Individuals using assistive technology may not be able to fully access the information contained in this file. For assistance, please call 800-835-4709 or 240-402-8010, extension 1. CBER Consumer Affairs Branch or send an e-mail to: ocod@fda.hhs.gov and include 508 Accommodation and the title of the document in the subject line of your e-mail.

Summary Basis for Regulatory Action

Date:	July 19, 2023
From:	Ze Peng, PhD, Chair Of the review Committee, Office of Therapeutic Products (OTP), Office of Plasma Protein Therapeutics CMC, Division of Hemostasis, Hemostasis Branch 1
BLA STN:	125776/0
Applicant:	OCTAPHARMA Pharmazeutika Produktionsges.m.b.H.
Submission Receipt Date:	July 28, 2022
Action Due Date:	July 28, 2023
Proper Name:	Prothrombin complex concentrate, human-lans
Proprietary Name:	BALFAXAR
Indication:	Urgent reversal of acquired coagulation factor deficiency induced by Vitamin K antagonist (VKA, e.g., warfarin) therapy in adult patients with need for an urgent surgery/invasive procedure.

Recommended Action: The Review Committee recommends approval of this product.

Acting Director, Office of Clinical Evaluation, Office of Therapeutic Products, Center for Biologics Evaluation and Research

Discipline Reviews	Reviewer / Consultant - Office/Division
CMC • CMC Product (Product Office and OCBQ/DBSQC) • Facilities review (OCBQ/DMPQ) • Establishment Inspection Report (OCBQ/DMPQ and Product Office) • QC, Test Methods, Product Quality (OCBQ/DBSQC)	Ze Peng, PhD, CBER/OTP/OPPT Obinna Echeozo, MPH, MBA CBER/OCBQ/DMPQ Emnet Yitbarek, PhD, CBER/OCBQ/DBSQC Hyesuk Kong, PhD, CBER/OCBQ/DBSQC Parmesh Dutt, PhD, CBER/OCBQ/DBSQC Marie Anderson, PhD, CBER/OCBQ/DBSQC
Clinical • Clinical (Product Office) • Postmarketing safety (Epidemiological review (OBPV/DE) • BIMO	Karl Kasamon, MD, CBER/OTP/OCE Margarita M Gomez Lorenzo, MD, CBER/OBPV/DPV/PB2 Triet M. Tran, PharmD, BCSCP, CBER/OCBQ/DIS/BMB
Statistical	Jiang Hu, PhD, CBER/OBPV/DB
Non-clinical/Pharmacology/Toxicology • Toxicology (Product Office) • Developmental toxicology (Product Office) • Animal pharmacology	Rondine Allen, PhD, CBER/OTP/OPT
Clinical Pharmacology	Xiaofei Wang, PhD, CBER/OTP/OCE
Labeling • Promotional (OCBQ/APLB) • Carton/Containers (OTP/ OPPT, OTP/ ORMRR)	Kristine Khuc, PharmD, CBER/OCBQ/DCM/APLB Ze Peng, PhD, CBER/OTP/OPPT Eden Chane, MS, CBER/OTP/ORMRR
Other Review(s) not captured above categories, for example: • Consults • Devices	Mikhail V. Ovanesov, PhD, CBER/OTP/OPPT Oluchi Elekwachi, PharmD, MPH, CBER/OCBQ/DCM/APLB David Wolloscheck, CDRH/OPEQ/OHTIII/DHTIIIC

Table of Contents

1. Introduction

Octapharma Pharmaceuticals submitted a Biologics License Application (BLA), STN BL 125776, for prothrombin complex concentrate (PCC), human-lans. The proprietary name is BALFAXAR. BALFAXAR is a four-factor human plasma-derived PCC which contains vitamin-K dependent clotting factors (II, VII, IX, and X) as well as coagulation inhibitors, protein C and S. The manufacturing process for BALFAXAR includes solvent-detergent treatment and nanofiltration for pathogen inactivation and removal. BALFAXAR is labeled and dosed based on the factor IX activity.

BALFAXAR is supplied in a package with a single-dose vial of lyophilized powder and a vial of diluent (sterile Water For Injection, sWFI), together with a transfer device. The reconstituted product is administered intravenously. It is available at a strength of 500 IU

Range (20 mL reconstitution volume) and 1000 IU Range (40 mL reconstitution volume) per vial and has a shelf-life of 3 years at +2°C to +25°C. The actual potency is labelled on each product vial and its carton.

BALFAXAR is indicated for the urgent reversal of acquired coagulation factor deficiency induced by Vitamin K antagonist (VKA, e.g., warfarin) therapy in adult patients with need for an urgent surgery/invasive procedure.

This document summarizes the basis for approval of BALFAXAR. Data from 105 subjects from one adequate and well controlled Phase 3 study, study LEX-209, provide the primary evidence of effectiveness and safety of BALFAXAR in this BLA. The recommendation for approval is based on demonstration of non-inferiority in the primary endpoint of hemostatic efficacy compared to treatment with a comparator PCC product that is licensed for the same indication. The major risk of treatment with BALFAXAR is occurrence of thromboembolic events.

The review team recommends approval of this BLA with a post-marketing requirement (PMR) for an observational study to assess the risk of thromboembolic events and overall mortality with use of BALFAXAR.

2. Background

There are many indications for anticoagulation with vitamin K antagonist (VKA) therapy, such as previous venous or arterial thrombosis, heart valvular lesions, or atrial fibrillation. The mechanism of action of VKA is induction of acquired deficiency of vitamin K dependent clotting factors (FII, FVII, FIX, or FX).

Patients treated with VKA may need to undergo urgent surgical interventions and therefore require interruption of VKA. The administration of vitamin K is often inadequate to reestablish hemostasis in a timely manner. Fresh Frozen Plasma (FFP) use requires thawing of FFP that can cause significant delays, and the large volume of FFP that may be required if the international normalized ratio (INR) is high presents significant risks. PCCs offer an advantage over FFP including timely coagulopathy correction and the absence of volume overload risk. Kcentra® is a PCC that has been licensed since 2013. Availability of additional PCCs would help increase consumer choice and prevent possible shortages.

Product marketing background

BALFAXAR has been marketed in Germany since 2003, and subsequently licensed in 87 other countries. Currently, there is another PCC product (Kcentra® manufactured by CSL Behring) licensed in the U.S. for the urgent reversal of acquired coagulation factor deficiency induced by VKA therapy in adult patients with need for an urgent surgery/invasive procedure. BALFAXAR will be the second member of this product class in the U.S. for this indication.

Table 1. Regulatory History

Regulatory Events / Milestones	Date
1. Pre- IND Meeting	May 18, 2006
2. IND submission (IND 013323)	March 19, 2007
3. Orphan Drug designation granted	February 01, 2008
4. Fast Track designation granted	September 30, 2010
5. Pre-BLA meeting	February 22, 2022
6. BLA 125776/0 submission	July 28, 2022
7. BLA filed	September 22, 2022
8. Mid-Cycle communication	January 26, 2023
9. Late-Cycle meeting	March 31, 2023
10. Action Due Date	July 28, 2023

The product in this BLA was classified as a combination product. As such, CBER consulted the Center for Drug Evaluation Center (CDER) at the pre-BLA meeting stage for an assessment of human factors (HF) study, and the Center for Devices and Radiological Health (CDRH) during the review of this BLA for the evaluation of the Nextaro transfer device used to reconstitute BALFAXAR powder with its diluent.

All identified issues were adequately resolved during the review. The review team determined that the applicant has satisfactorily addressed all substantive issues and recommends approval of the original BLA for BALFAXAR.

3. Chemistry Manufacturing, and Controls (CMC)

a. Product Quality

BALFAXAR is a human plasma-derived, purified, virus-inactivated and nanofiltered non-activated PCC. It is manufactured at Octapharma's facility at Oberlaaer Strasse 235, A-1100 Vienna, Austria. Several manufacturing steps including visual inspection of drug product vials, labeling, and secondary packaging are also performed at Octapharma's facility in (b) (4) BALFAXAR is produced from pooled U.S. human (b) (4) Plasma by using a sequence of (b) (4) and filtration steps. During the manufacturing process of BALFAXAR, satisfactory viral reduction is obtained via a combination of two dedicated virus inactivation/removal steps: S/D treatment and nanofiltration (20 nm).

The active ingredients of BALFAXAR include the vitamin K dependent pro-coagulation factors, FII, FVII, FIX, and FX as well as the anti-coagulation proteins, Protein C and Protein S. The other ingredients include the excipients heparin (b) (4) and sodium citrate. This product is offered in two dosage strengths, 500 IU or 1000 IU per vial. Dosage of BALFAXAR is based on FIX potency. FIX potency is measured using the (b) (4) assay against a reference standard. The reference standards used are either, (b) (4)

Manufacturing process steps

(b) (4)

Description of the manufacturing process

(b) (4)

Source material quality and control

BALFAXAR is manufactured from human (b) (4) Plasma obtained from FDA-approved U.S. plasmapheresis centers. The plasma donations used for BALFAXAR are tested and found to be negative using serological assays for hepatitis B surface antigen (HBsAg), and antibodies against Human Immunodeficiency Virus (HIV) – Type 1 and Type 2 (1/2) and Hepatitis C Virus (HCV). (b) (4) are excluded from further manufacture.

In addition, the (b) (4) plasma (b) (4) is tested for (b) (4) during the manufacturing process. Furthermore, the manufacturing pool should be non-reactive according to specified sensitivity of the analytical methods for (b) (4) (b) (4) The limit for B19V DNA in the manufacturing pool is $<10^4$ IU/mL.

The excipient heparin (b) (4) used to manufacture BALFAXAR is manufactured from (b) (4) Heparin (b) (4) is qualified based on a (b) (4) that specifically includes the (b) (4) (b) (4)

All other source materials used for BALFAXAR manufacture are qualified according to the monographs of the USP, National Formulary, or European Pharmacopoeia (Ph. Eur.), and do not contain animal- or human-derived materials that could potentially introduce contamination with adventitious agents. All these source materials are purchased from approved suppliers and released against the approved specifications.

Critical process parameters and their control

Critical process parameters (CPPs) for the manufacturing process and their acceptable ranges were initially determined during process development. The acceptance ranges were further verified and adjusted during the optimization of the process steps and production of full-scale GMP batches. Operating parameters for each unit operation in the BALFAXAR process were examined for criticality prior to the execution of the conformance campaigns. These CPPs and their acceptance criteria have been justified.

Process validation

The Process Performance Qualification (PPQ) of BALFAXAR manufacturing process included the production of three 500 IU (b) (4) and three 1000 IU (b) (4) conformance DP batches, covering the minimum and maximum process time. To produce the bulk used for manufacture of batch (b) (4) For the implementation of an alternative (b) (4) used in (b) (4) conformance DP batches (b) (4) were produced to cover both dosage strengths. The results of in-process control and quality control testing for all the

conformance batches complied with prospectively defined acceptance criteria, demonstrating that process validation was successful.

CMC Comparability Assessment

Octapharma confirmed in the amendment to the BLA submitted on 23 January 2023, that DP used in the pivotal clinical study LEX-209 was manufactured by the proposed commercial process. Therefore, no CMC comparability assessment is needed for this BLA.

Analytical methods for product quality

Suitable analytical methods have been validated to support quality control testing throughout manufacture, final product release, and stability monitoring. Clarifications were obtained through requests of additional documentation. All identified issues were adequately addressed by Octapharma and resolved during the review process.

Impurities

The impurity profile of BALFAXAR final drug product (FDP) is described in Report No. *020STD26x 28x.713/00*. The product-related impurities include (b) (4) (b) (4) These impurities were found below the detection limits of the assays in the BALFAXAR FDP. The process-related impurities include (b) (4) (b) (4) potential leachables from the (b) (4) and (b) (4) materials used for the processing of BALFAXAR. The process-related impurities were either below the limit of detection of the assays or present in amounts that did not present a risk to the patient.

Specification for final drug product

The following release specifications are considered adequate to confirm product quality and manufacturing consistency.

Table 2. Specification for final drug product

Product quality attributes	Specifications	Test methods
Appearance	A white to ice-blue powder or friable mass, very hygroscopic	Visual inspection
Solubility	The preparation dissolved completely in 20 mL (500 IU) or 40 mL (1000 IU) of water for injection by gentle swirling within 1-5 minutes at 20 – 25°C, giving a clear solution that may be colored	Visual inspection
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
Water	(b) (4)	(b) (4)

		(b) (4)
Sterility	Sterile	(b) (4)
Endotoxin	(b) (4)	(b) (4)
Heparin	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
FII	17 – 25 IU/mL	(b) (4)
FVII	12 – 20 IU/mL	(b) (4)
FIX	20 – 32 IU/mL	(b) (4)
FX	15 – 27 IU/mL	(b) (4)
Protein C	16 – 28 IU/mL	(b) (4)
Protein S	12 – 30 IU/mL	(b) (4)
(b) (4)	(b) (4)	(b) (4)
Specific activity	(b) (4)	Calculation
(b) (4)	(b) (4)	Calculation
Confidence limits	FIX and FVII: within (b) (4) of the estimated potency FII and FX: within (b) (4) of the estimated potency	Calculation
Citrate	16.8 – 23.4 mmol/L	(b) (4)
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
(b) (4)		

Stability Studies

The available stability data showed no critical trends during the observed long-term storage period (BALFAXAR DS: (b) (4) at (b) (4) BALFAXAR DP: 36 months at 2°C to 8°C, 25°C/(b) (4) Relative Humidity (RH), or (b) (4) RH).

- For BALFAXAR DS, the data support a shelf-life of (b) (4) months at (b) (4)
- For BALFAXAR DP, the data support the proposed shelf-life of 36 months when stored at 2º to 25ºC. After reconstitution, the solution should be administrated immediately, or within 8 hours when stored at 20º to 25ºC, provided sterility is maintained.

Combination product

BALFAXAR is a co-packaged combination product consisting of three different constitute parts: a lyophilized powder of BALFAXAR in a product container, sWFI in a separated

container, and a transfer device (Nextaro). For this reason, CBER consulted with Dr. David Wolloscheck from CDRH for evaluation of the Nextaro device used in this combination product, and Dr. Ebony Whaley from CDER for evaluation of the HF study. The data to support device use for the reconstitution of BALFAXAR are summarized as follows:

- Nextaro, which contains integrated 15 µm filters on both the solvent and the active ingredient sides and is used for the reconstitution of BALFAXAR product, has been cleared under 510(k) No. K183187.

- To support use of the Nextaro device with BALFAXAR, Octapharma submitted a use-related risk assessment, a risk management report, the instructions for use of the device, a threshold analysis, and a design traceability matrix. In addition, a device compatibility study was provided. Our CDRH colleague concluded that the data from these assessments/studies support that the use of the Nextaro reconstitution device does not have a significantly adverse impact on the quality of BALFAXAR FDP.

- Our CDER colleagues reviewed the information related to device used for the reconstitution of BALFAXAR product in terms of the HF study under IND 13323/116. Based on the evaluation, they agreed with the revisions in the Instruction-For-Use made by the sponsor, and recommended that submission of additional HF data is not required.

Evaluation of Product Safety with respect to Adventitious Agents

Production processes are performed according to cGMP regulations and are controlled and monitored by specified process control parameters. Production processes have been investigated and validated concerning their ability to reduce microbes.

Residual microbes are reduced by in-process (b) (4) steps and removed by the validated (b) (4) sterile filtration of the (b) (4) Thereafter, aseptic filling is performed, and the product is freeze-dried. The final release tests include those for sterility and endotoxin.

As stated above, all plasma donations, (b) (4) and manufacturing pools, are tested for viral markers in compliance with the requirements of FDA.

Additionally, the potential for viral contamination of BALFAXAR is mitigated by two dedicated viral clearance steps: S/D treatment (b) (4) at (b) (4) and 20 nm nanofiltration (Planova 20N or Pegasus SV4). Octapharma has evaluated these steps in (b) (4)-scale studies. The enveloped viruses selected in the studies include HIV-1; Pseudorabies virus (PRV, model for enveloped DNA viruses including HBV); and Bovine viral diarrhea virus (BVDV, model virus for enveloped RNA viruses). The non-enveloped viruses selected in the studies include HAV; and Porcine parvovirus (PPV, model virus for B19V). These viruses were chosen to resemble viruses which may contaminate the BALFAXAR, and to represent a wide range of physicochemical properties in order to test the ability of the manufacturing process to eliminate viruses. (b) (4)-scale studies of the relevant steps resulted in at

least the following total log reduction factors (in parenthesis) for the following viruses: HIV-1 (≥ 8.93), PRV (≥ 11.78), BVDV (≥ 10.97), HAV (5.24), and PPV (3.98). These results are sufficient to support the effectiveness of viral clearance in the commercial manufacturing process.

Table 3. Total virus reduction factors (log_{10}) for inactivation/removal of various viruses achieved by the BALFAXAR manufacturing process

Manufacturing steps	Virus reduction factor (log10)				
	Enveloped viruses			Non-enveloped viruses	
	HIV-1	PRV	BVDV	HAV	PPV
S/D treatment	≥ 4.35	≥ 5.77	≥ 5.96	Not applicable	Not applicable
Planova 20N nanofiltration	≥ 4.58	≥ 6.01	≥ 5.95	≥ 5.36	5.79
Total log reduction factors (S/D treatment + Planova 20N nanofiltration)	≥ 8.93	≥ 11.78	≥ 11.91	≥ 5.36	5.79
S/D treatment	≥ 4.35	≥ 5.77	≥ 5.96	Not applicable	Not applicable
Pegasus SV4 nanofiltration	≥ 4.82	≥ 6.13	≥ 5.01	≥ 5.24	3.98
Total log reduction factors (S/D treatment + Pegasus SV4 nanofiltration)	≥ 9.17	≥ 11.90	≥ 10.97	≥ 5.24	3.98

b. CBER Lot Release (DBSQC)

The lot release protocol template was submitted to CBER for review and found to be acceptable after revisions. A lot release testing plan was developed by CBER and will be used for routine lot release.

c. Testing Specifications (DBSQC)

The analytical methods and their validations and/or qualifications reviewed for BALFAXAR drug substance and drug product were found to be adequate for their intended use.

d. Facilities Review / Inspection (DMPQ)

Facility information and data provided in the BLA were reviewed by CBER and found to be sufficient and acceptable. The facilities involved in the manufacture of Balfaxar are listed in the table below. The activities performed and inspectional histories are noted in the table.

Table 4. Manufacturing Facilities for Balfaxar [Prothrombin Complex Concentrate, Human]

Name/Address	FEI number	DUNS number	Inspection/ Waiver	Justification /Results
Octapharma Pharmazeutika Produktionsges.m.b.H., Oberlaaer Strasse 235, A-1100, Vienna, Austria (Octapharma Vienna) *Drug substance manufacturing, drug product manufacturing and final release testing*	3002809097	301119178	Waiver	ORA/OBPO December 2022 VAI
Octapharma (b) (4) (b) (4) *Drug product manufacturing and primary labeling*	(b) (4)	(b) (4)	Waiver	ORA (b) (4) VAI
(b) (4) *Diluent manufacturing and final release testing*	(b) (4)	(b) (4)	Waiver	(b) (3) (b) (4) Satisfactory
(b) (4) *Diluent final release testing*	(b) (4)	(b) (4)	Waiver	ORA (b) (4) NAI

OBPO – Office of Biological Products Operations; ORA – Office of Regulatory Affairs; NAI – No Action Indicated; VAI – Voluntary Action Indicated.

ORA/OBPO performed a surveillance inspection of the Octapharma Vienna facility in December 2022, and a Form FDA 483 was issued at the end of the inspection. All inspectional issues appear to have been resolved, and the inspection was classified VAI.

ORA conducted a surveillance inspection of the Octapharma (b) (4) facility in (b) (4) A Form FDA 483 was issued at the end of the inspection. The firm responded to the observations, and corrective actions were reviewed and found to be adequate. All inspectional issues appear to have been resolved, and the inspection was classified VAI.

The most recent inspection of (b) (4) was conducted by the (b)(4), (b)(3) (b)(4), (b)(3) in (b)(4), (b)(3) DMPQ obtained and reviewed the inspection report from the (b)(4), (b)(3) via the Mutual Recognition Agreement. No observation report was submitted, and the inspection was classified "satisfactory".

ORA performed a surveillance inspection of the (b) (4) (b) (4) facility in (b) (4) A Form FDA 483 list of observations was not issued, and the inspection was classified NAI.

e. Container/Closure System (DMPQ)

The 500 IU and 1000 IU presentations of the lyophilized Balfaxar DP are each filled into 30 mL and 50mL (b) (4) glass vials (supplied by (b) (4) respectively, and stoppered with sterilized gray 20mm (b) (4) bromobutyl rubber stoppers coated with (b) (4) coating (supplied by (b) (4) . The stoppered product vial is sealed with a 20 mm aluminum seal with blue plastic flip off cap manufactured by (b) (4) Octapharma Vienna performed the container closure integrity testing (CCIT) of filled and sealed DP vials at the Vienna, Austria facility, employing the (b) (4) (b) (4) and (b) (4) methods; all acceptance criteria were met.

The water for injection (WFI) diluent is supplied in 20 mL and 50 mL (b) (4) glass vials (supplied by (b) (4)) for the reconstitution of the lyophilized 500 IU and 1000 IU Balfaxar DP presentations, respectively. The WFI vials are stoppered with 20 mm gray (b) (4) bromobutyl rubber stoppers supplied by (b) (4) (b) (4) and sealed with aluminum flip off caps manufactured by (b) (4) (b) (4) performed the CCIT of the WFI vials at the (b) (4) facility, employing the (b) (4) method (b) (4) (b) (4) method). A second CCIT using the (b) (4) method was performed by (b) (4) (b) (4) (acquired by (b) (4)) at the (b) (4) facility. All CCIT results met the acceptance criteria.

A single-use needleless transfer device (Nextaro) with an integrated 15 µm (nominal) filter is co-packaged with the lyophilized DP and WFI vials. This device is cleared under FDA 510(k) No. K183187 and is used to transfer the WFI diluent into the DP vial for reconstitution.

f. Environmental Assessment

The BLA included a request for categorical exclusion from an Environmental Assessment under 21 CFR 25.31c. The FDA concluded that this request is justified as the manufacture of this product will not significantly alter the concentration and distribution of naturally occurring substances, and no extraordinary circumstances exist that would require an environmental assessment.

Recommendation:

The manufacturing process for BALFAXAR is considered validated at the commercial

scale and is sufficiently controlled to assure consistent manufacture of commercial product meeting acceptable release specifications. The reviewers from the Division of Hemostasis, the Division of Manufacturing and Product Quality, and the Division of Biological Standards and Quality Control conclude that Octapharma has provided sufficient data and information on chemistry, manufacturing, and controls to support the licensure of BALFAXAR.

4. Nonclinical Pharmacology/Toxicology

The reversal of Phenprogamma® 3-induced anticoagulation was evaluated in a study comparing BALFAXAR to Beriplex (human prothrombin complex) in healthy rats. Following pre-treatment with Phenprogamma®, intravenous administration of 500 IU of BALFAXAR or Beriplex increased concentrations of Factors II, IX, Protein S and Protein C, normalized bleeding time and the international normalized ratio (INR), a standardized measure of blood clotting time and clot stability, and increased the thromboplastin time (TPT) in comparison to saline-administered control animals.

Nonclinical *in vitro* and *in vivo* studies evaluated the risk for BALFAXAR to cause thrombosis. The thrombogenic potential, activity, and concentration of (b) (4) coagulation Factors II, VII, IV, and X were determined for heparin-containing and (b) (4) batches of BALFAXAR. Thrombogenic potential was evaluated by determining the partial thromboplastin time, thrombin generation time (TGt_{50}), non-activated partial thromboplastin time (NAPTT), and thrombin fibrinogen coagulation time. BALFAXAR was considered non-thrombogenic in each thrombogenicity test. Regarding (b) (4) content was below (b) (4) and (b) (4) for heparin containing and (b) (4) batches, respectively. (b) (4) activity was below (b) (4) for all batches of BALFAXAR. (b) (4) content was (b) (4) for all BALFAXAR batches.

The Wessler stasis test was used to evaluate thrombus formation in rats (Report No. Dec 1996) following infusion of 100 IU/kg, 200 IU/kg, and 400 IU/kg of BALFAXAR 500 IU. Thrombogenic scores for both (b) (4) and heparin containing batches of BALFAXAR were below the thrombogenic threshold. Three additional studies were conducted in rabbits (Report Nos. 26621/49, 30503, and 37157) to determine the thrombogenic potential of BALFAXAR using the Wessler stasis test. No thrombosis was observed for BALFAXAR 500 or 1000 IU when intravenously administered at 400 IU/kg.

Two studies (Report Nos. SL-LT-221/11 and 37158) were conducted to evaluate local skin reactions to BALFAXAR 500 IU following (b) (4) intravenous administration, or (b) (4) (b) (4) in rabbits. No test article-related macroscopic changes were reported in either study.

Animal reproductive and developmental toxicity and carcinogenicity studies were not conducted with BALFAXAR, which is acceptable based on the product type, safety profile, and proposed indication.

5. Clinical Pharmacology

BALFAXAR is a blood coagulation factor replacement product to be administered as a single dose intravenous (IV) infusion. The administration of BALFAXAR provides a rapid increase in plasma levels of the vitamin K-dependent coagulation factors (FII, FVII, FIX, FX) and antithrombotic proteins C and S.

After a single dose IV infusion, BALFAXAR was distributed, metabolized, and excreted in the same manner as the endogenous proteins. The pharmacokinetic assessment results from a Phase 2, prospective, single arm open-label study in subjects with acquired deficiency of vitamin K dependent coagulation factors is summarized in below Table 5:

Table 5. Pharmacokinetic Parameters and Recovery of Coagulation Factors, Protein C and Protein S

Parameter	FII	FVII	FIX	FX	Protein C	Protein S
C_{max} (%)	62.42/1.33 (37.00-118.00)	30.58/1.55 (13.00-81.00)	57.57/1.55 (27.00-130.00)	51.03/1.41 (30.00-120.00)	59.95/1.35 (38.00-109.00)	63.20/1.39 (30.00-115.00)
$C_{max,norm}$ (%/IU/kg)	2.38/1.23 (1.38-2.96)	1.16/1.51 (0.48-2.11)	2.19/1.65 (0.84-4.71)	1.94/1.26 (1.08-2.74)	2.28/1.31 (1.17-3.45)	2.41/1.41 (0.90-3.95)
Incremental Recovery** (%/IU/kg)	1.73/1.33 (0.81-2.42)	0.68/1.88 (0.11-1.62)	1.17/1.83 (0.26-2.52)	1.47/1.34 (0.73-2.38)	1.25/0.54* (0.00-2.22)	1.47/1.52 (0.59-2.35)
Absolute Recovery*** (%)	75.70/1.34 (32.65-116.98)	29.64/1.90 (4.45-78.35)	51.36/1.82 (13.54-115.58)	64.39/1.37 (29.68-114.8)	54.95/24.60* (0.00-107.04)	64.26/1.55 (23.74-113.66)
t_{max}	0.17 (0.17-3.00)	0.17 (0.17-1.00)	0.50 (0.17-3.00)	0.17 (0.17-3.00)	0.17 (0.00-3.00)	0.17 (0.17-3.00)

Note: Values reported as geometric mean/geometric SDs (range), except for t_{max} which is reported as median (min-max)
*Mean values SD (due to zero values, the geometric mean could not be calculated)
**The incremental recovery is defined as the rise in the plasma concentrations (%) achieved with 1 IU BALFAXAR/kg BW.
***The absolute recovery is defined as the rise in the plasma concentrations (%) achieved by the dose.

In a Phase 3, randomized, double-blind, controlled study in adult subjects needing urgent surgery with significant bleeding risk, the international normalized ratio (INR) was determined at varying time points after the end of infusion, and compared to another PCC product, Kcentra. As shown in Table 6, the median INR was 3.0 prior to the infusion and decreased to a median value of 1.30 by the 30-minute time point after the end of infusion in both groups. After 24 hours the median INR was 1.25 in the BALFAXAR group. The change of INR from baseline was similar between BALFAXAR and Kcentra treatment groups.

Table 6. Median INR (Min-Max) After End of Infusion in Urgent Surgery RCT

Treatment	Baseline	30 min	2 hr	4 hr	12 hr	24 hr
BALFAXAR (N=105)	3.05 (2.0 – 21.1)	1.30 (1.0 – 3.1)	1.28 (1.0 – 2.5)	1.30 (1.0 – 2.0)	1.30 (0.9 – 2.7)	1.25 (0.8 – 3.4)
KCENTRA (N=103)	3.00 (2.0 – 11.3)	1.30 (0.9 – 2.7)	1.29 (0.9 – 3.5)	1.30 (0.9 – 3.5)	1.38 (0.9 – 3.5)	1.29 (0.9 – 4.1)

6. Clinical/Statistical

a. Clinical Program

To support licensure of BALFAXAR, Octapharma, Inc., submitted data from a Phase 3. The clinical team's recommendation for approval of BALFAXAR is based on review of efficacy and safety data from this Phase 3 study of 105 treated subjects with VKA anticoagulation who required urgent surgery with high risk of bleeding.

The Phase 3 study was designed to demonstrate that the efficacy of BALFAXAR was not clinically inferior to that of Kcentra. The efficacy and safety of BALFAXAR were compared with those of Kcentra, currently the only FDA approved PCC therapy indicated for the urgent reversal of acquired coagulation factor deficiency induced by VKA.

The study was a prospective, parallel, randomized, controlled study in patients needing urgent surgery and judged to carry significant risk of intraoperative/procedural hemorrhage. The primary objective of the study was to determine that the efficacy of BALFAXAR as a reversal agent in patients under VKA therapy with significant bleeding risk was clinically non-inferior to Kcentra.

To meet the study eligibility criteria patients had to be aged ≥ 18 years; anticoagulated with VKA to INR ≥ 2 and admitted to the hospital for urgent surgery (i.e., needed within 24h of the start of treatment infusion) that carries significant bleeding risk (≥50 mL expected blood loss in normal coagulation state); where VKA withdrawal and use of vitamin K to reverse anticoagulation is deemed too slow.

Patients with life expectancy ≤ 48 hours; bleeding disorder or thrombocytopenia (of <80,000/µL or history of heparin-induced thrombocytopenia); history of TEEs, myocardial infarction, unstable angina pectoris, critical aortic stenosis, cerebrovascular accident, transient ischemic attack within preceding 90 days, were excluded from the study.

The primary efficacy endpoint was hemostatic efficacy rating following surgery. This was assessed by the investigator at the end of the surgery based on a 4-point hemostatic efficacy scale considering blood loss and transfusion requirements in the context of the surgery and also assessed by an independent efficacy assessment board (IEAB). The dichotomized final adjudicated hemostatic efficacy rating from the IEAB served as the primary efficacy variable for the statistical analysis. Secondary efficacy endpoints evaluated correction of INR between baseline and 30 minutes after end of BALFAXAR infusion, and changes in levels of coagulation factors. Main safety parameters included RBC transfusion requirements, adverse events (AE) including seroconversion for

parvovirus, thromboembolic events (TEE), and mortality. The study duration for each participant was 45 days.

BALFAXAR dose depended on the body weight (BW) and baseline international normalized ratio (INR) of the patient and was calculated by the responsible treating investigator based on 3 tiers of INR prolongation, with corresponding maximal dose cap.

Efficacy Results

The primary efficacy was evaluated based on non-inferiority of the proportion of subjects achieving effective hemostasis in the BALFAXAR group compared to that in the Kcentra group. The non-inferiority margin was pre-specified at -15%. The study was stopped at the pre-specified interim analysis due to statistically significant efficacy results. At the interim analysis, 94.6% (88/93) of the subjects in the BALFAXAR group and 93.5% (86/92) of the subjects in the Kcentra group achieved effective hemostasis. The proportion difference (98% CI) of 1.1% (-9.2%, 11.5%) was statistically significant ($p<0.001$) at the pre-specified one-sided 0.01 significance level, i.e., the lower bound of the CI was above the pre-specified noninferiority margin of -15%, indicating that BALFAXAR was non-inferior to Kcentra. At the conclusion of the study, the updated proportions of subjects with effective hemostasis were 94.3 % (99/105) in the BALFAXAR group and 94.2 % (97/103) in the Kcentra group, resulting in a difference (95% CI) of 0.1% (-8.0%, 8.2%).

In the descriptive analyses of the secondary efficacy endpoints, numerically similar results between the two treatment groups were observed in the proportion of patients achieving an INR ≤1.5, 30 minutes after the end of the IP infusion as well as in the change from baseline in INR.

A numerically similar, and low, proportion of patients received RBC during surgery (3.8% in the BALFAXAR group and 2.9% in Kcentra group), with similar volumes administered (5.99 mL/kg and 5.76 mL/kg, respectively).

In summary, substantial evidence of effectiveness of BALFAXAR in adults on VKA who require urgent surgery was demonstrated in an adequate and well-controlled trial (LEX-209). The results support approval for BALFAXAR.

b. Bioresearch Monitoring (BIMO) – Clinical/Statistical/Pharmacovigilance

A Bioresearch Monitoring inspection was conducted for one foreign clinical study site, and a Remote Regulatory Assessment (RRA) was conducted for another foreign clinical study site that participated in the conduct of the Phase 3 study. The inspection and RRA did not reveal any issues that impact the data submitted in support of this original BLA.

c. Pediatrics

This application is exempt from Pediatric Research Equity Act (PREA) because it is intended for a biologic product for which orphan designation has been granted. This product is not indicated in pediatric subjects.

d. Other Special Populations

BALFAXAR has not been studied in special populations.

7. Safety and Pharmacovigilance

The primary safety population included 105 subjects in a Phase 3 study who were treated with BALFAXAR at a median dose of 25 IU of FIX/kg over 12 minutes (range 8-50 minutes). Treatment-emergent adverse events (TEAEs) were defined as all adverse events occurring after initiation of the product administration to Day 45 visit.

Summary of safety findings:

The proportion of subjects with treatment emergent adverse events (TEAEs) was similar between treatment arms: 81.9% for BALFAXAR vs. 77.7% for Kcentra.

Most commonly reported TEAEs by preferred term (>5% in either group) included procedural pain in 47.6% of patients, postoperative wound complication in 14.3%, asthenia in 12.4%, and anemia 5.7%. Generally, the incidence of TEAEs was similar across the treatment groups.

The incidence of adverse drug reactions was low: 1 patient (1.0%) in the BALFAXAR group had 2 such events (unstable angina and chest pain).

A total of 24 severe events (12 of which were serious adverse events [SAEs]) were reported in 9 patients (8.6%) in the BALFAXAR group and 19 severe events (7 of which were SAEs) in 8 patients (7.8%) in the Kcentra group.

Thirteen patients (12.4%) in the BALFAXAR group and 6 (5.8%) in Kcentra group had SAEs. One of the SAEs in the BALFAXAR group (angina unstable) was considered to be drug-related; it occurred 5 days after receiving BALFAXAR. Five patients (4.8%) in the BALFAXAR group and 1 (1.0%) in Kcentra group had SAEs with a fatal outcome. All deaths were considered not related to BALFAXAR. Numerically, more TEEs were reported in the BALFAXAR arm than the Kcentra arm, as summarized in the table below.

Table 7. Subjects with Thromboembolic Events (TEEs) per Treatment Arm

Type of Thromboembolic Event	BALFAXAR N=105 (%)	Kcentra N=103 (%)
Number of Subjects with TEEs per MedDRA SMQ embolic and thrombotic events	3 (2.9)	0
Number of Subjects with TEEs possibly causally related to IP	1 (1.0)	0

Given the imbalance in the reported TEEs and the known risk of thrombosis associated with treatments that are used to reverse anticoagulation, a prospective observational post-marketing study to evaluate the serious risk of TEEs with use of BALFAXAR will be

required upon product approval. The risk of thromboembolic events is also included as a boxed warning in BALFAXAR Prescribing Information.

a. Pharmacovigilance

Post licensure safety surveillance activities will include:
1. Routine pharmacovigilance: Adverse event reporting in accordance with 21 CFR 600.80.

2. Enhanced surveillance under 21 CFR 600.80 (c)(1)(i) for TEEs for 3 years following approval:

- Submission of all post-marketing reports of thromboembolic events (TEEs), regardless of seriousness or expectedness, as expedited (15-day) reports
- Provision of aggregate assessment (based on interval and cumulative data) of TEEs in periodic safety reports.

3. Post marketing requirement (PMR) under Section 505(o) of the Federal Food, Drug, and Cosmetic Act (FDCA) to conduct the following study to assess a known serious risk of TEEs after BALFAXAR:

- Post-marketing, prospective observational study to assess the risk of thromboembolic events (TEEs) following Vitamin K Antagonist (VKA) reversal among patients treated with BALFAXAR or comparator in the setting of urgent surgery or an invasive procedure. Study subjects will be evaluated for the primary endpoint of proportion of patients with TEEs within 45 days following VKA reversal treatment with BALFAXAR and the secondary endpoint of proportion of patients who die from any reason within 45 days following VKA reversal treatment with BALFAXAR. The study will enroll at least 3574 subjects randomized 1:1 to BALFAXAR or comparator.

Data available at this time do not suggest any safety signals that warrant a Risk Evaluation and Mitigation Strategy (REMS) for this product. There is no post-marketing commitment for a safety study for this product.

8. Labeling

The proposed proprietary name, BALFAXAR, was reviewed by Advertising and Promotional Labeling Branch (APLB) on October 26, 2022 and was found acceptable. CBER communicated the acceptability of the proprietary name to the applicant November 17, 2022. The proper name suffix, -lans, was designated on March 13, 2023, making (prothrombin complex concentrate-lans) the proper name.

APLB reviewed the proposed Prescribing Information, and package and container labels on April 18, 2023, and found them acceptable.

9. Advisory Committee Meeting

No advisory committee meeting was held because initial review of information submitted in the BLA did not raise concerns or controversial issues that would have benefited from an advisory committee discussion.

10. Other Relevant Regulatory Issues

BALFAXAR has received Orphan Drug and Fast Track Designations.

11. Recommendations and Benefit/Risk Assessment

a. Recommended Regulatory Action

The Applicant provided substantial evidence of effectiveness and reasonable assurance of safety based an adequate and well controlled clinical investigation. The review team recommends approval of BALFAXAR.

b. Benefit/Risk Assessment

BALFAXAR administration resulted in an effective hemostasis rate that was non-inferior to that of Kcentra treatment in subjects on VKA anticoagulation undergoing urgent surgery. The most notable risk identified with BALFAXAR was thrombosis. This risk is acceptable when compared to the substantial benefit of effective hemostasis. Therefore, the overall benefit-risk profile of BALFAXAR is favorable.

The clinical trial data do not suggest a safety concern that would necessitate a Risk Evaluation and Mitigation Strategy (REMS). Given the imbalance in occurrence of thromboembolic events observed in the clinical trial, a post-marketing safety study will be required to assess the serous risk of thromboembolic events following treatment with BALFAXAR.

c. Recommendation for Post-marketing Activities

In addition to routine and enhanced pharmacovigilance activities (with adverse event reporting as required under 21 CFR 600.80), the applicant will do the following study as a post-marketing requirement (PMR) under Section 505(o) of the FDCA to assess a known serious risk of thromboembolic events:

A prospective, observational, cohort study to be conducted using electronic medical records (EMR) linked with administrative claims data, to assess the known risk of thromboembolic events after administration of BALFAXAR. The study will enroll minimum of 3,574 patients (with 1787 patients exposed to BALFAXAR and 1787 patients exposed to a comparator treatment).

The study will be conducted on the following schedule:

- Protocol submission date: 12/31/2023
- Study completion date: 12/31/2031
- Final report submission date: 06/30/2032.