

Clinical Pharmacology BLA Review

Division of Clinical Evaluation General Medicine
Office of Clinical Evaluation
Office of Therapeutic Products, CBER, FDA

BLA 125776/0
Applicant OCTAPHARMA Pharmazeutika Produktionsges.m.b.H.
Product Balfaxar (Prothrombin Complex Concentrate (Human), Octaplex)
Powder & Solvent for Intravenous Use (500 IU/ 1000 IU)
Proposed Indication Urgent reversal of acquired coagulation factor deficiency induced by
Vitamin K antagonist (VKA, e.g., warfarin) therapy in adult patients
with (b) (4) need for an urgent surgery/invasive
procedure
Date Received July 28, 2022
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1 EXECUTIVE SUMMARY

OCTAPHARMA Pharmazeutika Produktionsges.m.b.H. seeks approval of its Biologics License Application (BLA) for its BALFAXAR (Prothrombin Complex Concentrate (Human), Octaplex) for urgent reversal of acquired coagulation factor deficiency induced by Vitamin K antagonist (VKA, e.g., warfarin) therapy in adult patients with (b) (4) need for an urgent surgery/invasive procedure. BALFAXAR is supplied as a lyophilized powder for reconstitution for intravenous use. The proposed dose of BALFAXAR is individualized based on the patient's baseline International Normalized Ratio (INR) value and body weight, ranging from 25 to 50 (units of Factor IX/kg), with a maximum dose at 5000 (units of Factor IX).

The clinical pharmacology evaluation of this BLA is based on data from 4 clinical studies. After a single dose intravenous infusion, BALFAXAR was distributed, metabolized, and excreted in the same manner as the endogenous proteins. The change from baseline in the international normalized ratio (INR) was similar between BALFAXAR and Kcentra treatments.

The proposed dosing regimen of BALFAXAR administered by IV infusion has demonstrated clinical effectiveness with a tolerable safety profile; therefore, the proposed dose is acceptable. From clinical pharmacology standpoint, the data presented in the BLA are adequate and acceptable to support approval.

2 RECOMMENDATIONS

The clinical pharmacology information in this BLA is acceptable, provided that satisfactory agreement is reached between the sponsor and the FDA regarding the language in Section 12 of the package insert. Please refer to Section 4 for detailed Labeling Recommendations.

3 INTRODUCTION

BALXAFAR is a human plasma-derived prothrombin complex concentrate containing the coagulation factors II, VII, IX and X and Proteins C and S. BALFAXAR is supplied as a lyophilized powder for reconstitution for intravenous use. BALFAXAR is a "co-packaged" combination product consisting of three different constituent parts: BALFAXAR powder, water for injection and transfer device Nextaro[®].

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 (b) (4) (b) (4) need for an urgent surgery/invasive procedure.

(b) (4)

(b) (4)

the Applicant started an additional clinical study, a Phase 3, randomized, double-blind study to evaluate the efficacy and safety of BALFAXAR for the reversal of Vitamin K antagonist induced anticoagulation in patients needing urgent surgery with significant bleeding risk (Study LEX-209). OCTAPHARMA (b) (4)

(b) (4)

On July 28, 2022, OCTAPHARMA submitted current application, BLA125776 for BALFAXAR (Prothrombin Complex Concentrate (Human), BALFAXAR), for urgent reversal of acquired coagulation factor deficiency induced by vitamin K antagonist (VKA, e.g., warfarin) therapy in adult patients with (b) (4) need for an urgent surgery/invasive procedure.

The clinical pharmacology of BALFAXAR includes four clinical studies. Please refer to Section 6.1 for detailed information.

4 SUMMARY OF IMPORTANT CLINICAL PHARMACOLOGY FINDINGS

After a single dose IV infusion, BALFAXAR was distributed, metabolized, and excreted in the same manner as the endogenous proteins. The pharmacokinetic parameters of the components of BALFAXAR are summarized as below:

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)

After a single IV 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 the end of infusion. After 24 hours it was 1.25 in the BALFAXAR group. The change of INR from baseline was similar between BALFAXAR and KCENTRA treatment groups.

5 LABELING COMMENTS

The clinical pharmacology reviewer has reviewed the package insert for BLA 125776/0 and finds it acceptable pending the following revisions shown below.

Comments to Applicant:

1. Please only report the PK results of BALFAXAR from your study in subsection 12.3.
2. Please delete the first 3 paragraphs in Section 12.2.

Below is the labeling incorporated with reviewer's comments.

12. CLINICAL PHARMACOLOGY

12.1. Mechanism of Action

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. Together they are referred to/known as the prothrombin complex. BALFAXAR can temporarily correct the coagulation defect of patients with deficiency of one or several of these factors.

12.2. Pharmacodynamics

In the randomized controlled trial in urgent surgery, the INR was determined at varying time points after the 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 the end of infusion. After 24 hours it was 1.25 in the BALFAXAR group (see [Table 6](#)).

The relationship between these or other INR values and clinical hemostasis in patients has not been established [*see Clinical Studies (14)*].

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)

12.3. Pharmacokinetics

Since BALFAXAR is given intravenously, bioavailability is proportional to the dose administered. BALFAXAR is distributed, metabolized, and excreted in the same manner as the endogenous proteins (see [Table 7](#)).

Table 7 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.

6 COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

6.1 Overview of Clinical Pharmacology Evaluation

Clinical Studies with Clinical Pharmacology Evaluation

- LEX-201: a Phase 2/3, prospective, open-label, single-arm, multi-center study evaluating the safety and efficacy of BALFAXAR in patients with single or multiple congenital deficiencies in Factor II, VII, IX and X.
- LEX-202: a Phase 2, prospective, non-randomized, open-label, single-arm, multi-center study assessing the efficacy and safety of BALFAXAR in patients with acquired deficiency of vitamin K dependent coagulation factors.
- LEX-203: a Phase 3, prospective, non-randomized, single-arm, open-label, multi-center study evaluating the efficacy and safety of BALFAXAR in patients under oral anticoagulant therapy and undergoing surgery or invasive procedures.
- LEX-209: a Phase 3, randomized, double-blind, multicenter study to assess the efficacy and safety of BALFAXAR in comparison with Kcentra in patients needing urgent surgery with significant bleeding risk.

Reviewer's Comments:

In Study LEX-201, the PK analysis was only available for FVII and FIX. In Study LEX-203, the PK analysis was only available for FII, FVII, FIX, and FX, but not protein C and Protein S.

The PK analysis of FII, FVII, FIX, FX, Protein C and Protein S was conducted in Study LEX-202. The international normalized ratio (INR) of BALFAXAR was also evaluated and compared to Kcentra in LEX-209.

6.2 General Pharmacology and Pharmacokinetics

The pharmacokinetic of the components of BALFAXAR was assessed in Study LEX-202, a Phase 2, prospective, non-randomized, non-controlled, open-label study in subjects with acquired deficiency of vitamin K dependent coagulation factors. A single dose of BALFAXAR was given to 20 subjects. The median dose of BALFAXAR administered in 10 subjects treated during surgical interventions was 29.0 IU/kg, and the median dose in 10 subjects treated to control bleedings was 21.3 IU/kg. After a single dose IV infusion, BALFAXAR was distributed, metabolized, and excreted in the same manner as the endogenous proteins. Table 1 Summarizes the PK parameters of the components in BALFAXAR.

Table 1. 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.

Source: Applicant. Module 2, section 2.7.2. Summary of Clinical Pharmacology Studies.

In a Phase 3, randomized, double-blind, controlled study in subjects needing urgent surgery with significant bleeding risk, the international normalized ratio (INR) was determined at varying time points post-infusion, and compared to comparator, Kcentra. 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 the end of infusion in both groups. After 24 hours it was 1.25 in the BALFAXAR group. The change of INR from baseline was similar between BALFAXAR and Kcentra treatment groups.

Table 2. 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)	1.39 (0.9 - 4.1)

Source: Applicant. Module 5, section 5.3.5.1. Clinical Study Report for LEX-209.

Reviewer's Comments:

Because the PK sampling schedule was not long enough, accurate half-life values for all the components of BALFAXAR cannot be calculated. Per the Applicant proposed labeling of Section 2.1 Dosage, *“The safety and effectiveness of repeat dosing have not been established and it is not recommended”*.

7 APPENDIX - INDIVIDUAL STUDY

7.1 Study LEX-201

Clinical End: January 28, 1999

Title: Safety and Efficacy of BALFAXAR in patients with single or multiple congenital deficiencies in Factor II, VII, IX and X.
Objectives: To determine the efficacy, the pharmacokinetic parameters, thrombogenic potential, tolerability, immunogenicity and viral safety during a six months period of treatment.
Methodology: This was a prospective, open-label, non-controlled, multi-national multi-centre phase II/III study.
Number of Subjects: Planned: 10; Enrolled: 10; Completed and analyzed: 10.
Diagnosis and Criteria for Inclusion: Severe deficit in FII, VII, IX or X; Age > 12 years. At least 10 previous exposure days to FII, VII, IX or X containing preparations.
Study Treatments Test product: BALFAXAR 500, S/D and virus-filtered human prothrombin complex concentrate, freeze-dried. Dose: For pharmacokinetic and recovery evaluation 50 IU/kg. For the 6 months treatment period, according to the instructions for use and the investigator's evaluation of clinical needs (prophylaxis, bleeding, surgical procedures). Administration Route: Intravenous Batch Number: The following 3 batches were used during the study: 703002265, 7030032651, 7120042651.
Pharmacokinetic Sampling Times Blood samples were collected at pre-dose (baseline) and then at 10 min, 30 min, 1, 3, 6, 9, 12, 24, 32, 48, and 72 hours after first injection and at 6 months for FIX deficiencies and pre-dose (baseline) and at 5 min, 10 min, 30 min, 45 min, 1, 2, 3, 6, 9, 12, and 24 hours after first injection and at 6 months for FVII deficiencies.
Clinical Pharmacology Results: The PK profile was assessed in 10 male patients (6 hemophilia B and 4 FVII-deficient patients from which 2 dropped-out), aged between 11 and 67 years of age (mean age, 21 years) with severe deficit in FIX and FVII, respectively, who had received at least 10 past exposure days to FIX- or FVII-containing preparations (median previous exposure was 150 days [range, 15 to 600 days]). For FVII deficient patients, the calculated terminal half-life ranges from 5.4 to 8.25 hours. For FIX deficient patients, the calculated terminal half-life ranges from 28.7 to 49.1 hours depending on the number of time-points considered for the regression. FVII recovery ranges from 0.84 to 1.24%/IU/kg (35.5 – 53.4%). FIX recovery ranges from 0.80 to 1.42%/IU/kg (38.6 – 61.0%).

Source: Applicant. Module 5, section 5.3 Clinical Study Reports.

7.2 Study LEX-202

Clinical End: February 14, 2001

Title: Efficacy and Safety of BALFAXAR in patients with acquired deficiency of vitamin K dependent coagulation factors.
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<p>Objectives:</p> <p>Primary: To assess the efficacy of BALFAXAR in patients with major bleeds or in case of surgical or invasive procedures during treatment with anticoagulants of coumarin or indandion type.</p> <p>Secondary:</p> <ul style="list-style-type: none"> To access the clinical safety and tolerability of BALFAXAR.
<p>Methodology:</p> <p>This was a Phase 2, prospective, non-randomized, open-label, multi-center study.</p>
<p>Number of Subjects:</p> <p>Planned: 20; Enrolled: 20; Analyzed: 20</p>
<p>Diagnosis and Criteria for Inclusion:</p> <p>Patients with major bleeds attributable to, or complicated by, oral anticoagulants; or who need urgent reversal of anticoagulant treatment in case of surgical or invasive procedures.</p> <p><u>Inclusion Criteria</u></p> <p>Patients receiving anticoagulants of coumarin or indandion type. For major bleeds: INR > 5. For surgical or invasive procedures: INR > 3. Age > 18 years. Freely given written informed consent.</p> <p><u>Exclusion Criteria</u></p> <p>Recent history of DIC, hyperfibrinolysis. Known congenital coagulation disorder. Present or past inhibitor activity. Previous allergic thrombocytopenia (type II) induced by heparin. Administration of other plasma derived or blood products 4 months before study entry. History of intolerance to plasma derived or blood products. Participation in another clinical study currently or during the past four weeks. Pregnancy or lactation.</p>
<p>Test Product</p> <p>BALFAXAR 500, S/D and virus-filtered human prothrombin complex concentrate, freeze-dried powder for injection after dissolution in water (Water for Injection, (b) (4)).</p> <p>Dose: An initial dose of about 25 to 50 IU/kg BW was recommended. Since the dosage depends on the clinical status of the patient or the kind of surgery it was to be calculated individually. Single administrations or multiple doses were appropriate.</p> <p>Administration Route: Intravenous</p> <p>Batch Number: 0060042611 (Haifa, Israel), 0060022611 (Tel-Hashomer, Holon and Tel Aviv, Israel), 0060032611 (St. Petersburg, Russia).</p>
<p>Pharmacokinetic Sampling Time Points</p> <p>Blood samples were collected at pre-dose (baseline) and at 10 min, 30 min, 1, and 3 hours post-infusion.</p>
<p>Clinical Pharmacology Results:</p> <p>PK parameters for FII, FVII, FIX, FX, Protein C and Protein S. Please refer to Section 6.2 Table 1 for details.</p>

Source: Applicant. Module 5, section 5.3 Clinical Study Reports.

7.3 Study LEX-203

Clinical End: July 2005

<p>Title: Efficacy and Safety of BALFAXAR in Patients Under Oral Anticoagulant Therapy and Undergoing Surgery or Invasive Procedures – A Prospective, Non-Randomised, Non-Controlled, Open-Labelled, Multi-Centre, Phase III – Study</p>
<p>Objectives:</p> <p>Primary: To investigate the efficacy of BALFAXAR in patients undergoing surgical or invasive procedures being under treatment with anticoagulants.</p> <p>Secondary: To assess investigate the safety and tolerability of BALFAXAR</p>
<p>Methodology:</p> <p>The study is a prospective, non-randomized, non-controlled, open-labelled, multi-center study.</p>

Number of Subjects:

Planned: 60; Enrolled: 60, Analyzed per protocol: 56.

Diagnosis and Criteria for Inclusion:Inclusion Criteria

- Patients receiving anticoagulants of coumarin or indandion type and in whom a surgery or invasive procedure is indicated.
- Patients requiring BALFAXAR to control bleeding during surgery or invasive procedures who have a PT (Quick) < 50%.
- Patients who have given written informed consent or for whom written informed consent has been obtained from the patient's legal representative on their behalf.
- Patients able and willing to comply with the procedures laid out in the study protocol.

Exclusion Criteria

- Patients with a recent history of DIC, or hyperfibrinolysis.
- Patients with a known congenital coagulation disorder.
- Patients with present or past inhibitor activity.
- Patients with previous allergic thrombocytopenia (type II) induced by heparin.
- Patients with a history of exposure to viral hepatitis during the last 6 months prior to study entry.
- Patients who received plasma-derived or blood products within 30 days prior to study inclusion.
- Patients with a history of hypersensitivity to plasma-derived or blood products.
- Pregnant and nursing women.
- Patients participating in another clinical study currently or during the past 3 months prior to study inclusion.

Study Treatments**Test Product**

BALFAXAR 500, to be reconstituted with 20 mL Water for Injection (b) (4)

The BALFAXAR dose depended on the clinical status of the patient and the kind of surgery/invasive procedure, and was therefore calculated individually, based on the assumption that 1 IU of BALFAXAR per kg BW raises the PT value by 1.0%.

The following formula was used to calculate the initial BALFAXAR dose:

$$(PT \text{ endpoint} - PT \text{ baseline}) * kg \text{ BW} = IU \text{ BALFAXAR to be infused}$$

BALFAXAR intravenous infusion was to be started at a speed of 1 mL per minute, followed by 2-3 mL per minute, using an aseptic technique.

Batch number(s): No. 312 005 261; No. 324 012 261; No. 328 020 261; No. 328 021 261, No. 407 003 261; No. 414 006 261, No. 511 005 261.

Clinical Pharmacology Results:Pharmacokinetic:

The PK parameters were calculated using data from 12 subjects who had available concentration data up to 48 hours post-dose.

Study LEX-203: Pharmacokinetic Parameters

Parameter	FII N=11	FVII N=12	FIX N=11	FX N=12
t _{1/2} (h)	39.21 (10.77)	21.64 (22.04)	63.29 (117.03)	45.75 (52.80)
AUC _{0-inf} (%*h)	4730.0 (1833.2)	1478.5 (1566.3)	2739.8 (3806.2)	4311.4 (3050.8)
MRT _{0-inf} (h)	57.31 (15.51)	37.43 (36.87)	95.63 (168.46)	68.91 (83.76)
CL (IU/%/h)	0.76 (0.25)	3.39 (3.60)	2.78 (2.37)	0.64 (0.28)
V _Z (IU/%)	40.20 (9.32)	37.25 (17.10)	81.06 (24.53)	30.38 (9.66)
V _{SS} (IU/%)	40.79 (9.55)	43.73 (21.22)	86.38 (22.42)	31.18 (10.38)

Values reported as mean (SD); PK parameters were calculated on baseline adjusted data only for patients with 24 hour or 48 hour results (12 of 59 patients).

AUC = area under the concentration-time curve extrapolated to infinity; CL = total clearance; MRT = mean residence time; SD = standard deviation; t_{1/2} = terminal half-life; V_{SS} = volume of distribution at steady state; V_Z = volume of distribution

Study LEX-203: Maximum Concentration and Factor Recoveries

Full set population (N = 59)

C _{max} (%)	108.31 (28.08)	82.33 (39.10)	89.02 (34.72)	95.93 (31.63)
C _{max,norm} (%/IU/kg)	2.66 (1.02)	3.73 (2.48)	2.67 (1.54)	3.18 (1.31)
Recovery (%/IU/kg)	1.97 (0.61)	2.05 (1.07)	1.27 (0.58)	2.58 (0.91)

All patients with at least a 24 h measurement (N = 12)

C _{max} (%)	107.25 (21.55)	86.37 (51.88)	81.69 (23.12)	91.42 (18.31)
C _{max,norm} (%/IU/kg)	2.59 (0.55)	3.93 (2.33)	2.45 (1.15)	3.15 (0.76)
Recovery (%/IU/kg)	1.99 (0.22)	2.48 (1.48)	1.15 (0.40)	2.65 (0.56)

Values reported as mean (SD) and were calculated up to 3 hours post infusion

C_{max} = maximum concentration ; SD = standard deviation

The PK parameters from *Study LEX-203* should be interpreted with caution for the following reasons:

- Limited sample size
- Due to the study indication (patients under oral anticoagulant therapy and undergoing surgery or invasive procedure), most patients presented a substantial baseline (pre-infusion) level of coagulation factors. Therefore, the concentration vs. time profiles of the 12 patients were baseline adjusted to capture the effect of the rise in factor levels due to the infused product. Post-infusion concentration values that fell below the baseline values were set to missing. Due to this adjustment, derived PK parameters may not be comparable with PK parameters in other situations (e.g., factor deficient patients).
- Dosing of patients was done by the investigator on an individual level to achieve a desired target level of PT. Therefore, individual values of AUCs are not comparable even between study patients.
- Clinical circumstances (patients undergoing a surgical procedure, concomitant administration of IV fluids, blood products, or other concomitant medications etc.) may potentially influence the concentration of the coagulation factor levels. Thereby the long-term elimination patterns of *BALFAXAR* constituents will likely be affected.

Source: Applicant. Module 5, section 5.3 Clinical Study Reports.

7.4 Study LEX-209

Clinical End: November 08, 2021

<p>Title: A Phase III, randomized, double-blind, multicenter study to assess the efficacy and safety of BALFAXAR, a four-factor prothrombin complex concentrate (4F-PCC), compared to the 4F-PCC Beriplex® P/N (Kcentra), for the reversal of vitamin K antagonist induced anticoagulation in patients needing urgent surgery with significant bleeding risk.</p>
<p>Objectives: Primary: To demonstrate that the efficacy of BALFAXAR as a reversal agent in patients under VKA therapy with the need for urgent surgery with significant bleeding risk is clinically non-inferior to Beriplex® P/N (Kcentra). Secondary: To assess investigate the safety and tolerability of BALFAXAR compared to Beriplex® P/N (Kcentra) in patients under VKA therapy with the need for urgent surgery with significant bleeding risk.</p>
<p>Methodology: The study was designed as a Phase 3, randomized, double-blind non-inferiority study comparing BALFAXAR with Beriplex® P/N (Kcentra).</p>
<p>Number of Subjects: Planned: 370 (185 per treatment group); Enrolled: 370, Randomized: 208; Analyzed per protocol: 202.</p>
<p>Diagnosis and Criteria for Inclusion: <u>Inclusion Criteria</u> Male or female patients at least 18 years of age. Patients currently on oral anticoagulation treatment with VKA of coumadin or warfarin type. Patients admitted to the hospital or currently hospitalized where:</p> <ul style="list-style-type: none">• 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. <p>Patients with an international normalized ratio (INR) of 2.0 or above at the time of decision to reverse the anticoagulation status.</p> <p><u>Exclusion Criteria</u> The following criteria led to exclusion of patients from enrollment in the study: Patients with a life expectancy of less than 48 hours; with a known congenital bleeding disorder, antiphospholipid antibody syndrome, present or past specific factor inhibitor activity, or thrombocytopenia (of $< 80,000/\mu\text{L}$ 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).</p>
<p>Study Treatments Test Product BALFAXAR (500 IU) was reconstituted with 20 mL Water for Injection. The BALFAXAR dose depended on the body weight (BW) and baseline international normalized ratio (INR) (INR0) of the patient and was calculated by the responsible treating investigator as follows:</p>

Baseline INR (rounded to the first decimal place)	2 to <4	4-6	>6
Dose (IU of Factor IX/kg BW) (BW rounded to the nearest whole kilogram)	25	35	50
Maximum dose (IU of Factor IX)	2500	3500	5000

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

Batch numbers:
K619B2816, K631E2812, K650A2815, K706A2811, K826C2816, K908A2817.

Control Product
Beriplex® P/N (Kcentra) (500 IU) was reconstituted with 20 mL Water for Injection. The Beriplex® P/N (Kcentra) dose depended on the BW and INR0 of the patient and was calculated by the responsible treating investigator as follows:

Baseline INR (rounded to the first decimal place)	2 to <4	4-6	>6
Dose (IU of Factor IX/kg BW) (BW rounded to the nearest whole kilogram)	25	35	50
Maximum dose (IU of Factor IX)	2500	3500	5000

Beriplex® P/N (Kcentra) was administered by IV infusion at a rate of 0.12 mL/kg/min (~3 units/kg/min), up to a maximum rate of 8.4 mL/min (~210 units/min).

Batch numbers:
G5260111C, H0960111A, H3860111F, H4160111C, H5960111E, K0260111C, J3660111A, J8360111A, J8360111B, K9660111B, P100033909, P100078154

Clinical Pharmacology Results:
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 groups. After 24 hours it was 1.25 in the BALFAXAR group. The change of INR from baseline was similar between BALFAXAR and Kcentra treatment groups. Please refer to Section 6.2 Table 2 for details.

Source: Applicant. Module 5, section 5.3 Clinical Study Reports.