**DEPARTMENT OF HEALTH AND HUMAN SERVICES** Public Health Service

Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Biostatistics and Epidemiology
Division of Biostatistics

# STATISTICAL REVIEW AND EVALUATION
# BLA (FINAL)

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| **BLA Supplement Number:** | STN 125421 |
| **Product Name:** | Kcentra®, Prothrombin Complex Concentrate (Human) |
| **Indication(s):** | For patients with acute major bleeding |
| **Applicant:** | CSL Behring |
| **Date(s):** | March 30, 2012 |
| **Review Priority:** | Standard |
| **Statistical Branch:** | Therapeutics Evaluation Branch (TEB) |
| **Primary Statistical Reviewer:** | Jessica Hu PhD., Visiting Scientist |
| **Concurring Reviewer (1):** | Renée C. Rees, PhD., Acting Team Leader, Therapeutics Evaluation Branch, (HFM-219) |
| **Concurring Reviewer (2):** | Boguang Zhen, PhD., Branch Chief, Therapeutics Evaluation Branch, (HFM-219) |
| **Medical Office/Division:** | OBRR/DBA |
| **Clinical Reviewer(s):** | Leland Ross Pierce, MD |
| **Project Manager:** | Beth Walton |

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# 1. EXECUTIVE SUMMARY

CSL Behring (CSLB) submitted a biologic license application (BLA 125421) for Kcentra®, Prothrombin Complex Concentrate (Human) which contains the vitamin K dependent coagulation Factors II, VII, IX and X (FII, FVII, FIX, FX) and proteins C and S. The proposed indication for Kcentra is: The urgent reversal of vitamin K antagonist (VKA) therapy in patients with acute major bleeding.

## 1.1 Conclusions and Recommendations

This memo serves as the complete final statistical memo for BLA 125421. This statistical reviewer reviewed the primary efficacy analyses, secondary efficacy analyses, as well as the safety analyses of Kcentra. The product met the pre-specified efficacy criteria. The safety of the proposed product was comparable with the placebo in most aspects. A Phase IV post market clinical trial is recommended to continue studying the safety of Kcentra.

## 1.2 Brief Overview of Clinical Studies

Two pivotal studies, BE1116_3002 and BE1116_3003, are discussed in this memo. BE1116_3002 is the pivotal Phase IIIb study for reversal of VKA therapy in subjects with acute major bleeding. BE1116_3003 is an ongoing Phase IIIb study for reversal of VKA therapy in subjects with an urgent surgical procedure. The sponsor provided efficacy and safety data from BE1116_3002 and interim safety data from ongoing BE1116_3003 in this submission.

## 1.3 Major Statistical Issues and Findings

This statistical reviewer verified the sponsor's efficacy result of the proposed product provided in the study results of BE1116_3002. The BE1116_3002 results meet the pre-specified non-inferiority criterion (compare to plasma) for both the primary and co-primary efficacy endpoint. Secondary efficacy analyses, safety analyses, as well as subgroup analyses are also included in this memo.

# 2. INTRODUCTION

## 2.1 Overview

According to the sponsor, Kcentra is a human prothrombin complex containing the blood coagulation Factors II, VII, IX and X, as well as anti-thrombotic proteins C and S. It is a heat-treated, virus filtered and lyophilized plasma protein concentrate made from pooled human plasma. The preparation is sterile, pyrogen-free, and does not contain any antimicrobial preservative.

CSLB submits this marketing authorization application for the use of Kcentra in the urgent reversal of VKA (e.g., warfarin) therapy in patients with acute major bleeding. VKAs are routinely administered to patients with atrial fibrillation, prosthetic heart valves, deep vein thrombosis or other risk factors for arterial or venous thromboembolism. The anticoagulants disrupt synthesis of FII, FVII, FIX, FX and proteins C and S, thereby diminishing the risk of thromboembolic events. Although the VKAs are effective anticoagulants, they have a narrow therapeutic range and pharmacokinetics sensitive to multiple intrinsic and extrinsic variables. Consequently, close monitoring of the deficiencies of the vitamin K-dependent factors using the international normalized ratio (INR) is required. The increased rate of bleeding and mortality associated with elevated INR values has provided the rationale for reversing anticoagulation as a standard step in the management of bleeding patients receiving VKAs. No alternative products have been approved by FDA for the urgent reversal of VKA therapy in patients with acute major bleeding besides plasma.

Kcentra with its current manufacturing and quality profile was introduced into the European market in 1996 when it was approved by Germany and had virus filtration added to the production process as a second virus removal step. A marketing authorization has been granted in 24 countries. CSLB started the Kcentra development program with FDA in 2006. On June 7, 2007, the sponsor submitted the BB-IND 13398 application for Kcentra that contained the clinical protocol for Study 3002. On January 21, 2008, CSLB submitted an IND amendment that split the original clinical study into two separate studies aligned by indication: Study 3002 (acute major bleeding) and Study 3003 (urgent surgical procedure). On April 11, 2008, the FDA provided comments regarding both Study 3002 and Study 3003 that included: revising the co-primary endpoint time for evaluation of INR decrease to be 30 minutes after the end of infusion, including all adverse events (AEs)/serious adverse events (SAEs) regardless of investigator assessment, justifying the non-inferiority margin of 10% and that the intention-to-treat (ITT) population for the two co-primary endpoints will be considered for the final analysis. On June 30, 2011, the sponsor submitted a Type B Pre-BLA meeting background package concerning the BLA submission plan. The teleconference was held on August 3, 2011. On September 1, 2011, FDA responded to the sponsor via email to clarify the following issues: additional INR analyses, revised SAP to include methods for handling missing data and analyze primary endpoint using the evaluable for efficacy (ITT-E) population including/excluding the two subjects already enrolled. These issues were accepted by the sponsor and reflected in the final protocol Amendment 3.0 dated September 7, 2011.

### 2.2 Data Sources

The sponsor submitted its batch-analyses in pdf files as an eCTD submission located in the FDA's Electronic Document Room (EDR) at the following link:
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# 3. STATISTICAL EVALUATION

### 3.1 Evaluation of Efficacy

Two efficacy studies, Study 3002 (BE1116_3002) and Study 3003 (BE1116_3003) were conducted by the sponsor. However, efficacy data from the ongoing Study 3003 will not be available until the study is complete. The interim study results of Study 3003 were included in this submission for the safety analysis only. The current efficacy report provided by the sponsor includes one IND study (Study 3002) and four single arm, non-IND studies. Each study includes subjects who have been treated with oral VKAs and who require urgent replacement of their vitamin K-dependent clotting factors.

The four non-IND studies include:

1. Study BE1116_3001 – an open-label, single-arm, multi-center Phase III study. There were 43 subjects treated with Kcentra. The primary endpoint was the rapid decrease of the INR (i.e. INR ≤ 1.3 within 30 minutes after end of Kcentra infusion). Forty of 43 subjects reached an INR of 1.3 or lower.

2. Study BE1116/7D-201KO (Study 201 KO) – an open-label, single-arm, multi-center Phase II study. There were 30 subjects treated with Kcentra. The primary efficacy variables included factor levels, in vivo recovery (IVR), and Quick's value. Descriptive statistics of this study were reported in Section 5.3.5.2.2.2 of the sponsor's submission.

3. The Preston investigator-initiated study (Study Preston 2002) – an open-label, single arm study in 42 subjects. The primary efficacy outcome was the rate of correction of the INR. The dose of Kcentra (25 IU/kg, 35 IU/kg, 50 IU/kg) was determined by the baseline INR. Complete INR correction (decreased to < 1.3) was achieved within 20 minutes in 33 patients. For the remaining 9 patients, the INR decreased to 1.30 to 1.90, 20 minutes after receiving Kcentra. The median pre-treatment INR was 3.98, with a range from 2.0 to 27.6.

4. The Evans investigator-initiated study (Study Evans 2001) – an open-label, single arm study in 10 subjects. The primary outcome variables were clinical response, INR, and factor levels. Descriptive statistical results were included in Section 5.3.5.2.5.1 of the sponsor's submission. The median pre-treatment INR was >20 (range from 8.9 to >20). All INRs measured 30 minutes after treatment were ≤1.3 with completion of the infusion within 10 to 15 minutes. At 30 minutes, median FII, FIX, and FX levels were greater than 50 IU/dL. However, the median FVII level was only 30 IU/dL at 30 minutes and did not reach 50 IU/dL until the 6-8 hour time point.

The overall efficacy profile in this submission summarizes all five studies (in Section 2.7.3.2). This statistical memo reviews the efficacy result of Study 3002 only.

**Study Design and Endpoints**

Study 3002 was entitled as "An open-label, randomized, multicenter Phase IIIb study to assess the efficacy, safety and tolerance of Kcentra compared with plasma for rapid

reversal of coagulopathy induced by coumarin derivatives in subjects with acute major bleeding".

The study is designed as a prospective, randomized, open-label, active-controlled, non-inferiority, multicenter, Phase IIIb clinical trial. The randomization ratio is 1:1. Each subject received a single dose of Kcentra or plasma intravenously on day 1, based on subject's baseline INR value and body weight. The dose of Kcentra also depends on the amount of FIX. Each subject was followed up to 90 days. Data were collected on day 1, day 10 (7-11 days after start of infusion), day 45 (43-51 days after start of infusion), and day 90 (86-96 days after start of infusion).

The primary objective of this study is to compare the hemostatic efficacy of Kcentra and plasma in ceasing spontaneous or traumatically-induced major bleeding in subjects who have a deficiency of vitamin K-dependent FII, FVII, FIX, and FX, as well as the proteins C and S, acquired from oral anticoagulation therapy.

The co-primary objective of this study is to compare the efficacy of Kcentra and plasma in rapidly reducing the INR values at 30 minutes after end of infusion.

The secondary objectives are to compare between the two treatment groups:

- Plasma levels of FII, FVII, FIX, FX and proteins C and S.
- Hemostatic efficacy of Kcentra and plasma for visible and muscular/skeletal nonvisible bleeding, with measures taken at 3 and 6 hours from start of infusion.
- Time from start of infusion until INR correction.
- Time from randomization until INR correction.
- Total number of RBC transfusions, and the proportion of subjects with one or more RBC transfusions.
- Use of non-study-prescribed blood products and/or hemostatic agents.
- All-cause mortality at 45 days after treatment.
- Safety and tolerability of Kcentra and plasma.

The primary hemostatic efficacy endpoint was assessed for the time period from the start of infusion of Kcentra or plasma until 24 hours after the start of the infusion. It is a binary endpoint of effective or non-effective hemostasis, where "effective" is a hemostatic efficacy rating of excellent or good, and "non-effective" is a hemostatic efficacy rating of poor or none. The definition of the primary rating of hemostatic efficacy is provided in Table 5 in Section 9 of the Study Report for BE1116_3002 (submission Section 5.3.5.1.3). The primary efficacy endpoint was assessed by the Endpoint Adjudication Board (EAB), a blinded independent board.

The co-primary endpoint was the proportion of subjects who achieve an INR of 1.3 or lower within 30 minutes after infusion completion.

Secondary efficacy variables include:

- Secondary rating of hemostatic efficacy,

- Response and IVR of FII, FVII, FIX, FX, protein C, and protein S,
- 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,
- Transfusions of red blood cells.

The four analysis populations, Intention-to-treat (ITT), Intention-to-treat for Safety (ITT-S), Evaluable-for-efficacy (ITT-E), and Per-protocol (PP), were defined as follows:

- *Intention-to-treat (ITT) population:*

  All subjects who are randomized to one of the two treatment groups constitute the ITT population regardless of whether the subjects received Kcentra or had any post-baseline evaluations. In the ITT population, subjects were analyzed "as randomized".

- *Intention-to-treat safety (ITT-S) population:*

  Subjects are evaluated for safety if they are part of the ITT population and have received any portion of a dose of Kcentra; this subgroup constitutes the ITT-S population. ITT subjects for whom it cannot be verified that at least a portion of a dose of Kcentra was administered will not be included in safety presentations and incidence rate calculations. It is anticipated that the ITT-S population will be identical to the ITT population. In the ITT-S population, subjects were analyzed "as treated".

- *Evaluable-for-efficacy (ITT-E) population:*

  The ITT-E population consists of those subjects in the ITT-S population who presented with acute major bleeding and had an INR > 1.3 prior to infusion with Kcentra for the bleeding event that qualified the subject for participation in the study. The subjects to be included in the ITT-E population were determined by the process described in the EAB charter. In addition, subjects from the visible bleeding and non-visible musculoskeletal bleeding groups who were enrolled before protocol Amendment 3.0 and for whom the EAB has insufficient information for adjudication of the primary endpoint shall be assigned a hemostatic efficacy rating of "poor/none" but will be excluded from the ITT-E population. In the ITT-E population, subjects were analyzed "as randomized".

- *Per-protocol (PP) population:*

  The PP population consists of all subjects in the ITT-E population, excluding subjects who have major protocol deviations. Typical major protocol deviations in this study include missing key primary efficacy variables or the pre-infusion INR is less than 2.

**Patient Disposition, Demographic and Baseline Characteristics**

The ITT population consisted of 216 subjects (107 in the Kcentra group and 109 in the plasma group) enrolled in the study.

The ITT-S population included 212 subjects (104 in the Kcentra group and 108 in the plasma group). Subject 314011 was randomized to Kcentra, but was actually treated with plasma, and is therefore included in the Kcentra group for the ITT and ITT-E populations,

and in the plasma group for the safety (ITT-S) population. Hence the ITT-S population as treated is comprised of 103 Kcentra and 109 plasma subjects. There were four subjects (three in the Kcentra group: 018010, 041001, and 601006; and one in the plasma group: 011005) excluded from the ITT-S, ITT-E and PP populations because they were randomized and not treated.

The ITT-E population included 202 subjects (98 in the Kcentra group and 104 in the plasma group). There were 10 subjects in ITT-S population excluded from the ITT-E population (6 in the Kcentra group 029001, 030030, 052009, 314020, 316004, 501003; and 4 in the plasma group 030007, 030022, 314002, 314017). Among the 10 subjects, 8 subjects excluded because they did not have acute major bleeding and 2 subjects (both non-visible muscular/skeletal bleeding) were excluded because they were missing key primary efficacy variables, due to enrollment prior to the final variable definitions in Amendment 3.0.

The PP population included 190 subjects (93 in the Kcentra group and 97 in the plasma group). There were 15 subjects (7 in the Kcentra group and 8 in the plasma group) excluded from the PP population for major protocol deviations. In the Kcentra group, four subjects had missing key primary efficacy variables, two subjects had pre-infusion INR <2, and one received treatment different from randomization. In the plasma group, three subjects had missing key primary efficacy variables, four subjects received < 70% for the planned amount of study product (plasma), and one subject had pre-infusion INR <2. Subject 314011 (randomized to Kcentra, treated with plasma, see ITT-S description above) did not affect the PP population as this subject was excluded from the PP population.

The Table 1 summarizes all four analysis populations in Study 3002.

**Table 1. Subject Disposition by Analysis Population**

| Population | Kcentra (N=107) | Plasma (N=109) | Overall (N=216) |
|---|---|---|---|
| ITT | 107 | 109 | 216 |
| ITT-S | 103 | 109 | 212 |
| ITT-E | 98 | 104 | 202 |
| PP | 93 | 97 | 190 |

The sponsor summarized the demographic (Table 2) and disease (Table 3) characteristics of the ITT-E analysis population in Study 3002:

**Table 2. ITT-E Population Demographic Characteristics**

| Subgroup | Kcentra (N=98) | Plasma (N=104) |
|---|---|---|
| Age | | |
| <65 years | 33 | 31 |
| ≥ 65 and < 75 years | 24 | 29 |
| ≥75 years | 41 | 44 |
| Gender | | |
| Male | 50 | 51 |
| Female | 48 | 53 |
| Race | | |
| White | 93 | 88 |
| Non-white | 5 | 16 |
| Ethic Group | | |
| Not Hispanic or Latino | 90 | 99 |
| Hispanic or Latino | 8 | 5 |
| Country/region | | |
| Europe | 30 | 32 |
| United States | 68 | 72 |

**Table 3. ITT-E Population Disease Characteristics**

| | Kcentra (N=98) | Plasma (N=104) |
|---|---|---|
| **Type of acute bleeding** | | |
| Non-visible gastrointestinal | 55 | 58 |
| Visible | 16 | 21 |
| Intracranial hemorrhage | 12 | 12 |
| Other non-visible | 8 | 6 |
| Non-visible muscular/skeletal | 7 | 7 |
| **Reason for oral VKA therapy** | | |
| Arrhythmia | 56 | 53 |
| Thromboembolic event | 18 | 21 |
| Artificial heart valve or joint | 13 | 13 |
| Vascular disease | 10 | 13 |
| Other | 1 | 4 |

## Statistical Methodologies

The aim of the study was to show non-inferiority of Kcentra compared to plasma for both the primary and co-primary endpoints. The lower limit of the 2-sided 95% confidence interval using the method of Farrington and Manning was used to test for non-inferiority. The non-inferiority hypotheses were:

$$H_0: p_1 - p_2 \leq \delta \text{ vs. } H_1: p_1 - p_2 > \delta,$$

where $p_1$ and $p_2$ are the proportions of subjects achieving a hemostatic efficacy rating of effective under Kcentra or plasma, respectively. Hemostatic efficacy is a binary endpoint in which a rating is assigned for “effective” or “non-effective” hemostasis.

The non-inferiority margin, δ, was chosen as -0.10. That is, to support non-inferiority, the lower confidence limit for the difference of Kcentra minus plasma in the proportion of subjects with effective hemostasis had to exceed -0.10. If the lower limit of the 95% CI for the difference of Kcentra minus plasma is higher than 0, $H_0$ would be rejected and it will be concluded that Kcentra is superior to plasma with respect to hemostatic efficacy.

According to the SAP, non-inferiority of the co-primary endpoint (the effect of Kcentra compared to that of plasma on the proportion of subjects who have a rapid decrease of INR) would be tested if non-inferiority has been demonstrated for the primary endpoint (hemostatic efficacy). The method to test for non-inferiority will be the same as for hemostatic efficacy, including hypotheses, test procedure, maximum type I error, and non-inferiority margin. In this study, the claim of non-inferiority requires rejection of the null hypothesis in the ITT-E population.

With 83 subjects in each group, the lower limit of the observed one-sided 97.5% confidence interval was expected to exceed -0.10 with greater than 80% power when it is assumed that 85% of the hemostatic efficacy assessments in the plasma group ($p_2 = 0.85$) and 90% of the hemostatic efficacy assessments in the Kcentra group ($p_1 = 0.90$) will be rated effective; results are based on the Miettinen-Nurminen likelihood score test to construct the confidence interval. With an assumed rate of drop-outs of approximately 10%, the total target sample size was chosen as184 subjects.

However, the observed hemostatic efficacies in this study were lower than the assumptions applied in the above sample size calculation. The sponsor should recalculate the sample size and the power calculation based on the observed values.

In the last amendment of the protocol (Amendment 3.0), the primary endpoint was changed for subjects with visible musculoskeletal bleeding. As a consequence 28 subjects (enrolled prior to Amendment 3.0) were identified as potentially lacking sufficient data. In order to preserve the power of the study, the total enrollment was increased from 184 to 212, with 103 subjects in Kcentra group and 109 subjects in the plasma group.

**Results and Conclusions**

Primary Efficacy Analyses

(1) Hemostatic Efficacy

The primary efficacy analysis of Study 3002 was a test of the non-inferiority of Kcentra versus plasma, comparing the proportion of subjects with effective (excellent or good) hemostasis as rated by the blinded EAB. The proportion of subjects with effective hemostasis was 72.4% in the Kcentra group and 65.4% in the plasma group. Analysis of the treatment difference confirmed the non-inferiority of Kcentra compared to plasma treatment. The results shown in Table 4 were calculated by this statistical reviewer, and are consistent with the study report.

**Table 4. Primary Endpoint: Proportion of Subjects with Hemostasis Rated Effective**

| Effective rate | | Difference in %: Kcentra – Plasma |
|---|---|---|
| Kcentra | Plasma | |
| 72.4 (71/98) | 65.4 (68/104) | 7.1 (-5.62, 19.82)* |

*: 95% confidence interval

As stated in the SAP, if non-inferiority is shown, an additional procedure will be conducted to test for superiority of the effect of Kcentra compared to that of plasma. However, the efficacy result of the primary endpoint does not support the superiority of Kcentra over plasma.

(2) Rapid Decrease in INR

The co-primary endpoint was the proportion of subjects with a rapid decrease in INR defined as less than or equal to 1.3 within 30 minutes after the end of infusion. The proportion of subjects with a rapid decrease in INR was 62.2% in the Kcentra group and 9.6% in the plasma group (Table 5). The rapid increase in coagulation factors reaffirms that the clinical effects of Kcentra are non-inferior to plasma (lower bound of 95% confidence interval exceeds -10).

**Table 5. Co-Primary Endpoint: Rapid Decrease of INR**

| Rapid decrease | | Difference in %: Kcentra – Plasma |
|---|---|---|
| Kcentra | Plasma | |
| 62.2 (61/98) | 9.6(10/104) | 52.6 (41.5, 63.7)* |

*: 95% confidence interval

Using the pre-specified analyses outlined in the SAP, results from the pivotal Study 3002 met the non-inferiority criteria (non-inferiority margin of 10%) for both the primary and co-primary endpoints. The efficacy results were consistent with those of the single-arm supportive studies.

(3) Sensitivity Analyses

The sponsor conducted two sets of sensitivity analyses (Table 6). The first set of two sensitivity analyses (Analysis 1.1 and 1.2) were each a repeat of the primary analysis of hemostatic efficacy in the ITT-E population with the two subjects (enrolled prior to Amendment 3.0 and excluded from the ITT-E population because the EAB had insufficient information to adjudicate the hemostatic efficacy rating) now included in the analysis and given:

Analysis 1.1: the hemostatic efficacy rating “poor/none”
Analysis 1.2: the EAB’s secondary rating of hemostatic efficacy if it exists

The purpose of the second set of sensitivity analyses was to assess whether the evaluations of the investigator at the 1 hour or 4 hour time point only in place of the EAB evaluations affected the outcome of the primary analysis. Analysis 2.1 and 2.2 were each

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 those in the non-visible muscular/skeletal and visible bleeding groups. For these subjects, the EAB assessment was replaced with:

Analysis 2.1: the 4 hour CRF assessment as described in the SAP
Analysis 2.2: the 1 hour CRF assessment as described in the SAP

**Table 6. Sensitivity Analyses for the Primary Efficacy Endpoint (ITT-E Population)**

| Analysis | Effective rate | | Difference in %: Kcentra–Plasma |
|---|---|---|---|
| | Kcentra | Plasma | |
| 1.1 | 71.0 (71/100) | 65.4 (68/104) | 5.6 (-7.1, 18.4)* |
| 1.2 | 73.0 (73/100) | 65.4 (68/104) | 7.6 (-5.0, 20.2) |
| 2.1 | 66.3 (65/98) | 62.5 (65/104) | 3.8 (-9.4, 17.0) |
| 2.2 | 61.2 (60/98) | 58.7 (61/104) | *2.6 (-10.9, 16.1)* |

*: 95% confidence interval

A sensitivity analysis of the co-primary endpoint was also conducted at the request of the FDA in which 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 (Table 7).

**Table 7. Sensitivity Analyses of Rapid Decrease of the INR**

| | Kcentra | Plasma | Difference in %: Kcentra - Plasma |
|---|---|---|---|
| Rapid decrease | 61.2 (60/98) | 9.6 (10/104) | 51.6 (40.4, 62.8)* |

*: 95% confidence interval

At the request of the clinical reviewer, this statistical reviewer performed two additional sensitivity analyses for the primary efficacy endpoint regarding missing EAB worksheets. There were 28 subjects whose EAB worksheets (source documents) were missing in the original submission. In the first analysis (Table 8), the hemostatic efficacy rating was assigned as "poor/none" for Kcentra subjects with missing EAB worksheets , while the hemostatic efficacy rating was assigned as "excellent" for plasma subjects with missing EAB worksheets . In the second analysis (Table 9), all subjects with missing EAB worksheets were assigned a hemostatic efficacy rating of "poor/none".

**Table 8. Missing EAB Worksheet Sensitivity Analysis 1 for Hemostatic Efficacy**

| Effective rate | | Difference in %: Kcentra – Plasma |
|---|---|---|
| Kcentra | Plasma | |
| 63.3 (62/98) | 73.1 (76/104) | -9.8 (-22.6, -2.98)* |

*: 95% confidence interval

**Table 9. Missing EAB Worksheet Sensitivity Analysis 2 for Hemostatic Efficacy**

| Effective rate | | Difference in %: Kcentra – Plasma |
|---|---|---|
| Kcentra | Plasma | |
| 63.3 (62/98) | 60.6 (63/104) | 2.7 (-10.7, 16.1)* |

*: 95% confidence interval

Note that the lower limit of the 95% confidence interval for both additional analyses does not exceed -10. However, the analyses using the above two approaches for missing data imputation could be conservative and the results based on the post-hoc analyses should be interpreted with caution.

Secondary Efficacy Analyses

All secondary endpoints were analyzed in the ITT-E and PP populations. The following tables are results of the ITT-E analysis. The sponsor also provided the results for the PP populations in the submission.

(1) Secondary Rating of Hemostatic Efficacy

The secondary rating of hemostatic efficacy was a repetition of the primary analysis of hemostatic efficacy, using the EAB's secondary rating of hemostatic efficacy in place of the EAB's primary rating for the subgroup of subjects in the non-visible muscular/skeletal and the visible bleeding groups; for subjects not in the non-visible muscular/skeletal and the visible bleeding groups, the EAB's primary rating of hemostatic efficacy was retained in this analysis. The purpose of this secondary analysis was to assess whether the change in the definition of hemostatic efficacy resulting from protocol Amendment 3.0 affected the outcome of the primary analysis. The results using the secondary rating of hemostatic efficacy are reported in Table 10.

**Table 10. Analyses of Secondary Rating of Hemostatic Efficacy**

| | Kcentra (N=98) | Plasma (N=104) | Difference in %: Kcentra - Plasma |
|---|---|---|---|
| Secondary rating of hemostatic efficacy | 72 | 70 | 6.2 (-6.4, 18.9)* |
| 3 hour assessment | 67 | 66 | 4.9 (-8.1, 18.0) |
| 6 hour assessment | 70 | 69 | 5.1 (-7.6, 17.8) |
| 3 hour assessment, when missing, imputing with 6 hour assessment | 67 | 65 | 5.8 (-7.2, 19.0) |
| 3 hour assessment, missing considered "effective" | 67 | 66 | 4.9 (-8.1, 18.0 ) |

*: 95% confidence interval

(2) Response and In Vivo Recovery of Factors II, VII, IX, X, and Proteins C and S

The incremental IVR and the classical IVR were determined for FII, FVII, FIX, FX, and for proteins C and S. The incremental IVR responses ranged from 1.29 (FIX) to 2.17 (protein S) while the classical IVR ranged from 56% (FIX) to 96% (FVII) . Table 11 summarizes the IVR measurement.

**Table 11. Comparison of incremental IVR and classical IVR for Kcentra (ITT-E population)**

| Factor and Proteins | | N | Mean (SD) | Min/Max |
|---|---|---|---|---|
| Factor II | Incremental IVR | 97 | 2.00 (0.879) | -0.3/4.8 |
| | Classical IVR | 91 | 85.83 (37.208) | -13.9/224.8 |
| Factor VII | Incremental IVR | 97 | 2.15(2.958) | -1.8/20.9 |
| | Classical IVR | 91 | 96.09(139.192) | -74.5/987.6 |
| Factor IX | Incremental IVR | 97 | 1.29(0.711) | -0.7/4.0 |
| | Classical IVR | 91 | 55.98(32.422) | -31.4/174.6 |
| Factor X | Incremental IVR | 97 | 1.96(0.871) | -0.2/4.7 |
| | Classical IVR | 91 | 84.72(36.622) | -8.0/221.8 |
| Protein C | Incremental IVR | 97 | 2.04(0.958) | -0.5/5.0 |
| | Classical IVR | 91 | 88.59(41.848) | -22.6/235.1 |
| Protein S | Incremental IVR | 97 | 21.7(1.661) | -2.2/9.7 |
| | Classical IVR | 91 | 92.91(76.539) | -99.1/504.7 |

(3) Plasma Levels of Factors II, VII, IX, X, and Proteins C and S

Plasma levels of FII, FVII, FIX, FX and proteins C and S were measured at various times after the end of infusion. The sponsor provided the measurement at pre-infusion, 30 minutes, 1 hour, 3 hours, 6 hours, 12 hours and 24 hours after the infusion. For Kcentra, all factors showed marked increases with low to moderate variability and typically were greater than 50% at 30 minutes after the start of infusion. In contrast, increases in factor levels after plasma administration were much lower.

The sponsor submitted the descriptive statistics (mean and SD) in the study report (Table 29 and Figures 14.2.2-1 to 14.2.2-6 in the study report).

(4) Time to INR Correction from Start of Infusion and from Randomization

The sponsor submitted a Kaplan-Meier plot of time to INR correction from start of infusion (Figure 1) and a Kaplan-Meier plot of time to INR correction from randomization (Figure 2). Both KM plots were calculated based on the ITT-E population.

**Figure 1. Kaplan-Meier Plot of Time to INR Correction from Start of Infusion**

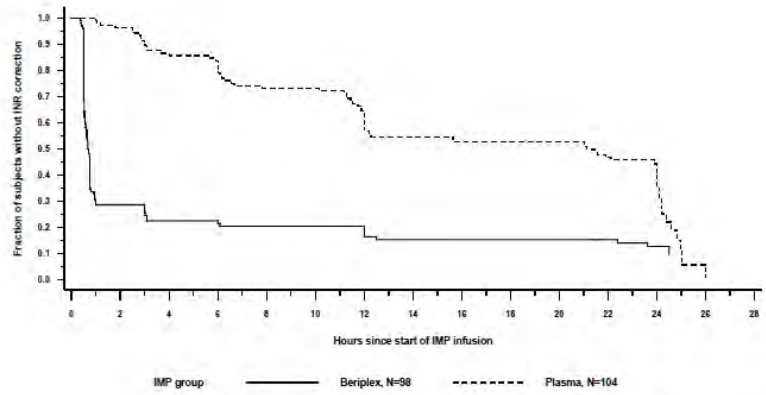
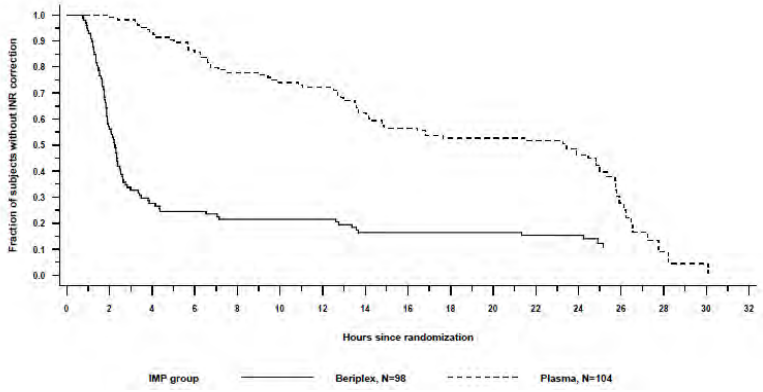



**Figure 2. Kaplan-Meier Plot of Time to INR Correction from Randomization**




(5) Transfusion of Packed Red Blood Cells

The mean ± SD transfused PRBC units per subject were 1.4 ± 1.77 in the Kcentra group and 1.2 ± 1.57 in the plasma group. No significant difference was detected.

(6) Use of Other Blood Products and Hemostatic Agents (Not Including PRBCs)

The mean ± SD units of other blood products used by subjects up to 24 hours after the start of infusion were 0.3 ± 1.36 in the Kcentra group and 0.3 ± 0.87 in the plasma group. No statistically significance difference was detected.

(7) 45-day All-cause Mortality

At 45 days, there were 9 deaths in the Kcentra group and 5 in the plasma group in the ITT-E population. The 45-day all-cause mortality risk ratio was 1.91, with the 95% CI as (0.66, 5.50).

## 3.2 Evaluation of Safety

The sponsor performed the safety analyses using data from both Study 3002 and Study 3003.

In Study 3002, 212 subjects received a single infusion of either Kcentra (103) or plasma (109). The overall incidences of treatment-emergent adverse event (TEAEs) in the Kcentra (64.1%) and plasma (65.1%) groups were similar (Table 12). The overall incidence of TEAEs considered by the investigator to be at least possibly related to Kcentra and plasma were 9.7% and 21.1%, respectively.

**Table 12. Number of Subjects with TEAEs in Study 3002**

| | **Kcentra, N=103(%)** | **Plasma, N=109(%)** |
|---|---|---|
| Any TEAE | 66(64.1) | 71(65.1) |
| Serious TEAEs | 21(20.4) | 15(13.8) |
| Moderate TEAEs | 35(34.0) | 21(19.3) |
| Mild TEAEs | 55(53.4) | 62(56.9) |
| At least possibly treatment-related TEAEs | 10(9.7) | 23(21.1) |
| TEAEs leading to treatment discontinuation | 0 | 3(2.8) |
| SAEs | 33(32.0) | 26(23.9) |
| At least possibly treatment-related SAEs | 2(1.9) | 4(3.7) |
| SAEs leading to treatment discontinuation | 0 | 0 |
| Death by day 45 | 11(10.7) | 5(4.6) |
| At least possibly treatment related (Investigator) | 1(1.0) | 0 |
| At least possibly treatment related (EAB) | 1(1.0) | 0 |
| Possible thromboembolic events | 9 (8.7) | 6 (5.5) |

There were a total of 15 deaths between administration of study product and Day 45; 10 subjects died in the Kcentra group and 5 subjects died in the plasma group. The death rates at Day 30 were similar for the two groups: 6 subjects died in the Kcentra group and 5 subjects died in the plasma group. One death (Day 7, sudden death) was considered possibly related to Kcentra by the blinded safety adjudication board (SAB). One additional death (on Day 46, 3 days following an ischemic stroke) occurred after completion of the study on Day 45. The SAE was considered possibly related to Kcentra by the investigator.

The sponsor also analyzed possible thromboembolic events (TEs). There are 15 subjects who had possible 16 TEs, including one subject had 2 TEs). Among the 15 subjects, 9 from the Kcentra group and 6 from the plasma group, giving a 95% CI of the difference of TE's incidence between the Kcentra arm and the plasma arm as (-3.70%, 10,16%). Among these 15 subjects with possible thromboembolic TEAEs, 9 subjects had SAEs: 5 in the Kcentra group and 4 in the plasma group.

SAEs were reported for 33 subjects (32%) in the Kcentra group and 26 subjects (23.9%) in the plasma group. SAEs considered at least possibly related to treatment by the investigator were reported for two subjects (1.9%) in the Kcentra group and four subjects

(3.7%) in the plasma group. The SAE of ischemic stroke was considered possibly related to Kcentra by the investigator and the SAE and death were considered not related to Kcentra by the SAB. No deaths were considered possibly related to plasma by the investigator or the SAB. Most deaths did not share significant features with other deaths except for the frequent finding of a high co-morbid burden, advanced age and death after being placed on comfort care (12 of 15 subjects).

Study 3003 is an ongoing, open-label, randomized, multicenter, Phase IIIb study to assess the efficacy, safety and tolerance of Kcentra compared with plasma for rapid reversal of coagulopathy induced by VKAs in subjects requiring an urgent surgical or urgent invasive procedure. Interim safety data is available for 114 subjects (56 Kcentra, 58 plasma). The overall incidence of TEAEs in the Kcentra (55.4%) and plasma (60.3%) groups were similar (Table 13). The overall incidence of TEAEs considered by the investigator to be at least possibly related to Kcentra and plasma were 7.1% and 19.0%, respectively.

**Table 13. Number of Subjects with TEAEs in Study 3003**

| | **Kcentra, N=56(%)** | **Plasma, N=58(%)** |
|---|---|---|
| Any TEAE | 31(55.4) | 35(60.3) |
| Serious TEAEs | 7(12.5) | 9(15.5) |
| Moderate TEAEs | 15(26.8) | 14(24.1) |
| Mild TEAEs | 25(44.6) | 29(50.0) |
| At least possibly treatment-related TEAEs | 4(7.1) | 11(19.0) |
| TEAEs leading to treatment discontinuation | 0 | 0 |
| SAEs | 12(21.4) | 13(22.4) |
| At least possibly treatment-related SAEs | 1(1.8) | 3(5.2) |
| Death by day 45 | 3(5.4) | 7(12.1) |
| At least possibly treatment related (Investigator) | 0 | 0 |
| At least possibly treatment related (Investigator) | 0 | 0 |
| Possible thromboembolic events | 2(3.6) | 6(10.3) |

SAEs were reported for 12 subjects (21.4%) in the Kcentra group and 13 subjects (22.4%) in the plasma group. SAEs considered at least possibly related to treatment by the investigator were reported for one subject (1.8%) in the Kcentra group and three subjects (5.2%) in the plasma group. There were a total of nine deaths between the start of administration of study product and up to and including Day 45: two in the Kcentra group and seven in the plasma group. One death, in a plasma-treated subject, followed an acute myocardial infarction on Day 8, and was considered to be a TE and possibly related to plasma by the SAB. The remaining deaths followed non-TEs, occurred among different system organ classes, and could be attributed to underlying disease or conditions. The incidence of possible thromboembolic events were 3.6% for the Kcentra group and 10.3% for the plasma group, giving the 95% CI of the difference as (-15.99%, 2.45%).

This statistical reviewer compared the mortality rate between the Kcentra group and the plasma group with one-sided and two-sided Pearson tests. The mortality rate of the Kcentra group is significantly higher than that of the plasma group in Study 3002 with a one-sided Pearson test at alpha level = 0.05. However the mortality rates in Study 3003

and the pooled data do not support the significant increase. The results are reported in Table 14.

**Table 14. Mortality Rates in Studies 3002, 3003, and the Pooled Data**

| | Kcentra | Plasma | 1-sided p-value | 2-sided p-value |
|---|---|---|---|---|
| Study 3002 | 11/103 | 5/109 | 0.0466 | 0.0933 |
| Study 3003 | 3/56 | 7/58 | 0.1027 | 0.2054 |
| Pooled | 14/159 | 12/167 | 0.2948 | 0.5896 |

At the request of the clinical reviewer, this statistical reviewer also compared frequency of TEs between the subgroup with prior medical history of TE and the subgroup without prior medical history of TE (Table 15) for Study 3002.

**Table 15. Number of Thromboembolic Events by Medical History in Study 3002**

| | Kcentra (%) | Plasma (%) | Difference in % Kcentra - Plasma |
|---|---|---|---|
| Subjects with prior medical history | 9/69 (13.0) | 3/79 (3.8) | 9.2 (-0.8, 20.4)* |
| Subjects without prior medical history | 1/34 (2.9) | 3/30 (10.0) | -7.1 (-25.0, 8.9) |

*: 95% confidence interval

The descriptive statistics shows that subjects with prior medical history of TE in the Kcentra arm have the highest risk for TE event. Further safety studies for TE events might be useful to estimate the risk of TE event between the subjects with prior medical history of TE and subjects the without prior medical history of TE.

## 3.3 Gender, Race, Age and Other Special/Subgroup Populations

The sponsor conducted subgroup analyses for the co-primary endpoints (Tables 16 and 17).

**Table 16. Subgroup Analysis of Hemostatic Efficacy**

| Subgroup | Kcentra (N=98) % | Plasma (N=104) % | Difference in %: Kcentra – Plasma |
|---|---|---|---|
| Country region | | | |
| Europe | 66.7 (20/30) | 68.8 (22/32) | *-2.1 (-25.3, 21.2)** |
| USA | 75.0 (51/68) | 63.9 (46/72) | 11.1 (-4.0, 26.2) |
| Age | | | |
| <65 years | 60.6 (20/33) | 64.5 (20/31) | *-3.9 (-27.6, 19.8)* |
| ≥ 65 and < 75 years | 83.3 (20/24) | 51.7 (15/29) | 31.6 (8.1, 55.1) |
| ≥75 years | 75.6 (31/41) | 75.0 (33/44) | *0.6 (-17.7, 18.9)* |
| Gender | | | |
| Male | 77.1 (37/48) | 71.7 (38/53) | *5.4 (-11.6, 22.4)* |

| **Subgroup** | **Kcentra** (N=98)<br>% | **Plasma** (N=104)<br>% | **Difference in %:**<br>Kcentra – Plasma |
|---|---|---|---|
| Female | 68.0 (34/50) | 58.8 (30/51) | 9.1 (-9.5, 27.9) |
| Reason for VKA therapy | | | |
| Arrhythmia | 69.6 (39/56) | 66.0 (35/53) | *3.6 (-13.4, 21.1)* |
| Thromboembolic | 77.8 (14/18) | 76.2 (16/21) | *1.6 (-24.9, 28.0)* |
| Type of major bleeding | | | |
| Non-visible gastrointestinal | 74.5 (41/55) | 75.9 (44/58) | *-1.3 (-17.2, 14.6)* |
| Visible | 75.0 (12/16) | 57.1 (12/21) | *17.9 (-12.1, 47.9)* |

*: 95% confidence interval

It is observed in Table 16 that for hemostatic efficacy, the non-inferiority criterion fails in the following subgroups: European sites, age < 65 years, age ≥ 75 years, males, reasons for VKA therapy, and type of major bleeding. However, since the study was not powered to test this endpoint in these subgroups, these results should be interpreted with caution.

**Table 17. Subgroup Analysis of Rapid Decrease of INR**

| **Subgroup** | **Kcentra** (N=98)<br>% | **Plasma** (N=104)<br>% | **Difference in %:**<br>Kcentra - Plasma |
|---|---|---|---|
| Country region | | | |
| Europe | 50.0 (15/30) | 3.1 (1/32) | 46.8 (28.0, 65.8)* |
| USA | 67.6 (46/68) | 12.5 (9/72) | 55.1 (41.7, 68.6) |
| Age | | | |
| <65 years | 57.6 (19/33) | 12.9 (4/31) | 44.7 (24.1, 65.3) |
| ≥ 65 and < 75 years | 54.2 (13/24) | 13.8 (4/29) | 40.4 (16.8, 63.9) |
| ≥75 years | 70.7 (29/41) | 4.5 (2/44) | 66.2 (51.0, 81.4) |
| Gender | | | |
| Male | 66.7 (32/48) | 11.3 (6/53) | 55.3 (39.5, 71.2) |
| Female | 58.0 (29/50) | 7.8 (4/51) | 50.2 (34.6, 65.7) |
| Reason for VKA therapy | | | |
| Arrhythmia | 67.9 (38/56) | 7.5 (4/53) | 60.3 (45.2, 74.5) |
| Thromboembolic | 61.1 (11/18) | 9.5 (2/21) | 51.6 (25.8, 77.4) |
| Type of major bleeding | | | |
| Non-visible gastrointestinal | 69.1 (38/55) | 8.6 (5/58) | 60.5 (46.3, 74.7) |
| Visible | 50.0 (8/16) | 9.5 (2/21) | 40.5 (12.9, 68.0) |

*: 95% confidence interval

According to the results shown in Table 17, non-inferiority was supported in all subgroups regarding rapid decrease of INR. However, since the study was not powered to test this endpoint in these subgroups, these results should be interpreted with caution.

# 4. SUMMARY AND CONCLUSIONS

## 4.1 Statistical Issues and Collective Evidence

Regarding Study 3002, the primary and co-primary efficacy endpoint met the pre-specified non-inferiority margin of 10%. This statistical reviewer verified the primary efficacy analyses, secondary efficacy analyses, as well as the subgroup analyses for the primary efficacy endpoints. All point and confidence interval estimations included in this memo were computed by this statistical reviewer.

For safety, the statistical results show that the number of TEAEs and SAEs between the Kcentra groups and the plasma groups are comparable. However in Study 3002, the mortality rate in the Kcentra group is significantly higher than that of the plasma group (one-sided p-value: 0.0466). The overall analysis on mortality obtained by pooling the data from both Study 3002 and Study 3003 shows that the mortality rate between the Kcentra group and the plasma group are similar to each other.

## 4.2 Conclusions and Recommendations

The statistical evidence supports the licensure application of Kcentra® as an urgent reversal of vitamin K antagonist therapy in patients with acute major bleeding. For efficacy, statistical analyses show that Kcentra is not inferior to plasma (the current placebo) in the primary endpoint (hemostatic efficacy) and the co-primary endpoint (rapid decrease of INR). The safety data were also examined and no serious defects of Kcentra were detected.

A Phase IV post-market trial is recommended to continue the investigation of the safety of Kcentra, especially the mortality rate.

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