversal of vitamin K antagonist (e.g., warfarin) therapy in patient's with acute major bleeding. Other PCCs have been licensed in the U.S. for treatment of hemophilia A and B but their use has been largely supplanted by purified plasma-derived and, more recently, recombinant Factor VIII and Factor IX products. Bleeding during warfarin or other vitamin K antagonist (VKA) anticoagulation occurs not uncommonly due to trauma and variability in the degree of anticoagulation over time due to such factors as changes in concomitant medications, such as antibiotics and many others, which interact with warfarin. The standard of care for reversal of vitamin K antagonist (e.g., warfarin) therapy in patients with acute major bleeding depends on the urgency of the need for reversal of VKA anticoagulation. Mild bleeding may be managed with conservative measures and [temporary] withdrawal of VKA therapy. Moderate degrees of bleeding are managed with withdrawal of VKA therapy and oral, subcutaneous, or IV vitamin K administration. In the U.S., moderate to severe bleeding is managed with withdrawal of VKA therapy, vitamin K administration, and administration of fresh frozen plasma (FFP). FDA recognizes the indications for FFP and for

24 hour plasma listed in the American Association of Blood Banks (AABB) circular as equivalent to FDA-approved indications. The AABB circular recognizes urgent reversal of VKA anticoagulation for bleeding and also in VKA anticoagulated patients who require urgent surgery as legitimate indications for FFP and for 24 hour plasma despite the fact that the efficacy for neither of these indications has been demonstrated in adequate and well-controlled clinical trials.

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. Beriplex is currently authorized for marketing in 24 countries outside the U.S., including Canada and the U.K. It is widely recognized in the literature and in the foreign package inserts of PCC products that they are associated with thrombogenic risk, which must be taken into account when deciding whether to use FFP or a PCC product in combination with vitamin K and withdrawal of VKA antagonist therapy in patients with an urgent need for reversal of VKA anticoagulation who are bleeding or require urgent surgery or an invasive procedure. Although PCC products have certain practical and theoretical advantages over FFP of (1) no need to thaw the product, (2) no need to perform a cross-matching procedure, and (3) administration of the therapeutic dose in a smaller volume in a shorter period of time, and (presumed theoretical greater viral safety due to the presence of dedicated viral inactivation procedures commonly employed in the manufacture of PCC products, no head-to-head randomized clinical trial comparisons of FFP and PCC products have been published, despite many calls for the need for performance of such studies in standard hematology textbooks.

CSL ----------(b)(4)---------- have been conducting phase 3 randomized, plasma-controlled clinical trials under U.S. INDs in patients requiring urgent reversal of VKA anticoagulation for bleeding or because of the need for urgent surgery of urgent performance of an invasive procedure. (b)(4) sponsors had originally approached FDA during "pre-BLA" (actually pre-IND) meetings during which they had hoped to convince FDA to accept BLA applications 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 to (b)(4) sponsors they undertake randomized, FFP-controlled clinical trials to provide substantial evidence of effectiveness and safety in support of BLAs for these indications. FFP was chosen as the comparator because of its use as standard of care in the U.S. 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.

The clinical efficacy data in this application are based primarily on 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 data are submitted from 6 uncontrolled single arm non-IND studies. Additional safety data are provided from an interim safety analysis of ongoing pivotal phase 3 surgery study BE1116_3003. This review focuses on the 2 RCTs conducted under IND: safety and efficacy data from completed bleeding patient study BE1116_3002 and interim safety data from ongoing surgery/invasive procedure patient study BE1116_3003. Additional PCC class safety data from an interim safety analysis of -----(b)(4)----- PCC, ---(b)(4)--- from IND --(b)(4)-- are also discussed.

Summary of **Protocol BE1116_ 3002** Design

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 a single intravenous dose of Beriplex or plasma (including FFP and 24-hour plasma) which varied in 3 steps depending on the baseline INR. INR, CBC and clinical assessments of hemostasis and of markers of intravascular coagulation were assessed frequently over a 24 hour period, then clinical and/or laboratory examinations were conducted on days , 10, 20, 45, and 90.

Protocol BE1116_ 3002 had the following objectives:

Primary:

> To compare the hemostatic efficacy of Beriplex® *PIN* 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 Objective:

To compare the efficacy of Beriplex® P*I*N and plasma in rapidly reducing the international normalized ratio (INR, i.e. INR $\leq$ 1.3) values between the 2 treatment groups at 30 minutes after end of infusion.

The study had additional "other" objectives mirrored by the "other" efficacy endpoints listed below.

PRIMARY EFFICACY VARIABLE

The primary efficacy variable was the hemostatic efficacy with respect to the adequacy of stopping an ongoing major bleed. The primary efficacy endpoint was assessed by the blinded Independent Endpoint Adjudication Board (EAB) implemented by the data and safety monitoring board (DSMB) as excellent, good, or poor/none, based on pre-specified definitions. 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)."

The primary endpoint assessment covered 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 any additional hemostatic treatments. The efficacy of only the planned study treatment was to be assessed. 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.

See the body of this review for tables defining excellent, good, and poor/none ratings for the primary hemostatic efficacy variable. Specific

criteria were established a priori depending on whether bleeding was visible or fell into each 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)

Statistical Analysis of the Primary (Hemostatic) Efficacy Endpoint

The primary endpoint is hemostatic efficacy, assessed for the time from start of infusion of Beriplex P/N or plasma until 24 hours after the start of the infusion. The primary analysis will use the method of Farrington and Manning of the C.I. for the difference in the proportions of subjects with a rating of effective hemostasis (excellent or good) in the 2 treatment groups, where p_1 is that proportion in the Beriplex group and p_2 is that proportion in the FFP group.

Null Hypothesis: $p_1 - p_2 \leq$ delta

Alternative Hypothesis: $p_1 - p_2 >$ delta

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

According to the protocol and statistical analysis plan (SAP), Beriplex®P/N can 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 Beriplex® P*I*N compared to that of plasma on each of the two primary endpoints.

According to the protocol and statistical analysis plan (SAP), superiority could not be claimed unless Beriplex was found superior to plasma for both the primary hemostatic efficacy endpoint and the co-primary (INR correction) endpoint.

CO- PRIMARY EFFICACY VARIABLE

The co-primary efficacy variable was the proportion of subjects who had a rapid decrease of the INR (i.e. to an INR value ≤ 1.3) at 30 minutes after end of infusion.

If the INR at 30 min +/- 15 min post infusion is missing, the subject was counted as having "no rapid decrease" (ITT-E analysis).

If the INR at 30 min +/- 15 min post infusion is ≤ 1.3, but additional Beriplex, plasma, or other coagulation factor products were used after the start of the infusion and prior to the 30 min post-end-of-infusion blood draw, then the subject was counted as having "no rapid decrease."

SECONDARY EFFICACY VARIABLES

The following secondary efficacy endpoint was added in amendment 3:

• 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:

Table Contrasting 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	Cessation of bleeding > 1 and ≤ 4 hrs after end of infusion and no additional coagulation intervention	Cessation of bleeding > 4 hrs after end of infusion and no additional coagulation intervention
Secondary Rating of Hemostatic Efficacy	Cessation of bleeding ≤ 3 hrs after start of infusion and no additional coagulation intervention	Cessation of bleeding > 3 and ≤ 6 hrs after start of infusion and no additional coagulation intervention	Cessation of bleeding > 6 hrs after start of infusion and/or additional coagulation intervention[1]

[1] e.g., plasma, whole blood (WB), PRBC, 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,

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

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

• Transfusion of red blood cells.

The following endpoint was moved from secondary to "other" by protocol amendment:

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

Reviewer Note: During the IND phase, it was noted that the large number of secondary and additional efficacy analyses seems more in keeping with a phase 2 rather than a "phase 3b) protocol. FDA communicated the following to the sponsor during the IND phase:

In view of the large number (8) of secondary endpoints and the lack of provision for correction for multiplicity of endpoints in their statistical analyses, we may discourage you from including the results of these analyses, and/or their p values, except where it may impact potential product safety, in the package insert for the product.

Other 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

The following additional "other" (exploratory) endpoints were added to the final SAP but not to the study protocol:

- Responder Analysis among subjects with visible bleeding (SAP page 30/59).

- Healthcare Utilization
  - ER time
  - Inpatient time
  - Critical Care unit/ICU time
  - General Ward time

The following analysis was added at the request of the DSMB but was not included in the protocol or final SAP:

- Re-hospitalization due to study drug related complications within 45/90 days.

Safety Variables

- Adverse events AEs
- Vital signs (blood pressure, pulse rate, and respiration rate)
- Physical examination
- Hematology (hemoglobin (Hb), hematocrit (Hct), and platelet count)
- Transfusion requirement
- Thrombogenicity (lab markers, including F1+2, TAT, D—Dimers) and clinical signs and symptoms)
- Viral safety (viral Antibody titers before and after treatment). HBsAg, antibodies to HIV-1&2, HCV, HAV (IgG and IgM), parvovirus B19 by IgM. (b)(4) for B19V, HACV, HBV, HCV, and HIV-1.
- For ICH subjects: Modified Rankin Score at day 45, Glasgow Coma Score (GCS)
- For subarachnoid hemorrhage (SAH) subjects: Hunt and Hess grade

The sponsor made a number of changes to planned analyses, only some of which were reflected in the final SAP. The most important of these are detailed in the body of this review.

The sponsor did not follow the procedure required by the protocol for blinded assignment of subjects to the various analysis populations (ITT, ITT-E, PP, and ITT-S). The protocol stated that "The determination of each subject's membership (yes/no) in each of the study populations will be accomplished during the Blinded Data Review Meeting (BDRM), before database lock and before the unblinding of the primary/secondary efficacy ratings. The assignments will be documented in the BDRM meeting minutes." Instead, as documented on p 74 of 4514 of the study report (section 9.8.2.6), "The determination of the subject's membership in the ITT-E population was partially done after the unblinding of the primary/secondary efficacy ratings since the corresponding information (eligibility of subjects, efficacy rating of 'poor/none' due to missing information for subjects with visible or non-visible muscular/skeletal bleeding enrolled before Amendment 3) was not available until the Clinical Research Organization managing the adjudication data provided the unblinded assessments to the Clinical Research Organization managing the clinical database." Reviewer Comment: There is potential for bias when decisions concerning exclusion from key efficacy analysis populations are not made in a blinded fashion. See letter-ready comments and 05 Sept 2011 Addendum to BiMo Inspection Assignment for this BLA.

RANDOMIZATION

Biased coin minimization method, using validated software was utilized centrally using a 24-hour randomization service center. Randomization was stratified according to the following 5 bleeding sites:

- Gastrointestinal bleeding
- Visible bleeding (such as hematuria or epistaxis)
- Intracranial hemorrhage
- Muscular/skeletal bleeding
- All other non-visible bleeding

The biased coin minimization method sought to approach balance within each center (presumably in the number of subjects in each treatment group) and to achieve balance across treatment groups in the distribution of bleeding types.

RESULTS – DEMOGRAPHICS AND SUBJECT DISPOSITION (Study _3002)

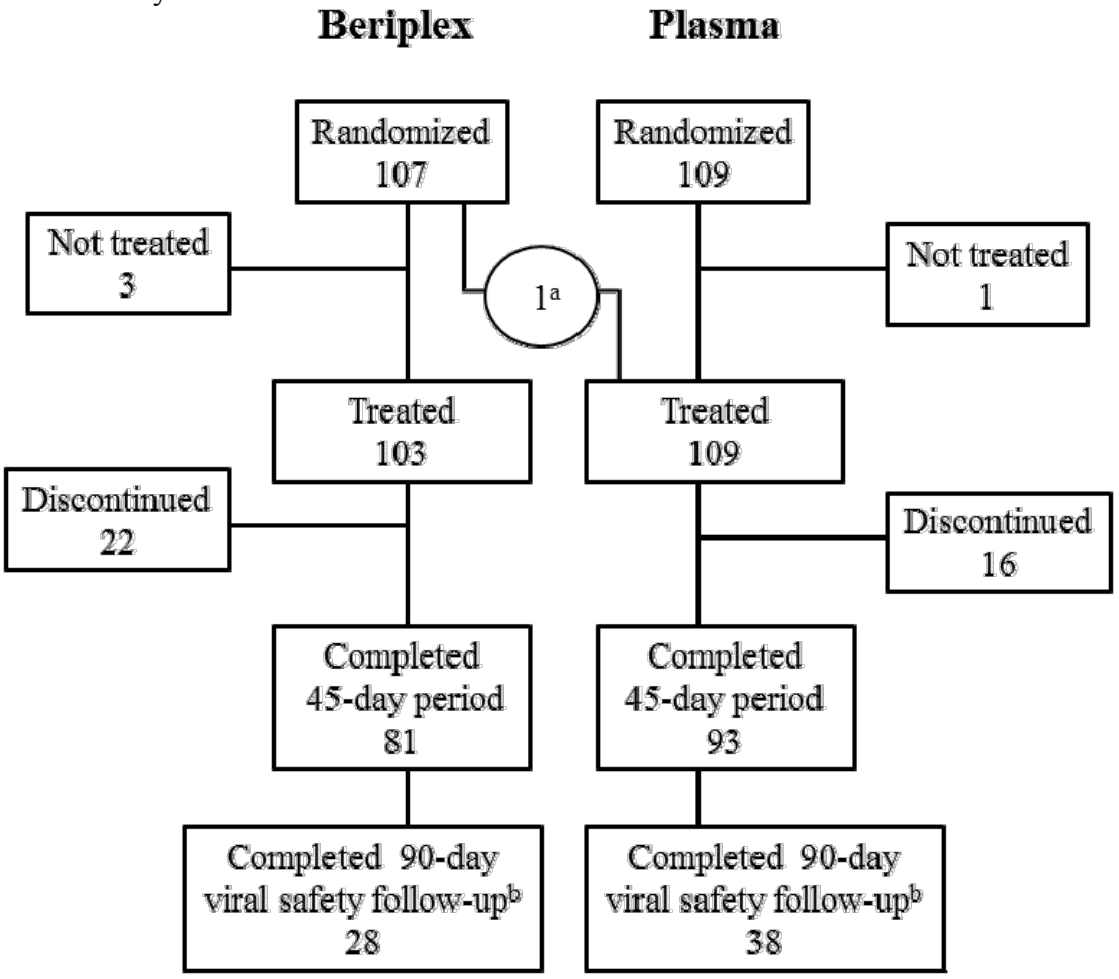
Subject Disposition in Study _3002 and Analysis Populations

Sponsor's Table 10 – Subject disposition by study population

Population	No. (%) of subjects		
	Beriplex	**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.

Sponsor's Figure 1: Summary of Subject Disposition (ITT Population)



[a] Subject 314011 was randomized to Beriplex but treated with plasma.
[b] Only added subsequent to Amendment 3.0.

DEMOGRAPHICS

Good balance was achieved in the ITT-E population between randomization groups in sex, age, site location (U.S. vs. European), and BMI, but the number of non-whites was over 3x greater in the plasma group (16 vs. 5). I am not aware of any mechanism by which the imbalance in non-whites would be expected to impact study outcomes, but the theoretical possibility could be considered, though it would seem unlikely.

Major Protocol Deviations (ITT Population)

There were 7 subjects in the Beriplex randomization group and 8 subjects in the Plasma randomization group who had major protocol violations. Four subjects in the Beriplex and 3 in the plasma group were missing key primary efficacy variables. Fur subjects in the plasma group and zero in the Beriplex group received < 70% of the intended dose of the investigational product. One subject randomized to Beriplex received plasma instead.

RESULTS – EFFICACY (Study _3002)

Sponsor's Table 6: Primary endpoint: Proportion of subjects with hemostasis rated effective (ITT-E population) (Study BE1116_3002)

Rated Effective[a] n/N (%)		Difference (%): Beriplex – Plasma (95% CI for difference)[b]
Beriplex	**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] Beriplex non-inferior to plasma: lower limit of the 95% CI exceeds –10%;
Beriplex 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.
Source: Module 5.3.5.1.1.2, Table 14.2.1-1.1b

Three of 4 sensitivity analyses of the primary efficacy endpoint supported the non-inferiority of Beriplex in relation to plasma and in all 4 the point estimate was numerically better for Beriplex.

Because the lower bound of the 95% confidence interval was -5.8, meaning that the trial results are consistent with a 2.5% probability that Beriplex may be inferior to Plasma in the proportion of subjects rated effective for the hemostatic efficacy co-primary endpoint by an absolute margin of 5.8% or greater, the statistical test for superiority of Beriplex over Plasma failed.

Results– Co-Primary Efficacy Endpoint (A Surrogate Endpoint Measure)

Sponsor's Table 9: Co-primary endpoint: Rapid decrease in INR (ITT-E population) (Study 3002)

Rapid Decrease[a] n/N (%)		Difference (%): Beriplex – Plasma (95% CI for difference)[b]
Beriplex	**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]Beriplex non-inferior to plasma: lower limit of the 95% CI exceeds –10%;
Beriplex 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

Because Beriplex was not found to be superior to plasma for <u>both</u> the primary and co-primary endpoint in the ITT-E population, the protocol provided that no conclusion of superiority of Beriplex over plasma can be drawn (as regards efficacy).

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 PRBCs 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 61.2% of subjects in the Beriplex group and 9.6% of subjects in the FFP group showing rapid decrease in INR at 30 min post end of CTM infusion.

<u>Results of Secondary Efficacy Endpoints</u> – Pivotal Bleeding Study _3002

45-Day Mortality from All Causes

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 Beriplex/Plasma Risk Ratio 0.66 to 5.50). There were 9 deaths out of 98 Beriplex subjects and 5 deaths out of 104 Plasma subjects in the ITT-E population, giving 45 day mortality rates of 9.2% and 4.8&, respectively.

Secondary Assessment of hemostatic efficacy by EAB

"The proportion of subjects with effective hemostasis under the secondary rating was 73.5% in the Beriplex group and 67.3% in the plasma group (Table 24). The difference between groups was 6.2% in favor of Beriplex, and the lower limit of the 95% CI was −6.5%. Analysis of the treatment difference confirmed the non-inferiority of Beriplex treatment compared to plasma treatment (lower limit of 95% CI was > –10%), but did not demonstrate superiority (lower limit of 95% CI was not > 0%)."

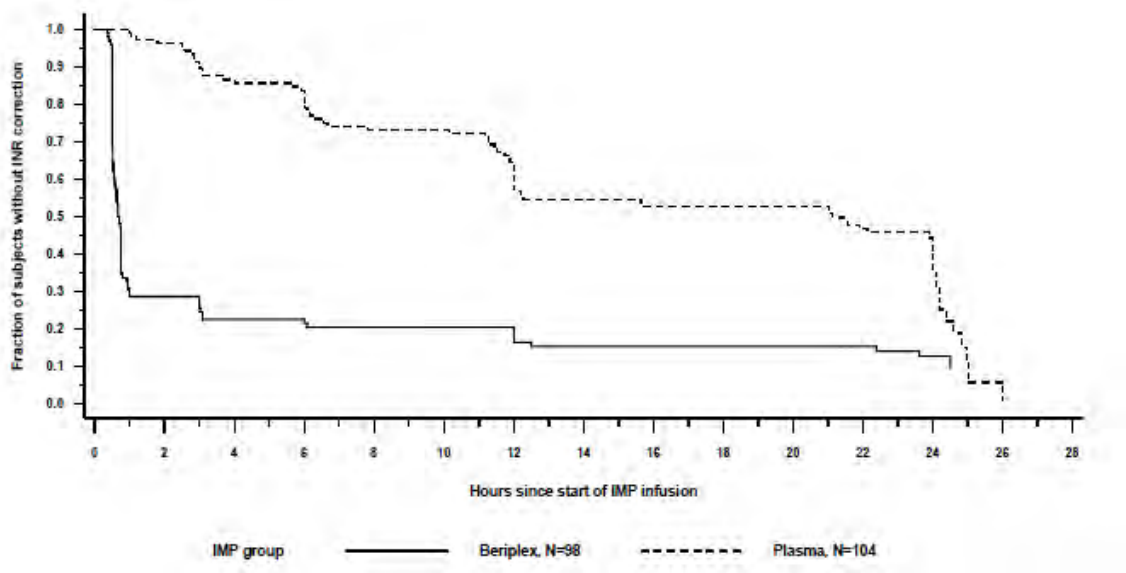
Sponsor's Table 27: Comparison of incremental IVR (response) and classical IVR for Beriplex for each component (ITT-E population)

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

Parameter	N	Mean (SD)	Min/Max
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.

Sponsor's Fig 2 – Kaplan-Meier Plot of Time to INR Correction from Start of Infusion (ITT-E Population)



RBC Transfusions

The mean +/- SD number of transfused units of PRBCs was 1.4 +/- 1.77 and 1.2 +/- 1.57 units in Beriplex and Plasma groups, respectively and did not differ by the Wilcoxon Rank Sum test (p = 0.4462). Volumes of transfused units of PRBCs were available for 21 subjects in the Beriplex group and 23 subjects in the plasma group. The mean volume of all transfused units was 308.3 mL. Normalization of transfusion volumes to this standard volume per unit also revealed no statistically significant difference between randomization groups (p = 0./4995 by Wilcoxon Rank Sum test).

Results of Other [Tertiary, Exploratory] Efficacy Endpoints – Pivotal Bleeding Study _3002

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.

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).

Use of Other Blood Products (besides PRBCs)

The numbers of units of other blood products used by subjects in Beriplex (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). Results excluding center 314 were similar.

Decrease of INR to 1.3 or less at 30 minutes after the start of infusion

Fifty-eight (59.2$) of Beriplex group subjects and none of plasma group subjects had an INR $\leq$ 1.3 at 30 min after the start of randomized test product infusion.

Visible bleeding responder analysis

Sixteen Beriplex group and 21 plasma group subjects had visible bleeding. The proportion in each group who were classified in the primary hemostatic endpoint analysis as responders (cessation of bleeding within 24 hours of start of infusion) was 15/16 (85.7%) in the Beriplex group and 18 of 21 (85.7%) in the plasma group, giving an absolute difference of 8.1% in favor of Beriplex (NS, p = 0.62)

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 1 Beriplex group and 2 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

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

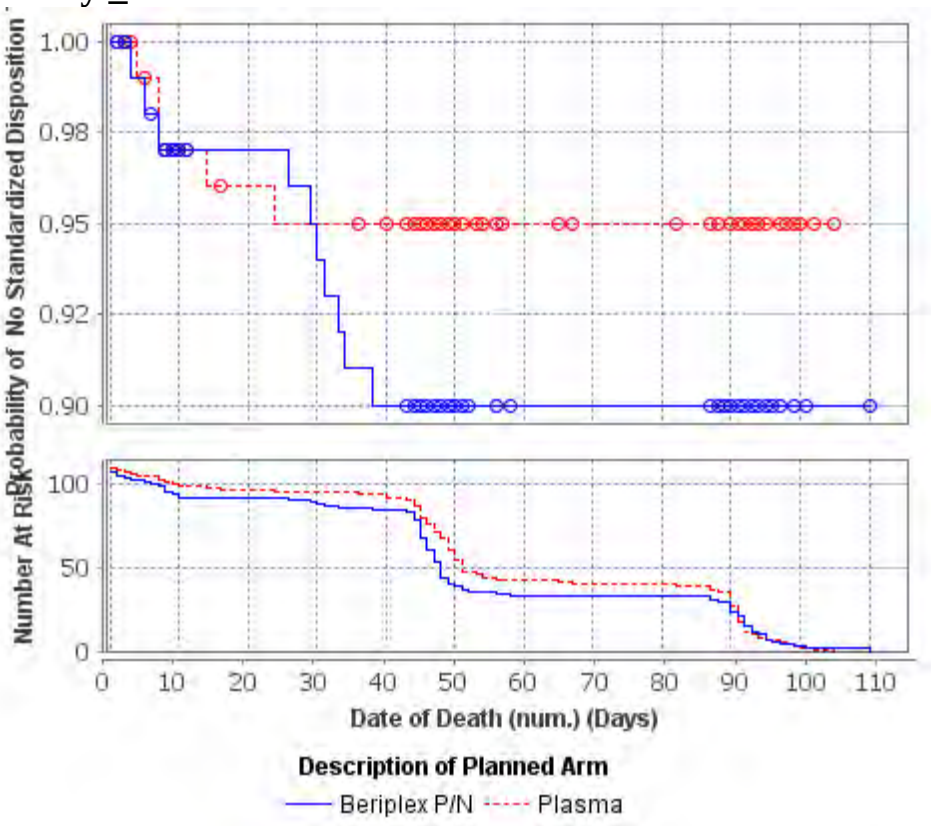
Among the 9 subjects in each treatment group with mRS data at day 45, eight subjects achieved good mRS scores (pre-defined as <5). Using a mRS value of <4 to define a good response, 6 of 9 Beriplex and 7 of 9 plasma group subjects had a good response. The differences in changes from baseline in mRS between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

SAFETY RESULTS

Safety Results from Study BE1116_3002:

There were 11 deaths (10.7%) out of 103 Beriplex subjects compared to 5 deaths (4.6%) out of 109 FFP subjects. The ratio of the excess deaths among subjects randomized to Beriplex to those randomized to control plasma treatment was 2.33. The unmasked investigator and masked safety adjudication board concluded that only 1 death (in the Beriplex group) was at least possibly treatment-related.

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



It can be seen from the above Kaplan-Meier survival plot that while the rate of deaths in the 2 treatment arms was roughly balanced during the first 30 days of the study, a number of late deaths occurring between days 30 and 45 contributed to a trend of imbalance with excess overall 45-day mortality in the Beriplex group.

I undertook a blinded analysis of the adverse events reported for each subject who died and the time of onset, severity, and duration of these associated adverse events in order to assign a 3-point ordinal death causality score to each subject who died. After eliminating subjects who had little to no evidence of causality in my opinion based on the review of the timing and nature of AEs reported for these subjects (score of zero), the number of remaining subjects who died in each treatment group (with blinded death causality scores of 1 or 2) was 8 subjects in the Beriplex group and 2 subjects in the plasma group.

Blinded Assessment of Potential for Relationship of Death to Study Product

Comparison	Beriplex	Plasma
Subjects with Score[a] = 0	2	3
Subjects with Score = 1	3	0
Subjects with Score = 2	5	2
Subjects with Score = 1 or 2	8	2
Total Score	13	4

[a]Blinded Death Causality Score Definitions:
0 = Little to no Relationship;
1 = Some Possible Relationship;
2 = Plausible Relation to Study Product

Serious Adverse Events (SAEs) were numerically more frequent in the Beriplex group (32.0%) compared to the FFP group (23.9%). AEs leading to premature discontinuation of treatment numbered 3 with FFP and zero in the Beriplex group. It should be noted that because FFP takes on average 7 times longer to infuse than Beriplex, the time during which the risk of any event, including an AE leading to premature discontinuation of study product, is proportionately greater with FFP, could confound the interpretation of the difference in subjects who discontinued CTM due to an AE. Overall, treatment-emergent adverse events (TEAEs, hereinafter referred to as AEs) were 1% greater in the FFP group 65.1% of subjects) than in the Beriplex group (64.1% of subjects). However, **severe and moderate AEs were notably more frequent in the Beriplex Group (20.4% vs 13.8% and 34.0% vs. 19.3%, respectively**. AEs considered by the investigator at least possibly related to study treatment were twice as frequent in the FFP group (23/109 = 21.1% for FFP vs. 10/103 = 9.7% for Beriplex). The open-label study design may possibly have biased some investigators' assignments of causality.

Thrombotic and Thromboembolic (TE) Events

Consolidated Table Adapted from Sponsor's Table 49 - Number of subjects with possible thromboembolic TEAEs (SMQ and SAB) by preferred term (ITT-S population) with grouping of related terms

Preferred Term[a]	**No. (%) of subjects**	**No. (%) of subjects**
	Beriplex (N = 103)	**Plasma (N = 109)**
Possible thromboembolic events according to SMQ		
Ischemic stroke/CVA/ Cerebrovascular disorder	3 (2.9)	2 (1.8)
Deep vein thrombosis /Venous thrombosis limb/ Thrombophlebitis	3 (2.9)	1 (0.9)
Thrombosis in device	1 (1.0)	1 (0.9)
Myocardial infarction/ Acute myocardial infarction	1 (1.0)[c]	2 (1.8)
Additional possible thromboembolic events according to SAB		
Myocardial ischemia	0	2 (1.8)
Total subjects with possible thromboembolic events	**8 (7.8)**[d]	**7 (6.4)**[e]

As shown in the above table, the overall incidence of thrombotic events appears to be roughly balanced between the 2 treatment groups with a 1.3% absolute excess in the Beriplex group. Among the subset of 9 subjects with TEEs considered SAEs, cerebrovascular accidents (CVA) were more frequent in the Beriplex group (3 vs. 1). There was one MI considered an SAE in each treatment group.

Volume or Fluid Overload/CHF/Pulmonary Edema/Pleural Effusion/Dyspnea/Edema Peripheral/Respiratory Failure AEs

Respiratory, thoracic, and mediastinal disorders were reported for 21/103 Beriplex subjects (20.4%) and for 16/109 FFP subjects (14.7%).

Cardiac disorders were reported for 15 subjects in each randomization group (14.6% for Beriplex and 13.8% for FFP).

Table of AEs Which May Relate to Possible Volume Overload – Study _3002

AE	Beriplex N of Subjects with AE	Beriplex % of Subjects with AE	FFP N of Subjects with AE	FFP % of Subjects with AE
Pleural Effusion	5	4.9	1	0.9
Respiratory Failure	3	2.9	2	1.8
Cardiac Failure Congestive	2	1.9	5	4.6
Pulmonary Edema	2	1.9	4	3.7
Dyspnea	2	1.9	2	2.8
Fluid Overload	0	0	4	3.7
Total	14 (not necessarily unique)		18 (not necessarily unique)	

Late Bleed Serious Adverse Events

Potential late bleeding events were reviewed by the blinded safety adjudication board (SAB). Late bleeding was defined by the DSMB as SAEs of bleeding occurring between 24 hours and 10 days after the start of study product administration. Five cases were reviewed and 3 confirmed as late bleeds: 2 in the Beriplex group and 1 in the plasma group.

Laboratory Safety Data

Hb and Hct changes at 3 and 24 hours were consistent with the study population experiencing major bleeding. Mean values were slightly lower at 3 hours for the plasma group (n = 109) compared to the Beriplex group (n = 103) (mean Hb change from baseline – 0.7 +/- 1.4 vs. 0.0 +/- 1.1 and mean Hct change from baseline -2.2 +/- 4.2 vs. 0.2+/- 3.2, respectively.

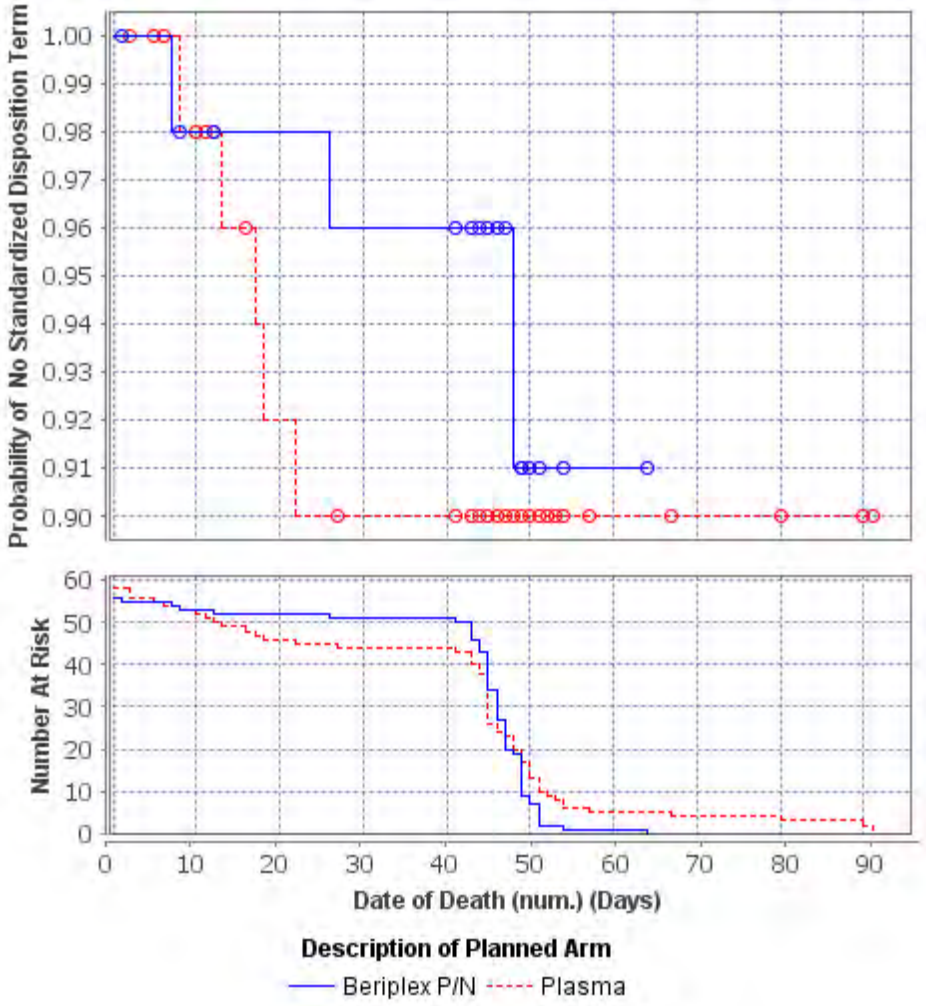
Study Title:

> 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.

The FDA JReview tool indicates that 10 AEs resulted in death as of the interim analysis of the surgery study included in the original submission.

The Kaplan-Meier Plots below of all subjects by randomization group in the interim analysis of surgery study _3003 reveal more subjects in the plasma group died through day 45 than was seen in the Beriplex PCC group (7 vs. 3) in bleeding study _3002. In both studies, deaths tended to occur earlier in the plasma randomization group. No additional deaths were identified in the safety updated included in amendment 01 to this BLA.

Kaplan-Meier Plots of All subjects by Randomized Treatment Group – Study _3003



In summary, Beriplex PCC has been shown to be non-inferior to plasma in terms of the hemostatic efficacy primary endpoint and most of the supportive secondary endpoints in the randomized, open-label, plasma controlled IND study BE1116_3002. Although the product was able to be administered a mean of 145.5 minutes more rapidly than the full protocol-determined FFP dose, this difference did not translate into a statistically significant advantage in terms of clinical efficacy. Thus, it has not been demonstrated that the reduced preparation time, lack of need for cross-matching, and faster administration time with Beriplex translates into any meaningful clinical advantage to patients over the use of plasma in terms of hemostatic outcome.

As regards safety in the target population for the indication being sought, data from study _3002 show an adverse trend for all-cause mortality through day 45. The imbalance occurred mainly between days 30 and 45 and thus may be less likely to be product related. Nevertheless, the potential safety finding of a numerical excess in mortality should be viewed in the context of

safety information from the other RCT involving Beriplex vs. plasma in the related indication for patients requiring urgent reversal of VKA anticoagulation for surgery, and for the class of PCC products. Interim safety data from ongoing surgery study BE1116_3003 showed a smaller total number of deaths with trend in the opposite direction favoring Beriplex. Totaling the deaths in both Beriplex IND RCTs, there is still a small numerical excess of deaths in the combined Beriplex randomization treatment groups (**n = 14 total deaths among Beriplex subjects and 12 total deaths among plasma subjects).** **----------**

----------(b)(4)----------

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Surprisingly, the number of possible thrombotic and thrombo-embolic events was roughly balanced between treatment groups in bleeding study _3002. There appears to be a non-statistically significant numerical excess of subjects in the plasma group for whom AEs consistent with volume overload were reported.

Conclusions and Discussion (Executive Summary)

- Beriplex has been shown in one adequate and well-controlled trial to be non-inferior to plasma in the urgent reversal of VKA anticoagulation in patients with major bleeds as defined in protocol BE1116_3002.

- There is a potential safety signal from RCT bleeding BE1116_3002 in terms of a non-statistically significant > 2-fold excess 45-day all-cause mortality. As well as being a safety endpoint, all-cause 45 mortality was a pre-specified efficacy endpoint. The imbalance in favor of plasma persisted after sequentially removing subjects whose deaths were attributed to (a) malignancy or (b) sepsis in an *unblinded* post-hoc analysis conducted by this reviewer. The imbalance in deaths became more pronounced in a reviewer-conducted *blinded* analysis of deaths potentially causally related to administration of the test products.

- The potential safety signal for increased mortality was not reflected in interim data from ongoing RCT BE1116_3003 in which subjects who require urgent reversal of VKA anticoagulation due to the need for urgent surgery or an invasive procedure are randomly treated with Beriplex or plasma in the same doses as were used in completed bleeding study BE1116_3003. The number of deaths (n = 11) in the ongoing surgery study was less than that in the completed bleeding study (n = 16), but the direction of the imbalance was reversed in favor of Beriplex. This imbalance persisted in *unblinded* reviewer conducted analyses removing sequentially deaths attributed by the investigator to (a) malignancy or (b) sepsis. The imbalance in favor of Beriplex became more pronounced in a reviewer-conducted *blinded* analysis of deaths potentially causally related to administration of the test products.

- Although it may be tempting to pool deaths across bleeding and surgery RCTs, we need to recognize that there may be factors which would lead to different risks of the test products in the 2 different settings. In the surgery setting, unlike in the bleeding setting, subjects have their INR corrected before surgery is undertaken and subjects may have different surgery-related outcomes due to the nature of the surgery and associated care by the anesthesiologist and other surgical team members. The teams managing bleeding subjects are likely to be primarily drawn from the medical rather than surgical specialties and the perturbations to the clotting system (consumption coagulopathy) as a result of non-surgical bleeding may be different from those in the surgical setting.

Brief Description of BLA Submission Contents

This submission for a lyophilized formulation from CSL Behring has been submitted electronically. It appears to be compliant with FDA guidance for electronic submission. The table of contents is navigable. The submission contains the following:

Files/Folders	Information
Files	(a) Cover letter, (b) Form 356h, (c) Form 3674

Folders/ Files	Module 1 for ICH CTD • Labeling (section 1.14) • Debarment Certification (item 16)* • User fee cover sheet - Form 3397 (item 18)* • Financial information (item 19) • Other Table of Contents (item 20)** Module 2 for ICH CTD • Summaries of Clinical Efficacy and Safety, Literature References • ICH CTD Module 2.3 Quality Overall Summary • ICH CTD Module 2.4 Nonclinical Overview • ICH CTD Module 2.6 Nonclinical Written and Tabulated Summaries Module 5 for ICH CTD • Clinical information • Statistical information • Case report tabulations • Case report forms

*Single document item or folder; **This is item 19 instead of item 20 in *Guidance for Industry: Providing Regulatory Submissions to the Center for Biologics Evaluation and Research (CBER) in Electronic Format — Biologics Marketing Applications*

The indication in the proposed package insert is:

"Beriplex®, Prothrombin Complex Concentrate (Human) is indicated for the urgent reversal of vitamin K antagonist (e.g., warfarin) therapy in patients with acute major bleeding."

Materials for Administrative/Labeling information as well as the Overviews and Summaries appear to contain the required information for review.

- **The proposed labeling (package insert) conforms to the PLR format under 21 CFR 201.57 (71 FR 3922-3997; January 24 2006), and has been provided in both annotated (in pdf) and clean (in Microsoft Word) versions. The SPL version has also been included.**

- **Financial certification and disclosure information (Form 3454 and 3455) have been submitted. The sponsor states that 3 investigators were "found to have received financial interests" for non-IND**

clinical study BE1116_3001 (Drs. Wolfgang Korte, Ingrid Pabinger-Fasching, and Claudia Spies). Dr. Korte received significant payment worth more than ---(b)(4)--- for lab research support. Dr. Pabinger-Fasching indicated that the amount of compensation for the conduct of study BE1116_3001 could be influenced by the outcome of the study and that the investigator received significant payment worth more than ---(b)(4)--- for being a coordinating investigator and as an unrestricted grant to fund research. Dr. Spies received significant payment worth more than ---(b)(4)--- for a clinical trial. The sponsor states that no other investigators of the above 4 studies received financial interests. The applicant certifies that there have been no arrangements where the value of the compensation could have been affected by the outcome of the study. A list of Investigators for studies BE1116_1001, BE1116_3001, BE1116_3002, BE1116_3003 is included in the Financial Information folder.

For study BE1116_3002, investigators are listed in the financial info section for the following sites:

046
077
502
035
033
029
002
101
021
003
311
043
402
103
039
013
051
052
053
018
038
501
104

072
015
050
040
030
009
316
404
314
601
304
011
027

Total sites for study BE1116_3002 for which investigators are listed in financial section: 36

For Beriplex study BE1116_3003, the following investigator sites are listed in the financial info section:

502
061
303
029
002
111
063
311
103
013
051
052
053
019
501
050
005
030
204
313
316
314
006

310

Total sites for study BE1116_3003 for which investigators are listed in financial section: 24

- **Under Module 1, section 1.9, Applicant requests full waiver for conducting pediatric studies.**

Reviewer Comment: I recommend the sponsor's full waiver request for pediatric studies be granted because it is unlikely that the requisite number of pediatric subjects could be enrolled in efficacy and safety studies in a reasonable timeframe of several years.

CMC and Nonclinical data (ICH CTD Modules 3 and 4) are being reviewed by:

ZE PENG (Committee Chair, Product Reviewer)
ROMAN DREWS (Consult Product Reviewer) and

LA NISSA BAKER-BROWN (Pharm/Tox Reviewer), respectively.

The clinical study reports (ICH CTD Module 5) are being reviewed by me as the Clinical Reviewer, and by the Statistical reviewer (JIANG HU), the Clinical Pharmacology Reviewer (IFTEKHAR MAHMOOD), the Clinical Pharmacology Reviewer (IFTEKHAR MAHMOOD), and the BiMo Reviewer (ANTHONY HAWKINS).

Clinical Information

The clinical material is located in Modules 2 (2.5, 2.7) and 5:

- Module 2 contains the Clinical Overview (2.5) and Clinical Summary (2.7)

- Module 5 consists of the following sections:

Volume(s)	Information
5.2	List of clinical studies
5.3.3	Code and Title of PK study report, if applicable.
5.3.5	Code and Title of Clinical study reports
5.3.7	Case report forms and case report tabulations
5.4	Literature references

LIST OF COMPLETED AND ONGOING CLINICAL STUDIES

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./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 reversal for bleeding	INR correction
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,	No/No/None	10/ Receiving VKA	Clinical Response,

Study No./ Phase/ IND?	Randomized?/Double-Blind?/Control	No./Type of Subjects	(Co-) Primary endpoint(s)
investigator - sponsored)		and INR $\geq$ 8 and urgent need for reversal	INR, factor levels

Ongoing Study in Subjects Requiring Surgery or Invasive Procedure:

Study No./Phase	Randomized?/Double-Blind?/IND?/Control	No./Type of Subjects	(Co-) Primary endpoint(s)
BE1116_3003	Yes/No/Yes/Plasma	114 as of data cutoff date; 56 Beriplex 58 Plasma /VKA, elevated INR, and need for urgent surgery or invasive procedure	INR correction, Hemostatic Efficacy

The objectives and design of the pivotal clinical study for the bleeding indication was judged during the IND stage to be adequate to potentially support licensure of the product for the requested indication.

Characteristics of Clinical Trials for which Data are Submitted:

Sponsor's Table 1 - Efficacy Variables Analyzed in Beriplex Studies
Studies 3002, 3001, 201KO, Preston 2002, Evans 2001

Study Assessment	Pivotal Trial 3002a (N=202)	3001 (n=43)	201KO (N=30)	Preston 2002 (N=42)	Evans 2001 (N=10)
Blinded Endpoint Adjudication Board (EAB) assessment of hemostatic efficacy	X	–	–	–	–
Unblinded investigator or treating physician assessment of clinical efficacy and/or judgment of adequacy	X	X	X	–	X
INR assessment	X	X	–	X	X
Quick's value assessment – –	–	–	X	–	–
IVR and response for Factors II, VII, X X IX, X, and Proteins C and S	X	X	Xb	–	–

Sponsor's Table 1 - Efficacy Variables Analyzed in Beriplex Studies
Studies 3002, 3001, 201KO, Preston 2002, Evans 2001

	Pivotal Trial	201KO	Preston	Evans

a Study 3002 included 104 plasma-treated subjects in the ITT-E population.
b Study 201KO did not assess Protein S.
INR = international normalized ratio; IVR = in vivo recovery
N = Number of subjects treated with study product.

Pivotal Protocol ID for Indication Being Sought: BE1116_3002

Protocol Name:

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

Pivotal Trial: YES

Investigator(s):

Coordinating Investigator: Ravindra Sarode, MD, U. Texas Southwest Medical Center, Dallas, TX

Site(s): Multinational

SUMMARY OF PROTOCOL BE1116_ 3002

Objectives:

Primary:

To compare the hemostatic efficacy of Beriplex® *PIN* 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 Objective:

To compare the efficacy of Beriplex® P*I*N and plasma in rapidly reducing the international normalized ratio (INR, i.e. INR $\leq$ 1.3) values between the 2 treatment groups at 30 minutes after end of infusion.

Secondary Objectives:

• To compare the plasma levels of coagulation factors II, VII, IX, and X, protein C and S between the 2 treatment groups,

• To document the time from start of infusion until INR correction for both treatment groups,

• To document the time from randomization until INR correction for both treatment groups,

• To compare the use of non-study-prescribed blood products and/or hemostatic agents in both treatment groups,

• All-cause mortality at 45 days after treatment,

• To determine the safety and tolerability of Beriplex® *PIN* compared to that of plasma.

Other [Tertiary, Exploratory] Objectives

• To evaluate the neurological outcome as assessed by modified Rankin Scale (mRS) for intracranial hemorrhage (ICH) subjects at 24 hours, time of hospital discharge, and at day 45.

• To compare INR values between the 2 treatment groups at 30 minutes from the start of infusion

• To compare the investigator's assessment of hemostatic efficacy between the 2 treatment groups.

Eligibility Criteria:

Inclusion Criteria

• Male and female subjects $\geq$ 18 years,

• Subjects who have received anticoagulation therapy (warfarin, acenocoumarol or phenprocoumon)
• Subjects who have acute major bleeding, defined as one of the following:

o Life-threatening or potentially life-threatening,
o Acute bleeding associated with a fall in Hb level ≥ *2g/dL,*
o 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,
• Acute trauma for which reversal of vitamin K antagonists alone would not be expected to control the acute bleeding event,
• For patients with ICH:

o Glasgow coma score <7
o Intracerebral hematoma volume> 30cc as assessed by *ABC/2*1
o For subdural hematomas: maximum thickness > 10 mm, midline shift > 5 mm,
o For subarachnoid hemorrhage: any evidence of hydrocephalus,
o Infratentorial ICH location,
o Epidural hematomas,
o Intraventricular extension of hemorrhage,
o Modified Rankin score of >3 prior to ICH,

• 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,
• Known history of antiphospholipid antibody syndrome or lupus anticoagulant antibodies,
• Suspected or confirmed sepsis at time of enrollment,
• Administration of whole blood, plasma, plasma fractions or platelets within 2 weeks prior to inclusion into the study
o Note: Administration of packed red blood cells is not an exclusion criterion,
• Large blood vessel rupture (e.g. in advanced cancer patient),
• Pre-existing progressive fatal disease with a life expectancy of

less than 2 months,
• Known inhibitors to coagulation factors II, VII, IX, or X; or hereditary protein C or protein S deficiency; or heparin induced, type II thrombocytopenia,
• Treatment with any other investigational medicinal product within 30 days prior to inclusion into the study,
• Presence or history of hypersensitivity to components of the study medication,
• Pregnant or breast-feeding women,
• 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.

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

Planned Number of Centers: 30 in US and ~ 30 international.

Intended Study duration for each subject: 90 day f/u visit (for viral studies).

Dose Escalation Scheme/Treatment Plan:

Beriplex P.N 500 is to be dosed as follows:

Baseline INR	Beriplex P/N 500 Dosage (IU FIX per kg)
2 - < 4	25
4 - 6	35
>6	50

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

FFP will be dosed as follows:

Baseline INR	FFP Dosage (mL per kg)
2 - < 4	10
4 - 6	12
>6	15

Note that, depending on baseline INR, the dose of Beriplex varies over a 2-fold range, whereas the FFP dose varies by 50%.

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

The maximum rate of administration of Beriplex according to the protocol was 3 IU/kg/min (based on Factor IX content).

No minimum or maximum rate of administration of plasma was specified in the protocol.

The protocol required all subjects to receive slow IV vitamin K_1. The dose of vitamin K was based on local clinical practice. Adherence to ACCP guidelines was recommended.

PRIMARY EFFICACY VARIABLE

The primary efficacy variable was the hemostatic efficacy with respect to the adequacy of stopping an ongoing major bleed. The primary efficacy endpoint was assessed by the blinded Independent Endpoint Adjudication Board (EAB) implemented by the data and safety monitoring board (DSMB) as excellent, good, or poor/none, based on pre-specified definitions. 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)."

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. 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.

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
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 < 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 < 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. **.* 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 refer 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).

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.

Pages 45-51 and 67-68 of redline-strikeout version of protocol from IND amendment 46 contained the revised primary endpoint hemostatic efficacy definitions. See the section further below regarding sponsor correspondence in response to FDA request in regard to the primary hemostatic efficacy endpoint definitions.

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 VARIABLE

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

If the INR at 30 min +/- 15 min post infusion is missing, the subject was counted as having "no rapid decrease" (ITT-E analysis).

If the INR at 30 min +/- 15 min post infusion is $\leq$ 1.3, but additional Beriplex, plasma, or other coagulation factor products were used after the start of the infusion and prior to the 30 min post-end-of-infusion blood draw, then the subject was counted as having "no rapid decrease."

If the baseline INR was missing, the variable "rapid decrease of INR" was set to:

- "No rapid decrease" if the INR measurement at 30 min was > 1.3.
- Missing (not evaluable) if the INR at 30 min is $\leq$ 1.3.

SECONDARY EFFICACY VARIABLES

The following secondary efficacy endpoint was added in amendment 3:

• 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:

Table Contrasting 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	Cessation of bleeding > 1 and ≤ 4 hrs after end of infusion and no additional coagulation intervention	Cessation of bleeding > 4 hrs after end of infusion and no additional coagulation intervention
Secondary Rating of Hemostatic Efficacy	Cessation of bleeding ≤ 3 hrs after start of infusion and no additional coagulation intervention	Cessation of bleeding > 3 and ≤ 6 hrs after start of infusion and no additional coagulation intervention	Cessation of bleeding > 6 hrs after start of infusion and/or additional coagulation intervention[1]

[1] e.g., plasma, whole blood (WB), PRBC, 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,

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

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

• Transfusion of red blood cells.

The following endpoint was moved from secondary to "other" by protocol amendment:

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

Reviewer Note: During the IND phase, it was noted that the large number of secondary and additional efficacy analyses seems more in keeping with a phase 2 rather than a "phase 3b) protocol. FDA communicated the following to the sponsor during the IND phase:

In view of the large number (8) of secondary endpoints and the lack of provision for correction for multiplicity of endpoints in their statistical analyses, we may discourage you from including the results of these analyses, and/or their p values, except where it may impact potential product safety, in the package insert for the product.

Other Efficacy Variables

- Proportion of subjects who have a decreased INR (i.e. INR $\leq$ 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 Day 45

The following additional "other" (exploratory) endpoints were added to the final SAP but not to the study protocol:

- Responder Analysis among subjects with visible bleeding (SAP page 30/59).
- Healthcare Utilization
  - ER time
  - Inpatient time
  - Critical Care unit/ICU time
  - General Ward time

The following analysis was added at the request of the DSMB but was not included in the protocol or final SAP:

- Re-hospitalization due to study drug related complications within 45/90 days.

Safety Variables

- Adverse events AEs
- Vital signs (blood pressure, pulse rate, and respiration rate)
- Physical examination
- Hematology (hemoglobin (Hb), hematocrit (Hct), and platelet count)
- Transfusion requirement
- Thrombogenicity (lab markers, including F1+2, TAT, D—Dimers) and clinical signs and symptoms)
- Viral safety (viral Antibody titers before and after treatment). HBsAg, antibodies to HIV-1&2, HCV, HAV (IgG and IgM), parvovirus B19 by IgM. -(b)(4)- for B19V, HACV, HBV, HCV, and HIV-1.
- For ICH subjects: Modified Rankin Score at day 45, Glascow Coma Score (GCS)
- For subarachnoid hemorrhage (SAH) subjects: Hunt and Hess grade

RANDOMIZATION

Biased coin minimization method, using validated software was utilized centrally using a 24-hour randomization service center. Randomization was stratified according to the following 5 bleeding sites:

- Gastrointestinal bleeding
- Visible bleeding (such as hematuria or epistaxis)
- Intracranial hemorrhage
- Muscular/skeletal bleeding
- All other non-visible bleeding

The biased coin minimization method sought to approach balance within each center (presumably in the number of subjects in each treatment group) and to achieve balance across treatment groups in the distribution of bleeding types. It was modified after amendment 3 to include a procedure for minimizing possible imbalance in the number of subjects with a missing redefined primary hemostatic endpoint.

Monitoring:

Subjects are assessed at time points indicated in the flow sheet on p 20 of the protocol. Assessments are at various times on day 1 and also on days 2, 20 and 45.

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	
Day 45 (43-51 days after start of infusion)		Viral Assessment	

Treatment Modifications:

There were no specific subject stopping criteria in the original protocol, but study stopping procedures are discussed on p 31 of the protocol.

There are no specific study stopping criteria, but study stopping procedures are discussed on p 28 of the protocol.

Statistical Analytic Plan:

PRIMARY ENDPOINT / CONFIRMATORY ANALYSIS:

The primary efficacy analysis in this study will be a test for the Non-inferiority of the effect of Beriplex® P/N 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) at 24 hours after the start of the infusion. Originally, a 1-sided, 2-sample, Miettinen/Nurminen, Chi-square test will be used to test for noninferiority, using the following hypotheses with a type I error of alpha = 0.025 was to be used:

Ho: p2 $-P_1 \geq$ delta,

H1: $p_2 - p_1 <$ delta,

where P_1 and P_2 represent the binary hemostatic efficacy data under Beriplex® *PIN* or plasma, respectively.

The primary endpoint was changed by amendment to read as follows: The primary endpoint is hemostatic efficacy, assessed for the time from start of infusion of Beriplex P/N or plasma until 24 hours after the start of the infusion. The primary analysis will use the method of Farrington and Manning of the C.I. for the difference in the proportions of subjects with a rating of effective hemostasis (excellent or good) in the 2 treatment groups, where p_1 is that proportion in the Beriplex group and p_2 is that proportion in the FFP group.

Null Hypothesis: $p_1 - p_2 \leq$ delta

Alternative Hypothesis: $p_1 - p_2 >$ delta

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

According to the protocol and statistical analysis plan (SAP), Beriplex® P/N can 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 Beriplex® *PIN* compared to that of plasma on each of the two primary 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 ($p_1 = 0.90$) will have a score of good or excellent. The acceptable delta will be 0.10 (10%). The power to show non-inferiority with the above assumptions will be greater than 80% for 2 treatment groups of 80. Although the primary analysis will be done for the ITT population, this sample size will be chosen for the per protocol population in order to have enough power to show noninferiority also in the secondary 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).

A secondary analysis of the primary endpoint was to be conducted using the investigators' assessments, if there were at least one divergent for the primary endpoint between the investigator and the DSMB. As per the protocol and SAP, The assessment from the DSMB was used as the primary assessment.

CO-PRIMARY ENDPOINT / CONFIRMATORY ANALYSIS:

The proportion of subjects with a rapid decrease of INR, (i.e., INR $\leq$ 1.3 at 30 minutes after end of Beriplex® P/N or plasma infusion), Was also examined as a co-primary endpoint for non-inferiority in the Beriplex® P/N group compared to the plasma group. The test, hypotheses, maximum type I error, and non-inferiority margin were identical to the method described for hemostatic efficacy.

"For the primary and co-primary endpoints, a combination of hierarchical and closed testing procedures was used…Therefore, no correction for multiplicity of testing was required." **Reviewer Comment: FDA agreed that since non-inferiority needed to be shown for both the primary hemostatic and co-primary efficacy endpoints in order to claim non-inferiority to plasma that no adjustment of the p values of the primary and co-primary endpoints for multiplicity was required.**

Non-inferiority and superiority

The protocol and SAP stated that Beriplex®P/N can be successfully claimed non-inferior to plasma if non-inferiority were shown for both the primary and co-primary endpoints in the ITT population.

It stated if non-inferiority were shown, an additional test would be performed for the superiority of the effect of Beriplex® P/N compared to that of plasma on each of the two primary endpoints.

INTERIM ANALYSIS: A descriptive interim analysis of efficacy and safety was originally to have been performed when 50% of planned number of subjects completed the study, but the sponsor elected by protocol amendment not to conduct the interim analysis.

SECONDARY ENDPOINTS

The secondary endpoints were analyzed descriptively. No hierarchical testing or correction of p values for multiplicity of testing was applied by the sponsor to statistical tests of secondary endpoints.

CHANGES TO THE PLANNED ANALYSES MADE BY THE SPONSOR

(See also Protocol Amendments section below.)

The sponsor renamed 3 of the analysis populations for the study:

- The modified ITT or "protocol defined" ITT population in the protocol was renamed the ITT population. The ITT population was revised to comprise all subjects who were (1) *eligible for the study* and had (2) signed informed consent and were randomized to 1 of the 2 treatment groups regardless of whether the subjects received study product.
- The ITT population in the protocol was renamed the ITT-E population.
- The safety population in the protocol was renamed the ITT-S population.

The sponsor did not follow the procedure required by the protocol for blinded assignment of subjects to the various analysis populations (ITT, ITT-E, PP, and ITT-S). The protocol stated that "The determination of each subject's membership (yes/no) in each of the study populations will be accomplished during the Blinded Data Review Meeting (BDRM), before database lock and before the unblinding of the primary/secondary efficacy ratings. The assignments will be documented in the BDRM meeting minutes." Instead, as documented on p 74 of 4514 of the study report (section 9.8.2.6), "The determination of the subject's membership in the ITT-E population was partially done after the unblinding of the primary/secondary efficacy ratings since the corresponding information (eligibility of subjects, efficacy rating of 'poor/none' due to missing information for subjects with visible or non-visible muscular/skeletal bleeding enrolled before Amendment 3) was not available until the Clinical Research Organization managing the adjudication data provided the unblinded assessments to the Clinical Research Organization managing the clinical database."

The following changes not reflected in the protocol were made "post-hoc" and incorporated into the final statistical analysis plan (SAP) dated 26 Jan 2011:

· According to Section 9.4.1.4.1 of the protocol, the proportion of subjects with mRS < and ≥ 5 at Day 45 were to be compared between treatment arms. This was changed by request of FDA to mRS < and ≥ 4 at Day 45. The mRS assessment was only applicable for subjects with ICH (there were only few ICH subjects enrolled), and this objective was only changed after Amendment 3.0.

· A subgroup analysis was added by start time of TEAE with respect to the start of infusion (previously only with respect to the end of infusion) for a final set of 4 subgroups described as: TEAEs that began during or within 24 hours after the start or end of infusion; TEAEs that began during or within 72 hours after the start or end of infusion. [It is unclear why the sponsor performed subgroup analyses of AEs which started in relation to the start time of the infusion in addition to analyzing AEs which began during or within fixed intervals after the end of test product infusion.]

The following changes were made to the sponsor's analysis methodologies without either protocol amendment or inclusion in the final statistical analysis plan:

1. The Intent-to-Treat (ITT) population was re-defined as noted above.

2. The population membership determination for each subject was not determined during the blinded data review meeting as required by the protocol.

3. All planned AE subgroup analyses were performed independently of the numbers of subjects included (rather than only if at least 20% of each treatment group were included in each subgroup).

4. Definition of primary efficacy variable:

Addition of: In case that a subject received any additional plasma, blood products or coagulation factor products (excluding PRBCs and platelets) within 24 hours after start of infusion of study product, the rating of hemostatic efficacy was set to 'poor/none' regardless of the rating of the EAB.

5. INR measurement at 30 minutes after start of infusion:
Original: If the INR measurement at the 30-minute time point post infusion is missing or was not obtained within the permitted 15 minute window following the 30-minute time point, the subject will be counted as having "no rapid decrease" (ITT-E population).
Revised: Was also performed for the ITT and PP populations.

6. INR ≤ 1.3 at 30 minutes after start of infusion:
Change: **In the calculation of INR ≤ 1.3 at the 30-minute time point after start of infusion, if** a subject's INR value was missing, or **the assessment time was more than 45 minutes prior to start of infusion** or if the assessment time was more than 15 minutes after the scheduled 30 minutes post infusion, **the subject was counted as having "no rapid decrease" of INR.**

7. Additional vital sign measurements were added at 1 and 4 hours after the end of infusion for subjects with visible or non-visible muscular/skeletal bleeding.

8. The 2 pre-planned robustness analyses of the primary hemostatic efficacy endpoint were changed as follows:

> *Original:* The following sensitivity analyses will be performed to assess the robustness of the primary rating of hemostatic efficacy for subjects with non-visible muscular/skeletal bleeding or visible bleeding:
> **Hemostatic efficacy 4 hours after the end of infusion:**
> The primary analysis will be repeated for the specified subgroup using the hemostatic efficacy assessment at 4 hours after the end of infusion, as recorded in the CRF, as the sole determinant of the hemostatic efficacy rating (see Note below).
> **Hemostatic efficacy 1 hour after the end of infusion for subjects with prolonged infusions:**
> The primary analysis will be repeated for the specified subgroup using the hemostatic efficacy rating at 1 hour after the end of infusion, as recorded in the CRF, as the sole determinant of the hemostatic efficacy rating (see Note below). For subjects who do not have an assessment recorded within the allowed time window for the 1 hour assessment, the missing assessment will be imputed by using the assessment at 4 hours after the end of infusion unless the infusion was prolonged for lack of

tolerability or an intervention for lack of efficacy occurred or the 4 hour assessment is also missing, in which cases, the hemostatic efficacy rating at 1 hour after the end of the infusion shall be set to “noneffective” (poor/none).

Revised: Two sensitivity analyses will be performed to assess the robustness of the primary rating of hemostatic efficacy; each analysis is a repeat of the primary analysis of hemostatic efficacy in each of the ITT, ITT-E, and PP populations, keeping the EAB primary rating of hemostatic efficacy for all subjects except:

Analysis (1): for subjects in the non-visible muscular/skeletal bleeding group and subjects in the visible bleeding group, the EAB assessment is replaced with the 4-hour CRF assessment;

Analysis (2): for subjects in the non-visible muscular/skeletal bleeding group and subjects in the visible bleeding group, the EAB assessment is replaced with the 1-hour CRF assessment. For subjects who do not have an assessment recorded within the allowed time window for the 1 hour assessment, the missing assessment will be imputed by using the assessment at 4 hours after the end of infusion unless the infusion was prolonged for lack of tolerability or an intervention for lack of efficacy occurred or the 4-hour assessment is also missing, in which cases the hemostatic efficacy rating at 1-hour after the end of the infusion shall be set to “non-effective” (poor/none).

9. Definition of effective hemostasis – primary rating:
The following was added to the definition of effective: hemostasis was also defined as effective if "No change" is checked for "Signs of bleeding" provided that "Improved" was checked at the 1-hour assessment and the conditions for "Pain" and "Swelling" are fulfilled.

10. Co-primary efficacy analysis:
Addition: Sensitivity analyses (overall and by the pre-defined subgroups) will be performed for the co-primary efficacy variable where a subject will be evaluated as having no rapid decrease of the INR in case that he/she received any additional plasma, blood

products, or coagulation factor products (excluding PRBCs and platelets) within 24 hours after start of infusion of study product.

PROTOCOL AMENDMENTS – (Study _3002)

The original protocol, which included both bleeding subjects and subjects requiring urgent surgery or an invasive procedure requiring urgent reversal of VKA anticoagulation was split at FDA request into 2 separate studies ---(b)(4)--- (bleeding study _3002 and surgery/invasive procedure study _3003).

Amendment 1 to study _3002 dated 13 May 2008 included the following changes:

· The non-inferiority margin for the primary non-inferiority analysis was decreased from originally 0.15 to 0.10 as per a request of FDA.

· The sample size had to be recalculated to reflect this revision of the non-inferiority margin (increased from 160 to 176 subjects; The number of planned study sites was increased from 50 to 60 sites.

· A uniform transfusion trigger was implemented at FDA request to enhance evaluability of hemostatic efficacy for non-visible bleeding. Transfusions now had to be initiated at Hb levels $\leq 8 \pm 1$ g/dL.

· The co-primary objective and the co-primary efficacy variable were modified at FDA request: the time window for evaluation of INR decrease was revised from originally 30 minutes after start of infusion to 30 minutes after end of infusion.

· The related secondary objective and corresponding secondary efficacy variable were changed to compare the INR values between the 2 treatment groups at 30 minutes from the start of infusion,
· An additional secondary objective and secondary efficacy variable were added to include the evaluation of neurological outcomes (mRS at Day 45) as a measure of efficacy in the ICH subset of subjects,

· The exclusion criteria for ICH subjects were modified to exclude severe ICH bleeding subjects who would be unlikely to benefit from either treatment with respect to the neurological outcome,

· The dosage regimen was specified more precisely to document accurate dosage per body weight.

Amendment 2 to study _3002 dated 29 Sept 2008 included the following changes:

· Inclusion criteria were modified to include a definition for the term "acute major bleeding" using the following new inclusion criterion,

— Subjects who have acute major bleeding, defined as 1 of the following:

- ♦ Life-threatening or potentially life-threatening
- ♦ Acute bleeding associated with a fall in Hb level ≥ 2 g/dL
- ♦ Bleeding requiring blood product transfusions (blood products include plasma, red blood cells and other coagulation factor products).

· Exclusion criteria 1-5 were modified and summarized to exclusion criteria 1-4.

· Two exclusion criteria were newly added:

— Known history of antiphospholipid antibody syndrome or lupus anticoagulant antibodies,
— Suspected or confirmed sepsis at time of enrolment.

· The required concomitant vitamin K was specified to vitamin K1, and adherence to the ACCP guidelines was recommended. A note was added that vitamin K1 was provided to sites in countries were the product was not marketed.

· An addition was made to the table defining the rating criteria for hemostatic efficacy ("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 ICH subjects, the GCS was to be additionally to be documented at Day 45.

Amendment 3 dated 15 Oct 2009 included the following changes:

· Based on an FDA request, the primary endpoint was modified for those subjects with visible bleeding or non-visible muscular/skeletal bleeding. "None of the parties directly involved in the study (CSL Behring as sponsor, investigators, boards, and committees) suggested or drove that decision… No formal or informal interim analysis and no data reviews had been performed for the ongoing or any related studies. Thus the decision on the change in endpoints is not based on newly gathered or accumulated data from current studies conducted by CSL Behring." This change comprised the timing of the assessment of the bleeding status as basis for the rating of the hemostatic efficacy from 3 and 6 hours after start of infusion to 1 and 4 hours after end of infusion.

· The modification of the primary endpoint required an adaptation of the sample size (increase from 176 to 184 subjects. The number of planned study sites was increased from 60 to 80 sites.

· If the proportion of subjects randomized before Amendment 3.0 with a missing new primary endpoint would have been unbalanced between the 2 treatments, the randomization scheme (balanced coin design) had to be modified. This was to be done by reducing the increment of the balanced coin in the respective arm by the number of subjects with a missing value for the primary endpoint.

· The primary efficacy endpoint was originally to be assessed by the DSMB. The DSMB was replaced by a blinded, independent EAB. Remaining tasks of the DSMB were specified.

· The primary efficacy analysis for non-inferiority was modified (Protocol Section 9.8.2.2).

· An initially planned descriptive interim analysis on 50% of the subjects was skipped.

· A secondary objective and the corresponding secondary efficacy variable were added to include the evaluation of hemostatic efficacy according to the

previous primary endpoint definition in the protocol. The additional secondary objective was:

— To compare the hemostatic efficacy of Beriplex and plasma for visible and muscular/skeletal non-visible bleeding between the 2 treatment groups at 3 and 6 hours from start of infusion.

· A new secondary objective and the corresponding efficacy variable were added at FDA request regarding PRBC transfusions. The additional objective was:

— To compare the total number of PRBC transfusions and the proportion of subjects with 1 or more PRBC transfusions.

· "Other objectives" were added to the protocol; including 2 previous secondary objectives and 1 new "other" objective. Previous secondary objectives which became "other objectives" were:

— To compare INR values between the 2 treatment groups at 30 minutes from the start of
infusion,
— To evaluate the neurological outcome as assessed by mRS for ICH subjects at Day 45.

The additional "other" objective was:

— To compare investigator assessment of hemostatic efficacy.

· The following exclusion criterion was added to the protocol to exclude heparin use:

— Use for unfractionated or low molecular weight heparin use from 24 hours prior to enrollment or expected need 24 hours after start of infusion.

· Regarding the subjects' informed consent, it was clarified that in emergency situations, subjects might have been enrolled under an abbreviated informed consent as allowed by the IEC/IRB in countries where such a procedure was permitted. In this case, the subject had to be re-consented and to sign the applicable informed consent form as soon as possible to continue participation in the trial.

· The dose calculation for Beriplex and plasma was modified; the INR closest to start of infusion (up to 3 hours before start of infusion) had to be used for dose calculation.

· Regarding concomitant vitamin K1 injections, it was specified that if vitamin K1 had been administered for the current bleeding event prior to enrollment, an additional dose was not needed unless indicated by local clinical practice or the above guidelines.

· The duration of follow-up for virus safety was increased from 45 days to 90 days; an additional virus safety assessment at Day 90 was added to the study schedule.

· Additional time points at 1 and 4 hours after start of the infusion were added to assess the following: hemostatic efficacy, vital signs, concomitant medication, AEs. mRS had to be additionally assessed at the discharge from hospital.

· Additional criteria were added for excluding subjects from the PP population (Protocol Section 9.8.2.5).

RESULTS – DEMOGRAPHICS AND SUBJECT DISPOSITION (Study _3002)

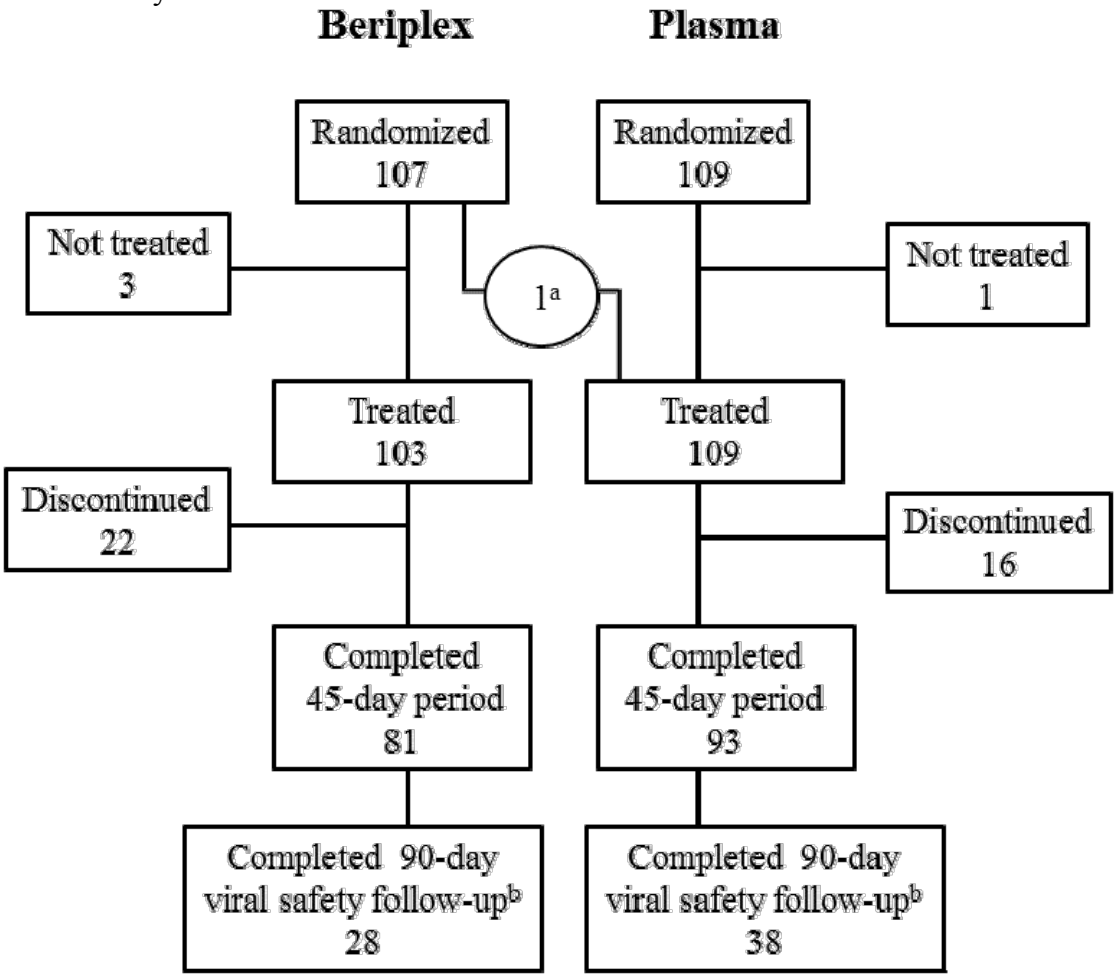
Subject Disposition in Study _3002 and Analysis Populations

Sponsor's Table 10 – Subject disposition by study population

Population	**No. (%) of subjects**		
	Beriplex	**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.

Sponsor's Figure 1: Summary of Subject Disposition (ITT Population)



[a] Subject 314011 was randomized to Beriplex but treated with plasma.
[b] Only added subsequent to Amendment 3.0.

Results – Demographics (Study _3002)

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

Parameter	Beriplex (N = 98)	Plasma (N = 104)
Males (N)	50	51
Females (N)	48	53
Mean Age (years)	69.8	69.8
Age < 65 (N (%))	33 (33.7)	31 (29.8)
Age 65 to < 75 (N (%))	24 (24.5)	29 (27.9)
Age >= 75 (N (%))	41 (41.8)	44 (42.3)
White (N)	93	88
Non-White (N (%))	5 (5.1)	16 (15.4)
European Site	30	32
U.S. Site	68	72
Weight kg (Mean,	78.7 (45.2-200.5)	78.4 (46.4 – 142.3)

Parameter	Beriplex (N = 98)	Plasma (N = 104)
Range)		
BMI (Mean (SD))	27.7 (8.5)	27.6 (6.5)

PROTOCOL VIOLATIONS/DEVIATIONS (Study _3002)

Major protocol violations were defined in the protocol and SAP, were adjudicated at a blinded data review meeting, and required exclusion from the per-protocol (PP) population. Seven Beriplex group subjects and 8 plasma group subjects had major protocol violations.

Sponsor's Table 9 – Major Protocol Deviations (ITT Population)

Protocol deviation	No. of subjects (Subject ID)	
	Beriplex (N = 107)	Plasma (N = 109)
Subjects with a major protocol deviation[a]	**7**	**8**
Missing key primary efficacy variables	**4** (018002, 029001[b], 052009[b], 601001)	**3** (018008, 027001, 030006)
Subject received < 70% of planned amount of study product[c]	**0**	**4** (002006, 002016, 030022, 101010)
Pre-infusion INR < 2	**2** (030020, 038004)	**1** (013005)
Subject received treatment different from randomization	**1** (314011)	**0**

[a] As determined at the blinded data review meeting prior to database lock. Subjects could have more than 1 deviation.
[b] Subjects 029001 and 052009 were excluded from both the ITT-E and the PP populations (non-visible muscular/skeletal bleeding enrolled before Amendment 3.0).
[c] Except if a consequence of intolerance to study product, AE or medical condition.
INR = international normalized ratio; ITT = intention-to-treat; N = total number of subjects. Source: Table 14.1.1-4a, Listing 16.2.2-1

Section 10.2.2 of the study report states in part "The majority of minor protocol deviations were related to visits performed outside the visit window or not done; blood samples not obtained; and Beriplex, plasma, or vitamin K dosing irregularities."

Four Beriplex group and 2 plasma group subjects did not receive vitamin K during the study as required by the protocol. Eight Beriplex group and 3 plasma group subjects received vitamin K only by a route other than IV.

Five Beriplex group subjects and one plasma group subject received a Beriplex dose based on an INR obtained > 3 hours prior to the start of investigational medicinal product (IMP) infusion. Four additional Beriplex

subjects had their Beriplex dose calculated incorrectly (Subjects 018005, 030021, 101001, and 314013).

"Other deviations in plasma administration (greater than ± 10%) commonly resulted from the challenges of administering a product supplied in non-standardized volumes and from decisions by investigators to prematurely discontinue administration: local standard of practice/pack size (9 subjects); AE/concomitant condition (6 subjects); other, including insufficient supply (6 subjects); decision of clinical care team (5 subjects); or miscalculation (2 subjects)."

Thirteen Beriplex group subjects had a faster Beriplex infusion rate than permitted by the protocol, but the actual maximum infusion rates did not exceed 120% of the maximum recommended rate.

RESULTS – EFFICACY (Study _3002)

Note:

With regard to the definitions of the primary rating of hemostatic efficacy:

"First, during the conduct of the study, the FDA requested … a modification to the primary endpoint for subjects with visible bleeding or non-visible muscular/skeletal bleeding and in response, CSLB submitted the revised protocol dated 15 October 2009 (Amendment 3.0). The pre-specified time-points for measurements were modified from the original 3 and 6 hours after the start of infusion to 1 and 4 hours after the end of infusion. The modification in the timing of the primary rating of hemostatic efficacy was introduced to provide primary efficacy data that represents the activity of the complete dose of study product (and discounts rapidity of factor replacement from the efficacy evaluation). The 2-hour difference in timing of evaluation was chosen to maximize consistency among subjects enrolled before and after Amendment 3.0 (assuming approximately a 2-hour infusion time for administration of plasma). The originally specified endpoint, relative to the start of infusion, was retained as a secondary rating of hemostatic efficacy… In addition, after the study conduct was completed, the FDA requested … that the Statistical Analysis Plan (SAP) be modified and that all subjects be assigned a "poor/none" rating for hemostatic efficacy if they received non-study related plasma, whole blood, or coagulation factor products within 24 hours of the start of infusion, regardless of investigator or EAB assessment ([Sponsor's] Table 2 does not include this modification)."

[-source: BLA section 2.7.3]

"The primary analysis of hemostatic efficacy was via calculation of a 2-sided 95% confidence interval (CI), using the method of Farrington and Manning, for the difference (Beriplex minus plasma) in the proportions of subjects with a rating of effective hemostasis. The non-inferiority margin (δ) was −0.10. If the lower limit of the 95% CI was >–0.10, then the null-hypothesis was rejected and it was concluded that Beriplex was non-inferior to plasma. A claim of non-inferiority required rejection of the null hypothesis in the ITT-E population ([BLA] Section 2.7.3.1.3). If noninferiority was shown, Beriplex was also tested for superiority compared to plasma. Superiority was to be concluded if the lower limit of the 2-sided 95% CI using the method of Farrington and Manning exceeded 0 for the ITT-E population."

[-source: BLA section 2.7.3, p 23]

Sponsor's Table 6: Primary endpoint: Proportion of subjects with hemostasis rated effective (ITT-E population) (Study BE1116_3002)

Rated Effective[a] n/N (%)		Difference (%): Beriplex – Plasma (95% CI for difference)[b]
Beriplex	**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] Beriplex non-inferior to plasma: lower limit of the 95% CI exceeds –10%; Beriplex 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.
Source: Module 5.3.5.1.1.2, Table 14.2.1-1.1b

Because the lower bound of the 95% confidence interval was -5.8, meaning that the trial results are consistent with a 2.5% probability that Beriplex may be inferior to Plasma in the proportion of subjects rated effective for the hemostatic efficacy co-primary endpoint by an absolute margin of 5.8% or greater, the statistical test for superiority of Beriplex over Plasma failed.

One of 4 sensitivity analyses of the primary hemostatic efficacy endpoint conducted by the sponsor failed to demonstrate non-inferiority of Beriplex 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 Beriplex than for FFP in each of the 4 sensitivity analyses.

Surrogate Endpoint Measure – Co-Primary Efficacy Endpoint

"A co-primary endpoint, the proportion of subjects with a reduction of INR to ≤1.3 at 30 minutes after the end of infusion, was tested for non-inferiority of Beriplex vs. plasma if non-inferiority had been demonstrated for the primary [hemostatic] endpoint. The test, hypotheses, and non-inferiority margin were identical to the method described for hemostatic efficacy. If non-inferiority was shown, Beriplex was also to be tested for superiority compared to plasma. The study was considered a success if the non-inferiority of Beriplex to plasma was demonstrated for both the primary and coprimary endpoint in the ITT-E population. Because a pre-specified hierarchy of hypothesis testing was used, no correction for multiplicity of testing was necessary."

[-source: BLA section 2.7.3, p 23]

"The INR provides a robust, quantitative, and objective measure of VKA-related factor deficiencies. However, a liability of the INR as a clinical study endpoint is that it is disproportionately sensitive to deficiencies in some factor levels such as Factors II, VII, and X as compared to Factor IX. Nevertheless, it provides a method for evaluating multiple vitamin K dependent factor deficiencies using a single assay. Each of the clinical studies of Beriplex included the INR (or Quick's value - the reciprocal of the test sample prothrombin time compared to normal plasma) as a bioanalytical evaluation of coagulation."

[-source: BLA section 2.7.3., p 15]

Sponsor's Table 9: Co-primary endpoint: Rapid decrease in INR (ITT-E population) (Study 3002)

Rapid Decrease[a] n/N (%)		Difference (%): Beriplex – Plasma (95% CI for difference)[b]
Beriplex	**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]Beriplex non-inferior to plasma: lower limit of the 95% CI exceeds –10%;

Beriplex 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

Because Beriplex was not found to be superior to plasma for <u>both</u> the primary and co-primary endpoint in the ITT-E population, the protocol provided that no conclusion of superiority of Beriplex over plasma can be drawn (as regards efficacy).

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 PRBCs 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 61.2% of subjects in the Beriplex group and 9.6% of subjects in the FFP group showing rapid decrease in INR at 30 min post end of CTM infusion.

Results of Secondary Efficacy Endpoints – Pivotal Bleeding Study _3002

Secondary Rating of Hemostatic Efficacy by EAB

> "The proportion of subjects with effective hemostasis under the secondary rating was 73.5% in the Beriplex group and 67.3% in the plasma group (Table 24). The difference between groups was 6.2% in favor of Beriplex, and the lower limit of the 95% CI was −6.5%. Analysis of the treatment difference confirmed the non-inferiority of Beriplex treatment compared to plasma treatment (lower limit of 95% CI was > –10%), but did not demonstrate superiority (lower limit of 95% CI was not > 0%)."
>
> "As for the primary efficacy endpoint rating, results for the subjects excluding Center 314 were consistent with those for those for all subjects and confirmed the non-inferiority of Beriplex to plasma."
>
> The purpose of the secondary rating of hemostatic efficacy was to determine if changing the timing of assessment of non-visible muscular/skeletal and visible bleeding in protocol amendment #3 made a difference in the primary endpoint.

Sponsor's Table 27: Comparison of incremental IVR (response) and classical IVR for Beriplex 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.

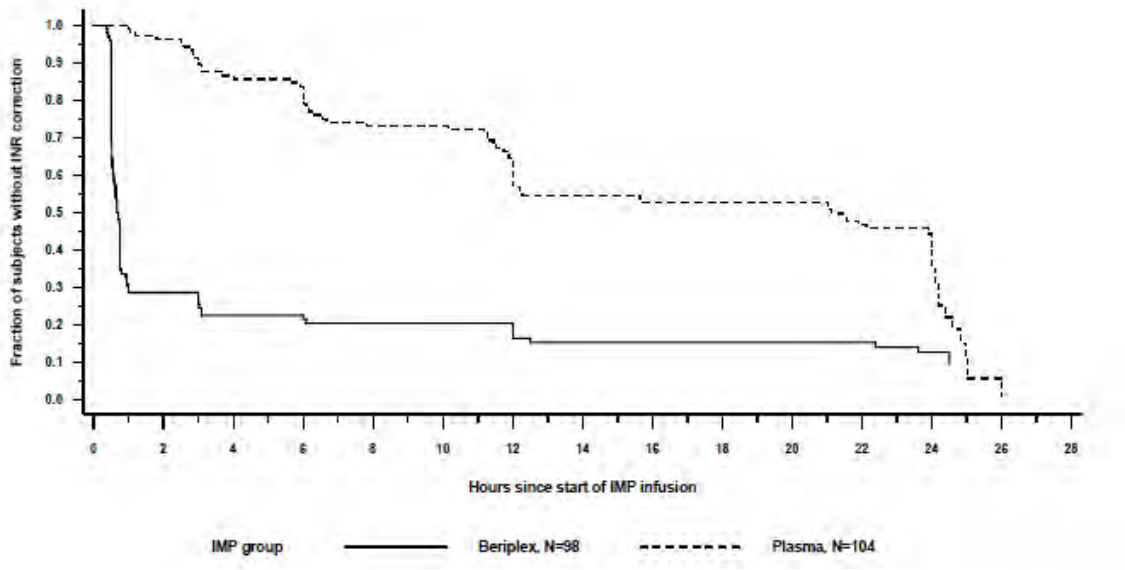
Sponsor's Table 29: Plasma levels of Factors II, VII, IX, X, and Proteins C and S up to 24 hours after start of infusion (ITT-E population) Study BE1116_3002

Analyte	Group	Mean (SD) plasma levels at time after start of infusion (%)						
		Pre-infusion	30 min	1 hour	3 hours	6 hours	12 hours	24 hours
Factor II	Beriplex	20.1 (14.56)	87.5 (44.48)*	83.7 (29.92)*	84.2 (26.25)*	80.0 (26.04)*	77.4 (22.16)*	77.1 (22.06)*
	Plasma	22.3 (22.39)	31.9 (22.55)	35.3 (19.55)	43.9 (18.86)	47.4 (18.95)	52.2 (17.46)	58.1 (19.55)

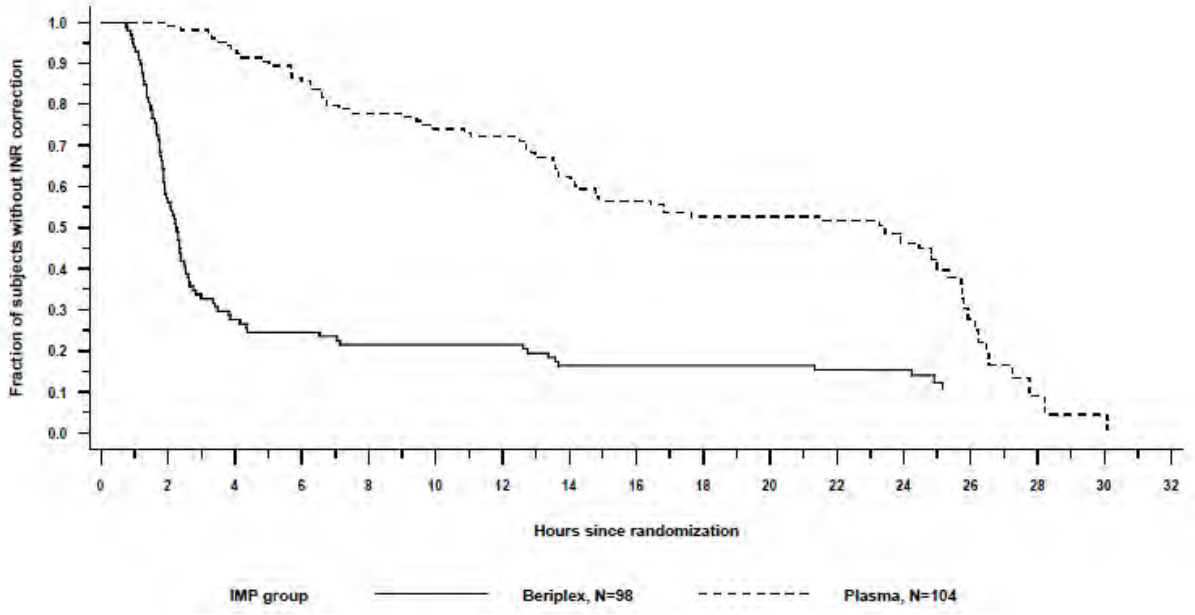
Analyte	Group	Mean (SD) plasma levels at time after start of infusion (%)						
		Pre-infusion	30 min	1 hour	3 hours	6 hours	12 hours	24 hours
Factor VII	Beriplex	25.9 (35.01)	60.5 (45.23)*	59.7 (55.35)*	64.4 (65.98)*	58.0 (30.10)	81.1 (105.97)	114.8 (165.28)
	Plasma	23.5 (23.45)	34.6 (26.18)	36.6 (23.44)	55.6 (77.61)	53.9 (29.21)	80.8 (68.89)	101.3 (79.01)
Factor IX	Beriplex	36.1 (22.56)	76.8 (35.47)*	72.7 (27.12)*	72.8 (25.74)*	77.0 (29.47)*	82.3 (31.39)	88.5 (35.65)
	Plasma	39.0 (27.56)	47.7 (26.78)	49.1 (26.66)	57.2 (24.33)	65.9 (23.12)	77.6 (25.60)	93.0 (29.95)
Factor X	Beriplex	13.0 (11.25)	99.8 (56.07)*	93.5 (38.13)*	91.9 (31.06)*	87.9 (32.20)*	84.2 (27.00)*	83.7 (27.05)*
	Plasma	14.7 (18.83)	23.9 (20.40)	26.9 (17.12)	37.4 (20.38)	41.5 (21.59)	48.6 (18.99)	58.2 (21.78)
Protein C	Beriplex	39.3 (17.15)	110.3 (47.37)*	104.0 (30.56)*	100.6 (27.29)*	95.1 (29.12)*	91.4 (26.84)*	90.3 (27.19)*
	Plasma	41.1 (18.84)	50.9 (24.78)	52.0 (19.32)	60.5 (19.49)	64.7 (20.51)	75.0 (25.87)	82.8 (24.34)
Protein S	Beriplex	27.8 (11.34)	59.4 (28.56)*	49.1 (18.43)*	52.5 (22.62)*	49.3 (18.83)*	54.7 (20.27)	47.8 (16.54)
	Plasma	29.6 (12.97)	38.6 (20.45)	33.5 (15.30)	39.1 (14.75)	42.2 (15.85)	49.6 (17.78)	45.4 (16.00)

Similar results to those in the above table were obtained after exclusion of data from study center 314.

Sponsor's Fig 2 – Kaplan-Meier Plot of Time to INR Correction from Start of Infusion (ITT-E Population)



Sponsor's Fig – Kaplan-Meier Plot of Time to INR Correction from Randomization (ITT-E Population)



RBC Transfusions

The mean +/- SD number of transfused units of PRBCs was 1.4 +/- 1.77 and 1.2 +/- 1.57 units in Beriplex and Plasma groups, respectively and did not differ by the Wilcoxon Rank Sum test (p = 0.4462). Volumes of transfused units of PRBCs were available for 21 subjects in the Beriplex group and 23 subjects in the plasma group. The mean volume of all transfused units was 308.3 mL. Normalization of transfusion volumes to this standard volume per unit also revealed no statistically significant difference between randomization groups (p = 0./4995 by Wilcoxon Rank Sum test). Similar results were obtained excluding data from center 314.

Results of Other [Tertiary, Exploratory] Efficacy Endpoints – Pivotal Bleeding Study _3002

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	
	Beriplex	**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 ecellent/good and poor/none)."

Use of Other Blood Products (besides PRBCs)

The numbers of units of other blood products used by subjects in Beriplex (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). Results excluding center 314 were similar.

45-Day Mortality from All Causes

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 Beriplex/Plasma Risk Ratio 0.66 to 5.50). There were 9 deaths ourt of 98 Beriplex subjects and 5 deaths out of 104 Plasma subjects in the ITT-E population, giving 45 day mortality rates of 9.2 and 4.8, respectively.

Decrease of INR to 1.3 or less at 30 minutes after the start of infusion

Fifty-eight (59.2$) of Beriplex group subjects and none of plasma group subjects had an INR $\leq$ 1.3 at 30 min after the start of randomized test product infusion. "A sensitivity analysis was performed by the sponsor at the request of FDA where subjects requiring any additional units of plasma, blood products and/or coagulation factor products (excluding PRBCs and platelets) during 24 hours after start of infusion were scored as having no rapid decrease of INR. Results were similar with 56 (57.1%) subjects in the Beriplex group compared to none in the plasma group with an INR of $\leq$ 1.3 at 30 minutes after the start of the infusion."

Visible bleeding responder analysis

Sixteen Beriplex group and 21 plasma group subjects had visible bleeding. The proportion in each group who were classified in the primary hemostatic endpoint analysis as responders (cessation of bleeding within 24 hours of start of infusion) was 15/16 (85.7%) in the Beriplex group and 18 of 21 (85.7%) in the plasma group, giving an absolute difference of 8.1% in favor of Beriplex (NS, p = 0.62)

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 1 Beriplex group and 2 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

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

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 Beriplex 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.

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

Time after Start Infusion	Beriplex (N = 98)		Plasma (N = 104)		p-value[a]
	n	Mean INR	n	Mean INR	
Pre-inf	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).

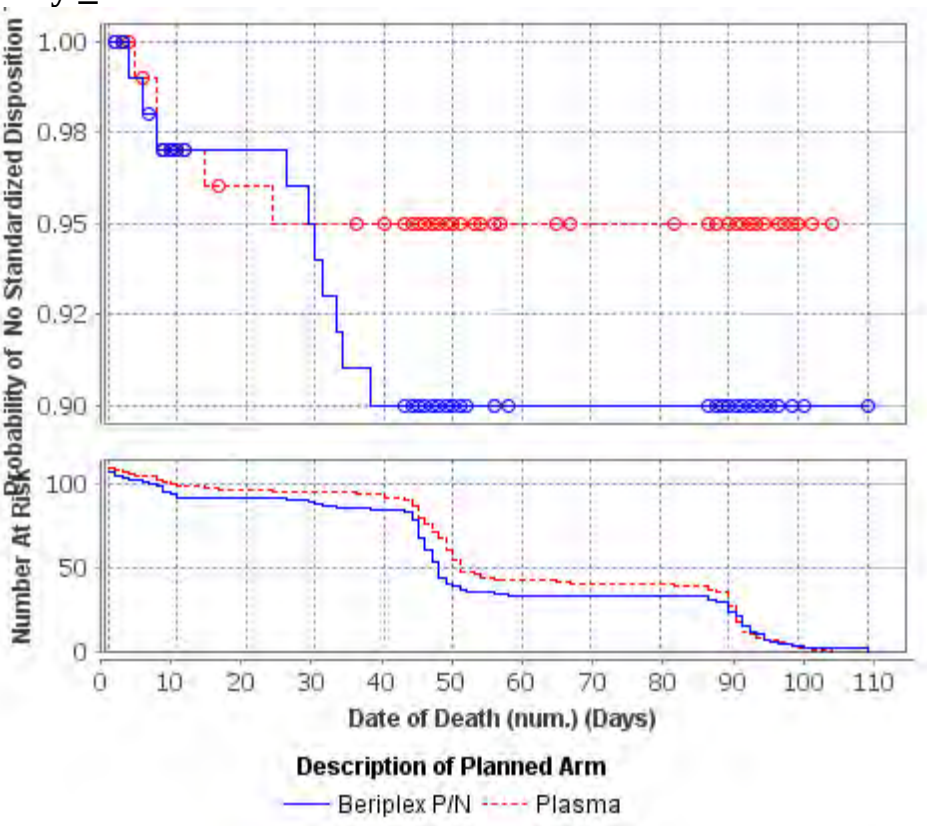
INR = international normalized ratio; ITT-E = evaluable for efficacy; N = total number of subjects; n = number of subjects.

SAFETY RESULTS

Safety Results from Study BE1116_3002:

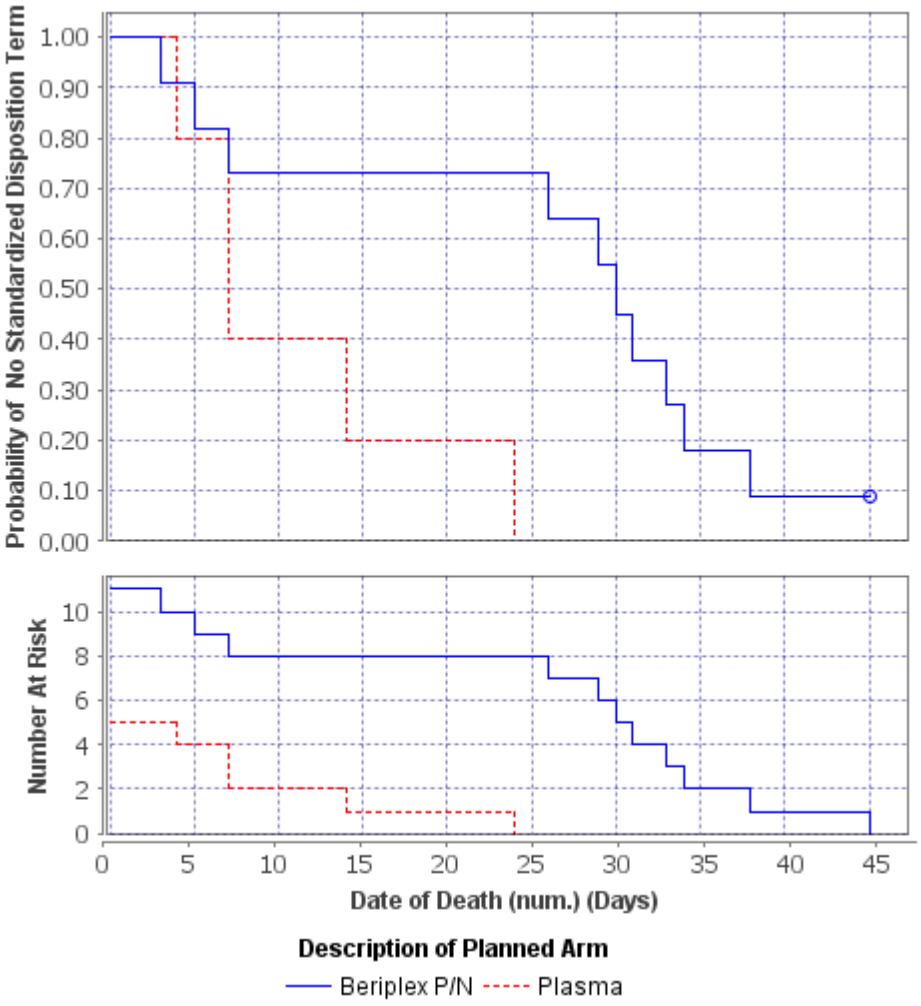
There were 11 deaths (10.7%) out of 103 Beriplex subjects compared to 5 deaths (4.6%) out of 109 FFP subjects. The ratio of the excess deaths among subjects randomized to Beriplex to those randomized to control plasma treatment was 2.33. The unmasked investigator and masked safety adjudication board concluded that only 1 death (in the Beriplex group) was at least possibly treatment-related.

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

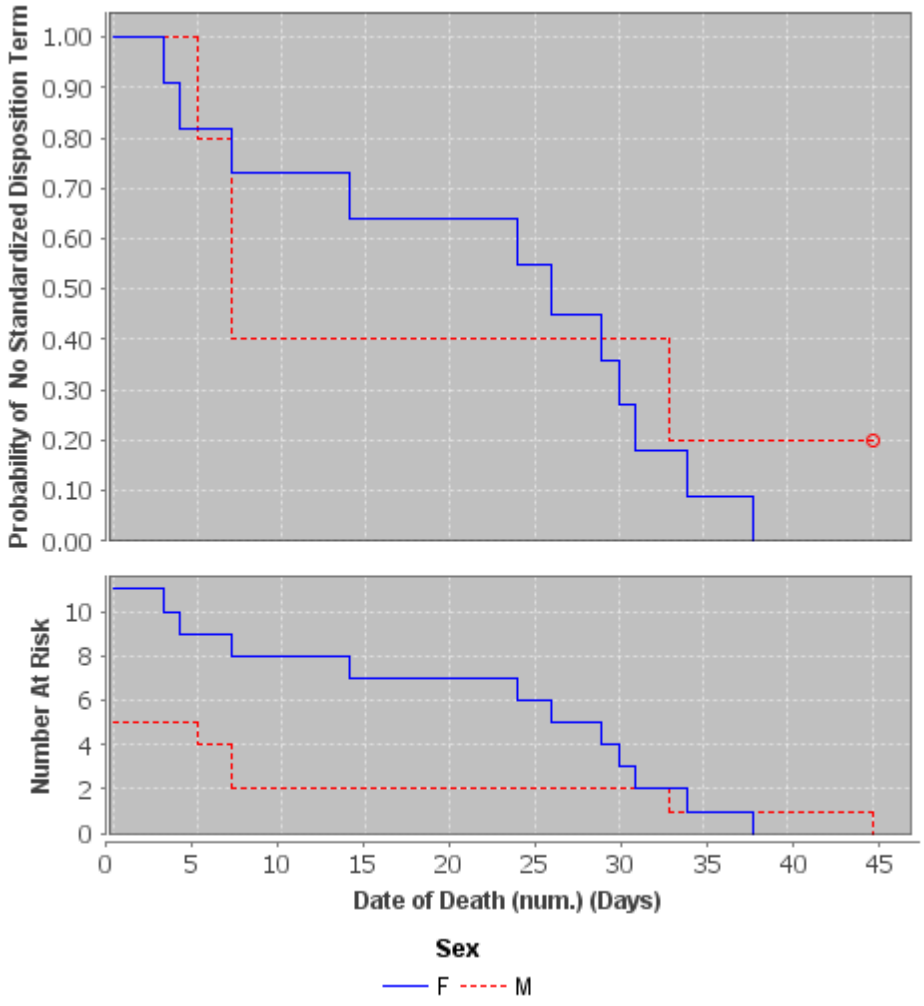


It can be seen from the Kaplan-Meier survival curves below for men and women pooled across randomization groups for study _3002 that there were more women who died by day 45 than men (11 vs. 5) and that proportionately more women died somewhat later during the observation period than was the case for men.

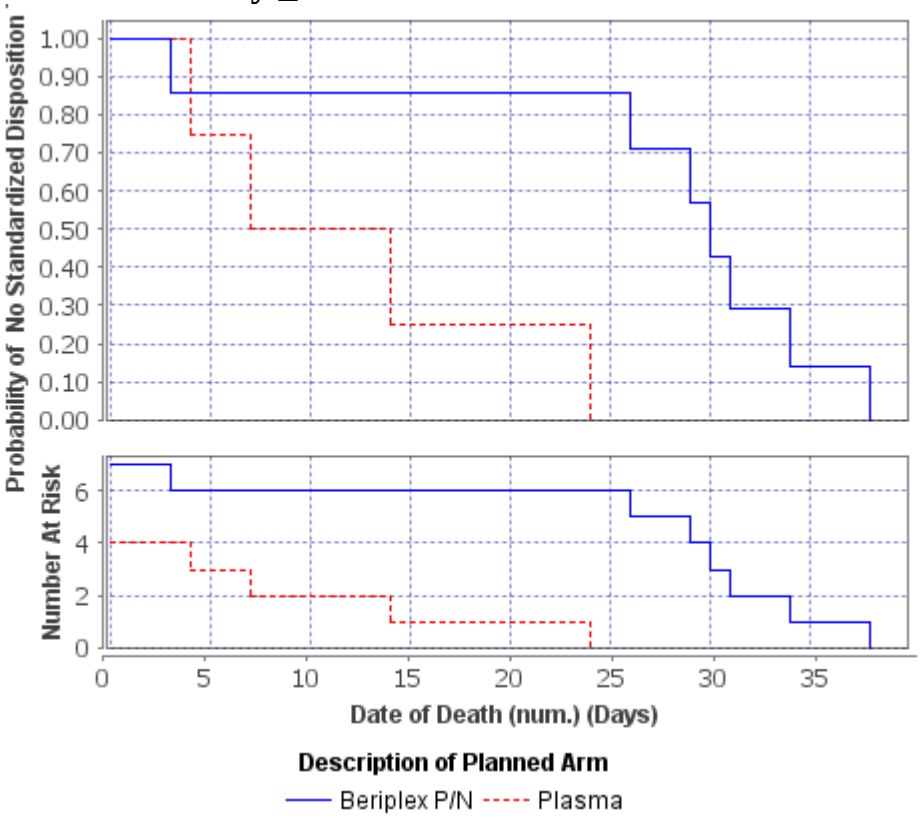
Kaplan-Meier Plot by Randomized Treatment Group Limited to Subjects Who Died – Study _3002



Kaplan-Meier Plot of Pooled Treatment Groups by Sex Limited to Subjects Who Died – Study _3002



Kaplan-Meier Plot by Treatment Group Limited to Female Subjects Who Died – Study _3002



Overall, treatment-emergent adverse events (TEAEs, hereinafter referred to as AEs) were 1% greater in the FFP group 65.1% of subjects) than in the Beriplex group (64.1% of subjects). However, severe and moderate AEs were notably more frequent in the Beriplex Group (20.4% vs 13.8% and 34.0% vs. 19.3%, respectively). AEs considered by the investigator at least possibly related to study treatment were twice as frequent in the FFP group (23/109 = 21.1% for FFP vs. 10/103 = 9.7% for Beriplex). It should be noted that the study was open-label which may possibly have biased some investigators' assignments of causality. Serious Adverse Events (SAEs) were numerically more frequent in the Beriplex group (32.0%) compared to

the FFP group (23.9%). AEs leading to premature discontinuation of treatment numbered 3 with FFP and zero in the Beriplex group. It should be noted that because FFP takes on average 7 times longer to infuse than Beriplex, the time during which the risk of any event, including an AE leading to premature discontinuation of study product, is proportionately greater with FFP, could confound the interpretation of the difference in subjects who discontinued CTM due to an AE.

Thrombotic and Thromboembolic (TE) Events

Consolidated Table Adapted from Sponsor's Table 49 - Number of subjects with possible thromboembolic TEAEs (SMQ and SAB) by preferred term (ITT-S population) with grouping of related terms

Preferred Term[a]	**No. (%) of subjects**	**No. (%) of subjects**
	Beriplex (N = 103)	**Plasma (N = 109)**
Possible thromboembolic events according to SMQ		
Ischemic stroke/CVA/ Cerebrovascular disorder	3 (2.9)	2 (1.8)
Deep vein thrombosis /Venous thrombosis limb/ Thrombophlebitis	3 (2.9)	1 (0.9)
Thrombosis in device	1 (1.0)	1 (0.9)
Myocardial infarction/ Acute myocardial infarction	1 (1.0)[c]	2 (1.8)
Additional possible thromboembolic events according to SAB		
Myocardial ischemia	0	2 (1.8)
Total subjects with possible	**8 (7.8)**[d]	**7 (6.4)**[e]

Preferred Term[a]	**No. (%) of subjects**	**No. (%) of subjects**
	Beriplex (N = 103)	**Plasma (N = 109)**
thromboembolic events		

Table Adapted from Sponsor's Table 49 - Number of subjects with possible thromboembolic TEAEs (SMQ and SAB) by preferred term (ITT-S population)

Preferred Term[a]	**No. (%) of subjects**	**No. (%) of subjects**
	Beriplex (N = 103)	**Plasma (N = 109)**
Possible thromboembolic events according to SMQ		
Ischemic stroke	3 (2.9)	0
Venous thrombosis limb	2 (1.9)	0
Deep vein thrombosis	1 (1.0)	0
Thrombosis in device	1 (1.0)	1 (0.9)
Myocardial infarction	1 (1.0)[c]	1 (0.9)
Acute myocardial infarction	0	1 (0.9)
Cerebrovascular accident	0	1 (0.9)
Cerebrovascular disorder	0	1 (0.9)
Thrombophlebitis	0	1 (0.9)
Additional possible		

Preferred Term[a]	**No. (%) of subjects**	**No. (%) of subjects**
	Beriplex (N = 103)	**Plasma (N = 109)**
thromboembolic events according to SAB		
Myocardial ischemia	0	2 (1.8)
Total subjects with possible thromboembolic events	**8 (7.8)**[d]	**7 (6.4)**[e]

[a] TEAEs are listed in descending order based on frequency in Beriplex total group and are coded according to MedDRA 12.0.
Multiple thromboembolic event entries per subject possible.
[c] The SAB did not confirm the SAE of myocardial infarction to be a thromboembolic event "as there is neither compatible history nor documentation of one " (Subject 043004).
[d] Subject 013008 experienced 2 separate possible thromboembolic events of DVT.
[e] Subject 002010 experienced 2 possible thromboembolic events: thrombophlebitis and myocardial ischemia
DVT = deep vein thrombosis; ITT-S = safety population; MedDRA = Medical Dictionary for Regulatory Activities; N = total number of subjects; SAB = Safety Adjudication Board; SAE = serious adverse event; SMQ = Standardized MedDRA Query; TEAE = treatment-emergent adverse event.
Source: Table 14.3.1-12

All SAEs considered possible TE events were reviewed to confirm the AE and to assess relatedness to the investigational product or FFP control by a blinded Safety Adjudication Board (SAB), which had been created at the request of the unblinded DSMB. Of 15 subjects with possible TE AEs, only 9 were reported to have SAEs. This means that there were 6 subjects who had TE AEs which were not assessed by the SAB.

Of the 9 subjects with TE SAEs, 5 subjects had received Beriplex as follows:

Subject ID No.	Thrombotic/Thromboembolic SAE	Onset of TE SAE in Relation to Product Infusion
002003	Ischemic CVA	
002005	Ischemic CVA	
035001	Ischemic CVA	
013008	Deep Venous Thrombosis (DVT)	

Subject ID No.	Thrombotic/Thromboembolic SAE	Onset of TE SAE in Relation to Product Infusion
043004	Myocardial Infarction (MI)	

Of the 9 subjects with TE SAEs, 4 subjects belonged to the FFP group as follows:

Subject ID No.	Thrombotic/Thromboembolic SAE	Onset of TE SAE in Relation to Product Infusion
002010	Myocardial Ischemia (Misch)	
002011	Myocardial Ischemia (Misch)	
013016	Myocardial Infarction (MI)	
030032	CVA	

Volume or Fluid Overload/CHF/Pulmonary Edema/Pleural Effusion/Dyspnea/Edema Peripheral/Respiratory Failure AEs

Respiratory, thoracic, and mediastinal disorders were reported for 21/103 Beriplex subjects (20.4%) and for 16/109 FFP subjects (14.7%).

Cardiac disorders were reported for 15 subjects in each randomization group (14.6% for Beriplex and 13.8% for FFP).

AE	Beriplex N of Subjects with AE	Beriplex % of Subjects with AE	FFP N of Subjects with AE	FFP % of Subjects with AE
Pleural Effusion	5	4.9	1	0.9
Respiratory Failure	3	2.9	2	1.8
Cardiac Failure Congestive	2	1.9	5	4.6
Pulmonary Edema	2	1.9	4	3.7
Dyspnea	2	1.9	2	2.8
Fluid Overload	0	0	4	3.7
Total	14 (not		18 (not	

AE	Beriplex N of Subjects with AE	Beriplex % of Subjects with AE	FFP N of Subjects with AE	FFP % of Subjects with AE
	necessarily unique)		necessarily unique)	

AEs which might relate to findings of volume overload

Subject ID	Treatment/ Age, Sex	Start time of AE in relation to Infusion	AE Preferred Term/ Verbatim	Serious/ Severity	Outcome
002001	Beriplex 85, F	4.6 days	Pulmonary edema	No/Moderate	Recovered with sequellae
002001	Beriplex 85, F	7.6 days	Pulmonary edema	No/Moderate	Recovered
002013	Beriplex	17 hrs	Respiratory Distress	Yes/Severe	Recovered with Sequellae
002015	Beriplex 85, M	1.2 days	Edema, peripheral/ LE Edema	No/Mild	Recovered
002015	Beriplex 85, M	5.9 days	Rales/Crackles in lung	No/Mild	Recovered
011002	Beriplex 79, M	9 days	Dyspnea/SOB	No/Mild	Recovered
-(b)(6)-	Beriplex 79, M	27 days	Respiratory Failure/ Respiratory Failure	Yes/Severe	Fatal
-(b)(6)-	Beriplex 82, F	1.6 hrs	Respiratory Failure/ Respiratory Failure	No/Severe	Not recovered (Fatal)
013011	Beriplex 56, F	1.8 days	Edema peripheral/ Trace edema	No/Mild	Recovered

Subject ID	Treatment/ Age, Sex	Start time of AE in relation to Infusion	AE Preferred Term/ Verbatim	Serious/ Severity	Outcome
			LEs		
015002	Beriplex 61, M	0 days	Rales/Bibasilar Rales	No/Mild	Recovered
015002	Beriplex 61, M	9.7 days	Pleural Effusion	No/Moderate	Recovered
-(b)(6)-	Beriplex 75, M	3 days	Cardiac failure/ Gradual worsening of cardiogenic heart failure	Yes/Severe	Fatal
029001	Beriplex 73, F	3.5 days	Respiratory failure/ Respiratory Failure	Yes/Moderate	Recovered

Late Bleed Serious Adverse Events

The DSMB requested late bleeding SAEs be reviewed by the blinded SAB. Late bleeding was defined by the DSMB as SAEs of bleeding occurring between 24 hours and 10 days after the start of study product administration. Five cases were revewed and 3 confirmed as late bleeds: 2 in the Beriplex group and 1 in the plasma group. One of these in each group was attributed to re-anticoagulation and one case in the Beriplex group was attributed to a fall. No late rebleeds were considered product related.

Viral Safety (Study _3002)

AEs Among Subjects Who Died Study _3002

			Start Time of AE	

Unique Subject Identifier	Dictionary-Derived Term	Reported Adverse Event	Relative to IMP Start	Severity/Intensity
----------				
-(b)(6)----	Sudden death	sudden death	6 days	SEVERE
----------	Hepatitis b antigen positive	positive -(b)(4)- test for hepatitis B pre-infusion	-0.5 hrs	MILD
-(b)(6)----	Chest pain	chest pain	2 days	MILD
	Respiratory failure	respiratory failure	27 days	SEVERE
	Skin ulcer	Ulcer left ancle and (R) foot 2nd toe, chronic in nature due to PVD	3 days	MILD
	Peripheral vascular disorder	intravascular volume depletion	4.1 days	SEVERE
	Hepatic enzyme increased	elevated liver enzymes	5 days	MILD
	Blood potassium decreased	serum potassium decreased	8.7 days	MILD
	Dyspnoea	shortness of breath	9 days	MILD
----------			-0.2	
-(b)(6)----	Vomiting	vomiting	hrs	MILD
	Blood glucose increased	elevated glucose	-1.3 hrs	MILD
	Respiratory failure	respiratory failure	1.6 hrs	SEVERE
	Haemorrhage intracranial	Increased size of intracranial hemorrhage.	1.6 hrs	SEVERE
	Pyrexia	fever following admission	7.8 hrs	MILD
----------			42	
-(b)(6)----	Ischaemic stroke	acute ischemic stroke	days	SEVERE
----------			1.7	
-(b)(6)----	Oedema peripheral	edema left hand	days	MODERATE
	Skin disorder	skin breakdown - sacral area	11.8 hrs	MILD
	Convulsion	seizure	20.3 hrs	MILD
	Convulsion	seizure	21.1 hrs	MILD
	Cardiac failure	gradual worsening of cardiogenic heart failure	3 days	SEVERE
	Urine output decreased	decreased urine output	3.8 hrs	MODERATE
	Pyrexia	fever	9.8 hrs	MILD
----------			1.1	
-(b)(6)----	Hypermagnesaemia	hypermagnesemia	days	MILD
	Hyponatraemia	hyponatremia	1.7 days	MILD
	Hyperphosphataemia	hyperphosphatemia	10.9 hrs	MILD
	Renal failure	worsening renal insufficiency	10.9 hrs	MODERATE
	Mental status changes	intermittent mental status changes	17.6 hrs	MODERATE
	Lung carcinoma cell type unspecified stage iv	stage IV lung cancer	19.6 days	SEVERE
	Hypoglycaemia	reccurrent Hypoglycemia	2.1	MODERATE

			Start Time of AE	
Unique Subject Identifier	Dictionary-Derived Term	Reported Adverse Event	Relative to IMP Start	Severity/Intensity
			days	
	Cardioactive drug level increased	elevated digoxin level	2.4 days	MILD
	Respiratory failure	respiratory failure	3.5 days	MODERATE
	Hypocalcaemia	hypocalcemia	4.2 days	MILD
	Urinary tract infection	urinary tract infection	4.4 days	MILD
----------			12.0	
-(b)(6)----	Dyspnoea	increased shortness of breath	hrs	MILD
	Hepatic enzyme increased	elevated liver enzymes	12.2 hrs	MILD
	Blood potassium decreased	decreased potassium (serum) level	2.6 days	MILD
	Constipation	constipation	3.1 days	MILD
	Lung cancer metastatic	worsening metastatic lung cancer	5 days	SEVERE
----------			1.4	
-(b)(6)----	Hypotension	worsening of hypotension	days	MODERATE
	Liver function test abnormal	exacerbation of increased liver function test	1.5 hrs	MODERATE
	Mobility decreased	not moving right hand or fingers	2.3 days	MILD
	Staphylococcal sepsis	sepsis (staph infection uncertain etiology)	3 days	SEVERE
	Thrombosis in device	fistula clot	4.3 hrs	MODERATE
----------			10.2	
-(b)(6)----	Metastases to liver	probable liver metastasis	days	SEVERE
	Peripheral ischaemia	peripheral vascular ischemia	10.7 days	MILD
	Pneumonia	pneumonia	11.6 days	MILD
	Hypotension	worsening hypotension	2.9 days	MILD
	Hypercoagulation	hypercoagulopathy	3.6 days	MODERATE
	Septic shock	septic shock	3.6 days	SEVERE
	Decubitus ulcer	decubitus ulcer	3.9 days	MILD
	Hyperglycaemia	hyperglycemia	4.5 days	MILD
	Diarrhoea	diarrhea	8.1 days	MILD
	Hyperkalaemia	hyperkalemia	9.5 days	MILD
	Hypotension	worsening hypotension	9.6 days	MILD
----------			1.4	
-(b)(6)----	Hypophosphataemia	hypophosphatemia	days	MODERATE

			Start Time of AE	
Unique Subject Identifier	Dictionary-Derived Term	Reported Adverse Event	Relative to IMP Start	Severity/Intensity
	Metabolic acidosis	metabolic acidosis	1.4 days	MODERATE
	Facial palsy	right facial droop	15.2 hrs	MILD
	Arthralgia	right wrist pain	2.2 days	MODERATE
	Bone cyst	bone cysts in right distal radius	2.6 days	MODERATE
	Contusion	left upper extremity bruising	3 days	MILD
	Peroneal nerve palsy	bilateral slight foot drop	3 days	MILD
	Constipation	constipation	3.5 days	MILD
	Anxiety	anxiety	3.6 hrs	MODERATE
	Gastritis	gastritis	3.8 days	MODERATE
	Gastric polyps	polyp in the stomach	3.8 days	MODERATE
	Myocardial infarction	myocardial infarction	37 days	SEVERE
	Skin discolouration	brown discoloration of skin on left hip	4 days	MILD
	Hyperkalaemia	hyperkalemia	6.7 days	MODERATE
---------- -(b)(6)----	Abdominal pain	abdominal pain	1.2 days	MILD
	Oral pain	pain in mouth	2 days	MILD
	Cardio-respiratory arrest	cardio pulmonary arrest	29.7 days	SEVERE
	Agitation	agitation	3.7 days	MILD
	Headache	intermittent headaches	9.0 days	MILD
---------- (b)(6)----	Melaena	melena	1.2 days	MILD
	Hepatic failure	worsening hepatic failure	22 days	SEVERE
	Confusional state	confusion	5 days	MILD
---------- -(b)(6)----	Pancreatic carcinoma	pancreatic cancer	2 days	SEVERE
	Back pain	back pain	2.4 days	MILD
	Insomnia	insomnia	3.2 days	MILD
---------- -(b)(6)----	Hypernatraemia	hypernatremia	2.1 days	MILD
	Renal failure acute	acute renal failure	24 days	SEVERE
	Skin laceration	skin tear (top of anus and gluteal cleft)	4.6 days	MILD
	Hypoventilation	hypoventilation of the lungs	5	MILD

Unique Subject Identifier	Dictionary-Derived Term	Reported Adverse Event	Start Time of AE Relative to IMP Start days*	Severity/Intensity
---------- -(b)(6)---- ----------	Haemorrhagic anaemia	progression of post hemorrhagic anemia	24.0 hrs	SEVERE
-(b)(6)----	Infection	systemic infection	1.4 days	SEVERE
	Haematocrit decreased	hematocrit decreased	3.4 hrs	MILD
	Haemoglobin decreased	hemoglobin decreased	3.4 hrs	MILD

Blinded Assessment of Potential for Relationship of Death to Study Product - Study BE1116_3002
(0 = Little to no Relationship; 1 = Some Possible Relationship; 2 = Plausible Relation to Study Product)

Subject ID	Reviewer's Assessment of Possible Relationship	Randomized Treatment Group
---(b)(6)---	2	B
---(b)(6)---	0	B
---(b)(6)---	2	B
---(b)(6)---	0	B
---(b)(6)---	2	B
---(b)(6)---	1	B
---(b)(6)---	0	P
---(b)(6)---	2	B
---(b)(6)---	2	P
---(b)(6)---	2	B
---(b)(6)---	1	B
---(b)(6)---	0	P
---(b)(6)---	0	B
---(b)(6)---	1	B
---(b)(6)---	2	P
---(b)(6)---	0	P
N = 16	17/16 = 1.0625	

Comparisons of the Reviewer's death potential relatedness scores determined by my blinded analysis of the timing of associated adverse

events for each treatment group and the number of subjects in each treatment group with scores of 0, 1, and 2 are given in the following table.

Reviewer's Death Potential Relatedness Scores - Study BE1116_3002

Comparison	Beriplex	Plasma
Subjects with Score[a] = 0	3	3
Subjects with Score = 1	3	0
Subjects with Score = 2	5	2
Subjects with Score = 1 or 2	8	2
Total Score	13	4

[a]Blinded Death Causality Score Definitions:
0 = Little to no Relationship;
1 = Some Possible Relationship;
2 = Plausible Relation to Study Product

Reviewer's Post-Hoc Analysis of Deaths by Treatment Group Excluding Deaths Attributed to Malignancy - - Study BE1116_3002

Comparison	Beriplex	Plasma
Total Deaths	11	5
Deaths Attributed to Malignancy	2	1
Deaths Excluding Those Attributed to Malignancy	9	4

Subject IDs where Death was attributed to Malignancy:
Beriplex: ---(b)(6)--- ("stage IV lung cancer"); ---(b)(6)--- ("pancreatic carcinoma")
Plasma: ---(b)(6)--- ("worsening metastatic lung cancer");
Note that Plasma subject ---(b)(6)--- death was attributed to septic shock, so she was not counted as a death attributed to malignancy despite the fact that the subject was considered to have "probable liver metastasis."

Listed Causes of Death with Relative Start Time of Serious Adverse Event Reported to be the Cause of Death - Study BE1116_3002

Subject ID	Randomized Treatment Group	Listed Cause of Death[a]	Relative Start Time of AE to which Death was Attributed[c]
---(b)(6)---	B	Sudden Death	6 days
---(b)(6)---	B	Respiratory Failure	6 days
---(b)(6)---	B	Intracranial Hemorrhage	1.6 hours
---(b)(6)---	B	Acute Ischemic Stroke	42 days
---(b)(6)---	B	Cardiac Failure	3 days
---(b)(6)---	B	Stage IV Lung Cancer	19.6 days
---(b)(6)---	B	Pancreatic Carcinoma	2 days
---(b)(6)---	B	Staphylococcal Infection Uncertain Etiology	3 days
---(b)(6)---	B	Acute Renal Failure	24 days
---(b)(6)---	B	Myocardial Infarction	37 days
---(b)(6)---	B	Cardio-Pulmonary Arrest	29.7 days
---(b)(6)---	P	Worsening Hepatic Failure	22 days
---(b)(6)---	P	Septic Shock	9.4 days
---(b)(6)---	P	Progression of Post-Hemorrhagic Anemia	24 hours
---(b)(6)---	P	Systemic Infection	1.8 days
---(b)(6)---	P	Lung Cancer	5 days

[a]Source: Sponsor's data listing
[b] B = Beriplex; P = Plasma randomization treatment group
[c]This is not necessarily the same as the relative day of death.

Reviewer's Post-Hoc Analysis of Deaths by Treatment Group Excluding Deaths Attributed to Malignancy or Sepsis - Study BE1116_3002

Comparison	Beriplex	Plasma
Total Deaths	11	5
Deaths Attributed to Malignancy	3	3
Deaths Excluding Those Attributed to Malignancy	8	2

Subject IDs where Death was attributed to Malignancy or Sepsis:
Beriplex: -(b)(6)- ("stage IV lung cancer"); -(b)(6)- ("pancreatic carcinoma"); -(b)(6)- ("staphyloccal infection uncertain etiology")
Plasma: -(b)(6)- ("worsening metastatic lung cancer"); -(b)(6)- (systemic infection"); -(b)(6)- ("septic shock")
Note that Plasma subject -(b)(6)- death was attributed to septic shock, so she was not counted as a death attributed to malignancy despite the fact that the subject was considered to have "probable liver metastasis."

Subject ---(b)(6)--- was a 56 year old WHITE M.
The subject experienced a FATAL adverse event Sudden death initially reported as sudden death on study day 7

Safety Results – Clinical Laboratory Findings

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.

SAFETY ANALYSES OF INTERIM DATA FROM ONGOING SURGERY/INVASIVE PROCEDURE STUDY BE1116_3003

Brief Summary of Interim Safety Results from Ongoing Surgery IND Study BE1116_3003 (Original BLA)

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.

See section below for summary of protocol design for the ongoing surgery IND study BE1116_3003.

Interim safety data from the surgery study are presented for a total of 114 subjects (56 randomized to Beriplex and 58 randomized to plasma) for this ongoing study ----------(b)(4)----------.

The overall incidence of treatment-emergent Adverse Events (TEAEs, AEs) was 55.4% in the Beriplex group and 60.3% in the plasma group.

Within the severity categories of mild, moderate, and severe, AEs were approximately equally balanced across randomization groups.

AEs considered by the investigator to be at least possibly related were reported in 7.1% of subjects in the Beriplex group and 19.0% in the plasma group. The open-label design of the study may have biased some or all investigators' opinions regarding causality.

No subjects in either group discontinued treatment due to an AE.

There were 2 deaths in the Beriplex group and 7 in the plasma group between start of administration of study product and day 45 follow-up. Of this total of 9 deaths, only 1 death (in the plasma group) was considered at least possibly treatment related by the blinded safety adjudication board.

Serious Adverse Events (SAEs) were reported for 12 subjects (21.4%) in the Beriplex group and in 13 subjects (22.4%) in the plasma group.

As in bleeding study BE1116_3002, there were a number of possible thrombotic or thromboembolic AEs (TE events) which were not classified as SAEs. A total of 8 possible TE events were identified: 2 in the Beriplex group and 6 in the plasma group, of which only 4 were classified as SAEs.

The number of possible TE events considered by the investigator to be at least possibly related to the test treatment was 2 in each randomization group.

SAEs which are considered thrombotic or thromboembolic AEs were as follows:

SAE	No. (%) Subjects with SAE in Beriplex Group (N = 56)	No. (%) Subjects with SAE in Plasma Group (N = 58)
Ischemic Stroke	1 (1.8)	0
Embolic cerebral infarction	0	1 (1.7)
Venous thrombosis limb/deep venous thrombosis	1 (1.8)	1 (1.7)

"Non-serious" possible TE events reported for the plasma group include 2 subjects with MI, 1 pulmonary embolism, and 1 TIA. The SAB did not confirm the PE report to be a possible TE event.

GI disorders were more frequent in the Beriplex group (15 subjects, 27%) compared to the plasma group (9 subjects, 16%). Cardiac disorders were reported for 9 Beriplex subjects (16%) vs. 9 plasma subjects (19%). Respiratory, thoracic, and mediastinal disorders were reported fro 8 Beriplex subjects (14%) and 11 plasma subjects (19%). Vascular disorders were equal in both groups (7 subjects, 12%).

Hypokalemia was the most frequently reported preferred AE term in both groups (6 subjects, 11% for Beriplex, 4 subjects, 7% for plasma). Hypotension was more frequently reported in the Beriplex group (6 subjects, 11%) than in the plasma group (2 subjects, 3%), as was acute renal failure (3 subjects, 5% with Beriplex vs. 1 subject, 2% with plasma). There were 2 MIs in the plasma group and none in the Beriplex group, 2 cases of respiratory failure in the plasma group vs. 1 in the Beriplex group, 2 cases each of rales and dyspnea in the plasma group vs. zero for each in the Beriplex group. CHF was reported for 2 plasma subjects and for 1 Beriplex subject.

There was a numerical excess of AEs possibly related to fluid overload in the plasma group, however there was no pre-planned analysis in the protocol for this analysis.

Reviewer Comment: Among AEs listed in module 2, section 2.7.4 (Summary of Clinical Safety) Table 15, "Possible thromboembolic TEAEs by preferred term and relatedness (investigator assessment) (Study _3003)" are acute myocardial infarction, deep venous thrombosis, pulmonary embolism, and transient attack. These do not appear in Table 14, "Treatment related TEAEs by decreasing frequency (Study 23003)" of the same section because the investigator/EAB/sponsor did not consider them treatment related. Also, the total number of subjects with product-related acute pulmonary edema (n = 1) and cardiac failure, congestive (n = 1) appearing in Table 14 are different from the total number of subjects for which these AEs are reported in Table 15 (n = 5 for pulmonary edema and n = 3 for cardiac failure, congestive).

Summary of Design of Protocol BE1116_3003:

Protocol Number: BE1116_3003

Note: Changes from this and prior amendments are indicated by strikeout for deletions and underscore for additions.

Protocol Name:

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

Pivotal Trial: yes

Protocol Design:

Note: Changes by current and previous amendments are indicated by strikeout for deletions and underscore for additions.

Prospective, R, open-label, active-controlled (fresh frozen plasma (FFP)), non-inferiority, multicenter Phase IIIb trial

Study Sites: ~ 30 in US and ~ 30 International.

Study Size: The total number of subjects planned is between 100 and 210, depending on the results of the interim analysis.

Objectives:

Primary:

To compare hemostatic efficacy of Beriplex P/N and plasma in preventing excessive hemorrhages during emergency surgical or invasive interventions in subjects who have a deficiency of vitamin K-dependent coagulation factors II, VIII, IX, X, and proteins C and S acquired from oral anticoagulation.

Co-Primary Objective:

To compare efficacy of Beriplex P/N and plasma in rapidly reducing pre-operative international normalized ratio (INR) values between the 2 treatment groups at 30 minutes after the end of infusion.

Secondary Objectives:

- To compare the plasma levels of coagulation factors II, VI, IX, and X, protein C, and protein S between the 2 treatment groups.
- To document time from start of infusion until INR correction for both treatment groups
- To document time from randomization until INR correction for both treatment groups
- To compare INR between treatment groups at 30 min from start of infusion
- To compare use of non-study prescribed blood products, additional FFP and/or hemostatic agents for coagulation in both treatment groups
- To compare predicted estimated blood loss versus actual estimated blood loss for intended procedure between the 2 treatment groups
- To compare transfusion requirement intraoperatively and during the 24 hours from start of infusion
- To compare the volume and duration of wound drainage
- To determine the safety and tolerability of Beriplex P/N compared to that of plasma.

Other Objectives:

- To compare the procedure related differences in blod loss (ABL [excluding unexpected blood loss from surgical complications] – PBL) by randomization group.
- To compare the INR between both treatment groups at 30 min from the start of infusion of IMP.
- For ICH subjects only, to evaluate the neurological outcome change from baseline as assessed by the Mofified Rankin Scale (mRs) at 24 hours, hospital discharge, and day 45.
- To compare the use of newly prescribed (defined as new treatment or increased dose of existing treatment) diuretics within 24 hours of start of IMP.
- To assess the total amount of diuretics (mg/diuretic) administered within 24 hours of the start of IMP.

Eligibility Criteria:

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.

- 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 assesmenet, 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 prodedure-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 therapay 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 Ab 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.

Number of Subjects: 176

Number of Centers: 60 (half in US, half international)

Estimated study duration: 22-36 months, including 45 day f/u visit.

Coordinating Investigator: Ravindra Sarode, MD, U. Texas Southwest Medical Center, Dallas, TX

Dose Escalation Scheme/Treatment Plan:

Subjects are randomized 1:1 to receive either Beriplex P/N 500 (reconstituted with 20 mL SWI, containing on average 25 IU FIX per mL) or fresh-frozen plasma (FFP).

Beriplex P.N 500 is to be dosed as follows:

Baseline INR	Beriplex P/N 500 Dosage (IU FIX per kg)
2 - < 4	25
4 - 6	35
>6	50

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

FFP will be dosed as follows:

Baseline INR	FFP Dosage (mL per kg)
2 - < 4	10
4 - 6	12
>6	15

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

The requirement for urgent reversal of the vitamin K antagonist must be balanced with the potential risk of **transfusion associated circulatory overload.** The investigator or responsible party should determine the infusion rate based on urgency of reversal and volume of plasma to be administered as well as the subject's weight, age, underlying clinical conditions, and other risks for plasma induced fluid overload.

All subjects will receive oral or slow IV vitamin K as early as possible. The dose of vitamin K should be based on ~~local clinical practice~~ ACCP guidelines (e.g., 2 – 10 mg. Further vitamin K may be required and should be administered according to local clinical practice (e.g., q 12 – 24 hours). Concomitant vitamin K should be properly documented.

Note: Vitamin K should not be administered during this study by either the subcutaneous or intramuscular routes due to the potential for inconsistent bioavailability.

PRIMARY EFFICACY ENDPOINT

Hemostatic efficacy, assessed for the time period from the start of infusion of IMP until the end of the urgent surgical or urgent invasive procedure in preventing excessive bleeding during emergency surgical

or invasive intervention (the "procedure"). The components of the hemostatic efficacy ratings of excellent, good, and poor/none are presented in sponsor's Table 4.

CO- PRIMARY EFFICACY ENDPOINT

Decrease of the INR to ≤ 1.3 within 30 min after the end of infusion of IMP.

SECONDARY EFFICACY VARIABLES

- Response and in-vivo recovery of the plasma levels of coagulation factors II, VI, IX, and X, and protein C, and protein S.
- Time from start of infusion of IMP until INR correction (INR ≤ 1.3).
- Time from randomization until INR correction (INR ≤ 1.3).
- Proportion of subjects who have a decrease in INR (INR ≤ 1.3) at 1, 3, 6, and 24 hours from start of infusion (only using results obtained preoperatively).
- Intraoperative hemostasis of the subject (normal, mildly abnormal, or severely abnormal) assessed by the surgeon or the physician who performed the procedure imme3diately after the end of the urgent surgical or urgent invasive procedure (last skin suture or equivalent).
- Need for additional products providing coagulation factors (plasma, whole blood, coagulation factor products) administered from randomization through 24 hours after start of infusion and/or end of urgent or invasive procedure (this definition excludes platelets and PRBCs).
- Use of non-study prescribed ~~blood products and~~ non-study hemostatic agents from randomization through 24 hours from start of IMP infusion and/or end of urgent surgical or invasive procedure.
- Number of intra-operative PRBC transfusions required.
- Comparison of pre-surgery predicted estimated blood loss (EBL) versus actual estimated blood loss for intended procedure To compare transfusion requirement interoperatively and during the 24 hours from start of infusion
- 45 day all-cause mortality ~~by treatment group~~
- Volume of wound drainage

- Time between last suture and cessation of wound drainage.
- To determine the safety and tolerability of Beriplex P/N compared to that of plasma.
- Comparison between treatment groups, by type of surgery, of differences in actual blood loss (ABL) and predicted blood loss (PBL); two analyses: (1) ABL (including unexpected blood loss from surgical complications) – PBL; and, (2) ABL (including unexpected blood loss from surgical complications) – PBL.
- **Comparison of ABL between randomization groups using the type of surgery and PBL as covariates**.
- Number of units of packed red blood cells from start of surgery through 24 hours from the start of surgery
- Proportion of subjects receiving packed red blood cells from start of surgery through 24 hours from the start of surgery

Other Efficacy Endpoints (as listed by the sponsor)

- Comparison of the procedure related differences in blod loss (ABL [excluding unexpected blood loss from surgical complications] – PBL) by randomization group.
- Proportion of subjects who have a decreased INR to < 1.3 at 30 min from the start of infusion of IMP.
- For ICH subjects only, assessment of the neurological outcome change from baseline as assessed by the Modified Rankin Scale (mRs) at 24 hours, hospital discharge, and day 45.
- Proportion of subjects newly prescribed (defined as new treatment or increased dose of existing treatment) diuretics within 24 hours of start of IMP.
- Total amount of diuretics (by product) administered within 24 hours of the start of IMP.
- Number of units of packed red blood cells from start of administration of the IMP through 24 hours from start of administration of the IMP or the end of surgery, whichever is later.
- Proportion of subjects receiving packed red blood cells from the start of administration of the IMP through 24 hours from start of administration of the IMP or the end of surgery, whichever is later.
- Comparison between treatment groups of the total volume of wound drainage (sanguinous or serosanguinous)

Safety Variables

- 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. -(b)(4)- 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.

Randomization:

Biased coin minimization method, using validated software. Randomization is stratified on 2 levels as described on pp 35-36 of the protocol. The 1st level is 5 strata of surgery type. The 2nd level is oral vitamin K < or > 2 mg and any dose of IV vitamin K1.

Monitoring:

Three (3) retained samples (1 mL serum each) will be obtained as back up samples for virology or required study specific retesting prior to infusion of Beriplex® *PIN* and 10 and 45 days after the infusion. Samples will be deep frozen at -20 deg C or lower.

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	

Pharmacokinetic Evaluation (if applicable): not in TOC

Dose Escalation Scheme/Treatment Plan:

Additional Beriplex must not be given during the study after the randomized IMP dose is given**.**

Additional blood products and hemostatic agents given from randomization through 24 hours after start of IMP infusion and or end of surgery/invasive procedure must be documented on the appropriate CRF page**.**

Resumption of anticoagulant therapy should be considered as soon after the procedure as medically appropriate and the rationale for the decision must be documented on the CRF up to day 45 (43-51 days post IMP infusion).

All anticoagulation treatments given up to 2 weeks before randomization will be recorded as concomitant medications**.**

Treatment Modifications:

There are no specific subject stopping criteria, but study stopping procedures are discussed on p 30 of the protocol. Subjects who are withdrawn prior to the primary efficacy assessment will be replaced.

There are no specific study stopping criteria, but study stopping procedures are discussed on p 28 of the protocol.

Statistical Analytic Plan:

The study is an active controlled, non-inferiority study with a once-only administration of the IMP to each subject. The design includes superiority testing if non-inferiority is shown. The study has a primary endpoint, a co-primary endpoint, and a specified hierarchy of hypothesis testing: non-inferiority of Beriplex P/N versus plasma with regard to the co-primary endpoint will be tested if non-inferiority with regard to the primary endpoint is shown.

Secondary analyses of the primary endpoint will be conducted in the per – protocol population and also using the investigators' assessments, if there is at least 1 "divergent" for the primary endpoint between the investigator and the DSMB.

The analysis for the co-primary endpoint, proportion of subjects with INR < 1.3 at 30 min after end of the test product infusion will be done the same way as for hemostatic efficacy.

Non-inferiority of Beriplex P/N to FFP can be claimed if non-inferiority was claimed for both the primary and the co-primary endpoints in the ITT population.

If non-inferiority is shown, an additional test will be performed for the superiority of the effect of Beriplex P/N compared to that of plasma on each of the 2 primary endpoints.

Assumptions

Estimated effect size – The sponsor assumes a response rate of 0.90 for Beriplex and 0.85 for FFP.

Planned Enrollment – With 80 subjects per group, the lower limit of the observed 97.5 CI will be expected to exceed -0.10 with greater than 80% power4 when it is assumed that 85% of the hemostatic efficacy assessments in the plasma group (p2 = 0.85) and 90% of the hemostatic efficacy assessments in the Beriplex P/N group (p1 = 0.990) will be rated effective; results are based on the Newcombe-Wilson score method to construct the CI. With an assumed rate of drop-outs of approximately 10%, the total target sample size will be n = 176.

Provision for Dropouts - none

Power – 80% in the ITT population

Identification of study populations – intent-to-treat for primary analysis (and PP)

List of specific protocol violations to exclude subjects from per-protocol analysis

Secondary efficacy analyses - descriptive

Data Monitoring Committee: yes

Summary of Appendix 7 to Protocol : Information on laboratory methods for coagulation factors

Equipment used:
I) ----------(b)(4)----------
----
2) ----------(b)(4)----------

The following specifications are available:

Parameter	Product Name	Measurement method	WHO standard* Reference values standard*
		(b)(4)	
		(b)(4)	
		(b)(4)	
		(b)(4)	
		(b)(4)	
			(b)(4)
		(b)(4)	

Depending on the charge used as standard for calibration of the individual parameters adjustment of the WHO standard may be necessary. If others than the above mentioned WHO standards are used the Reference values standard will be adjusted accordingly.

Excerpt from sponsor correspondence in regard to request from FDA for change to study protocol relating to primary hemostatic endpoint:

CSLB will revise Study No. BEl116_3003 Hemostasis CRF page so that the categories of hemostasis are: Normal; Mildly abnormal; and, Moderately to severely abnormal. CSLB believes that the following hemostatic efficacy rating algorithm captures all aspects of the revisions to the definitions for hemostatic efficacy

requested by CBER in CBER's comments of 30 March 2009 and reiterated in CBER's comments of20 July 2011 (corrected as suggested above).

The hemostatic efficacy rating algorithm is defined in Table 1 below; the terminology appearing in column headings is to be interpreted as:

Additional product required:
Subject received no additional transfusion of coagulation-containing products (defined as plasma, whole blood, or other products containing coagulation factors but not including PRBCs or platelets) from the start of IMP infusion until the start of the urgent surgical procedure. (Yes or No.)

Hemostasis:
The subjective rating of hemostasis, qualified as:

> ***Normal**: Subject exhibited normal hemostasis, defined as achieving hemostasis comparable to that expected after a similar procedure in a non-coagulopathy patient;*
>
> ***Mildly abnormal**: Subject exhibited mildly abnormal hemostasis, defined as somewhat increased bleeding compared to that expected after a similar procedure in a non-coagulopathy patient in terms of quantity andlor quality (e.g., slight oozing or prolonged time to hemostasis);*
>
> ***Moderately to severely abnormal**: Subject exhibited moderately to severely abnormal hemostasis, defined as moderately to substantially increased bleeding compared to that expected after a similar procedure in a non-coagulopathy patient in terms of quantity andlor quality (e.g. moderate to severe hemorrhage that is difficult to control).*

ABL:

ABL = actual blood loss; PBL = predicted blood loss. ABL includes unexpected blood loss due to surgical or procedural complications. ABL will be determined by the anesthesiologist's estimate of ABL,

however, if an anesthesiologist was not present during an emergency invasive procedure, ABL win be the estimate made by the physician performing the procedure.

***ABL < 1.2 PBL**: Subject's estimated ABL during surgery or procedure is not greater than 20% higher than the estimated PBL for the intended surgy! or procedure;*

***1.2 PBL < ABL≤ 1.3 PBL**: Subject's estimated ABL during surgery or procedure is greater than 20% but not greater than 30% higher than the estimated PBL for intended surgery or procedure;*

***ABL > 1.3 PBL**: Subject's estimated ABL during surgery or procedure is greater than 30% higher than the estimated PBL for intended surgery or procedure.*

***Hemostatic Efficacy Rating**:*
Reading from left to right across the table, the hemostatic efficacy rating is determined via the algorithm by the outcomes in the three categories (additional product required, subjective rating of hemostasis, and quantification of blood loss);
*three ratings are defined by the algorithm: **Excellent**; **Good**; and, **Poor/None**. Two categories of these ratings are presented: (1) the absolute difference between ABL and PBL is greater than 50 mL; and, (2) the absolute difference between ABL and PBL is less than or equal to 50 mL. The purpose of these two categories is to address the issue of potentially misleading assessments of hemostatic efficacy driven by the quantification criteria for ABL in the algorithm table in the case of procedures that result in little or no predicted blood loss in non-coagulopathy patients.*

From Sponsor's Table 1. Hemostatic Efficacy Rating Algorithm:

Rating is Poor/None if additional Product required.

Rating is Poor/None if Hemostasis is moderate to severely abnormal.

Rating is Poor/None if ABL>1.3x PBL, EXCEPT if [ABL-PBL] is ≤ 50 mL, in which case rating is Good provided no additional product required and Hemostasis Normal or Mildly abnormal..

Rating is Excellent only if (1) no additional product required, (2) Hemostasis is Normal, (3) ABL < 1.2 x PBL, regardless of whether [ABL-PBL] is > or ≤ 50 mL.

**For ll intracranial, spinal, and intraocular surgeries, if ABL > PBL, the rating will be assessed as "poor/none" regardless of subjective rating of hemostasis.*

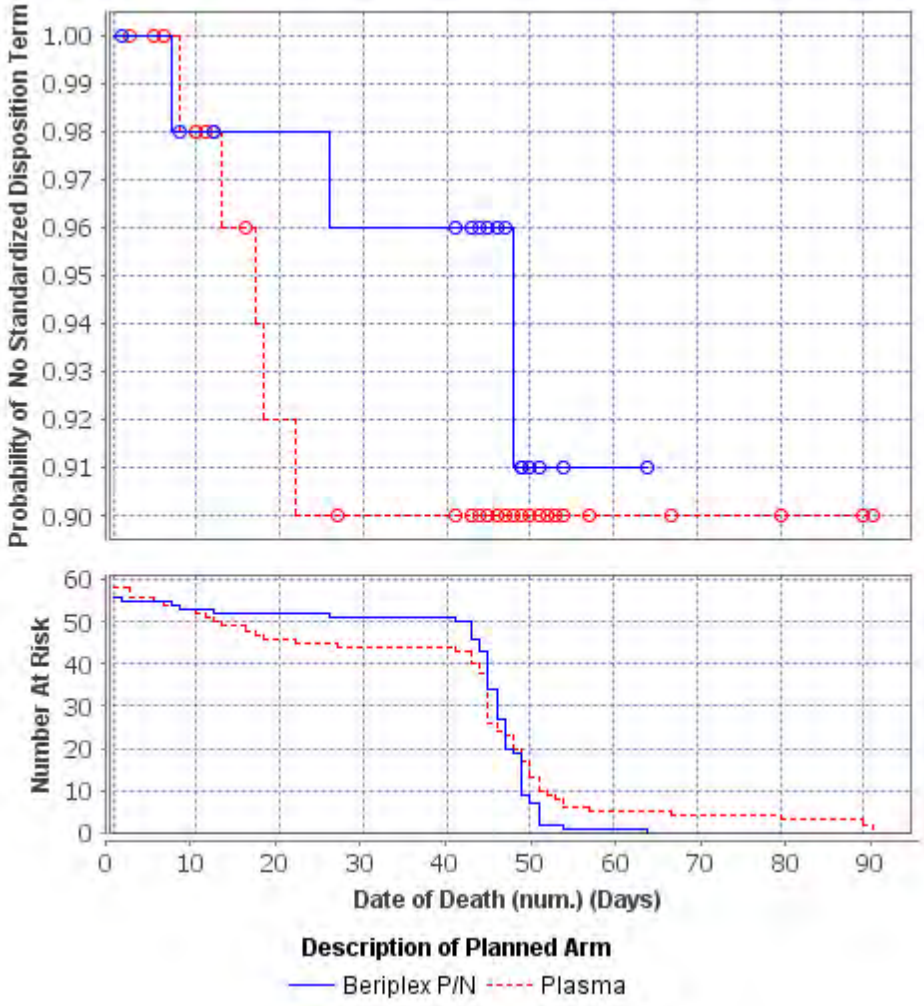
CSLB agrees to perform separate robustness efficacy analyses for subjects who participated prior to this revision and those who win participate after implementation of amendment 3.

Results – Safety – Study BE1116_3003 (Source: Original BLA)

The FDA JReview tool indicates that 10 AEs resulted in death as of the interim analysis of the surgery study included in the original submission.

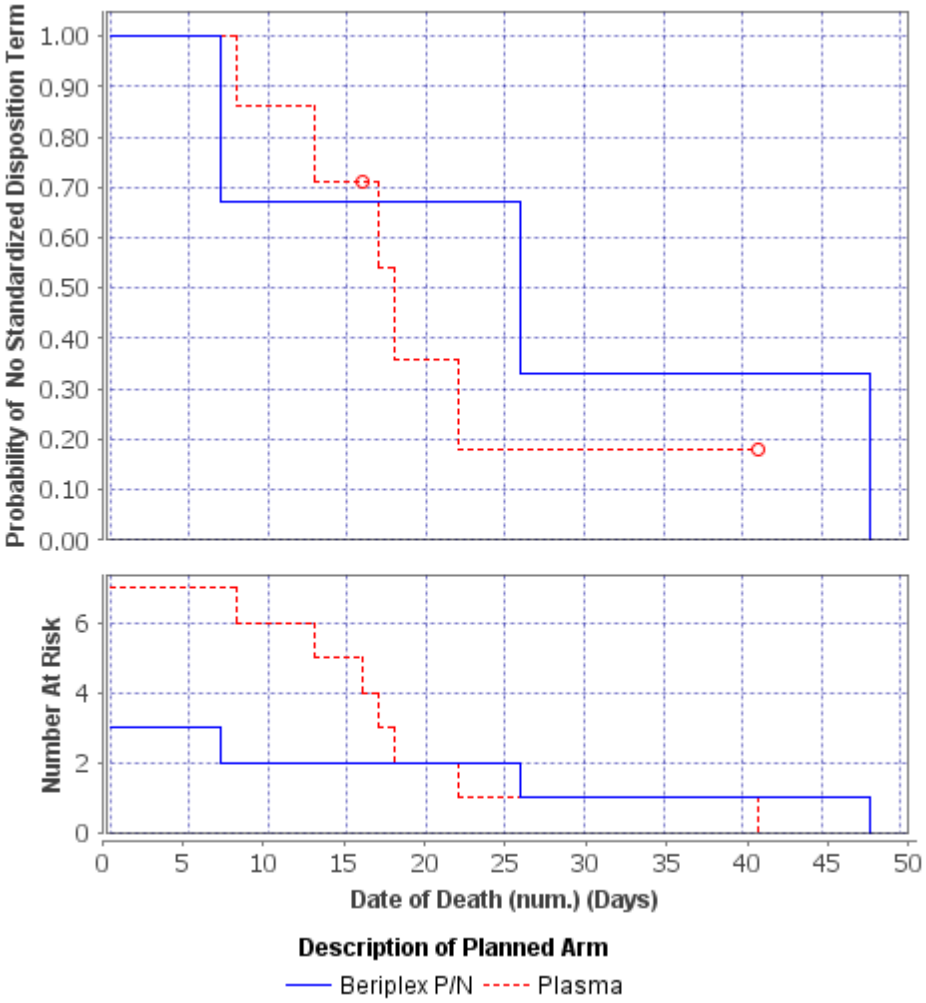
The Kaplan-Meier Plots below of all subjects by randomization group in the interim analysis of surgery study _3003 reveal more subjects in the plasma group died through day 45 than was seen in the Beriplex PCC group (7 vs. 3) in bleeding study _3002. In both studies, deaths tended to occur earlier in the plasma randomization group.

Kaplan-Meier Plots of All subjects by Randomized Treatment Group – Study _3003 (Original BLA)



Note: The above Kaplan-Meier analysis, generated from J-Review using the original BLA data listings, does not include 1 additional death for a Beriplex subject (No.--(b)(6)--) which appears in a listing from the 10 week safety updated submitted in BLA Amendment 01

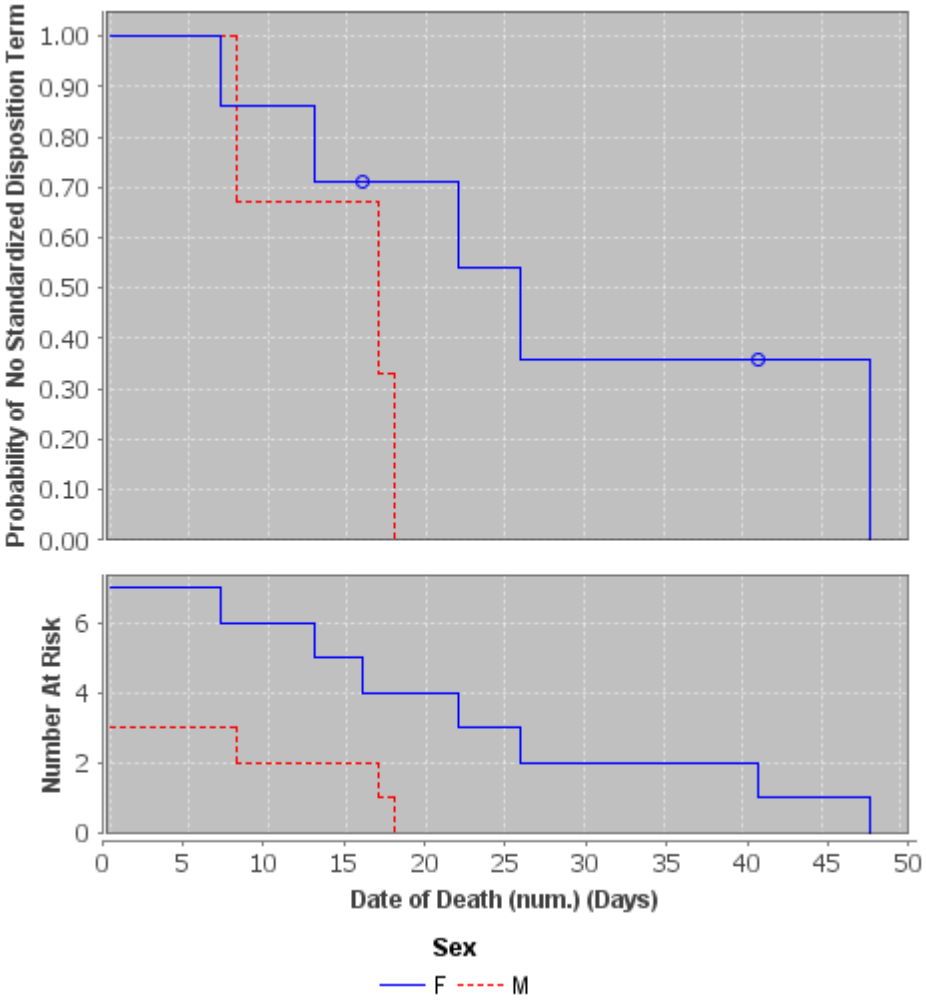
Kaplan-Meier Plots Limited to Subjects Who Died by Randomized Treatment Group – Study BE1116_3003 (Original BLA)



Note: The above Kaplan-Meier analysis, generated from J-Review using the original BLA data listings, does not include 1 additional death for a Beriplex subject (No. --(b)(6)--) which appears in a listing from the 10 week safety updated submitted in BLA Amendment 01

It can be seen from the Kaplan-Meier survival curves below for men and women pooled across randomization groups for the interim analysis of study _3003 included in the original BLA submission that there were more women who died by day 45 than men (7 vs. 3) and that proportionately more women died somewhat later during the observation period than was the case for men. Recall that this same pattern was observed in pivotal bleeding study _3002.

Kaplan-Meier Plots by Sex of Subjects Who Died – Interim Analysis Study _3003 (Original BLA Submission)



Note: The above Kaplan-Meier analysis, generated from J-Review using the original BLA data listings, does not include 1 additional death for a Beriplex subject (No. --(b)(6)--) which appears in a listing from the 10 week safety updated submitted in BLA Amendment 01.

AEs Among Subjects Who Died Study BE1116_3003[a]

Unique Subject Identifier	Dictionary-Derived Term	Reported Adverse Event	Start Time of AE Relative to IMP Start	Severity/ Intensity
----------(b)(6)----	Death	death	16 days	SEVERE
----------(b)(6)---	Atelectasis	atelectasis	10.8 hrs	MILD

Unique Subject Identifier	Dictionary-Derived Term	Reported Adverse Event	Start Time of AE Relative to IMP Start	Severity/ Intensity
-				
	Dyspepsia	indigestion	10.8 hrs	MILD
	Oedema peripheral	right leg swelling	10.8 hrs	MILD
	Disorientation	change in orientation	10.8 hrs	MILD
	Oedema genital	right labial majora swelling and redness	10.8 hrs	MILD
	Tachycardia	tachycardia	10.8 hrs	MILD
	Confusional state	confused/impaired recent recall	10.8 hrs	MILD
	Delirium	sundowning episode	10.8 hrs	MILD
	Vomiting	intermittent vomiting	10.8 hrs	MILD
	Pulmonary embolism	pulmonary embolus	10.8 hrs	MILD
	Vulval haemorrhage	left labial majora bruising	10.8 hrs	MILD
	Hyponatraemia	hyponatremia	10.8 hrs	MILD
	Confusional state	confused/impaired recent recall	10.8 hrs	MILD
	Oedema genital	right labial majora swelling and redness	10.8 hrs	MILD
	Rales	bibasilar crackles	10.8 hrs	MILD
	Oedema peripheral	right leg swelling	10.8 hrs	MILD
	Atelectasis	atelectasis	10.8 hrs	MILD
	Confusional state	intermittently confused	10.8 hrs	MILD
	Rales	bibasilar crackles	10.8 hrs	MILD
	Disorientation	change in orientation	10.8 hrs	MILD
	Dyspnoea exertional	shortness of breath with activity	10.8 hrs	MILD
	Hyponatraemia	hyponatremia	10.8 hrs	MILD
	Hypocalcaemia	hypocalcemia	10.8 hrs	MILD
	Vulval haemorrhage	left labial majora bruising	10.8 hrs	MILD
	Tachycardia	tachycardia	10.8 hrs	MILD
	Dyspepsia	indigestion	10.8 hrs	MILD
	Pulmonary embolism	pulmonary embolus	10.8 hrs	MILD
	Delirium	sundowning episode	10.8 hrs	MILD
	Vomiting	intermittent vomiting	10.8 hrs	MILD
	Nausea	intermittent nausea	10.8 hrs	MILD
	Confusional state	intermittently confused	10.8 hrs	MILD
	Dyspnoea exertional	shortness of breath with activity	10.8 hrs	MILD
	Hypocalcaemia	hypocalcemia	10.8 hrs	MILD
	Nausea	intermittent nausea	10.8 hrs	MILD
	Hyponatraemia	hyponatremia	2.2 days	MILD
	Delirium	sundowning episode	2.2 days	MILD
	Pulmonary	pulmonary embolus	2.2	MILD

Unique Subject Identifier	Dictionary-Derived Term	Reported Adverse Event	Start Time of AE Relative to IMP Start	Severity/ Intensity
	embolism		days	
	Hypocalcaemia	hypocalcemia	2.2 days	MILD
	Dyspepsia	indigestion	2.2 days	MILD
	Vomiting	intermittent vomiting	2.2 days	MILD
	Dyspnoea exertional	shortness of breath with activity	2.2 days	MILD
	Oedema peripheral	right leg swelling	2.2 days	MILD
	Confusional state	confused/impaired recent recall	2.2 days	MILD
	Atelectasis	atelectasis	2.2 days	MILD
	Oedema genital	right labial majora swelling and redness	2.2 days	MILD
	Disorientation	change in orientation	2.2 days	MILD
	Rales	bibasilar crackles	2.2 days	MILD
	Confusional state	intermittently confused	2.2 days	MILD
	Nausea	intermittent nausea	2.2 days	MILD
	Vulval haemorrhage	left labial majora bruising	2.2 days	MILD
	Tachycardia	tachycardia	25 days*	SEVERE
	Nausea	intermittent nausea	25 days*	SEVERE
	Vomiting	intermittent vomiting	25 days*	SEVERE
	Hyponatraemia	hyponatremia	25 days*	SEVERE
	Disorientation	change in orientation	25 days*	SEVERE
	Pulmonary embolism	pulmonary embolus	25 days*	SEVERE
	Rales	bibasilar crackles	25 days*	SEVERE
	Atelectasis	atelectasis	25 days*	SEVERE
	Tachycardia	tachycardia	25 days*	SEVERE
	Dyspnoea exertional	shortness of breath with activity	25 days*	SEVERE
	Dyspepsia	indigestion	25 days*	SEVERE
	Confusional state	intermittently confused	25	SEVERE

Unique Subject Identifier	Dictionary-Derived Term	Reported Adverse Event	Start Time of AE Relative to IMP Start	Severity/ Intensity
			days*	
	Delirium	sundowning episode	25 days*	SEVERE
	Vulval haemorrhage	left labial majora bruising	25 days*	SEVERE
	Oedema peripheral	right leg swelling	25 days*	SEVERE
	Oedema genital	right labial majora swelling and redness	25 days*	SEVERE
	Hypocalcaemia	hypocalcemia	25 days*	SEVERE
	Confusional state	confused/impaired recent recall	25 days*	SEVERE
	Delirium	sundowning episode	3 days	MILD
	Vomiting	intermittent vomiting	3 days	MILD
	Nausea	intermittent nausea	3 days	MILD
	Tachycardia	tachycardia	3 days	MILD
	Vulval haemorrhage	left labial majora bruising	3 days	MILD
	Rales	bibasilar crackles	3 days	MILD
	Pulmonary embolism	pulmonary embolus	3 days	MILD
	Nausea	intermittent nausea	3 days	MILD
	Oedema peripheral	right leg swelling	3 days	MILD
	Hyponatraemia	hyponatremia	3 days	MILD
	Atelectasis	atelectasis	3 days	MILD
	Delirium	sundowning episode	3 days	MILD
	Confusional state	confused/impaired recent recall	3 days	MILD
	Disorientation	change in orientation	3 days	MILD
	Oedema genital	right labial majora swelling and redness	3 days	MILD
	Pulmonary embolism	pulmonary embolus	3 days	MILD
	Rales	bibasilar crackles	3 days	MILD
	Confusional state	intermittently confused	3 days	MILD
	Disorientation	change in orientation	3 days	MILD
	Atelectasis	atelectasis	3 days	MILD
	Tachycardia	tachycardia	3 days	MILD
	Dyspnoea exertional	shortness of breath with activity	3 days	MILD
	Vulval haemorrhage	left labial majora bruising	3 days	MILD
	Oedema peripheral	right leg swelling	3 days	MILD
	Hypocalcaemia	hypocalcemia	3 days	MILD
	Confusional state	confused/impaired recent recall	3 days	MILD
	Hypocalcaemia	hypocalcemia	3 days	MILD
	Oedema genital	right labial majora swelling	3 days	MILD

Unique Subject Identifier	Dictionary-Derived Term	Reported Adverse Event	Start Time of AE Relative to IMP Start	Severity/ Intensity
		and redness		
	Dyspnoea exertional	shortness of breath with activity	3 days	MILD
	Confusional state	intermittently confused	3 days	MILD
	Vomiting	intermittent vomiting	3 days	MILD
	Hyponatraemia	hyponatremia	3 days	MILD
	Dyspepsia	indigestion	3 days	MILD
	Dyspepsia	indigestion	3 days	MILD
	Nausea	intermittent nausea	3.2 days	MILD
	Vulval haemorrhage	left labial majora bruising	3.2 days	MILD
	Confusional state	intermittently confused	3.2 days	MILD
	Hyponatraemia	hyponatremia	3.2 days	MILD
	Delirium	sundowning episode	3.2 days	MILD
	Dyspepsia	indigestion	3.2 days	MILD
	Vomiting	intermittent vomiting	3.2 days	MILD
	Dyspnoea exertional	shortness of breath with activity	3.2 days	MILD
	Dyspepsia	indigestion	3.2 days	MILD
	Oedema genital	right labial majora swelling and redness	3.2 days	MILD
	Disorientation	change in orientation	3.2 days	MILD
	Rales	bibasilar crackles	3.2 days	MILD
	Atelectasis	atelectasis	3.2 days	MILD
	Tachycardia	tachycardia	3.2 days	MILD
	Pulmonary embolism	pulmonary embolus	3.2 days	MILD
	Vulval haemorrhage	left labial majora bruising	3.2 days	MILD
	Confusional state	confused/impaired recent recall	3.2 days	MILD
	Oedema peripheral	right leg swelling	3.2 days	MILD
	Confusional state	confused/impaired recent recall	3.2 days	MILD
	Hypocalcaemia	hypocalcemia	3.2 days	MILD
	Hyponatraemia	hyponatremia	3.2	MILD

Unique Subject Identifier	Dictionary-Derived Term	Reported Adverse Event	Start Time of AE Relative to IMP Start	Severity/ Intensity
			days	
	Oedema genital	right labial majora swelling and redness	3.2 days	MILD
	Nausea	intermittent nausea	3.2 days	MILD
	Vomiting	intermittent vomiting	3.2 days	MILD
	Hypocalcaemia	hypocalcemia	3.2 days	MILD
	Confusional state	intermittently confused	3.2 days	MILD
	Delirium	sundowning episode	3.2 days	MILD
	Oedema peripheral	right leg swelling	3.2 days	MILD
	Dyspnoea exertional	shortness of breath with activity	3.2 days	MILD
	Atelectasis	atelectasis	3.2 days	MILD
	Disorientation	change in orientation	3.2 days	MILD
	Rales	bibasilar crackles	3.2 days	MILD
	Pulmonary embolism	pulmonary embolus	3.2 days	MILD
	Tachycardia	tachycardia	3.5 days	MILD
	Atelectasis	atelectasis	3.5 days	MILD
	Pulmonary embolism	pulmonary embolus	3.5 days	MILD
	Vulval haemorrhage	left labial majora bruising	3.5 days	MILD
	Confusional state	intermittently confused	3.5 days	MILD
	Delirium	sundowning episode	3.5 days	MILD
	Oedema peripheral	right leg swelling	3.5 days	MILD
	Dyspepsia	indigestion	3.5 days	MILD
	Vomiting	intermittent vomiting	3.5 days	MILD
	Oedema genital	right labial majora swelling and redness	3.5 days	MILD
	Dyspnoea exertional	shortness of breath with activity	3.5 days	MILD
	Hypocalcaemia	hypocalcemia	3.5 days	MILD
	Nausea	intermittent nausea	3.5	MILD

Unique Subject Identifier	Dictionary-Derived Term	Reported Adverse Event	Start Time of AE Relative to IMP Start	Severity/ Intensity
			days	
	Hyponatraemia	hyponatremia	3.5 days	MILD
	Tachycardia	tachycardia	3.5 days	MILD
	Confusional state	confused/impaired recent recall	3.5 days	MILD
	Rales	bibasilar crackles	3.5 days	MILD
	Disorientation	change in orientation	3.5 days	MILD
	Vomiting	intermittent vomiting	4 days	MILD
	Atelectasis	atelectasis	4 days	MILD
	Rales	bibasilar crackles	4 days	MILD
	Nausea	intermittent nausea	4 days	MILD
	Pulmonary embolism	pulmonary embolus	4 days	MILD
	Vulval haemorrhage	left labial majora bruising	4 days	MILD
	Delirium	sundowning episode	4 days	MILD
	Confusional state	confused/impaired recent recall	4 days	MILD
	Hyponatraemia	hyponatremia	4 days	MILD
	Oedema genital	right labial majora swelling and redness	4 days	MILD
	Disorientation	change in orientation	4 days	MILD
	Dyspepsia	indigestion	4 days	MILD
	Confusional state	intermittently confused	4 days	MILD
	Dyspnoea exertional	shortness of breath with activity	4 days	MILD
	Tachycardia	tachycardia	4 days	MILD
	Oedema peripheral	right leg swelling	4 days	MILD
	Hypocalcaemia	hypocalcemia	4 days	MILD
	Hypocalcaemia	hypocalcemia	4.3 days	MILD
	Disorientation	change in orientation	4.3 days	MILD
	Atelectasis	atelectasis	4.3 days	MILD
	Rales	bibasilar crackles	4.3 days	MILD
	Tachycardia	tachycardia	4.3 days	MILD
	Pulmonary embolism	pulmonary embolus	4.3 days	MILD
	Nausea	intermittent nausea	4.3 days	MILD
	Vulval haemorrhage	left labial majora bruising	4.3 days	MILD

Unique Subject Identifier	Dictionary-Derived Term	Reported Adverse Event	Start Time of AE Relative to IMP Start	Severity/ Intensity
	Vomiting	intermittent vomiting	4.3 days	MILD
	Delirium	sundowning episode	4.3 days	MILD
	Hyponatraemia	hyponatremia	4.3 days	MILD
	Oedema genital	right labial majora swelling and redness	4.3 days	MILD
	Oedema peripheral	right leg swelling	4.3 days	MILD
	Dyspepsia	indigestion	4.3 days	MILD
	Confusional state	confused/impaired recent recall	4.3 days	MILD
	Confusional state	intermittently confused	4.3 days	MILD
	Dyspnoea exertional	shortness of breath with activity	4.3 days	MILD
	Disorientation	change in orientation	4.5 days	MILD
	Rales	bibasilar crackles	4.5 days	MILD
	Pulmonary embolism	pulmonary embolus	4.5 days	MILD
	Nausea	intermittent nausea	4.5 days	MILD
	Vulval haemorrhage	left labial majora bruising	4.5 days	MILD
	Delirium	sundowning episode	4.5 days	MILD
	Hyponatraemia	hyponatremia	4.5 days	MILD
	Confusional state	confused/impaired recent recall	4.5 days	MILD
	Oedema genital	right labial majora swelling and redness	4.5 days	MILD
	Dyspepsia	indigestion	4.5 days	MILD
	Oedema peripheral	right leg swelling	4.5 days	MILD
	Confusional state	intermittently confused	4.5 days	MILD
	Dyspnoea exertional	shortness of breath with activity	4.5 days	MILD
	Hypocalcaemia	hypocalcemia	4.5 days	MILD
	Vomiting	intermittent vomiting	4.5 days	MILD
	Nausea	intermittent nausea	4.5 days	MILD

Unique Subject Identifier	Dictionary-Derived Term	Reported Adverse Event	Start Time of AE Relative to IMP Start	Severity/ Intensity
	Disorientation	change in orientation	4.5 days	MILD
	Tachycardia	tachycardia	4.5 days	MILD
	Rales	bibasilar crackles	4.5 days	MILD
	Pulmonary embolism	pulmonary embolus	4.5 days	MILD
	Vulval haemorrhage	left labial majora bruising	4.5 days	MILD
	Atelectasis	atelectasis	4.5 days	MILD
	Vomiting	intermittent vomiting	4.5 days	MILD
	Tachycardia	tachycardia	4.5 days	MILD
	Atelectasis	atelectasis	4.5 days	MILD
	Oedema peripheral	right leg swelling	4.5 days	MILD
	Confusional state	confused/impaired recent recall	4.5 days	MILD
	Hyponatraemia	hyponatremia	4.5 days	MILD
	Oedema genital	right labial majora swelling and redness	4.5 days	MILD
	Delirium	sundowning episode	4.5 days	MILD
	Dyspepsia	indigestion	4.5 days	MILD
	Confusional state	intermittently confused	4.5 days	MILD
	Dyspnoea exertional	shortness of breath with activity	4.5 days	MILD
	Hypocalcaemia	hypocalcemia	4.6 days	MILD
	Tachycardia	tachycardia	4.6 days	MILD
	Pulmonary embolism	pulmonary embolus	4.6 days	MILD
	Rales	bibasilar crackles	4.6 days	MILD
	Nausea	intermittent nausea	4.6 days	MILD
	Vulval haemorrhage	left labial majora bruising	4.6 days	MILD
	Vomiting	intermittent vomiting	4.6 days	MILD
	Oedema peripheral	right leg swelling		

Unique Subject Identifier	Dictionary-Derived Term	Reported Adverse Event	Start Time of AE Relative to IMP Start	Severity/ Intensity
	Atelectasis	atelectasis	4.6 days	MILD
	Delirium	sundowning episode	4.6 days	MILD
	Confusional state	confused/impaired recent recall	4.6 days	MILD
	Hyponatraemia	hyponatremia	4.6 days	MILD
	Oedema genital	right labial majora swelling and redness	4.6 days	MILD
	Dyspepsia	indigestion	4.6 days	MILD
	Dyspnoea exertional	shortness of breath with activity	4.6 days	MILD
	Hypocalcaemia	hypocalcemia	4.6 days	MILD
	Disorientation	change in orientation	4.6 days	MILD
	Confusional state	intermittently confused	4.6 days	MILD
	Vulval haemorrhage	left labial majora bruising	5 days	MILD
	Vomiting	intermittent vomiting	5 days	MILD
	Delirium	sundowning episode	5 days	MILD
	Confusional state	confused/impaired recent recall	5 days	MILD
	Oedema peripheral	right leg swelling	5 days	MILD
	Hyponatraemia	hyponatremia	5 days	MILD
	Pulmonary embolism	pulmonary embolus	5 days	MILD
	Oedema genital	right labial majora swelling and redness	5 days	MILD
	Dyspepsia	indigestion	5 days	MILD
	Confusional state	intermittently confused	5 days	MILD
	Dyspnoea exertional	shortness of breath with activity	5 days	MILD
	Hypocalcaemia	hypocalcemia	5 days	MILD
	Disorientation	change in orientation	5 days	MILD
	Atelectasis	atelectasis	5 days	MILD
	Rales	bibasilar crackles	5 days	MILD
	Tachycardia	tachycardia	5 days	MILD
	Nausea	intermittent nausea	5 days	MILD
	Confusional state	confused/impaired recent recall	6.4 hrs	MILD
	Hyponatraemia	hyponatremia	6.4 hrs	MILD
	Oedema genital	right labial majora swelling and redness	6.4 hrs	MILD
	Dyspepsia	indigestion	6.4 hrs	MILD
	Confusional state	intermittently confused	6.4 hrs	MILD

Unique Subject Identifier	Dictionary-Derived Term	Reported Adverse Event	Start Time of AE Relative to IMP Start	Severity/ Intensity
	Hypocalcaemia	hypocalcemia	6.4 hrs	MILD
	Disorientation	change in orientation	6.4 hrs	MILD
	Atelectasis	atelectasis	6.4 hrs	MILD
	Rales	bibasilar crackles	6.4 hrs	MILD
	Tachycardia	tachycardia	6.4 hrs	MILD
	Dyspnoea exertional	shortness of breath with activity	6.4 hrs	MILD
	Pulmonary embolism	pulmonary embolus	6.4 hrs	MILD
	Nausea	intermittent nausea	6.4 hrs	MILD
	Vulval haemorrhage	left labial majora bruising	6.4 hrs	MILD
	Vomiting	intermittent vomiting	6.4 hrs	MILD
	Oedema peripheral	right leg swelling	6.4 hrs	MILD
	Delirium	sundowning episode	6.4 hrs	MILD
	Confusional state	confused/impaired recent recall	6.4 hrs	MILD
	Hyponatraemia	hyponatremia	6.4 hrs	MILD
	Oedema genital	right labial majora swelling and redness	6.4 hrs	MILD
	Confusional state	intermittently confused	6.4 hrs	MILD
	Dyspnoea exertional	shortness of breath with activity	6.4 hrs	MILD
	Hypocalcaemia	hypocalcemia	6.4 hrs	MILD
	Dyspepsia	indigestion	6.4 hrs	MILD
	Disorientation	change in orientation	6.4 hrs	MILD
	Atelectasis	atelectasis	6.4 hrs	MILD
	Rales	bibasilar crackles	6.4 hrs	MILD
	Tachycardia	tachycardia	6.4 hrs	MILD
	Pulmonary embolism	pulmonary embolus	6.4 hrs	MILD
	Nausea	intermittent nausea	6.4 hrs	MILD
	Vulval haemorrhage	left labial majora bruising	6.4 hrs	MILD
	Vomiting	intermittent vomiting	6.4 hrs	MILD
	Oedema peripheral	right leg swelling	6.4 hrs	MILD
	Delirium	sundowning episode	6.4 hrs	MILD
----------(b)(6)----	Pneumonia	ventilator - associated - pneumonia	1.2 days	SEVERE
	Decubitus ulcer	sacral decubitus ulcer	1.2 days	SEVERE
	Cardiac arrest	cardiac arrest	1.2 days	SEVERE
	Hypernatraemia	hypernatremia	1.2 days	SEVERE
	Respiratory failure	respiratory failure	1.2 days	SEVERE
	Respiratory failure	respiratory failure	11.8 days	MILD

Unique Subject Identifier	Dictionary-Derived Term	Reported Adverse Event	Start Time of AE Relative to IMP Start	Severity/ Intensity
	Pneumonia	ventilator - associated - pneumonia	11.8 days	MILD
	Decubitus ulcer	sacral decubitus ulcer	11.8 days	MILD
	Cardiac arrest	cardiac arrest	11.8 days	MILD
	Hypernatraemia	hypernatremia	11.8 days	MILD
	Respiratory failure	respiratory failure	16.6 days	SEVERE
	Pneumonia	ventilator - associated - pneumonia	16.6 days	SEVERE
	Decubitus ulcer	sacral decubitus ulcer	16.6 days	SEVERE
	Cardiac arrest	cardiac arrest	16.6 days	SEVERE
	Hypernatraemia	hypernatremia	16.6 days	SEVERE
	Respiratory failure	respiratory failure	4.9 days	MILD
	Pneumonia	ventilator - associated - pneumonia	4.9 days	MILD
	Decubitus ulcer	sacral decubitus ulcer	4.9 days	MILD
	Cardiac arrest	cardiac arrest	4.9 days	MILD
	Hypernatraemia	hypernatremia	4.9 days	MILD
	Respiratory failure	respiratory failure	7.9 days	SEVERE
	Pneumonia	ventilator - associated - pneumonia	7.9 days	SEVERE
	Decubitus ulcer	sacral decubitus ulcer	7.9 days	SEVERE
	Cardiac arrest	cardiac arrest	7.9 days	SEVERE
	Hypernatraemia	hypernatremia	7.9 days	SEVERE
--------(b)(6)----------	Sepsis	severe sepsis	10.8 days	SEVERE
	Respiratory failure	respiratory failure	10.8 days	SEVERE
	Shock	circulatory failure	10.8 days	SEVERE
	Coma	coma	10.8 days	SEVERE
	Pneumonia	ventilator associated pneumonia	10.8 days	SEVERE
	Septic shock	septic shock	10.8 days	SEVERE

Unique Subject Identifier	Dictionary-Derived Term	Reported Adverse Event	Start Time of AE Relative to IMP Start	Severity/ Intensity
	Pancreatic abscess	pancreatic abscess	10.8 days	SEVERE
	Anaemia	secondary anemia	10.8 days	SEVERE
	Grand mal convulsion	Tonic - clonic seizures	10.8 days	SEVERE
	Grand mal convulsion	Tonic - clonic seizures	19.7 days	SEVERE
	Respiratory failure	respiratory failure	19.7 days	SEVERE
	Shock	circulatory failure	19.7 days	SEVERE
	Coma	coma	19.7 days	SEVERE
	Sepsis	severe sepsis	19.7 days	SEVERE
	Pneumonia	ventilator associated pneumonia	19.7 days	SEVERE
	Septic shock	septic shock	19.7 days	SEVERE
	Pancreatic abscess	pancreatic abscess	19.7 days	SEVERE
	Anaemia	secondary anemia	19.7 days	SEVERE
	Grand mal convulsion	Tonic - clonic seizures	23.0 hrs	MILD
	Respiratory failure	respiratory failure	23.0 hrs	MILD
	Shock	circulatory failure	23.0 hrs	MILD
	Coma	coma	23.0 hrs	MILD
	Sepsis	severe sepsis	23.0 hrs	MILD
	Pneumonia	ventilator associated pneumonia	23.0 hrs	MILD
	Septic shock	septic shock	23.0 hrs	MILD
	Pancreatic abscess	pancreatic abscess	23.0 hrs	MILD
	Anaemia	secondary anemia	23.0 hrs	MILD
	Grand mal convulsion	Tonic - clonic seizures	3.9 days	MODERATE
	Shock	circulatory failure	3.9 days	MODERATE
	Coma	coma	3.9 days	MODERATE
	Sepsis	severe sepsis	3.9 days	MODERATE
	Septic shock	septic shock	3.9 days	MODERATE
	Pancreatic abscess	pancreatic abscess	3.9 days	MODERATE
	Anaemia	secondary anemia	3.9 days	MODERATE

Unique Subject Identifier	Dictionary-Derived Term	Reported Adverse Event	Start Time of AE Relative to IMP Start	Severity/ Intensity
	Pneumonia	ventilator associated pneumonia	3.9 days	MODERATE
	Respiratory failure	respiratory failure	3.9 days	MODERATE
	Grand mal convulsion	Tonic - clonic seizures	4.0 days	SEVERE
	Respiratory failure	respiratory failure	4.0 days	SEVERE
	Shock	circulatory failure	4.0 days	SEVERE
	Coma	coma	4.0 days	SEVERE
	Pneumonia	ventilator associated pneumonia	4.0 days	SEVERE
	Septic shock	septic shock	4.0 days	SEVERE
	Pancreatic abscess	pancreatic abscess	4.0 days	SEVERE
	Grand mal convulsion	Tonic - clonic seizures	4.0 days	SEVERE
	Respiratory failure	respiratory failure	4.0 days	SEVERE
	Shock	circulatory failure	4.0 days	SEVERE
	Sepsis	severe sepsis	4.0 days	SEVERE
	Pneumonia	ventilator associated pneumonia	4.0 days	SEVERE
	Septic shock	septic shock	4.0 days	SEVERE
	Pancreatic abscess	pancreatic abscess	4.0 days	SEVERE
	Anaemia	secondary anemia	4.0 days	SEVERE
	Grand mal convulsion	Tonic - clonic seizures	4.0 days	MILD
	Respiratory failure	respiratory failure	4.0 days	MILD
	Coma	coma	4.0 days	SEVERE
	Anaemia	secondary anemia	4.0 days	SEVERE
	Shock	circulatory failure	4.0 days	MILD
	Coma	coma	4.0 days	MILD
	Sepsis	severe sepsis	4.0 days	MILD
	Pneumonia	ventilator associated pneumonia	4.0 days	MILD

Unique Subject Identifier	Dictionary-Derived Term	Reported Adverse Event	Start Time of AE Relative to IMP Start	Severity/ Intensity
	Sepsis	severe sepsis	4.0 days	SEVERE
	Septic shock	septic shock	4.0 days	MILD
	Pancreatic abscess	pancreatic abscess	4.0 days	MILD
	Anaemia	secondary anemia	4.0 days	MILD
	Grand mal convulsion	Tonic - clonic seizures	4.2 days	MODERATE
	Respiratory failure	respiratory failure	4.2 days	MODERATE
	Shock	circulatory failure	4.2 days	MODERATE
	Coma	coma	4.2 days	MODERATE
	Sepsis	severe sepsis	4.2 days	MODERATE
	Pneumonia	ventilator associated pneumonia	4.2 days	MODERATE
	Septic shock	septic shock	4.2 days	MODERATE
	Pancreatic abscess	pancreatic abscess	4.2 days	MODERATE
	Anaemia	secondary anemia	4.2 days	MODERATE
	Grand mal convulsion	Tonic - clonic seizures	Unknown	MODERATE
	Respiratory failure	respiratory failure	Unknown	MODERATE
	Shock	circulatory failure	Unknown	MODERATE
	Coma	coma	Unknown	MODERATE
	Sepsis	severe sepsis	Unknown	MODERATE
	Pneumonia	ventilator associated pneumonia	Unknown	MODERATE
	Septic shock	septic shock	Unknown	MODERATE
	Pancreatic abscess	pancreatic abscess	Unknown	MODERATE
	Anaemia	secondary anemia	Unknown	MODERATE
----------(b)(6)----	Ventricular tachycardia	non - sustained VT	1.4 days	MODERATE
	Acute myocardial infarction	ST segment elevation myocardial infarction	1.4 days	MODERATE
	Acute pulmonary oedema	flash pulmonary edema	1.4 days	MODERATE

Unique Subject Identifier	Dictionary-Derived Term	Reported Adverse Event	Start Time of AE Relative to IMP Start	Severity/ Intensity
	Nausea	nausea	1.4 days	MODERATE
	Cough	cough	1.4 days	MODERATE
	Incision site pain	incision pain	1.4 days	MODERATE
	Ventricular tachycardia	non - sustained VT	2 days	MILD
	Acute pulmonary oedema	flash pulmonary edema	2 days	MILD
	Acute myocardial infarction	ST segment elevation myocardial infarction	2 days	MILD
	Nausea	nausea	2 days	MILD
	Cough	cough	2 days	MILD
	Incision site pain	incision pain	2 days	MILD
	Ventricular tachycardia	non - sustained VT	2.3 hrs	MODERATE
	Acute myocardial infarction	ST segment elevation myocardial infarction	2.3 hrs	MODERATE
	Nausea	nausea	2.3 hrs	MODERATE
	Cough	cough	2.3 hrs	MODERATE
	Incision site pain	incision pain	2.3 hrs	MODERATE
	Acute pulmonary oedema	flash pulmonary edema	2.3 hrs	MODERATE
	Ventricular tachycardia	non - sustained VT	3.4 days	SEVERE
	Acute pulmonary oedema	flash pulmonary edema	3.4 days	SEVERE
	Acute myocardial infarction	ST segment elevation myocardial infarction	3.4 days	SEVERE
	Nausea	nausea	3.4 days	SEVERE
	Cough	cough	3.4 days	SEVERE
	Incision site pain	incision pain	3.4 days	SEVERE
	Ventricular tachycardia	non - sustained VT	4 days	MODERATE
	Acute pulmonary oedema	flash pulmonary edema	4 days	MODERATE
	Acute myocardial infarction	ST segment elevation myocardial infarction	4 days	MODERATE
	Nausea	nausea	4 days	MODERATE
	Cough	cough	4 days	MODERATE

Unique Subject Identifier	Dictionary-Derived Term	Reported Adverse Event	Start Time of AE Relative to IMP Start	Severity/ Intensity
	Incision site pain	incision pain	4 days	MODERATE
	Ventricular tachycardia	non - sustained VT	5 days	MODERATE
	Acute pulmonary oedema	flash pulmonary edema	5 days	MODERATE
	Acute myocardial infarction	ST segment elevation myocardial infarction	5 days	MODERATE
	Nausea	nausea	5 days	MODERATE
	Cough	cough	5 days	MODERATE
	Incision site pain	incision pain	5 days	MODERATE
----------(b)(6)-----	Tumour haemorrhage	tumor hemorrhage	39.3 days	SEVERE
---------- (b)(6)----	Vena cava injury	post procedure rupture of vena cava inferior	2.1 days	SEVERE
	Intestinal obstruction	bowel obstruction	2.1 days	SEVERE
	Gastrointestinal haemorrhage	gastro-intestinal bleeding	2.1 days	SEVERE
	Renal failure acute	acute renal failure	2.1 days	SEVERE
	Vena cava injury	post procedure rupture of vena cava inferior	3.5 days	SEVERE
	Intestinal obstruction	bowel obstruction	3.5 days	SEVERE
	Gastrointestinal haemorrhage	gastro-intestinal bleeding	3.5 days	SEVERE
	Renal failure acute	acute renal failure	3.5 days	SEVERE
	Vena cava injury	post procedure rupture of vena cava inferior	4.4 days	SEVERE
	Intestinal obstruction	bowel obstruction	4.4 days	SEVERE
	Gastrointestinal haemorrhage	gastro-intestinal bleeding	4.4 days	SEVERE
	Renal failure acute	acute renal failure	4.4 days	SEVERE
	Vena cava injury	post procedure rupture of vena cava inferior	4.8 days	SEVERE
	Intestinal obstruction	bowel obstruction	4.8 days	SEVERE
	Gastrointestinal haemorrhage	gastro-intestinal bleeding	4.8 days	SEVERE
	Renal failure acute	acute renal failure	4.8 days	SEVERE
---------- (b)(6)----	Hepatic mass	liver mass	1 day	MODERATE

Unique Subject Identifier	Dictionary-Derived Term	Reported Adverse Event	Start Time of AE Relative to IMP Start	Severity/ Intensity
	Oedema peripheral	trace pedal edema	1 day	MODERATE
	Back pain	left mild back pain	1 day	MODERATE
	Hallucination	mild hallucinations	1 day	MODERATE
	Lung carcinoma cell type unspecified stage iv	worsening advanced stage lung cancer	1 day	MODERATE
	Confusional state	confusion	1 day	MODERATE
	Arthralgia	left knee pain	1 day	MODERATE
	Arthralgia	left knee pain	11.9 hrs	MILD
	Hepatic mass	liver mass	11.9 hrs	MILD
	Oedema peripheral	trace pedal edema	11.9 hrs	MILD
	Back pain	left mild back pain	11.9 hrs	MILD
	Hallucination	mild hallucinations	11.9 hrs	MILD
	Lung carcinoma cell type unspecified stage iv	worsening advanced stage lung cancer	11.9 hrs	MILD
	Confusional state	confusion	11.9 hrs	MILD
	Arthralgia	left knee pain	14.8 hrs	MILD
	Hepatic mass	liver mass	14.8 hrs	MILD
	Oedema peripheral	trace pedal edema	14.8 hrs	MILD
	Back pain	left mild back pain	14.8 hrs	MILD
	Hallucination	mild hallucinations	14.8 hrs	MILD
	Lung carcinoma cell type unspecified stage iv	worsening advanced stage lung cancer	14.8 hrs	MILD
	Confusional state	confusion	14.8 hrs	MILD
	Arthralgia	left knee pain	2.0 days	MILD
	Hepatic mass	liver mass	2.0 days	MILD
	Oedema peripheral	trace pedal edema	2.0 days	MILD
	Back pain	left mild back pain	2.0 days	MILD
	Hallucination	mild hallucinations	2.0 days	MILD
	Lung carcinoma cell type unspecified stage iv	worsening advanced stage lung cancer	2.0 days	MILD
	Confusional state	confusion	2.0 days	MILD
	Arthralgia	left knee pain	5.0 days	MILD

Unique Subject Identifier	Dictionary-Derived Term	Reported Adverse Event	Start Time of AE Relative to IMP Start	Severity/ Intensity
	Hepatic mass	liver mass	5.0 days	MILD
	Oedema peripheral	trace pedal edema	5.0 days	MILD
	Back pain	left mild back pain	5.0 days	MILD
	Hallucination	mild hallucinations	5.0 days	MILD
	Lung carcinoma cell type unspecified stage iv	worsening advanced stage lung cancer	5.0 days	MILD
	Confusional state	confusion	5.0 days	MILD
	Arthralgia	left knee pain	5.4 hrs	MILD
	Hepatic mass	liver mass	5.4 hrs	MILD
	Oedema peripheral	trace pedal edema	5.4 hrs	MILD
	Back pain	left mild back pain	5.4 hrs	MILD
	Hallucination	mild hallucinations	5.4 hrs	MILD
	Lung carcinoma cell type unspecified stage iv	worsening advanced stage lung cancer	5.4 hrs	MILD
	Confusional state	confusion	5.4 hrs	MILD
	Arthralgia	left knee pain	Unknown	SEVERE
	Hepatic mass	liver mass	Unknown	SEVERE
	Oedema peripheral	trace pedal edema	Unknown	SEVERE
	Back pain	left mild back pain	Unknown	SEVERE
	Hallucination	mild hallucinations	Unknown	SEVERE
	Lung carcinoma cell type unspecified stage iv	worsening advanced stage lung cancer	Unknown	SEVERE
	Confusional state	confusion	Unknown	SEVERE
---------- (b)(6)----	Embolic cerebral infarction	Embolic L frontal infarct.	1.0 day	MILD
	Cardiac failure congestive	worsening congestive heart failure	1.0 day	MILD
	Oedema peripheral	edema LLE and RUE	1.0 day	MILD
	Hypoxia	hypoxia: decreased oxygen levels noted.	1.0 day	MILD
	Labile blood pressure	unstable blood pressure	1.0 day	MILD
	Pulmonary oedema	pulmonary edema noted.	1.0 day	MILD
	Blood creatine increased	elevated creatine levels	1.0 day	MILD

Unique Subject Identifier	Dictionary-Derived Term	Reported Adverse Event	Start Time of AE Relative to IMP Start	Severity/ Intensity
	Dysphagia	pharyngeal dysphagia - delayed and weakability to swollow	1.0 day	MILD
	Tachyarrhythmia	irregular tachycardia	1.0 day	MILD
	Labile blood pressure	unstable blood pressure	1.4 days	MODERATE
	Cardiac failure congestive	worsening congestive heart failure	1.4 days	MODERATE
	Oedema peripheral	edema LLE and RUE	1.4 days	MODERATE
	Embolic cerebral infarction	Embolic L frontal infarct.	1.4 days	MODERATE
	Hypoxia	hypoxia: decreased oxygen levels noted.	1.4 days	MODERATE
	Pulmonary oedema	pulmonary edema noted.	1.4 days	MODERATE
	Blood creatine increased	elevated creatine levels	1.4 days	MODERATE
	Dysphagia	pharyngeal dysphagia - delayed and weakability to swollow	1.4 days	MODERATE
	Tachyarrhythmia	irregular tachycardia	1.4 days	MODERATE
	Cardiac failure congestive	worsening congestive heart failure	2.2 days	MILD
	Oedema peripheral	edema LLE and RUE	2.2 days	MILD
	Hypoxia	hypoxia: decreased oxygen levels noted.	2.2 days	MILD
	Labile blood pressure	unstable blood pressure	2.2 days	MILD
	Pulmonary oedema	pulmonary edema noted.	2.2 days	MILD
	Blood creatine increased	elevated creatine levels	2.2 days	MILD
	Dysphagia	pharyngeal dysphagia - delayed and weakability to swollow	2.2 days	MILD
	Tachyarrhythmia	irregular tachycardia	2.2 days	MILD
	Embolic cerebral infarction	Embolic L frontal infarct.	2.2 days	MILD
	Cardiac failure congestive	worsening congestive heart failure	22.8 hrs	MILD
	Oedema peripheral	edema LLE and RUE	22.8 hrs	MILD
	Embolic cerebral infarction	Embolic L frontal infarct.	22.8 hrs	MILD
	Hypoxia	hypoxia: decreased oxygen levels noted.	22.8 hrs	MILD

Unique Subject Identifier	Dictionary-Derived Term	Reported Adverse Event	Start Time of AE Relative to IMP Start	Severity/ Intensity
	Labile blood pressure	unstable blood pressure	22.8 hrs	MILD
	Pulmonary oedema	pulmonary edema noted.	22.8 hrs	MILD
	Blood creatine increased	elevated creatine levels	22.8 hrs	MILD
	Dysphagia	pharyngeal dysphagia - delayed and weakability to swollow	22.8 hrs	MILD
	Tachyarrhythmia	irregular tachycardia	22.8 hrs	MILD
	Cardiac failure congestive	worsening congestive heart failure	3 days	SEVERE
	Oedema peripheral	edema LLE and RUE	3 days	SEVERE
	Embolic cerebral infarction	Embolic L frontal infarct.	3 days	SEVERE
	Hypoxia	hypoxia: decreased oxygen levels noted.	3 days	SEVERE
	Labile blood pressure	unstable blood pressure	3 days	SEVERE
	Pulmonary oedema	pulmonary edema noted.	3 days	SEVERE
	Blood creatine increased	elevated creatine levels	3 days	SEVERE
	Dysphagia	pharyngeal dysphagia - delayed and weakability to swollow	3 days	SEVERE
	Tachyarrhythmia	irregular tachycardia	3 days	SEVERE
	Cardiac failure congestive	worsening congestive heart failure	3.2 days	MILD
	Oedema peripheral	edema LLE and RUE	3.2 days	MILD
	Embolic cerebral infarction	Embolic L frontal infarct.	3.2 days	MILD
	Labile blood pressure	unstable blood pressure	3.2 days	MILD
	Pulmonary oedema	pulmonary edema noted.	3.2 days	MILD
	Blood creatine increased	elevated creatine levels	3.2 days	MILD
	Dysphagia	pharyngeal dysphagia - delayed and weakability to swollow	3.2 days	MILD
	Tachyarrhythmia	irregular tachycardia	3.2 days	MILD
	Hypoxia	hypoxia: decreased oxygen levels noted.	3.2 days	MILD
	Cardiac failure congestive	worsening congestive heart failure	3.2 days	MILD
	Oedema peripheral	edema LLE and RUE	3.2 days	MILD
	Embolic cerebral	Embolic L frontal infarct.	3.2	MILD

Unique Subject Identifier	Dictionary-Derived Term	Reported Adverse Event	Start Time of AE Relative to IMP Start	Severity/ Intensity
	infarction		days	
	Hypoxia	hypoxia: decreased oxygen levels noted.	3.2 days	MILD
	Labile blood pressure	unstable blood pressure	3.2 days	MILD
	Pulmonary oedema	pulmonary edema noted.	3.2 days	MILD
	Blood creatine increased	elevated creatine levels	3.2 days	MILD
	Dysphagia	pharyngeal dysphagia - delayed and weakability to swollow	3.2 days	MILD
	Tachyarrhythmia	irregular tachycardia	3.2 days	MILD
	Cardiac failure congestive	worsening congestive heart failure	3.5 days	MODERATE
	Oedema peripheral	edema LLE and RUE	3.5 days	MODERATE
	Embolic cerebral infarction	Embolic L frontal infarct.	3.5 days	MODERATE
	Hypoxia	hypoxia: decreased oxygen levels noted.	3.5 days	MODERATE
	Labile blood pressure	unstable blood pressure	3.5 days	MODERATE
	Pulmonary oedema	pulmonary edema noted.	3.5 days	MODERATE
	Blood creatine increased	elevated creatine levels	3.5 days	MODERATE
	Dysphagia	pharyngeal dysphagia - delayed and weakability to swollow	3.5 days	MODERATE
	Tachyarrhythmia	irregular tachycardia	3.5 days	MODERATE
	Pulmonary oedema	pulmonary edema noted.	3.9 days	MILD
	Blood creatine increased	elevated creatine levels	3.9 days	MILD
	Dysphagia	pharyngeal dysphagia - delayed and weakability to swollow	3.9 days	MILD
	Tachyarrhythmia	irregular tachycardia	3.9 days	MILD
	Cardiac failure congestive	worsening congestive heart failure	3.9 days	MILD
	Oedema peripheral	edema LLE and RUE	3.9 days	MILD
	Embolic cerebral infarction	Embolic L frontal infarct.	3.9 days	MILD
	Hypoxia	hypoxia: decreased oxygen levels noted.	3.9 days	MILD

Unique Subject Identifier	Dictionary-Derived Term	Reported Adverse Event	Start Time of AE Relative to IMP Start	Severity/ Intensity
	Labile blood pressure	unstable blood pressure	3.9 days	MILD
---------- (b)(6)----	Cardio-respiratory arrest	worsening of cardiopulmonary disease	47.2 days	SEVERE

[a]**Note that Beriplex subject --(b)(6)-- did not appear in this J-Review-generated table of AEs in subjects who died; therefore this subject was not included in the Reviewer's blinded analyses of deaths.**

Reviewer's Blinded Assessment of Possible Relationship between Death and Test Product Administration Based on Timing of Adverse Events[b]

Subject ID	Possible Relationship to Test Product Administration[a]	Randomized Treatment Group
--(b)(6)--	1	P
--(b)(6)--	2	P
--(b)(6)--	0	P
--(b)(6)--	0	P
--(b)(6)--	2	P
--(b)(6)--	0	P
--(b)(6)--	0	B
--(b)(6)--	0	B
--(b)(6)--	2	P
--(b)(6)--	0	B (death 47.2 days)
N = 10 (N = 9 who died within 45 days)	7/8 = 0.875 (among subjects who died within 45 days	

[a]**Reviewer's Death Potential Relatedness Score Definitions: 1 = No to little Relationship; 1 = Some possible Relationship; 2 = Possible Relationship to Test Product Administration)**

[b] **Note that Beriplex subject --(b)(6)-- did not appear in the J-Review-generated table of AEs in subjects who died, which was based on the datasets included in the original BLA submission; therefore this subject was not included in the Reviewer's blinded analyses of deaths.**

Comparisons of the total potential death relatedness scores determined by my blinded analysis of the timing of associated adverse events for each treatment group and the number of subjects in each treatment group with scores of 0, 1, and 2 are given in the following table.

Reviewer's Death Potential Related Scores by Treatment Group[b] - Study BE1116_3003

Comparison	Beriplex	Plasma
Subjects with Score[a] = 0	3	3
Subjects with Score = 1	0	1
Subjects with Score = 2	0	3
Subjects with Score = 1 or 2	0	4
Total Score	0	7

[a]Blinded Death Causality Score Definitions:
0 = Little to no Relationship;
1 = Some Possible Relationship;
2 = Plausible Relation to Study Product

[b]**Note that Beriplex subject --(b)(6)-- did not appear in the J-Review-generated table of AEs in subjects who died; therefore this subject was not included in the Reviewer's blinded analyses of deaths.**

Reviewer's Post-Hoc Analysis of Deaths by Treatment Group Excluding Deaths Attributed to Malignancy - Study BE1116_3003

Comparison	Beriplex	Plasma
Total Deaths	4	7
Deaths Attributed to Malignancy	1	1
Deaths Excluding Those Attributed to	3	6

Comparison	Beriplex	Plasma
Malignancy		

Subject IDs where Death was attributed to Malignancy:
Beriplex: --(b)(6)-- ("worsening advanced stage lung cancer")
Plasma: --(b)(6)-- ("tumor hemorrhage")

Reviewer's Post-Hoc Analysis of Deaths by Treatment Group Excluding Deaths Attributed to Malignancy or Sepsis - Study BE1116_3003

Comparison	Beriplex	Plasma
Total Deaths	4	7
Deaths Attributed to Malignancy	1	2
Deaths Excluding Those Attributed to Malignancy	3	5

Subject IDs where Death was attributed to Malignancy:
Beriplex: --(b)(6)-- ("worsening advanced stage lung cancer");
Plasma: --(b)(6)-- ("tumor hemorrhage"); --(b)(6)-- ("septic shock")

Listed Causes of Death with Relative Start Time of Serious Adverse Event Reported to be the Cause of Death[a] - Study BE1116_3003

Subject ID	Randomized Treatment Group	SAE to which Death was Attributed	Relative Start Time of AE to which Death was Atrributed[b]
--(b)(6)--	P	Death	16 days
--(b)(6)--	P	Pulmonary Embolus	25 days[d]
--(b)(6)--	P	Cardiac Arrest	16.6 days
--(b)(6)--	P	Septic Shock	19.7 days
--(b)(6)--	P	ST Segment Elevation Acute Myocardial Infarction	3.4 days[e]
--(b)(6)--	P	Tumor Hemorrhage	39.3 days
--(b)(6)--	P	Worsening Congestive Heart Failure	3 days
--(b)(6)--	B	Worsening Advanced Stage Lung Cancer	1 day
--(b)(6)--	B (death 47.2 days)	Worsening of CardioPulmonary Disease	47.2 days
--(b)(6)--[c]	B	GI Hemorrhage	4.8 days
--(b)(6)--	B	Intestinal Obstruction	4.4 days[f]

[a]Source: Sponsor's Listing 16.2.7 from 10 week Safety Update Interim Analysis Report (BLA Amendment 1); .

[b]Not necessarily the same as the relative date of death

[c] Note that Beriplex subject --(b)(6)-- did not appear in the J-Review-generated table of AEs in subjects who died; therefore this subject was not included in the Reviewer's blinded analyses of deaths

[d]Note that subject (b)(6) also had reported a leg DVT with relative start time of 15.9 hours managed with an IVC filter, said to have resolved.

[e]Note that subject (b)(6) also had reported acute pulmonary edema with a relative start time of 2.3 hours, said to have resolved.
[f]Note that subject (b)(6) also had reported acute renal failure with a relative start time of 3.5 days.

Review of Safety Update (BLA Amendment 01 Received 31 May 2012) – Interim Safety Analysis Ongoing Surgery Study BE1116_3003 ("Interim CSR")

No additional deaths were reported in the interim analysis included in amendment 01 not already included in the earlier interim analysis of study _3003 included in the original BLA. The safety update includes safety data from 155 treated subjects (77 Beriplex and 78 plasma) through the data cutoff date of 16 Nov 2011.

FOREIGN POSTMARKETING SURVEILLANCE

Beriplex was first marketed overseas in 1996. It is currently registered for marketing in 24 foreign countries. Review of an in-progress spreadsheet provided by Dr. Sukhminder Sandhu from DBA reveals ~ 24 postmarketing cases of thrombotic and thromboembolic events in patients who had received Beriplex. Due to disparate postmarketing surveillance mechanisms in different foreign countries, no estimate of under-reporting is available.

Conclusion and Recommendations

- Beriplex has been shown in one adequate and well-controlled trial to be non-inferior to plasma in the urgent reversal of VKA anticoagulation in patients with major bleeds as defined in protocol BE1116_3002.

- There is a potential safety signal from RCT bleeding BE1116_3002 in terms of a non-statistically significant > 2-fold excess 45-day all-cause mortality. As well as being a safety endpoint, all-cause 45 mortality was a pre-specified efficacy endpoint. The imbalance in favor of plasma persisted after sequentially removing subjects whose deaths were attributed to (a) malignancy or (b) sepsis in an *unblinded* post-hoc analysis conducted by this reviewer. The imbalance in

deaths became more pronounced in a reviewer-conducted *blinded* analysis of deaths potentially causally related to administration of the test products.

- The potential safety signal for increased mortality was not reflected in interim data from ongoing RCT BE1116_3003 in which subjects who require urgent reversal of VKA anticoagulation due to the need for urgent surgery or an invasive procedure are randomly treated with Beriplex or plasma in the same doses as were used in completed bleeding study BE1116_3003. The number of deaths (n = 11) in the ongoing surgery study was less than that in the completed bleeding study (n = 16), but the direction of the imbalance was reversed in favor of Beriplex. This imbalance persisted in *unblinded* reviewer conducted analyses removing sequentially deaths attributed by the investigator to (a) malignancy or (b) sepsis. The imbalance in favor of Beriplex became more pronounced in a reviewer-conducted *blinded* analysis of deaths potentially causally related to administration of the test products.

- Although it may be tempting to pool deaths across bleeding and surgery RCTs, we need to recognize that there may be factors which would lead to different risks of the test products in the 2 different settings. In the surgery setting, unlike in the bleeding setting, subjects have their INR corrected before surgery is undertaken and subjects may have different surgery-related outcomes due to the nature of the surgery and associated care by the anesthesiologist and other surgical team members. The teams managing bleeding subjects are likely to be primarily drawn from the medical rather than surgical specialties and the perturbations to the clotting system (consumption coagulopathy) as a result of non-surgical bleeding may be different from those in the surgical setting.

RECOMMENDATIONS:

- Presentation of the safety and efficacy data to BPAC with the questions:

    - "Given the similar hemostatic efficacy outcomes in the single randomized, open-label, plasma-controlled study to urgently reverse vitamin K antagonist (VKA) anticoagulation in

bleeding patients, BE1116_3002 and the available safety findings showing an unfavorable trend for Beriplex Human Prothrombin Complex Concentrate in 45-day mortality in this study and for another Human Prothrombin Complex Concentrate product in an interim analysis of an ongoing surgery study in patients requiring urgent VKA anticoagulation reversal, do you recommend additional safety data, including mortality data, be collected in order to provide substantial evidence of safety for Beriplex for the indication being sought?

- If not, what additional postmarketing study/studies and/or changes to the pharmacovigilance plan for Beriplex do you recommend to better characterize the comparative safety profile of Beriplex to plasma/FFP?

- This application at the present time triggers PREA because the sponsor's orphan product designation is currently being held in abeyance (see 09 March 2012 letter from Orphan Products). The sponsor requests a **full waiver** from conducting studies using Beriplex for the urgent reversal of vitamin K antagonist (e.g., warfarin) therapy in pediatric patients with acute major bleeding. "CSLB has determined that the necessary studies are impossible or highly impracticable and the product is not likely to be used in a substantial number of patients." **I recommend the sponsor's full waiver request for pediatric studies be granted because it is unlikely that the requisite number of pediatric subjects could be enrolled in efficacy and safety studies in a reasonable timeframe of several years.**

Reviewer's Discussion Regarding Safety and Efficacy

The safety and efficacy results from study BE1116_3002 for Beriplex PCC demonstrate that the product is non-inferior to plasma for the bleeding indication being sought, but was associated with a ~ 2-fold higher total mortality, a slightly higher incidence of suspected thrombotic and thromboembolic AEs, and a somewhat lower incidence of volume-overload-associated AEs. The prospectively planned statistical test for superiority for the co-primary hemostatic efficacy endpoint was did not support any

conclusion that Beriplex may be more effective than plasma for the requested bleeding indication. The fact that a much larger percentage of the Beriplex group subjects than the plasma group subjects had normalized their INR values to ≤ 1.3 at 30 min following the end of test product infusion did not translate into a significant superiority for hemostatic efficacy seems consistent with the findings in the retrospective study of Goldstein et al. (Timing of fresh frozen plasma administration and rapid correction of coagulopathy in warfarin-related intracebral hemorrhage. Stroke. 2006:37:151-155), which found no improvement in clinical outcome among those patients whose INR was corrected by 24 hours compared to those patients had not been corrected by that time point.

One possible bias in the design of pivotal study BE1116_3002 was that the protocol-prescribed range of doses of Beriplex expressed on a FIX IU/kg basis varied over a 2-fold range (from 25 to 50 IU/kg), depending on the subject's baseline INR value, whereas the dose of plasma varied over only a 1.5-fold range (from 10 to 15 mL/kg), also dependent on the subject's baseline INR value. The sponsor points out that in the study report that, although the selected dosing scheme for plasma "falls within a range that may be expected in clinical practice (Baker 2004, American Society of Anesthesiologists Task Force on Blood Component Therapy 1996, Chowdhury 2004, Makris 2001, Silberstein 1989, Goodnough 2011)," there is no universal standard for selecting plasma dose for the requested indication. The fact that the clear superiority of Beriplex over plasma in achieving the co-primary endpoint of INR reduction to ≤ 1.3 at 30 minutes post end of infusion did not translate into a significant superiority in hemostatic efficacy suggests one or more of the following possibilities:

- INR reduction to ≤ 1.3 is not an appropriate surrogate endpoint for assessment of hemostatic efficacy of PCC in this setting.

- Adequate hemostasis may be achieved in this setting using plasma with an INR reduction to a level > 1.3.

- The possibility also exists that adequate hemostasis may be achieved in this setting using PCC with an INR reduction to a level > 1.3.

Indeed, some centers use an INR threshold of 1.5 for the urgent reversal of VKA anticoagulation in patients requiring urgent surgery or invasive procedures. However, it is not at all clear that this threshold is data driven.

Some studies have been done suggesting that lowering the INR from values greater than 1.5 prior to performing some invasive procedures such as percutaneous liver biopsy is not medically necessary. Whether that also applies to the bleeding indication being sought is plausible, but unknown. It is reasonable to assume, however, that at some level of INR perturbation from VKA therapy, reversal of the hemostatic deficit in a bleeding patient will confer benefit in helping to arrest bleeding. However, the minimal and optimal threshold for such INR reduction that will confer benefit remains unknown, and there may well be differences between the ability of the INR to correlate with bleeding risk after the INR has been lowered with a PCC product as opposed to lowering by stopping VKA therapy with or without vitamin K therapy. In other words, the nature and slope of the curve of hemostatic impairment vs. INR values may be different in patients who have received PCC products vs. patients who have received plasma, or just had their VKA therapy withheld.

APPENDICES

Appendix 1

Summary of Sponsor's Priority Review Request

"In warfarin-associated acute critical bleeding situations and in acute care in general, patients need urgent, controlled reversal of the anticoagulation effect by rapid replacement of vitamin K-dependent coagulation proteins."

"The population with an acute intracranial hemorrhage has a high mortality rate and requires rapid control of hemorrhage. The American Heart Association /American Stroke Association guidelines recommend correction of the International Normalized Ratio (INR) as rapidly as possible for patients receiving oral anticoagulants with bleeding such as intracranial hemorrhage [Morgenstern et al. 2010]. In the setting of acute and emergency care, the goal is to stop bleeding as quickly as possible in order to reduce the burden of hemorrhage (shock load reduction) and consequently reduce the amount of administered blood products. The shorter infusion time of Beriplex compared to FFP will provide prompt onset of care by urgently reversing the anticoagulant effects of vitamin K antagonists in subjects requiring emergency treatment to stop major bleeding [Speed of Administration]."

"Withholding vitamin K antagonists and administering vitamin K are routine interventions that may correct an elevated INR after 24hours. However, when urgent correction is required, fresh frozen plasma (FFP) or Prothrombincomplex concentrates (PCCs) are recommended [Baglin 1998, Makris et al. 2001]. In the US, FFP is regarded as standard therapy for patients requiring urgent reversal of over-anticoagulation despite its many safety concerns and preparation/administration drawbacks."

"Currently, 3 main therapeutic options exist to treat or prevent bleeding in these patients:

- Substitution with FFP
- Vitamin K preparations and
- Prothrombin complex concentrates.

"Fresh frozen plasma seems to have limited efficacy and particular safety concerns in the correction of coagulation factor levels compared to PCC's. In the fiscal year (FY) 2009, the transfusion related fatalities reported (by complication) to the FDA [FDA 2009] and listed by decreasing numbers of reports are:

- Transfusion related acute lung injury (TRALI)
- Hemolytic Transfusion Reactions
- Transfusion Associated Circulatory Overload (TACO) and
- Microbial Infection."

"Transfusion associated respiratory distress can be related to fluid overload, allergic reactions or TRALI and occurs more in older patients with a history of congestive heart failure."

"The Beriplex dose needed to reverse the effects of vitamin K antagonists can be administered in a significantly smaller volume (~20 to 40 mL) compared to a standard unit of FFP (250 to 600 mL). In addition to volume overload, transfusion of large volumes of FFP may result in progressive hyperkalemia, hypocalcaemia and acidosis."

"Plasma contains all plasma proteins as well as anaphylatoxins possibly leading to allergic reactions [Contreras et al. 1992, Sonntag et al. 1997]. When FFP is used for the reversal of the effect of vitamin K antagonists, patients are concomitantly administered a high load of unwanted proteins."

Risk of Virus Transmission

Risks of viral transmission with plasma are estimated at approximately 1 in 3 x 105 for HBV and 1 in 2 x 106 for HCV and HIV [Bihl et al. 2007]. All plasma used in the manufacture of Beriplex is obtained from US donors and must pass virus screening before being used in manufacturing. All US donors are tested for serological markers including HBsAg, antibodies against HIV-1/2 and HCV. In addition, --(b)(4)-- of donated plasma are tested for the presence genomic material of HAV, HBV, HCV, HIV-1, and high titers of B19V by nucleic acid testing. All manufacturing pools are tested for anti-HIV 1/2 and HBsAg and for genomic material of HAV, HBV, HCV, HIV-1 and high titers of B19V.

"Beriplex's manufacturing process and testing (in-process, release and stability) provide consistent quality assurance for each lot. The manufacturing process incorporates various steps that contribute to the reduction or inactivation of enveloped and non-enveloped viruses, including heat treatment of the preparation in aqueous solution at 60°C for 10 hours, adsorption and virus filtration (nanofiltration)."

Transfusion Related Acute Lung Injury

Plasma has been implicated in TRALI [Silliman et al. 2005] which is an acute lung injury occurring within 6 hours of transfusion. TRALI has been reported with a frequency of 1:7,896 to 1:74,000 for FFP transfusions [Kleinman et al. 2004] and 1:5,000 for platelet and FFP transfusions [Bux 2005]… Because the injury is provoked by anti-HLA antibodies and leukoagglutinins present in the transfused product, the American Association of Blood Banks recently recommended that transfusion services take measures to exclude women with a history of pregnancy from the donor pool [Popovski et al. 2010]. The intervention reduced incidence of TRALI to approximately 1 in 12,000

Transfusion Associated Circulatory Overload

"Although, there is no universal standard for the volume of FFP to be used for reversal of vitamin K antagonists, a volume of 10-15 mL/kg is common [Goodnough et al. 2011, Anesthesiology 1996, Chowdhury et al. 2004]. For a 70 kg patient, this is approximately 700-1050 mL or 3 to 5 units of FFP.

While such volumes may be acceptable and tolerated by an individual with normal cardiac function, the risk of circulatory overload increases when a patient has compromised cardiac function, as is commonly the case in the population receiving vitamin K antagonists (e.g., atrial fibrillation, artificial cardiac valves, etc.) [Li et al. 2011]. The risk of TACO increases when FFP is administered rapidly, as is typical when acute major bleeding is present [Li et al. 2011]. Even if administration of 4 units of FFP could be tolerated at an infusion rate of 10 mL/min, the time to complete the transfusion would be approximately 1.5 hours. The advantage of Beriplex is the high concentration of vitamin K dependent coagulation factors with a reduced total volume of product that enables a faster administration rate."

Speed of Administration

"Due to significant differences in volume between Beriplex and FFP, a therapeutic dose of Beriplex can be safely administered in a much shorter period of time than one unit of FFP… In the BLA pivotal clinical Study No. BE1116_3002, the mean infusion duration of Beriplex (approximately 24 minutes) was substantially less than FFP (approximately169 minutes) in this comparative study. Beriplex can be administered about 7-fold faster with only 12% of the infused volume required for treatment with FFP."

Preparation and Administration

"When FFP is used, it needs to be thawed which requires additional time and costs [Makris et al. 2001]… Thawing, requires a technician to be involved, typically takes approximately 30 to 45 minutes and can creates delays that are unacceptable in cases where FFP administration is urgent. Beriplex can be stored up to 36 months at temperatures between (2 to 25○C) and reconstituted quickly for administration. In emergency room settings, this provides a major convenience benefit over FFP's longer preparation time which includes blood typing, thawing of frozen plasma, transport from the blood bank storage and administration."

Hemolytic Transfusion Reactions

"Therapy with FFP requires transfusions according to ABO-isoagglutinin. FFP must be administered to patients according to ABO blood group in order to prevent hemolysis by passively transfused antibodies [Contreras et al. 1992, Urbaniak et al. 1977]… Identifying a patient's blood type can

require up to an hour including the time to order the test, collect the blood specimens and perform the typing reactions [Goodnough et al. 2011]."

Rapidity of INR response to a level < 1.3

Also, the INR level after the start of infusion showed a more rapid decrease at 30 minutes in the Beriplex group compared to the FFP group with a statistically significant difference up to 12 hours.

Discussion of Sponsor's Priority Review Request

Criteria for granting priority review by CBER are as follows (see Appendix for Ref):

> The product would be a significant improvement in the safety or effectiveness of the treatment, diagnosis or prevention of a serious or life-threatening disease. Examples include:
>
> - documented improvement in patient compliance
> - elimination or significant reduction of a treatment-limiting drug reaction
> - ***demonstration*** [emphasis added] of safety or effectiveness in a new subpopulation of patients with the disease.

I concluded that the data provided in the BLA have not established that with Beriplex, in comparison to fresh frozen plasma, there would be a significant improvement in the safety or effectiveness of the treatment, of a serious or life-threatening disease. For priority review, the theoretical possibility of providing [greater] safety or effectiveness in a new subpopulation [or the entire population] of patients with the disease should have been demonstrated, i.e. shown with statistical and clinical significance. This is not the case for Beriplex for the indication being sought.

The protocol and prospective statistical analysis plan had provision for both non-inferiority and superiority testing for hemostatic efficacy for Beriplex vs. FFP. As regards the hemostatic efficacy co-primary endpoint of the pivotal study BE11116_002, while non-inferiority of Beriplex in relation to

FFP was demonstrated, Beriplex was not found to be statistically significantly superior to FFP.

Although the product was able to be administered a mean of 145.5 minutes more rapidly than the full protocol-determined FFP dose, this difference did not translate into a statistically significant advantage in terms of efficacy. Thus, it has not been demonstrated that the reduced preparation time, lack of need for cross-matching, and faster administration time with Beriplex translates into any meaningful clinical advantage to patients in terms of hemostatic outcome.

The sponsor has not presented evidence of effectiveness in a new subpopulation of patients with the disease as compared to FFP.

FFP was chosen as the positive comparator for the pivotal trials for Beriplex because FDA endorses the AABB product circular with regard to indications for FFP. This is considered equivalent to FFP carrying an FDA-approved indication for urgent reversal of Warfarin anticoagulation in actively bleeding patients – the indication being sought in this BLA.

The sponsor has not presented data demonstration of [greater, in relation to FFP] safety in a new subpopulation of patients with the disease.

There was a small numerical excess of patients in the FFP group compared to the Beriplex group who developed volume overload/CHF/pulmonary edema. However, the numerical difference is too small to be statistically significant. In addition, safety among subjects with a history of congestive heart failure was not prospectively examined. The small numerical excess of volume overload/CHF/pulmonary edema AEs in the FFP group appears to be offset by a small numerical excess of TE events in the Beriplex group with some indication that some of the TE events in the FFP group were milder than in the Beriplex group (myocardial ischemia with FFP vs. MI with Beriplex).

APPENDIX 2

Brief Summaries of Each Amendment to BLA

Amendment 01 – Submitted and Received by FDA 31 May 2012

Safety Update from ongoing RCT BE1116_3003 including data from 155 subjects (78 Beriplex and 78 plasma) through data cutoff 16 Nov 2011.

Updated Risk Mgmt Plan

Updated annotated and clean draft PI

Updated clinical overview and summary

Updated Integrated Summary of Safety (ISS)

Postmarketing data – PSUR #7 and Summary Bridging Report 2005 - 2012

Amendment 02 - Submitted and Received by FDA 28 June 2012

Response to email FDA information request dated 28 June 2012 regarding clinical, PVP, and lot release product samples.

Revised tables in Clinical Study BE1116_3002 report

- Actual Beriplex dose (IU/kg) listed for some some subjects in Tables 50 (TE events) and 52 (deaths up to day 45) were in error and have been corrected to be consistent with data in subject listings and narratives.

APPENDIX 3

Summary of changes to protocol in IND amendment 19

- **Inclusion criteria changed to define acute major bleeding as any one of the following:**
  - **Life-threatening or potentially life-threatening**
  - **Acute bleeding with fall in Hb by** UU≥UU **2 g/dL**
  - **Bleeding requiring blood product transfusion (including plasma, RBCs and other coagulation factors)**
- **Lobar location only is eliminated from ICH locations listed in inclusion criteria (correction).**

- **Exclusion criteria were modified, including**
  - **changing "acute polytrauma (e.g., major motor vehicle accidents, penetrating injury or fall of > 20 feet…)" to "Acute trauma for which reversal of Vitamin K antagonists alone would not be expected to control the acute bleeding event."**
  - **Only ABC/2 will be used to estimate intra cerebral hemorrhage (ICH) volume**
  - **Correction of subdural hematoma maximum thickness of ≥ 10 mm or midline shift of ≥ 5 mm rather than < these values**
  - **Epidural hemorrhage is added**
  - **Intracerebral hemorrhage is added according to attachment 6 to amendment 19, but only intracerebral hematomas > 30 cc are added to exclusion criteria according to the protocol.**
  - **Modified Rankin score of >3 prior to ICH is added**
  - **Ambulatory without assistance prior to ICH is eliminated**
  - **Acute MI, DIC, angina, sepsis, or severe ischemic vascular disorder is changed to history of thrombotic event, MI, DIC, CVA, TIA, unstable angina pectoris, or severe peripheral vascular disease within 3 months of enrollment.**
  - **Life expectancy of < 2 months is eliminated. Life expectancy < 3 days is retained.**
  - **Known history of antiphospholipid antibody syndrome or lupus anticoagulant Ab is added.**
  - **Suspected or confirmed sepsis at time of enrollment is added.**
  - **PRBC transfusion is not an exclusion criterion.**
  - **Subject may not have been previously enrolled in [this or] any CSLB sponsored Beriplex study.**
- **Adherence to the 7th ACCP Conference on Antithrombotic and Thrombolytic Therapy Guidelines is recommended for the administration of vitamin K IV.**
- **Vitamin K1 will be provided in countries where the product is not marketed.**
- **Study flow chart is changed.**
- **The statement "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."**
- **Modified Rankin score is assessed at baseline.**
- **Glasgow Coma Score assessment is added at day 45.**
- **Calculation of ER time is corrected.**
- **"Signs and symptoms of bleeding, including non-visible bleeding (e.g., pain, swelling) should be documented in the baseline assessment. Only worsening of these symptoms should be recorded as adverse events" is added.**
- **The ACCP conference reference is added (Chest 2004; 126:204-23).**
- **Most study personnel are identified in the investigators' study files rather than in the protocol.**

Appendix 4

FDA Information Request dated 01 June 2012 with Sponsor Replies and Reviewer Comments on Sponsor Resposnes

1. There are AEs listed in module 2, section 2.7.4 (Summary of Clinical Safety) Table 15, "Possible thromboembolic TEAEs by preferred term and relatedness (investigator assessment) (Study 3003)" (acute myocardial infarction, deep venous thrombosis, pulmonary embolism, transient attack) which do not appear in Table 14, "Treatment related TEAEs by decreasing frequency (Study 3003)" of the same section. Also, the total number of subjects with acute pulmonary edema (n = 1) and of cardiac failure, congestive (n = 1) appearing in Table 14 are different from the total number of subjects for which these AEs are reported in Table 15 (n = 5 for pulmonary edema and n = 3 for cardiac failure, congestive). Please reconcile these apparent discrepancies.

Sponsor Response:

In Module 2.7.4 (30 March 2012 BLA), the differences in adverse event tabulations between

· Table 14 *Treatment-related TEAEs by decreasing frequency (Study 3003)* and

· Table 15 *Possible thromboembolic TEAEs by preferred term and relatedness (investigator assessment) (Study 3003)* and between Table 14 and

· Table 16 *Fluid overload and similar cardiac events (Study 3003)* correspond to differences between treatment related TEAEs (Table 14) and total TEAEs (Tables 15 and 16). Acute myocardial infarction, deep vein thrombosis, pulmonary embolism, transient ischemic attack, and cardiac failure congestive adverse events are correctly represented in Tables 14, 15, and 16. Of note, the term "pulmonary edema" (n=3 plasma, related) in Table 16 comprises the preferred terms "pulmonary edema" (n=2 plasma, related) and "acute pulmonary edema" (n=1 plasma, related) from Table 14.

Reviewer Comment:

Noted.

2. Please provide the location in the application where copies of the abbreviated informed consent forms which were utilized for study BE1116_3002. You state in section 5.3 of the study report that "In emergency situations when treatment of the subject was time critical, the subject was allowed to be enrolled under an abbreviated informed consent as allowed by the IEC/IRB in countries where such a procedure was permitted." Please provide a table of the subject ID numbers for those subjects enrolled under an abbreviated informed consent and the countries in which their study sites were located.

Sponsor Response:

One subject (050002) in the United States signed the abbreviated informed consent form (ICF) for Study 3002 on 12 August 2010 then signed the full ICF on 18 August 2010. The abbreviated informed consent form used for this subject has been added to the BLA as Appendix 16.1.3-2.6 in Module 5.3.5.1.1.

Reviewer Comment:

Noted.

3. Please provide for study BE1116_3002 a table showing the subject ID numbers and volume of plasma from each unit for each plasma unit administered for which the blood bank did not provide the volume of the plasma units furnished.

Sponsor Response:

Table 1 provides Study 3002 subject ID numbers, number of plasma units and the volume of each unit of plasma not provide by the blood bank.

Table 1: Clinical Study BE1116_3002 Plasma Unit Volumes

Subject ID	Number of plasma units	Volume of each unit of plasma (mL)	Total Dose volume (mL)	Comments
314009	4	200 200 200 230	830	IMP listing (16.2.5 - 2.1) states that the total volume of these units was administered to the subject.
314011	3	300 200 200	674	IMP listing (16.2.5 - 2.1) states that 674 mL of the total volume of these units was administered to the subject.
314012	2	250 250	500	Both unit lot numbers were specified, but unit volumes were unknown and assumed to be half the total dose (i.e. 250 mL). Pack size of 500 mL was a transcription error from the CRF. IMP listing (16.2.5 – 2.1) states that 500 mL represents the total volume administered to the subject from the 2 units.

Reviewer Comment:

Noted.

4. The define.pdf in BLA module 5, section 5.3.5.1.25.3.3 does not appear to list expanded dataset definitions for all fields for data tabulation datasets, but rather only for analysis datasets for study BE1116_3002. Please provide or describe the location of expanded dataset definitions for all fields for data tabulation datasets for all submitted studies.

Sponsor Response:

For IND-Studies 3002 and 3003, define.pdf files were provided for the analysis datasets and define.xml files were provided for the tabulation datasets (SDTMs). For non-IND Studies (3001, 1001, 7D-201KO), define .xml files were provided. The define.xml contains the definitions for all fields for data tabulation datasets. The ISS and ISE datasets include the define.pdf files. The location of each

define.pdf and define.xml file for the Beriplex BLA studies is listed in Table 2.

Table 2: Datasets' Location and Format for Beriplex BLA Studies

Clinical Study Number	Path	File name
BE1116_3002	0000\m5\datasets\be1116-3002\analysis\datasets	define.pdf
BE1116_3002	0000\m5\datasets\be1116-3002\tabulations\sdtm\datasets	define.xml
BE1116_3003	0001\m5\datasets\be1116-3003\analysis\datasets	define.pdf
BE1116_3003	0001\m5\datasets\be1116-3003\tabulations\sdtm\datasets	define.xml
BE1116_3001	0000\m5\datasets\be1116-3001\tabulations\sdtm\datasets	define.xml
BE1116_1001	0000\m5\datasets\be1116-1001\tabulations\sdtm\datasets	define.xml
Clinical Study Number	Path	File name
BE1116_7D-201KO	0000\m5\datasets\be1116-7d-201ko\tabulations\sdtm\datasets	define.xml
ISS	0001\m5\datasets\iss\analysis\datasets	define.pdf
ISE	0000\m5\datasets\ise\analysis\datasets	define.pdf

Reviewer Comment:

Noted.

Appendix 5

Priority Review – Summary of FDA Guidance and SOPPs Germane to Priority Review Request

The following is a quote from CBER SOPP 8405: Complete Review and Issuance of Action Letters, Version #4 dated 20 Sept 2004:

Priority Applications

The product, if approved by CBER or the Center for Drug Evaluation and Research (CDER), would be a significant improvement in the safety or effectiveness of the treatment, diagnosis or prevention of a serious or life-threatening disease. In addition, for drug products under CDER's jurisdiction, the product, if approved, would be a significant improvement in the treatment, diagnosis or prevention of a non-serious disease. Examples include:

- documented improvement in patient compliance
- elimination or significant reduction of a treatment-limiting drug reaction
- demonstration of safety or effectiveness in a new subpopulation of patients with the disease.

The following is a quote from the FDA Fast Track Guidance:

Because fast track products are intended to treat serious or life-threatening conditions and must demonstrate the potential to address unmet medical needs for such conditions, a BLA or NDA for a product in a fast track drug development program ordinarily will be eligible for priority review (see CBER and CDER procedures in Appendix 3).

It is foreseeable that, for certain products in fast track drug development programs, it will become apparent over the course of drug development that the development programs do not continue to meet the criteria for fast track designation. A product in a fast track development program may not continue to meet the criteria if the drug no longer (1) demonstrates a potential to address unmet medical needs…

It may no longer demonstrate a potential to address unmet needs, for example,…**if emerging clinical data failed to show that the product in a fast track development program had the anticipated advantage over existing therapy [emphasis added]**.

Above-referenced Appendix 3 to Fast Track Guidance documents:

> Center for Biologics Evaluation and Research
> Manual of Standard Operating Procedures and Policies
> SOPP 8405, Complete Review and Issuance of Action Letters, June 11, 1998
>
> Center for Drug Evaluation and Research
> Manual of Policies and Procedures
> MaPP 6020.3, Priority Review Policy, April 22, 1996