octapharma

CLINICAL STUDY PROTOCOL

STUDY TITLE

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 Beriplex® P/N (Kcentra), for the reversal of vitamin K antagonist induced anticoagulation in patients needing urgent surgery with significant bleeding risk.

Investigational Product:	OCTAPLEX
Indication:	Reversal of anticoagulation due to vitamin K antagonists in patients needing urgent surgery associated with significant bleeding risk.
Study Design:	Prospective, multi-center, randomized, double-blind, active-control, group-sequential, non-inferiority study.
Sponsor:	Octapharma Pharmazeutika Produktionsges.m.b.H Oberlaaer Strasse 235 A-1100 Vienna, Austria
Study Number:	LEX-209
EudraCT and/or IND Number:	2016-002649-41/BB IND: 13323
Development Phase:	Phase III
Planned Clinical Start:	Quarter 4 2016
Planned Clinical End:	Quarter 2 2021
Date of Protocol:	19 Jan 2018
Version:	04
Coordinating Investigator:	[redacted] UT Southwestern Medical Center, 5323 Harry Hines Blvd Dallas, TX 75390, USA

STUDY OUTLINE

Name of Sponsor/Company: Octapharma Pharmazeutika Produktionsges.m.b.H Oberlaaer Strasse 235 A-1100 Vienna, Austria	
Name of Investigational Product: OCTAPLEX **Name of Comparator:** Beriplex® P/N (Kcentra)	**Protocol Identification Code:** LEX-209
Name of Active Ingredient: Four-factor prothrombin complex concentrate	**Date of Final Protocol:** 19-Jan-2018

Title of Study:
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 Beriplex® P/N (Kcentra), for the reversal of vitamin K antagonist induced anticoagulation in patients needing urgent surgery with significant bleeding risk.

Indication:
Reversal of vitamin K antagonist (VKA) induced anticoagulation in patients needing urgent surgery associated with significant bleeding risk.

Number of Study Centre(s):
Approximately 70 centers will participate in the study worldwide.

Objectives:
Primary
The primary objective of the study is to demonstrate that the efficacy of OCTAPLEX 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
The secondary objective of the study is to investigate the safety and tolerability of OCTAPLEX compared to Beriplex® P/N (Kcentra) in patients under VKA therapy with the need for urgent surgery with significant bleeding risk.

Study Design:
This study is a prospective, multi-center, randomized, double-blind, active-control, group-sequential, non-inferiority study.

Number of Patients:
Enrollment of a total of 370 patients is planned (185 patients per treatment group).

Patient Selection Criteria:
Inclusion Criteria
1. Male or female patients at least 18 years of age.
2. Patients currently on oral anticoagulation treatment with VKA of coumadin or warfarin type.
3. Patients being admitted to the hospital or currently hospitalized where:
   - an urgent surgery carrying significant bleeding risk (≥50 mL expected blood loss in normal coagulation state) is required as part of routine clinical care within 24 hours of the start of investigational medicinal product;
   - VKA withdrawal and use of oral or parenteral vitamin K alone to reverse anticoagulation is deemed too slow or inappropriate for reversal;

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4. Patients with an international normalized ratio (INR) of 2.0 or above at the time of decision to reverse the anticoagulation status.
5. Patients who have given written informed consent and who are able and willing to comply with the procedures described in the study protocol.

Exclusion Criteria

1. Patients with a life expectancy of less than 48 hours per physician's judgment (e.g. patients with a Glasgow Coma Scale equal to 3 or a Head Abbreviated Injury Score of 6, patients requiring continuous inotropic or pressor support, and patients whose status is post cardiac arrest).
2. Patients for whom the planned surgery or procedure is commonly associated with a very low bleeding risk (e.g. catheter placement, gastroscopy).
3. Patients with a history of thromboembolic events (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. (Note: ongoing thrombosis in-situ or severe unilateral peripheral arterial disease (PAD) undergoing surgical intervention is not an exclusion criterion).
4. Patients with a known congenital bleeding disorder.
5. Patients with a known antiphospholipid antibody syndrome.
6. Patients with present or past specific factor inhibitor activity.
7. Patients with thrombocytopenia of <80,000/µL or history of heparin-induced thrombocytopenia.
8. Patients who have received more than 5000 units of systemic unfractionated heparin (UFH), any dose of low-molecular-weight heparin (LMWH) or any dose of non-VKA anticoagulant (i.e. direct oral anticoagulant) within 24 hours prior to enrollment into the study or with potential need to receive these medications in mentioned doses before completion of hemostasis evaluation at the end of surgery.
9. Patients who have received prothrombin complex concentrates (PCCs), fresh frozen plasma or vitamin K within 72 hours prior to enrollment into the study.
10. Patients receiving P2Y12 platelet inhibitors (e.g. Clopidogrel, Prasugrel, Ticagrelor)
11. Patients with a known history of hypersensitivity to plasma-derived products.
12. Patients requiring urgent surgical procedures where according to the surgeon's clinical judgment an accurate estimate of expected blood loss and transfusion requirements is not possible, e.g.:
    a. Surgeries requiring massive transfusion protocols (e.g., major polytrauma, major injuries, organ transplant surgeries),
    b. Patients with acute major bleeding (e.g., gastrointestinal bleeds, obstetric haemorrhage),

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c. Surgeries with unpredictable intraoperative blood loss (e.g., ruptured aneurysm, primary surgery for intracranial hemorrhage (ICH)).

13. Pregnant or nursing women.
14. Patients participating in another interventional clinical study currently or during the past 30 days prior to enrollment into this study.
15. Patients previously enrolled in this study.

Test Product, Dose, Mode of Administration, and Batch Number(s):
OCTAPLEX (500 IU) is to be reconstituted with 20 mL Water for Injection.
The OCTAPLEX dose will depend on the body weight (BW) and baseline INR (INR_0) of the patient and will be calculated by the responsible treating investigator according to the following dosing table. BW should be rounded to the nearest whole kilogram number for IMP dose calculation. Baseline INR value should be rounded to the 1st decimal place.

Baseline INR	2 to <4	4-6	>6
Dose (IU of Factor IX/kg BW)	25	35	50
Maximum dose (IU of Factor IX)	2500	3500	5000

OCTAPLEX will be 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). The total OCTAPLEX volume used and time of infusion will be recorded. Batch numbers for OCTAPLEX will be reported in the final clinical study report.

Reference Therapy, Dose, Mode of Administration, and Batch Number(s):
Beriplex® P/N (Kcentra) (500 IU) is to be reconstituted with 20 mL Water for Injection. The Beriplex® P/N (Kcentra) dose will depend on the BW and INR_0 of the patient and will be calculated by the responsible treating investigator according to the following dosing table. BW should be rounded to the nearest whole kilogram number for IMP dose calculation. Baseline INR value should be rounded to the 1st decimal place.

Baseline INR	2 to <4	4-6	>6
Dose (IU of Factor IX/kg BW)	25	35	50
Maximum dose (IU of Factor IX)	2500	3500	5000

Beriplex® P/N (Kcentra) will be 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). The total Beriplex® P/N (Kcentra) volume used and time of infusion will be recorded. Batch numbers for Beriplex® P/N (Kcentra) will be reported in the final clinical study report.

Duration of Treatment:
Only a single administration of study drug is planned per patient. The dose of study drug will depend on the baseline INR and patient BW, and will conform to the dosing table. Both

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treatments will be administered in a blinded fashion. A concomitant administration of vitamin K is to be administered, unless the patient requires resumption of VKA anticoagulation within 24 hours after surgery. Vitamin K should be administered within 1 hour before or within 1 hour after investigational medicinal product (IMP) infusion at a dose of 2, 5, or 10 mg according to local clinical practice. The preferred route for vitamin K administration is by slow IV infusion. If vitamin K is not administered, the reason must be documented.

Study Outcome Parameters (Efficacy and Safety Endpoints):

Efficacy:

The primary efficacy endpoint is the hemostatic efficacy rating at the end of the surgery.

Efficacy will be rated by the investigator at the end of the surgery in a blinded manner based on a 4-point hemostatic efficacy scale taking into account blood loss and transfusion requirements in the context of the surgery.

The hemostatic efficacy rating will also be assessed by an independent endpoint adjudication board (IEAB) consisting of clinical experts. All adjudications will be conducted in a blinded manner and the IEAB will be provided with all relevant details (e.g., duration of surgery, co-medication, medical history, predicted and actual blood loss, and transfusion information) of the patient and the actual procedure performed[1] covering the time period up to the end of the surgery, as documented in the anesthesia record. To ensure the effectiveness of blinding and avoid potential bias, the INR and prothrombin time values will not be provided to the IEAB. The dichotomized final adjudicated hemostatic efficacy rating from the IEAB will serve as the primary efficacy variable for the statistical analysis. The concordance or discordance of the investigator and the IEAB ratings will also be determined as part of the final analysis; the IEAB will be kept blinded to the investigator's rating.

Secondary efficacy endpoints are:

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

[1] A detailed description of the information to be provided to the IEAB will be developed with the clinical experts and will be included in an IEAB charter.

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Exploratory endpoints are:

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

Safety:

Clinical safety will be assessed using the following endpoints:

- 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 IMP for patients with negative baseline virology test).

Summary of Study Procedures and Statistical Analysis Plan:

Study Procedures:

A maximum of 370 patients will be enrolled (185 patients per treatment group). One group will receive OCTAPLEX and the other group will receive Beriplex® P/N (Kcentra).

Patients will be on oral anticoagulant therapy with VKA and will need to undergo an urgent surgery that bears a significant risk of bleeding (≥50 mL expected blood loss).

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The intent of the physician performing the procedure is to start the surgery within 3 hours after the end of 4F-PCC administration.

At least 40% of all patients enrolled will be scheduled for an urgent surgery with expected blood loss of ≥200 mL. At least 20% of all patients enrolled will be scheduled for an urgent surgery with expected blood loss of ≥100 mL but <200 mL. At most 40% of all patients enrolled will be scheduled for an urgent surgery with expected blood loss ≥50 mL but <100 mL.

After determination of the acceptability for the study, patients have to give their written informed consent and must meet the inclusion criteria of the study. Written informed consent must be obtained from the patient.

The qualifying INR (INR available at the time of decision to reverse the anticoagulation status) should be used for the decision to enroll a patient into the study. Treatment allocation will then be performed by an Interactive Response Technology (IRT) where the patient will be assigned to one of the 2 treatment groups with equal probability (i.e., 1:1). In order to achieve a balance between the 2 treatment groups with respect to the planned type of surgery and history of TEE, the treatment allocation by the IRT will be stratified according to the parameters 'Expected blood loss ("≥200 mL", "≥100 mL but <200 mL" or "≥50 mL but <100 mL")', 'History of TEE ("yes" or "no")' and 'Type of planned surgery ("orthopaedic surgery", "cardiothoracic surgery" or "other surgery"). To ensure that the intended proportions of patients enrolled are kept for subgroups of expected blood loss, the IRT will preclude enrollment into the subgroup once its targeted number of enrolled patients is reached. The same applies to the population considered in the interim analysis.

Details on the patient's medical history (especially occurrence of previous 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 should be recorded. Baseline measurements will be performed for all relevant parameters within 3 hours before administration of study drug.

The dose of study drug to be administered will be calculated by the responsible treating investigator based on the patient's BW and baseline INR according to the recommended dosing table. Based on the calculated dose and the assigned treatment code, the IMP will be prepared in a manner that will blind the investigator to the study treatment.

After baseline measurements, blood samples and the administration of IMP, blood samples will be taken for safety assessments, coagulation tests and for factor level measurements at pre-defined time points. All relevant details of the surgery will be recorded. The time and

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amount of all blood and plasma products given during and after the surgery will be recorded in the Case Report Form, as well as the reason and timing for their administration. An assessment of the hemostatic efficacy of the study treatments based on the provided guidance document (see Section 7.2.1), including the 4-point hemostatic efficacy scale, will be recorded by the investigator after the surgery.

Clinical safety will be assessed by monitoring vital signs, laboratory parameters, and by documenting AEs and vital status.

Statistical Analysis:

The primary efficacy variable is the hemostatic efficacy as assessed by the IEAB. The hemostatic efficacy is to be assessed based on objective criteria in the categories 'excellent', 'good', 'moderate' or 'none'. Ratings of 'excellent' and 'good' will be considered as 'effective' hemostasis, while a rating of 'moderate' and 'none' will be considered as 'ineffective' hemostasis.

The dichotomous 'hemostatic success' variable will be used in the analyses.

To demonstrate that treatment with OCTAPLEX is clinically not inferior to treatment with Beriplex® P/N (Kcentra) with respect to hemostatic success, a two-sample, one-sided test of the pair of hypotheses:

$$H_0: \quad p_K - p_O \geq \delta \text{ (inferiority)}$$
$$\text{vs.} \quad H_1: \quad p_K - p_O < \delta \text{ (non-inferiority)}$$

will be carried out with a type I error probability of $\alpha = 0.025$ and clinical non-inferiority margin of $\delta = 0.15$. Whereby p_O and p_K present the probabilities of hemostatic success of OCTAPLEX and Beriplex® P/N (Kcentra), respectively.

The study employs a sequential design that allows one pre-planned interim analysis using the data from the first 50% of randomized patients. The interim analysis will be performed on the cohort of the first 185 randomized patients after documentation of the primary endpoint has been performed. See Section 9.4 for details.

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

The primary analysis will be performed on the intent-to-treat (ITT) population. Additional analyses will be performed for the modified intent-to-treat (mITT) and per-protocol (PP) population.

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In case of non-inferiority in the ITT, mITT and the PP population a "tipping point" analysis will be done to determine the robustness of the results. Iteratively patients excluded from the mITT analysis assigned to the control arm will be considered as treatment successes, and patients excluded from the mITT analysis and assigned to the OCTAPLEX arm will be considered as treatment failures, to determine the number of such imputed outcomes required to "tip" the study result from positive to negative in the randomized population.
Farrington's and Manning's test for difference in proportions will be used to test the secondary variables on proportions. Point estimates and two-sided 95% CIs will be presented in addition to descriptive statistics for these endpoints.
Analysis of the secondary and further exploratory endpoints will be done on the ITT and mITT, and PP populations unless indicated otherwise. These analyses will be exploratory, by presenting descriptive statistics.
Safety analyses will be performed for the Safety Analysis Set. Analyses will generally be descriptive. For TEEs and mortality, a possible difference between treatment groups will be estimated by a risk ratio with 95% CI and Kaplan-Meier estimates for time to event will be calculated and graphically presented.
The Statistical Analysis Plan details the full analysis to be performed. This analysis plan is available as a separate document.

The study assessments and scheduled time points are summarized in the Flow Chart:

FLOW CHART

Table 1: Overview of Study Assessments and Time Points

		Before Infusion		Infusion	After END of Infusion					OP [1]				POST OPERATIVE [2]			FOLLOW-UP		
		Screening / Randomisation	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			
IMP dose calculation, Randomization		X [4]																	
IMP 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			
	Pregnancy Test	X [8]																	
C. Lab	**Coagulation Factors**		X		X	X	X	X	X										
	Virology tests		X														X [9]		
Vitamin K Administration			X [10]																
IMP 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] ----------																

[1] Time of surgery start is time of anesthesia initiation. Time of surgery end is surgical end time of principal procedure.

[2] Assessments at Days 1, 2, or 4 are done if patient remains hospitalized. Discharge assessments should be done at the day of discharge. If discharge falls on Days 1, 2, or 4, schedule of discharge assessments should be followed.

[3] Baseline information includes collection of demographics, medical history, prior and concomitant medication use, determination of vitamin K administration details (see Section 7.1).

[4] If baseline INR value is not available when patient must be randomized to initiate preparation of IMP, qualifying INR (used for inclusion of the patient) can be used. Baseline INR test can be skipped if qualifying INR is taken within 3 hours before IMP infusion start and was analyzed by local laboratory participating in the study. If initial IMP dose calculation was based on qualifying INR and later Baseline INR was performed it must be checked whether IMP dose requires adjustment due to INR change. If required, IMP dose must be adjusted to Baseline INR and revised INR and IMP dose registered using IRT.

[5] Results of hematology and coagulation factors blood tests performed as part of standard patient care should be documented in eCRF.

[6] Prior OP/Post OP **coagulation** samples can be skipped if one of the After the END of Infusion samples is scheduled within its time window.

[7] Samples will not be done if patient has been discharged earlier. Discharge visit samples should be taken at the day of discharge.

[8] Urine or blood pregnancy test should be done only in women of childbearing potential (WOCBP). See Section 7.3.9 for definition of WOCBP status.

[9] Day 9 Virology tests should only be done in patients who had at least one negative result of Baseline Virology tests (See Section 7.3.7)

[10] Vitamin K can be administered within timeframe ±1h of IMP infusion. For patients with mechanical heart valve, LVAD or any other hypercoagulable/prothrombotic condition administration of vitamin K is not mandatory.

[11] If reconstituted IMP not used within 4 hours following reconstitution it should be discarded and new IMP assigned via IRT.

[12] Transfusions should be collected during hospitalization for the original admission.

[13] Only concomitant medications related to ongoing AE should be recorded.

[14] AEs are to be followed-up until Day 4. Serious adverse events (SAEs) are to be followed-up until Day 45. Note: If TEEs are suspected at any time during the study, appropriate examinations according to local standards should be performed (e.g. Doppler scan using color duplex, X-ray) and the results documented.

PROTOCOL SIGNATURES

Signature of the Sponsor's Representative

This study is intended to be conducted in compliance with the protocol, Good Clinical Practice and the applicable regulatory requirements.

[redacted] [redacted] 19.01.2018

[redacted] Signature Date

on behalf of the Sponsor
Octapharma Pharmazeutika Produktionsges.m.b.H
Oberlaaerstr. 235, A-1100 Vienna, Austria
[redacted]

Signature of the Principal Coordinating Investigator

This study is intended to be conducted in compliance with the protocol, Good Clinical Practice and the applicable regulatory requirements.

[redacted] [redacted] 1.19.2018

Coordinating Investigator Signature Date

[redacted]
University of Texas – Southwestern Medical Center
5323 Harry Hines Blvd, Dallas, TX 75390, United States
[redacted]

Signature of the Author of the Protocol / Clinical Project Manager

This study is intended to be conducted in compliance with the protocol, Good Clinical Practice and the applicable regulatory requirements.

[redacted] [redacted] 19-JAN -2018

[redacted] Signature Date

Octapharma Pharmazeutika Produktionsges.m.b.H
Oberlaaerstr. 235, A-1100 Vienna, Austria
[redacted]

Signature of the Biostatistician

This study is intended to be conducted in compliance with the protocol, Good Clinical Practice and the applicable regulatory requirements.

[redacted] [redacted] 19-JAN -2018

[redacted] Signature Date

Octapharma Pharmazeutika Produktionsges.m.b.H
Oberlaaerstr. 235, A-1100 Vienna, Austria
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LIST OF ABBREVIATIONS

Abbreviation	Description
:C	Concentration
4F-PCC	Four-Factor Prothrombin Complex Concentrate
ADR	Adverse Drug Reaction
AE	Adverse Event
ASA	American Society of Anesthesiologists
aPTT	Activated Partial Thromboplastin Time
BUN	Blood Urea Nitrogen
BW	Body Weight
CI	Confidence Interval
CRF/eCRF	Case Report Form/electronic Case Report Form
DVT	Deep Vein Thrombosis
EDC	Electronic Data Capture
FII	Coagulation factor II
FVII	Coagulation factor VII
FIX	Coagulation factor IX
FX	Coagulation factor X
FAS	Full Analysis Set
FDA	Food and Drug Administration
FFP	Fresh Frozen Plasma
GCP	Good Clinical Practice
Hct	Hematocrit
Hgb	Hemoglobin
HIT	Heparin-induced Thrombocytopenia
IB	Investigator's Brochure
ICH	Intracranial Hemorrhage
IDMC	Independent Data Monitoring Committee
IEAB	Independent Endpoint Adjudication Board
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IND	Investigational New Drug
INR	International Normalized Ratio
INR_0	Baseline International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology

ITT	Intention-To-Treat
IU	International Units
IV	Intravenous
LDH	Lactic Acid Dehydrogenase
LMWH	Low-Molecular-Weight Heparin
LVAD	Left Ventricular Assist Device
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified Intent-To-Treat
OP	Operation
PAD	Peripheral Arterial Disease
PC	Protein C
PCC	Prothrombin Complex Concentrate
PE	Pulmonary Embolism
PK	Pharmacokinetic
PP	Per Protocol
PS	Protein S
PT	Prothrombin time
RAND	Randomized population
RBC	Red Blood Cells
SAE	Serious Adverse Event
SAF	Safety Analysis Population
SAP	Statistical Analysis Plan
SDV	Source Data Verification
SOP	Standard Operating Procedure
SMQ	Standardized MedDRA query
TEAE	Treatment Emergent Adverse Event
TEE	Thromboembolic Events
UFH	Unfractionated Heparin
US	United States
TIA	Transient Ischemic Attack
VKA	Vitamin K Antagonist
WBC	White Blood Cell (count)
WOCBP	Women Of Childbearing Potential

GLOSSARY OF TERMS AND TRADEMARKS

Beriplex® P/N (Kcentra)	CSL Behring

1 INTRODUCTION

1.1 Background

Freeze-dried human prothrombin complex concentrate (PCC) 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). It is prepared from human plasma by fractionation.

PCC can be used for the substitutive therapy of patients with either inherited or acquired single or multiple deficiency in coagulation factors II, VII, IX, or X. Acquired deficiency of coagulation factors is seen in conjunction with a prophylactic, oral anticoagulant therapy using the coumadin or warfarin type drugs to prevent thrombosis/embolism in patients at high risk (e.g. previous venous or arterial thrombosis, heart valvular lesions or atrial fibrillation).

Patients treated with oral anticoagulants who need to undergo surgical interventions represent a special risk population. If anticoagulant therapy is not interrupted before the surgical intervention, the risk of bleeding is high. The desirable therapeutic range of the international normalized ratio (INR) for patients needing anticoagulation, appears to be 2-3 for most clinical situations except perhaps for prosthetic heart valves, which appear to benefit from a slightly higher target range of 2.5-3.5. Nevertheless, the incidence of adverse bleeding on warfarin rises 4 fold with INRs over 4.5 (1) and each 0.5 increase in the INR increases the risk of intracranial bleeding by 1.43 (2). Almost half of all warfarin-related bleeds occur with INRs less than 4 (3). In a recent study, mortality from all causes of death was strongly related to the INR level. Minimum risk of death was attained at 2.2 INR for all patients and 2.3 INR for patients with mechanical heart valve prostheses. A high INR was associated with an excess mortality: with an increase of 1 unit of INR above 2.5, the risk of death from cerebral bleeding (149 deaths) and from any cause was about doubled (4).

Special attention should be paid to emergency patients who are treated with anticoagulants. These patients need additional interventions for a rapid reversal of oral anticoagulant therapy to avoid major bleeding.

Three approaches have been recommended in cases where bleeding occurring peri-operatively needs to be treated. One strategy involves injection of vitamin K. However, vitamin K injection attains full effect after 12 to 24 hours, which might be too long for effective substitution. A second approach involves the administration of fresh frozen plasma (FFP). A third approach involves the use of PCC. In the latter two cases, between 20-50 International Units (IU) of each factor/kg body weight (BW) should be administered but this is dependent on the initial INR of the patient. It has been shown that individualized dosing dependent on the INR of the patient is a more effective way of dosing PCCs (5). FFP attains full effect shortly after the appropriate volume of infusion has been completed; however, the thawing of FFP could add a significant time delay, especially in emergency situations. Another major disadvantage with plasma is the large volume required to reduce a high INR to below 2.0, with the consequence that patients treated with this alternative may have a residual anticoagulant effect and the hemorrhage may progress (6).

PCC administration is an effective treatment modality for the correction of warfarin anticoagulation in the urgent setting (5, 7, 8). Advantages over FFP include more timely correction, absence of volume overload and potentially more complete correction (9). The use of PCC provides a simple and convenient tool for a quick and predictive correction of the depleted coagulation factors.

These products contain all factors needed for quick reversal of VKA anticoagulant related bleeding in predefined activities. It is, therefore, possible to attain a full effect with an optimal reduced time to the correction of the coagulation deficit.

OCTAPLEX is a four-factor prothrombin complex concentrate (4F-PCC) being developed by Octapharma. In the current study, the control will consist of Beriplex® P/N (Kcentra), a 4F-PCC developed and marketed by CSL Behring.

1.1.1 OCTAPLEX

1.1.1.1 Efficacy of OCTAPLEX

Octapharma has carried out 6 clinical trials with OCTAPLEX in patients.

Study LEX-201 included patients with single or multiple congenital deficiencies in coagulation factors II, VII, IX and X. The results of the clinical study have shown that OCTAPLEX is an efficient preparation for the chronic substitutive treatment of patients with congenital deficiencies of these coagulation factors. With respect to safety, OCTAPLEX was well tolerated. No viral seroconversion was observed. The very sensitive markers of thrombogenicity, which were tested, did not indicate any thrombogenicity of the product. No inhibitor development was observed, and recovery and terminal half-life measured in 10 patients after 6 months of treatment did not suggest immunogenicity of the product.

Study LEX-202 included patients either undergoing major surgery or having major bleeding during treatment with anticoagulants of coumadin or warfarin type. The results indicate that OCTAPLEX, given as single dose, is a valuable, new alternative to achieve a profound rise in prothrombin time (PT) associated with a profound decrease of the INR and having a good overall clinical efficacy. In this study, two patients seroconverted for Parvovirus B19, however, without any clinical symptoms. Otherwise no safety concerns have been raised during the clinical testing.

Study LEX-203 concluded that the clinical efficacy of OCTAPLEX administered in appropriate doses could be demonstrated conclusively: 51 of the 56 patients in the per protocol population (91.1%) showed an efficacy response, i.e., reached the efficacy endpoint of a post infusion PT value equal to or larger than the desired and corrected PT value pre-defined by the investigator. In all responders these post infusion PT values could be measured within 10 minutes after administration of the calculated dosage. Even in five remaining patients the clinical response was adequate. The individual coagulation factor levels showed a sufficient rise from baseline into the therapeutic range. All patients showed an excellent clinical response, in particular, no complications caused by uncontrollable bleeding were observed after OCTAPLEX treatment. The clinical tolerability of the product was excellent. In this study OCTAPLEX appears to be an efficacious treatment for the prophylaxis and treatment of bleeding in acquired deficiency of the prothrombin complex coagulation factors.

Study LEX-204 was an observational study in patients with prothrombin complex factor deficiency in Germany and Study LEX-206 was conducted in in patients with intracranial hemorrhage related to oral anticoagulant therapy in France. Results for these studies are summarized in the Investigator's Brochure (IB).

Study LEX-205 was a randomized, open-label, efficacy and safety study of OCTAPLEX and fresh frozen plasma (FFP) in patients under vitamin K antagonist (VKA) therapy with the need for urgent surgery or invasive procedures. Correction of INR to a value below 1.5 within

15 minutes of the end of study infusion was achieved for 76% of the OCTAPLEX-treated patients and 30% of the FFP-treated patients.

This new clinical study (LEX-209) will be conducted to facilitate marketing authorization in the US; the rationale for conducting this study is provided in Section 1.2.

1.1.1.2 Safety of OCTAPLEX

OCTAPLEX has received marketing authorization in 76 countries worldwide. Between March 2003 andSeptember 2017, more than [redacted] of OCTAPLEX have been sold. Assuming a mean single dose of about 30 IU/kg BW and a mean patient weight of 70 kg, this figure represents about [redacted] of OCTAPLEX.

OCTAPLEX is not to be administered to patients with:

- Hypersensitivity to the active substance or to any of the excipients.
- Known allergy to heparin or history of heparin induced thrombocytopenia.

Patients receiving a VKA may have an underlying hyper-coagulation state and infusion of PCC may exacerbate this.

If allergic or anaphylactic-type reactions occur, the infusion should be stopped immediately. In case of shock, standard medical treatment for shock should be implemented.

There is a risk of thrombosis or disseminated intravascular coagulation when patients, with either congenital or acquired deficiency are treated with human prothrombin complex, particularly with repeated dosing. Patients given human prothrombin complex should be observed closely for signs or symptoms of intravascular coagulation or thrombosis. Because of the risk of thromboembolic complications, close monitoring should be exercised when administering human prothrombin complex to patients with a history of coronary heart disease, to patients with liver disease, to peri- or postoperative patients, to neonates, or to patients at risk of thromboembolic events (TEE) or disseminated intravascular coagulation. In each of these situations, the potential benefit of treatment should be weighed against the risk of these complications.

The known risks of treatment with OCTAPLEX are consistent with the inclusion and exclusion criteria in this study, which minimize the risk to patients enrolled in this study.

1.1.2 Beriplex® P/N (Kcentra)

Beriplex® P/N (Kcentra) (CSL Behring), Prothrombin Complex Concentrate (Human), is a blood coagulation factor replacement product indicated for the urgent reversal of acquired coagulation factor deficiency induced by VKA (e.g., warfarin) therapy in adult patients with:

- acute major bleeding (approved April 2013 in the US) or
- need for an urgent surgery/invasive procedure (approved April 2013 in the United States [US]).

Full details on Beriplex® P/N (Kcentra) are available in the respective US Prescribing Information and local labeling.

1.1.2.1 Efficacy of Beriplex® P/N (Kcentra)

Of particular relevance to the current OCTAPLEX study, the efficacy of Beriplex® P/N (Kcentra) was evaluated in a prospective, open-label, active-controlled, non-inferiority,

multicenter randomized controlled trial in subjects who had been treated with VKA therapy and who required urgent replacement of their Vitamin K-dependent clotting factors because of their need for an urgent surgery/invasive procedure.

A total of 181 subjects with acquired coagulation factor deficiency due to oral VKA therapy were randomized to a single dose of Beriplex® P/N (Kcentra) or plasma. One hundred seventy-six (176) subjects received Beriplex® P/N (Kcentra) or plasma because of their need for an urgent surgery/invasive procedure in the setting of a baseline INR ≥2.0 and recent use of a VKA anticoagulant. The doses of Beriplex® P/N (Kcentra) (25 IU/kg, 35 IU/kg, or 50 IU/kg) based on nominal Factor IX content and plasma (10 mL/kg, 12 mL/kg, or 15 mL/kg) were calculated according to the subject's baseline INR (2–< 4, 4–6, >6, respectively). The observation period lasted for 90 days after the infusion of Beriplex® P/N (Kcentra) or plasma. The modified efficacy (ITT-E) population for Beriplex® P/N (Kcentra) included 87 subjects and for plasma included 81 subjects. Additionally, oral or intravenous (IV) Vitamin K was administered.

The efficacy endpoint was hemostatic efficacy for the time period from the start of infusion of Beriplex® P/N (Kcentra) or plasma until the end of the urgent surgery/invasive procedure. Criteria for effective hemostasis were based upon the difference between predicted and actual blood losses, subjective hemostasis rating, and the need for additional blood products containing coagulation factors. The proportion of subjects with effective hemostasis was 89.7% in the Beriplex® P/N (Kcentra) group and 75.3% in the plasma group. The lower limit of the 95% confidence interval (CI) for the difference in proportions of Beriplex® P/N (Kcentra) minus plasma was 2.8%, which exceeded -10% and thereby demonstrated the non-inferiority of Beriplex® P/N (Kcentra) versus plasma (the study's primary objective). Because the lower limit of the CI was greater than 0, the prospectively defined criterion for superiority of Beriplex® P/N (Kcentra) for hemostatic efficacy (a secondary objective) was also met.

An additional endpoint was the reduction of INR to ≤1.3 at 30 minutes after the end of infusion of Beriplex® P/N (Kcentra) or plasma for all subjects that received study product. The proportion of subjects with this decrease in INR was 55.2% in the Beriplex® P/N (Kcentra) group and 9.9% in the plasma group. The 95% CI for the difference in proportions of Beriplex® P/N (Kcentra) minus plasma was 31.9% to 56.4%. The lower limit of the 95% CI of 31.9% demonstrated superiority of Beriplex® P/N (Kcentra) versus plasma for this endpoint. The relationship between a decrease in INR to less than or equal to 1.3 and clinical hemostatic efficacy was not established.

A summary of this study, including key safety findings, is provided in the Beriplex® P/N (Kcentra) US Prescribing Information and local labeling, and the results have also been published (10).

1.1.2.2 Safety of Beriplex® P/N (Kcentra)

The following "black box warning" is included in the Kcentra US Prescribing Information:

WARNING: ARTERIAL AND VENOUS THROMBOEMBOLIC COMPLICATIONS

> Patients being treated with VKA therapy have underlying disease states that predispose them to thromboembolic events. Potential benefits of reversing VKA should be weighed against the potential risks of thromboembolic events, especially in patients with the history of a thromboembolic event. Resumption of anticoagulation should be carefully considered as soon as the risk of TEE outweighs the risk of acute bleeding.

- Both fatal and non-fatal arterial and venous thromboembolic complications have been reported with Kcentra in clinical trials and post marketing surveillance. Monitor patients receiving Kcentra for signs and symptoms of thromboembolic events.
- Kcentra was not studied in subjects who had a thromboembolic event, myocardial infarction, disseminated intravascular coagulation, cerebral vascular accident, transient ischemic attack (TIA), unstable angina pectoris, or severe peripheral vascular disease within the prior 3 months. Kcentra may not be suitable in patients with TEE in the prior 3 months.

Kcentra is contraindicated in patients with:

- Known anaphylactic or severe systemic reactions to Kcentra or any components in Kcentra including heparin, Factors II, VII, IX, X, Proteins C and S, Antithrombin III and human albumin.
- Disseminated intravascular coagulation.
- Known heparin-induced thrombocytopenia (HIT). Kcentra contains heparin.

These warnings and contraindications are consistent with the exclusion criteria in this study, which exclude such patients from enrollment in this study.

Warnings and Precautions for Kcentra:

- Hypersensitivity reactions may occur. If necessary, discontinue administration and institute appropriate treatment.
- Arterial and venous thromboembolic complications have been reported in patients receiving Kcentra. Monitor patients receiving Kcentra for signs and symptoms of thromboembolic events. Kcentra was not studied in subjects who had a thrombotic or TEE within the prior 3 months. Kcentra may not be suitable in patients with TEE in the prior 3 months.
- Kcentra is made from human blood and may carry a risk of transmitting infectious agents, e.g., viruses, the variant Creutzfeldt-Jakob disease agent, and theoretically, the Creutzfeldt-Jakob disease agent.

Adverse Reactions with Kcentra

- The most common adverse reactions (frequency ≥2.8%) observed in subjects receiving Kcentra were headache, nausea/vomiting, hypotension, and anemia.
- The most serious adverse reactions were TEE including stroke, pulmonary embolism, and deep vein thrombosis.

1.2 Rationale for Conducting the Study

To evaluate the efficacy and safety of OCTAPLEX, the Food and Drug Administration (FDA) proposed a prospective, parallel, randomized, controlled trial in patients needing urgent surgery and judged to carry significant risk of intraoperative/procedural hemorrhage. FDA advised that the control group should receive a product licensed for this indication. The trial should achieve greater statistical power than LEX-205.

This adequately powered study is intended to meet these requests by demonstrating that the efficacy of OCTAPLEX is not clinically inferior to that of Beriplex® P/N (Kcentra). The efficacy and safety results will be compared with those of Beriplex® P/N (Kcentra), the only

currently FDA-approved PCC therapy indicated for the urgent reversal of acquired coagulation factor deficiency induced by VKA.

This study will be conducted in compliance with the protocol, International Council on Harmonisation-Good Clinical Practice (ICH-GCP), and other regulatory requirements.

1.3 Dose Rationale

The dosage recommended in the current US Prescribing Information of Beriplex® P/N (Kcentra) will be used for both OCTAPLEX and Beriplex® P/N (Kcentra) in this study. This dose allows blinding for both groups as the same amount of product would be injected.

The dose of investigational medicinal product (IMP) will depend on the BW and baseline INR (INR_0) of the patient and will be calculated by the responsible treating investigator according to the following dosing table. BW should be rounded to the nearest whole kilogram number for IMP dose calculation. Baseline INR value should be rounded to the 1st decimal place.

Baseline INR	2 to <4	4-6	>6
Dose (IU of Factor IX/kg BW)	25	35	50
Maximum dose (IU of Factor IX)	2500	3500	5000

IMP will be 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). The total volume of IMP used and time of infusion will be recorded. Batch numbers will be reported in the final clinical study report.

1.4 Benefit-Risk Statement

To date, 6 clinical trials with OCTAPLEX have been performed resulting in marketing authorization in Europe and other non-US countries. The tolerability and efficacy of the product was good. The active control in this study, Beriplex® P/N (Kcentra), is approved in the US for the indication under investigation. Demonstration of the efficacy of OCTAPLEX in the targeted indication would add another independent 4F-PCC treatment option, which is of particular importance for such medicinal products that are prepared from human blood or plasma.

Currently available efficacy data indicate that treatment with OCTAPLEX should be non-inferior to Beriplex® P/N (Kcentra) in the targeted indication. To minimize the risk of treating patients with a non-efficacious treatment, the study will be conducted in 2 stages, with one un-blinded interim analysis after enrollment of 50% of the planned sample size, allowing for an early stopping of the study for demonstrated non-inferiority of OCTAPLEX or futility to achieve this. Any decision to prematurely terminate the study will be made in consultation with the relevant regulatory authorities.

For both 4F-PCC preparations, the following adverse reactions may occur:

1. Allergic or anaphylactic reactions in rare cases. Symptoms of an increased sensitivity can vary from fever, chills, nausea, urticaria, chest tightness, shortness of breath, and hypotension up to anaphylactic shock.
2. There is a risk of thrombosis or disseminated intravascular coagulation when patients are treated with PCC. Close monitoring should be exercised when administering OCTAPLEXPCC to patients with a history of coronary heart disease, to patients with liver disease, or to patients at risk of TEE or disseminated intravascular coagulation.

3. Very rarely, a sudden, allergy induced reduction of the blood platelet count below 100,000/µL or 50% of the starting count may be observed (HIT; thrombocytopenia type II). In patients not previously hypersensitive to heparin, this decrease in platelets may occur 6 to 14 days after the start of treatment. In patients with previous heparin hypersensitivity this reduction may happen within a few hours. This severe form of blood platelet reduction may be accompanied by, or result in, arterial thrombosis, thromboembolism, severe clotting disorder (consumptive coagulopathy), skin necrosis at injection site, petechia, purpura or melaena. Also, a reduction of the anticoagulant effect of heparin may occur (heparin-tolerance). Patients with the specified allergic reactions must immediately stop administration with the IMP and should not use medication containing heparin in the future.
4. Development of antibodies to one or more of the prothrombin complex factors.
5. As for all medicinal products prepared from human blood or plasma, infectious diseases due to transmission of infective agents cannot be totally excluded. This applies also to pathogens of hitherto unknown origin. However, in the current manufacturing process for both OCTAPLEX and Beriplex® P/N (Kcentra), various steps are included that contribute towards the reduction/inactivation of viruses.

The inclusion and exclusion criteria in this study have been selected to minimize the risk to patients enrolled in this study. Safety will be continuously monitored throughout the study as it accrues, including monitoring of unblinded safety data by an Independent Data Monitoring Committee (IDMC).

In conclusion, the benefit/risk analysis for this study is acceptable for the patient population to be enrolled.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of the study is to demonstrate that the efficacy of OCTAPLEX 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).

2.2 Secondary Objective

The secondary objective of the study is to investigate the safety and tolerability of OCTAPLEX compared to Beriplex® P/N (Kcentra) in patients under VKA therapy with the need for urgent surgery with significant bleeding risk.

3 INVESTIGATIONAL PLAN

3.1 Primary and Secondary Endpoints

3.1.1 Primary Endpoint

The primary efficacy endpoint is the hemostatic efficacy rating at the end of the surgery.

Efficacy will be rated by the investigator at the end of the surgery in a blinded manner based on a 4-point hemostatic efficacy scale taking into account blood loss and transfusion requirements in the context of the surgery.

The hemostatic efficacy rating will also be assessed by an independent endpoint adjudication board (IEAB) consisting of clinical experts. See Section 7.2.1 for details. All adjudications will be conducted in a blinded manner and the IEAB will be provided with all relevant details (e.g., duration of surgery, co-medication, medical history, predicted and actual blood loss, and transfusion information) of the patient and the actual procedure performed[1] covering the time period up to the end of the surgery, as documented in the anesthesia record. To ensure the effectiveness of blinding and avoid potential bias, the INR and PT values will not be provided to the IEAB. The dichotomized final adjudicated hemostatic efficacy rating from the IEAB will serve as the primary efficacy variable for the statistical analysis. The concordance or discordance of the investigator and the IEAB ratings will also be determined as part of the final analysis; the IEAB will be kept blinded to the investigator's rating.

3.1.2 Secondary Endpoints

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

3.1.3 Further Exploratory Endpoints

- Change in INR from baseline.
- Change in Protein C (PC), and Protein S (PS) from baseline to 30 (± 15 min) after the end of infusion.
- Change in coagulation factor levels (FII, FVII, FIX, FX, PCC, and PS) from baseline to 2 h, 4 h, 12 h, and 24 h after end of infusion.
- Assessment of blood loss after end of surgery.
- Proportion of patients receiving plasma and platelets transfusions initiated during the surgery.

[1] A detailed description of the information to be provided to the IEAB will be developed with the clinical experts and be included in an IEAB charter.

- Total volume of RBC and other blood product transfusions initiated during the surgery normalized by patient's BW.
- Change in hematological parameters (hemoglobin (Hgb), hematocrit (Hct), RBC, white blood cell (WBC), platelets) from the beginning to the end of the surgery.
- RBC transfusion corrected change from baseline in Hgb at 12 and 24 hours after start of surgery.
- Proportion of patients experiencing surgical wound hematoma requiring surgical evacuation.
- Ratio of actual estimated blood loss as documented after surgery to the pre-operative predicted blood loss for the type of planned surgery.

3.1.4 Clinical safety

- Occurrence of 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 IMP).

3.2 Overall Study Design and Plan

This study is a prospective, multi-center, randomized, double-blind, active-control, group-sequential, non-inferiority Phase III study. The study is planned to start in Q4 2016 and be completed by Q2 2021, and will be performed at sites in the US and Europe.

A maximum of 370 patients (male and female patients at least 18 years of age) will be enrolled (185 patients per treatment group). One group will receive OCTAPLEX and the other group will receive Beriplex® P/N (Kcentra). Patients will be on oral anticoagulant therapy with VKAs and will need to undergo an urgent surgery that bears a significant risk of bleeding (≥50 mL expected blood loss). The intent of the physician performing the procedure is to start the surgery within 3 hours after the end of 4F-PCC administration.

At least 40% of all patients enrolled will be scheduled for an urgent surgery with expected blood loss of ≥200 mL. At least 20% of all patients enrolled will be scheduled for an urgent surgery with expected blood loss of ≥100 mL but <200 mL. At most 40% of all patients enrolled will be scheduled for an urgent surgery with expected blood loss ≥50 mL but <100 mL.

After determination of the acceptability for the study, patients have to give their written informed consent (see Section 10.3) and must meet the inclusion criteria of the study. Written informed consent must be obtained from the patient. The INR value available at the time of decision to reverse the anticoagulation status (qualifying INR) should be used for the decision to enroll a patient into the study. Treatment allocation will then be performed by an Interactive Response Technology (IRT), where the patient will be assigned to one of the 2 treatment groups with equal probability (i.e., 1:1). In order to achieve a balance between the 2 treatment groups with respect to the planned type of surgery and history of TEE, the treatment allocation by the IRT will be stratified according to the parameters 'Expected blood loss ("≥200 mL", "≥100 mL but <200 mL" or "≥50 mL but <100 mL")', 'History of TEE ("yes" or "no")' and 'Type of planned surgery ("orthopaedic surgery", "cardiothoracic surgery" or "other surgery"). To ensure that the intended proportions of patients enrolled are kept for subgroups of expected blood loss, the IRT will preclude enrollment into the subgroup once its targeted number of

enrolled patients is reached. The same applies to the population considered in the interim analysis.

Details on the patient's medical history (especially occurrence of previous TEEs), the current clinical status, the expected amount of blood loss (mL) due to the surgery (average and maximum blood loss and expected average and maximum transfusion requirements for non-anticoagulated patients undergoing the same type of surgical procedure), the reason for, duration and time of last administration of anticoagulant therapy and details about concomitant medication should be recorded. Baseline measurements will be performed for all relevant parameters within 3 hours before administration of study drug.

The dose of study drug to be administered will be calculated by the responsible treating investigator based on the patient's BW and baseline INR according to the recommended dosing table. Based on the calculated dose and the assigned treatment code, the IMP will be prepared and infused in a manner that will blind the investigator to the study treatment.

A concomitant administration of vitamin K is to be administered, unless the patient requires resumption of VKA anticoagulation within 24 hours after surgery. Patients not requiring concomitant vitamin K administration are those with:

- Presence of a mechanical heart valve
- Presence of a Left Ventricular Assist Device (LVAD)
- Presence of a hypercoagulable/prothrombotic condition identified by the treating physician and documented with audit trail prior to surgery as an indication for the resumption of VKA treatment within 24 hours.

Vitamin K should be administered within 1 hour before IMP infusion or within 1 hour after IMP infusion, at a dose of 2, 5, or 10 mg according to local clinical practice. The preferred route for vitamin K administration is by slow IV infusion. If vitamin K is not administered, the reason must be documented.

After baseline measurements, blood samples and the administration of IMP, blood samples will be taken for safety assessments, coagulation tests and for factor level measurements at pre-defined time points. All relevant details of the surgery will be recorded. The time, reason, and amount of all blood and plasma products given during the hospital stay for the primary procedure will be recorded. An assessment of the hemostatic efficacy of the study treatments based on the provided guidance (see Section 7.2.1), including the 4-point hemostatic efficacy scale, will be recorded by the investigator after the surgery.

Clinical safety will be assessed by monitoring vital signs, laboratory parameters, and by documenting AEs.

An IDMC will continually monitor safety during the study (see Section 8.6).

An IEAB will be established to determine the primary efficacy outcome for the study (see Section 3.3.11).

One un-blinded interim analysis will be conducted after enrollment of 50% of the planned sample size. The critical values of the chosen group sequential method (11) will protect the overall type I error but allow an early stopping of the study for demonstrated non-inferiority of OCTAPLEX or futility to achieve this.

3.3 Discussion of Study Design and Choice of Control Group

3.3.1 Study Design

Octapharma designed the study to use a randomized double-blind non-inferiority design comparing OCTAPLEX with Beriplex® P/N (Kcentra). A further consideration was to have a study design and patient population that would allow comparison with the Beriplex® P/N (Kcentra) confirmatory trial, which demonstrated that Beriplex® P/N (Kcentra) is non-inferior and superior to plasma for rapid INR reversal and effective hemostasis (10); this is the only published confirmatory trial comparing 4F-PCC with plasma (the standard agent for rapid reversal of VKA-induced anticoagulation). There are no published confirmatory trials comparing 4F-PCC with placebo.

3.3.2 Control Group

The FDA advised that the control group in this study should receive a product licensed for this indication in the US. Beriplex® P/N (Kcentra) is the only currently FDA-approved 4F-PCC therapy indicated for the urgent reversal of acquired coagulation factor deficiency induced by VKA and is therefore used as the control in this study.

3.3.3 Patient Population

Patients requiring rapid reversal of VKA-induced anticoagulation needing urgent surgery associated with significant bleeding risk are to be enrolled in this study. At least 40% of all patients enrolled will be scheduled for an urgent surgery with expected blood loss of ≥200 mL. At least 20% of all patients enrolled will be scheduled for an urgent surgery with expected blood loss of ≥100 mL but <200 mL. At most 40% of all patients enrolled will be scheduled for an urgent surgery with expected blood loss ≥50 mL but <100 mL. This patient population should also be comparable to that described for the Beriplex® P/N (Kcentra) confirmatory study (10).

In the selected clinical setting, patients may require resumption of VKA anticoagulation within 24 hours after surgery. To facilitate inclusion of such patients into this study, criteria to waive concomitant vitamin K administration were included in the study, with the stipulation that the reason(s) must be documented in the Case Report Form (CRF).

3.3.4 Primary Endpoint

The chosen hemostatic efficacy endpoint with blinded, perioperative hemostatic efficacy rating by an independent adjudication board captures all clinical aspects of the restoration of hemostasis. See Section 7.2.1 for details.

3.3.5 Rationale for Choice of Non-Inferiority Margin

In the publication of Goldstein et al. (10), an absolute difference in hemostatic efficacy of 15% of the planned control drug (Beriplex® P/N [Kcentra]) over FFP was reported (90% versus 75%). Therefore, demonstrating non-inferiority to Beriplex® P/N (Kcentra) based on a 15% non-inferiority margin would necessarily imply a hemostatic efficacy that is not less than that of FFP, which is another FDA approved agent for this indication. The positive demonstration of non-inferiority to the control drug (Beriplex® P/N [Kcentra]) will, of course, require that the point estimate for the difference in success rates between Beriplex® P/N (Kcentra) and OCTAPLEX be substantially below the non-inferiority margin. When assuming a success rate for Beriplex® P/N (Kcentra) comparable to the one cited in the publication of Goldstein et al.

(10), the point estimate for the success rate with OCTAPLEX will be substantially higher than the point estimate for FFP. Finally, the current clinical use of both the control drug (Beriplex® P/N [Kcentra]) and FFP for the reversal of VKA anticoagulation in the US, given the observed 15% higher efficacy with Beriplex® P/N (Kcentra), demonstrates that a 15% difference in clinical success rates lies within a range that is clinically similar.

3.3.6 Study Procedures

The study procedures were selected based on standards for the clinical setting, the procedures used in the OCTAPLEX LEX-205 study and Beriplex® P/N (Kcentra) confirmatory study (10), and to provide the data required to allow assessment of the selected efficacy and safety endpoints.

A follow-up sample will be taken for Parvovirus B19 PCR and anti-Parvovirus B19 IgM Ab assessments at 9 days (-2/+5 days) following administration of IMP for patients seronegative at baseline. This time point was chosen as it has been shown that at this time post-infection, significant concentrations of both virus and IgM antibodies directed against the virus can be detected in blood. Patients seropositive at baseline do not need to have repeat Parvovirus B19 serology performed.

3.3.7 Dose Justification

The dose justification is provided in Section 5.4.

The maximum infusion rate (8.4 mL per minute) is consistent with that recommended in the Kcentra US Prescribing Information.

3.3.8 Sample Size Justification

See Section 9.1.

3.3.9 Use of an Interim Analysis

One un-blinded interim analysis will be conducted after enrollment of 50% of the planned sample size, to allow for an early stopping of the study for demonstrated non-inferiority of OCTAPLEX or for an early stopping for futility. Any decision to prematurely terminate the study will be made in consultation with the relevant regulatory authorities. The interim analysis is detailed in Section 9.4.

3.3.10 Stratification of Randomization

Patients receiving a VKA generally have an underlying higher risk of TEEs, the reason for administration of the antagonist. Withdrawal of the antagonist and restoration of coagulation via administration of PCC can therefore raise the risk of TEEs, with the risk being more pronounced in those patients who have experienced TEEs in the past. To balance this factor that may impact on safety comparisons between the treatment groups, randomization will be stratified by 'History of TEE (yes/no)'.

As the type of surgery and expected blood loss volume may impact on efficacy comparisons 'Expected blood loss ("≥200 mL", "≥100 mL but <200 mL" or "≥50 mL but <100 mL")' and 'Type of planned surgery ("orthopaedic surgery", "cardiothoracic surgery" or "other surgery")' will be a further stratification factors.

3.3.11 Independent Committees

The primary efficacy endpoint will be the assessment of clinical hemostasis as assessed by the blinded IEAB. In order to adjudicate the primary efficacy endpoint, the IEAB will receive the pre-operative documented expected average and maximum blood loss (both recorded irreversibly prior to randomization), the estimated actual blood loss, and all information on any transfusions and administration of "rescue" clotting factor-containing products. Additionally the IEAB will be provided with all available Hgb and Hct values and information on volume of hemorrhagic would drainage. INR and PT values will not be provided to help ensure the effectiveness of blinding and avoid potential bias. IEAB will be blinded to Investigator's clinical hemostasis rating. A detailed description of the information to be provided to the IEAB will be developed with the clinical experts and will be included in an IEAB charter.

An IDMC will be established by the Sponsor and will routinely monitor safety in the study. The IDMC will also advise on the further conduct/stopping of the study once the interim analysis has been performed. Details are provided in Section 8.6 and Section 9.4.

4 STUDY POPULATION

4.1 Population Base

Patients under VKA therapy who need urgent surgery associated with significant bleeding risk will be eligible for study inclusion.

The studied patient population is appropriate since these patients have an acquired prothrombin complex factor deficiency caused by anticoagulant therapy. This puts them at risk of excessive bleeding either spontaneously, due to trauma, or during surgery. The population to be studied would be most vulnerable since they would not have time to have their anticoagulation therapy reversed by administration of vitamin K in order to prevent the possibility of excessive bleeding during surgery. Patients needing urgent surgery can be defined as those that cannot be postponed until reversal of anticoagulation can be safely performed by vitamin K administration.

Sites will identify patients for enrollment in this active-controlled prospective study. Independent Ethics Committee (IEC) / Institutional Review Board (IRB) approval will be obtained at all participating sites before start of enrollment.

4.1.1 Inclusion Criteria

Patients who meet all of the following criteria are eligible for the study:

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

4.1.2 Exclusion Criteria

Patients who do meet any of the following criteria are not eligible for the study:

1. Patients with a life expectancy of less than 48 hours per physician's judgment (e.g., patients with a Glasgow Coma Scale equal to 3 or a head Abbreviated Injury Score of 6, patients requiring continuous inotropic or pressor support, and patients whose status is post cardiac arrest).
2. Patients for whom the planned surgery or procedure is commonly associated with a very low bleeding risk (e.g., catheter placement, gastroscopy).
3. Patients with a history of TEEs, myocardial infarction (MI), unstable angina pectoris, critical aortic stenosis, cerebrovascular accident, TIA, severe peripheral vascular disease (e.g. Fontaine IV) or disseminated intravascular coagulation within 3 months of

enrollment. (Note: ongoing thrombosis in-situ or severe unilateral peripheral arterial disease (PAD) undergoing surgical intervention is not an exclusion criterion).
4. Patients with a known congenital bleeding disorder.
5. Patients with a known antiphospholipid antibody syndrome.
6. Patients with present or past specific factor inhibitor activity.
7. Patients with thrombocytopenia of <80,000/μL or history of heparin-induced thrombocytopenia.
8. Patients who have received more than 5000 units of systemic unfractionated heparin (UFH), any dose of low-molecular-weight heparin (LMWH) or any dose of non-VKA anticoagulant (i.e. direct oral anticoagulant) within 24 hours prior to enrollment into the study or have potential need to receive these medications in mentioned doses before completion of hemostasis evaluation at the end of surgery.
9. Patients who have received PCCs, FFP or vitamin K within 72 hours prior to enrollment into the study.
10. Patients receiving P2Y12 platelet inhibitors (e.g. Clopidogrel, Prasugrel, Ticagrelor)
11. Patients with a known history of hypersensitivity to plasma-derived products.
12. Patients requiring urgent surgical procedures where according to the surgeon's clinical judgment an accurate estimate of expected blood loss and transfusion requirements is not possible, e.g.:
    a. Surgeries requiring massive transfusion protocols (e.g., major polytrauma, major injuries, organ transplant surgeries),
    b. Patients with acute major bleeding (e.g., gastrointestinal bleeds, obstetric haemorrhage),
    c. Surgeries with unpredictable intraoperative blood loss (e.g., ruptured aneurysm, primary surgery for intracranial hemorrhage (ICH)).
13. Pregnant or nursing women.
14. Patients participating in another interventional clinical study currently or during the past 30 day prior to enrollment into this study.
15. Patients previously enrolled in this study.

4.2 Prior and Concomitant Therapy

4.2.1 Prior Treatment

Details on medications taken within 30 days prior to enrollment and any concomitant medications taken during the study, including any over the counter medications, herbal supplements, vitamins, IV fluids, blood products, must be recorded in the CRF.

4.2.2 Permitted Concomitant Therapy

Concomitant administrationsof therapies not interfering with the primary objectives of the study are permitted.

Patients taking acetylsalicylic acid concomitantly with Warfarin are eligible.

Administration of vitamin K is permitted within 1 hour before IMP infusion or within 1 hour after IMP infusion, at a dose of 2, 5, or 10 mg according to local clinical practice.

4.2.3 Forbidden Concomitant Therapy

Patient taking P2Y12 platelet inhibitors (e.g. Clopidogrel, Prasugrel, Ticagrelor) concomitantly with VKA are not eligible for the study. P2Y12 platelet inhibitors must not be used until completion of hemostasis evaluation at the end of surgery.

UFH in dose above 5000 units, LMWH and/or non-VKA anticoagulant (i.e. direct oral anticoagulant) in any dose, **must not be used** from the time 24 hours before enrollment into the study and until completion of hemostasis evaluation at the end of surgery.The reconstituted IMP should not be mixed with other drugs. This could lead to an activation or inactivation of coagulation factor(s).

Generally, administration of blood products should be avoided if possible. However, it is up to the treating physician to decide whether a surgical procedure can start or if additional pre-operative administration of coagulation treatment is required per standard of care (eg, PCC, single coagulation factors, plasma). If used, all details must be documented (eg, product name, reason for administration, dose etc.).

4.3 Withdrawal and Replacement of Patients

4.3.1 Premature Patient Withdrawal

Patients have the right to withdraw from the study at any time for any reason, without the need to justify their decision. The investigator also has the right to withdraw patients in case of AEs, poor compliance, or other reasons. Since an excessive rate of withdrawal can render the study non-interpretable, the unnecessary withdrawal of patients must be avoided.

For any discontinuation after study entry, the investigator will obtain all the required details and document the reason(s) for discontinuation. If the reason for withdrawal of a patient is an AE, the main specific event or laboratory test will be recorded and the investigator will make thorough efforts to clearly document the outcome.

4.3.2 Patient Replacement Policy

Patients withdrawn from the study because of safety or efficacy reasons will not be replaced.

4.4 Assignment of Patients to Treatment Groups

Each patient will receive a patient number (in numeric order per center) after having signed a written informed consent form. The site will enter the patient number and the initials of each patient in the CRF and in the confidential patient identification list.

Each patient will be randomized to receive IMP (either OCTAPLEX or Beriplex® P/N [Kcentra]). In order to achieve a balance between the 2 treatment groups with respect to the planned type of surgery and history of TEE, the treatment allocation by the IRT will be stratified according to the parameters 'Expected blood loss ("≥200 mL", "≥100 mL but <200 mL" or "≥50 mL but <100 mL")', 'History of TEE ("yes" or "no")' and 'Type of planned surgery ("orthopaedic surgery", "cardiothoracic surgery" or "other surgery"). To ensure that the intended proportions of patients enrolled are kept for subgroups of expected blood loss, the IRT will preclude enrollment into the subgroup once its targeted number of enrolled patients is reached.

4.5 Relevant Protocol Deviations

In the case of any major protocol deviation the investigator and Octapharma will decide on the further participation of the patient in this study, after having discussed all relevant aspects. All major protocol deviations should be notified to IEC/IRBs or regulatory authorities if required by local regulation.

Each patient who has received IMP will be included in the safety population. With respect to the Per-Protocol efficacy analysis, protocol deviations will be handled on an individual basis. After each study part the decision on membership of the patients in a particular analysis population will be made at a blinded data review meeting, prior to database lock.

4.6 Subsequent Therapy

Any patient who discontinues from the study should continue medical treatment according to local standards.

5 INVESTIGATIONAL MEDICINAL PRODUCTS

5.1 Characterization of Investigational Products

Commercially available investigational products will be used in this study: OCTAPLEX 500IU (in all participating countries), Kcentra 500 IU (in the US), Beriplex® P/N 500 IU (in all participating countries except the US). All products are supplied as a powder for solution for injection together with a solvent (20 mL Water for Injection), which should be used for the reconstitution of the investigational products. The batch number(s) used will be recorded in the clinical study report.

5.1.1 OCTAPLEX 500 IU

The reconstituted solution contains the following ingredients as shown in Table 2:

Table 2: Ingredients in the Reconstituted OCTAPLEX 500IU Solution

Ingredients	**Quantity per vial (20 mL)**	**Quantity per mL reconstituted solution**
Total protein	260-820 mg	13 – 41 mg/mL
Active substances		
1. Coagulation factors		
Human coagulation factor II (FII)	220 – 760 IU	11 – 38 IU/mL
Human coagulation factor VII (FVII)	180 – 480 IU	9 – 24 IU/mL
Human coagulation factor IX (FIX)	400 – 620 IU	20 – 31 IU/mL
Human coagulation factor X (FX)	360 – 600 IU	18 – 30 IU/mL
2. Further active ingredients		
Protein C	140 – 620 IU	7 – 31 IU/mL
Protein S	140 – 640 IU	7 – 32 IU/mL
Excipients		
Heparin	100 – 250 IU	5 – 12.5 IU/mL
Sodium citrate	0.34 – 0.54 mmol	0.017 – 0.027 mmol/mL

5.1.2 Kcentra 500 IU

The reconstituted solution contains the following ingredients as shown in Table 3:

Table 3: Ingredients in the Reconstituted Kcentra 500 IU Solution

Ingredients	Quantity per vial (20 mL)	Quantity per mL reconstituted solution
Total protein	120 – 280 mg	6 – 14 mg/mL
Active substances		
1. Coagulation factors		
Human coagulation factor II (FII)	380 – 800 IU	19 – 40 IU/mL
Human coagulation factor VII (FVII)	200 – 500 IU	10 – 25 IU/mL
Human coagulation factor IX (FIX)	400 – 620 IU	20 – 31 IU/mL
Human coagulation factor X (FX)	500 – 1020 IU	25 – 51 IU/mL
2. Further active ingredients		
Protein C	420 – 820 IU	21 – 41 IU/mL
Protein S	240 – 680 IU	12 – 34 IU/mL
Excipients		
Heparin	8 – 40 IU	0.4 – 2 IU/mL
Antithrombin III	4 – 30 IU	0.2 – 1.5 IU/mL
Human albumin	40 – 80 mg	2 – 4 mg/mL
Sodium chloride	60 – 120 mg	3 – 6 mg/mL
Sodium citrate	40 – 80 mg	2 – 4 mg/mL
HCL	Small amounts	Small amounts
NaOH	Small amounts	Small amounts

5.1.3 Beriplex® P/N 500 IU

The reconstituted solution contains the following ingredients as shown in **Table 4**:

Table 4: Ingredients in the Reconstituted Beriplex ® P/N 500 IU Solution

Ingredients	Quantity per vial (20 mL)	Quantity per mL reconstituted solution
Total protein	120 – 280 mg	6 – 14 mg/mL
Active substances		
1. Coagulation factors		
Human coagulation factor II (FII)	400 – 960 IU	20 – 48 IU/mL
Human coagulation factor VII (FVII)	200 – 500 IU	10 – 25 IU/mL
Human coagulation factor IX (FIX)	400 – 620 IU	20 – 31 IU/mL
Human coagulation factor X (FX)	440 – 1020 IU	22 – 60 IU/mL
2. Further active ingredients		
Protein C	300 – 900 IU	15 – 45 IU/mL
Protein S	240 – 760 IU	12 – 38 IU/mL
Excipients		
Heparin	8 – 40 IU	0.4 – 2 IU/mL
Antithrombin III	4 – 30 IU	0.2 – 1.5 IU/mL
Human albumin	40 – 80 mg	2 – 4 mg/mL
Sodium chloride	60 – 120 mg	3 – 6 mg/mL
Sodium citrate	40 – 80 mg	2 – 4 mg/mL
HCL	Small amounts	Small amounts
NaOH	Small amounts	Small amounts

5.2 Packaging and Labeling

Commercially available IMPs will be re-packed and additionally labeled according to local regulations.

5.3 Conditions for Storage and Use

IMP should be stored at ≥ 2°C (35°F) and ≤25°C (77°F) protected from light and must not be frozen. The investigator must ensure that the IMP is stored under appropriate temperature conditions and in a reasonably secure area of restricted access.

Reconstituted product must be used within 4 hours following reconstitution. Reconstituted product can be stored at 2-25°C (35°F -77°F). If cooled, the solution should be warmed to 20-25°C prior to administration. Do not freeze the reconstituted product. Discard partially used vials.

5.4 Dose and Dosing Schedule

The dose of IMP to be administered should be determined based on BW and baseline INR. BW should be rounded to the nearest whole kilogram number for IMP dose calculation. Baseline INR value should be rounded to the 1st decimal place. If the baseline INR value is not available at the time when patient must be randomized to initiate preparation of IMP, qualifying INR (used for inclusion of the patient) can be used. If the qualifying INR is within 3 hours of IMP infusion start and was analyzed by the laboratory participating in the study it can serve as the baseline INR and additional baseline INR testing is not mandatory. Otherwise baseline INR must be obtained. If the baseline INR value compared to qualifying INR value used for initial IMP dose calculation falls within different IMP dosing ranges, the dose of IMP should be adjusted to baseline INR using IRT.

The dose of IMP will depend on the BW and baseline INR of the patient and will be calculated by the responsible treating investigator according to the following dosing table.

Baseline INR	2 to <4	4-6	>6
Dose (IU of Factor IX/kg BW)	25	35	50
Maximum dose (IU of Factor IX)	2500	3500	5000

The nominal IMP potency of 25 IU/mL of factor IX will be used for volume calculation (each vial has ~500 IU of OCTAPLEX or Beriplex® P/N (Kcentra) and is reconstituted in 20 mL of Water for Injection).

IMP will be 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). The total volume of IMP used and time of infusion will be recorded.

One infusion of IMP will be given according to the table above.

5.5 Preparation and Method of Administration

The preparation is dissolved with water for injection, by transferring it into the vial containing the concentrate using the Mix2Vial™ transfer set.

Before the IMP is infused, the solution must be warmed up to room temperature. The preparation must be used immediately after dissolution, and any unused solution must be discarded. If reconstituted IMP is not used within 4 hours following reconstitution, it should be discarded and new IMP assigned via IRT. Usually, the solution is clear or slightly opalescent. Do not use solutions that are cloudy or have deposits. The reconstitution time is less than 10

minutes at room temperature. During the procedure described, aseptic technique must be maintained.

The total volume used and time of start and end of infusion will be recorded.

Infusion line should be flushed with 0.9% sodium chloride.

5.6 Blinding and Breaking the Study Blind

Following randomization, IMP will be assigned using IRT and will be prepared for infusion by unblinded site personnel. IMP will be prepared and infused in a manner that will blind the investigator and other blinded site personnel to the study treatment. Unblinded site personnel must not communicate to the investigator or other blinded site personnel which product was assigned to the patient.

Breaking of blinding in individual patients is only permitted in case of a SAE or unexpected adverse drug reaction (ADR), when knowledge of the type of the administered IMP is required for therapeutic decisions regarding this event.

Emergency patient unblinding will be managed in a dedicated IRT system. In the event an investigator needs to unblind a study patient, authorized study personnel at the site will log into IRT to request access to the unblinded randomization code for the patient in question. In order to do so, the investigator will have to acknowledge the serious nature of unblinding. Upon taking these steps, the dedicated web-based system will then provide the investigator the specific treatment arm for that patient. Upon exiting the dedicated web-based system, an email notification of this action will automatically be sent to appropriate management and safety officials acknowledging the patient unblinding without providing the specific treatment arm. This information will also be captured in the study audit trail.

5.7 Treatment Compliance

5.7.1 Drug Dispensing and Accountability

IMP will be delivered to all sites by a central distribution facility or local depot. A drug dispensing log will be kept up-to-date by each investigator, detailing the dates and quantities of the IMP administered to each patient. The inventory will be available to the monitor to verify drug accountability during the study. Any unused IMP and empty bottles will be disposed locally if allowed by local regulation or returned to Sponsor's designee for disposal.

5.7.2 Assessment of Treatment Compliance

IMP will be infused at the study site under the guidance of the investigator. The number of vials used will be documented together with IMP batch numbers.

6 STUDY CONDUCT

6.1 Observations by Visit

6.1.1 Screening and Randomization

The following assessments will be performed during screening:

- Obtain voluntarily given, written (signed and dated) informed consent
- Screening registration
- Collection of baseline information:
  - demographics (including weight and height measurements) (see Section 7.1)
  - medical history (see Section 7.1)
  - prior and concomitant medication use (see Section 7.1 and 4.2.1)
- planned vitamin K administration (see Section 7.1)Check and document compliance with inclusion and exclusion criteria
- Urine or blood pregnancy test for women of childbearing potential (WOCBP) (see Section 7.3.9)
- Initial hemostatic assessment (see Section 7.2.1)
- Calculate IMP dose (see Section 5.4) and randomize patient via IRT
- Assign IMP following randomization using IRT, prepare product for infusion, document time of reconstitution. IMP reconstitution should start within 4 hours prior to infusion.

The expected average and maximum blood loss and expected average and maximum transfusion requirements for non-anticoagulated patients undergoing the same type of surgical procedure need to be documented with audit trail prior to randomization.

Patients with ongoing thrombosis in-situ or severe unilateral peripheral arterial disease (PAD) undergoing intervention must be consulted with the Sponsor/Sponsor's designee medical monitor before randomization. Contact details will be provided in the Investigator File.

6.1.2 Baseline

The following baseline assessments will be performed within 3 hours before the administration of IMP:

- Vital signs
- Physical examination (see Section 7.3.5)
- Blood sampling for local lab (see Section 7.2.2.1 and Section 7.3.6)
- Blood sampling for central lab (see Section 7.3.6) including viral markers
- Vitamin K administration 1 hour before IMP infusion and at the latest within 1 hour after IMP infusion. Document dose and administration time. For patients with the following clinical conditions, vitamin K administration is not mandatory:
  - mechanical heart valve

- Left Ventricular Assist Device (LVAD)
- any other hypercoagulable/prothrombotic condition identified by the treating physician

If vitamin K is not administered, the clinical reason for non-administration must be documented in the CRF.

- Document vital status, AEs

6.1.3 Infusion of IMP

- Check time of IMP reconstitution. If IMP was reconstituted more than 4 hours before infusion it should be discarded and new IMP assigned using IRT.
- Infuse IMP 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). The total volume of IMP used, time, and speed of infusion will be recorded.
- Document AEs, vital status
- Document concomitant medications and transfusions.

6.1.4 Procedures After End of Infusion

The following assessments will be performed after the End of Infusion of IMP:

- Vital signs (30 min and 2 hours after the end of infusion)
- Blood sampling for local lab (see Section 7.3.6) (30 min, 2 hours, 4 hours, 12 hours, and 24 hours after end of infusion).
- Blood sampling for central lab (see Section 7.3.6) (30 min, 2 hours, 4 hours, 12 hours, and 24 hours after end of infusion).
- Document AEs, vital status, concomitant medications, and transfusions

If TEEs are suspected at any time during the study, appropriate examinations according to local standards should be performed (e.g. Doppler scan using color duplex, X-ray) and the results documented in CRF.

6.1.5 Procedures Prior to Surgery

The following assessments will be performed within 1 hour prior to surgery start:

- Blood sampling for local lab (see Section 7.3.6)
- Document AEs, vital status, concomitant medications, and transfusions (see Section 7.2.2.3).
- Hematoma assessment (see Section 7.2.2.5)

The time of start of surgery is defined as the time of initiation of anesthesia, as documented in the anesthesia protocol.

6.1.6 Procedures After Surgery

The following assessments will be performed within 1 hour post-surgery end:

- Blood sampling for local lab (see Section 7.3.6)
- Document AEs, vital status (see Section 7.3), concomitant medications (see Section 4.2) and transfusions (see Section 7.2.2.3).

- Hemostatic assessment (see Section 7.2.1)
- Hematoma assessment (see Section 7.2.2.5)
- Wound drainage evaluation

The time of surgery end is defined as the surgery end time of the principal procedure.

6.1.7 Procedures 12 and 24 hours After Start of Surgery

The following assessments will be performed 12 and 24 hours after the start of surgery:

- Hematoma assessment including documentation of cases that require surgical evacuation (see Section 7.2.2.5).
- Document AEs, vital status (see Section 7.3), concomitant medications (see Section 4.2) and transfusions (see Section 7.2.2.3).
- Blood sampling for local lab (see Section 7.3.6)
- Wound drainage evaluation

6.1.8 Procedures in Post-Operative Period

The following assessments will be performed in the days after surgery:

- Vital signs (Day 2, discharge)
- Physical examination (Day 2, discharge)
- Blood sampling for local lab (see Section 7.3.6) (Day 2, discharge)
- Document AEs, vital status, concomitant medications and transfusions (see Section 7.2.2.3) (Day 2, 4, discharge)

Assessments at Days 2 or 4 are done if the patient remains hospitalized. Discharge assessments should be done on the day of discharge. If discharge falls on Days 2 or 4, the schedule of discharge assessments should be followed.

6.1.9 Follow-up Assessments

The following follow-up assessments will be performed:

- Blood sampling for central lab to test for Parvovirus B19 (Day 9) in patients with negative results for one or both Parvovirus B19 Baseline tests (see Section 7.3.7)
- Document vital status (Day 9, 21, and 45)
- Follow-up for serious AEs (Day 9, 21, and 45) and concomitant medication (documentation of concomitant medication at Days 9, 21, and 45 is only required if AEs are ongoing)

If no blood collection is required and it is otherwise deemed appropriate by the investigator (e.g. there is no need for any onsite follow up) these assessments can be done via phone.

6.1.10 Interpretation of time windows in this study

The allowed time windows in this study are outlined in the Flow Chart.

6.2 Duration of Study

6.2.1 Planned Duration for an Individual Patient

The duration of the entire study for each patient will be approximately 45 days. Patients randomized, but given no IMP, will be withdrawn from the study. All patients who received IMP, but whose surgery was cancelled due to any reason, should complete all protocol procedures with the exception of OP procedures (prior OP, post OP, 12h after START and 24h after START), which will be skipped. Post operative time points (Day 2, Day 4, and Discharge) will be calculated from the day of IMP infusion.

6.2.2 Planned Duration for the Study as a Whole

The study will be considered completed, when all patients have completed the final examination (Day 45 follow-up).

The estimated start of the study (enrollment of first patient) is Q4 2016, and the estimated end of the study (last visit of last patient) is Q2 2021. As one un-blinded interim analysis will be performed after enrollment of 50% of the planned sample size, early stopping of the study for demonstrated non-inferiority of OCTAPLEX or futility to achieve this could occur.

6.2.3 Premature Termination of the Study

Both the investigator and the Sponsor reserve the right to terminate the study at any time. Should this be necessary, the procedures will be arranged on an individual study basis after review and consultation by both parties. In terminating the study, the Sponsor and the investigator will ensure that adequate consideration is given to the protection of the patients' interests.

Regulatory authorities and IECs/IRBs will be informed according to national regulations.

Should the study be prematurely terminated, all study materials (IMPs, laboratory kits etc.) must be returned to the Sponsor or disposed at the study site if approved by the Sponsor.

7 ASSESSMENTS AND METHODS

7.1 Background / Baseline Information

The following information will be captured at Screening and upon enrollment:

Demographics: including sex, age, weight and height (calculated Body Mass Index), and ethnic origin. Weight must be measured using weighing scales, estimating or asking the patients for their weight is not acceptable.

Medical history: obtained by interviewing the patient. Records of past diseases and treatments (e.g., hospital discharge letters) will be obtained for the study files if available. As history of TEEs, estimated blood loss, and type of surgery are stratification factors for randomization in this study, this information must be carefully checked and entered in the CRF.

Previous and concomitant medication: obtained by interviewing the patient

Vitamin K administration: documentation of time and dose. If vitamin K is not administered, the clinical reason for non-administration must be documented in the CRF.

7.2 Efficacy Assessments

7.2.1 Assessments for Primary Efficacy Endpoints

During screening, an initial hemostatic assessment will be conducted and documented with an audit trail before randomization. This evaluation will include determination of the nature of the operation and the predicted estimated blood loss and anticipated transfusion requirements. Details to be documented include the expected average and maximum blood loss and expected average and maximum transfusion requirements for non-anticoagulated patients undergoing the same type of surgical procedure. Cell saver blood is to be accounted for when assessing the predicted volume of transfusions. The surgeon will also note any extenuating circumstances that may affect the estimated blood loss or transfusion requirements (e.g., prior surgery with resulting adhesions, limited or extensive surgery). Any planned adjunct therapy should also be recorded prior to surgery.

At the conclusion of the surgical procedure the actual estimated blood loss (by local practice) and transfusion requirements will be documented. Efficacy will be rated by the investigator at the end of the surgery in a blinded manner based on a 4-point hemostatic efficacy scale.

The hemostatic efficacy rating will also be assessed by an IEAB consisting of clinical experts. All adjudications will be conducted in a blinded manner and the IEAB will be provided with all relevant details (e.g. duration of surgery, co-medication, medical history, predicted and actual blood loss, transfusion information, details of hemorrhagic wound drainage) of the patient and the actual procedure performed covering the time period up to the end of the surgery, as documented in the anesthesia record. To ensure the effectiveness of blinding and avoid potential bias, the INR and PT values will not be provided to the IEAB. The IEAB will also be blinded to Investigator's clinical hemostasis rating.

The hemostatic efficacy of the study treatments is to be assessed in the categories 'excellent', 'good', 'moderate' or 'none'. Ratings of 'excellent' and 'good' will be considered as 'effective' hemostasis, while a rating of 'moderate' and 'none' will be considered as 'ineffective' hemostasis.

Assessment should be guided by clinical experience, the specifics of the surgery actually performed, additional transfusion requirements and blood loss occurred during the surgery. The criteria below involve aspects of intraoperative blood loss and transfusions.

Hemostatic Efficacy Scale (assessment at the end of the surgery – as documented in the anesthesia record)*:

- **Excellent**: Intra-operative blood loss and transfusion requirements were lower than or equal to the average expected ones 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 ones 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 ones 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 will not be taken into consideration when assessing intra-operative efficacy. These include:

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).

When quantifying the deviation between average and actual intra-operative blood loss and transfusions, unexpected transfusions of plasma, red cells, platelets and coagulation factor products due to surgical complications should be excluded. For example:

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),
4. Treatment of pre-existing conditions like anemia.

Transfusions for pre-existing anemia will be excluded only if the number of units of red cells to be transfused for this purpose is clearly documented prior to administration of the IMP and before the start of surgery.

7.2.2 Assessments for Secondary and Further Exploratory Efficacy Endpoints

7.2.2.1 Measurement of INR

INR will be calculated from the PT results. The INR system is used to standardize variability of response of different thromboplastin reagents to warfarin. The INR is calculated from the PT ratio of test plasma to the geometric mean normal PT, to the power of the international

sensitivity index of the thromboplastin, using the following formula: **INR = (patient PT/GMNPT)^{ISI}**.

Baseline INR will be determined within 3 hours prior to the start of the first infusion of IMP. Samples will also be drawn for INR determination at 30 minutes (±15 minutes), 2 hours (±30 minutes), 4 hours (±30 minutes), 12 hours (±1 hour), and 24 hours (±2 hours) after the end of IMP infusion, prior OP (within 1 hour prior surgery start) and post OP (within 1 hour after surgery end) and at any point considered necessary by the investigator. All tests performed per standard of care should be documented in CRF.

Certified portable INR monitoring devices may only be used for qualifying INR measurements. All study specific INR measurements must be tested in local laboratory.

7.2.2.2 Measurement of Coagulation Factor Levels (FII:C, FVII:C, FIX:C, FX:C, PC, and PS)

Baseline will be determined within 3 hours prior to the start of the first infusion of IMP. Samples will also be drawn for these determinations at 30 minutes (±15 minutes), 2 hours (± 30 minutes), 4 hours (± 30 minutes), 12 hours (± 1 hour), and 24 hours (± 2 hours) after the end of infusion or at any point considered necessary by the investigator.

7.2.2.3 Red Blood Cell, Plasma and Platelets Transfusions Initiated During the Surgery

The time, amount (units and mL) and reason of all intra-operative RBC, plasma, and platelet transfusions during surgery will be recorded and analyzed. All blood and plasma products given throughout the hospitalization for the original admission and the reason for their administration will be captured on a CRF page designed specifically for this purpose. This will include any blood product and/or volume expanders. Blood products will be defined as autologous blood, allogenic whole blood, whole blood, RBC, FFP, platelets, and cryoprecipitate (14) (American Society of Anesthesiologists 2006).

Cell saver blood is to be accounted for when assessing the volume of transfusions.

The ASA (American Society of Anesthesiologists) recommendations for triggering a RBC transfusion will be used to assess the need for RBC transfusions. These guidelines recommend RBC transfusion when Hg levels fall acutely below 6 g/dL and no transfusion when Hg levels are above 10 g/dL (14) (ASA 2006). The determination of whether intermediate Hgb concentrations (i.e., 6–10 g/dL) justify or require red blood cell transfusion should be based on any ongoing indication of organ ischemia, potential or actual ongoing bleeding (rate and magnitude), the patient's intravascular volume status, and the patient's risk factors for complications of inadequate oxygenation. These risk factors include a low cardiopulmonary reserve and high oxygen consumption indicated by decreased urine output, unstable vital signs, evidence of myocardial ischemia, increased lactate or base deficit, change in level of consciousness, orthostatic signs (dizziness or decreased blood pressure with standing), or with impending blood loss (expected for the scheduled surgery). If there is a deviation from this guideline the physician/surgeon will be asked to document the justification for any transfusion outside of these guidelines.

7.2.2.4 Change in hematological parameters

Hematological parameters (Hgb, Hct, RBC, WBC, platelets) will be determined at the local laboratory within 3 hours prior to the start of the first infusion of IMP. Samples will also be drawn for determination of these parameters at 30 minutes (±15 minutes) and 24 hours (±2 hours) after the end of IMP infusion, prior OP (within 1 hours prior surgery start) and post OP (within 1 hours after surgery end), at 12 and 24 hours after start of operation and at Day 2, Discharge, or at any point considered necessary by the investigator.

7.2.2.5 Incidence of Hematoma and Proportion of Patients with Surgical Wound Hematomas That Need Evacuation

The patient will be initially assessed for the presence of hematoma. The extent of hematomas after surgery will be evaluated. The need for evacuation of any hematoma post-surgery will be evaluated and recorded.

7.3 Safety Assessments

The following drug safety information shall be collected:

- AEs and SAEs temporally associated with administration of IMP, or comparator (definitions and reporting requirements see Section 7.3.1)
- Pregnancies, drug overdose, interaction, medication error, lack of efficacy, post study SAEs (see Section 7.3.9).
- Occurrence of TEEs
- Vital status (alive vs dead)
- Physical examination
- Vital signs
- Clinical laboratory tests
- Viral markers

7.3.1 Adverse Events

7.3.1.1 Definitions

Adverse event (AE): An AE is any untoward medical occurrence in a study patient receiving an IMP and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an IMP, whether or not related to the IMP.

Adverse drug reaction (ADR): An ADR is any noxious and unintended response to an IMP related to any dose. The phrase "response to an IMP" means that a causal relationship between the IMP and an AE carries at least a reasonable possibility, i.e., the relationship cannot be ruled out.

Other significant AEs: Any marked laboratory abnormalities or any AEs that lead to an intervention, including withdrawal of drug treatment, dose reduction or significant additional concomitant therapy.

Withdrawal due to AE/ADR: AE/ADR leading to discontinuation of treatment with IMP. Any such events will be followed up by the investigator until the event is resolved or until the medical condition of the patient is stable. All follow-up information collected will be made available to the Sponsor.

7.3.1.2 Collection

The condition of the patient will be monitored throughout the study. At each visit, whether scheduled or unscheduled, AEs will be elicited using a standard non-leading question such as "How have you been since the last visit / during the previous study period?".

Any AE or ADR which occurs during the study will be noted in detail on the appropriate pages of the CRF. If the patient reports several signs or symptoms, representing one syndrome or diagnosis, the diagnosis should be recorded in the CRF. The investigator will grade the severity of all AEs or ADRs (mild, moderate or severe), the seriousness (non-serious or serious) and causality, as defined below (Sections 7.3.1.3, 7.3.1.4 and 7.3.2). The Sponsor is responsible to assess the expectedness of each ADR (expected or unexpected), as defined below (Section 7.3.1.4).

In the event of clinically significant abnormal laboratory findings, the tests will be confirmed and followed-up until they have returned to normal and/or an adequate explanation is available.

Diseases, signs and symptoms and/or laboratory abnormalities already existing before the first administration of IMP are not considered as AEs when observed at a later stage unless they represent an exacerbation in intensity or frequency (worsening).

The investigator should always provide detailed information concerning any abnormalities and the nature of, and reasons for any necessary action(s), as well as any other observations or comments, which are useful for the interpretation and understanding of the patients' AEs or ADRs.

7.3.1.3 Severity

The intensity/severity of all AEs will be graded as follows:

- mild: an AE, usually transient, which causes discomfort but does not interfere with the patient's routine activities;
- moderate: an AE which is sufficiently discomforting to interfere with the patient's routine activities;
- severe: an AE which is incapacitating and prevents the pursuit of the patient's routine activities.

Grading of an AE is up to the medical judgment of the investigator and will be decided on a case by case basis.

7.3.1.4 Causality

The relationship of AEs to the administered IMP will be assessed by the investigator:

- probable: reports including good reasons and sufficient documentation to assume a causal relationship, in the sense of plausible, conceivable, likely, but not necessarily highly probable. A reaction that follows a reasonable temporal sequence from administration of the IMP; or that follows a known or expected response pattern to the suspected medicine; or that is confirmed by stopping or reducing the dosage of the medicine and that could not reasonably be explained by known characteristics of the patient's clinical state.
- possible: reports containing sufficient information to accept the possibility of a causal relationship, in the sense of not impossible and not unlikely, although the connection is uncertain or doubtful, for example because of missing data or insufficient evidence. A reaction that follows a reasonable temporal sequence from administration of the IMP; that follows a known or expected response pattern to the suspected medicine; but that could readily have been produced by a number of other factors.
- unlikely: reports not following a reasonable temporal sequence from IMP administration. An event which may have been produced by the patient's clinical state or by environmental factors or other therapies administered.
- not related (unrelated): events for which sufficient information exists to conclude that the etiology is unrelated to the IMP.
- unclassified: reports which for one reason or another are not yet assessable, e.g., because of outstanding information (can only be a temporary assessment).

Classification of ADRs:

ADRs will be classified by the Sponsor as either expected or unexpected:

- expected: an ADR that is listed in the current edition of the Investigator's Brochure.
- unexpected: an ADR that is not listed in the current edition of the Investigator's Brochure, or that differs because of greater severity or greater specificity.

7.3.1.5 Outcome

The outcome of all reported AEs has to be documented as follows:

1. recovered, resolved
2. recovering, resolving
3. not recovered, not resolved
4. recovered, resolved with sequelae
5. fatal
6. unknown

NOTE: A patient's **death** per se is not an event, but an outcome. The event that resulted in a patient's death must be fully documented and reported, even in case the death occurs within 45 days after IMP treatment end, and without respect of being considered treatment-related or not.

7.3.1.6 Action(s) taken

AEs requiring action or therapy must be treated with recognized standards of medical care to protect the health and well-being of the patient. Appropriate resuscitation equipment and medicines must be available to ensure the best possible treatment in an emergency situation.

The action taken by the investigator must be documented:

a) **in general**

- none
- medication (other than IMP) or other (e.g., physical) therapy started
- test performed
- other (to be specified)

b) **on IMP**

- none
- product withdrawn
- dose reduced
- dose increased

The investigator will follow-up each AE until it is resolved or until the medical condition of the patient is stable, and all relevant follow-up information will be reported to the Sponsor.

7.3.2 Serious Adverse Events

An SAE is any untoward medical occurrence that at any dose:

- results in death,
- is life-threatening,
- requires hospitalization (with the exception of hospitalizations for surgeries that were planned prior to study enrollment) or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity,
- is a congenital anomaly/birth defect,
- is another important medical event.

NOTE: The term "life-threatening" refers to an event in which the patient was — in the view of the reporting investigator — at immediate risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

Medical judgment should be exercised in deciding whether an AE/reaction is serious in other situations: Important AEs/ADRs that are not immediately life-threatening or do not result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definitions above, should also be considered serious.

In addition, although not classified under the seriousness criteria, all suspected transmissions of an infectious agent should be reported as SAE. A suspected virus transmission means that virus antigen has been detected in the patient. A passive transmission of antibodies alone does not constitute a suspected virus transmission.

SAE reporting timelines

All SAEs, whether suspected to be related to study treatment or not, are to be reported by telephone, fax or e-mail immediately to the Sponsor and the Sponsor's designee. An SAE form must be completed and submitted to the Sponsor and the Sponsor's designee within 24 hours after recognition of the event.

Sponsor contact details for SAE reporting:

Octapharma's Corporate Drug Safety Unit:
OCTAPHARMA Pharmazeutika Produktionsges.m.b.H.
Oberlaaer Strasse 235, 1100 Vienna, Austria
[redacted]

Sponsor's designee contact details for SAE reporting:

[redacted]

Waiver from SAE reporting requirement:

These exceptions/waivers include surgeries that are elective or planned before study entry, and prolongation of the existing hospitalizations due to economic or social reasons, but not medical reasons. These should not be considered as SAEs.

7.3.3 Occurrence of TEEs

As a component of the assessment of AE, the investigator will be questioned regarding the occurrence of TEEs. These are defined according to the Standardized Medical Dictionary for Regulatory Activities (MedDRA) query (SMQ) "Embolic and thrombotic events". TEEs will be captured on a specific page of the CRF. All TEEs must also be recorded on the AE page of the CRF. If TEEs is suspected at any time during the study, appropriate examinations according to local standards should be performed (e.g. Doppler scan using color duplex, X-ray) and the results documented.

7.3.4 Vital Status

Vital status (alive or dead) will be documented from consent through the 45-day follow-up or discontinuation of the patient to allow determination of all-cause mortality.

7.3.5 Physical Exam

A standard physical exam will be performed at baseline, and at post-operative day 2 or discharge (whichever comes first).

7.3.6 Laboratory Tests

The *actual* time of blood sampling must be documented and recorded in the CRF.

Details of test parameters to be collected are listed in Table 5.

Coagulation, hematology, electrolytes, liver enzymes, Blood Urea Nitrogen (BUN) (or Urea), and creatinine tests will be performed at the respective local laboratories.

Tests for coagulation parameters and virology will be performed at a central laboratory.

Samples for the central laboratory will be taken, processed, stored, and shipped in accordance with the laboratory manual provided by the central laboratory.

Lab samples will be drawn at the time frames noted in the Flow Chart, until patient discharge, with the exception of parvovirus B19 virology samples in patients with negative results for either PCR or IgM test at Baseline. These patients will need to be called back at Day 9 for the completion of virology tests.

Table 5: Details of Laboratory Tests

Parameter	Investigational Site
Coagulation parameters	
INR, PT	Locally
aPTT	Locally
FII:C, FVII:C, FIX:C, FX:C	Central lab
PC, PS	Central lab
Hematology	
Hematocrit	Locally
Hemoglobin	Locally
Blood cell count (WBC, RBC, platelets)	Locally
Liver Function & Electrolytes Others	
LDH	Locally
Sodium, potassium	Locally
Kidney Function	
BUN (or Urea) and Creatinine	Locally
Virology	
Anti-Parvovirus B19 IgM Ab	Central lab
Parvovirus B19 PCR	Central lab
Pregnancy test	
Urine or blood pregnancy test	Locally

The methods used for each parameter and the normal ranges of each determination at each laboratory involved will be provided in the Clinical Study Report.

7.3.7 Viral Safety Tests

Viral marker samples are taken at the baseline visit and at Day 9 (-2/+5 days) after the last administration of IMP.

At the baseline visit, all patients will undergo serologic testing for Parvovirus B19 (anti-Parvovirus B19 IgM Ab), as well as PCR for Parvovirus B19.

At Day 9 (-2/+5 days) following the study infusion of IMP, a follow-up sample will be taken for Parvovirus B19 PCR and anti-Parvovirus B19 IgM Ab assessments in patients who had negative results of one or both Parvovirus B19 tests at baseline. Patients with positive results of both baseline tests do not need to have Parvovirus B19 testing repeated on Day 9.

The virus safety samples will be analyzed in the central laboratory. In case there is a change from baseline of the viral status of a patient and a suspected seroconversion, the viral tests will be repeated by the laboratory on back up aliquots of the Baseline and Day 9 samples.

7.3.8 Vital Signs

Safety evaluation will include monitoring of vital signs, i.e., body temperature, heart rate, blood pressure, and respiratory rate. Measurements will be carried out at baseline (just prior to infusion), and at the time points specified in the Flow Chart. Hemodynamic changes are frequently observed during surgery. For this reason, only alterations in heart rate or blood pressure *not* coinciding with periods of rapid blood loss and/or deemed significant by the physician will be recorded as AEs. In case fever occurs, temperature will be measured every morning until normalized. Fever will be defined as a body temperature >37.8°C orally (or >38.2°C rectally or >38.0°C axillary) and will be documented as an AE.

7.3.9 Other Relevant Safety Information

Post-study related safety reports:

Any SAE that occurs up to 4 weeks after the completion of the study should be reported by the investigator to the Sponsor if the investigator becomes aware of it. Proactive monitoring for post study SAEs is not required.

If a post study SAE is identified, the investigator should complete an SAE form. Relation to the clinical study should be stated on the report.

If a patient dies within up to 45 days after the last IMP administration, this should be reported as well, regardless of being considered treatment-related or not.

Pregnancies

Every effort will be made to avoid a pregnancy during the use of an IMP. A pregnancy test will be done for all WOCBP to exclude pregnant patients.

WOCBP is defined as fertile woman, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

Pregnancies occurring during the study (fetal exposure to the IMP) need to be reported by the investigator using a pregnancy notification form. The form must be submitted to Sponsor and Sponsor's designee following SAE reporting instructions provided in Section 7.3.2.

Follow-up information on the outcome of both mother and fetus will be requested by a Sponsor representative.

Overdose, interaction, medication error and lack of efficacy:

The following safety relevant information should be reported as AE or, if the reaction fulfils one of the criteria for seriousness, as SAE.

Drug overdose:

An overdose is a deliberate or inadvertent administration of a treatment at a dose higher than specified in the protocol and higher than the known therapeutic dose and of clinical relevance. The reaction must be clearly identified as an overdose.

Interaction:

A drug interaction is a situation in which a substance/medicinal product affects the activity of an IMP, i.e., the effects are increased or decreased, or they produce an effect that none of the products exhibits on its own. The reaction must be clearly identified as drug interaction.

Medication error:

Medication error involves the inadvertent administration or unintended use of a medicinal product which may be caused by the naming, presentation of pharmaceutical form/packaging, instructions for use/labeling. The reaction must be clearly identified as a medication error.

7.4 Appropriateness of Measurements

Since the ultimate goal of the administered treatments is to restore a clinically satisfactory hemostasis for the duration of the surgery/invasive procedure, the clinical assessment of hemostatic efficacy provides the key clinical information on treatment efficacy. Blinded assessment of hemostatic efficacy has therefore been chosen as the primary endpoint. The secondary and further exploratory endpoints will provide further information on the clinical comparability of OCTAPLEX and Beriplex® P/N (Kcentra).

8 DATA HANDLING AND RECORD KEEPING

8.1 Documentation of Data

8.1.1 Source Data and Records

Source data are defined as all the information related to clinical findings, observations, or other activities in the study, provided in original records or certified copies of original records allowing reconstruction and evaluation of the clinical study.

The investigator will maintain adequate source records (e.g. case histories or patient files for each patient enrolled). Source records should be preserved for the maximum period of time required by local regulations.

For each patient enrolled, the investigator will indicate in the source records that the patient participates in this study.

All data entered in the CRF must be supported by source data in the patient records.

The investigator will permit study-related monitoring, audit(s), IEC/IRB review(s) and regulatory inspection(s), by providing direct access to source data/records.

The investigator may authorize site staff (e.g. sub-investigators, nurses) to enter study data into the CRF. This must be documented in the "Delegation of Authority Log", signed by the investigator.

8.1.2 Case Report Forms

For each patient enrolled, an electronic CRF (eCRF) will be completed within the Electronic Data Capture (EDC) system and approved by the investigator or an authorized sub-investigator.

Study site staff (e.g. research nurse) will be responsible for entering patient data into the validated EDC system. All site personnel will be trained on the EDC system and study specific eCRFs prior to receiving access to the live database for data entry. The site is also provided with the approved eCRF Completion Guidelines which will assist in data entry and data issues/questions. The site will be notified once the database is active to begin data entry. Additional site training may be provided as refreshers throughout the study, if needed. All persons allowed to enter or change eCRF data must appear on the delegation of authority log.

If any errors in the eCRFs are found during the data review process discrepancies will be generated programmatically within the EDC system, and 'manual' queries will be generated by either a monitor or Data Management. The programmed checks fire automatically once an eCRF page is saved within the system. The outputs of the programmed checks are referred to as 'discrepancies'. Discrepancies are generated by the input of illogical eCRF data with the purpose to clarify the context or insertion of illogical or missing data with the site or designee.

All discrepancies (programmed and manual) will be submitted to the site personnel or monitor for the site within the EDC system. Once the site responds to a discrepancy, Data Management or the monitor will review the new or changed data to ensure an appropriate response and close the discrepancy within the system.

8.1.3 Changes to Case Report Form Data

Monitors will perform source data verification (SDV) as defined for the study.

Errors occurring on the EDC system can only be corrected by the investigator(s) or other authorized site personnel. An audit trail documents all changes to the data over the entire study period. If data is changed as a result of a query, a comment must be supplied within the query's text, stating the reason for the change, prior to closing. The study monitor should provide guidance to investigators and the investigators' designated representatives on making such corrections. In addition, any changes to a previously saved eCRF page that has not had a query generated will need to have a reason specified for the data change. This is handled within the EDC system and relevant prompts appear once any changes are made.

Once queries have been resolved by the site staff, the resolutions are assessed by Data Management. If the query response provided confirms the data as correct, the discrepancy will be closed. If the response does not adequately address the question raised, a new query will be issued for further clarification.

Manual checks are performed and programs are run throughout the study until the data is clean and the database is ready for lock. All discrepancies will be resolved prior to database lock. There will be a final run of the programmed checks to ensure all discrepancies are closed out, SDV will be confirmed as complete by the monitor, and all eCRFs will be approved by the investigator prior to database lock.

8.2 Information of Investigators

An IB will be handed out to the investigator before the start of the study. This Brochure contains all information in the Sponsor's possession necessary for the investigator to be fully and accurately informed about the safety of the IMP under evaluation and the respective benefit-risk ratio.

The IB will be updated by the Sponsor at regular intervals and in case new information concerning the IMP becomes available.

The investigators will be informed about the methods for rating relevant study outcomes and for completing CRFs in order to reduce discrepancies between participating investigators and study sites.

The investigator will be kept informed of important data that relate to the safe use of the IMP as the study proceeds.

8.3 Responsibilities

The principal investigator is accountable for the conduct of the clinical study. Responsibilities may be delegated to appropriately qualified persons.

A "Delegation of Authority Log" will be filled in and signed by the investigator. In accordance with this authority log, study site staff (e.g. sub-investigators, nurses) are authorized to perform tasks relating to the study.

8.4 Investigator's Site File

At each study site, the investigator is responsible for maintaining all records to enable the conduct of the study to be fully documented. Essential documents as required by GCP guidelines and regulations (e.g., copies of the protocol, study approval letters, all original informed consent forms, site copies of all CRFs, drug dispensing and accountability logs, correspondence pertaining to the study, etc.) should be filed accurately and kept by the investigator for the maximum period of time required by local regulations.

The investigator is responsible for maintaining a confidential patient identification code list, which provides the unique link between named source records and CRF data for the Sponsor. The investigator must arrange for the retention of this confidential list for the maximum period of time required by local regulations.

No study document should be destroyed without prior written agreement between the investigator and the Sponsor. Should the investigator elect to assign the study documents to another party, or move them to another location, the Sponsor must be notified in writing.

8.5 Provision of Additional Information

On request, the investigator will supply the Sponsor with additional data relating to the study, or copies of relevant source records, ensuring that the patient's confidentiality is maintained. This is particularly important when CRFs are illegible or when errors in data transcription are encountered. In case of particular issues or governmental queries, it is also necessary to have access to the complete study records, provided that the patient's confidentiality is protected in accordance with applicable regulations.

8.6 Independent Data Monitoring Committee

An IDMC will be established by the Sponsor. The IDMC will be composed of recognized experts in the field of clinical care who are not actively recruiting patients and an independent statistician.

A study specific IDMC charter will define in detail the composition, responsibilities and procedures of the IDMC.

This Committee will have the following tasks:

- To review all **serious AEs** in a timely manner;
- To review all **non-serious AEs** on a regular basis;
- Review interim analysis results and give recommendations whether to continue the study or not;
- To give advice on the continuation, modification or termination of the study.

The IDMC will have access to the Investigator's Brochure for Octaplex and the current package insert for Beriplex® P/N (Kcentra), which includes all the ADRs that have been observed with the investigational product.

The IDMC will review individual unblinded safety data in order to monitor the accruing data for safety. IDMC review determinations will be communicated to investigators by the Sponsor/the Sponsor's designee.

9 STATISTICAL METHODS AND SAMPLE SIZE

9.1 Determination of Sample Size

The statistical analysis of the primary variable hemostatic success will be based on the probabilities of hemostatic success (derived from the blinded rating by the IEAB of OCTAPLEX and Beriplex® P/N (Kcentra) (p_O and p_K).

To demonstrate that the treatment with OCTAPLEX is clinically not inferior to the treatment with Beriplex® P/N (Kcentra) with respect to hemostatic success, a two-sample, one-sided test of the pair of hypotheses:

$$H_0: \quad p_K - p_O \geq \delta \quad \text{vs.} \quad H_1: \quad p_K - p_O < \delta$$

will be carried out with a type I error probability of $\alpha = 0.025$ and clinical non-inferiority margin of $\delta = 0.15$.

Farrington's and Manning's test for difference in proportions will be used to assess the primary hypothesis in an interim and in the final analysis.

Based on this method and a one-sided overall type I error probability $\alpha = 0.025$, power $1 - \beta = 0.8$, and a non-inferiority margin of $\delta = 0.15$, the table below presents the estimated sample sizes per treatment group for the one-sided testing problem taking into account one planned interim analysis after half of the planned patients are enrolled for different constellations of OCTAPLEX and Beriplex® P/N (Kcentra) hemostatic success probabilities. The calculations are based on the following additional assumptions:

- A multiple one-sided significance level (family-wise error rate) of 0.025 for the interim and final analysis
- An α-spending function according to Hwang, Shi and Cani (11) with parameter γ=-0.8 which allows an early efficacy stop if p <0.01.
- A β-spending function according to Hwang, Shi and Cani (11) with parameter γ=-4.584 which allows a non-binding futility stop if p> 0.5.

Beriplex® P/N (Kcentra) hemostatic success probability	89%	85%			90%			95%		
OCTAPLEX hemostatic success probability	85%	85%	90%	95%	85%	90%	95%	85%	90%	95%
sample size per group	166	100	51	28	193	75	37	615	135	50
actual power	80.3	80.5	81.5	82.2	80.7	80.8	80.6	80.1	80.6	82.0

Conservatively assuming an OCTAPLEX hemostatic success probability of at least 85% and a Beriplex® P/N (Kcentra) hemostatic success probability of at most 89%, it is planned to enrol 185 patients in each treatment arm, i.e. 370 patients in total.

Assuming a proportion of about 10% randomized patients who were not treated or did not undergo the surgical procedure for administrative reasons; this would ensure that data on at

least 166 patients per treatment group in the modified ITT (mITT) population will be available for the final statistical analysis as derived from the sample size calculation.

9.2 Statistical Analysis

A formal statistical analysis plan (SAP) describing all details of the analyses to be performed will be prepared by the study statistician and approved by the Sponsor prior to the start of the statistical analysis.

9.2.1 Population for Analysis

The randomized population (RAND) will include all randomized patients irrespective of whether they received treatment. This is the intent-to-treat (ITT) population according to the most rigid definition of ITT.

The safety analysis population (SAF) will include all randomized patients who received at least one dose of IMP. Patients receiving different study treatments than originally randomized will be considered according to the treatment actually received (rather than that of the original randomization).

For further statistical analysis of the efficacy parameters, a modified Intention-to-Treat population (mITT) is defined: All randomized patients who received at least one infusion of IMP, and who had the surgery initiated or for whom the surgery was not initiated for medical reasons related to insufficient coagulation. Patients in whom the surgery was not initiated due to technical reasons/aesthesia/etc (i.e., not related to insufficient coagulation) will be excluded from the mITT, whereas patients in whom the surgery was not initiated for coagulation-related reasons will be considered as treatment failures.

The Per-protocol (PP) population: This analysis population will consist of all patients in the mITT population, excluding patients with major protocol deviations potentially affecting the primary endpoint. The following patients will be excluded:

- Patients who receive an IMP different to the IMP assigned by randomization
- Patients who receive less than 70% of the planned dose
- Patients who significantly violate inclusion/exclusion criteria
- Patients with missing primary efficacy assessment
- Start of surgery more than 5 hours after end of infusion of IMP

A final decision about the classification of protocol deviations as major and minor and their consequences regarding assignment of patients to analysis populations will be made during the blinded data review meetings prior to unblinding of patient cohorts for the interim and final analyses. Decisions and outcome will be approved by the Sponsor.

The analysis of safety will be based on the SAF.

The primary efficacy analysis will be based on all randomized subjects (RAND=ITT).

9.2.2 In addition the primary endpoint will also be analysed using the mITT and the PP population. Efficacy Analysis Plan

9.2.2.1 Primary Endpoint: Hemostatic Efficacy

The primary efficacy variable is the hemostatic efficacy as assessed by the IEAB. The hemostatic efficacy is to be assessed based on objective criteria in the categories 'excellent', 'good', 'moderate' or 'none'. Ratings of 'excellent' and 'good' will be considered as 'effective' hemostasis, while a rating of 'moderate' and 'none' will be considered as 'ineffective' hemostasis.

The dichotomous 'hemostatic success' variable will be used in the analyses. This variable will be imputed as 'ineffective' under the following two circumstances:

- If hemostatic efficacy value is missing, then hemostatic efficacy will be considered 'none' for the analysis. This can occur in the RAND population if the patient is randomized and not treated (or does not undergo surgery), also in the mITT population if the patient is treated but does not undergo surgery due to insufficient coagulation.
- If patient receives additional coagulation treatment (e.g. PCC, single coagulation factors, plasma) after initial IMP infusion, then hemostatic efficacy will be considered 'none' for the analysis.

To demonstrate that treatment with OCTAPLEX is clinically not inferior to treatment with Beriplex® P/N (Kcentra) with respect to hemostatic success, a two-sample, one-sided test of the pair of hypotheses:

$$H_0: \quad p_K - p_O \geq \delta \text{ (inferiority)}$$

$$\text{vs.} \quad H_1: \quad p_K - p_O < \delta \text{ (non-inferiority)}$$

will be carried out with a type I error probability of $\alpha = 0.025$ and clinical non-inferiority margin of $\delta = 0.15$. Whereby p_O and p_K present the probabilities of hemostatic success of OCTAPLEX and Beriplex® P/N (Kcentra) respectively.

Farrington's and Manning's test for difference in proportions will be used to assess the primary hypothesis in an interim and in the final analysis. One-sided p-values and the corresponding nominal and repeated CIs for the difference in hemostatic success probabilities will be presented.

The primary analysis will be performed on the RAND population. Additional analyses will be performed for the mITT and the PP population.

In case of non-inferiority in the RAND, mITT and the PP population a "tipping point" analysis will be done to determine the robustness of the results. Iteratively patients excluded from the RAND/mITT/PP analysis assigned to the control arm will be considered as treatment successes, and patients excluded from the RAND/mITT/PP analysis and assigned to the OCTAPLEX arm will be considered as treatment failures, to determine the number of such imputed outcomes required to "tip" the study result from positive to negative in the randomized population.

A sensitivity analysis will be conducted in the RAND, mITT, and PP populations based on the hemostatic efficacy rating by the investigators at the end of surgery.

A concordance analysis will be done to assess the agreement between the assessment by the IEAB and the investigator assessment.

9.2.2.2 Secondary Endpoints

The following measurements will be considered as exploratory secondary endpoints in the analysis of the efficacy of the study treatments:

- Proportion of patients with an INR value of less or equal to 1.5 to 30 minutes (± 15 minutes) after the end of infusion.
- Change in coagulation factor levels from baseline to 30 minutes (± 15 minutes) after the end of infusion:
  - Factor FII
  - Factor FVII
  - Factor FIX
  - Factor FX
- Proportion of patients receiving RBC during the surgery

The primary analysis of secondary endpoints will be based on the ITT population, except for the proportion of patients receiving RBC during surgery, this will be based on subset of patients undergoing surgery. Additionally the same analyses will be done on the mITT and PP populations.

Farrington's and Manning's test for difference in proportions will be used to test the secondary variables on proportions. Point estimates and two-sided 95% CIs will be presented in addition to descriptive statistics for these endpoints.

The change in the individual coagulation factors from baseline to end of infusion will be tested with the Wilcoxon rank-sum test between OCTAPLEX and Beriplex® P/N (Kcentra). The Hodges-Lehmann estimator of the median difference of the intra-individual change in the individual coagulation factors from baseline to end of infusion between OCTAPLEX and Beriplex® P/N (Kcentra) and the corresponding 95% CI will be calculated.

9.2.2.3 Further Exploratory Endpoints

Analysis of the further exploratory endpoints will be done on the ITT, mITT, and PP population unless indicated otherwise. All analyses will be exploratory, by presenting descriptive statistics.

- Change in INR from baseline.
- Change in PC, and PS from baseline to the end of infusion.
- Change in coagulation factor levels (FII, FVII, FIX, FX, PC, and PS) from baseline to 2 h, 4 h, 12 h and 24 h after end of infusion
- Assessment of blood loss after end of surgery.
- Proportion of patients receiving plasma and platelets transfusions initiated during the surgery.
- Total volume of RBC and other blood product transfusions initiated during the surgery normalized by patient's BW.
- Change in hematological parameters (Hgb, Hct, RBC, WBC, platelets) from the beginning to the end of the surgery.
- RBC transfusion corrected change from baseline in Hgb at 12 and 24 hours after start of surgery
- Proportion of patients experiencing surgical wound hematoma requiring surgical evacuation

- Ratio of actual estimated blood loss as documented after surgery to the pre-operative predicted blood loss for the type of planned surgery

9.2.2.4 Subgroup Analyses for Efficacy

To study the sensitivity of the efficacy results subgroup analysis will be performed for the primary and the secondary efficacy endpoints based on the following characteristics:

- expected blood loss ("≥200 mL", "≥100 mL but <200 mL" or "≥50 mL but <100 mL") according to information provided at randomisation
- type of planned surgery ("orthopaedic surgery", "cardiothoracic surgery" or "other surgery")gender (male/female)
- age in years (<=60, 60+)
- race
- history of TEE (yes/no)
- baseline INR (2 to <4 / 4 to <6 / ≥6)
- concomitant treatment with Vitamin K (yes/no)

These subgroup analyses are considered to be exploratory and will involve no type I error adjustment. The subgroup analyses will be based on the primary analysis population for efficacy.

9.2.3 Safety Analysis Plan

Safety analyses will be performed for the SAF.

9.2.3.1 Adverse Events

AEs will be coded according to the latest MedDRA version as specified in the Data Management Plan. The analysis will focus on treatment emergent adverse events (TEAEs), i.e., AEs that started or worsened after start of infusion with IMP. All TEAEs, related TEAEs (i.e. AEs probably or possibly related to the IMP), and serious TEAEs will be summarized and tabulated according to primary system organ class and preferred term. TEAEs leading to death and TEAEs resulting in withdrawal from the study, respectively, will be tabulated using frequency tables if a reasonable number of events of this type are observed.

Patient listings will be provided for patients with SAEs, AEs leading to withdrawal from study, and AEs leading to death. The listings will also include patients enrolled but not randomized.

9.2.3.2 Thromboembolic Events

The number of patients with TEEs overall and within 3, 21 and 45 days after end of surgery will be summarized. A possible difference between treatment groups will be estimated by a risk ratio with 95% CI. Kaplan-Meier estimates for time to first occurrence of a TEE event will be calculated and graphically presented.

9.2.3.3 Mortality

The number of patients who died overall and within 3, 21 and 45 days after end of surgery will be summarized. A possible difference between treatment groups will be estimated by a risk

ratio with 95% CI. Kaplan-Meier estimates for time to death will be calculated and graphically presented.

9.2.3.4 Routine Laboratory Data

All laboratory values will be classified as normal or abnormal according to the laboratories' normal ranges and indicated as clinically significant or not clinically significant by the investigator. The following approaches will be taken for each laboratory parameter for the statistical analysis:

- Quantitative data will be examined for trends using descriptive analysis (number of patients, number of missing values, mean, SD, median, quartiles, minimum, maximum) of actual values at each visit and changes from baseline to each visit over time
- Qualitative data based on reference ranges will be described according to the categories (i.e., low, normal, high)
- Shift tables illustrating changes with respect to the laboratories' normal ranges between baseline and a defined visit
- Number and frequency of patients with clinically significant laboratory values. A separate patient listing will be provided

9.2.3.5 Vital Signs

Blood pressure (systolic/diastolic), pulse rate, and body temperature will be presented by time point.

9.2.3.6 Viral Safety

The incidence of Parvovirus B19 seroconversion will be calculated. Parvovirus B19 seroconversion is defined as the percentage of patients who have a positive post-baseline value but were negative at baseline. Seroconversion rates will be by treatment group both for serology and nucleic acid tests.

9.2.3.7 Subgroup Analyses for Safety

Subgroup analysis will be performed for overall number of TEAEs, related TEAEs and serious TEAEs, overall TEE and mortality rates based on the following characteristics:

- any TEE in medical history
- occurrence of any TEE within 1 year prior to surgery (yes/no),
- gender (male/female),
- baseline INR (2 to <4 / 4 to <6 / ≥6),
- concomitant treatment with vitamin K (yes/no)

These subgroup analyses are considered to be exploratory and will involve no type I error adjustment.

9.2.4 Handling of Missing Data

In general, missing data will not be imputed.

Patients for whom the primary efficacy endpoint 'hemostatic success' can't be assessed will be considered as having clinical hemostasis rated as "none". This efficacy analysis is performed with the RAND population (as primary), and additionally with the mITT and PP.

9.3 Randomization / Stratification / Code Release

The IMPs will be administered only to patients for whom a signed written IC form is available.

Eligible patients will be randomly assigned to receive either OCTAPLEX or Beriplex® P/N (Kcentra). To ensure balance between the two treatment groups with respect to type of surgery, estimated blood loss and history of TEE, randomization will be stratified by type of surgery, estimated blood loss and presence or absence of TEE in the medical history.

Randomization will be implemented by site staff using an IRT system. Randomization allocation will be 1:1 to OCTAPLEX or Beriplex® P/N (Kcentra), respectively.

Patients will be identified using a sequential numbering system.

9.4 Interim Analysis

The study employs a sequential design that allows one pre-planned interim analysis using the data from the first 50% of randomized patients. The interim analysis will be performed on the cohort of the first 185 randomized patients after documentation of the primary endpoint has been performed.

The interim analysis will focus on the analysis of hemostatic success probabilities based on the independent adjudication in the ITT population. The allocation of patients in the ITT population will be done in a blinded data review meeting prior to unblinding.

After the interim analysis, a positive outcome for non-inferiority test may be claimed and enrollment may be stopped if the primary test statistic in the ITT population is greater than the adjusted critical value $z_1 = 2.33$ corresponding to an adjusted significance level of $\alpha_1 = 0.01$ (efficacy stop). If a p-value > 0.5 is observed, the study may be stopped for futility (non-binding futility stop). The worst effect of a possible overrunning on the final result will be assessed if the result suggests a termination of the study. Individual patient data relevant to the interpretation of interim results will be listed.

The interim analysis will be performed by a statistical team which is independent from the study team. An IDMC will be established to review the interim analysis results and give recommendations whether to continue the study or not.

Details on the composition and charter of the IDMC will be provided before study start. A final analysis including all study data will be performed and reported if enrollment is stopped after the interim analysis. Otherwise, the study will continue until the maximum sample size is reached, and the final analysis will be performed as described above.

Further details of the interim analysis will be described in the respective sections of the SAP.

10 ETHICAL / REGULATORY, LEGAL AND ADMINISTRATIVE ASPECTS

10.1 Ethical / Regulatory Framework

This study will be conducted in accordance with the ethical principles laid down in the Declaration of Helsinki. The study protocol and any subsequent amendment(s) will be submitted to an Independent Ethics Committee (IEC) / IRB and to the Regulatory Authority. The study will be conducted in compliance with the protocol, GCP regulations and applicable regulatory requirements.

The regulatory application or submission for regulatory approval will be made by the Sponsor or designated third party (e.g. Contract Research Organization) as required by national law.

10.2 Approval of Study Documents

The study protocol, a sample of the patient information and informed consent form, any other materials provided to the patients, and further requested information will be submitted by the Sponsor or the investigator to the appropriate IEC/IRB and the Regulatory Authority. The study approval letter must be available before any patient is exposed to a study-related procedure.

The Sponsor, the investigator and any third party (e.g., Contract Research Organization) involved in obtaining approval, must inform each other in writing that all ethical and legal requirements have been met before the first patient is enrolled in the study.

10.3 Patient Information and Informed Consent

The investigators will obtain a freely given written consent from each patient. Children are not to be included in this study.

The investigators will explain that the subjects are completely free to refuse to enter the study or to withdraw from it at any time, without any consequences for the subject's further care and without the need to justify. The investigator will complete the informed consent section of the CRF for each subject enrolled.

Each patient will be informed that their source records may be reviewed by the study monitor, a quality assurance auditor or a health authority inspector, in accordance with applicable regulations, that the investigator will protect any personal information not related to the study, and that these persons are bound by confidentiality obligations.

10.4 Protocol Amendments

Any prospective change to the protocol will be agreed between the investigator (co-ordinating investigator in multi-centre studies) and the Sponsor prior to its implementation. Any such amendments will be submitted to the IEC(s/IRB) and/or competent authority responsible as required by applicable regulations. IEC(s)/IRB approval will at a minimum be requested for any change to this protocol which could affect the safety of the patients, the objective/design of the study, any increase in dosage or duration of exposure to the IMP an increase in the number of patients treated, the addition of a new test or procedure, or the dropping of a test intended to monitor safety.

10.5 Confidentiality of Patients´ Data

The investigator will ensure that the patient's confidentiality is preserved. On CRFs or any other documents submitted to the Sponsor, the patients will not be identified by their names, but by a unique patient number. Documents not for submission to the Sponsor, i.e., the confidential patient identification code list, original consent forms and source records will be maintained by the investigator in strict confidence.

11 QUALITY CONTROL AND QUALITY ASSURANCE

11.1 Periodic Monitoring

The monitor will contact and visit the investigator periodically to review all study-related source data/records, verify the adherence to the protocol and the completeness, correctness and accuracy of all CRF entries compared to source data. The investigator will cooperate with the monitor to ensure that any discrepancies identified are resolved.

For this study, the first monitoring visit shall take place shortly after the inclusion of the first patient. Thereafter, monitoring frequency will depend on study progress.

The monitor must be given direct access to source documents (original documents, data and records). Direct access includes permission to examine, analyze, verify and reproduce any records and reports that are important to the evaluation of the clinical study. Source data will be available for all data in the CRFs, including all laboratory results.

11.2 Audit and Inspection

The investigator will make all study-related source data and records available to a qualified quality assurance auditor mandated by the Sponsor, or to IEC/IRB/regulatory inspectors, after reasonable notice. The main purposes of an audit or inspection are to confirm that the rights and welfare of the patients have been adequately protected, and that all data relevant for the assessment of safety and effectiveness of the IMP have been reported to the Sponsor.

12 REPORTING AND PUBLICATION

12.1 Clinical Study Report

A clinical study report (in accordance with relevant guidelines and Sponsor's Standard Operating Procedure) will be prepared by the Sponsor after the completion of the study. The coordinating investigator will approve the final study report after review.

12.2 Publication Policy

The results of this study may be published or presented at scientific meetings. If this is envisaged by an investigator, the investigator agrees to inform the Sponsor and to submit all manuscripts or abstracts to the Sponsor prior to submission to an editorial board or scientific review committee. This will allow the Sponsor to protect proprietary information and to provide comments based on information that may not yet be available to the investigator.

In accordance with standard editorial and ethical practice, the Sponsor will support publication of multi-centre studies only in their entirety and not as individual centre data. Authorship will be determined by mutual agreement.

13 LIABILITIES AND INSURANCE

In order to cover any potential damage or injury occurring to a patient in association with the IMP or the participation in the study, the Sponsor will contract insurance in accordance with local regulations.

The investigator is responsible for dispensing the IMP according to this protocol, and for its secure storage and safe handling throughout the study.

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15 APPENDICES

Not applicable.