Octapharma

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.

Statistical Analysis Plan

Version: 03

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STATISTICAL ANALYSIS PLAN

SIGNATURE PAGE

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Protocol No: LEX-209

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1 Introduction

1.1 Preface

The objective of this document is to detail the statistical methodology to be used for the interim and the final statistical analysis of Octaplex study LEX-209.

The statistical analysis plan is based on the following information and documents:

Current Study Protocol	19 January 2018 – Version 04
Amendments to Study Protocol / Observational Plan	Original protocol dated: 1 April 2016 Version 02 dated: 1 Oct 2016 Version 03 dated: 21 October 2016

1.2 Timing of statistical analyses

The following statistical analyses are planned for this study:

- Interim analysis: one interim analysis after half of the patients are randomized and adjudication of the primary endpoint is available
- Safety analyses: quarterly safety analyses to be provided to Independent Data Monitoring Committee (IDMC)
- Final analysis: after all patients completed the study and the database is locked

2 Modification History

2.1 Changes to the study protocol

The statistical analysis as specified in this SAP is consistent with the statistical analysis as specified in the study protocol dated 21-Oct-2016, version 03.

2.2 Changes to previous SAP versions

Version (Date)	Revision
01 (01-Apr-2016)	Initial version
02 (27-Oct-2016)	Updated for consistency with protocol dated 21-Oct-2016, version 03
03 (06-Jan-2021)	Updates following review of SAP before execution of the interim analysis

3 Study Design

Indication	Reversal of vitamin K antagonist (VKA) induced anticoagulation in patients needing urgent surgery associated with significant bleeding risk.
Design	Prospective, multi-center, randomized, parallel group, double-blind, active-controlled, group-sequential non-inferiority
Phase	III
Primary Objective(s)	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 Objective(s)	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.
Treatments	OCTAPLEX, Beriplex® P/N (Kcentra)
Number of patients	370 (185 per treatment group)
Interim analysis	One interim analysis after half of the patients are randomized and adjudication of the primary endpoint is available

3.1 Sample size estimation

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 independent endpoint adjudication board (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 [1] 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 [1] 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 enroll 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.

3.2 Randomization, blinding and unblinding procedures

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 receiving a VKA generally have an underlying higher risk of thromboembolic events (TEEs), the reason for administration of the antagonist. Withdrawal of the antagonist and restoration of coagulation via administration of prothrombin complex concentrates (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 factor.

Regarding expected blood loss:

- 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.

4 Analysis Populations

Enrolled Analysis Population

The enrolled analysis population includes all patients who provided informed consent.

Randomized Population (RAND)

The randomized population will include all randomized patients irrespective of whether they received treatment. Following the intent-to-treat principle all patients will be analysed according to the treatment group to which they were randomized. This is the intent-to-treat (ITT) population according to the most rigid definition of ITT.

Safety Analysis Population (SAF)

The safety analysis population (SAF) will include all randomized patients who received investigational medicinal product (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).

Modified Intention-to-Treat Population (mITT)

The mITT population will consist of all randomized patients who received IMP, and who had the surgery initiated or for whom the surgery was not initiated for medical reasons related to insufficient coagulation.

Per Protocol Population (PP)

The PP population will consist of all those 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.

All patients excluded from the different analysis populations will be listed together with the reason for exclusion. The listing will also be presented by study site.

All safety analyses will be based on the SAF population. The primary efficacy analysis will be based on the RAND population.

Furthermore, additional efficacy analyses will be performed using the mITT and the PP populations, as specified in section 10 Efficacy. Demographic and background characteristics will be presented on the SAF, RAND and mITT. In case of only minor differences between

any analysis set, it will be discussed during the blind data review meeting to omit the creation of individual sets and use the next available set for the given analyses.

If not otherwise stated in the respective section, the statistical analyses will be performed for the following analysis populations:

Analyses	RAND (ITT)		mITT	PP	SAF
Demographics and background characteristics	✓				✓
Exposure and compliance	✓				✓
Previous and concomitant therapies	✓				✓
Surgery information	✓				
Efficacy: Primary	✓		✓	✓	
Efficacy: Secondary	✓		✓	✓	
Efficacy: Exploratory	✓				
Efficacy: Subgroup analysis	✓				
Safety					✓

5 General Statistical Methods and Definitions

5.1 General statistical methods

The statistical analyses will be presented by treatment group for the different analysis populations as defined in section 4 Analysis Populations.

Summary tables will usually be structured with a column for each treatment in the order Beriplex® P/N (Kcentra) and OCTAPLEX. For demographic and background characteristics a "Total" column will be additionally provided.

In general, continuous variables will be summarized using descriptive statistics, i.e. generally displaying number of patients in the respective analysis population, number of patients with data, number of patients with missing values, mean, standard deviation, minimum, lower quartile, median, upper quartile, and maximum.

Categorical variables will be summarized by using frequency counts and percentages. In addition, the number of patients with missing values will be displayed. Percentages usually relate to the number of patients with data. This includes data obtained by the respective missing data replacement strategy (see section 5.4 Missing data).

Means, medians, and standard deviations will be presented by 1 additional decimal place than the standard presentation level of the respective patient data. Minimum and maximum values will be presented using the same number of decimal places as the patient data. Percentages will be presented to 1 decimal place if not otherwise stated.

In listings, data will be sorted by treatment, site, and patient, and when appropriate by visit or other identifiers for sequence or type of observation.

If not otherwise specified, all statistical tests will be two-sided. The significance level of one sided tests will be divided by two to ensure comparability with two-sided tests.

The confidence level for calculation of confidence intervals will be chosen as (1-significance level) of the respective statistical test.

5.2 Strata

Treatment allocation by the IRT will be stratified according to the following three parameters, documented as baseline prior to randomization.

History of TEE

Presence or absence of any embolic or thrombotic event, defined according to the Standardized MedDRA query (SMQ) “Embolic and thrombotic event”, in the medical history of the patient.

Type of surgery

The type of surgery will be categorized into one of the following: “orthopaedic surgery”, “cardiothoracic surgery” or “other surgery”.

Expected Blood Loss

Expected blood loss will be categorized into one of the following: "≥200 mL", "≥100 mL but <200 mL" or "≥50 mL but <100 mL".

5.3 Subgroups

The following subgroups will be defined:

1. expected blood loss ("≥200 mL", "≥100 mL but <200 mL" or "≥50 mL but <100 mL") according to information provided at randomisation
2. gender (male/female)
3. baseline INR (2 to <4 / 4 to <6 / ≥6)
4. concomitant treatment with vitamin K (yes/no)
5. any TEE in medical history (yes/no)
6. occurrence of any TEE within 1 year prior to surgery (yes/no)
7. type of planned surgery ("orthopaedic surgery", "cardiothoracic surgery" or "other surgery")
8. age in years (<=60, 60+)
9. race

To study the sensitivity of the efficacy results subgroup analysis will be performed for the primary and the secondary efficacy endpoints for the first four subgroups. Results for the different subgroups will be presented descriptively by presenting the results separately for each subgroup and its complement.

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.

Regarding safety, subgroup analysis will be performed for overall number of treatment emergent adverse events (TEAEs), related TEAEs and serious TEAEs, overall TEE and mortality rates for the subgroups 2-6.

5.4 Missing data

Missing data will not be imputed except for analyses of the primary efficacy endpoint (see section 10.1 Primary efficacy analysis and 10.2 Secondary efficacy analyses for details) and partial and missing dates as specified below.

Partial or missing dates and times

Where the start date of an event or medical condition is missing or partially missing, the event will be assumed to be started after the start of IMP, unless there is clear evidence (through comparison of partial dates/times) to suggest otherwise.

In case of a partial or missing end date the medical condition will be assumed to be ongoing after start of IMP except if the partial date indicates that the condition stopped prior to start of IMP.

5.5 Observation and analysis times

Study days

Study day is defined as the number of days since start of infusion of IMP and, for a particular date, and is calculated as:

Study day = Assessment date – Date of start of infusion of IMP + 1.

Therefore, the date of infusion of IMP will be Day 1.

Study periods

Start and End of infusion and start and end of surgery define important timepoints during the course of the study. The following study periods are defined using these timepoints:

- Before start of infusion, comprises screening and baseline period: all observations until start of infusion of IMP
- Before start of surgery: from start of infusion till start of surgery
- During surgery: all observation during surgery
- After end of surgery to Day 4/discharge
- Follow-up: all observations after Day 4/discharge to end of study (day 45)

Definition of baseline values

The baseline value is in general defined to be the last value which was assessed before the start of infusion.

For INR the baseline value is defined as the INR value used for dose calculation.

Definition of analysis timepoints or time windows

The definition of analysis timepoints / time windows is specified in the following table.

Measurement	Analysis Timepoint	Time window
Coagulation Factors	30 min after end of infusion	30 min ± 15 min
	2h after end of infusion	2 h ± 15 min
	4h after end of infusion	4 h ± 30 min
	12h after end of infusion	12 h ± 1h
	24h after end of infusion	24 h ± 2 h
Virology	Day 9	Day 9 - 2 days/+ 5 days
Rate of TEE/Mortality	Day 4	Day 4
	Day 21	Day 21 ± 1 week
	Day 45	Day 45 ± 1 week

6 Patient Accounting and Disposition

6.1 Patient accounting

The number and relative frequencies of patients in each analysis population as defined in section 4 Analysis Populations will be presented overall and by randomized treatment, country and site. The enrolled population will only be presented overall.

Furthermore the number and percentage of patients in each analysis population will be presented overall and by treatment group including individual reasons of exclusion from the respective analysis population.

A list of patients with all randomization assignment information will be generated in order to confirm that the randomization was performed according to the randomization plan.

6.2 Disposition and withdrawals

The number and relative frequency will be presented for

- Patients not undergoing surgery and reasons thereof
- Patients who prematurely discontinued the study,
- Reasons for discontinuation.

Patients who discontinued the study will be listed.

6.3 Major protocol deviations

Major protocol deviations leading to exclusion from the per-protocol population are specified in section 4 Analysis Populations.

The number and relative frequency of patients with major protocol deviations leading to exclusion from the per-protocol population will be presented by treatment group, country, and study site for RAND.

In addition, all deviations of the in-/exclusion criteria will be summarized by treatment group and study site for the RAND.

All patients with protocol deviations as specified above will be listed.

7 Demographics and Background Characteristics

Demographic and baseline characteristics as specified in detail below will be presented descriptively by treatment group.

A statistical testing for baseline differences is not considered appropriate in a randomized study. In randomized controlled studies, randomization ensures that, on average, the distribution of baseline covariates will be similar between the different treatment groups.

7.1 Demographics

The following demographic characteristics will be presented

- Sex (male/female)
- Age (years), as entered in the eCRF
- Race (Caucasian, African (black), Asian, Other)
- Weight (kg) at baseline
- Height (cm) at baseline
- BMI (kg/m^2) at baseline = weight in kg / (height in cm)^2× 10000

The demographic data will be listed.

7.2 Disease characteristics

The following disease characteristics will be presented

- Pre-infusion anti-coagulation therapy
- History of TEE
- Type of planned surgery
- Estimated blood loss

7.3 Medical history

The diseases are coded according to Medical Dictionary for Regulatory Activities (MedDRA®) Version 18.1 or higher and will be classified as follows:

- Previous medical conditions, i.e. medical conditions that stopped prior to start of treatment
- Ongoing (concomitant) medical conditions, i.e. medical conditions still present after start of treatment

The frequency of diseases recorded from medical history will be presented after classification into previous and concomitant conditions by system organ class (SOCs) as well as the frequencies of preferred terms (PT) within each SOC. If patients have more than one disease within a SOC or PT they will be counted only once for the respective SOC or PT.

Additionally, all PTs occurring in the MedDRA SMQ “Embolic and thrombotic events” will be presented. For patients with a history of TEE, time (in months) since occurrence of last TEE event before enrollment will be presented with descriptive statistics.

8 Exposure and Compliance

8.1 Treatment groups

Treatments will be labelled as follows:

- KCentra
- Octaplex

For the RAND and mITT, patients will be assigned to the treatment groups they were randomized to and for the SAF to the treatment they actually received.

The number and percentage of patients will be presented by treatment group, study site and analysis population.

Deviations from the randomized treatment will be presented in the protocol deviation listing, see section 6.3 Major protocol deviations.

8.2 Dosage

Descriptive statistics for the total dose of IMP per patient will be presented by treatment group for the RAND, mITT and SAF. Both dose (IU) and weight adjusted dose (IU/kg) will be analyzed.

8.3 Infusion duration

The infusion duration will be calculated in minutes as:

Duration of exposure (minutes) = (time of stop of infusion – time of start of infusion)

Descriptive statistics for the infusion duration will be presented.

8.4 Discontinuations from study therapy

The number and percentage of patients who discontinued the infusion prematurely will be presented by treatment group.

Patients who discontinued study prematurely will be listed by study site and treatment group (Annex V to the CSR according to ICH E3 [2]). The listing will include age, sex, last visit, day of discontinuation, duration of treatment, and reason of discontinuation.

8.5 Compliance

IMP will be infused at the study site under the guidance of the investigator. However, compliance will be analysed and number of subjects who have received a miscalculated dose will be evaluated.

9 Previous and Concomitant Therapies

Previous and concomitant medications are coded according to WHO drug dictionary (Version SEP 16) and stored with ATC codes and generic names.

Therapies will be classified as previous if they stopped before start of infusion and as concomitant if taken after start of first infusion.

The number and frequency of previous and concomitant medications will be given per ATC level 2. Additionally, previous anti-coagulant therapy will be presented per ATC level 3. If a patient has received more than 1 drug within an ATC class, he/she will be counted only once for this ATC class.

The number of patients with Vitamin K administration will be presented, including descriptive statistics on the dose level administered. The number of patients who did not receive Vitamin K will be presented, with the reason of non-administration. Patients for whom a Vitamin K administration was planned and did not receive it will also be presented.

10 Efficacy

10.1 Primary efficacy 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. For details on the derivation see CSP Section 7.2.1 (Assessments for Primary Efficacy Endpoints).

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 confidence intervals 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 using the mITT and PP populations.

All patient data related to the primary efficacy analysis will be listed.

Handling of Missing Data

Patients with missing information on the primary efficacy endpoint (for example, patient for whom the surgery was not initiated due to an insufficient coagulation), will be assessed as having no hemostasis (i.e., hemostatic efficacy will be considered ‘none’ for the analysis).

Sensitivity and Robustness Analyses

In order to assess the treatment effect using different assumptions from those in the RAND analysis, the primary efficacy analysis will also be performed using the mITT and PP populations.

In case of non-inferiority in the mITT and the PP populations a "tipping point" analysis will be done to determine the robustness of the results

Iteratively patients excluded from the mITT/PP analysis assigned to the control arm will be considered as treatment successes, and patients excluded from the 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 RAND 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. This analysis will be conducted with the same methods as described above for the primary efficacy endpoint.

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

10.2 Secondary efficacy analyses

The secondary efficacy endpoints will be tested for differences between OCTAPLEX and Beriplex® P/N (Kcentra). No confirmatory hypotheses testing will be done. Treatment will be compared exploratorily, point estimates and corresponding 95% confidence intervals will be presented in addition to descriptive statistics.

The following measurements will be considered as exploratory secondary endpoints:

- Proportion of patients with an INR value of less 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

The primary analysis of secondary endpoints will be based on the RAND 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% confidence intervals will be presented in addition to descriptive statistics for these endpoints.

The change in the individual coagulation factors from baseline to 30 minutes after the 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 30 minutes after

the end of infusion between OCTAPLEX and Beriplex® P/N (Kcentra) and the corresponding 95% CI will be calculated.

Missing data will not be imputed.

All patient data related to the secondary efficacy analyses will be listed.

10.3 Further exploratory efficacy analyses

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

- Change in INR from baseline.
- Change in Protein C, and Protein S from baseline to 30 (± 15) minutes after the end of infusion.
- Change in coagulation factor levels (FII, FVII, FIX, FX, Protein C, and Protein S) from baseline to 2, 4, 12 and 24 hours after end of infusion
- Assessment of blood loss after end of surgery.
- Proportion of 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 body weight.
- Change in hematological parameters (hemoglobin, hematocrit, RBC, WBC, platelets) from the beginning to the end of the surgery.
- RBC transfusion corrected change from baseline in hemoglobin at 12 and 24 hours after start of surgery

  Correction of change will be calculated as follows:

$$corrected\ change\ (\frac{g}{dL}) = change\ in\ Hb\ (\frac{g}{dL}) - \frac{volume\ transfused}{200mL} * \frac{1g}{dL}$$

- 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

11 Safety

11.1 Adverse events

Adverse events (AE) will be coded using MedDRA®) Version 18.1 or higher and presented by primary System Organ Class (SOC) and Preferred Term (PT).

Treatment-emergent adverse events

The analysis will focus on treatment emergent adverse events (TEAEs), i.e., AEs that started or worsened after start of infusion with IMP.

Number and frequencies of patients with TEAEs and number of events will be given by SOC and by PT within each SOC for the following:

- All TEAEs by treatment group
- All TEAEs considered at least possibly related (i.e. considered as possibly or probably related) by treatment group
- Serious TEAEs by treatment group
- Serious TEAEs considered at least possibly related (i.e. considered as possibly or probably related) by treatment group
- TEAEs with fatal outcome by treatment group
- TEAEs leading to study discontinuation by treatment group

Number and frequencies of patients with TEAEs will be given by SOC and by PT within each SOC for the following:

- All TEAE by maximum intensity by treatment group

Number and frequencies of patients with TEAEs will be given by PTs by decreasing frequency for the following:

- All TEAEs by treatment group
- All TEAEs considered at least possibly related (i.e. considered as possible, probable or definite related) by treatment group
- Serious TEAEs by treatment group
- Serious TEAEs considered at least possibly related (i.e. considered as possible, probable or definite related) by treatment group
- All TEAEs by maximum intensity and by treatment group
- TEAEs with fatal outcome by treatment group
- TEAEs leading to study discontinuation by treatment group

If severity is missing, the event will not be included in the frequency tables presenting events by intensity. If relationship to study drug is missing, the event will be assessed as unrelated if it started before start of infusion; in all other cases it will be assumed to be related.

Patient listings will be provided for patients with adverse events, serious adverse events, for all patients with adverse events leading to discontinuation of IMP, and for all adverse events with fatal outcome. The listings will also include patients enrolled but not randomized.

Thromboembolic events (TEE)

The number of patients with TEE 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% confidence interval. Kaplan-Meier estimates for time to first occurrence of a TEE event will be calculated and graphically presented. If the patient did not experience a TEE, the time to first occurrence will be censored at the last visit for the patient.

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% confidence interval. Kaplan-Meier estimates for time to death will be calculated and graphically presented. The last information date on vital status will be taken as censoring date for patients who did not die.

Additionally, deaths will be summarized by MedDRA primary system organ class and preferred term of the principal cause of death. All deaths will be listed.

11.2 Clinical safety laboratory

Hematology and clinical chemistry

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

Data from unplanned determinations, i.e. usually determinations where the investigator felt follow-up was necessary, will be included in the number and frequency counts of clinically significant values. They will also be included in the data listings.

Laboratory values that are outside the normal range will also be flagged in the data listings, along with corresponding normal ranges. Any out-of-range values that are identified by the investigator as being clinically significant will also be shown in a data listing.

11.3 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.

11.4 Vital signs

The values measured at each timepoint as well as the change from baseline in vital signs will be summarized over time with n, mean, standard deviation, and median, quartiles, minimum, and maximum.

11.5 Physical examination

All available data will be listed.

12 Interim Analyses

12.1 Objective(s) of the interim analyses

The study will be conducted in 2 stages, with one un-blinded interim analysis 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 to allow for an early stopping due to futility to achieve this. Any decision to prematurely terminate the study will be made in consultation with the relevant authorities.

12.2 Timing of interim analyses

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.

12.3 Interim analysis populations

Cut-off date: The cut-off date for the interim analysis is defined as the date when the primary endpoint of the first 185 randomized patients is available.

The assignment of patients to analysis population will follow the rules provided in Section 4 Analysis Populations.

12.4 Stopping rules and adaptations

A sequential design with α- and β-spending function according to Hwang, Shi and Cani will be used.

After the interim analysis, a positive outcome for non-inferiority test may be claimed and enrollment may be stopped (after consultation between the IDMC and relevant parties, see section 9.4 of the CSP) if the primary test statistic in the RAND 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), as reported in the table below. 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.

Operational Characteristics of Study Design

		Significant Boundaries	
	n per arm	Z-value	p-Value
Interim	83	2.33216	0.00985
Final	166	2.07753	0.01888

If study success can be claimed on the interim results, enrollment of additional patients may be discontinued prematurely. In this case, all patients enrolled until a decision to stop the study has been made will be observed until the end of follow-up period. A final analysis and study report including all data collected during the study will be prepared.

12.5 Documentation of the interim analysis and disclosure of results

The interim analysis will be performed by a statistical team which is independent from the study team.

The results of the interim analysis will be presented to the IDMC. The following statistical summaries and listings will be presented:

- Analysis of patient populations and withdrawal status
  (Number and percentage of patients in the enrolled population, RAND, SAF, and withdrawals)
- A statistical summary of important demographic and baseline data for the RAND.
- Descriptive statistics and statistical test results including the p-value, point estimates and confidence intervals for the RAND of the primary efficacy variable.
- Descriptive statistics of the secondary efficacy variables
- An analysis of AEs for the SAF. This will include frequency tables of TEAEs and TEAEs assessed by the investigator as related (i.e. any possibly, probably, or definitely related TEAEs) according to primary SOC and preferred term. Serious TEAEs, TEAEs with fatal outcome, and TEAEs resulting in withdrawal from the study will be tabulated using frequency tables if a reasonable number of AEs of this type are observed.
- Frequency tables of TEEs
- Patient listings will be provided for all AEs reported, for patients with SAEs, for all patients with AEs leading to study discontinuation and for all AEs with fatal outcome. The listings will include all patients in the SAF and will show the investigator verbatim term and the MedDRA coded term simultaneously.

13 Statistical Analyses for Safety Monitoring

The statistical analysis for safety monitoring is specified in a separate IDMC charter.

14 Software

If not stated otherwise, the data will be analysed using SAS Version 9.3 or higher.

15 Abbreviations

4F-PCC	Four-Factor Prothrombin Complex Concentrate
AE	Adverse Event
BMI	Body Mass Index
CI	Confidence Interval
CSP	Clinical Study Protocol
CSR	Clinical Study Report
eCRF	Electronic Case Report Form
FII	Coagulation Factor II
FVII	Coagulation Factor VII
FIX	Coagulation Factor IX
FX	Coagulation Factor X
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IEAB	Independent Endpoint Adjudication Board
IMP	Investigational Medicinal Product
INR	International Normalized Ratio
IRT	Interactive Response Technology
ITT	Intention-to-Treat Population
IU	International Unit
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intention-to-Treat Population
PCC	Prothrombin Complex Concentrate
PP	Per Protocol Population
PT	Preferred Term
RAND	Randomized Population
RBC	Red Blood Cell Count
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAF	Safety Analysis Population
SD	Standard Deviation

SMQ	Standardized MedDRA query
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
TEE	Thromboembolic events
VKA	Vitamin K antagonist
WBC	White Blood Cell Count

16 References

1. Hwang IK, Shih WJ, De Cani JS. Group sequential designs using a family of type I error probability spending functions. Stat Med. 1990 Dec; 9(12):1439-45.
2. ICH Harmonised Tripartite Guideline E3, Structure and Content of Clinical Study Reports. 1995.