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Review Completion Date / Stamped Date	
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Applicant	OCTAPHARMA
Established Name	Prothrombin Complex Concentrate (Human)
(Proposed) Trade Name	BALFAXAR
Pharmacologic Class	
Formulation(s), including Adjuvants, etc	Prothrombin Complex Concentrate (Human), containing coagulation factors II, VII, IX, and X and antithrombotic Proteins C and S
Dosage Form(s) and Route(s) of Administration	Sterile, lyophilized powder for reconstitution for intravenous injection
Dosing Regimen	Calculated by the baseline International Normalized Ratio (INR_0) value and body weight.
Indication(s) and Intended Population(s)	The urgent reversal of vitamin K antagonist (VKA) therapy in adult patients with need for an urgent surgery/invasive procedure

Table of Contents

GLOSSARY

4F-PCC	Four-factor Prothrombin Complex Concentrate
Ab	Antibody
AE	Adverse Event
ASA	American Society of Anesthesiologists
BW	Body Weight
CI	Confidence Interval
CRF	Case Report Form
CRO	Contract Research Organization
FII, FVII, FIX, FX	Coagulation Factors II, VII, IX, X
FFP	Fresh Frozen Plasma
GCP	Good Clinical Practice
GMNPT	Geometric Mean Normal Prothrombin Time
Hct	Hematocrit
Hgb	Hemoglobin
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IDMC	Independent Data Monitoring Committee
IEAB	Independent Endpoint Adjudication Board
IEC	Independent Ethics Committee
IgM	Immunoglobulin M
INR	International Normalized Ratio
IP	Investigational Product
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISI	International Sensitivity Index
ITT	Intent-to-Treat
IU	International Unit
IV	Intravenous
LMWH	Low-Molecular-Weight Heparin
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat
PCC	Prothrombin Complex Concentrate
PCR	Polymerase chai
PP	Per Protocol
PT	Preferred Term
RAND	Randomized (Population)
RBC	Red Blood Cells
SAE	Serious Adverse Event
SAF	Safety Analysis (Population)
SAP	Statistical Analysis Plan
SD	Standard Deviation
SMQ	Standardized Medical Query
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
TEE	Thromboembolic Event

VKA   Vitamin K Antagonist
WBC   White Blood Cell

1. Executive Summary

This original Biologics License Application (BLA) submission seeks marketing authorization of BALFAXAR, a blood coagulation factor-replacement product with the indication of the urgent reversal of acquired coagulation factor deficiency induced by Vitamin K antagonist (VKA, e.g., warfarin) therapy in adult patients for an urgent surgery/invasive procedure. It is a prothrombin complex concentrate (PCC, human), which is a plasma protein fraction containing coagulation Factor IX (FIX) and comparable quantities of coagulation Factor II (FII), Factor VII (FVII), and Factor X (FX).

This statistical review memo focuses on the efficacy analysis and safety analysis of the pivotal phase 3 Study LEX-209 only. Data analyses for the phase 3 Study LEX-205 were reviewed in the statistical memo of (b) (4)   in (b) (4) The result in Study LEX-205 (b) (4)

Study LEX-209 was a Phase 3, non-inferiority study to assess the efficacy and safety of BALFAXAR compared with Kcentra for patients needing urgent surgery with a significant risk of bleeding (≥50 mL expected blood loss). The primary endpoint was the hemostatic efficacy rating at the end of the surgery. The non-inferiority margin was -15% for the difference in effective hemostasis rate between the BALFAXAR and the Kcentra groups. The planned enrollment was 370 subjects, with one interim analysis (IA) scheduled after half of the patients were randomized and had available primary endpoint results. At the interim analysis, 185 patients were randomized with 93 to BALFAXAR and 92 to Kcentra. The effective hemostasis rates were 94.6% and 93.5% for the BALFAXAR and Kcentra groups, respectively. The non-inferiority analysis for the proportion difference (98% confidence interval [CI]) of 1.1% (-9.2%, 11.5%) was statistically significant (p-value <0.001, 0.15 inferiority margin). The z-value was 3.62 and higher than the pre-specified critical value of 2.33 for IA corresponding to a one-side alpha level of 1%. As a result, Study LEX-209 was terminated early following the IA due to the efficacy. In the final study report submitted with the BLA, the updated final analysis included 208 patients, with 105 in the BALFAXAR group and 103 in the Kcentra group. The effective hemostasis rates were 94.3% (99/105) in the BALFAXAR group versus 94.2% (97/103) in the Kcentra group, with a proportion difference (95% CI) of 0.1% (-8.0%, 8.2%). These efficacy analysis results have provided adequate statistical evidence to demonstrate that BALFAXAR is non-inferior to Kcentra as a VKA therapy for patients with the need for urgent surgery and at risk for significant bleeding.

There were five deaths occurred in the BALFAXAR group and one death occurred in the Kcentra group. There were 13 (12.4%) patients experienced 21 serious adverse events (SAEs) in the BALFAXAR group and 6 (5.8%) patients experienced 9 SAEs in the Kcentra group. SAEs were most commonly reported in Injury, Poisoning and Procedural complications (3.8%), Cardiac Disorders (2.9%), and Gastrointestinal Disorders (2.9%) in the BALFAXAR group; and Blood and Lymphatic System Disorders (1.9%) and Gastrointestinal Disorders (1.9%) in the Kcentra group.

Overall, the statistical analyses of Study LEX-209 support the efficacy of BALFAXAR as an urgent reversal of VKA therapy in adult patients with need for an urgent surgent/invasive procedure. I defer to the clinical team on the acceptance of the safety profile of BALFAXAR.

2. Clinical and Regulatory Background

2.1 Disease or Health-Related Condition(s) Studied

BALFAXAR® is a four-factor, human plasma-derived prothrombin complex concentrate (PCC) which has undergone solvent-detergent treatment and nanofiltration (20 nm) for pathogen inactivation/removal. It is a second-generation PCC developed by Octapharma to comply with the requirements for viral safety as outlined in international guidelines on plasma-derived medicinal products.

The main therapeutic indication for BALFAXAR is the treatment of (b) (4) peri-operative prophylaxis of bleeding in acquired deficiency of the prothrombin complex coagulation factors, such as deficiency caused by treatment with vitamin K antagonists (or liver failure), when rapid correction of the deficiency is required or the use of vitamin K is inefficacious.

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

FDA has approved a four-factor prothrombin complex concentrates (4F-PCC) product Kcentra for urgent reversal of acquired coagulation deficiency induced by vitamin K antagonists (VKA) therapy in adult patients with acute major bleeding or need for an urgent surgery or invasive procedure in 2013.

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

BALFAXAR was first approved in Germany in March 2003 and registered in about 87 countries worldwide. Between March 2003 and March 2022, a total of more than (b) (4) IU of BALFAXAR have been sold.

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

BALFAXAR was evaluated under Investigational New Drug (IND) application 13323. It received Orphan Drug Designation in the US for the treatment of "Reversal of anticoagulation therapy in patients needing treatment of serious or life-threatening bleeding and/or needing urgent surgery or invasive procedures" on 01 February 2008. The Fast Track Designation was granted by FDA on 30 September 2010. The applicant submitted (b) (4)

The applicant submitted the protocol of phase 3 Study LEX-209 on 18 April 2016. The pre-BLA meeting (CRMTS 13686) request was submitted on 21 September 2021. On 22 February 2022, FDA sent the written response, in which FDA agreed that LEX-209 could be stopped early and that the data might be sufficient for a BLA submission.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

This submission was adequately organized for conducting a complete statistical review without unreasonable difficulty.

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

All data sources are included in the applicant's eCTD submission located in the FDA/CBER Electronic Document Room (EDR).

5.1 Review Strategy

This review memo focuses on both efficacy and safety analyses of the Phase 3 Study LEX-209.

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

The following documents in the BLA 125776 were reviewed:
- 1.6 Meetings
- 1.14 Labeling
- 2.2 Introduction
- 2.5 Clinical Overview
- 2.7 Clinical Summary
- 5.3.5 Clinical report (LEX-209)
- 5.3.5 Protocol (LEX-209)
- 5.3.5 Statistical methods (LEX-209)

5.3 Table of Studies/Clinical Trials

There were six clinical studies within the clinical development plan for BALFAXAR. Study LEX-201 recruited patients with severe FII, FVII, FIX, and FX deficiency and assessed the pharmacokinetic profile and clinical efficacy in bleeding episodes. Clinical efficacy in patients on VKA in need of urgent surgery with significant bleeding risk was formally assessed in the pivotal phase 3 Study LEX-209, with supplementary data from phase 3 Study LEX-205 and supportive studies LEX-202, LEX-203, and LEX-206. A summary of these five studies is provided in Table 1.

Table 1: Description of Clinical Efficacy and Safety Studies

Study Code	Study Design	Dose, Route, & Regimen	Primary Endpoint(s)	Number of Subjects
LEX-202	Prospective, open label, noncontrolled, multi-center Phase 2 study	Mean (range) BALFAXAR dose 27 IU/kg BW (13.7-43.8), IV infusion, single administration	Correction of prothrombin time and INR	20 subjects Included and subjects treated 11 male/ 9 female Age 43 to 83 years
LEX-203	Prospective, open label, noncontrolled, multi-center Phase 3 study	Median (range) dose of BALFAXAR 41 IU/kg BW (11.1-83.3), IV infusion, single administration	Correction of INR, activated partial thromboplastin time , thrombin time, fibrinogen; incremental recovery of coagulation Factors (FII, FVII, FIX, FX, PC); Investigator evaluation on 3-point VRS	60 subjects included, 60 subjects 33 male / 27 female Age 24 to 93 years
LEX-205	Prospective, randomized, active controlled, open label, multi-center Phase 3 study	BALFAXAR dose (mL/kg BW) = ln(INR0/1.4) / 0.52, I.V. infusion Control: FFP, IV infusion Single administration	Correction of INR to <1.5, 15 min after infusion of BALFAXAR of FFP Number of intraoperative RBC units transfused	207 subjects included, 200 subjects Treated Age 18 years and above
LEX-206	Prospective, multi-center,	BALFAXAR 25 IU/kg or	Correction of PT, plasma	59 subjects included,

	randomized, open label, controlled Phase 3 study	40 IU/kg, IV infusion, single administration	levels of coagulation Factors (FII,FVII, FIX, FX, PC, PS); Hematoma volume; Glasgow Coma Scale; Clinical outcome (various scales); quality of life; overall clinical response	59 subjects treated: 42 male / 17 female Age 46 to 92 years
LEX-209	Prospective, multi-center, randomized, double-blind, active controlled, group sequential, non-inferiority study	BALFAXAR or Kcentra, dose depending on BW and baseline INR, IV infusion, Single administration	Hemostatic efficacy rating at the end of the surgery	208 subjects included, 208 subjects treated Age 18 years and above

Source: Adapted from BLA 125776/0/Module 2.7: summary-clin-efficacy.pdf, Table 1, page 15-17.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Trial #1: Study LEX-209

Study LEX-209 was a phase III, randomized, double-blind, multicenter study to assess the efficacy and safety of BALFAXAR compared to Kcentra, for the reversal of vitamin K antagonist induced anticoagulation in patients needing urgent surgery with significant bleeding risk.

6.1.1 Objectives

The primary objective of this study was to demonstrate that the efficacy of BALFAXAR as a reversal agent in patients under VKA therapy with the need for urgent surgery with significant bleeding risk is non-inferior to Kcentra.

The secondary objective of this study was to investigate the safety and tolerability of BALFAXAR compared to Kcentra in patients under VKA therapy with the need for urgent surgery with significant bleeding risk.

6.1.2 Design Overview

This was a prospective, multi-center, randomized, double-blind, active-control, group-sequential, non-inferiority Phase III study conducted at sites in the US and Europe.

The planned enrollment was a maximum of 370 patients (male and female patients at least 18 years of age) with 185 patients per treatment group, BALFAXAR or Kcentra. Patients were on oral anticoagulant therapy with VKAs and needed to undergo an urgent surgery with a significant risk of bleeding (≥ 50 mL expected blood loss). Surgeons had to intend to start the surgery of each patient within 3 hours after the end of 4F-PCC administration.

The following patients with allocations were to be enrolled, based on the expected blood loss during surgery:
- ≥ 40% of patients with an expected blood loss of ≥200 mL.
- ≥ 20% of patients with an expected blood loss of ≥100 mL but <200 mL.
- < 40% of patients with expected blood loss ≥50 mL but <100 mL.

6.1.3 Population

Patients who met all of the following criteria were eligible for the study:
1. Male or female patients at least 18 years of age.
2. Patients currently on oral anticoagulation treatment with VKA of coumadin or warfarin type.
3. Patients being admitted to the hospital or currently hospitalized where:
   - an urgent surgery carrying significant bleeding risk (≥50 mL expected blood loss in normal coagulation state) was required as part of routine clinical care within 24 hours of the start of IP;
   - VKA withdrawal and use of oral or parenteral vitamin K alone to reverse anticoagulation is deemed too slow or inappropriate for reversal.
4. Patients with an International Normalized Ratio (INR) of 2.0 or above at the time of decision to reverse the anticoagulation status.
5. Patients who had given written informed consent and who were able and willing to comply with the procedures laid out in the study protocol.

6.1.4 Study Treatments or Agents Mandated by the Protocol

The dose of both BALFAXAR and Kcentra was calculated by the responsible treating investigator based on the patient's body weight (BW) and baseline INR.

Both BALFAXAR and Kcentra were administered by intravenous (IV) infusion at a rate of 0.12 mL/kg/min (~3 units/kg/min), up to a maximum rate of 8.4 mL/min (~210 units/min).

6.1.6 Sites and Centers

This study was conducted at 27 sites from 6 countries (Belarus, Georgia, Romania, Russia, Ukraine, and United States).

6.1.7 Surveillance/Monitoring

An independent data monitoring committee (IDMC) was set up to monitor safety data. The IDMC also advised on the further conduct/stopping of the study once the interim analysis had been performed.

6.1.8 Endpoints and Criteria for Study Success

Primary Efficacy Endpoints
The primary efficacy endpoint is the hemostatic efficacy rating at the end of the surgery. The hemostatic efficacy was to be assessed based on objective criteria in the categories as: excellent, good, moderate and none. Ratings of excellent and good will be considered as effective hemostasis, while a rating of moderate or none will be considered as ineffective hemostasis.

Secondary efficacy endpoints:
- Proportion of patients with an INR value of less or equal to 1.5 at 30 min (± 15 min) after the end of infusion.
- Change in coagulation factor levels from baseline to 30 (± 15 min) after the end of infusion: FII, FVII, FIX, and FX
- Proportion of patients receiving red blood cells (RBC) during the surgery

Further exploratory endpoints:
- Change in INR from baseline.
- Change in Protein C, and Protein S from baseline to 30 (± 15 min) after the end of infusion.
- Change in coagulation factor levels (FII, FVII, FIX, FX, Protein C, and Protein S) from baseline to 2 h, 4 h, 12 h, and 24 h after end of infusion.
- Assessment of blood loss after end of surgery.
- Proportion of patients receiving plasma and platelets transfusions initiated during the surgery.
- Total volume of RBC and other blood product transfusions initiated during the surgery normalized by patient's BW.
- Change in hematological parameters (hemoglobin, hematocrit, RBC, white blood cells [WBC], platelets) from the beginning to the end of the surgery.
- RBC transfusion corrected change from baseline in hemoglobin at 12 and 24 hours after start of surgery.
- Proportion of patients experiencing surgical wound hematoma requiring surgical evacuation.
- Ratio of actual estimated blood loss as documented after surgery to the pre-operative predicted blood loss for the type of planned surgery.

Safety Endpoints
- Occurrence of adverse events.
- Occurrence of thromboembolic events (TEEs; overall, within 3, 21 and 45 days after end of surgery).
- Mortality (overall, within 3, 21 and 45 days after end of surgery).

Page 10

- Monitoring vital signs, laboratory parameters.
- Viral safety (at baseline, and Day 9 (±1 day) after administration of IMP for patients seronegative at baseline).

Success Criterion
This study was designed to demonstrate that treatment with BALFAXAR is not inferior to treatment with Kcentra. The success criterion was defined as the difference of the hemostatic success rate between the BALFAXAR group and Kcentra group does not exceed the inferiority margin of $\delta = -0.15$, with a one-sided type I error $\alpha = 0.025$. The null and the alternative hypotheses were defined as the following in the statistical analysis plan (SAP):
$$H_0: p_B - p_K \leq \delta \text{ versus } H_1: p_B - p_K > \delta,$$
where p_B and p_K represent the hemostatic success rate of BALFAXAR and Kcentra respectively.

6.1.9 Statistical Considerations & Statistical Analysis Plan

Sample Size Determination
Based on the one-sided overall type I error probability $\alpha = 0.025$, power $1 - \beta = 0.8$, the non-inferiority margin of $\delta = -0.15$, the hemostatic success probabilities of 0.85 for the BALFAXAR group and 0.89 for the Kcentra group, and the chosen α-spending and β-spending functions, a sample size of 166 per group would provide 80.3% power. To account for an assumed 10% dropout rate, the applicant proposed to enroll 185 subjects in each group, that is, 370 subjects in total.

Analysis Populations
Randomized Population (RAND): The randomized population were to include all randomized patients irrespective of whether they received treatment. Following the intent-to-treat principle all patients were to be analyzed according to the treatment group to which they were randomized. This would be the intent-to-treat (ITT) population according to the most rigid definition of ITT.

Safety Analysis Population (SAF): The safety analysis population (SAF) were to include all randomized patients who received investigational medicinal product (IMP). Patients receiving different study treatments than originally randomized were be considered according to the treatment actually received.

Modified Intention-to-Treat Population (mITT): The mITT population were to consist of all randomized patients who received IMP, and who had the surgery initiated or for whom the surgery was not initiated for medical reasons related to insufficient coagulation.

Per Protocol Population (PP): The PP population were to consist of all those patients in the mITT population, excluding patients with major protocol deviations potentially affecting the primary endpoint.

The primary efficacy analysis was to be performed using the RAND population. All safety analyses were to be performed using the SAF population. Additional efficacy analyses were to be performed using the mITT and the PP populations.

Reviewer's comment: Since ITT analysis tends to bias towards the null, hypothesis testing of non-inferiority may be counter-conservative. Therefore, additional evaluation using the mITT and PP populations to ensure the robustness of the study results is necessary.

Primary Efficacy Analyses
The primary efficacy variable was the hemostatic efficacy as assessed by the Independent Endpoint Adjudication Board (IEAB). The hemostatic efficacy was to be assessed based on objective criteria in the categories "excellent", "good", "moderate" or "none". Ratings of "excellent" and "good" were to be considered as "effective" hemostasis, while a rating of "moderate" and "none" were to be considered as "ineffective" hemostasis.

Farrington and Manning test for difference in proportions was to be used to assess the primary hypothesis in the interim and final analyses. One-sided p-values and the corresponding nominal and repeated confidence intervals for the difference in hemostatic success probabilities were to be presented.

Interim Analysis
One unblinded interim analysis after enrollment of 50% of the planned sample size was to be conducted for LEX-209, allowing for an early stopping for demonstrated non-inferiority of BALFAXAR or an early stopping due to futility. The interim analysis was performed by a statistical team which is independent from the study team and the results were presented to the IDMC. A sequential design with α- and β-spending functions according to Hwang, Shi and Cani was used. After the interim analysis, a positive outcome for non-inferiority test could be claimed and enrollment may be stopped if the primary test statistic in the RAND population is greater than the adjusted critical value z = 2.33, corresponding to a one-side alpha level of 1%. If a p-value > 0.5 is observed, the study could be stopped due to futility (non-binding futility stop). The adjusted critical value for the final analysis was calculated as 2.08, given all 370 planned sample size are enrolled.

6.1.10 Study Population and Disposition

6.1.10.1   Populations Enrolled/Analyzed
In total, 214 patients were enrolled. There were 6 screen failures and 208 patients were randomized, 105 to the BALFAXAR group and 103 to the Kcentra group. All patients were treated and underwent surgery. A summary of the analysis populations is provided in Table 2.

Table 2: Analysis Populations

	BALFAXAR N (%)	Kcentra N (%)	Overall N (%)
RAND	105 (100)	103 (100)	208 (100)
SAF	105 (100)	103 (100)	208 (100)
mITT	105 (100)	103 (100)	208 (100)
PP	103 (98.1)	99 (96.1)	202 (97.1)

Source: Adapted from BLA 125776/0 Module 5.3.5.1/LEX-209: report-body.pdf, Table 8, page 62.

6.1.10.1.1 Demographics

Demographic characteristics were similar in the two treatment groups. Overall, the mean (SD) age was 66.2 (11.5) years with 74.5% of patients older than 60 years. There was a higher proportion of male patients (56.7% versus 43.3% female patients), and the majority were white (99.5%), with 4.3% of Hispanic ethnicity. Overall, the mean (SD) height was 170.2 (9.2) cm, mean (SD) weight was 83.01 (18.54) kg, and mean (SD) body mass index was 28.629 (5.953) kg/m^2 (Table 3).

Table 3: Demographic Characteristics (RAND)

	BALFAXAR N=105	Kcentra N=103	Overall N=208
Age			
Mean (SD)	65.6 (11.8)	66.8 (11.2)	66.2 (11.5)
Median (Q1, Q3)	67.0 (60.0, 72.0)	68.0 (62.0, 73.0)	67.5 (60.0, 73.0)
Min, Max	31, 90	32, 92	31, 92
Height (cm)			
Mean (SD)	170.2 (9.3)	170.2 (9.0)	170.2 (9.2)
Median (Q1, Q3)	170.0 (164.0, 178.0)	170.0 (164.0, 176.0)	170.0 (164.0, 176.5)
Min, Max	152, 192	148, 195	148, 195
Weight (kg)			
Mean (SD)	81.53 (18.21)	84.52 (18.84)	83.01 (18.54)
Median (Q1, Q3)	80.00 (70.00, 90.00)	84.00 (72.00, 93.00)	81.00 (71.00, 90.70)
Min, Max	50.0, 152.0	54.0, 165.0	50.0, 165.0
BMI (kg/m^2)			
Mean (SD)	28.132 (5.817)	29.136 (6.075)	28.629 (5.953)
Median (Q1, Q3)	26.830 (24.030, 31.140)	28.410 (24.860, 31.910)	27.760 (24.560, 31.325)
Min, Max	18.65, 51.98	19.38, 57.09	18.65, 57.09
Sex			
Male (%)	58 (55.2)	60 (58.3)	118 (56.7)
Female (%)	47 (44.8)	43 (41.7)	90 (43.3)
Race			
Asian (%)	0	1 (1.0)	1 (0.5)
White (%)	47 (44.8)	43 (41.7)	90 (43.3)
Ethnicity			
Hispanic or Latino	3 (2.9)	6 (5.8)	9 (4.3)
Not Hispanic or Latino	101 (96.2)	97 (94.2)	198 (95.2)
Unknown	1 (1.0)	0	1 (0.5)
Age Group			
≤ 60	28 (26.7)	25 (24.3)	53 (25.5)
>60	77 (73.3)	78 (75.7)	155 (74.5)

Source: Adapted from BLA 125776/0 Module 5.3.5.1/LEX-209: report-body.pdf, Table 9, page 63.

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population
All patients had pre-infusion anticoagulation therapy with a VKA, as per the study's inclusion criteria. The majority (87.6% in the BALFAXAR group and 82.5% in the Kcentra group) did not have a history of TEE. Approximately one half (50.5%) had an estimated average blood loss of ≥200 mL (the protocol required at least 40%), 24.5% with ≥100 mL but <200 mL (the protocol required

at least 20%), and 25.0% with ≥50 mL but <100 mL (the protocol required ≤40%). In the majority of patients, it was planned that Vitamin K would be administered during surgery (75.2% in the BALFAXAR group and 68.9% in the Kcentra group). Median INR was similar in both groups (3.050 and 3.000, respectively)

Table 4: Baseline Characteristics in Medical (RAND)

	BALFAXAR N=105 n (%)	Kcentra N=103 n (%)	Overall N=208 n (%)
Pre-infusion anticoagulation therapy			
Sol. fraxiparine (nadroparin calcium)	1 (1.0)	0	1 (0.5)
Vitamin K antagonist	105 (100)	103 (100)	208 (100)
History of TEE			
Presence of embolic or thrombotic event	13 (12.4)	18 (17.5)	31 (14.9)
Absence of embolic or thrombotic event	92 (87.6)	85 (82.5)	177 (85.1)
Type of surgery			
Cardiothoracic Surgery	5 (4.8)	4 (3.9)	9 (4.3)
Orthopaedic Surgery	7 (6.7)	5 (4.9)	12 (5.8)
Others	93 (88.6)	94 (91.3)	187 (89.9)
Estimated average blood loss			
≥ 200 mL	55 (52.4)	50 (48.5)	105 (50.5)
≥ 100 mL but <200 mL	26 (24.8)	25 (24.3)	51 (24.5)
≥ 50 mL but <100 mL	24 (22.9)	28 (27.2)	52 (25.0)
Estimated maximum blood loss			
≥ 200 mL	71 (67.6)	69 (67.0)	140 (67.3)
≥ 100 mL but <200 mL	30 (28.6)	29 (28.2)	59 (28.4)
≥ 50 mL but <100 mL	4 (3.8)	5 (4.9)	9 (4.3)
Planned Vitamin K administration during OP			
Yes	79 (75.2)	71 (68.9)	150 (72.1)
No	26 (24.8)	32 (31.1)	58 (27.9)
Baseline INR			
Mean (SD)	3.959 (2.769)	3.559 (1.821)	3.761 (2.351)
Median (Q1, Q3)	3.050 (2.400, 4.028)	3.000 (2.400, 4.100)	3.025 (2.400, 4.044)
Min, Max	1.97, 21.10	2.00, 11.30	1.97, 21.10

Source: Adapted from BLA 125776/0 Module 5.3.5.1/LEX-209: report-body.pdf, Table 10, page 64.

6.1.10.1.3 Subject Disposition
All 208 randomized patients were included in the RAND, SAF, and mITT populations. The reasons for exclusion from the PP population in the BALFAXAR group were surgery starting more than 5 hours after the end of the IP infusion in 1 patient and a major protocol violation in another patient. In the Kcentra group, the reasons were receiving 143% of planned dose in 1 patient, surgery starting more than 5 hours after the end of the IP infusion in 1 patient, and a major protocol violation in 2 patients.

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint
In the interim analysis, 185 patients were randomized, 93 to the BALFAXAR group and 92 to the Kcentra group. The hemostasis was effective in 94.6% (88/93) of patients in the BALFAXAR group versus 93.5% (86/92) in the Kcentra group. The non-inferiority analysis for the proportion difference (98% CI) of 1.1% (-9.2%, 11.5%) was statistically significant (p-value <0.001) at the one-sided 1% significance level. The z-value was 3.62 and therefore greater than the adjusted critical value of 2.33 and the lower bound of the CI was above the pre-specified non-inferiority margin of -0.15, indicating the study success criterion for non-inferiority was met. As a result, enrollment stopped following the interim analysis.

In the final analysis and as an update to the interim analysis, 208 randomized patients were included. There were 99 of 105 subjects achieved effective hemostasis in the BALFAXAR group while 97 of 103 subjects achieved effective hemostasis in the Kcentra group. The BALFAXAR group hemostasis was effective in 94.3% of patients versus 94.2% in the Kcentra group. The proportion difference (95% CI) was 0.1% (-8.0%, 8.2%).

Reviewer's Comment:

- *According to SAP v3.0, the IA result supported an early stop of LEX-209 due to efficacy. However, the enrollment was continued until FDA agreed to stop the study on 2/22/2022. Consequently, the final analysis included 208 patients, much less than the planned sample size 370. The data contributed to the decision-making at interim analysis are considered as the primary evidence for the efficacy evaluation. The final updated analysis, using all available data at the end of the study, is considered as a supportive analysis and presented in a descriptive manner.*

- *While the proportions of subjects achieving effective hemostasis were similar between the two treatment groups, it is noted that the proportion of subjects achieving the "excellent" category of hemostasis was numerically*

lower in the BALFAXAR group (39.0%) compared with that in the Kcentra group (48.5%).

The PP analysis yielded consistent results as those in the primary RAND analysis:
1. In the IA, the BALFAXAR group hemostasis was effective in 94.5% (86/91) of patients versus 94.3% (83/88) in the Kcentra group. The non-inferiority analysis for the proportion difference (98% CI) of 0.2% (-7.8%, 8.2%) was statistically significant (p-value <0.001 and z-value 3.43) at the one-sided 1% significance level.

2. In the final analysis, the BALFAXAR group hemostasis was effective in 94.2% (97/103) of patients versus 94.9% (94/99) in the Kcentra group. The proportion difference (95% CI) was -0.7% (-7.6%, 6.1%).

6.1.11.2 Analyses of Secondary Endpoints
Proportion of Patients with an INR ≤1.5 at 30 Minutes After the End of the Infusion
There were 82 of 105 patients from the BALFAXAR group and 74 of 103 patients from the Kcentra group achieved an INR ≤1.5 at 30 minutes after the end of the infusion, resulting in the proportions of 78.1% and 71.8% for the BALFAXAR group and the Kcentra group respectively. The proportion difference was 6.3% (95%CI: -5.5%, 18.0%)

Reviewer's comment: The applicant presented a difference of 6.3% (95%CI: -5.6%, 18.1%) in the CSR. This result appears to be based on the Farrington-Manning method constrained by a specified non-inferiority margin of 0.15 (as used in the primary analysis), which does not apply for this endpoint. I recalculated the 95% CI using the Normal approximation method and obtained (-5.5%, 18.0%).

Change in INR
The mean (SD) baseline (i.e., within 3 hours prior to IP infusion) INR was 3.96 (2.77) in the BALFAXAR group and 3.56 (1.83) in the Kcentra group. INR values (SD) decreased to 1.38 (0.35) and 1.40 (0.34), respectively, 30 minutes after the end of infusion and remained stable up to the final assessment at 1 hour post-surgery.

Change in Coagulation Factor Levels from Baseline
Table 5 summarizes the mean baseline activity of all tested coagulation factors (FII, FVII, FIX, and FX). The results were numerically similar between the two treatment groups. In both groups, there were numerical increases in FII, FVII, and IX activity levels from baseline to 30 minutes after the end of the infusion.

Table 5: Summary of Change in Coagulation Factor Levels from Baseline

Endpoint	BALFAXAR	N*	Kcentra	N**	Median difference (95% CI)
FII activity					
Mean baseline (SD)	33.7 (19.8)	104	34.4 (19.6)	101	
Mean change (SD)	56.5 (29.4)	104	55.6 (28.7)	100	1.00 (-7.00: 9.00)
FVII activity					
Mean baseline (SD)	27.6 (25.1)	105	27.3 (23.1)	102	
Mean change (SD)	40.9 (32.8)	105	32.8 (34.4)	102	8.00 (2.00: 15.00)
FIX activity					
Mean baseline (SD)	53.0 (32.2)	105	53.6 (31.4)	102	
Mean change (SD)	36.9 (37.6)	105	36.5 (33.2)	102	0.00 (-7.00: 8.00)
FX activity					
Mean baseline (SD)	24.4 (17.6)	103	24.0 (18.6)	100	
Mean change (SD)	56.0 (29.8)	103	69.0 (32.3)	99	-13.00 (-21.00: 4.00)

*: number of patients with available data in the BALFAXAR group;
**: number of patients with available data in the Kcentra group
Source: Adapted from BLA 125776/0 Module 5.3.5.1/LEX-209: report-body.pdf, Table 15, page 74.

Red Blood Cells Received During Surgery
A low proportion of patients received RBC during surgery (3.8% [4 patients] in the BALFAXAR group and 2.9% [3 patients] in the Kcentra group [proportion difference of 0.9%; 95% CI -4.0%, 5.8%]). All patients who received RBC during surgery were in the expected maximum blood loss ≥ 200 mL subgroup and received concomitant treatment with vitamin K; the other subgroup results were unremarkable.

6.1.11.3 Subpopulation Analyses
Subgroup analyses of the primary endpoint by sex, age group, race, region, expected blood loss, baseline INR, and concomitant treatment with vitamin K were performed on RAND. Table 6 summarizes subgroup analyses results. The proportions of subjects achieving effective hemostasis were in general numerically similar between the BALFAXAR and Kcentra groups.

Table 6: Subgroup analyses of hemostasis efficacy (RAND)

	BALFAXAR N=105	Kcentra N=103	P-value
Sex			
Male	91.4 (53/58)	93.3 (56/60)	0.012
Female	97.9 (46/47)	95.3 (41/43)	0.002
Age group			
≤ 60	89.3 (25/28)	96.0 (24/25)	0.151
>60	96.1 (74/77)	93.4 (73/78)	<0.001
Race			
Asian (%)	0	100 (1/1)	-
White (%)	94.3 (99/105)	94.1 (96/102)	<0.001
Expected average blood loss			
≥ 200 mL	94.5 (52/55)	92.0 (46/50)	0.002
100 mL - <200 mL	96.2 (25/26)	96.0 (24/25)	0.028
50 mL - <100 mL	91.7 (22/24)	96.4 (27/28)	0.107
Expected maximum blood loss			
≥ 200 mL	95.8 (68/71)	92.8 (64/69)	<0.001
100 mL - <200 mL	90.0 (27/30)	96.6 (28/29)	0.128
50 mL - <100 mL	100 (4/4)	100 (5/5)	-
Baseline INR			
2 - < 4	92.3 (72/78)	96.1 (74/77)	0.008
4 - < 6	100 (12/12)	83.3 (15/18)	0.013
>6	100 (15/15)	100 (0/0)	-
Concomitant Treatment with Vitamin K			
Yes	92.4 (73/79)	93.0 (66/71)	0.002
No	100 (26/26)	96.9 (31/32)	0.009

Source: Adapted from BLA 125776/0 Module 5.3.5.1/LEX-209: report-body.pdf, Table 14.2.1.1, page 2030-2042.

6.1.12 Safety Analyses

6.1.12.3 Deaths

There were five deaths (4.8%) occurred in the BALFAXAR group and one death (1.0%) occurred in the Kcentra group. Among the BALFAXAR group, four deaths occurred in the 22 to 45 days post-surgery, and 1 death occurred after 45 days post-surgery. The death in the Kcentra group occurred in the 4 to 21 days post-surgery. The difference is not statistically significant at the 5% level. However, I defer to the clinical reviewer on determining the clinical significance of the observed imbalance.

6.1.12.4 Nonfatal Serious Adverse Events

A numerically higher proportion of patients experienced SAEs in the BALFAXAR group (13 patients [12.4%] experienced 21 SAEs) versus the Kcentra group (6 patients [5.8%] experienced 9 SAEs).

6.1.12.5 Adverse Events of Special Interest (AESI)

The most commonly reported Treatment-Emergent Adverse Events (TEAEs) by System Organ Class (SOC) (>10% in either group) were: injury, poisoning and procedural complications (in 69.5% of patients in the BALFAXAR group and 65.0% in the Kcentra group), general disorders and administration site conditions (in 20.0% and 25.2%, respectively), gastrointestinal disorders (in 10.5% and 18.4%, respectively), and investigations (in 0% and 11.7%, respectively).

The most commonly reported TEAEs by Preferred Term (>5% in either group) were: procedural pain (in 47.6% of patients in the BALFAXAR group and 48.5% in the Kcentra group), postoperative wound complication (in 14.3% and 14.6%, respectively), asthenia (in 12.4% and 17.5%, respectively), and anemia (in 5.7% and 5.8%, respectively). Generally, the incidence of TEAEs by PT was similar across the two treatment groups.

In Four TEEs were reported in 3 patients (2.9%) in the BALFAXAR group; no TEEs were reported in the Kcentra group. None of the TEEs were reported in the 3 days after the end of surgery, 2 of the TEEs were reported in the 4 to 21 days post-surgery, and 2 were reported in the 22 to 45 days post-surgery.

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

This statistical review memo focuses on the efficacy analysis and safety analysis of the pivotal phase 3 study LEX-209.

Study LEX-209 was a Phase 3, group sequential with one IA, non-inferiority study including subjects on oral anticoagulant therapy with VKAs who needed to undergo an urgent surgery carrying a significant risk of bleeding to compare BALFAXAR with Kcentra. The primary endpoint was the hemostatic efficacy rating at the end of the surgery. In the IA, 185 patients were randomized with 93 to BALFAXAR and 92 to Kcentra. The effective hemostasis rates were 94.6% and 93.5% for BALFAXAR and Kcentra respectively. The non-inferiority analysis for the proportion difference (98% CI) of 1.1% (-9.2%, 11.5%) was statistically significant with a pre-specified non-inferiority margin of -15% (p-value <0.001). The z-value was 3.62 and higher than the pre-specified critical value of 2.33, showing that Study LEX-209 could be stopped following the IA due to a statistically significant efficacy result. In the final analysis report submitted on 07/28/22, 208 patients were randomized, with 105 to the BALFAXAR group and

103 to the Kcentra group. The effective hemostasis rate was 94.3% (99/105) in the BALFAXAR group versus 94.2% (97/103) in the Kcentra group, with a proportion difference (95% CI) of 0.1% (-8.0%, 8.2%). These analysis results have provided adequate statistical evidence to demonstrate that BALFAXAR was non-inferior to Kcentra as a VKA therapy for patients who are in need for urgent surgery with significant bleeding risk.

There were five deaths occurred in the BALFAXAR group and one death occurred in the Kcentra group. There were 13 (12.4%) patients experienced 21 SAEs in the BALFAXAR group and 6 (5.8%) patients experienced 9 SAEs in the Kcentra group. SAEs were most commonly reported in Injury, Poisoning and Procedural complications (4), and Cardiac Disorders (3) and Gastrointestinal Disorders (3) in the BALFAXAR group, and Blood And Lymphatic System Disorders (2) and Gastrointestinal Disorders (2) in the Kcentra group.

10.2 Conclusions and Recommendations

The statistical analysis of Study LEX-209 provides adequate evidence to support the efficacy of BALFAXAR as a VKA therapy for adult patients with (b) (4) (b) (4) surgery procedure. I defer to the clinical reviewer on the acceptance of the safety profile of BALFAXAR.