BLA Clinical Review Memorandum

<table>
<tr><td>Application Type</td><td>Biologic license application (BLA)</td></tr>
<tr><td>STN</td><td>125776/0</td></tr>
<tr><td>CBER Received Date</td><td>July 28, 2022</td></tr>
<tr><td>PDUFA Goal Date</td><td>July 28, 2023</td></tr>
<tr><td>Division / Office</td><td>OTAT</td></tr>
<tr><td>Priority Review (Yes/No)</td><td>No</td></tr>
<tr><td>Reviewer Name(s)</td><td>Karl Kasamon MD</td></tr>
<tr><td>Supervisory Concurrence</td><td>Prasad Mathew MD Branch Chief, BHB, OTP, CBER

Celia Witten MD, PhD Acting Division Director DCEH</td></tr>
<tr><td>Applicant</td><td>Octapharma Pharmazeutika Produktionsges.m.b.H</td></tr>
<tr><td>Established Name</td><td>prothrombin complex concentrate (Human)-lans</td></tr>
<tr><td>(Proposed) Trade Name</td><td>BALFAXAR</td></tr>
<tr><td>Pharmacologic Class</td><td></td></tr>
<tr><td>Formulation(s), including Adjuvants, etc.</td><td>Lyophilized Powder for Reconstitution</td></tr>
<tr><td>Dosage Form(s) and Route(s) of Administration</td><td>BALFAXAR dosing should be individualized based on the patient’s baseline International Normalized Ratio (INR) value, and body weight. For intravenous use after reconstitution</td></tr>
<tr><td>Dosing Regimen</td><td>
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<tr><th>Pre-treatment INR</th><th>2-< 4</th><th>4-6</th><th>> 6</th></tr>
<tr><td>Dose of BALFAXAR (units of Factor IX) / kg body weight</td><td>25</td><td>35</td><td>50</td></tr>
<tr><td>Maximum dose‡ (units of Factor IX)</td><td>Not to exceed 2500</td><td>Not to exceed 3500</td><td>Not to exceed 5000</td></tr>
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<tr><td>Indication(s) and Intended Population(s)</td><td>For the urgent reversal of acquired coagulation factor deficiency induced by Vitamin K</td></tr>
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	antagonist (VKA, e.g., warfarin) therapy in adult patients with need for an urgent surgery/invasive procedure
Orphan Designated (Yes/No)	Yes

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GLOSSARY

4F-PCC	Four-Factor Prothrombin Complex Concentrate
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BW	body weight
CFR	Code of Federal Regulations
CI	confidence interval
CMC	chemistry, manufacturing, and controls
CR	complete response
CSR	clinical study report
CT	computed tomography
eCTD	electronic Common Technical Document
EU	European Union
FII	Coagulation Factor II
FVII	Coagulation Factor VII
FIX	Coagulation Factor IX
FX	Coagulation Factor X
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICF	informed consent form
ICH	International Conference on Harmonisation (of Technical Requirements for Registration of Pharmaceuticals for Human Use)
iDMC	independent data monitoring committee
INR	International Normalized Ratio
IV	intravenous
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
OBE	Office of Biostatistics and Epidemiology
OSE	Office of Surveillance and Epidemiology
PD	pharmacodynamics
PeRC	Pediatric Review Committee (CDER)
PI	package insert
PK	pharmacokinetics
PMR	postmarketing requirement
PREA	Pediatric Research Equity Act
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAF	Safety analysis population
SAP	Statistical Analysis Plan
SD	Standard deviation
SMQ	Standardized MedDRA Queries
SOC	System Organ Class
TEAE	Treatment emergent adverse event
TEE	Thromboembolic event

TRALI	transfusion related acute lung injury
US	United States
VKA	Vitamin K antagonist

1. Executive Summary

Octapharma Pharmazeutika Produktionsges m.b.H submitted this Biologics License Application (BLA), STN 125776/0, for the licensure of BALFAXAR (with trade name BALFAXAR) for the reversal of anticoagulation due to vitamin K antagonists (VKAs) in patients needing urgent surgery associated with significant bleeding risk.

BALFAXAR is a human plasma-derived prothrombin complex concentrate (PCC) containing the coagulation factors II, VII, IX and X and Proteins C and S. BALFAXAR is manufactured from U.S. (b) (4) plasma and supplied as a lyophilized powder for reconstitution for intravenous use; the diluent for reconstitution is Water for Injection. BALFAXAR is a "co-packaged" combination product consisting of the three different constituent parts: biologic (BALFAXAR powder), water for injection, and a transfer device.

An identified safety risk[1] of PCCs, including BALFAXAR, is arterial and venous thrombosis and thromboembolism (TEE).

To obtain marketing authorization the applicant submitted results of study LEX-209, a noninferiority comparison of BALFAXAR efficacy to that of a licensed PCC product, Kcentra, for rapid reversal of oral anticoagulation by vitamin K antagonists in patients with need for urgent surgery or invasive procedures. Treatment with BALFAXAR met the non-inferiority criterion compared with Kcentra, demonstrating effectiveness. Safety outcomes were as expected following surgical procedures, however higher rates of TEEs and overall deaths were reported among BALFAXAR recipients. The benefit risk profile is positive leading the review team to approve BALFAXAR for the stated indication. The primary medical reviewer concurs with the recommendations of the division of biostatistics and epidemiology to have a post marketing requirement (PMR) study to generate more precise estimate of the risk of TEE and mortality.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

Of 214 subjects enrolled, there were six screen failures, and the remaining 208 subjects randomized, with 105 to BALFAXAR arm and 103 to Kcentra. All these were treated and proceeded to surgery. Demographic characteristics were similar in the two treatment groups, with mean (SD) age of 66.2 (11.5) years and 74.5% of patients older than 60 years. Males outnumbered females 56.7% versus

1 Dentali F. *Thrombosis and Haemostasis* 106:429-438 (2011); Lusher JM, *Seminars in Hematology* 28:3-5 (1991).

43.3%. As the study was done largely in eastern Europe, the majority of subjects were white (99.5%), with 4.3% of Hispanic ethnicity.

1.2 Patient Experience Data

N/A

Data Submitted in the Application

Check if Submitted	Type of Data	Section Where Discussed, if Applicable
☐	Patient-reported outcome	
☐	Observer-reported outcome	
☐	Clinician-reported outcome	
☐	Performance outcome	
☐	Patient-focused drug development meeting summary	
☐	FDA Patient Listening Session	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☐	Other: (please specify)	
☒	**If no patient experience data were submitted by Applicant, indicate here.**	
Check if Considered	**Type of Data**	**Section Where Discussed, if Applicable**
☐	Perspectives shared at patient stakeholder meeting	
☐	Patient-focused drug development meeting	
☐	FDA Patient Listening Session	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☐	Other: (please specify)	

3. Clinical and Regulatory Background

BALFAXAR is a blood coagulation factor-replacement product developed for the indication of the urgent reversal of acquired coagulation factor deficiency induced by VKA therapy in adult patients with a need for an urgent surgery/invasive procedure. BALFAXAR 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).

The first marketing authorization for BALFAXAR was granted in March 2003. To date, BALFAXAR (Octaplex) is registered in 86 countries worldwide.

2.1 Disease or Health-Related Condition(s) Studied

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

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

Kcentra is the only approved agent. Other approaches include withdrawal of VKA therapy, fresh frozen plasma (FFP), P24 plasma.

2.3 Safety and Efficacy of Pharmacologically Related Products

A previously identified safety risk of Prothrombin Complex Concentrate (Human), including Octaplex, is arterial and venous thrombosis and thromboembolism[2,3]

While numerous international and U.S. practice guidelines recommend PCCs (or plasma) in conjunction with vitamin K and VKA withdrawal to treat acute major bleeding in patients requiring urgent reversal of VKA anticoagulation, these

2 Dentali F, Marchesi C, Giorgi Pierfranceschi M, Crowther M, Garcia D, Hylek E, Witt DM, Clark NP, Squizzato A, Imberti D, Ageno W. Safety of prothrombin complex concentrates for rapid anticoagulation reversal of vitamin K antagonists. A meta-analysis. Thromb Haemost. 2011 Sep;106(3):429-38. doi: 10.1160/TH11-01-0052. Epub 2011 Jul 28. PMID: 21800002.
3 Lusher JM. Thrombogenicity associated with factor IX complex concentrates. Semin Hematol. 1991 Jul;28(3 Suppl 6):3-5. PMID: 1780767.

recommendations are not evidence-based, and rely on the surrogate endpoint of INR correction, which has not been validated in animals or humans to reflect the actual status of hemostasis in the setting of PCC administration after anticoagulation with VKAs.

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

BALFAXAR has been approved in 86 countries since first being approved in Germany in 2003.

Foreign postmarketing experience with Octaplex: Safety Summary Report (spontaneous reports, March 2003-March 2022):

There has been a total of 66 serious and one non-serious initial reports indicative of TEE with BALFAXAR as suspect product. Seven of the 66 TEE events were fatal.

Distribution data/patient exposure: Since International Birth Date (14 March of 2003), a total of (b) (4) IU of Octaplex have been sold worldwide. The Applicant estimates that this corresponds to approximately (b) (4) patients exposed to Octaplex. (Data lock point: 31 March 2022).

In the INCH Trial (investigator initiated, Octaplex vs Fresh Frozen Plasma in patients treated with VKA who had intracerebral haemorrhage) not powered to show differences in safety profile, reported 6 TEEs observed among the recipients of Octaplex. See Pharmacovigilance review memo from the FDA Division of Biostatistics and Epidemiology for full details.

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

Regularity activity is presented in the following table

Activity	Date	Description
ND 013323 submission	March 19, 2007	IND #013323 was opened with first study LEX-205 for "Reversal of anticoagulant treatment for patients who have need for urgent surgery or invasive procedures."
Orphan Drug Designation (#06-2258)	Feb 01, 2008	Granted for "Reversal of anticoagulation therapy in patients needing treatment of serious or life-threatening bleeding and/or needing urgent surgery or invasive procedures."
Fast Track Designation	Sep 30, 2010	Granted for "Reversal of anticoagulation therapy in patients under Vitamin K Antagonist Therapy with the need for urgent surgery or invasive procedures."
(b) (4)	(b) (4)	

(b) (4)	(b) (4)	(b) (4)
Type B Meeting (written responses only)	Feb 03, 2016	Agreement on the study design and planned analysis for a new phase 3 randomized controlled study LEX-209. FDA recommended a pre-BLA meeting once Study LEX-209 reached interim analysis.
Study LEX-209 protocol submission	Apr 18, 2016	Octapharma submitted Study LEX-209 Protocol and SAP prepared according to FDA written responses to type B meeting questions
FDA feedback on the Study LEX-209 Protocol	Oct 06, 2016	Octapharma received FDA feedback on the Study LEX-209 Protocol and SAP
Study LEX-209 revised protocol and SAP submission	Nov 3, 2016	Octapharma submitted revised Study LEX-209 Protocol and SAP addressing comments received from the FDA on Oct 6, 2016
(b) (4)	(b) (4)	(b) (4)
Submission IND Amendment #105	Sep 22, 2021	Notification of the temporary recruitment on- hold based on iDMC recommendation after reviewing the results of the Interim Analysis
Pre-BLA, Type B meeting WRO including follow-up emails	Feb 22, 2022	FDA confirmation that study enrolment for LEX-209 can be stopped; data might be sufficient for BLA submission. FDA confirmed that HF study is not required.

2.6 Other Relevant Background Information

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

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

3.2 Compliance With Good Clinical Practices And Submission Integrity

See also BIMO review memo. Complicating inspections is the ongoing war by Russia against Ukraine, the latter being the country with most clinical sites enrolling subjects into LEX209, and the former, the second largest number of sites.

3.3 Financial Disclosures

Covered clinical study (name and/or number): LEX-209
Was a list of clinical investigators provided? ☒ Yes ☐ No (Request list from applicant)
Total number of investigators identified: 24
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): N/A Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in sponsor of covered study: _____ Is an attachment provided with details of the disclosable financial interests/arrangements? ☐ Yes ☐ No (Request details from applicant) Is a description of the steps taken to minimize potential bias provided? ☐ Yes ☐ No (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): _____ Is an attachment provided with the reason? ☐ Yes ☐ No (Request explanation from applicant)

The information submitted regarding potential financial conflicts of interest was reviewed. IR was sent to request disclosure forms for the primary investigators involved in conducting LEX209. FDA concluded the submitted information did not, in the aggregate, indicate significant financial conflict of interest among investigators of the pivotal clinical trial LEX209.

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

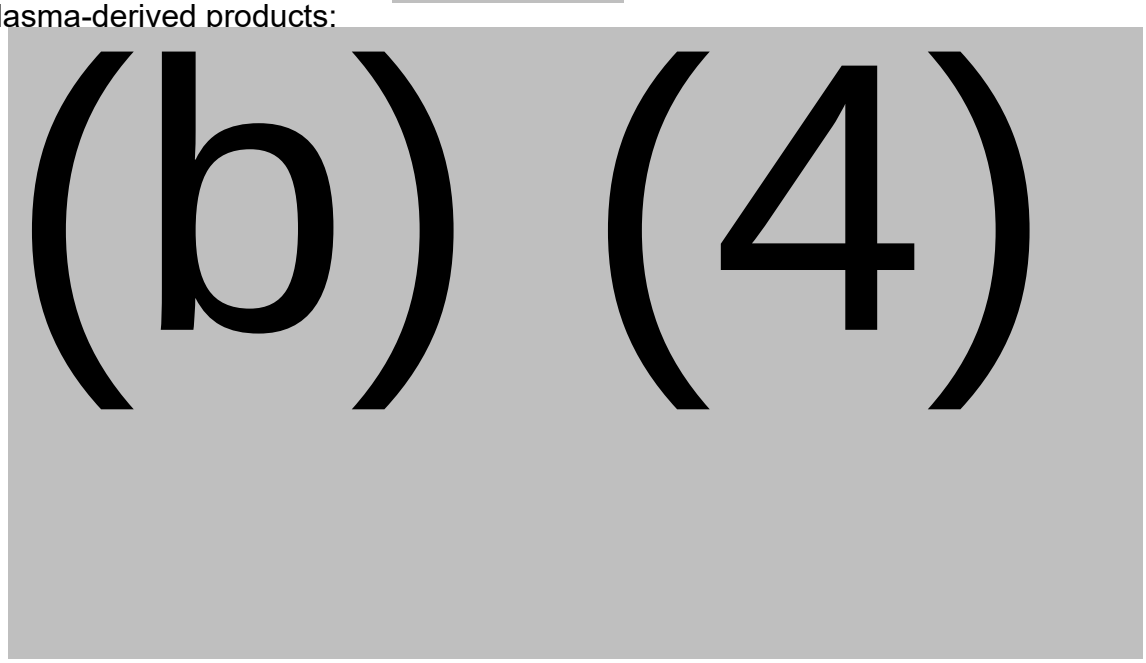
4.1 Chemistry, Manufacturing, and Controls

Balfaxar is technically considered by the Agency as a co-packaged combination product consisting of the three constituent parts: (1) Prothrombin Complex Concentrate powder (2) Water for injection; and (3) Transfer device, Nextaro. The product is supplied as a lyophilized powder for reconstitution with sterile Water for Injection (sWFI), and is administered intravenously.

The starting material for manufacture is Human plasma from USA ((b) (4) Plasma). The overall composition contains active ingredients: Factor IX, Factor II, Factor VII, Factor X, Protein C, and Protein S, plus excipients: Heparin (b) (4) and Sodium citrate.
It is produced with two dosage strengths (based on FIX activity):

- 500 FIX IU which is reconstituted in 20 mL sWFI/30-mL vial
- 1,000 FIX IU which is reconstituted in 40 mL sWFI/50-mL vial

Balfaxar manufacture utilizes (b) (4) -based purification schema for plasma-derived products:



This achieves high degree of virus reduction/inactivation.

For details on viral clearance, analytical methods to assess inactive ingredients, approach to release specifications, and determination of product stability, please see CMC memo.

4.3 Nonclinical Pharmacology/Toxicology

Early versions of the product were evaluated for thrombogenic potential using *in vitro* and *in vivo* (rats and rabbits), (b) (4) heparin, and no thrombosis was observed.
Coagulation activity of Balfaxar was also compared to Kcentra following intravenous (IV) administration in rats pre-treated with oral anticoagulant phenprocoumon, and this produced similar increases in concentrations of Factor II, IX, Protein S and Protein C. Both of these products normalized bleeding time, international normalized ratio (INR), and thromboplastin time (TPT) in these preclinical models.

No toxicology studies were conducted to evaluate the safety of Balfaxar. But toxicology studies evaluated the safety of (b) (4) which are used in viral inactivation steps.

A local tolerance study was conducted to determine the potential irritative effects of BALFAXAR following intravenous (b) (4) administration in rabbits. Procedure related findings (redness at the injection site or hematoma) were noted at both the test site and control site following (b) (4) (b) (4) intravenous infusion. Please see PT memo for more details

4.4 Clinical Pharmacology

The LEX-209 study evaluated changes in the international normalized ratio (INR) at varying time points after end of infusion. The median INR was 3.0 prior to the infusion and dropped to a median value of 1.30 by the 30-minute time point after start of infusion in both treatment arms. At 24 hours the INR was 1.25 in the BALFAXAR group. Please see clinical pharmacology memo for details.

4.4.1 Mechanism of Action

BALFAXAR contains the Vitamin K-dependent coagulation factors II, VII, IX, and X (FX), together known as the Prothrombin Complex, and the antithrombotic Protein C and Protein S. If the patient has an acquired coagulation factor deficiency where one or more of the Vitamin-K-dependent coagulation factors are deficient, bleeding may occur. A dose-dependent acquired deficiency of the Vitamin K-dependent coagulation factors occurs during Vitamin K antagonist treatment. Vitamin K antagonists exert anticoagulant effects by blocking carboxylation of glutamic acid residues of the Vitamin K-dependent coagulation factors during hepatic synthesis, lowering both factor synthesis and function. Kcentra infusion increases plasma levels of the Vitamin K-dependent coagulation Factors II, VII, IX, and X as well as the anti-thrombotic Proteins C and S.

4.4.2 Human Pharmacodynamics (PD)

Please see clinical pharmacology memorandum for details.

4.4.3 Human Pharmacokinetics (PK)

See clinical pharmacology review memorandum.

4.5 Statistical

The Biostatistics team reviewed study LEX-209, and reported that this was a prospective, randomized, double blind, active controlled (with Kcentra), multi-center, group sequential study with one IA (93 vs 94 at 1st stage), non-inferiority (with 0.15 inferiority margin), one primary endpoint (hemostatic efficacy), 370 subjects planned, and N=208 treated (105 vs 103), early stopped for non-inferiority. Please see statistics review memorandum.

4.6 Pharmacovigilance

Please see DPV memo for details. A post-marketing requirement (PMR) study to further evaluate TEE risk and mortality is being recommended by DPV.

5. Sources of Clinical Data and Other Information Considered in the Review

5.1 Review Strategy

The review focused on the most pertinent clinical trial for the requested indication, which was study LEX-209. The trial design was discussed with the sponsor, as it served as a replacement trial for LEX-205, an earlier study based on which the Applicant (b) (4) (b) (4) LEX-209 incorporated a clinical benefit efficacy endpoint and included measures to ensure eligibility of appropriate subjects as well as an acceptable control arm.

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

The main source of data came from the phase 3 study LEX209.

5.3 Table of Studies/Clinical Trials

The pivotal study for the requested peri-operative bleeding indication was LEX209, a study conducted overseas, except for one subject treated in USA.

5.4 Consultations

N/A

5.4.1 Advisory Committee Meeting (if applicable)

It was determined that no AC meeting was needed.

5.4.2 External Consults/Collaborations

N/A

5.5 Literature Reviewed (if applicable)

1. Dentali F, Marchesi C, Giorgi Pierfranceschi M, Crowther M, Garcia D, Hylek E, Witt DM, Clark NP, Squizzato A, Imberti D, Ageno W. Safety of prothrombin complex concentrates for rapid anticoagulation reversal of vitamin K antagonists. A meta-analysis. Thromb Haemost. 2011 Sep;106(3):429-38. doi: 10.1160/TH11-01-0052. Epub 2011 Jul 28. PMID: 21800002.
2. Lusher JM. Thrombogenicity associated with factor IX complex concentrates. Semin Hematol. 1991 Jul;28(3 Suppl 6):3-5. PMID: 1780767.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Trial #1

LEX209

A Phase III, randomized, double-blind, multicenter study to assess the efficacy and safety of Octaplex, a four-factor prothrombin complex concentrate (4F-PCC), compared to the 4F-PCC Kcentra, for reversal of VKA induced anticoagulation in patients needing urgent surgery with significant bleeding risk.

6.1.1 Objectives (Primary, Secondary, etc.)

Objectives:

Primary Objective:

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

Secondary Objectives:

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

6.1.2 Design Overview

The study was designed as a randomized, double-blind non-inferiority study comparing BALFAXAR with Kcentra. During screening, details of the subject's medical history (especially occurrence of previous thromboembolic events [TEEs]), the current clinical status, the expected amount of blood loss (mL) due to the surgery, the reason for, duration and time of last administration of anticoagulant therapy, and details about concomitant medication were recorded. Eligible subjects were randomized to one of the two treatment groups (1:1) using Interactive Response Technology (IRT), with stratification by expected blood loss, history of TEE, and type of planned surgery. Baseline measurements were performed within 3 hours before administration of investigational product (IP). The surgeon had the intention to start the procedure within 3 hours after the end of 4F-PCC administration. After administration of IP, blood samples were taken for safety assessments, coagulation tests, and for factor level measurements at pre-defined time points. Details of the surgery were recorded, including the time and amount of all blood and plasma products given during and after the surgery, as well as the reason for administration. Hemostatic efficacy was assessed by the investigator using a 4-point hemostatic efficacy scale after the surgery (assessed 1 hour after the end of surgery). The hemostatic efficacy rating was also assessed in a blinded manner by an independent endpoint adjudication board (IEAB) consisting of clinical experts. Safety assessments were done on Days 2, 4, and on discharge, and longer-term follow up on Days 9, 21, and 45.

Enrollment of a maximum of 370 subjects was planned (185 subjects per treatment group). The following proportions of subjects were to be enrolled, based on the expected blood loss during surgery:

- ≥40% of subjects with an expected blood loss of ≥200 mL
- ≥20% of subjects with an expected blood loss of ≥100 mL but <200 mL.
- <40% of subjects with expected blood loss ≥50 mL but <100 mL.

If the targeted number of enrolled subjects was reached in a subgroup, IRT was to preclude further enrollment into that subgroup. In total, following early termination of the study after the primary endpoint was met in the interim analysis, 208 subjects were randomized to study treatment and included in the randomized (RAND), safety analysis (SAF), and modified intent-to-treat (mITT) populations; 202 were included in the per-protocol (PP) population.

Reviewer comment:
Study design is reasonable, focusing on demonstrating non-inferiority to licensed PCC comparator, and incorporated design recommendations from the Agency. The protocol stipulated populations with sufficient bleeding expected to robustly demonstrate effectiveness. Ultimate population size was discussed between sponsor and the statistical team and the study was stopped with the interim analysis. Please see statistical review memorandum for justification of this agreement.

6.1.3 Population

Adults ≥ 18 years of age who were currently on oral anticoagulation treatment with VKA of coumadin or warfarin type. Subjects admitted to the hospital or currently hospitalized where:

- an urgent surgery carrying significant bleeding risk (≥50 mL expected blood loss in normal coagulation state) is 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. Subjects with an international normalized ratio (INR) of 2.0 or above at the time of decision to reverse the anticoagulation status.

The following criteria led to exclusion of subjects from enrollment in the study: Subjects with a life expectancy ≤48 hours; with a known congenital bleeding disorder, antiphospholipid antibody syndrome, present or past specific factor inhibitor activity, or thrombocytopenia (<80,000/μL or history of heparin-induced thrombocytopenia); with a history of TEEs, myocardial infarction, unstable angina pectoris, critical aortic stenosis, cerebrovascular accident, transient ischemic attack, severe peripheral vascular disease (e.g., Fontaine IV), or disseminated intravascular coagulation within 3 months of enrollment; who received more than 5000 units of systemic unfractionated heparin, any dose of low-molecular-weight heparin, or any dose of non-VKA anticoagulant (i.e., direct oral anticoagulant) within 24 hours prior to enrollment into the study or had potential need to receive these medications before completion of hemostasis evaluation at the end of surgery; who received PCCs, fresh frozen plasma, or vitamin K within 72 hours

prior to enrollment; or who were receiving P2Y12 platelet inhibitors (e.g., clopidogrel, prasugrel, ticagrelor).

Reviewer comment: exclusion of subjects with recent history of TEE is reasonable as these would be expected to have the greatest risk of recurrent thrombosis, and likewise were excluded from studies of Kcentra. This issue will be included in the USPI.

6.1.4 Study Treatments or Agents Mandated by the Protocol

Commercially available IPs were used in this study: BALFAXAR 500 IU (in all participating countries) Kcentra 500 IU in the US or Beriplex outside the US.

1.1.1.1.1 Dosing of Investigational Product

6.1.5 Directions for Use

The nominal IP potency of 25 IU/mL of FIX was used for volume calculation. A single infusion of IP was administered per subject. The dose was determined based on body weight (BW) and baseline INR and calculated by investigator according to the details in Table 1. BW was rounded to the nearest whole kilogram for IP dose calculation. Baseline INR value was rounded to one decimal place. If the qualifying INR was within 3 hours of IP infusion start and was analyzed by the laboratory participating in the study it could serve as the baseline INR and additional baseline INR testing was not mandatory. Otherwise, baseline INR had to be obtained. If the baseline INR value resulted in a different dosing category compared to the qualifying INR value used for initial IP dose calculation, the dose of IP was adjusted to baseline INR using IRT.

Table 1 Dosing of Investigational Products

Pre-treatment INR	2-< 4	4-6	> 6
Dose of BALFAXAR (units of Factor IX) / kg body weight	25	35	50
Maximum dose (units of Factor IX)	Not to exceed 2500	Not to exceed 3500	Not to exceed 5000

Source: reproduced from LEX-209 Study report, page 22.

After signing the written informed consent form, each subject received a subject number (in numeric order per center). The site entered the subject number and the initials of each subject in the CRF and in the confidential subject identification list. Each subject was randomized to receive IP (either BALFAXAR or Kcentra in 1:1 ratio). To achieve a balance between the two treatment groups with respect to the planned type of surgery and history of TEE, the treatment allocation by the IRT was stratified according to the following parameters:

- Expected blood loss: ≥200ml, ≥100ml but <200ml, or ≥50 ml but <100ml
- History of TEE: yes or no

- Type of planned surgery: orthopedic, cardiothoracic, or other surgery

To ensure that the intended proportions of subjects enrolled were kept for subgroups of expected blood loss, the IRT was to preclude enrollment into the subgroup once its targeted number of enrolled subjects was reached.

Blinding:
Following randomization, IP was assigned using IRT and prepared for infusion by unblinded site personnel. Investigational product was prepared and infused in a manner that blinded the investigator and other blinded site personnel to the study treatment. The IP was either transferred to an IV infusion bag or administered with a syringe pump. The infusion bag or syringe(s) were covered with a pouch/bag to obscure the contents and were labelled by the unblinded pharmacist with the blinded study label. Unblinded site personnel were not to communicate to the investigator or other blinded site personnel which product was assigned to the subject. Breaking of blinding in individual subjects was only permitted in case of a serious adverse event (SAE) or unexpected adverse drug reaction, when knowledge of the type of the administered IP was required for therapeutic decisions regarding this event. Emergency unblinding did not occur.

Reviewer comment:
The dosing is per package label for commercial IP at non-US sites, and the nominal concentration of both products is the same. Dose is determined based on weight of the subject and their baseline INR, as per provided table. These provisions are acceptable. Blinding was described and appears acceptable.

6.1.6 Sites and Centers

Approximately 70 centers worldwide were planned. In total, 87 centers were initiated, and subjects were enrolled at 24 sites as follows: 6 sites in Russia, 5 sites in Georgia, 1 site in Belarus, 9 sites in Ukraine, 2 sites in Romania and a single site in USA.

Reviewer comment: The distribution of the study centers as mostly in former Iron Block countries, especially in Ukraine and Russia, complicates possible inspection of facilities by FDA during ongoing hostile activities.

6.1.7 Surveillance/Monitoring

The study population was closely observed for safety, as per the schedule of activities shown in the figures below. Efficacy evaluation was primarily performed within the hospital stay, until day of discharge, and included vital signs as well as laboratory parameters including hemoglobin assessment. Wound drainage and hematoma evaluation were continued to be assessed until Day 45 +/- one week.

Reviewer comment:
The schedule of surveillance and monitoring as summarized in the figure below, appears reasonable.

Figure 1 Schedule of Assessments

		Before Infusion		Infusion	After END of Infusion					OP[1]				POST OPERATIVE[2]			FOLLOW-UP		
		Screening / Randomization	Baseline		30 min after END	2h after END	4h after END	12h after END	24h after END	Prior OP	Post OP	12h after START	24h after START	Day 2	Day 4	Discharge	Day 9	Day 21	Day 45
			within 3h prior infusion		±15 min	±30 min	±30 min	±1 h	±2 h	-1h	+1h	±3h	±3h				-2/+5 days	±1 week	±1 week
Informed Consent		X																	
Collect Baseline Information		X[3]																	
Inclusion/Exclusion Criteria		X																	
Hemostatic Assessment		X									X								
Screening Registration		X																	
Physical Examination			X											X		X			
IP dose calculation, Randomization		X[4]																	
IP assignment, preparation		X																	
Vital Signs			X		X	X								X		X			
Local Lab	Coagulation Factors[5] PT, INR, aPTT		X[4]		X	X	X	X	X	X[6]	X[6]								
	Hematology[5] Hct, Hgb, RBC, WBC, Platelets		X		X				X	X	X	X	X	X[7]		X			
	Liver Function & Electrolytes LDH, Sodium, Potassium		X						X					X[7]		X			
	Kidney Function BUN or Urea, Creatinine		X						X					X[7]		X			

		Before Infusion		Infusion	After END of Infusion					OP[1]				POST OPERATIVE[2]			FOLLOW-UP		
		Screening / Randomization	Baseline		30 min after END	2h after END	4h after END	12h after END	24h after END	Prior OP	Post OP	12h after START	24h after START	Day 2	Day 4	Discharge	Day 9	Day 21	Day 45
			within 3h prior infusion		±15 min	±30 min	±30 min	±1 h	±2 h	-1h	+1h	±3h	±3h				-2/+5 days	±1 week	±1 week
	Pregnancy Test	X[8]																	
C. Lab	Coagulation Factors		X		X	X	X	X	X										
	Virology tests		X														X[9]		
Vitamin K Administration			X[10]																
IP Infusion				X[11]															
Wound Drainage Evaluation											X	X	X						
Hematoma Assessment										X	X	X	X						
Concomitant Medications and Transfusions[12]				X	X	X	X	X	X	X	X	X	X	X	X	X	X[13]	X[13]	X[13]
AEs, Vital Status			X[14]																

AE=adverse event; aPTT=activated partial thromboplastin time; BUN=blood urea nitrogen; C. Lab=central laboratory; eCRF=electronic case report form Hct=hematocrit; Hgb=hemoglobin; IP=investigational product; INR=international normalized ratio; IRT=interactive response technology; LDH=lactate dehydrogenase PT=prothrombin time; RBC=red blood cells; SAE=serious adverse event; TEE=thromboembolic event; WBC=white blood cells.

1 Time of surgery start was time of anesthesia initiation. Time of surgery end was surgical end time of principal procedure.

2 Assessments at Days 1, 2, or 4 were done if patient remained hospitalized. Discharge assessments were done on the day of discharge. If discharge fell on Days 1, 2, or 4, the schedule of discharge assessments was followed.

3 Baseline information included collection of demographics, medical history, prior and concomitant medication use, and recording details of vitamin K administration

4 If baseline INR value was not available when patient had to be randomized to initiate preparation of IP, qualifying INR (used for inclusion of the patient) could be used (see Section 9.4.1 for details).

5 Results of hematology and coagulation factors blood tests performed as part of standard patient care were documented in eCRF.

6 Prior OP/Post OP coagulation samples could be skipped if one of the After the END of Infusion samples was scheduled within its time window.

7 Samples were not done if patient had been discharged earlier. Discharge visit samples were taken at the day of discharge.

8	Urine or blood pregnancy test was done only in women of childbearing potential.
9	Day 9 Virology tests were only done in patients who had at least one negative result of Baseline Virology tests.
10	Vitamin K could be administered within timeframe ±1h of IP infusion. For patients with a mechanical heart valve, Left Ventricular Assist Device, or any other hypercoagulable/prothrombotic condition administration of vitamin K was not mandatory.
11	If reconstituted IP was not used within 4 hours following reconstitution it had to be discarded and new IP assigned via IRT.
12	Transfusions were collected during hospitalization for the original admission.
13	Only concomitant medications related to ongoing AEs were recorded.
14	AEs were to be followed-up until Day 4. SAEs were to be followed-up until Day 45. If TEEs were suspected at any time during the study, appropriate examinations according to local standards were performed (e.g., Doppler scan using color duplex, X-ray) and the results documented.

Source: copied from study report Page 26, 27, 28

6.1.8 Endpoints and Criteria for Study Success

The investigator and the IEAB members were to employ a standard 4-point Hemostatic Efficacy Scale to assess outcome of surgical procedure:

- **Excellent:** Intra-operative blood loss and transfusion requirements were lower than or equal to the average expected for the type of procedure performed in a patient with normal hemostasis and of the same sex, age, and stature.
- **Good:** Intra-operative blood loss and transfusion requirements were higher than the average expected but lower or equal to the maximal expected blood loss and transfusion requirements for the type of procedure in a patient with normal hemostasis.
- **Moderate:** Intra-operative blood loss and transfusion requirements were higher than the maximal expected for the type of procedure performed in a patient with normal hemostasis, but hemostasis was controlled.
- **None:** Hemostasis was uncontrolled necessitating a change in clotting factor replacement regimen.

For all ratings (excellent, good, moderate, and none), unexpected blood loss due to surgical complications were not taken into consideration when assessing intra-operative efficacy. These included:

1. Direct injury to a vessel (artery or vein).
2. Vessel injury not adequately responding to routine surgical procedures achieving hemostasis.
3. Accidental injury of parenchymatous tissue (e.g., liver, lung).

For efficacy analysis, the above score was dichotomized as follows into two possible outcomes:

- Ratings of 'excellent' and 'good' were considered as 'effective' hemostasis, while ratings of 'moderate' and 'none' were considered as 'ineffective' hemostasis.

Lex-209 employed the following endpoints of efficacy:

Primary efficacy endpoint was the hemostatic efficacy rating at the end of the surgery as assessed by an IEAB.

Secondary efficacy endpoints were:

- Hemostatic efficacy rating at end of surgery as assessed by investigator;
- Proportion of subjects with an INR value ≤ to 1.5 at 30 (±15) minutes after the end of infusion.
- Change in coagulation factor levels (Factors FII, FVII, FIX and FX) from baseline to 30 (±15) minutes after the end of infusion
- Proportion of subjects receiving red blood cells (RBC) during the surgery

Exploratory efficacy endpoints:

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

Safety:

- Occurrence of adverse events (AEs).
- Occurrence of TEEs (overall, within 3, 21, and 45 days after end of surgery).
- Mortality (overall, within 3, 21, and 45 days after end of surgery).
- Monitoring vital signs, laboratory parameters.
- Viral safety (at baseline, and Day 9 (-2/+5 days) after administration of IP for subjects with negative baseline virology test).

Reviewer Comment:
The applicant selected the efficacy and safety endpoints with consideration of Agency recommendations, and these should provide evidence of effectiveness and inform of pertinent safety concerns of the IP.

6.1.9 Statistical Considerations & Statistical Analysis Plan

Statistical Methods:
The primary efficacy variable was the hemostatic efficacy as assessed by the IEAB. The hemostatic efficacy was assessed based on objective criteria in the categories 'excellent', 'good', 'moderate', or 'none'. Ratings of 'excellent' and 'good' were considered as 'effective' hemostasis, while ratings of 'moderate' and 'none' were considered as 'ineffective' hemostasis.
The dichotomous 'hemostatic success' variable was used in the analyses.

To demonstrate that treatment with BALFAXAR was clinically not inferior to treatment with Kcentra with respect to hemostatic success, a two-sample, one-sided test of the pair of hypotheses:
H0: $pK - pO \geq \delta$ (inferiority)
vs. H1: $pK - pO < \delta$ (non-inferiority)
was carried out with a type I error probability of $\alpha=0.025$ and clinical non-inferiority margin of $\delta=0.15$. Whereby pO and pK present the probabilities of hemostatic success of BALFAXAR and Kcentra, respectively.

The study employed a sequential design that allowed one pre-planned interim analysis using the data from the first 50% of randomized subjects. The interim analysis was performed on the cohort of the first 185 randomized subjects after documentation of the primary endpoint had been performed.
Farrington's and Manning's test for difference in proportions was used to assess the primary hypothesis in the interim and final analyses. One-sided p-values and the corresponding nominal and repeated confidence intervals (CIs) for the difference in hemostatic success probabilities were presented.
The primary analysis was performed on the RAND population. Additional analyses were performed for the mITT and PP population.
In case of non-inferiority in the mITT and the PP populations, a "tipping point" analysis was to be done to determine the robustness of the results. Iteratively subjects excluded from the mITT/PP analysis assigned to the control arm were considered as treatment successes, and subjects excluded from the mITT/PP analysis and assigned to the BALFAXAR arm were considered as treatment failures, to determine the number of such imputed outcomes required to "tip" the study result from positive to negative in the RAND population.
Farrington's and Manning's test for difference in proportions was used to test the secondary variables on proportions. Point estimates and two-sided 95% CIs were presented in addition to descriptive statistics for these endpoints.
Analysis of the secondary and further exploratory endpoints were done on the RAND, mITT, and PP populations unless indicated otherwise. These analyses were exploratory, by presenting descriptive statistics.
Safety analyses were performed for the SAF. Analyses were generally descriptive. For TEEs and mortality, a possible difference between treatment groups was estimated by a risk ratio with 95% CI, and Kaplan-Meier estimates for time to event were calculated and graphically presented.

Reviewer comment: Statistical plan appears reasonable. Please see Statistics memo for full details.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

LEX209 defines several study populations. These are defined in the table below:

Table 2 Analysis Populations

Enrolled Analysis Population	All subjects who provided informed consent.

Randomized (RAND) Population	All randomized subjects irrespective of whether they received treatment. Following the intent-to-treat (ITT) principle all subjects were analyzed according to the treatment group to which they were randomized. This is the ITT population according to the most rigid definition of ITT.
Safety Analysis (SAF) Population	All randomized subjects who received IP. Subjects receiving different study treatments than originally randomized were considered according to the treatment actually received (rather than that of the original randomization).
Modified Intent-to-Treat (mITT) Population	All randomized subjects who received IP and who had the surgery initiated or for whom the surgery was not initiated for medical reasons related to insufficient coagulation.
Per Protocol (PP) Population	Subjects in the mITT population, excluding subjects with major protocol deviations. The following subjects were excluded: • Subjects receiving an IP different than IP assigned by randomization. • Subjects who received less than 70% of the planned dose. • Subjects who significantly violated inclusion/exclusion criteria. • Subjects with a missing primary efficacy assessment. • Start of surgery more than 5 hours after the end of the infusion of IP. A final decision about the classification of protocol deviations as major and minor and their consequences regarding assignment of subjects to analysis populations was made during the blinded data review meeting prior to unblinding of subject cohorts for the interim and final analyses. Decisions and outcome were approved by Sponsor.

Source: collated by reviewer from Study Report, page 37.

For baseline summaries by the RAND and safety analysis sets were produced. The same applies to the efficacy summaries, where summaries by the RAND and mITT analysis set were produced. All 3 sets are identical. For exposure summaries, only the safety analysis set is presented.

6.1.10.1.1 Demographics

The mean (SD) age was 66.2 (11.5) years with 74.5% of subjects >60 years. There was a higher proportion of male subjects (56.7%), and almost all were White (99.5%), with 4.3% of Hispanic ethnicity. Overall, the mean (SD) weight was 83.01 (18.54) kg.

Table 3 LEX-209 Demographics (RAND set)

		BALFAXAR N=105 (SD)	Kcentra N=103 (SD)	Overall N=208 (SD)
Age (years)	Mean (SD)	65.6 (11.8)	66.8 (11.2)	66.2 (11.5)
Weight (Kg)	Mean (SD)	81.5 (18.2)	84.5 (18.8)	83 (18.5)
Gender n (%)	Male	58 (55.2)	60 (58.3)	118 (56.7)
Gender n (%)	Female	47 (44.8)	43 (41.7)	90 (43.3)
Race n (%)	White	105 (100)	103 (99)	207 (99.5)
Race n (%)	Asian	0	1 (1)	1 (0.5)
Ethnicity n (%)	Hispanic/Latino	3 (2.9)	6 (5.8)	9 (4.3)

Source: Derived by reviewer from ADSL dataset

Reviewer comment:
Although ethnic and racial variables are not likely to predict responses to PCCs, the study population was not very reflective of the demographics of the United

States population. The study was multinational, but most subjects were natives of eastern Europe, with 45% hailing from Ukraine, followed Romania (24.5%), Georgia (20.1%), Russia (5.7%), while a single White subject was American (0.5%).

6.1.10.1.2 Subject Baseline Characteristics

At baseline, all subjects were anticoagulated with a VKA, as per the eligibility criteria. The majority (87.6% in the BALFAXAR group and 82.5% in 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 subjects, 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 (3.1 and 3, respectively). These characteristics are in the table below:

Table 4 Baseline Characteristics of Study Populations (RAND set)

Parameter	**Baseline Characteristic**	**BALFAXAR N=105 n (%)**	**Kcentra N=103 n (%)**	**Overall N=208 n (%)**
Baseline anticoagulant	Nadroparin calcium	1 (1)	0	1 (0.5)
	VKA	105 (100)	103 (100)	208 (100)
TEE History	Presence of TEE History	13 (12.4)	18 (17.5)	31 (14.9)
	Absence of TEE History	92 (87.6)	85 (82.5)	177 (85.1)
Surgery Type	Cardiothoracic	5 (4.8)	4 (3.9)	9 (4.3)
	Orthopedic	7 (6.7)	5 (4.9)	12 (5.8)
	Other	93 (88.6)	94 (91.3)	187 (89.9)
Estimated avg. blood loss	≥200ml	55 (52.4)	50 (48.5)	105 (50.5)
	≥100ml but <200ml	26 (24.8)	25 (24.3)	51 (24.5)
	≥50ml but <100ml	24 (22.9)	28 (27.2)	52 (25)
Estimated max. blood loss	≥200ml	71 (67.6)	69 (67)	140(67.3)
	≥100ml 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 VKA resumption	Yes	79 (75.2)	71 (68.9)	150 (72.1)
	No	26 (24.8)	32 (31.1)	58 (27.9)
INR at baseline	Mean (SD)	4 (2.8)	3.6 (1.8)	3.8 (2.3)
	Median (Min, Max)	3.1 (2, 21.1)	3.0 (2, 11.3)	3.0 (2, 21.1)

Source: Compiled by reviewer from ADSL dataset

The past medical history of the subjects can affect study outcome and response or intolerance to IP, therefore, subjects' prior medical history was collected. Especially pertinent was prior TEE history, and in fact, subjects were allocated to treatment arms based on prior TEE history.
The most commonly reported previous conditions (>5% overall) were surgical and medical procedures in 24.0% of subjects, cardiac disorders in 8.7% of subjects (with a higher incidence in Kcentra group than in the BALFAXAR group of 14.6% versus 2.9%), and vascular disorders in 5.3%. Concomitant diseases were reported by 98.1% of subjects in both the BALFAXAR (103/105) group and Kcentra (101/103) group. The most commonly reported concomitant diseases (>20% overall) were cardiac disorders in 53.4% of subjects, vascular disorders in 44.7%, gastrointestinal disorders in 34.1%, infections and infestations in 23.1%, and hepatobiliary disorders in 21.2%.

Overall, 31 subjects (14.9%) had a history of TEE more than 3 months before enrolment, 12.4% in the BALFAXAR group and 17.5% in Kcentra group. There were 12 subjects (5.8%) with previous TEE (i.e., resolved before administration of IP), and 21 subjects (10.1%) with concomitant TEE (i.e., previously diagnosed and ongoing during the study); one subject in each treatment group had both a previous and a concomitant TEE. The most common concomitant TEEs were ischemic stroke (in 3.8% of subjects), deep vein thrombosis (in 1.9%), and myocardial infarction (in 1.4%). The median time since the last TEE was 86.7 months, ranging from 14 to 224 months, for the BALFAXAR group (n=12) and 42.5 months, ranging from 3 to 201 months, for Kcentra group (n=18).

Table 5 Embolic and Thrombotic Events, Subjects with prior TEE History (RAND set)

Preferred Terms	**BALFAXAR N=105 n (%)**	**Kcentra N=103 n (%)**	**Overall N=208 n (%)**
Subjects with TEE History*	13 (12.4)	18 (17.5)	31 (14.9)
Subjects with Previous TEE	4 (3.8)	8 (7.8)	12 (5.8)
Aortic Valve Replacement	0	1 (1.0)	1 (0.5)
Cerebrovascular Accident	0	1 (1.0)	1 (0.5)
Deep Vein Thrombosis	1 (1.0)	2 (1.9)	3 (1.4)
schemic Stroke	1 (1.0)	1 (1.0)	2 (1.0)
Myocardial Infarction	0	2 (1.9)	2 (1.0)
Pelvic Venous Thrombosis	1 (1.0)	0	1 (0.5)
Pulmonary Embolism	1 (1.0)	0	1 (0.5)
Thrombectomy	0	1 (1.0)	1 (0.5)
Transient Ischemic Attack	1 (1.0)	0	1 (0.5)
Vena Cava Filter Insertion	1 (1.0)	0	1 (0.5)
Venous Thrombosis Limb	0	1 (1.0)	1 (0.5)

*Previous: Embolic and Thrombotic Events is medical history that resolved before the IP
Source: Compiled by reviewer from ADMH dataset

Reviewer comment: *History of prior TEE, especially a recent TEE, are known risk factors for recurrent TEEs. Per protocol, no subject with TEE diagnosed within 3 months of screening was permitted into the study. The two treatment arms were fairly balanced with respect to a number of baseline health characteristics pertinent to thrombotic outcomes. However, the Kcentra arm had a modestly higher rate of overall TEEs, plus their rate of previous TEEs (I.e., those TEEs that resolved before IP infusion) was double the rate of BALFAXAR subjects. Additionally, the median time from last TEE was about twice as long among BALFAXAR recipients vs. the Kcentra cohort. These observations predict that the Kcentra subjects carried a higher antecedent risk of TEE into the study, because more of the Kcentra recipients had prior TEEs and their TEEs were more recent, compared with those who received Octaplex.*

Table 6 Embolic and Thrombotic Events, Subjects with Concurrent TEE History (RAND set)

Preferred Terms	BALFAXAR N=105 n (%)	Kcentra N=103 n (%)	Overall N=208 n (%)
Subjects with concomitant TEE*	10 (9.5)	11 (10.7)	21 (10.1)
Deep Vein Thrombosis	1 (1)	2 (2.9)	4 (1.9)
Ischemic Stroke	5 (4.8)	3 (2.9)	8 (3.8)
myocardial Infarction	1 (1.0)	2 (1.9)	3 (1.4)
Pulmonary Embolism	1 (1.0)	1 (1.0)	2 (1.0)
Hemiparesis	2 (1.9)	0	2 (1.0)
Intracranial Pressure Increased	1 (1.0)	0	1 (0.5)
Mitral Valve Replacement	0	1 (1.0)	1 (0.5)
Paraparesis	1 (1.0)	0	1 (0.5)
Peripheral Ischemia	1 (1.0)	0	1 (0.5)
Vena Cava Thrombosis	0	1 (1.0)	1 (0.5)
Vestibular Ataxia	1 (1.0)	0	1 (0.5)

*Concomitant: medical history that is present before and ongoing during the treatment.
Source: Compiled by reviewer from ADMH dataset

6.1.10.1.3 Subject Disposition

LEX 209 enrolled 214 subjects, of whom six were screen failures, leaving 208 randomized subjects, 105 to the BALFAXAR group and 103 to the Kcentra group. All subjects were treated and underwent surgery. Five subjects discontinued from the study prematurely, 4 (3.8%) in the BALFAXAR arm, and a single subject (1%) from Kcentra group, all due to fatal TEAEs. For baseline summaries (demographics, medical history, and baseline characteristics) The randomized subject set (RAND) safety subject set and the modified intention to treat (mITT) sets were identical. The table below lists these, in addition to those who had a major protocol violation vs. remained in the per protocol (PP) set.

Table 7 Summary of Analysis Populations (Enrolled Analysis Set)

Parameter	BALFAXAR n (%)	Kcentra n (%)	Overall n (%)
N enrolled			214
N failed screen			6
Subjects randomized (RAND)	105 (100)	103 (100)	208 (100)
Safety population (SAF)	105 (100)	103 (100)	208 (100)
Modified intention to treat population (mITT)	105 (100)	103 (100)	208 (100)
Per protocol population (PP)	103 (98.1)	99 (96.1)	202 (97.1)
Reason for exclusion from PP			
Received 143% of planned dose	0	1 (1)	1 (0.5)
Surgery start >5h after end of IP	1 (1)	1 (1)	2 (1)
Major protocol violation	1 (1)	2 (1.9)	3 (1.4)

Source: compiled by reviewer from ADSL and ADDV datasets

Protocol deviations:

There were 43 major protocol deviations among BALFAXAR and 40 among Kcentra subjects, including related to randomization deviations (30.1%), procedures/tests/assessment deviations (19.3%) and laboratory deviations (18.1%), with similar distribution between the two arms. Two subjects' protocol deviations that met exclusion criteria: one who had a history of TEE <3 months of enrollment, and another received vitamin K <72 h prior to enrolment and also received a prohibited platelet inhibitor (both were on Kcentra arm). The first subject was included in all analysis populations, the second in all but PP population.

The review team was especially interested in protocol deviations that had the potential to bias outcomes by skewing the expected severity of the surgery with respect to estimated blood loss. The protocol contained stipulations to achieve a balance between the two treatment groups with respect to the planned type of surgery (and history of TEE), the treatment allocation by the IRT was stratified according to the following parameters: Expected blood loss: ≥200 mL, ≥100 mL but <200 mL, or ≥50 mL but <100 mL. Several subjects had deviations related to the EBL.
The following subject (Kcentra arm) had major protocol deviations and was therefore excluded from the per protocol (PP) analysis:

- (b) (6) had average EBL corrected from 300 to 500 mL, and the maximum EBL corrected from 500 to 800 mL after randomization, which changed the hemostatic efficacy category from "ineffective" to "effective".

Another subject (b) (6) (on Kcentra arm) had deviation consisting of result of the hemostatic efficacy being changed from "effective" to "ineffective". However, the applied change was only the change in the location of the data fields. Initially, the investigator reported average EBL in the field for maximum EBL and vice versa:

- original data: average EBL 300 / maximum EBL 250
- corrected data: average EBL 250 / maximum EBL 300

Considering that the values were correct, the subject was also kept in the PP analysis set.

Reviewer comment: Actual intraoperative blood loss for (b) (6) *was 325ml. This is more than the maximum. Per protocol, actual EBL > maximal define "moderate" hemostatic outcome on the 4-point scale, and a moderate score is considered "ineffective" hemostasis.*

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

At the time of interim analysis 2, the hemostatic outcome among recipients of BALFAXAR was rated "effective" (i.e., hemostatic efficacy of excellent or good as assessed by the IEAB) in 94.3% compared with in 94.2% of Kcentra subjects. The individual hemostasis ratings were dichotomized into two possible results: effective or ineffective hemostasis. Please see the dichotomized outcomes tabulated below.

Table 8 Primary Efficacy Endpoint Outcomes (RAND population)

Parameter	BALFAXAR N=105 (%)	Kcentra N=103 (%)
Hemostatic efficacy excellent	41 (39)	50 (48.5)
Hemostatic efficacy good	58 (55.2)	47 (45.6)
Hemostatic efficacy moderate	6 (5.7)	6 (5.8)
Hemostatic efficacy none	0	0
Dichotomized efficacy Effective	99 (94.3)	97 (94.2)
Dichotomized efficacy Ineffective	6 (5.7)	6 (5.8)

Source: reviewer calculations from ADEFF dataset.

The per protocol (PP) analysis supported the results of the primary RAND analysis: In the BALFAXAR group hemostasis was effective in 94.2% and 94.9% of subjects in the Kcentra group.

Adjudication of Hemostasis Outcomes

Whereas the four-point hemostasis scale was the main metric to determine efficacy, the investigator and IEAB integrated other factors, such as blood loss, hematoma size, hemoglobin concentration change and RBC and FFP transfusion requirements into the overall score.

The reviewer identified eight cases where the actual EBL exceeded the maximal predicted EBL, thus would have been scored as moderate but nevertheless were scored by the investigator/IEAB as good. Analysis and review of these cases follows:

Subject LEX-209-(b) (6) the reviewer agrees with the score given considering that the Subject's EBL exceeded original predicted maximum by merely 10ml and subject's surgery was upgraded intraoperatively from laparoscopic to open thus expected to be bloodier.

For the remainder of subjects in this category, the sponsor provided justifications via IR, which suggest that the IEAB tended to give a more favorable score in situations where the subjects' EBL only modestly exceeded the predicted maximal, i.e., if the actual EBL were 25-50 ml over what had been projected. Below are listed subjects who had such "lenient" score given by the IEAB taking into account clinical features of the cases. However, as five of the affected subjects were Kcentra recipients and two were in the BALFAXAR arm, this nonstandard scoring favors Kcentra, therefore ruling out bias in favor of experimental arm. These cases are listed below:

LEX-209-(b) (6) Kcentra
LEX-209-(b) (6) Kcentra
LEX-209-(b) (6) Kcentra
LEX-209-(b) (6) Kcentra
LEX-209-(b) (6) Kcentra

LEX-209-(b) (6) BALFAXAR
LEX-209-(b) (6) BALFAXAR

There were other subjects where similar scoring discrepancy may change the score between excellent and good, but this would not alter primary efficacy analysis, which was prospectively based on the dichotomized score, and both good and excellent dichotomized outcomes would equal an effective hemostasis outcome.

Impact of Red Cell Transfusion Requirements on Hemostatic Score

The reviewer scrutinized subjects who required RBC transfusion after surgery, as substantial transfusion support requirement may indicate ongoing, occult bleeding, and imply incomplete or inadequate hemostasis. The impact of any such transfusion support was evaluated with respect to hemostatic score by the investigator and IEAB. The subjects are listed below with brief description (first BALFAXAR, followed by Kcentra subgroup). The reviewer's adjudicated score is provided where sufficient information obtained from IR responses and BLA submission was available to make a reasonable determination.

(BALFAXAR Subjects)

1. LEX-209-(b) (6) had EBL 100 ml < maximum of 150 ml, but transfused 1265 ml RBCs on Day 3 for acute bleeding. Subject also had 10 u FFP and 5 u pRBC,

and despite this Hb dropped by over 3 g/dL. (IAEB score moderate, after panel met.) **Reviewer gives moderate score.**

2. LEX-209-(b) (6) did get 1 U RBC on Day 4 and had extenuating circumstance of extensive surgery. EBL was 150, which is < maximum of 200. Subject had serosanguinous drainage. No RBCs were prospectively planned. **Reviewer gives score of good** (IEAB did too)
3. LEX-209-(b) (6) had 1 U RBC D1. He also had EBL of 300, and maximum was only 150, so that is moderate. IEAB gave moderate score**. Reviewer gives score of moderate.**
4. LEX-209-(b) (6) Had 1 U pRBC D8 and EBL was < maximum and <average, so was called good/excellent. Considering initial outcome that was good and only RBC at a much later time (Day 8), **Reviewer gives score of excellent.**
5. LEX-209-(b) (6) had 480 ml RBC on Day 1. Had extensive surgery. He was called excellent by iEAB and investigator. Subject was preplanned to need 700ml RBCs. **Reviewer gives score of excellent**
6. LEX-209-(b) (6) 1 U pRBC Day 3. EBL 200ml < maximum of 600 and < 150 ml average. So was called excellent by investigator and IEAB. Subject was preplanned to need 600 ml RBCs. **Reviewer gives score of excellent.**
7. LEX-209-(b) (6) had 340ml RBC Day1 and one on Day 3 but had extensive surgery and EBL 100 <200average and 400maximum. Investigator/IEAB score good. Subject was preplanned to need 600 ml RBCs. **Reviewer gives score of good.**
8. LEX-209-(b) (6) had 1 unit pRBC on Day1 for expansion of Operation and tech difficulties and 1 u pRBC Day1 for restoration of blood loss. He had extensive surgery and unexpected blood loss with large vol surgical intervention. He had 900ml EBL, more than maximum 500. Was given moderate score by investigator/iEAB. **Reviewer gives score of moderate.** No preplanned RBCs
9. LEX-209-(b) (6) 1 U pRBC on Day1. He had EBL 50 and Maximum 500, average 200. Thus, was good per investigator and excellent per IEAB. **Subject was preplanned to need 500 ml RBCs. Reviewer gives score of excellent.**
10. LEX-209-(b) (6) had 2 U Day1 of RBC and another unit Day2. (I.e., 3 U RBC). He had EBL of 430ml, which was < 500 maximum, but > 200 average. Investigator gave him score of moderate (likely due to the pRBC, but IEAB gave score of good. It was stated that his surgery was extensive. **Subject was preplanned to need 500 ml RBCs. Reviewer gives score of good.**

Reviewer comment
In the 10 BALFAXAR treated subjects who were also RBC recipients, review of clinical factors including prospectively preplanned/expected RBC transfusions, led the reviewer to account for the impact of observed RBC transfusions, and conclude that the IEAB hemostasis scores coincided with scores the review team adjudicated, considering the clinical factors, especially preplanned RBC volumes. Of note, this review team analysis was not blinded.

Kcentra RBC Recipients

1. LEX-209-(b) (6) Received pRBC only on Days 10, 13, 17 and 18 for wound debridement. With very low Hb levels of 6.5-8g/dL at those times (beyond scope of study visits). EBL was 50ml, maximum 2000, average 50ml. Thus, was scored

as excellent by investigator and IEAB. However, per IR reply, the 3 IEAB experts had divergent scores, and the panel voted to give excellent score**. Reviewer gives score of excellent**, as the bleed happened 10 Days post surgery, furthermore, some RBC transfusions were prospectively planned (600ml)

2. LEX-209-(b) (6) had RBC on Day1, Day2 (2 units), and Day3. And then more, on Days 11, 13, 16 (2 U), and D17 (2U) and D20. EBL 800ml equaled the predicted maximum, and > 500ml average. Was scored good by investigator and moderate by IEAB. And given the RBCs and the nearly exceeding maximum EBL**. Reviewer gives score of moderate.**
3. LEX-209-(b) (6) had RBC on Days 2, and had 3 units on Day 4 for acute posthemorrhagic anemia. EBL of 60ml, maximum of 100ml, was scored excellent by investigator and *moderate by IEAB.* He did not need RBC until Day 2. **Reviewer gives score of moderate, *on account of needing RBCs*.**

4. LEX-209-(b) (6) 1 U on Day 2. EBL was 90 vs 150 maximum, was scored excellent by investigator and good by IEAB. 350ml RBC was preplanned. **Reviewer gives score of good.**
5. LEX-209-(b) (6) D 22 had 1 U RBC. Had EBL 300 vs 700maximum, 400 average, was excellent by both investigator and IEAB. Preplanned 700ml of RBC. **Reviewer gives score of excellent**
6. LEX-209-(b) (6) RBC of 590ml on Day2. EBL 350, maximum 800, good by both investigator and IEAB. Maximum of 600 ml of RBC was pre-planned. **Reviewer gives score of good**
7. LEX-209-(b) (6) RBC Day1 and Day4, one 600ml. EBL 350, vs 650ml maximum. was scored as good by investigator and excellent by iEAB. Extensive surgery. maximum of 800 ml of RBC was preplanned. **Reviewer gives score of excellent.**
8. LEX-209-(b) (6) Day1 one unit RBC given for "Postrevascularization anemia." EBL 300 vs. 1000 maximum. Extensive surg. Good by investigator and IEAB. No drainage was noted. No RBCs were preplanned. It is unclear to review team why RBCs were required. The Hg only dropped by 0.6g/dl, but this includes the RBCs given (278 ml). **Reviewer score is moderate, due to requirement of unplanned RBC transfusion on Day1.**

9. LEX-209-(b) (6) had 1 U on *Day minus 1*. Excellent score. **Reviewer gives score of excellent**. 400ml of RBC were preplanned anyway. No post-OP transfusions.
10. LEX-209-(b) (6) required one U RBC on Day1. EBL 50 vs 600ml maximum. Did have extensive surgery. Excellent score from Investigator and from iEAB**. No RBC was pre planned. Hb did not change significantly (<1g/dL), no FFP given, no drainage reported. Reviewer gives a score of good, given RBC needs without extenuating circumstance other than extensive surgery.**
11. LEX-209-(b) (6) had one U pRBC Day1 and one Day2. EBL 250 vs 800 maximum was called moderate by both investigator and iEAB. Subject had extensive surgery. Per IR response, subject exceeded expected RBC transfusion by only 23ml (Maximum expected was 500ml). However, two IEAB

experts felt that the transfusions were substantial and without clear indication, hence IEAB gave score of moderate. **Reviewer score = moderate.**

12. LEX-209-(b) (6) had 2 U units of rbc on d1, another d2, and D 3. EBL 300, vs 500 maximum. Score was moderate by both investigator and iEAB. **Reviewer gives score of moderate**
13. LEX-209-(b) (6) had rbc on D 1 x 3 u, and then on D 2 and D 3. EBL was 520 vs 500 maximum, and 200 average. Score was moderate by both investigator and iEAB. Per IR, subject was expected to need no more than 2 U RBCs. Had extensive surgery. **Reviewer gives score of moderate**.

Reviewer comment:
In the case of two subjects in the control (Kcentra) arm, no RBCs were preplanned, but nevertheless subjects received a unit of RBCs for unclear reasons shortly following surgery. The IEAB scores in these cases did not appear to take into account the RBC transfusion requirements, rather were congruent simply with comparison of expected to actual EBL. The reviewer would take into account unplanned RBC transfusions postOP, in this case, the absolute and dichotomized scores would be lowered in the case of one of the subjects (LEX-209-(b) (6)). *(The other case,* LEX-209-(b) (6) *would not lead to lower dichotomized score, as IEAB scored outcome as excellent, and reviewer as good, but both would be dichotomized as successful hemostasis outcome). The other Kcentra subjects who received RBCs generally had been preplanned to need this, and therefore, the RBC transfusions would not diminish the score.*

Overall, the numbers of subjects in the BALFAXAR and Kcentra arms who required postoperative transfusions were similar, and RBCs were universally pre planned in the BALFAXAR arm, being mostly preplanned in the Kcentra arm. This argues against any bias favoring the experimental arm

FFP Transfusion

There were four subjects who required FFP administration postoperatively. Due to the mechanism of action of FFP, which overlaps with Octaplex, this intervention may be confounding to determination of hemostatic score, especially if FFP is needed shortly after surgery. The reviewer scrutinized outcomes of FFP recipients, who are listed below:

LEX-209-(b) (6) (Kcentra Arm) Received four units FFP on Day4. Based on EBL of 50, = average predicted of 50 and < Maximum of 2000, got excellent score from Investigator and IEAB. **Reviewer gives score of excellent**, considering that the FFP was not administered until Day 4.
LEX-209-(b) (6) (BALFAXAR arm) Received four units FFP on Day 2. Based on EBL of 100, >50 average, but < 150 maximum, was given good score per investigator. IEAB, however gave moderate score. **Reviewer gives score of moderate.**
LEX-209-(b) (6) (BALFAXAR subject) Received 10 units FFP on Day 3, four more on D 5, four on D 7 and four on D 8. Based on EBL of 150, with AVERAGE of 100 and Maximum 200, got score of good from Investigator and IEAB. (In the Panel Meeting dated Aug-25-2020, the committee requested additional information from the site asking why so many unexpected plasma transfusions were given; the case was

discussed again during an IEAB Panel meeting. The final decision of a score of "good," was made. The reviewer would consider the need for large volume of FFP to be of concern, however, the FFP was not needed until 3 days after surgery. **Reviewer score good.**

LEX-209-(b) (6) (BALFAXAR subject) Got one unit of FFP on Day 1. Was scored good by investigator and IEAB based on EBL of 150, 100 average, 200 maximum. **However, the reviewer would consider the need to administer even small volume of FFP on Day 1 to be of concern. Moderate score by reviewer due to FFP requirement on Day 1.**

Reviewer comment:
The score of good by the IEAB given to subject (b) (6) *does not adequately account for the extensive FFP requirements, however, the sponsor has provided all available information on this case, and the subject did not need any FFP for 3 days after surgery. With respect to subject* (b) (6) *who only received one unit FFP on Day 1, the FFP administration does not appear to have been incorporated into the score, if the score were to be adjusted downward by FDA for requiring of FFP, this would affect the overall BALFAXAR arm. See also below, in discussion of hemoglobin trend analysis.*

Analysis of Hemoglobin Concentration Trends

Although fraught with possible confounding secondary to hemodilution from adventitious fluid administration common perioperatively and postoperatively, analysis of subjects' hemoglobin trends could help uncover occult blood loss due to surgery. This might have efficacy implications for the IP. Analysis was conducted by review team and led to the identification of the following subjects with Hb decrease of ≥ 3g/dL (threshold Hb decrease was chosen on the basis of clinical experience). Of note, the ADLB data do not account for any confounding RBC transfusions. However, only the first subject on the list received any RBC transfusions post-surgery. The following subjects were found to have a marked decrease in Hb concentration of ≥ 3g/dl:

1. LEX-209-(b) (6) (also 10 units FFP and 5 of RBC & had > 6 g/dl drop in Hb)
2. LEX-209-(b) (6)
3. LEX-209-(b) (6)
4. LEX-209-(b) (6)
5. LEX-209-(b) (6)
6. LEX-209-(b) (6)
7. LEX-209-(b) (6) (also FFP x 2 units)
8. LEX-209-(b) (6)
9. LEX-209-(b) (6)
10. LEX-209-(b) (6)
11. LEX-209-(b) (6)
12. LEX-209-(b) (6)

The review team analyzed projected EBL volumes vs. actual EBL volumes. In cases where the scores determined by investigator and/or IEAB were not congruent with the 4 point score determination, we requested IR to seek further

explanation. Factors such as hematoma formation, need for FFP and RBC transfusions were also reviewed.

In the case of several subjects, the reviewer noted confounding by administration of FFP. This includes subject (b) (6) from BALFAXAR arm who received one transfusion of FFP (270 mL) about 5 hours after BALFAXAR for what the investigator called “bleeding prophylaxis”. No bleeding, physical or lab abnormalities reported in this subject, and the EBL was 150 ml, which exceeded average projected of 100 ml, but < 200 ml maximum projected. While the hemostasis was deemed effective (good), the use of FFP, which may confound effectiveness of BALFAXAR because FFP also contributes missing clotting factors, making determination of efficacy challenging

Wound Drainage Evaluation

Subject (b) (6)
Surgery (b) (6) Subject reported to have received 10 doses of FFP one day and 2 days after surgery for “anemia” Also had RBC transfusions on Day2 of 5 units, and was reported to have serosanguinous drainage on day of surgery equaling 100 ml, plus 400 ml of hemorrhage, as well as an additional 300ml of serosanguinous drainage.
Was given Not assessable score by one IEAB expert. “Postop bleed of unknown origin”. Was given “none” score by another IEAB expert, due to “large volume FFP post op for hemorrhage. While a 3rd reviewer from IEAB gave:
Moderate: Post OP bleed D 1-2 with 10 u FFP and 5 U RBC.
Therefore, IEAB panel met. Reviewer score of Moderate.

Subject (b) (6)
This subject had serosanguinous drainage 150ml Day1 and then 50ml Day2. And then more drainage that was serosanguinous. There was an extenuating circumstance, vessel injury unresponsive to therapy. And thus intraOP EBL was 700 ml Per IEAB doctor #1, This was scored as “moderate due to moderate blood loss in big surgery with blood transfusion”.
IEAB expert #2: Moderate: EBL > maximum, “but no transfusion except albumin”.
Reviewer score moderate.

Subject (b) (6)
Did get prospectively planned RBC transfusion intraoperatively; and more on Day 1 post surgery. And then more unexpected RBCs about a week later- about 8 units. Also had serosanguinous drainage on Day of surgery of about 350ml and more about a week later.
Score: Moderate maybe due to chronic anemia but high RBC use postOP Moderately large transfusion requirement, and “not assessable”. Lots of blood given the week after surgery. Was there an unexpected bleed??”
Therefore, Moderate score was determined. Reviewer score moderate.

Reviewer comments:
The above results indicate similar outcomes for the two treatment arms. The results were adjudicated by the IEAB. Confirmation of noninferiority of the BALFAXAR group vs. Kcentra was performed by statistics reviewer. Please see statistics note for details.

In a number of other subjects where the hemostasis met criteria for a score of good or excellent by the four-point scale, when the review team accounted for clinical features like bloody wound drainage, post operative RBC transfusions, or FFP administration, a moderate (ineffective) hemostatic score was assessed by FDA reviewer, coinciding with the IEAB's score.

In the case of two subjects, the review team adjudicated hemostasis score diverged from that given by the IEAB. Nevertheless, the noninferiority of BALFAXAR to Kcentra would be preserved even using the hemostatic scores adjudicated by the reviewer noting that subject (b) (6) *on the BALFAXAR arm required FFP infusion on Day 1 and this confounding intervention would bring down the subject's score from good to moderate. On the other hand, analysis of RBC transfusions in the case of subject* (b) (6) *led the reviewer to adjudicate a lower dichotomized score than the IEAB.*

Evaluation of hemostasis outcomes taking into account all available information did not lead the reviewer to conclude a different overall efficacy outcome than that given by the IEAB. Therefore, the reviewer agrees with the efficacy analysis.

6.1.11.2 Analyses of Secondary Endpoints

The proportion of subjects achieving an INR ≤ 1.5 by 30 minutes post end of infusion was similar between the two arms, with 78.1% of BALFAXAR group and 71.8% of Kcentra subjects achieving this endpoint. Similar results were obtained in the subgroup analyses of the proportion of subjects with INR ≤1.5 (by gender, expected blood loss, baseline INR, and concomitant treatment with vitamin K.)

Reviewer comment: While INR has been shown to be a predictive assay to instruct management of VKA dosing, it has not been validated as a predictor of normalized hemostasis with surgery following VKA reversal. This makes the applicability of these secondary efficacy outcomes questionable.

Change in coagulation factor levels

The study assessed the activity levels of coagulation factors FII, FVII, FIX, and FX at baseline, and then at prespecified times post infusion of DP. The mean baseline activity of all tested coagulation factors (FII, FVII, FIX, and FX) were similar in the two treatment groups and in both groups there were increases from baseline to 30 minutes after the end of the infusion.

Among the factors assessed, there was a higher increase in FVII activity in the BALFAXAR group (median difference of 8.00; and a higher increase in FX activity in the Kcentra group (median difference of -13.0: -21.00, -4.00).

Table 9 Factor activity change: baseline to 30 min post end of infusion (RAND population)

Parameter	BALFAXAR N=105	Kcentra N=103
Subjects with INR≤1.5 n (%)	82 (78.1)	74 (71.8)
FX activity mean baseline (SD)	N= 103 24.4 (17.6)	N=100 24.0 (18.6)
FX activity Mean change from baseline (SD)	56 (29.8)	69 (32.3)
FVII activity mean baseline (SD)	N=105 27.6 (25.1)	N=102 27.3 (23.1)
FVII activity Mean change from baseline (SD)	N=105 40.9 (32.8)	N=103 32.8 (34.4)

Source: reviewer calculations from ADLB dataset

Anticoagulant factors (Protein C and Protein S) were also evaluated in the study subjects. The analyses are presented in the table below:

Table 10 Change from Baseline in Protein C and Protein S (RAND population)

Parameter	BALFAXAR N=105	Kcentra N=103
Protein C mean baseline (SD)	N=105 44.8 (21)	N=102 46.3 (23.9)
Protein C mean change from baseline (SD)	45.9 (28.2)	55.3 (26)
Protein S activity actual/control (%) mean baseline (SD)	N=105 30 (17.6)	N=102 35.8 (22.6)
Protein S activity actual/control (%) mean change from baseline (SD)	N=105 23.7 (22.4)	N=101 25.6 (24.3)

Source: reviewer calculations from ADLB dataset

Reviewer comment:
Secondary efficacy endpoints were designed to support hemostatic efficacy outcomes, and these demonstrate comparable baseline activity levels of coagulation factors, along with increases in coagulation factors post infusion. Factors FX and FVII differed numerically in degree of change between the BALFAXAR and Kcentra groups. The clinical implications of this observation for efficacy are unclear, and it is unknown if relatively greater increases of one coagulation factor or another within a given PCC is meaningful.
Levels of anticoagulant factors Protein C and S were also evaluated, and analyses showed a relatively larger magnitude of increase in Protein C among Kcentra treated subjects compared with Octaplex. The relevance of this observation to efficacy or safety is unclear. Levels of clotting factors, and even levels of excipients such as heparin, have been reported to vary among PCCs

like BALFAXAR and Kcentra, and theoretically may confound impact of the changes in these measured parameters.

Transfusion of RBCs during surgery

A total of four subjects (3.8%) in BALFAXAR group received RBC transfusion during surgery, compared with 3 (2.9%) of Kcentra subjects. All RBC recipients were in the subgroup with expected maximal blood loss of ≥ 200 ml, and they had received concomitant vitamin K treatment. The mean volume of RBCs transfused intraoperatively was biologically equal in the two groups, with BALFAXAR subjects receiving 6 ml/kg and Kcentra subjects 5.8 ml/kg.

Reviewer comment: The intraoperative RBC transfusion needs were similar between arms. The reviewer also assessed number subjects in each arm who received at least on RBC transfusion postoperatively and found that 35 Kcentra and 13 BALFAXAR recipients received postoperative RBC transfusion.

Intra operative blood loss
Median intra-operative blood loss was higher in the BALFAXAR group (150 mL) than in the Kcentra group (120 mL), with four subjects in the BALFAXAR group having unexpected intra-operative blood loss (none in the Kcentra group) with a median volume of 400 mL. In one of these four subjects the unexpected blood loss was due to surgical complications whereby a vessel injury did not respond to routine hemostatic procedures.

Intraoperative platelet and plasma transfusions
Post-operative plasma transfusions were required in three BALFAXAR subjects vs. one Kcentra subject.

Reviewer comment:
The numbers are small and differences between the arms maybe due to chance, especially for number of RBC transfusions and intraoperative blood loss volume. While postoperative FFP was required in three BALFAXAR subjects vs. one in the Kcentra arm, these differences are small and may also be due to chance.

6.1.11.3 Subpopulation Analyses

Subjects were also analyzed including by subgroups of gender and baseline INR, as well as expected blood loss criteria. Efficacy outcomes were similar in these subgroups.

6.1.11.4 Dropouts and/or Discontinuations

Five subjects discontinued from the study, four were BALFAXAR recipients, whereas one was in the Kcentra arm. These were due to deaths (please see further exploration of deaths in the safety section which follows)

6.1.11.5 Exploratory and Post Hoc Analyses

Subject age as a variable was analyzed vs. IEAB dichotomized score and subjects who had effective hemostasis were of approximately the same median and mean age as those whose score was ineffective. This suggested little impact of this treatment relative to age.

6.1.12 Safety Analyses

6.1.12.1 Methods

FDA focused its review of safety on a Kcentra-controlled RCT: LEX-209

LEX-209 was an open-label, randomized, multicenter, active (Kcentra PCC) controlled clinical trial to assess the efficacy, safety and tolerance of Kcentra compared with Kcentra for rapid reversal of coagulopathy induced by vitamin K antagonists in subjects requiring an urgent surgical or urgent invasive procedure. The safety population included 208 subjects treated with IP (105 to BALFAXAR and 103 to Kcentra). Subjects were randomized 1:1 to receive either BALFAXAR or Kcentra. The dose of both products depended on subjects' weight and baseline INR.

Exposure to IP
All randomized subjects received treatment with IP. The median dose of IP was 25.0 IU of Factor IX/Kg in both treatment groups, ranging from 16 IU/Kg to 50 IU/kg in the BALFAXAR group and 15 IU/kg to 50 IU/kg in Kcentra arm. The median doses by baseline INR category reflected the protocol defined dosing.

Similar proportions of both groups reported TEAEs, with 81.9% of BALFAXAR recipients and 77.7% Kcentra subjects reporting TEAEs. Among the 105 subjects treated with BALFAXAR, 86 subjects reported 177 TEAEs, whereas 80 of the 103 Kcentra recipients went on to report a total of 212 TEAEs.

The most common TEAEs were comprised of events which are expected in a perioperative period, with pain due to procedure, wound complications, and anemia being most common. TEAEs reported in at least 3% of subjects are tabulated below in each arm, per SOC and PT.

Table 11 TEAEs Reported by ≥ 3% of BALFAXAR Recipients (N=105) and Kcentra Recipients (N=103)

System Organ Class **Preferred Term**	**BALFAXAR Subjects (N=105)** **n (%)**	**Kcentra Subjects (N=103)** **n (%)**
Blood and lymphatic system disorders		
Anemia	6 (5.7%)	6 (5.8%)
Gastrointestinal disorders		
Abdominal pain	3 (2.9%)	5 (4.9%)

General disorders and administration site conditions		
Asthenia	13 (12.4%)	18 (17.5%)
Catheter site related reaction	4 (3.8%)	2 (1.9%)
Injury, poisoning and procedural complications		
Postoperative wound complication	15 (14.3%)	15 (14.6%)
Procedural pain	50 (47.6%)	50 (48.5%)
Procedural vomiting	4 (3.8%)	0
Suture related complication	2 (1.9%)	4 (3.9%)
Investigations		
Blood pressure increased	0	5 (4.9%)
Body temperature increased	0	4 (3.9%)
Renal and urinary disorders		
Dysuria	5 (4.8%)	2 (1.9%)

Source: Derived by reviewer from ADAE dataset.

Reviewer Comment: the most commonly reported AEs reflect largely a surgical experience and no safety signal from the investigational product.

6.1.12.3 Deaths

LEX209 included six fatal outcomes, five in the BALFAXAR arm and one in the Kcentra arm, (this includes one death in the BALFAXAR arm on Day 47, after end of study 45 Day observation period.) Overall, despite somewhat limited details available for review from the submitted investigator and IDMC narratives, the reviewer does not believe the deaths are likely related to IP. The subjects in the BALFAXAR group who had SAEs with a fatal outcome were:

(b) (6) (89-year-old white female) died of a pulmonary embolism 37 days after receiving IP. Relevant medical history included hypertension, congestive heart failure, ischemic heart disease, permanent atrial fibrillation, non- rheumatic mitral valve stenosis and insufficiency with secondary pulmonary hypertension, acute vascular disorders of intestine (mesenteric artery thrombosis), and diabetes mellitus. The subject was enrolled into the study for urgent laparotomy for an intestinal obstruction (mesenteric artery thrombosis) requiring reversal of VKA therapy that the subject was receiving for permanent atrial fibrillation. In the postoperative period the subject received 5 days of antithrombotic prophylaxis with LMWH, but oral anticoagulation was not restarted. In the post-operative period, the subject also experienced SAEs of shock and acute respiratory failure (day 2), cerebral infarction (TEE, day 12), acute respiratory failure (day 35), and shock (day 37), and TEAEs of anemia, hypoalbuminemia, acute cor pulmonale, postoperative wound complication, hepatic failure, hypokalemia, hydrothorax, and pneumonia. The subject received multiple post-operative blood transfusions. She also received FFP in the post operative setting. All SAEs were assessed as not related to IP by the investigator and the Sponsor, as well as the review team.

Reviewer comment

The subject carried a history of high-risk competing diagnoses including: congestive heart failure, ischemic heart disease, permanent atrial fibrillation, non-rheumatic mitral valve stenosis and insufficiency with secondary pulmonary hypertension, and diabetes mellitus. Although she was not given oral anticoagulant, the subject received 5 days of LMWH prophylaxis against TEE. She was reported on Day 35 to have acute cor pulmonale, shock and then death on Day 37. Per response to IR, the investigator administered additional FFP during post operative course to assuage hepatic failure with hypoalbuminemia, which may potentiate TEE risk compared with administration of only PCC. The review team concluded that the SAEs of cerebral infarction and PE were unrelated to IP.

(b) (6) (a 90-year-old white male) died of (verbatim term was 'other ill-defined and unspecified causes of mortality') 35 days after receiving IP. Relevant medical history included a fall after slipping, contusion of the right knee, tripping and stumbling, chronic traumatic subdural hemorrhage, headache, hypersomnia, open wound in the area of the left eyebrow, ischemic heart disease, arterial hypertension, coronary heart disease, atrial fibrillation, chronic heart failure, pulmonary hypertension, and aortic valve stenosis. The subject was enrolled into the study for reversal of VKA (prescribed for atrial fibrillation) in preparation for urgent surgery.
Thirty minutes after IP, the baseline INR of 9.13 was normalized to 1.16 and the subject underwent an evacuation of the chronic subdural hematoma with drainage. The subject received 10 days of LMWH prophylaxis starting post-operative day 2 but oral anticoagulation was not restarted. On day 4, the subject experienced recurrence of the subdural hemorrhage that was managed conservatively considering the high risk of the intervention. The subject also experienced TEAEs of anemia, hypersomnia, and anxiety. He received 1 post-operative blood transfusion and was discharged on day 14 with the SAE of subdural hemorrhage not fully recovered. On day 45 during the follow up phone call, the investigator received information from the subject's relative that the subject had died a week previously. The relative did not provide any further information on the cause of death; no autopsy report was available. The investigator reported the cause of death as 'other ill-defined and unspecified causes of mortality'. Both SAEs were assessed as not related to IP by the investigator and the Sponsor.

<u>Reviewer comment</u>
*Although precise cause of death cannot be determined, the reviewer does **not** believe the death was related to IP, considering the highly morbid presenting problem, and especially due to the fact that the ICH recurred on Day 4. Moreover, though he was not given oral anticoagulant, the subject received 10 days of LMWH prophylaxis against TEE.*

Subject (b) (6) (a 73-year-old white female) died of chronic cardiac failure 24

days after receiving IP. Relevant medical history included ischemic heart disease, chronic cardiac failure (since 2010), diabetes mellitus, atrial fibrillation, and arterial hypertension. The subject was enrolled into the study for reversal of VKA therapy prescribed for thrombosis prophylaxis (atrial fibrillation). Baseline INR of 4.0 was normalized to 1.2 thirty minutes after IP and the subject underwent orthopedic surgery (hemiarthroplasty). In the postoperative period the subject experienced TEAEs of hyperthermia and postoperative anemia, which required 1 blood transfusion. LMWHs were given from day 1 until day 16 when the subject was discharged with prescription of oral anticoagulant. The investigator was informed of the subject's death at home on day 24. No autopsy was performed; the cause of death was reported by relatives based on the death certificate. The event was assessed as not related to IP by the investigator and the Sponsor.

Reviewer comment
Although exact cause of death is not determinable, the death occurred more than 3 weeks post IP and following 16 days of LMWH followed by prescription for oral anticoagulant. Subject had multiple serious comorbidities that competed with IP for possibly causing mortality. The reviewer does not believe the death was related to IP.

Subject (b) (6) (a 90-year-old white female) died of ischemic heart disease 30 days after receiving IP. Relevant medical history included rheumatoid arthritis, ischemic heart disease, arterial hypertension, chronic cardiac failure, Afib, and intertrochanteric fracture of the right femur. Subject was receiving VKA therapy considering presence of prothrombotic condition (paroxysmal form of Afib) and was enrolled into the study for reversal of VKA therapy in preparation for urgent surgery. Baseline INR of 6.7 was normalized to 1.18 thirty minutes after IP and the subject underwent orthopedic surgery (osteosynthesis with gamma nail). The subject received 1 intraoperative blood transfusion. In the post-OP period the subject experienced TEAEs of hypoproteinemia, paroxysm of Afib, and post-OP anemia, that required 1 postoperative blood transfusion. The subject received 10 days of postoperative thrombosis prophylaxis with LMWHs followed by a prescription of oral anticoagulant. The subject was discharged on day 12. The investigator was informed of the subject's death at home on day 30. No autopsy was performed; the cause of death was reported by relatives based on the death certificate. The SAE was assessed as not related to IP by the investigator and the Sponsor.

Reviewer comment
Although exact cause of death is not determinable, the death occurred more than 4 weeks post IP and following 10 days of LMWH and the prescription for oral anticoagulant. Subject also had multiple serious comorbidities that competed with IP as potential cause of mortality. The reviewer does not believe the death was related to IP.

Subject (b) (6) (74-year-old white male) died of multiple organ dysfunction syndrome 47 days after receiving IP and after completing the last study visit (study reporting period ended 45 days after IP administration). Medical history included ischemic stroke, left-sided hemiparesis, intracranial hypertension, arterial hypertension, ischemic heart disease, heart failure grade 2A, atrial fibrillation, rectal cancer (T3N1M0), and rectal bleeding. Subject was receiving VKA therapy considering high risk of thrombosis (medical history of stroke and atrial fibrillation) and was enrolled into the study for urgent reversal of VKA therapy in preparation for major surgery. Baseline INR of 2.48 was normalized to 1.42 thirty minutes after IP and the subject underwent an anterior resection of the rectum. In the postoperative period, the subject experienced an SAE of partial anastomotic failure (day 9) which required first local sanitation and then proximal resection of descending colon and sigma with sigmo-recto anastomosis. Subject received 4 post-operative albumin transfusions and LMWH until discharge on day 16 but oral anticoagulation was not restarted. The subject died at home on day 47. Both SAEs were assessed as not related to IP by the investigator and the Sponsor.

Reviewer comment
Although exact cause of death is not determinable, death occurred about 7 weeks post IP and following 16 days of LMWH (oral anticoagulant not resumed). Subject had multiple serious comorbidities that competed with IP as potential cause of mortality. The reviewer does not believe the death was related to IP.

The subject in the Kcentra arm who had a TEAE with a fatal outcome was: Subject (b) (6) (died of after receiving IP. Relevant medical history included varicose vein disease, hypertension, myocardial infarction, ischemic heart disease, and hypoproteinemia. The subject was receiving VKA therapy due to medical history of deep vein thrombosis and was enrolled into the study for urgent reversal of VKA therapy in preparation for major orthopedic surgery. Baseline INR of 3.11 was normalized to 1.08 thirty minutes after IP and the subject underwent orthopedic surgery (open reduction with intramedullary nailing of the left femur). The subject received 1 intraoperative transfusion of 2 RBC units. In the postoperative period the subject experienced an SAE of pneumonia (day 8, diagnosed as poly-segmental bilateral pneumonia based on CT results) and TEAEs of hyperglycemia, anemia (required 1 postoperative transfusion of 2 RBC units), hypo coagulable state, hyperthermia, bone pain, hypotension, renal failure, vomiting, and ventricular arrhythmia. LMWH was given starting day 1 until day 10 when the subject died in intensive care unit. Oral anticoagulation was not restarted. Based on the autopsy report the subject died of chronic coronary heart disease complicated by acute cardiovascular insufficiency. The investigator reported acute cardiac failure as the main cause of death. Both SAEs were assessed as not related to IP by the investigator and the Sponsor.

Reviewer comment

The cause of death per autopsy was chronic coronary heart disease, moreover death occurred in the intensive care unit after the subject suffered deterioration with extensive nosocomial pneumonia with multiple organ failure. The reviewer does not believe the death was related to IP.

Overall, none of the deaths were concluded to be related to IP.

6.1.12.4 Nonfatal Serious Adverse Events

Treatment emergent adverse events that met criteria for serious are listed in the table below, by body organ system class and preferred term and by study arm. Thirteen subjects (12.4%) in the BALFAXAR arm and six subjects (5.8%) in the Kcentra arm reported SAEs. Most common SAEs were in the SOC injury, poisoning and procedural complications (3.8%), and cardiac disorders and gastrointestinal disorders (2.9% each). While most of the SAEs in each arm were considered unrelated to the IP, several SAEs in the BALFAXAR arm need further discussion. These include the preferred term SAE of cerebral infarction and pulmonary embolism both reported in subject (b) (6) subdural hemorrhage and death in (b) (6) unstable anginal in (b) (6) and myocardial ischemia in (b) (6) Further detail is provided in the narratives below, and SAEs are tabulated below:

(b) (6) 89-year-old subject experienced two SAEs. The first was cerebral infarction 12 days after receiving IP and the second was pulmonary embolism 37 days after receiving IP, which had a fatal outcome. Both events were considered not related to IP by the investigator. Subject had a history of HTN, CHF, ischemic heart disease, Afib, valvular disease with pulmonary HTN, DM, and acute mesenteric artery thrombosis. She underwent surgery for bowel obstruction, 5 days LMHW prophylaxis. Ultimately, the SAEs of cerebral infarction and PE were considered unrelated to IP.

(b) (6) 90-year-old subject experienced two SAEs. Subject had a fall and a history of chronic traumatic subdural hemorrhage, headache, somnolence (hypersomnia), open wound in the area of the left eyebrow, ischemic heart disease, arterial hypertension, coronary heart disease, atrial fib, CHF, pulmonary HTN, and aortic valve stenosis. After surgery (drainage of intracranial hematoma), received 10 days of LMWH. On day 4, the subject experienced recurrence of the subdural hemorrhage (considered SAE) that was managed conservatively. He was discharged on day 14 with the SAE of subdural hemorrhage not fully recovered. On day 45 during the follow up phone call, family revealed that he had died a week previously. SAEs of subdural hemorrhage and SAE of death were unrelated.

(b) (6) 90 year old subject had myocardial ischemia on Day 30. Subject had a history of ischemic heart disease, HTN, CHF, Afib. Subject was given 10 days of LMWH prophylaxis and a prescription for VKA following hip fracture repair

surgery, prior to discharge on Day 12. Died at home Day 30, no autopsy performed, cause of death was reported by family based on death certificate. The AE was considered unrelated.

Table 12 Serious Treatment-Emergent Adverse Events by System

System Organ Class Preferred Term	BALFAXAR N=105 n (%)	Kcentra N=103 n (%)
All Serious TEAEs	13 (12.4)	6(5.8)
Blood and lymphatic system disorders	0	2(1.9)
Anemia	0	1(1)
Hemorrhagic anemia	0	1(1)
Cardiac disorders	3(2.9)	1(1)
Angina unstable	1(1)	0
Cardiac failure acute	0	1(1)
Cardiac failure chronic	1(1)	0
Myocardial ischemia	1(1)	0
Gastrointestinal disorders	3(2.9)	2(1.9)
Ileus	0	1(1)
Gastritis erosive	1(1)	0
Gastritis hemorrhagic	0	1(1)
Mesenteric hematoma	1(1)	0
Proctitis	1(1)	0
General disorders and administration site conditions	2(1.9)	0
Death	1(1)	0
Multiple organ dysfunction syndrome	1(1)	0
Infections and infestations	1(1)	1(1)
Orchitis	1(1)	0
Pneumonia	0	1(1)
Injury, poisoning and procedural complications	4(3.8)	1(1)
Anastomotic hemorrhage	1(1)	0
Failure to anastomose	1(1)	0
Joint dislocation	1(1)	0
Postoperative wound complication	0	1(1)
Subdural hemorrhage	1(1)	0
Musculoskeletal and connective tissue disorders		
Soft tissue hemorrhage	1(1)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	1(1)
Ovarian cancer stage IV	0	1(1)
Nervous system disorders	1(1)	0
Cerebral infarction	1(1)	0
Respiratory, thoracic and mediastinal disorders	2(1.9)	0
Acute respiratory failure	1(1)	0
Pulmonary embolism	1(1)	0
Pulmonary oedema	1(1)	0
Vascular disorders	1(1)	1(1)
Shock	1(1)	0

Shock hemorrhagic	0	1(1)

Source: calculated by reviewer from ADAE dataset

Reviewer comment: Despite the imbalance in SAEs rate between the arm, with more BALFAXAR subjects experiencing more SAEs than Kcentra subjects, most of the events were unrelated to IP. An SAE of death and SAEs categorized as TEEs were only reported among BALFAXAR recipients. These are further discussed in the next section on events of special interest.

6.1.12.5 Adverse Events of Special Interest (AESI)

Considering known thrombotic risks with PCCs, TEEs were considered an adverse event of special interest. Per protocol, TEEs were defined according to the MedDRA SMQ "Embolic and thrombotic events". Four TEEs were reported in 3 subjects (2.9%) in the BALFAXAR group, whereas no Kcentra recipients experienced any TEEs, which is shown in table below.

Table 13 TEEs Reported per Treatment Arm

Type of TEE	Octaplex	Kcentra
Total TEEs	4	0
TEE Adverse Reactions*	1	0

Source: Table generated by reviewer from data in ADAE dataset and narratives.
*Adverse Reactions were events adjudicated by reviewer to be at least possibly related to IP.

Although subjects all underwent a recent surgery along with withdrawal of VKA, which are known risks for TEEs; the provided narratives by the sponsor and the IDMC, as well as other data were reviewed by the Agency to adjudicate possible causality of the TEE with respect to the IP. The amount of detail provided in the some of the narratives was scant, making attribution adjudication challenging, but ultimately the review team considered the events not related to IP. Please see table below.

Table 14 TEE Attribution (Kcentra recipients)

Subject and TEE	Causality Attribution to IP
Subject (b) (6) 1. CVA Day 12 2. PE Day 37	1. CVA unrelated per FDA reviewer; unrelated per investigator. 2. PE considered unrelated.
Subject (b) (6) 3. Unstable angina Day 5	3. Possibly related per FDA reviewer, per investigator and per sponsor
Subject (b) (6) 4. MI Day 30	4. Unrelated per FDA, investigator and Sponsor

Source: Table generated by reviewer from data in ADAE dataset and narratives

Reviewer comment:
Competing factors, including comorbidities and recent surgery were present in all subjects, confounding FFP was given to some post operatively, while on the other hand several subjects were exposed to prophylactic LMWH and even VKA

following their surgery. The review team concluded that the TEEs were unrelated to IP.

The following subjects experienced TEEs:

Subject (b) (6) (an 89-year-old white female) experienced two TEEs: the first was cerebral infarction 12 days after receiving IP and the second TEE was pulmonary embolism 37 days after receiving IP, which had a fatal outcome. Both events were considered not related to IP by the investigator. The review team concluded the events were unrelated to IP.

Subject (b) (6) (63-year-old white male) had a TEE of unstable angina 5 days after receiving BALFAXAR infusion at a dose of 2500 IU. This SAE was moderate in intensity and considered possibly related to IP by the investigator; the subject recovered the same day. Medical history included arterial hypertension III (ESCESH), coronary artery disease, angioplasty and stenting (2018), permanent atrial fibrillation, heart failure, and laryngeal cancer. The subject was receiving VKA therapy considering high risk of thrombosis (permanent atrial fibrillation) and was enrolled into the study for urgent reversal of VKA therapy in preparation for major orthopedic surgery. Baseline INR of 2.0 was normalized to 1.26 thirty minutes after IP. The subject received concomitant injection of vitamin K (10 mg IV) and underwent orthopedic surgery (primary total left hip arthroplasty without the use of bone cement). There was no transfusion done during the intraoperative period. The subject received 10 days of postoperative thrombosis prophylaxis with LMWHs with re-start of oral anticoagulation on day 11. In the postoperative period, 2 days after receiving Octaplex, the subject experienced acute retrosternal pain, described as squeezing pressure, troponin test results showed 0.02 ng/mL. The cardiologist excluded myocardial infarction and prescribed solution analgini 50% 2mL as single dose IM. Two days later, 4 days after receiving Octaplex, the subject was again consulted by a cardiologist due to continuous pain and underwent coronography and stenting with diagnosis of unstable angina pectoris. The SAE and TEE of unstable angina was reported with seriousness criteria of prolonged hospitalization. The SAE/TEE was assessed as possibly related to IP by the Sponsor. This reviewer agrees that the event of unstable angina on Day 4 possibly related to IP.

Subject (b) (6) (a 90-year-old white female) had a TEE of myocardial ischemia 30 days after receiving IP which had a fatal outcome. The event was considered not related to IP by the investigator. Please refer to narrative above (TEAEs with a fatal outcome) for details. This reviewer believes the more likely cause of fatal MI at Day 30 was underlying ischemic heart disease. Not only did the subject receive 10 days of postoperative thrombosis prophylaxis with LMWH, but was also given a prescription of oral anticoagulant upon her discharge on Day 12. The investigator was informed of the subject's death at home on day 30, and cause of death was derived from death certificate.

Reviewer comment:
Subjects treated intrinsically carry a high risk for TEEs due to the acute need to reverse their chronic anticoagulation and due to recent surgical procedures. Study LEX 209 was not powered to analyze differences in safety outcomes. Chance could potentially explain differences observed although this was a randomized trial with comparable groups in each arm exposed to a PCC product. The small numbers of subjects reporting TEE events makes it difficult to ascertain if differences in the clotting factor composition, anticlotting proteins C and S, or adjuncts such as antithrombin III and heparin, may lead to the differing clinical safety profiles. The level of detail captured on study and available for review makes it difficult to adjudicate the contribution of BALFAXAR in the above TEEs. Considering the historically known risk of TEE from PCCs, and the skewed safety results where subjects treated with the comparator experienced no TEEs, a regulatory requirement to to collect additional safety data is considered reasonable and recommended by this reviewer. This additional assessment of serious risk of TEE will be conducted as a post-marketing requirement (PMR) study.

6.1.12.6 Clinical Test Results

Hematology

At all timepoints in both treatment groups, the highest proportions (between approximately 40% and 60%) were for subjects who did not have shifts out of the normal range in RBC and WBC parameters.

Most subjects did not have shifts outside of normal range for WBC and RBC parameters, however, the most common shifts in RBC parameters shifts from normal to low in both treatment groups (approximately 10% across the timepoints in both treatment groups).
For WBC, the most common shifts were seen from normal to high at most timepoints (between approximately 5% and 20% of subjects in the BALFAXAR group and between approximately 5% and 30% Kcentra arm. And at discharge, the most common shift in both groups was from high to normal (21.9% and 18.4%, respectively).
For platelets, the proportion of subjects remaining within the normal range was higher (generally over 60% of subjects in the BALFAXAR group and over 50% in the Kcentra arm, with no marked trends in shifts out of the normal range.

Reviewer comment:

6.1.12.7 Dropouts and/or Discontinuations

There were five discontinuations among Balfaxar recipients, and these were all due to death.

6.1.13 Study Summary and Conclusions

Table 15 Risk Benefit Table

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Urgent surgery in patients on VKA Anticoagulant requires reversing therapy with rapid onset of action. • Other treatments such as FFP are often not sufficiently potent, and may be associated with fluid overload • Vitamin K works slowly • Kcentra may be administered, but a second agent in this class may lower process and improve patient accessibility	• Other treatment options may not be adequate
Unmet Medical Need	• Although Kcentra is licensed and on the US market, its availability might not be guaranteed.	• With only a single product in class on the US market, supply may not be sufficient and prone to shortages
Clinical Benefit	• One clinical trial in adults who need urgent surgery while on VKA anticoagulant was submitted. The trial was well controlled, and primary efficacy endpoint of hemostatic efficacy of BALFAXAR was non-inferior to control.	• The clinical evidence for effectiveness of BALFAXAR is compelling.
Risk	• The most substantial risks of BALFAXAR are thromboembolic events. These were reported more frequently in the BALFAXAR arm compared to control	• RCT for perioperative management reported higher TEE rate for BALFAXAR compared with control arm.
Risk Management	• The most substantial risks BALFAXAR are thromboembolic events	• If BALFAXAR is approved, a post-marketing requirement (PMR) for observational study would be needed to further evaluate the serious risk of TEE.

11.2 Risk-Benefit Summary and Assessment

The reviewer concludes that the submitted evidence indicates that the benefit risk of BALFAXAR is favorable, with majority of subjects achieving successful hemostasis and the efficacy shown to be non-inferior vs. control. The safety profile observed in the clinical development program is acceptable in the context of the demonstrated product efficacy. An additional evaluation of the serious risk of TEE will be required after product approval.

11.3 Discussion of Regulatory Options

Licensure with a boxed warning for arterial and venous thromboembolic complications which include a statement regarding to weigh the risks of VKA reversal using BALFAXAR with the risks of TEE, particularly in patients with a history of TEE, as well as a statement that in subjects with a history of prior TEE, MI, DIC, CVA, TIA, unstable angina pectoris, or severe peripheral vascular disease within the prior 3 months has not been established because these subjects were not studied. PMR to better define risks of TEEs compared to Kcentra.

11.4 Recommendations on Regulatory Actions

BALFAXAR, Prothrombin Complex Concentrate, is recommended for licensure. The risk of thromboembolism will be further evaluated in a post marketing requirement (PMR) to evaluate the risks of TEE compared with treatment with control.

11.5 Labeling Review and Recommendations

The sponsor has agreed that a boxed warning be inserted in the label to inform of arterial and venous thromboembolic events.

11.6 Recommendations on Post-marketing Actions

The Applicant will be required to conduct a post-marketing study to evaluate the serious risk of TEEs and mortality rate with use of BALFAXAR.