octapharma

CLINICAL STUDY PROTOCOL

LEX-211

FActor REplacement in Surgery

Four-Factor Prothrombin Complex Concentrate versus Frozen Plasma in Bleeding Adult Cardiac Surgical Patients ("FARES-II" Study)

Investigational Product:	*Octaplex*
Indication:	Bleeding cardiac surgery patients requiring coagulation factor replacement
Study Design:	Multicentre, randomised, active-control, Phase 3 study
Sponsor:	Octapharma AG Seidenstrasse 2, CH-8853 Lachen, Switzerland
Study Number:	LEX-211
IND Number:	IND 28027
Development Phase:	Phase 3
Planned Clinical Start:	Quarter 4 2022
Planned Clinical End:	Quarter 4 2024
Date of Protocol:	25-Aug-2023
Version:	9.0
Previous Protocol Versions:	08 – 17 Apr 2023 (Canada only) 07 – 17 Apr 2023 (United States only) 06 – 12 Apr 2022 (Canada only) 05 – 12 Apr 2022 (United States only) 04 – 28 Jan 2022 (Canada only) 03 – 28 Jan 2022 (United States only) 02 – 28 Oct 2021 01 – 07 Sep 2021
Co-ordinating Investigator:	[redacted] Department of Anaesthesia and Pain Management

	Toronto General Hospital 200 Elizabeth Street, 3EN-460 Toronto, ON M5G 2C4 Canada

STUDY OUTLINE

Name of Sponsor/Company: Octapharma AG	
Name of Investigational Product: *Octaplex*	**Protocol Identification Code:** LEX-211
Name of Active Ingredient: Prothrombin complex concentrate, human	**Date of Final Protocol:** 25-Aug-2023

Title of Study:

Prospective, multicentre, active-control randomised trial comparing 4-factor prothrombin complex concentrate with frozen plasma in bleeding adult cardiac surgical patients

Indication:

Bleeding cardiac surgery patients requiring coagulation factor replacement

Number of Study Centre(s):

Approximately 10 hospitals in Canada and 2 in the United States

Objectives:

Primary Objective:

1. To demonstrate that the 4-factor prothrombin complex concentrate (PCC) *Octaplex* is clinically non-inferior to frozen plasma (FP) with respect to haemostatic effectiveness, as measured by the need for post-therapy haemostatic interventions.

Secondary Objectives:

1. To compare global haemostatic response between the *Octaplex* and FP groups, as measured by a composite of the need for post-therapy haemostatic interventions and drop in haemoglobin.
2. To compare the amount of bleeding as measured by the amount of chest tube drainage between the *Octaplex* and FP groups.
3. To compare the incidence of severe to massive bleeding between the *Octaplex* and FP groups.
4. To compare efficacy in terms of the total number of allogeneic blood components transfused between the *Octaplex* and FP groups.
5. To compare efficacy in terms of the incidence and number of individual allogeneic blood components transfused between the *Octaplex* and FP groups.
6. To compare the incidence of use of other coagulation factor products between the *Octaplex* and FP groups.

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7. To compare the incidence of other bleeding-related clinical endpoints, i.e., intracerebral haemorrhage, gastrointestinal haemorrhage and surgical re-exploration, between the *Octaplex* and FP groups.
8. To compare the effect of *Octaplex* versus FP administration on the international normalised ratio (INR) between the *Octaplex* and FP groups.
9. To compare the effect of *Octaplex* versus FP administration on other coagulation parameters.
10. To compare time from IMP initiation to arrival at ICU between the *Octaplex* and FP groups.
11. To compare safety as measured by serious treatment-emergent adverse events (TEAEs) between the *Octaplex* and FP groups.
12. To compare other secondary safety endpoints including duration of mechanical ventilation, duration of intensive care unit (ICU) stay, duration of hospitalisation, incidence of death and days alive and out of hospital between the *Octaplex* and FP groups.

Study Design:

This is a multicentre, randomised, active-control, prospective, Phase 3 study in adult cardiac surgery patients. Approximately 500 patients will be randomised at approximately 12 hospitals and the study will require approximately two years to complete.

The study will include adult (≥18 years old) patients who undergo cardiac surgery with cardiopulmonary bypass (CPB) and require coagulation factor replacement due to bleeding post-CPB and after adequate reversal of heparin with protamine (as assessed by the surgical staff based on clinical and laboratory criteria) during surgery, and who have a known (e.g., as indicated by INR) or suspected coagulation factor deficiency. Patients will be randomised to receive either 4-factor PCC (*Octaplex*) or FP when the blood bank/pharmacy receives the first order for coagulation factor replacement and determines patient eligibility with the study team based on the study inclusion and exclusion criteria. IMP will be administered once treatment indications are met. Patients will be treated according to their assigned group until the maximum dose of IMP is administered during the treatment period, which represents 24 hours after IMP initiation (defined as the start of IMP administration). If additional treatment is required after the maximum dose of IMP is administered or the treatment period has elapsed, patients in both groups will receive FP.

Other aspects of coagulation management will be according to a standardised transfusion algorithm. Measurements of INR and haemoglobin will be performed at

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preestablished time points, if not available already. No other aspects of care will be modified.

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Number of Patients:

The study is split in two stages. In the first stage, randomisation (1:1) will continue until 200 evaluable patients are obtained. Then, an administrative unblinded interim analysis will be carried out to re-estimate the sample size or stop for futility (non-binding) if necessary. The sample size in the second stage is limited to 210–800 evaluable patients. Accounting for 20% dropouts, the total sample size of the study will range between 513–1250 if the study is not stopped for futility at the interim.

Subject/Patient Selection Criteria:

Inclusion Criteria:

1. Adult (≥18 years old) patients undergoing any index cardiac surgery employing CPB
2. Coagulation factor replacement with PCC or FP ordered in the operating room for:

a. Management of bleeding, or

b. Anticipated bleeding in a patient who has been on-pump for >2 hours or has undergone a complex procedure (e.g., aortocoronary bypass [ACB] plus aortic valve replacement)

3. Coagulation factor deficiency, either known to exist (e.g., as indicated by elevated EXTEM clotting time [CT] or INR) or suspected based on the clinical situation
4. Patients who have given written informed consent[1]

Exclusion Criteria:

1. Undergoing heart transplantation, insertion or removal of ventricular assist devices (not including intra-aortic balloon pump [IABP]) or repair of thoracoabdominal aneurysm
2. Critical state immediately before surgery with high probability of death within 24 hours of surgery (e.g., acute aortic dissection, cardiac arrest within 24 hours before surgery)

[1] In Canada, informed consent will be obtained after randomisation, in accordance with Article 3.7A of the 2018 Tri-Council Policy Statement on the Ethical Conduct for Research Involving Humans.

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3. Severe right heart failure (clinical diagnosis ± echocardiography)
4. Known contraindications to heparin
5. PCC required for reversal of warfarin or direct oral anticoagulant (DOAC; dabigatran, rivaroxaban, apixaban or edoxaban) within 3 days prior to or during surgery
6. Known thromboembolic event (TEE) within 3 months prior to surgery
7. History of severe allergic reactions to PCC or FP
8. Individuals who have immunoglobulin A (IgA) deficiency with known antibodies against IgA
9. Refusal of allogeneic blood products
10. Known pregnancy
11. Currently enrolled in other interventional clinical trials

Test Product, Dose and Mode of Administration:

Octaplex and FP will be administered intravenously. For the first ordered dose, the blood bank/pharmacy will prepare and release either *Octaplex* or FP, as per the randomised group allocation. The dose for *Octaplex* will be 1500 IU for patients weighing ≤60 kg and 2000 IU for patients weighing >60 kg. The dose for FP will be 3 U for patients weighing ≤60 kg and 4 U for patients weighing >60 kg).

If a second order of coagulation factors is received during the treatment period of 24 hours after IMP initiation, the blood bank/pharmacy will release a second dose of *Octaplex* or FP as above. The maximum allowable dose of IMP will be: *Octaplex* 3000 IU if ≤60 kg or 4000 IU if >60 kg; FP 6 U if ≤60 kg or 8 U if >60 kg. If further doses of coagulation factors are required, non-IMP FP will be administered. That is, once the maximum dose of IMP (i.e., two doses) has been administered, if additional amounts of coagulation factors are ordered during the treatment period, and for any requests after the treatment period, the blood bank/pharmacy technologist will release FP (in 1–4 U increments at the discretion of the ordering physician) for both groups; these additional FP units will not be counted as part of the IMP.

Duration of Treatment:

Twenty-four hours from IMP initiation or until the maximum dose of the IMP has been administered, whichever occurs first.

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Reference Therapy, Dose and Mode of Administration:

Two methods of coagulation factor replacement will be compared in the study, with patients randomly assigned (1:1 ratio) to receive IV infusion of 1500 to 2000 of *Octaplex* or 3 to 4 units of FP. If a second order is received during the treatment period of 24 hours after IMP initiation, the blood bank/pharmacy will release a second dose of *Octaplex* or FP as above. If further doses of coagulation factors are required, all patients will receive non-IMP FP.

Study Outcome Parameters (Primary and Secondary Endpoints):

Efficacy Parameters:

Primary Endpoint:

1. Comparison of haemostatic treatment response to *Octaplex* versus FP, defined as 'effective' if no additional haemostatic intervention, such as administration of any systemic haemostatic agents (including platelets, cryoprecipitate, fibrinogen concentrate, activated recombinant factor VII, other coagulation factor products or a second dose of IMP) or any haemostatic interventions (including surgical re-opening for bleeding) is required from 60 minutes to 24 hours after initiation of the first dose of IMP.

Secondary Endpoints:

1. Comparison of global haemostatic response to *Octaplex* versus FP, defined as 'positive' if no additional haemostatic intervention (as per the primary endpoint) is required and haemoglobin levels decrease by <30% (after accounting for red cell transfusions) from 60 minutes to 24 hours after initiation of the first dose of IMP.
2. Comparison of the total amount of chest tube drainage at 12 and 24 hours after chest closure between the *Octaplex* and FP groups.
3. Comparison of the incidence of severe to massive bleeding, using a modification of the universal definition of perioperative bleeding (UDPB) in cardiac surgery and its individual components during the first 24 hours after start of surgery, after the end of CPB and after IMP initiation, between the *Octaplex* and FP groups.
4. Comparison of the mean number of <u>total</u> allogeneic blood components – including red cells, platelets and all (IMP and non-IMP) FP – administered during the first 24 hours after the end of CPB, between the *Octaplex* and FP groups.

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5. Comparison of the mean number of total non-IMP allogeneic blood components – including red cells, platelets and non-IMP FP – administered during the first 24 hours after the end of CPB, between the *Octaplex* and FP groups.
6. Comparison of the mean number of total non-IMP allogeneic blood components – including red cells, platelets, cryoprecipitate and non-IMP FP – administered during the first 24 hours and 7 days after IMP initiation, between the *Octaplex* and FP groups.
7. Comparison of the mean number of individual allogeneic blood components – including red cells, platelets, cryoprecipitate and non-IMP FP – administered during the first 24 hours and 7 days after the start of surgery, after the end of CPB and after IMP initiation, between the *Octaplex* and FP groups.
8. Comparison of the incidence of transfusion of individual allogeneic blood components – including red cells, platelets, cryoprecipitate and non-IMP FP – during the first 24 hours and 7 days after the start of surgery, after the end of CPB and after IMP initiation, between the *Octaplex* and FP groups.
9. Comparison of the incidence of administration of non-IMP coagulation factor products – including fibrinogen concentrate and activated recombinant factor VII – during the first 24 hours and 7 days after the start of surgery, after the end of CPB and after IMP initiation, between the *Octaplex* and FP groups.
10. Comparison of the incidence of intracerebral haemorrhage during the first 24 hours after start of surgery, after the end of CPB and after IMP initiation between the *Octaplex* and FP groups.
11. Comparison of the incidence of gastrointestinal haemorrhage during the first 24 hours after start of surgery, after the end of CPB and after IMP initiation between the *Octaplex* and FP groups.
12. Comparison of the incidence of surgical re-exploration during the first 24 hours after start of surgery, after the end of CPB and after IMP initiation between the *Octaplex* and FP groups.
13. Comparison of the change in INR, from within 30 minutes before to within 60 minutes after the initiation of IMP administration, between the *Octaplex* and FP groups; INR reduction will be considered successful if the magnitude of the reduction is >1.0 or the post-treatment level drops below 1.5.
14. Comparison of the changes in other coagulation parameters, including PT, aPTT, fibrinogen activity, ROTEM EXTEM CT and MCF, ROTEM FIBTEM MCF and platelets, from within 75 minutes before to within 75 minutes after the initiation of IMP administration, between the *Octaplex* and FP groups.

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15. Comparison of time elapsed from initiation of the first dose of IMP to arrival at the ICU room between the *Octaplex* and FP groups.

Safety Endpoints:

All adverse events (AEs) and serious AEs (SAEs) will be collected from beginning of surgery (defined as entry into OR) to POD-30.

1. Comparison of the incidence of serious treatment-emergent adverse events (TEAEs), individually and as composite where appropriate (e.g., TEEs, major adverse cardiac events), between the *Octaplex* and FP groups.
2. Comparison of the duration of mechanical ventilation (measured as duration of ventilation and ventilator-free days) up to POD-30 between the *Octaplex* and FP groups.
3. Comparison of the duration of ICU stay up to POD-30 between the *Octaplex* and FP groups.
4. Comparison of the duration of hospitalisation up to POD-30 between the *Octaplex* and FP groups.
5. Comparison of the incidence of death up to POD-30 between the *Octaplex* and FP groups.
6. Comparison of the number of days alive and out of hospital at POD-30 between the *Octaplex* and FP groups.

Study Procedures:

At the screening assessment, voluntarily given, written, informed consent will be obtained from the patient. Once consent has been obtained and the patient enrolled into the study, eligibility according to inclusion criteria 1 and 4 (i.e., patients ≥18 years old, undergoing any index cardiac surgery employing CPB, who have provided informed consent) and the exclusion criteria will be confirmed.

Only patients who bleed and require coagulation factor replacement therapy during surgery will be randomised to receive study drug, and undergo the following visits and assessments.

When the first order for PCC or FP is received by the blood bank/pharmacy while the patient is in the operating room, the blood bank/pharmacy technologist will confirm patient eligibility with the clinical team. Following confirmation of eligibility, the technologist will randomise the patient to PCC or FP according to the randomisation and

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dosing schedule and prepare and release the IMP in a tamper sealed container (with weight device in PCC containing boxes to ensure adequate concealment). Operating room personnel will remain blinded until the decision to administer the IMP is made.

IMP can be administered if bleeding is severe enough to necessitate treatment (meaning at least a grade 2 level [moderate] bleeding according to the validated Bleeding Severity Scale - see Appendix 1), heparin is adequately reversed (confirmed by the return of post-protamine activated clotting time [ACT] to within 10% of pre-pump ACT), and INR is ≥1.5. IMP can also be administered if bleeding is severe enough to require urgent therapy, in which case treatment can be initiated irrespective of the INR value. Once the decision is made to administer the IMP, the administering clinician will break the seal on the container, carry out routine safety checks, and initiate IMP administration according to the weight-based dosing recommendations.

A second dose of IMP can be administered if the patient continues to have at least moderate bleeding and a suspected coagulation deficiency (e.g. INR ≥1.5) after completion of the first dose. If an order for a second dose of coagulation factors is received within 24 hours after IMP initiation (either from the operating room or in the ICU after surgery), the blood bank/pharmacy technologist will release the IMP as determined by the randomisation schedule up to the maximum allowable dose, as per usual practice (a tamper-sealed container will not be used for these orders as clinicians will by now be unblinded).

If further doses of coagulation factors are required after the second dose of IMP, all patients will receive non-IMP FP. That is, for subsequent orders once the maximum dose of IMP has been administered (i.e., two doses), or after the 24-hour treatment period has elapsed, the technologist will release non-IMP FP for both groups.

The type of IMP administered will be recorded in a manner that will not unblind the outcome assessor. Patients will also be blinded to treatment allocation.

If any of the IMP doses is returned from the operating room without any part of the IMP being administered for any reason, the reason for return of the IMP and status of the seal on the tamper-sealed container will be recorded by the blood bank/pharmacy technologist. *Octaplex* will be accounted for and FP will be handled according to the local practice.

Study Visits:

Screening visit (maximum 28 days before surgery)

- Voluntarily given, written (signed and dated) informed consent obtained from patients

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- Determine eligibility according to inclusion criteria 1 and 4 (i.e., patients ≥18 years old, undergoing any index cardiac surgery employing CPB, who have provided informed consent) and the exclusion criteria
- If screening is performed before the day of surgery, exclusion criterion 3 (i.e., severe right heart failure [clinical diagnosis ± echocardiography]) will be rechecked on the day of surgery

The following visits will only be performed for patients who bleed and require coagulation factor replacement therapy during surgery

Visit 1: (POD 0 pre-randomization): Pre-randomisation visit (blood bank/pharmacy)

- Surgical staff records the patient's body weight

Visit 2: (POD 0 post-randomization and POD 1): First visit after IMP initiation (0 to 24 hours after IMP initiation)

- Collect baseline data
- Administer first dose of IMP
- Collect surgical data
- Collect laboratory, transfusion and haemostatic therapy, and bleeding data
- Administer second dose of IMP, if needed
- Collect extubation time
- Collect concomitant medications
- Collect AEs and SAEs

Visit 3: (POD 2-7): Days 2–7 after IMP initiation (or at discharge, if earlier)

- Collect laboratory, transfusion and haemostatic therapy, and bleeding data
- Record intracerebral haemorrhage, gastrointestinal haemorrhage and surgical re-exploration. Collect extubation time, length of stay in the ICU and hospital (if applicable)
- Collect concomitant medications
- Collect AEs and SAEs

Visit 4: (POD 30): Day 30 after IMP initiation (in person if in hospital or by phone)

- Collect concomitant medications
- Collect AEs and SAEs
- Collect extubation time, length of stay in the ICU, length of stay in the hospital (if extended), readmissions and 30-day mortality

Concomitant Therapies and Management:

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Transfusion of non-IMP blood components and all haemostatic agents will be administered according to a standardised transfusion management algorithm that will employ point-of-care and standard coagulation assays. Hospitals will also be provided with point-of-care INR assays to measure and document INR before and after IMP administration. Other than the treatment algorithm, and the haemoglobin and INR measurements at preestablished time points (if not available already), no other aspects of routine clinical care will be modified.

Ethics:

This is a prospective trial that compares two coagulation factor replacement therapies that are routinely used in the treatment of bleeding related to coagulation factor deficiency in multiple regions globally and in various settings. Informed consent will be obtained from the patient before the patient is exposed to any study-related procedure.

Statistical Analysis Plan:

The analysis of the primary efficacy endpoint will involve comparison of haemostatic treatment response to IMP, defined as 'effective' if no additional haemostatic intervention, such as administration of any systemic haemostatic agents (including platelets, cryoprecipitate, fibrinogen concentrate, activated recombinant factor VII, other coagulation factor products or a second dose of IMP) or any haemostatic interventions (including surgical re-opening for bleeding) is required from 60 minutes to 24 hours after initiation of the first dose of IMP.

Patients categorised as having an 'ineffective' haemostatic treatment response to IMP, due to requiring administration of any haemostatic intervention, including a second dose of IMP, in the time window from 60 minutes to 24 hours after initiation of the first IMP dose, will be considered as treatment failures.

Of the more than 100 patients studied in the FARES pilot study, approximately 75% of patients in the PCC group and 65% in the FP group demonstrated haemostatic treatment response from 60 minutes to 24 hours after initiation of the first IMP dose. Using a more conservative estimate of 70% versus 65%, it is estimated that 410 patients will be required to demonstrate non-inferiority with a one-sided α of 0.025, power of ≥90%, and non-inferiority margin of 0.10 when using a Farrington-Manning score test.

It is anticipated that up to 20% of randomised patients may not meet administration criteria (based on objective Bleeding Severity Scale and INR) due to cessation of haemorrhage between randomisation and delivery of IMP to the operating room and therefore will not receive the therapy.

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An administrative unblinded interim analysis will be carried out after approximately 200 patients have been randomised and treated and will be used to re-estimate the sample size or stop for futility (non-binding). Patient recruitment will continue during the conduct of the interim analysis. The study can only be stopped for futility and not for efficacy at the time of the interim analysis. The sample size re-estimation will be based on the evaluation of the conditional power making use of the observed response rates and inverse normal combination test statistic with equal weights given by $(\Phi^{-1}(1 - p_1) + \Phi^{-1}(1 - p_2))/\sqrt{2}$, where p_1 and p_2 denote the p-values for testing the non-inferiority null hypothesis for the first and the second stage of the trial, respectively. The aspired conditional power used for the new intended sample size will be 90%. The sample size in the second stage is limited to 210–800 evaluable patients. Accounting for dropouts as described above, the total sample size will range between 513–1250 if the study is not stopped for futility at the interim.

The non-inferiority of the primary endpoint 'haemostatic response' will be tested between the treatment groups by means of a Farrington-Manning score test with a non-inferiority margin of 0.10. At the end of the trial, the inverse normal test statistic with equal weights given by $(\Phi^{-1}(1 - p_1) + \Phi^{-1}(1 - p_2))/\sqrt{2}$ is calculated, where p_1 and p_2 denote the p-values for testing the non-inferiority null hypothesis for the first and the second stage of the trial, respectively. If the test statistic exceeds the value 1.96, non-inferiority is demonstrated. Only in case that non-inferiority is demonstrated, i.e., the null hypothesis is rejected at the one-sided 2.5% level of significance, superiority of PCC with regard to the primary endpoint will be investigated.

Descriptive statistics or frequency tables will be presented for all efficacy and safety data in addition to the inferences performed. The summary tables and exploratory inferences will be chosen according to the scaling level of the measurements, e.g., frequency tables for categorical responses, sampling statistics for continuous data. Safety endpoints will be analysed analogously to the primary endpoint, presenting point estimates and two-sided 95% CIs in addition to descriptive statistics. The Statistical Analysis Plan (SAP) will detail all analyses to be undertaken prior to study initiation.

The full analysis set (FAS) will consist of all consented and randomised patients who receive any amount of the intervention, which will serve as the primary analysis set. A secondary efficacy analysis will be performed for the per-protocol set (PPS), which will exclude all patients with major deviations. Consented, randomised but untreated patients will not be included in the efficacy or safety analyses, but will be followed for 30 days to determine between-group comparability in baseline characteristics and outcomes.

FLOW CHART OF ASSESSMENTS

Table 1: Flow Chart of Assessments Performed Throughout the Study

ASSESSMENTS	Screening visit (≤28 days before surgery)	Visit 1 POD 0 Pre-randomisation visit (blood bank/pharmacy)	Visit 2 POD 0-1 First visit after IMP initiation (0 to 24 h after IMP initiation)[1]	Visit 3 POD 2-7 after IMP initiation (or at discharge if earlier)	Visit 4 POD 30 after IMP initiation (in person if in hospital, or by phone)
Patient consent	X				
Inclusion and exclusion criteria	X[2]	X			
Blood bank/pharmacy receives PCC or FP order[3]		X			
Body weight		X			
Randomisation		X			
IMP (PCC or FP) administration[4]			X		
Baseline data					
Demographics			X		
Medical history			X		
Preoperative medications			X		
Laboratory assessments			X		
Surgical data					
Bleeding Score			X[2]		
Intraoperative medications			X		
CPB time			X		
Cross-clamp time			X		
Circulatory arrest			X		
Fluid intake and output monitoring			X		
Inotropes and vasopressors			X		
Start and end time of IMP administration			X		
OR length of stay			X		
Laboratory assessments					
Clinical chemistry[5]			X	X	
Haematology (CBC)[5]			X[6]	X[7]	
Coagulation measures[5,8]			X[9]	X	
Safety laboratory analyses[5]			X	X	
INR			X[10]		
Transfusions and haemostatic therapies and timings					
Second dose of PCC (IMP), if needed[11]			X		
Second dose of FP (IMP), if needed[11]			X		
FP (non-IMP)			X	X	
RBCs			X	X	
Pooled and apheresis platelets			X	X	
Cryoprecipitate			X	X	
Fibrinogen concentrate			X	X	
Activated recombinant factor VII			X	X	
Other haemostatic products			X	X	
Blood loss determination					

Total chest tube drainage at 1, 6 12 hours and 24 hours after chest closure			X	X	
Bleeding-related clinical endpoints					
Occurrence of intracerebral haemorrhage[12]			X	X	
Occurrence of gastrointestinal haemorrhage[12]			X	X	
Occurrence of surgical re-exploration[12]			X	X	
Extubation time			X	(X)	(X)
ICU length of stay				(X)	(X)
Hospital length of stay				(X)	(X)
Hospital readmissions					X
AEs and SAEs			X	X	X
Concomitant medications			X	X	X
Patient survival					X

AE, adverse event; aPTT, activated partial thromboplastin time; CBC, complete blood count; CPB, cardiopulmonary bypass; CT, clotting time; DC, discharge; FP, frozen plasma; ICU, intensive care unit; IMP, investigational medicinal product; INR, international normalised ratio (INR); MCF, maximum clot firmness; OR, operating room; PCC, prothrombin complex concentrate; POD, postoperative day; PT, prothrombin time; RBC, red blood cell; SAE, serious adverse event;

[1] For any specified activity that cannot be completed during the first visit after IMP initiation, additional visits will be made on postoperative day 1 until all study data are obtained

[2] Inclusion criteria 1 and 4, and all exclusion criteria checked for eligibility at the screening visit. If screening is performed before the day of surgery, exclusion criterion 3 (i.e., severe right heart failure [clinical diagnosis ± echocardiography]) will be rechecked on the day of surgery

[3] After the start of surgery

[4] IMP will be administered during surgery based on objective clinical criteria of bleeding status and point-of-care INR, as assessed by the surgical staff

[5] As per standard practice

[6] Measure haemoglobin within 30 minutes before and at 60 minutes after IMP initiation

[7] Measure haemoglobin at 24 hours after IMP initiation and document results

[8] For example: PT, aPTT, INR, plasma fibrinogen level, ROTEM EXTEM CT and MCF, FIBTEM MCF, platelet count and function (PlateletWorks). Either ROTEM or TEG can be used.

[9] Measured from within 75 minutes before to within 75 minutes after IMP initiation

[10] Measure INR within 30 minutes before and at 60 minutes after IMP initiation and document results

[11] If the patient continues to have at least moderate bleeding and a suspected coagulation deficiency (e.g. INR ≥ 1.5) after completion of the first dose

[12] Data collected during visit 2 (0–24 hours after IMP initiation)

( ) If needed

PROTOCOL SIGNATURES

Signature of the Coordinating Investigator

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

[redacted] [redacted]

Signature Date

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Signature of the Sponsor's Representative

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

[redacted]

[redacted]

Signature Date

[redacted]

Octapharma AG
Seidenstrasse 2
8853 Lachen
Switzerland

Signature of the Author of the Protocol

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

[redacted] [redacted]

Signature Date

[redacted]
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Seidenstrasse 2
8853 Lachen
Switzerland

Signature of the Clinical Project Manager

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

[redacted]

[redacted] Signature Date

[redacted]

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117 West Century Road
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Signature of the Biostatistician

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

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LIST OF ABBREVIATIONS

Abbreviation	Description
ACB	Aortocoronary Bypass
ACT	Activated Clotting Time
ADR	Adverse Drug Reaction
AE	Adverse Event
AKI	Acute Kidney Injury
ALT	Alanine Aminotransferase
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
BMI	Body Mass Index
CABG	Coronary Artery Bypass Grafting
CC	Community Consultation
CCA	Complete Case Analysis
CI	Confidence Interval
CPB	Cardiopulmonary Bypass
CRF	Case Report Form
CRO	Contract Research Organisation
CT	Clotting Time
DOAC	Direct Oral Anticoagulant
E-CABG	European Coronary Artery Bypass Grafting
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EXTEM	ROTEM Test Assessing the Extrinsic Coagulation Pathway
FIBTEM	Fibrin-Based ROTEM Test Extrinsically Activated with Tissue Factor and Containing the Platelet Inhibitor Cytochalasin D
GCP	Good Clinical Practice
HIV	Human Immunodeficiency Virus
IABP	Intra-Aortic Balloon Pump
IB	Investigator's Brochure
ICU	Intensive Care Unit
IDSMC	Independent Data and Safety Monitoring Committee
IgA	Immunoglobulin A
IMP	Investigational Medicinal Product
INR	International Normalised Ratio
IRB	Institutional Review Board
IV	Intravenous
KDIGO	Kidney Disease: Improving Global Outcomes
MACE	Major Adverse Cardiac Events
MCF	Maximum Clot Firmness

Abbreviation	Description
MedDRA	Medical Dictionary for Regulatory Activities
OR	Operating Room
PCC	Prothrombin Complex Concentrate
PD	Public Disclosure
PI	Package Insert
POD	Postoperative Day
PP	Per-Protocol
PRV	Pseudorabies Virus
PT	Prothrombin Time
RBC	Red Blood Cell
rFVIIa	Activated Recombinant Factor VII
ROTEM	Rotational Thromboelastometry
SAE	Serious Adverse Event
SAF	Safety Analysis Population
SBV	Schmallenberg Virus
SDV	Source Data Verification
SmPC	Summary of Product Characteristics
TACS	Transfusion Avoidance in Cardiac Surgery
TEAE	Treatment-Emergent Adverse Event
TEE	Thromboembolic Event
UDPB	Universal Definition of Perioperative Bleeding
WFI	Water for Injections

1 INTRODUCTION

1.1 Rationale for Conducting the Study

Bleeding in Cardiac Surgery

Cardiac surgery is frequently complicated by coagulopathic bleeding that often leads to excessive blood loss, blood product transfusion and bleeding-related complications [1-4]. Bleeding and transfusions are associated with increased morbidity and mortality, including up to an 8-fold increase in the odds of death [2], and patients with major bleeding are at particularly high risk of adverse outcomes (e.g., infection, heart failure and mortality) [5-17].

Coagulopathy during cardiac surgery is caused by several factors, including the contact of blood with the cardiopulmonary bypass (CBP) circuit, which activates the intrinsic and extrinsic coagulation pathways (despite the use of heparin and heparin-coated circuits), causing excessive clot formation and breakdown. Other contributory factors include haemodilution, hypothermia, blood loss, surgical trauma and use of foreign substances such as aortic grafts causing the consumption of coagulation factors [18-22]. These in turn can lead to excessive fibrinolysis, fibrinogen deficiency, platelet dysfunction and thrombocytopenia [20, 21]. Deficiency of enzymatic coagulation factors (e.g., vitamin K-dependent factors II, VII, IX, X and XI) is also an important cause of coagulopathy, leading to impaired generation of thrombin, which is a central component of the coagulation cascade [23, 24]. Activated thrombin converts soluble fibrinogen into insoluble strands of fibrin, which forms the basis of the clot, and it also catalyses numerous other coagulation-related reactions [25]. Consequently, replacement of coagulation factors is an important aspect of a multimodal approach to coagulopathy to reduce bleeding and transfusion [4, 26].

To replenish depleted coagulation factors and improve thrombin generation, two therapeutics, frozen plasma (FP) and prothrombin complex concentrate (PCC), are available. FP is currently the mainstay of therapy for patients with acquired coagulopathies in North America whereas PCC is the mainstay of therapy in much of Europe [27].

Frozen Plasma

FP is obtained from donated whole blood and contains all enzymatic coagulation factors, although some coagulation factor activity is lost during storage and processing (including freezing for storage and thawing prior to transfusion) [28]. FP utilised in North America is not commonly pathogen-reduced. FP is the mainstay of therapy for bleeding cardiac surgery patients requiring coagulation factor replacement in many countries and is administered in around 15% of all cardiac surgeries in the United States [29]. Despite being a mainstay of therapy, there is limited clinical trial evidence on the use of FP in bleeding cardiac surgery patients requiring coagulation factor replacement [30]. Nevertheless, it is recommended by current guidelines and is considered standard practice to transfuse FP in bleeding patients who have coagulation factor deficiency, as indicated by an elevated international normalised ratio (INR) >1.5, which indicates that one or more coagulation factor levels are below the 30% critical threshold [31-37].

The widespread use of FP needs to be considered in the context of the risks associated with its use [38, 39]. FP can cause serious adverse events (SAEs) including allergic reactions (which occur in 1–3% of transfusions, ranging from mild to life-threatening

anaphylaxis) [30]; transfusion-related acute lung injury (TRALI), which is a leading cause of transfusion-related death [30, 40]; and transfusion-associated circulatory overload (TACO), which occurs in approximately 5% of transfusions as a result of the large volume of transfusion (10–15 mL/kg) that is required to achieve therapeutic effect with FP [41]. FP transfusion can also lead to transmission of infectious diseases, as FP is not usually filtered or treated with solvent/detergent [42]. These adverse effects are often dose-dependent [43-46]. Another important consideration with FP use is that it requires ABO blood group compatibility matching and thawing, which can delay therapy. The large volumes of FP needed to achieve therapeutic effect can further delay time to haemostatic control and lead to substantial haemodilution, resulting in additional RBC transfusions [47]. Therefore, although FP is currently a mainstay of therapy in North America, due to the disadvantages and risks associated with its use, it could be considered to be an unsatisfactory treatment.

Prothrombin Complex Concentrate (PCC)

PCC offers a potential alternative to FP for treating bleeding cardiac surgery patients requiring coagulation factor replacement; however, no PCC product is currently approved for this indication in the United States. PCCs contain prothrombin and other enzymatic coagulation factors, the anticoagulant proteins C and S, and small amounts of heparin; thus, they are contraindicated in patients who are allergic to heparin or have a prior history of heparin-induced thrombocytopenia. PCCs are routinely defined as 3-factor (containing factors II, IX and X) or 4-factor (containing factors II, VII, IX and X) formulations [48]. PCCs are purified from human pooled plasma, which is fractionated into cryoprecipitate and cryoprecipitate-free plasma fractions through a process of slow thawing, then eluted from cryoprecipitate-free plasma [48]. The production of PCCs includes numerous pathogen inactivation steps using solvents, detergents, pasteurisation, nanofiltration and vapor-heated treatment [1, 48].

PCCs have several potential advantages over FP. Solvent/detergent treatment and filtering to remove pathogens substantially reduces the risk of transmission of infectious agents with PCCs. Indeed, a Consensus Conference recommended in 2007 that pathogen reduction technologies should be implemented to improve the safety of transfusion when they became available [49]. Unlike FP, PCCs do not require ABO compatibility matching or thawing, and can therefore be prepared and administered more quickly. PCCs are associated with a substantially lower risk of TRALI (due to pooling of the source donor plasma), and also a lower risk of TACO [38] as substantially lower volumes of PCC are required than with FP to achieve dose-equivalence for increasing thrombin generation (for example, in a 70-kg patient, a standard dose of 25 IU/kg PCC would be administered in a volume of 80 mL, whereas a standard dose of 15 mL/kg FP would be administered in a volume of 1000 mL) [47]. Finally, PCCs contain standardised levels of coagulation factors and thus have a more predictable therapeutic effect than FP, whose coagulation factor concentrations vary depending on the characteristics of the donor [50, 51].

On the other hand, PCCs do not contain the full balanced complement of procoagulants and anticoagulants present in FP [52] and it is therefore conceivable that they might be less effective, although *in vitro* studies suggest that PCCs may be more effective than FP in enhancing thrombin generation after cardiac surgery [47]. Also, because PCCs contain more procoagulants than anticoagulants, they may carry a higher risk of thrombotic events, disseminated intravascular coagulation and acute kidney injury (AKI) when administered in high doses [48, 53-57]. However, the FARES pilot study in adult patients who required coagulation factor replacement for bleeding during cardiac surgery showed that the rates

of adverse events (AEs; 77.8% in PCC group versus 87.2% in FP group) and thromboembolic events (TEEs; 7.4% in PCC group versus 8.2% in FP group) were similar between patients receiving PCC or FP [58]. Other prospective studies, as well as retrospective studies and meta-analyses, have also reported comparable rates of AEs and TEEs between cardiac surgery patients treated with PCC or FP [59-66]. Furthermore, some of these studies in cardiac surgery patients, including a recent meta-analysis [64], the PROPHESY pilot study (organ failure, including renal) [62] and the FARES pilot study [58], reported the risk of AKI with PCC to be similar to that with FP [61]. Outside of cardiac surgery, meta-analyses and Phase 3 studies have shown that PCC also has a favourable safety profile and is well tolerated in patients requiring anticoagulant reversal, with rates of AEs and TEEs comparable with FP [38, 67-69].

Review of the Literature

Few guidelines exist on the use of PCC in acquired coagulopathies. The European Society of Anaesthesiology recommends goal-directed therapy with coagulation factor concentrates, including PCC, suggesting that their use may reduce transfusions during cardiac surgery [70], and the American Society of Anaesthesiologists suggests PCCs for excessive bleeding in the presence of elevated INR [71]. Joint guidelines from the European Association for Cardio-Thoracic Surgery and the European Association of Cardiothoracic Anaesthesiology recommend PCC or FP in patients with bleeding related to coagulation factor deficiency and suggest that PCC may be preferred over FP in situations where rapid normalisation of coagulation factors is needed [72]. However, there is little high-quality clinical evidence to support these recommendations: there are few direct comparisons of PCC versus FP for managing coagulopathy resulting from coagulation factor deficiency during cardiac surgery (or other types of surgery) and randomised controlled trials are limited to small, pilot studies [58, 62].

An observational study that compared outcomes for patients at Toronto General Hospital who received FP (*n*=1151), PCC (*n*=79) or both (*n*=125) for management of coagulopathy after cardiac surgery was carried out between 2012 and 2016 [61]. Using propensity score matching, 117 patients who received FP were matched with 117 patients with similar risk and surgery profiles who received PCC (with or without FP). The odds ratio (OR) for red cell transfusion avoidance was 2.4-fold (95% confidence interval [CI] 1.2–4.8) higher for patients receiving PCC. In addition, incidences of massive transfusion (OR 0.58; 95% CI 0.33–1.0) and refractory bleeding (OR 0.49; 95% CI 0.24–1.03) tended to be lower in patients who received PCC. Results from this exploratory study suggest that PCC is potentially more efficacious than FP in avoiding transfusion, and AE profiles were similar between groups, suggesting a comparable safety profile.

These results are similar to those from other observational studies. A recent systematic review identified 4 observational studies – including our study noted above [61] – comparing perioperative PCCs to FP in cardiac surgery [64]. The meta-analysis showed that PCCs were associated with reduced risk of RBC transfusion (OR 2.22; 95% CI 1.45–3.40) and fewer units of RBCs transfused (OR 1.34; 95% CI 0.78–1.90). PCCs were not associated with increased hospital mortality (OR 0.94; 95% CI 0.59–1.49), stroke (OR 0.80; 95% CI 0.41–1.56) or AKI occurrence (OR 0.80; 95% CI 0.58–1.12). In one of the studies in the systematic review, Arnekian and colleagues [59] compared three groups of cardiac surgical patients: 24 who received only PCC, 26 who received only FP and 27 who received both products. In an unadjusted analysis, they found that RBC transfusions occurred least frequently in the PCC group and most frequently in patients who received

both products. However, given the small sample size and lack of risk-adjusted analysis, few conclusions can be drawn from this study. In another study that included only patients who underwent pulmonary endarterectomy with cardiopulmonary bypass (CPB), Ortmann and colleagues [63] compared transfusion requirements and outcomes between 55 patients who received only FP and 45 patients who received only PCC for management of post-CPB coagulopathic bleeding. In an unadjusted analysis, they found that the PCC group had lower blood loss than the FP group, but transfusion rates were similar. They conducted multivariable regression analysis for AEs and found no differences between the two groups. However, given its small sample size, limited generalisability and lack of risk-adjustment for efficacy outcomes, this study should be interpreted with caution. In a larger study involving 3,454 consecutive cardiac surgery patients, Cappabianca and colleagues [73] used propensity scores to match 225 patients who received PCC (with or without FP) to 225 patients who received only FP for management of post-CPB coagulopathy. Among the propensity-score matched pairs, RBC transfusion requirements were lower in the PCC group (84% versus 93%), as were multiple (more than two units) RBC transfusions (51% versus 70%) and number of units of RBCs transfused (3.4 versus 5.2 units). While there were no major between-group differences in adverse outcomes, in a regression analysis that incorporated the propensity score in a larger patient series, the authors noted an association between PCC use and AKI that led them to caution about this potential risk, though the difference was not statistically significant among the 225 matched pairs. Similarly, in a recent multicentre observational study not included in the above systematic review, Biancari and colleagues compared 101 patients who received FP following coronary artery bypass grafting (CABG) to 101 propensity-score-matched patients who received PCC with or without FP [74]. PCC was associated with a significant decrease in the rate of RBC transfusions (67.3% versus 83.2%) but was also associated with an increased risk of AKI as measured by the Kidney Disease: Improving Global Outcomes (KDIGO) score, though not with KDIGO AKI stage 3. The authors suggested that this could be related to a relative hypovolemia in patients treated with PCC compared with those receiving FP. However, there were many limitations to this study, including unknown differences in PCC dosage, bleeding severity and coagulopathy. Furthermore, in the group of patients that received both FP and PCC, it was not known what the order of administration was and so PCC could have been given as salvage therapy [74]. Together, these studies suggest that PCC may be more efficacious than FP in cardiac surgery; however, data from adequately powered, prospective, randomised trials are lacking.

Pilot Randomised Studies

There are now two completed pilot randomised trials that have compared 4-factor PCC with FP [58, 62]. The study by Green et al. included 50 patients who underwent cardiac surgery and required coagulation factor replacement, with 25 randomised to 4-factor PCC and 25 randomised to FP [62]. IMP dose was limited to 1000 IU (approximately 15 IU/kg) for PCC and 4 units (approximately 15 mL/kg) for FP. The study aimed to assess recruitment rate for a large trial and hypothesis testing was not carried out, but safety and efficacy event rates were similar between the groups.

A randomised pilot trial (the FARES study) [58] was carried out at two hospitals for the purpose of exploring feasibility. The study randomised 101 adult patients who required coagulation factor replacement for management of bleeding during cardiac surgery to *Octaplex* (N=54) or FP (N=47). IMP dosing was weight based: PCC dose was 1500 IU for patients weighing ≤60 kg) and 2000 IU for those weighing >60 kg), and for FP it was 3 U and 4 U, respectively. Dosing could be repeated only once as needed within 24 hours; FP was used for any subsequent doses in both groups. Patients and outcome assessors were

blinded to treatment allocation, but no other aspects of care were modified. Both hospitals employed a validated point-of-care based coagulation management algorithm for bleeding patients.

Overall, the PCC group received a median (IQR) of 24.9 (21.8–27.0) IU/kg of PCC [two patients (3.7%; 95% CI 0.4–12.7%) required FP after PCC], and the FP group received a median (IQR) of 12.5 (10.0–15.0) mL/kg of FP [four patients (8.5%; 95% CI 2.4–20.4%) required >2 doses of FP]. Median (IQR) 12-hour chest tube drainage was 310 (250–455) mL and 500 (310–750) mL in the PCC and FP groups, respectively (P<0.001). One of the primary measures of haemostatic effects was treatment response, based on receipt of any haemostatic therapies from 60 minutes to 4 and 24 hours after initiation of study treatment. Haemostatic therapy was not required at the 4-hour time point for 43 patients (79.6%) in the PCC group and 32 patients (68.1%) in the FP group (P=0.25), nor at the 24-hour time point for 41 patients (75.9%) in the PCC group and 31 patients (66.0%) in the FP group (P=0.28). Another primary outcome measure was cumulative and individual allogeneic blood component units administered within 24 hours after the start of surgery. Median (IQR) 24-hour post-bypass cumulative allogeneic transfusions, including red cells, platelets and all (IMP + non-IMP) FP were 5.0 (4.0–9.0) units in the PCC group and 12.0 (7.0–19.0) in the FP group; ratio 0.56, 95% CI 0.43–0.73; P<0.001. Excluding IMP FP, the median (IQR) cumulative allogeneic transfusions were 5.0 (4.0–9.0) and 8.0 (4.0-15.0) units, respectively; ratio 0.78, 95% CI 0.58–1.06; P=0.11. For red cells alone, the median (IQR) was 1.0 (0.0–2.0) and 2.0 (1.0–3.0) units, respectively; ratio 0.53, 95% CI 0.36–0.78; P<0.001. Adverse event profiles were similar.

This pilot study showed that 4-factor PCC may be a suitable substitute for FP for mitigation of bleeding in cardiac surgery and validated the study methodology and dosing that will be used for the proposed trial. It also clearly illustrated that a large, multicentre, confirmatory trial is warranted to determine the relative risk-benefit profiles of these two therapeutics.

Purpose of the Study

The purpose of the LEX-211 study is to determine whether the PCC, *Octaplex,* is clinically non-inferior to FP with respect to haemostatic effectiveness when used to treat bleeding in cardiac surgical patients requiring coagulation factor replacement. Haemostatic management in bleeding surgical patients is evolving from empirical therapy with non-purified allogeneic blood products to targeted therapy with purified products that have undergone treatment with pathogen reduction technologies [75]. The proposed study, by comparing two currently available but distinctly different therapies for treating bleeding surgical patients requiring coagulation factor replacement, is well aligned with this change.

Given the potential advantages of PCC over FP detailed above (viral inactivation, ease of administration, standardised dosing/predictable effect and substantially lower risk of TRALI and TACO due to smaller volume), as well as the haemostatic superiority signals detected in observational studies and the recently completed FARES pilot randomised trial [58], a large multicentre trial adequately powered to establish haemostatic superiority or non-inferiority is warranted. The need for such a trial was highlighted in a recent editorial [76], as it will have a profound impact on clinical practice, potentially altering the long-established practice of administering FP for coagulation factor replacement in bleeding patients. If the study is positive, it will lead to the adoption of PCC over FP as first-line therapy for the management of bleeding surgical patients requiring coagulation factor replacement. If it is negative, on the other hand, it will prevent the inappropriate adoption

of PCC over FP for this indication. Thus, the study will inform clinical practice and promote the rational use of healthcare resources.

Study Population

To ensure that the results of the study are clinically relevant and generalisable, the LEX-211 study aims to include a wide spectrum of cardiac surgery patients (including simple or complex procedures and elective or non-elective procedures). In particular, two important, interrelated risk factors for haemorrhage due to coagulation factor deficiency are complex surgery and prolonged CPB duration. Complex surgeries include combined procedures (e.g., CABG + valve or multiple valves) and surgery on the aorta, and these are the procedures that also require prolonged CPB duration. Another equally important risk factor is non-elective surgery, as the risk of haemorrhage is substantially higher in patients who require emergency cardiac surgery. Thus, it is important to include patients undergoing complex or non-elective cardiac surgery in clinical studies on management of haemorrhage during cardiac surgery to ensure that the findings are clinically relevant and generalisable to this important population.

Therefore, the study will include adult patients undergoing any type of cardiac surgery (excluding those undergoing highly specialised procedures where there is wide variability in clinical practice, such as heart transplantation) who require coagulation factor replacement due to haemorrhage in the operating room, post-CPB. Given that patients undergoing isolated CABG are at low risk for haemorrhage, with approximately 2.5–7.5% receiving coagulation factor replacement with FP [77], it is anticipated that the study will primarily include patients who develop haemorrhage after complex surgeries, non-elective surgery or both. Overall, cardiac surgery patients who require coagulation factor replacement due to haemorrhage represent a small proportion of those undergoing cardiac surgery. In the FARES pilot study, patients for whom coagulation factor replacement was ordered during surgery for management of bleeding represented approximately 12% (169 of 1360) of all adults who underwent cardiac surgery at the two study centres in Canada during the study period [58].

Importantly, the study will not involve treating patients prophylactically before surgery as a Cochrane review found no evidence to support the prophylactic administration of FP to patients without coagulopathy undergoing elective cardiac surgery [30].

In the study, IMP will be administered if bleeding is severe enough to necessitate treatment or require urgent therapy. The severity of bleeding will be graded according to the Bleeding Severity Scale [78], which fulfils US Food and Drug Administration requirements for a validated, clinician-reported scale to standardise bleeding in clinical studies of intraoperative bleeding. The scale was developed to assess the performance of haemostatic agents in clinical studies, in order to generate clinically relevant labelling claims and identify appropriate haemostatic agents for clinical use.

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

1.2 Dose rationale

The doses of PCC and FP selected for the study are the same doses used for the pilot FARES study. There is an absence of a consensus regarding PCC dosing in acquired coagulation factor deficiency; however, the study dose of PCC represents current

recommended dosing for bleeding indications in various settings and is consistent with doses used in other studies in cardiac settings [27, 61, 79, 80]. Moreover, the maximum dose is equal to or lower than doses of PCC that have demonstrated a good safety and tolerability profile in other clinical settings (e.g., factor Xa inhibitor reversal in major bleeding [81-83] and trauma [84]. Of note, neither PCC nor FP will be administered to patients unless they are deemed to be clinically indicated by the ordering physician based on objective clinical criteria that will ensure adherence to best blood management practices.

1.3 Benefit-Risk Statement

Substituting either PCC or FP for the other is not expected to pose any material risks to the participants. Patients will only be included in the trial when their clinicians have ordered coagulation factor replacement for treatment of bleeding according to clinical and laboratory criteria; thus, patients would have received one or the other therapy as part of their routine clinical care. The two coagulation factor replacement therapies, *Octaplex* (the PCC to be used in this study) and FP, are both commonly used therapies for this procedure in many regions, with an expected comparable clinical safety profile. *Octaplex* is currently approved for use in Canada (but not in the United States) for the "treatment of bleeding and perioperative prophylaxis of bleeding in acquired deficiency of prothrombin complex coagulation factors, such as deficiency caused by treatment with vitamin K antagonists, or in case of overdose of vitamin K antagonists, when rapid correction of the deficiency is required" [85]. This approved indication falls within the proposed use in this study. In contrast, in the United States, Octaplex is approved under the tradename Balfaxar for the urgent reversal of acquired coagulation factor deficiency induced by Vitamin K antagonist (VKA, e.g., warfarin) therapy in adult patients with need for an urgent surgery/invasive procedure.

The experience to date with this PCC has shown a favourable safety profile [81, 82, 86-88]. As discussed, PCC is pathogen-reduced, can be administered quickly and in predictable doses, and has a substantially lower risk of TRALI and TACO compared with FP, making its administration likely to be both safer than, and at least as efficacious as, FP. It is possible that treatment with PCC may not be as effective as FP given that it does not contain the full complement of clotting factors that plasma contains, but the study protocol will allow patients in the PCC group to receive FP if haemostatic control is not achieved after two doses of PCC. By limiting maximal PCC dosing to well within acceptable limits that have been proven safe in other settings [81, 82, 86-88], theoretical risks for thrombotic complications have been mitigated.

1.4 COVID-19 Benefit-Risk Statement

Patients in the LEX-211 study will attend hospital for either emergency or scheduled elective cardiac surgery. The patients will not receive any additional contact with study staff beyond those required for undergoing the surgical procedure. The final postoperative visit will be carried out by phone unless the patient is currently in hospital, in order to reduce contact between the patient and healthcare staff. All surgeries will be carried out using standard safety measures in place at the treatment centres in line with local requirements for COVID-19 risk management. The study therefore does not place patients at any additional risk, since emergency surgical procedures must take place immediately, and elective cardiac surgery likewise cannot be postponed for long periods of time and therefore would go ahead even during the COVID-19 pandemic.

Potential COVID-19 related risks for site and project management will be evaluated in advance and options such as alternative monitoring approaches will be implemented. In addition, for the support of the study processes (e.g., provision of the study medication), only well-established service providers are selected which have strong regional expertise and strict risk and quality guidelines in place, including with regards to potential COVID-19-related risks. The current regulations regarding transport and logistics will be continuously monitored for the countries participating in the study, and flexible solutions and longer lead times will be implemented wherever appropriate.

2 STUDY OBJECTIVES

2.1 Primary Objective

1. To demonstrate that the 4-factor prothrombin complex concentrate (PCC) *Octaplex* is clinically non-inferior to frozen plasma (FP) with respect to haemostatic effectiveness, as measured by the need for post-therapy haemostatic interventions.

2.2 Secondary Objectives

1. To compare global haemostatic response between the *Octaplex* and FP groups, as measured by a composite of the need for post-therapy haemostatic interventions and drop in haemoglobin.
2. To compare the amount of bleeding as measured by the amount of chest tube drainage between the *Octaplex* and FP groups.
3. To compare the incidence of severe to massive bleeding between the *Octaplex* and FP groups.
4. To compare efficacy in terms of the total number of allogeneic blood components transfused between the *Octaplex* and FP groups.
5. To compare efficacy in terms of the incidence and number of individual allogeneic blood components transfused between the *Octaplex* and FP groups.
6. To compare the incidence of use of other coagulation factor products between the *Octaplex* and FP groups.
7. To compare the incidence of other bleeding-related clinical endpoints, i.e., intracerebral haemorrhage, gastrointestinal haemorrhage and surgical re-exploration, between the *Octaplex* and FP groups.
8. To compare the effect of *Octaplex* versus FP administration on the international normalised ratio (INR) between the *Octaplex* and FP groups.
9. To compare the effect of *Octaplex* versus FP administration on other coagulation parameters.
10. To compare time from IMP initiation to arrival in the ICU between the *Octaplex* and FP groups.
11. To compare safety as measured by serious treatment-emergent adverse events (TEAEs) between the *Octaplex* and FP groups.
12. To compare other secondary safety endpoints including duration of mechanical ventilation, duration of intensive care unit (ICU) stay, duration of hospitalisation, incidence of death and days alive and out of hospital between the *Octaplex* and FP groups.

3 INVESTIGATIONAL PLAN

3.1 Primary and Secondary Endpoints

3.1.1 Primary Endpoint

1. Comparison of haemostatic treatment response to *Octaplex* versus FP, defined as 'effective' if no additional haemostatic intervention, such as administration of any systemic haemostatic agents (including platelets, cryoprecipitate, fibrinogen concentrate, activated recombinant factor VII, other coagulation factor products or a second dose of IMP) or any haemostatic interventions (including surgical re-opening for bleeding) is required from 60 minutes to 24 hours after initiation of the first dose of IMP.

3.1.2 Secondary Endpoints

1. Comparison of global haemostatic response to *Octaplex* versus FP, defined as 'positive' if no additional haemostatic intervention (as per the primary endpoint) is required and haemoglobin levels decrease by <30% (after accounting for red cell transfusions) from 60 minutes to 24 hours after initiation of the first dose of IMP.
2. Comparison of the total amount of chest tube drainage at 12 and 24 hours after chest closure between the *Octaplex* and FP groups.
3. Comparison of the incidence of severe to massive bleeding, using a modification of the universal definition of perioperative bleeding (UDPB) in cardiac surgery [89] and its individual components during the first 24 hours after start of surgery, after the end of CPB and after IMP initiation, between the *Octaplex* and FP groups.
4. Comparison of the mean number of <u>total</u> allogeneic blood components – including red cells, platelets and all (IMP and non-IMP) FP – administered during the first 24 hours after the end of CPB, between the *Octaplex* and FP groups.
5. Comparison of the mean number of <u>total non-IMP</u> allogeneic blood components – including red cells, platelets and non-IMP FP – administered during the first 24 hours after the end of CPB, between the *Octaplex* and FP groups.
6. Comparison of the mean number of total non-IMP allogeneic blood components – including red cells, platelets, cryoprecipitate and non-IMP FP – administered during the first 24 hours and 7 days after IMP initiation, between the *Octaplex* and FP groups.
7. Comparison of the mean number of individual allogeneic blood components – including red cells, platelets, cryoprecipitate and non-IMP FP – administered during the first 24 hours and 7 days after the start of surgery, after the end of CPB and after IMP initiation, between the *Octaplex* and FP groups.
8. Comparison of the incidence of transfusion of individual allogeneic blood components – including red cells, platelets, cryoprecipitate and non-IMP FP – during the first 24 hours and 7 days after the start of surgery, after the end of CPB and after IMP initiation, between the *Octaplex* and FP group.
9. Comparison of the incidence of administration of non-IMP coagulation factor products – including fibrinogen concentrate and activated recombinant factor VII –

during the first 24 hours and 7 days after the start of surgery, after the end of CPB and after IMP initiation, between the *Octaplex* and FP groups.

10. Comparison of the incidence of intracerebral haemorrhage during the first 24 hours after start of surgery, after the end of CPB and after IMP initiation between the *Octaplex* and FP groups.
11. Comparison of the incidence of gastrointestinal haemorrhage during the first 24 hours after start of surgery, after the end of CPB and after IMP initiation between the *Octaplex* and FP groups.
12. Comparison of the incidence of surgical re-exploration during the first 24 hours after start of surgery, after the end of CPB and after IMP initiation between the *Octaplex* and FP groups.
13. Comparison of the change in INR, from within 30 minutes before to within 60 minutes after the initiation of IMP administration, between the *Octaplex* and FP groups; INR reduction will be considered successful if the magnitude of the reduction is >1.0 or the post-treatment level drops below 1.5.
14. Comparison of the changes in other coagulation parameters, including PT, aPTT, fibrinogen activity, ROTEM EXTEM CT and MCF, ROTEM FIBTEM MCF and platelets, from within 75 minutes before to within 75 minutes after the initiation of IMP administration, between the *Octaplex* and FP groups.
15. Comparison of time elapsed from initiation of the first dose of IMP to arrival into the ICU between the *Octaplex* and FP groups.

3.1.3 Safety Endpoints

All AEs and serious AEs (SAEs) will be collected from beginning of surgery (defined as entry into OR) to POD-30.

1. Comparison of the incidence of serious treatment-emergent adverse events (TEAEs), individually and as composite where appropriate (e.g., TEEs, major adverse cardiac events), between the *Octaplex* and FP groups.
2. Comparison of the duration of mechanical ventilation (measured as duration of ventilation and ventilator-free days) up to POD-30 between the *Octaplex* and FP groups.
3. Comparison of the duration of ICU stay up to POD-30 between the *Octaplex* and FP groups.
4. Comparison of the duration of hospitalisation up to POD-30 between the *Octaplex* and FP groups.
5. Comparison of the incidence of death up to POD-30 between the *Octaplex* and FP groups.
6. Comparison of the number of days alive and out of hospital at POD-30 between the *Octaplex* and FP groups.

3.2 Overall Study Design and Plan

This is a multicentre, randomised, active-control, prospective, Phase 3 study in adult cardiac surgery patients. Approximately 500 patients will be randomised at approximately 12 hospitals (10 in Canada and two in the United States), and the study will require

approximately two years to complete. The study is planned to start in quarter 4, 2022 and to be completed in quarter 4, 2024.

The study will include adult (≥18 years old) patients who undergo cardiac surgery on CPB and require coagulation factor replacement due to bleeding post-CPB and after adequate reversal of heparin with protamine (as assessed by the surgical staff based on clinical and laboratory criteria) during surgery, and who have a known (e.g., as indicated by INR) or suspected coagulation factor deficiency. Patients will be randomised to receive either 4-factor PCC (*Octaplex*) or FP when the blood bank/pharmacy receives the first order for coagulation factor replacement and determines patient eligibility with the study team based on the study inclusion and exclusion criteria.

Following confirmation of eligibility, the technologist will randomise the patient to PCC or FP according to the randomisation and dosing schedule and prepare and release the IMP in a tamper sealed container. Operating room personnel will remain blinded until the decision to administer the IMP is made.

IMP can be administered if bleeding is severe enough to necessitate IMP (meaning at least a grade 2 level [moderate] bleeding according to the validated Bleeding Severity Scale [78]), heparin is adequately reversed (confirmed by the return of post-protamine activated clotting time [ACT] to within 10% of pre-pump ACT) and INR is ≥1.5. IMP can also be administered if bleeding is severe enough to require urgent therapy, in which case treatment can be initiated irrespective of the INR value. Once the decision is made to administer the IMP, the administering clinician will break the seal on the container, carry out routine safety checks and initiate IMP administration according to the weight-based dosing recommendations.

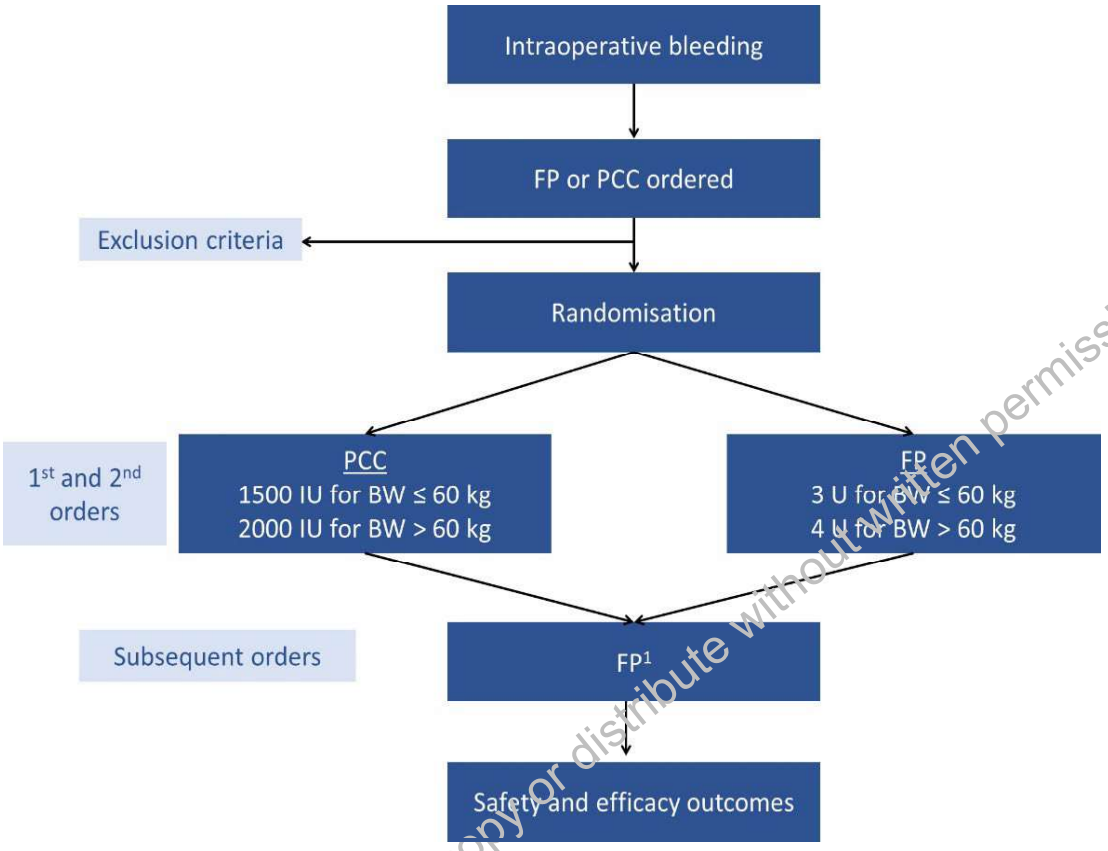
The recommended initial dose for *Octaplex* will be 1500 IU for patients weighing ≤60 kg and 2000 IU for patients weighing >60 kg. The recommended initial dose for FP will be 3 U for patients weighing ≤60 kg and 4 U for patients weighing >60 kg.

A second dose of IMP can be administered if the patient continues to have at least moderate bleeding and suspected coagulation deficiency (e.g., INR ≥1.5) after completion of the first dose. If an order for a second dose of coagulation factors is received within 24 hours after IMP initiation (either from the operating room or in the ICU after surgery), the blood bank/pharmacy technologist will release the IMP as determined by the randomisation schedule up to the maximum allowable dose (*Octaplex* 3000 IU if ≤60 kg or 4000 IU if >60 kg; FP 6 U if ≤60 kg or 8 U if >60 kg) (a tamper-sealed container will not be used for these orders as clinicians will by now be unblinded).

If further doses of coagulation factors are required after the second dose of IMP, all patients will receive non-IMP FP. That is, for subsequent orders once the maximum dose of IMP has been administered (i.e., 2 doses), or after the 24-hour treatment period has elapsed, the technologist will release FP for both groups (in 1–4 U increments as per the ordering physician); these additional FP units will not be counted as part of the IMP (**Figure 1**).

Transfusion of non-IMP blood components and all haemostatic agents will be according to a standardised transfusion management algorithm (**Figure 2**). Measurements of INR and haemoglobin will be performed at preestablished time points, if not available already. No other aspects of routine clinical care will be modified.

Figure 1: Study Flow



[1] FP in 1U increments as per the ordering physician

PCC, prothrombin complex concentrate; FP, frozen plasma; BW, body weight; IU, international units;

3.3 Discussion of Study Design and Choice of Control Group

3.3.1 Study Design

3.3.1.1 Criteria for Administration of IMP

The decision to administer the IMP will be based on objective clinical and laboratory criteria (**Section 6**). Incorporating these criteria in the study will standardise administration of IMP such that it is administered when clinically indicated.

3.3.1.2 Transfusion Protocol Standardisation

All participating hospitals will be required to follow an established transfusion management protocol for administration of non-IMP blood components and all haemostatic agents. Recognising that the intervention will occur during a very dynamic period (i.e., bleeding during surgery); however, the study employs a pragmatic design that will allow clinicians

to use best judgment within the context of the transfusion protocol. This will allow the surgical team flexibility while maintaining clinical practice standardisation that conforms to best clinical practices. This is important since other multicentre studies that have included a very strict design so far have failed when studied in later phase trials because of the inability of the sites to accurately follow the specified design, which itself has been criticised for not being consistent with usual clinical practice.

3.3.1.3 External Validity

This Phase 3 study will be performed in multiple hospitals with different characteristics. Moreover, patients will be randomised after the clinical team orders coagulation factor replacement and the only change to routine practice is dictating the choice of coagulation factor replacement amongst the two therapies that are currently available and used interchangeably. For these reasons, external validity should not be an issue.

3.3.1.4 Randomisation and Baseline Differences

Given the size of the study and random patient assignment stratified by centre, study groups should be reasonably balanced with respect to important clinical variables. The random allocation schedule will be prepared by a biostatistician not involved in the conduct of the trial, and neither the individual randomising nor any of the health care providers will know which treatment will be assigned to the patient when coagulation factor replacement is ordered.

3.3.1.5 Recruitment and Informed Consent

This is a pragmatic trial that compares two coagulation factor replacement therapies that are currently routinely used for the study indication in multiple regions globally and in various settings. It is not expected that participating in the trial will pose any risks to patients.

All patients ≥18 years old undergoing cardiac surgery with CPB at the study centres will be offered the chance to participate in the study prior to their surgery. Voluntarily given, written, informed consent will be obtained from the patient before the study procedures start. Once consent has been obtained and the patient enrolled into the study, eligibility according to inclusion criteria 1 and 4 (i.e., patients ≥18 years old, undergoing any index cardiac surgery employing CPB, who have provided informed consent) and the exclusion criteria will be confirmed. If screening is performed before the day of surgery, exclusion criterion 3 (i.e., severe right heart failure [clinical diagnosis ± echocardiography]) will be rechecked on the day of surgery[2].

Only patients who require coagulation factor replacement therapy during surgery will be randomised, receive study drug, and undergo the proceeding visits and assessments. When the first order for PCC or FP is received by the blood bank/pharmacy while the patient is in the operating room, the blood bank/pharmacy technologist will confirm patient eligibility with the clinical team. Following confirmation of eligibility, the technologist will randomise the patient to PCC or FP according to the randomisation and dosing schedule.

[2]In Canada, informed consent will be obtained after randomisation, in accordance with Article 3.7A of the 2018 Tri-Council Policy Statement on the Ethical Conduct for Research Involving Humans.

Randomisation (1:1) will continue until at least 410 evaluable patients are obtained (205 patients per group).

3.3.1.6 Blinding

Given that the products have quite different physical properties, it is not possible to blind treating clinicians to group assignment. To minimise bias, treating clinicians will be blinded to group assignment until immediately prior to IMP infusion. The blood bank/pharmacy technologist will randomise the patient to PCC or FP, according to the randomisation schedule, and prepare and release the product in a tamper sealed container (with weight device in PCC boxes to ensure adequate concealment). The operating room personnel will be blinded to group allocation until the tamper lock seal is broken in the operating room immediately prior to infusion. For subsequent orders, a tamper-sealed container will not be necessary, and the blood bank/pharmacy technologist will release IMP as determined by the randomisation schedule, as per usual practice. The type of IMP administered will be recorded in manner that will not unblind the outcome assessor. Patients will also be unaware of treatment allocation. These same processes were successful in the pilot study noted above.

3.3.1.7 Drop-outs and Crossovers

Drop-outs: Based on the results of the FARES pilot study, it is anticipated that approximately 20% of randomised patients will not receive the IMP due to cessation of bleeding or identification of other causes of bleeding by the time the IMP is received in the operating room. (Significant dropouts are not anticipated for any other reasons, including not having undergone an index cardiac procedure.) Since clinicians will be blinded to group assignment until the decision is made to administer the IMP, and the decision to administer the IMP will be based on objective criteria, exclusion of these randomised but untreated patients from the primary analysis set will not bias the results. Study sample size has been calculated to compensate for dropouts. To ensure between-group comparability in baseline characteristics and outcomes, data will be collected for these patients for 30 days after surgery.

Product switching: Other than the coagulation factor replacement order being cancelled, all patients will be treated according to the randomisation schedule up to the maximum allowable dose during the treatment period (24 hours after IMP initiation). Thereafter, all patients will receive non-IMP FP when coagulation factor replacement is required. To ensure minimal product switching, instructions will be entered into the blood bank/pharmacy information system to dictate the randomisation product for the 24 hours after IMP initiation and will flag the laboratory technologists if attempts are made to override the instruction. In the FARES pilot trial, all treated patients received the appropriate IMP; thus, product switching is not anticipated to be a significant problem.

3.3.1.8 Independent Data and Safety Monitoring Committee (IDSMC)

An IDSMC will review accumulating safety, endpoint and other study data (recruitment, retention and compliance, data quality and timeliness, risk versus benefit).

The function of the IDSMC will be to protect and serve the recruited patients particularly pertaining to patient safety as well as to assist and advise the Sponsor on medical questions and issues of study conduct and continuation. The IDSMC will be independent of the investigating team and the Sponsor in operating and formulating recommendations.

The responsibilities of the IDSMC are listed in **Section 8.6**.The full role of the IDSMC will be detailed in the IDSMC Charter.

3.3.2 Control Group

The trial will not include a placebo arm because delaying coagulation factor replacement in bleeding patients may expose them to the negative consequences of excessive blood loss, is not consistent with standard practice [90] and would withhold an effective treatment from patients and thus be unethical. Moreover, the question being addressed does not meet any of Freedman's five conditions that would justify the use of a placebo control, which are: 1) no standard treatment exists; 2) standard treatment is not better than placebo; 3) standard treatment is a placebo or no treatment; 4) new evidence has shown uncertainty of the risk-benefit profile of the standard treatment; and 5) effective treatment is not readily available due to cost or supply issues [91].

3.3.3 Study Parameters

A dichotomous classification of haemostatic effectiveness will be used to assess treatment response to PCC or FP in bleeding adult cardiac surgical patients. Treatment will be considered 'effective' if no additional haemostatic intervention is required in the time window from 60 minutes to 24 hours after initiation of the first IMP dose. The 60-minute time period will allow for the administration of the IMP and establishment of treatment effect. Patients will be assigned a haemostatic treatment response classification of 'ineffective' if their management required haemostatic interventions during the time window from 60 minutes to 24 hours after initiation of the first IMP dose.

Haemostatic intervention includes the administration of any systemic haemostatic agents (including platelets, cryoprecipitate, fibrinogen concentrate, activated factor VII, other coagulation factor products, or a second dose of IMP) or any haemostatic interventions (including surgical re-opening for bleeding). Because of the complexity and dynamic nature of cardiac surgery, as well as the multifactorial nature of haemorrhage during cardiac surgery, it is inherently not feasible to assess the specific haemostatic response to individual therapeutic agents.

The following secondary endpoints will be included to provide supportive evidence of haemostatic efficacy: global haemostatic response, INR reduction, the incidence and amount of individual allogeneic blood components transfused and the incidence of other bleeding-related clinical endpoints.

Global haemostatic response will be based on the haemostatic efficacy scale used successfully in a Phase 3b RCT by Sarode and colleagues [69] (in discussion with the Food and Drug Administration), modified to reflect the special considerations of haemorrhage during cardiac surgery.

4 STUDY POPULATION

4.1 Population Base

The study will include approximately 500 randomised bleeding adult (≥18 years old) cardiac surgical patients who require coagulation factor replacement after CPB. The study will continue until there are at least 410 evaluable patients, accounting for dropouts in both arms, with a minimum of 205 patients assigned to each of the two treatment groups.

4.1.1 Inclusion Criteria

Patients undergoing the following criteria will be eligible for inclusion in the study:

1. Adult (≥18 years old) patients undergoing any index cardiac surgery employing CPB
2. Coagulation factor replacement with PCC or FP ordered in the operating room for:
    a. Management of bleeding, or
    b. Anticipated bleeding in a patient who has been on-pump for >2 hours or undergone a complex procedure (e.g., aortocoronary bypass [ACB] plus aortic valve replacement)
3. Coagulation factor deficiency, either known to exist (e.g., as indicated by elevated EXTEM clotting time [CT] or INR) or suspected based on the clinical situation
4. Patients who have given written informed consent[3]

4.1.2 Exclusion Criteria

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

1. Undergoing heart transplantation, insertion or removal of ventricular assist devices (not including intra-aortic balloon pump [IABP]) or repair of thoracoabdominal aneurysm
2. Critical state immediately before surgery with high probability of death within 24 hours of surgery (e.g., acute aortic dissection, cardiac arrest 24 hours before surgery)
3. Severe right heart failure (clinical diagnosis ± echocardiography)
4. Known contraindications to heparin
5. PCC required for reversal of warfarin or direct oral anticoagulant (DOAC; dabigatran, rivaroxaban, apixaban or edoxaban) within 3 days prior to or during surgery
6. Known TEE within 3 months prior to surgery
7. History of severe allergic reactions to PCC or FP
8. Individuals who have IgA deficiency with known antibodies against IgA
9. Refusal of allogeneic blood products

[3] In Canada, informed consent will be obtained after randomisation, in accordance with Article 3.7A of the 2018 Tri-Council Policy Statement on the Ethical Conduct for Research Involving Humans.

10. Known pregnancy
11. Currently enrolled in any other interventional clinical trials

4.2 Prior and Concomitant Therapy

Details on medications taken within 1 week before enrolment and concomitant medications taken during the study (excluding drugs given for routine anaesthesia) will be recorded in the case report form (CRF).

4.2.1 Permitted Concomitant Therapy

Participating hospitals will use a standardised point-of-care based transfusion algorithm that will employ a targeted approach to correct coagulopathy (as per the validated TACS algorithm) [79], but with selection of PCC or FP determined according to the patient's assigned grouping and using the doses described in **Section 5.4**.

Concomitant administration of any therapies required as part of standard patient care is permitted but must be recorded in the CRFs. All haemostatic drugs or products administered (e.g., heparin and protamine dose, antifibrinolytic drugs, desmopressin, rFVIIa, idarucizumab, andexanet alpha or topical haemostatic agents) will be recorded, as well as all procedures that may influence amount of bleeding (e.g., retrograde autologous priming of CPB circuit, cell salvage). In addition, concomitant medications used to treat SAEs will be reported throughout the duration of follow-up (up to POD-30).

4.2.2 Forbidden Concomitant Therapy

No concomitant therapies are forbidden.

4.3 Withdrawal and Replacement of Patients

4.3.1 Premature Subject/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 for reasons such as intervention no longer indicated due to cessation of bleeding, randomisation of ineligible patients and adverse events attributed to previous doses of IMP. For any withdrawals after study entry, the Investigator will obtain all the required details and document the reason(s) for discontinuation, and report to the IDSMC and institutional review board (IRB) where indicated. 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 outcomes up to the time of withdrawal of participation.

4.3.2 Subject/Patient Replacement Policy

Patients withdrawn from the study for safety reasons will not be replaced.

4.4 Assignment of Patients to Treatment Groups

Patients will be assigned to treatment with either PCC or FP using a permuted-block, stratified (by centre) random allocation scheme prepared by a biostatistician not involved in the conduct of the trial. Group allocation will apply to the first two doses of IMP during the treatment period (up to 24 hours from IMP initiation). For any additional doses (i.e., the

third dose and thereafter), patients in both groups will receive FP. Patients are not permitted to re-enrol in the study.

4.5 Relevant Protocol Deviations

Classification of protocol deviations as minor and major will be defined *a priori*. Patients with major protocol deviations will be excluded from the per-protocol analyses. The Sponsor and IDSMC will review the number and nature of major protocol deviations and take appropriate measures to minimise the impact on the study.

4.6 Subsequent Therapy

Any subsequent haemostatic therapy will be according to institutional standard of care.

5 INVESTIGATIONAL MEDICINAL PRODUCT(S)

5.1 Characterisation of Investigational Product(s)

5.1.1 Octaplex

Octaplex is a product derived from human plasma containing the coagulation factors II, VII, IX and X and proteins C and S. It is manufactured by chromatographic purification of cryoprecipitate-poor plasma.

The *Octaplex* manufacturing process includes two dedicated virus inactivation/removal steps, by way of a solvent/detergent viral inactivation process and a virus removal nanofiltration step. The solvent/detergent treatment causes enveloped viruses such as pseudorabies virus (PRV), Schmallenberg virus (SBV) and human immunodeficiency virus (HIV) type 1 to be irreversibly destroyed. Nanofiltration removal of infectious agents from protein solutions on the basis of their size may be the only method to date permitting efficient removal of enveloped (e.g., HIV-1, SBV, PRV, bovine viral diarrhoea virus) and non-enveloped viruses (e.g., hepatitis A virus) under conditions where 90–95% of protein activity is recovered [92]. Other precautions against viral transmission include: selection of plasma donors, screening of donations and plasma pool, as well as quality control measurements of the final product.

5.1.1.1 Composition of Octaplex

Octaplex is a human PCC for intravenous (IV) use. The composition of Octaplex is described in the current edition of the IB. Differences in composition may exist between countries; please refer to the country-specific Summary of Product Characteristics (SmPC) and Package Insert (PI).

5.1.2 Frozen plasma

For patients randomised to FP, the blood bank/pharmacy will assign to the study, prepare and release FP for the first and second orders received during the treatment period (24 hours after IMP initiation). The recommended dose for FP will be 3 U for patients weighing ≤60 kg and 4 U for patients weighing >60 kg. While there is no maximum dose for FP, during the treatment period administration of up to 6 U for patients weighing ≤60 kg and up to 8 U for patients weighing >60 kg will be counted as part of the IMP.

FP will be provided by local supplier of blood components and will be stored, thawed and pooled by the blood bank/pharmacy according to current standards. FP will be infused as per standard hospital protocols at the participating institutions (i.e., infused using timing recommended in the current monograph through standard 140 µm blood infusing set).

5.2 Packaging and Labelling

Octaplex 500 IU and 1000 IU will be used in this study. *Octaplex* is supplied as a powder for solution for injection together with a solvent (20 mL or 40 mL Water for Injection, respectively), which should be used for the reconstitution. The batch number(s) used will be recorded in the Clinical Study Report. *Octaplex* will be labelled and packed as IMP according to the local regulations.

Final labelling will comply with the national requirements of the respective countries, Canada and the United States, where the study is to be conducted.

5.3 Conditions for Storage and Use

Octaplex must be stored at room temperature (not more than 25°C) and protected from light. The product must not be frozen. The Investigator/authorised personnel at the site will ensure that *Octaplex* is stored in appropriate conditions with restricted access and in compliance with national regulations.

FP is to be stored at the blood bank/pharmacy in line with the local standard practice.

5.4 Dose and Dosing Schedule

For patients randomised to *Octaplex,* the blood bank/pharmacy will prepare and release either 1500 or 2000 IU of *Octaplex* for the first and second orders received during the treatment period (24 hours after IMP initiation). The recommended dose for *Octaplex* will be 1500 IU for patients weighing ≤60 kg and 2000 IU for patients weighing >60 kg. The maximum dose of *Octaplex* will be 4000 IU. If requests for additional doses are received during the treatment period or at any time thereafter, FP will be used, which will not be counted as part of the IMP.

5.5 Preparation and Method of Administration

Each vial of *Octaplex* will be reconstituted with 20 mL or 40 mL WFI (as per the manufacturer's instructions) at room temperature (not more than 25°C). *Octaplex* dissolves at room temperature to an almost colourless and slightly opalescent solution within 10 minutes. It will not be used if it remains cloudy or contains particulates.

Octaplex will be administered intravenously, immediately after reconstitution as recommended, via free-flowing IV syringe injection. *Octaplex* should not be mixed with other medicinal products or crystalloid intravenous solutions.

FP will be thawed and administered according to the local standard.

5.6 Blinding, Emergency Envelopes and Breaking the Study Blind

This is a partially blinded randomised study, with patients and outcome assessors blinded to treatment allocation. Given the physical differences in the products and the emergency nature of the intervention, attending clinicians will not be blinded to the treatment. Thus, breaking the study blind is not an issue in this study.

The random allocation schedule will be prepared by a biostatistician not involved in the conduct of the trial (see **Section 9.3**). To minimise bias, neither the individual randomising nor any of the health care providers will know which treatment will be assigned to a given patient when coagulation factor replacement is ordered. Blood products will be transported to the OR in weighted temper-proof boxes to maintain the blind until IMP infusion.

The type of IMP administered will be recorded in a manner that will not unblind the outcome assessor. Patients will also be blinded to treatment allocation.

5.7 Treatment Compliance

5.7.1 Drug Dispensing and Accountability

A drug dispensing log and the inventory will be kept current by the Investigator, detailing the dates and quantities of *Octaplex* administered to each patient. The inventory and the drug dispensing log will be available to the monitor to verify drug accountability during the study. Used or partially used vials are to be destroyed at the site. Any unused *Octaplex* either not dispensed or returned from the operating room or the ICU will be accounted for. After the Sponsor has granted written approval of destruction, these can be destroyed either at the study site or returned to the depot for destruction. Destruction can be initiated only after accountability has been verified and fully reconciled by the monitor.

FP assigned to the study and dispensed accordingly will be tracked in an IMP FP dispensing log which will be available to the monitor to verify drug accountability during the study. FP returned unused from the operating room or the ICU will be handled according to the local practice.

5.7.2 Assessment of Treatment Compliance

Coagulation factor replacement will be ordered and administered by the clinical team in the hospital and will not be dependent on patient compliance. Treatment compliance for each patient will be based on calculating the ratio of total IMP administered to scheduled amount of IMP, expressed as a percentage.

6 STUDY CONDUCT

All patients ≥18 years old undergoing cardiac surgery with CPB at the study centres will be the potential patients in the study. Voluntarily given, written, informed consent will be obtained from the patient. Once consent has been obtained and the patients enrolled into the study, eligibility according to inclusion criteria 1 and 4 (i.e., patients ≥18 years old, undergoing any index cardiac surgery employing CPB, who have provided informed consent) and the exclusion criteria will be determined. If screening is performed before the day of surgery, exclusion criterion 3 (i.e., severe right heart failure [clinical diagnosis ± echocardiography]) will be rechecked on the day of surgery.

Only patients who require coagulation factor replacement therapy during surgery will be randomised, receive study drug, and undergo the proceeding visits and assessments.

When the first order for PCC or FP is received by the blood bank/pharmacy while the patient is in the operating room, the blood bank/pharmacy technologist will confirm patient eligibility with the clinical team. Following confirmation of eligibility, the technologist will randomise the patient to PCC or FP according to the randomisation and dosing schedule and prepare and release the IMP in a tamper sealed container (with weight device in PCC containing boxes to ensure adequate concealment). Operating room personnel will remain blinded until the decision to administer the IMP is made.

IMP can be administered if bleeding is severe enough to necessitate IMP (meaning at least a grade 2 level [moderate] bleeding according to the validated Bleeding Severity Scale [78] – see Appendix 1), heparin is adequately reversed (confirmed by the return of post-protamine ACT to within 10% of pre-pump ACT) and INR is ≥1.5 (using the Hemochron Signature Elite; Instrumentation Laboratory). IMP can also be administered if bleeding is severe enough to require urgent therapy, in which case treatment can be initiated irrespective of the INR value. Once the decision is made to administer the IMP, the administering clinician will break the seal on the container, carry out routine safety checks, and initiate IMP administration according to the weight-based dosing recommendations: For *Octaplex*: 1500 IU if ≤60 kg; 2000 IU if >60 kg. For FP: 3 U if ≤60 kg; 4 U if >60 kg.

Octaplex and FP will be administered intravenously. For the first ordered dose, the blood bank/pharmacy will prepare and release either *Octaplex* or FP, as per the randomised group allocation. The recommended dose for *Octaplex* will be 1500 IU for patients weighing ≤60 kg and 2000 IU for patients weighing >60 kg. The recommended dose for FP will be 3 U for patients weighing ≤60 kg and 4 U for patients weighing >60 kg.

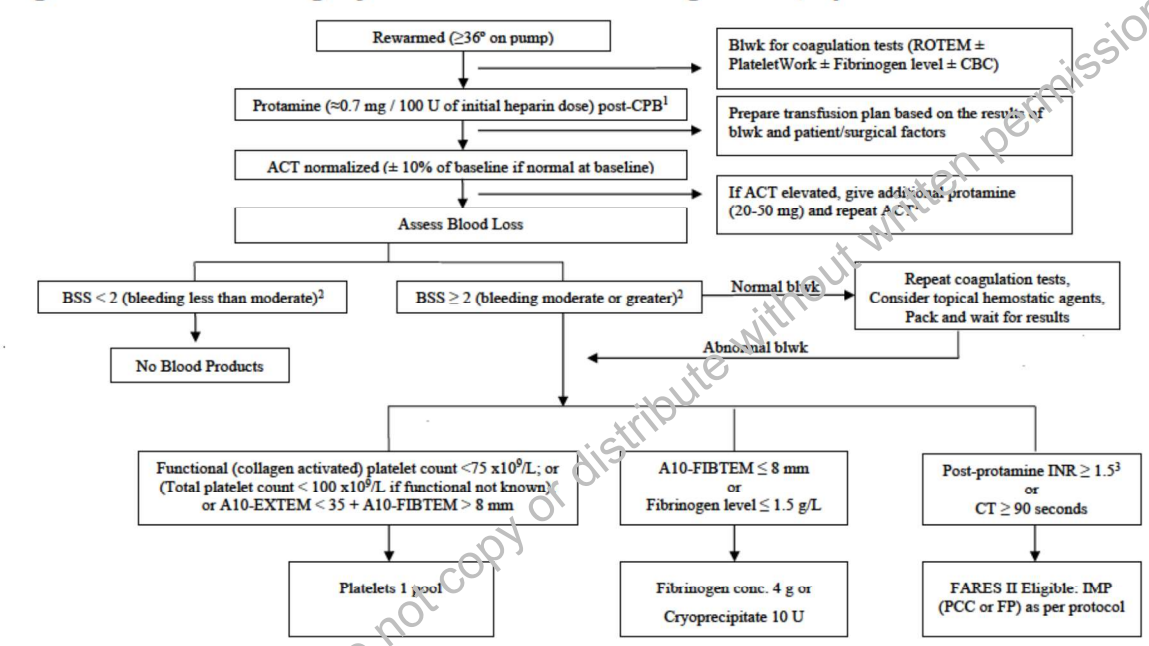
A second dose of IMP can be administered if the patient continues to have at least moderate bleeding and a suspected coagulation deficiency (e.g. INR ≥1.5) after completion of the first dose. If this second order of coagulation factors is received within 24 hours after IMP initiation (either from the operating room or in the ICU after surgery), the blood bank/pharmacy technologist will release the IMP as determined by the randomisation schedule up to the maximum allowable dose, as per usual practice (a tamper-sealed container will not be used for these orders as clinicians will by now be unblinded). The maximum allowable dose of IMP will be: *Octaplex* 3000 IU if ≤60 kg or 4000 IU if >60 kg; FP 6 U if ≤60 kg or 8 U if >60 kg.

If further doses of coagulation factors are required after two doses of IMP, all patients will receive non-IMP FP. That is, for subsequent orders once the maximum dose of IMP has been administered (i.e., two doses), or after the 24-hour treatment period has elapsed, the technologist will release FP (in 1–4 U increments as per the ordering physician) for both groups, but these will not be counted as part of the IMP (**Figure 1**). To maintain blinding

of outcomes assessors, the type of IMP administered will be recorded in a manner that will not unblind the outcome assessor.

Transfusion of non-IMP blood components and all haemostatic agents will be according to a standardised transfusion management algorithm (see **Figure 2**). Measurements of INR and haemoglobin will be performed at preestablished time points. No other aspects of routine clinical care will be modified.

Figure 2: Cardiac Surgery Blood Transfusion Algorithm, updated from TACS.



To determine need for RBC transfusion, consider patient status and haemoglobin. Transfuse red cells if Hb < 70 g/L during CPB; < 80 g/L post-CPB; and < 90 g/L in bleeding or unstable patients.

[1] In general, the initial protamine dose should not exceed 400 mg, irrespective of amount of heparin given. If an additional protamine dose does not shorten ACT, consider low fibrinogen levels or deficiency of enzymatic coagulation factors as a reason for prolonged ACT and treat according to the algorithm.

[2] BSS < 2 (less than moderate) = no therapy; BSS 2-3 (moderate-severe) = institute stepwise treatment; assess bleeding after each product; BSS 4 (life threatening) = administer therapy as necessary **without** waiting for laboratory results and combine therapies as appropriate.

[3] POC INR should be performed >10–15 minutes after protamine or results may be inaccurate.

ACT = activated clotting time; Blwk = bloodwork; BSS, bleeding severity scale; CBC = complete blood count; POC = point-of-care; CPB = cardiopulmonary bypass; CT = clotting time; IMP = investigational medicinal product; INR, international normalised ratio;

Standard and point-of-care coagulation measures will be obtained as per usual clinical practice, ideally within 75 minutes before and after each IMP administration.

All AEs and SAEs occurring until POD-30 will be recorded. Patients will be followed by research coordinators in each institution. All clinical outcomes will be obtained from patients' medical records and electronic records, history and physical where needed and via phone contact during the follow-up visits.

The flow chart of assessments by study visit is given in **Table 1**.

6.1 Observations by Visit

6.1.1 Screening visit (maximum 28 days before surgery)

At the screening assessment, voluntarily given, written (signed and dated) informed consent will be obtained from the patient.

Eligibility according to inclusion criteria 1 and 4 (i.e., patients ≥18 years old, undergoing any index cardiac surgery employing CPB, who have provided informed consent) and the exclusion criteria will be confirmed. If screening is performed before the day of surgery, exclusion criterion 3 (i.e., severe right heart failure [clinical diagnosis ± echocardiography]) will be rechecked on the day of surgery.

The following visits will only be performed for patients who bleed and require coagulation factor replacement therapy during surgery

6.1.2 Visit 1 (POD 0 pre-randomization): Pre-randomisation visit (blood bank/pharmacy)

First coagulation factor replacement order from the surgical team received at the blood bank/pharmacy

Surgical staff will confirm protocol criteria before the blood bank/pharmacy order is made.

Surgical staff will record the patient's body weight.

The blood bank/pharmacy technologist will confirm and document the following:

- All eligibility criteria are met

The blood bank/pharmacy technologist will then randomise patients to *Octaplex* or FP according to the randomisation schedule and prepare and release the product.

Note; if subsequent coagulation factor replacement orders are made within 24 hours from IMP initiation, the blood bank/pharmacy technologist will confirm and document that all contents of the order have been administered.

6.1.3 Visit 2 (POD 0 post-randomization and POD 1): First visit after IMP initiation (0 to 24 hours after IMP initiation)

For any specified activity that cannot be completed during the first visit after IMP initiation, additional visits will be made on postoperative day 1 until all study data are obtained.

- Collect baseline data
    - Demographics (sex, age, height and Body Mass Index [BMI])
    - Medical history
    - Preoperative concomitant medications
    - Laboratory assessments where available as part of routine care
        - Clinical chemistry (sodium, potassium, chloride, bicarbonate, pH)
        - Haematology (complete blood count)

        - Safety laboratory analyses if available (creatinine, liver function tests [ALT, ALP], bilirubin, troponin)

- Administer first dose of IMP
- Collect surgical data
    - Intraoperative concomitant medications
    - CPB start and end times
    - Cross-clamp time
    - Circulatory arrest start and end times
    - Fluid intake and output monitoring
    - Inotropes and vasopressors
    - Start and end time of IMP administration
    - Length of stay in the OR
- Collect laboratory assessments where available as part of routine care
    - Clinical chemistry (sodium, potassium, chloride, bicarbonate, pH)
    - Haematology (complete blood count)
    - Any coagulation measures (e.g. PT, aPTT, INR, plasma fibrinogen level, ROTEM EXTEM CT and MCF, ROTEM FIBTEM MCF, platelet count, platelet function) measured from within 75 minutes before to within 75 minutes after IMP initiation.
    - Safety laboratory analyses if available (creatinine, liver function tests [ALT, ALP], bilirubin, troponin)
- Measure haemoglobin within 30±15 minutes before and at 60±15 minutes after IMP initiation
- Measure INR within 30±15 minutes before and at 60±15 minutes after IMP initiation and document results
- Administer second dose of IMP, if needed
- Collect all transfusions and haemostatic therapies
- Collect chest tube drainage at 1, 6,12 and 24hours after chest closure
- Measure haemoglobin at 24 hours ±1 hour after IMP initiation and document results
- Collect extubation time
- Collect concomitant medications
- Collect AEs and SAEs

6.1.4 Visit 3 (POD 2-7): Days 2–7 after IMP initiation (or at discharge, if earlier)

- Collect daily laboratory assessments where available as part of routine care
    - Chemistry (sodium, potassium, chloride, bicarbonate, pH)

  - Haematology (complete blood count)
  - Coagulation profile (e.g. PT, aPTT, INR, plasma fibrinogen level, ROTEM EXTEM CT and MCF, ROTEM FIBTEM MCF platelet count, platelet function)
  - Safety labs (creatinine, liver function tests [ALT, ALP], bilirubin, troponin)
- Collect all transfusions and haemostatic therapies
- Record incidence of intracerebral haemorrhage, gastrointestinal haemorrhage and surgical re-exploration.
- Collect extubation time (if applicable)
- Collect length of stay in the ICU and hospital (if applicable)
- Collect concomitant medications
- Collect AEs and SAEs

6.1.5 Visit 4 (POD 30): Day 30 after IMP initiation (in person if in hospital, or by phone)

- Collect concomitant medications
- Collect AEs and SAEs
- Collect extubation time (if applicable)
- Collect length of stay in the ICU (if applicable)
- Collect length of stay in the hospital (if hospital stay is extended) and hospital readmissions
- Document patient outcome and survival at 30 days (still in hospital; dead or alive)

After Visit 4 or on POD-30, the clinical study is considered completed for the patient. No further study-related assessments will be performed, unless safety concerns (e.g., ongoing AEs) require follow-up.

6.1.6 Time Windows Used in this Study, including Tolerances

In this study, the following time windows and tolerances apply (**Table 2**):

Table 2: Time Windows Used in this Study

Time point	Time stated	Tolerance
Blood sampling for haemoglobin	Within 30 minutes of IMP initiation	N/A
	At 60 minutes after IMP initiation	±15 minutes
	At 24 hours after IMP initiation	±1 hour
Blood sampling for INR	Within 30 minutes of IMP initiation	N/A
	At 60 minutes after IMP initiation	±15 minutes
POD-30 follow-up		±2 days

IMP, investigational medicinal product; INR, international normalised ratio; N/A, not applicable; POD, postoperative day

6.2 Duration of Study

6.2.1 Planned Duration for an Individual Subject/Patient

The **duration of the treatment period** is 24 hours from initiation of IMP.

The **duration of the study** for an individual patient is 30 days from patient randomisation.

6.2.2 Planned Duration for the Study as a Whole

The study will be considered completed when at least 410 patients are consented, randomised, treated, and have finalised day 30 data. It is estimated that the study will take approximately two years for recruitment. The estimated start of the study (enrolment of first patient) is quarter 4 2022, and the estimated end of the study (last visit of last patient) is quarter 4 2024.

6.2.3 Premature Termination of the Study

The Sponsor, in consultation with the IDSMC, reserves the right to terminate the study at any time. In this event, any necessary procedures will be arranged on an individual study basis after review and consultation by both parties. In terminating the study, the Investigators will ensure that adequate consideration is given to the protection of the patients' interests.

Regulatory authorities and IRBs will be informed in accordance with national regulations.

Early termination of the study as a whole or by centre may apply for the following reasons:

6.2.3.1 Early Termination of the Entire Clinical Study

At any time, the study will be terminated prematurely if:

- New toxicological or pharmacological findings or safety reports invalidate the earlier positive benefit-risk-assessment.

6.2.3.2 Early Termination at an Individual Study Centre

At any time, the study can be terminated at an individual centre if:

- The centre cannot comply with the requirements of the protocol.
- The centre cannot comply with GCP standards.
- The a priori determined required recruitment rate is not met.

7 ASSESSMENTS AND METHODS

7.1 Demographic and Baseline Information

The baseline information and medical history will be recorded during Visit 1, i.e., as soon as possible after randomisation.

7.1.1 Demographic and baseline characteristics

The demographic and baseline characteristics are sex, age, height and BMI.

7.1.2 Medical history and prior/concomitant medications

The medical history will be obtained by interviewing the patient or from the medical records.

Prior and concomitant medications from within 1 week prior to surgery will be obtained.

7.2 Efficacy Assessments

7.2.1 Assessments for Primary Efficacy Endpoint

7.2.1.1 Haemostatic Treatment Response to IMP

A dichotomous classification of haemostatic effectiveness will be used to assess the primary endpoint of haemostatic treatment response to PCC or FP in bleeding cardiac surgical patients. Treatment will be considered 'effective' if no additional haemostatic intervention is required in the time window from 60 minutes to 24 hours after initiation of the first IMP dose (**Table 3**). The 60-minute time period will allow for the administration of the IMP and establishment of treatment effect. Patients will be assigned a haemostatic treatment response classification of 'ineffective' if their management required haemostatic interventions during the time window from 60 minutes to 24 hours after initiation of the first IMP dose.

Table 3: Objective Criteria for Determination of Haemostatic Treatment Response to IMP

Haemostatic Response	Haemostatic Intervention
Effective	No additional haemostatic interventions[1] administered between 60 minutes and 24 hours after initiation of infusion[2]
Ineffective	Additional haemostatic interventions[1] administered between 60 minutes and 24 hours after initiation of infusion[2]

[1] Administration of any systemic haemostatic agents (including platelets, cryoprecipitate, fibrinogen concentrate, activated recombinant factor VII, other coagulation factor products or a second dose of IMP) or any haemostatic interventions (including surgical re-opening for bleeding).

[2] The 60-minute period allows for the administration of the IMP and establishment of treatment effect.

Patients categorised as having an 'ineffective' haemostatic treatment response to IMP, due to requiring administration of any haemostatic intervention, including a second dose of IMP, in the time window from 60 minutes to 24 hours after initiation of the first IMP dose, will be considered as treatment failures.

7.2.2 Assessments for Secondary Efficacy Endpoints

7.2.2.1 Global Haemostatic Response

A secondary endpoint of global haemostatic response is included to provide supportive evidence of haemostatic effectiveness. This will be based on the haemostatic efficacy scale developed by Sarode and colleagues [69] (in discussion with the Food and Drug Administration), modified to reflect the special considerations of haemorrhage during cardiac surgery. Global haemostatic response will be considered as 'positive' if no additional haemostatic intervention (as per **Table 4**) is required *and* haemoglobin levels decrease by <30% (after accounting for red cell transfusions) in the time window from 60 minutes to 24 hours after initiation of the first IMP dose. Global haemostatic response will be considered as 'negative' if additional haemostatic intervention is required *or* haemoglobin levels decrease by ≥30% (after accounting for red cell transfusions) from 60 minutes to 24 hours after initiation of the first IMP dose.

Table 4: Objective Criteria for Determination of Global Haemostatic Response, Adapted from Sarode et al. 2013

Global Haemostatic Response	Haemostatic Intervention		Drop in Haemoglobin
Excellent (positive)	No additional coagulation interventions[1] administered between 1 and 24 hours after initiation of infusion[2]	AND	<15% decrease in haemoglobin between 1 and 24 hours after initiation of infusion[2,3]
Good (positive)	No additional coagulation interventions[1] administered between 1 and 24 hours after initiation of infusion[2]	AND	15% to <30% decrease in haemoglobin between 1 and 24 hours after initiation of infusion[2,3]
Poor (negative)	Additional coagulation interventions[1] administered between 1 and 24 hours after initiation of infusion[2]	OR	≥30% decrease in haemoglobin between 1 and 24 hours after initiation of infusion[2,3]

[1] Administration of any systemic haemostatic agents (including platelets, cryoprecipitate, fibrinogen concentrate, activated recombinant factor VII, other coagulation factor products or a second dose of IMP) or any haemostatic interventions (including surgical re-opening for bleeding).

[2] The 60-minute period allows for the administration of the IMP and establishment of treatment effect.

[3] Each unit of RBC transfused during this time period will be counted as a drop of 1.0 g/dL in haemoglobin.

7.2.2.2 Surgical and Surgery-Related Data

The following surgical data will be collected: details of procedure, CPB duration, CPB start and end times, cross-clamp duration, circulatory arrest duration, fluid intake and output, any medications administered, haemodynamic support (e.g., IABP), as well as any blood conservation methods used (e.g., haemoconcentration, retrograde prime, cell salvage), length of stay in the OR and need for surgical re-exploration.

In addition, extubation time, ICU length of stay and hospital length of stay will be documented. Data collected will be used for a pharmacoeconomic analysis to be conducted at a later date.

7.2.2.3 Transfusion Data

Details of all blood products and haemostatic agents released from the blood bank/pharmacy and transfused will be collected from the blood bank/pharmacy databases. These include allogeneic blood components (RBCs, pooled or apheresis platelets and plasma) and albumin. Other haemostatic agents include: desmopressin, fibrinogen concentrates, cryoprecipitate, rFVIIa, antithrombin, idarucizumab and andexanet alpha. Data collected will be used for a pharmacoeconomic analysis to be conducted at a later date.

7.2.2.4 Bleeding Data

Severity of bleeding before IMP administration according to the Bleeding Severity Scale by Lewis et al [78] will be collected during surgery.

The comparison of 'major' bleeding based on the universal definition of perioperative bleeding (UDPB) in cardiac surgery [89, 93] (**Table 5**Error! Reference source not found.) will be assessed. The UDPB is a multistage definition for perioperative bleeding based on easily measured clinical endpoints, including total blood loss from chest tubes at 12 hours and 24 hours after chest closure, allogeneic blood components transfused, surgical re-exploration including cardiac tamponade, delayed sternal closure and the need for salvage treatment. Modifications to the UDPB will include addition of fibrinogen concentrate to cryoprecipitate and exclusion of the category of delayed sternal closure.

Depending on these components, bleeding is graded as insignificant, mild, moderate, severe or massive (**Table 5Error! Reference source not found.**) [89].

Intracerebral and gastrointestinal haemorrhages will be documented.

Table 5: Bleeding categories according to the UDPB in adult cardiac surgery (if different categories indicate mixed definitions of bleeding, the worst definition applies) [89]

Bleeding definition	Postoperative chest tube blood loss within 12 h (mL)	RBC (units)	FP (units)	PLT (units)	Fibrinogen concentrate or Cryoprecipitate	PCC	rFVIIa	Re-exploration/ tamponade
Class 0 (insignificant)	<600	0	0	0	No	No	No	No
Class 1 (mild)	601–800	1	0	0	No	No	No	No
Class 2 (moderate)	801–1000	2–4	2–4	Yes	Yes	Yes	No	No
Class 3 (severe)	1001–2000	5–10	5–10	N/A	N/A	N/A	No	Yes
Class 4 (massive)	>2000	>10	>10	N/A	N/A	N/A	Yes	N/A

FP, frozen plasma; N/A, not applicable; PCC, prothrombin complex concentrate; PLT, platelets; rFVIIa, activated recombinant factor VII; UDPB, universal definition of perioperative bleeding.

To remove any potential bias from PCC and/or FP dosing, as their use is dictated by the randomisation schedule, a modified version of the UDPB will also be applied, with the following components of the score omitted: administration of PCC and transfusion of FP.

7.3 Safety Assessments

7.3.1 Assessments for Safety Endpoints

Any of the following drug safety information shall be collected:

- AEs and SAEs temporally associated with the administration of IMP (for definitions and reporting requirements, see **Sections 7.3.2, 7.3.3** and **7.3.4**.
- Pregnancies, drug overdose, interaction, medication error, lack of efficacy and post-study SAEs (see **Section 7.3.6**).

7.3.2 Adverse Events (AEs)

7.3.2.1 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 unfavourable 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. An AE is defined as a treatment-emergent AE (TEAE) if first onset or worsening is after the first treatment with study drug.
- **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.

7.3.2.2 Collection of AEs

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?". In addition, the Investigator/blinded outcome assessor will check the patient records for any documented event.

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 a single 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 the causality as defined below. The Sponsor is responsible for assessing the expectedness of each ADR (expected or unexpected) as defined below.

In the event of clinically significant abnormal laboratory findings, the tests will be confirmed and the patient followed up until the laboratory values have returned to normal and/or an adequate explanation for the abnormality has become available.

Diseases, signs and symptoms and/or laboratory abnormalities already present before the first administration of IMP will not be considered AEs unless an exacerbation in intensity or frequency (worsening) occurs.

The Investigator will provide detailed information about any abnormalities and about the nature of and reasons for any action taken, as well as any other observations or comments that may be useful for the interpretation and understanding of an AE or ADR.

7.3.2.3 Severity of AEs

The intensity/severity of 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

The grading of an AE is up to the medical judgement of the Investigator and will be decided on a case-by-case basis.

7.3.2.4 Causality of AEs

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 aetiology 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).

7.3.2.5 Classification of ADRs by Expectedness

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 (IB) or other reference safety information.
- **Unexpected:** an ADR that is not listed in the current edition of the IB or other reference safety information, or that differs because of greater severity or greater specificity.

7.3.2.6 Outcome of AEs

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 which resulted in the patient's death must be fully documented and reported, even in cases where the

death occurs within 4 weeks after IMP treatment end and regardless of whether or not it is considered treatment related.

7.3.2.7 Action(s) taken

AEs requiring action or therapy must be treated with recognised 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) General actions taken in the event of an AE

- None
- Medication (other than IMP) or other (e.g., physical) therapy started
- Test performed
- Other (to be specified)

b) IMP-related actions taken in the event of an AE

- None
- Product withdrawn
- Dose reduced
- Dose increased

The Investigator will follow up on each AE until it has resolved or until the medical condition of the patient has stabilised. Any relevant follow-up information will be reported to the Sponsor.

7.3.3 Serious Adverse Events (SAEs)

Standard statement:

A **serious AE (SAE)** is any untoward medical occurrence that at any dose:

- results in death,
- is life-threatening (see below),
- requires hospitalisation or prolongation of existing hospitalisation,
- 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 may hypothetically have caused death had it been more severe.

In deciding whether an AE/ADR is serious, medical judgment should be exercised. Thus, important AEs/ADRs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise 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 SAEs. 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.

7.3.4 SAE Reporting Timelines

All SAEs, whether or not they are suspected to be related to study treatment, are to be reported within 24 hours of recognition of the event by email to Ozmosis and to Octapharma Clinical by submitting the Serious Adverse Event Reporting Form:

[redacted]

The contact details will also be communicated at the study initiation visit.

Ozmosis Research will inform Octapharma's Safety Medical Expert and Octapharma's Central Drug Safety Unit (treatment emergent SAEs only) within 24 hours of receiving the event:

Octapharma Safety Medical Expert:

Email: [redacted]

Octapharma's Central Drug Safety Unit:

OCTAPHARMA Pharmazeutika Produktionsges.m.b.H.
Oberlaaer Straße 235, 1100 Vienna, Austria
Fax: [redacted]
Email: [redacted]
24 hours emergency telephone number: [redacted]
24 hours emergency telephone number: [redacted]

Waivers from SAE Reporting Requirement

Waivers from the SAE reporting requirement are surgical procedures that are elective or were planned before study entry, and prolongation of the existing hospitalisation that is performed for economic or social reasons and not for medical reasons. Such events should not be considered as SAEs.

7.3.5 Occurrence of TEEs

All TEEs (thrombotic, embolic, or thromboembolic events) must be recorded in the source data and reported as SAEs within 24 hours. If TEEs are suspected, appropriate examinations according to local standards (e.g. Doppler scan using color duplex, X-ray, CT scan) should be obtained and documented. Therapeutic measures for managing TEEs shall be initiated according to local clinical practice (e.g., anticoagulation).

As a component of the assessment of AEs, the Investigator will also be questioned regarding the occurrence of TEEs. These are defined according to the Standardized Medical Dictionary for Regulatory Activities (MedDRA) query “Embolic and thrombotic events”.

7.3.6 Laboratory Tests

The following laboratory parameters will be investigated during the study at the time points specified in **Section 6**.

7.3.6.1 Central Laboratory

No laboratory tests will be done at a central laboratory:

7.3.6.2 Local Laboratory

Table 6 summarises all test parameters performed as part of standard of care, the results of which will be collected as available.

Table 6 Test Parameters and Laboratories

Test	Material needed	Responsible Laboratory
Coagulation profile		
Point-of-care INR	Fresh blood	Local
(PT, aPTT, INR, fibrinogen activity via Clauss assay)	Citrated blood	Local
*ROTEM EXTEM CT	Citrated blood	Local
*ROTEM EXTEM MCF	Citrated blood	Local
*ROTEM FIBTEM MCF	Citrated blood	Local
PlateletWorks	Fresh blood	Local
Haematology – standard panel as per local lab	Citrated blood	Local
Clinical chemistry – standard panel as per local lab	Serum	Local
Safety laboratory analyses		
Troponin	Serum	Local
ALT/ALP	Serum	Local
Bilirubin	Serum	Local
Creatinine	Serum	Local

ALT, alanine aminotransferase; ALP, alkaline phosphatase; CT, clotting time; MCF, maximum clot firmness; PT, prothrombin time; aPTT, activated partial thromboplastin time; ROTEM, thromboelastometry

*ROTEM or TEG can be measured

The haemoglobin and INR measurements will be performed at preestablished time points (**Table 7**).

Table 7 Mandatory Test Parameters and Laboratories

Test	Material needed	Responsible laboratory
Coagulation profile		
Point-of-care INR	Fresh blood	Local
	Citrated blood	Local
Haematology		
Haemoglobin	Citrated blood	Local

Blood Sampling

All blood sampling will be performed as per standard practice at the local institution.

The *actual* time of blood sampling will be recorded. If the draw time is not recorded for samples processed in the laboratory, the draw time will be estimated based on the received time in the laboratory minus 10 minutes. For ROTEM and PlateletWorks, if the exact draw time is not recorded, the time for start of testing will be used for draw time.

Citrated and Fresh Blood

Citrated and fresh blood as required by the local laboratory will be collected and processed in accordance with local requirements.

Serum

Serum will be obtained for the determination of clinical chemistry, haematology, and safety labs (ALT, ALP, creatinine, bilirubin, troponin), where a serum blood sample has been collected.

Recording of Clinically Significant Abnormal Laboratory Values as AEs/ADRs

Other than abnormal laboratory values due to the underlying condition, the Investigator must assess the clinical significance of abnormal laboratory values outside the specified normal range. Any clinically significant abnormalities will be documented. All specified clinically significant abnormalities will be documented as AEs/SAEs and investigated.

Additional tests and other evaluations required to establish the significance or aetiology of specified abnormalities or to monitor the course of an AE will be obtained if clinically indicated. Follow-up will persist until resolution or up to the Study Completion Visit, whichever occurs first.

7.3.7 Other Relevant Safety Information

a) Post-study related safety reports

Proactive monitoring for post-study SAEs is not required.

In case a post-study SAE is identified, the Investigator should complete an SAE form and also state the relation to the clinical study in the report.

b) Pregnancies

Patients who are known to be pregnant will not be included in the study. In patients of reproductive age, pregnancy is ruled out prior to the cardiac surgery as part of standard of care.

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.

c) 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 that is of clinical relevance. The reaction must be clearly identified as an overdose.

d) Drug interaction

A drug interaction is a situation in which a substance or medicinal product affects the activity of an IMP, i.e., increases or decreases its effects, or produces an effect that none of the products would exhibit on its own. The reaction must be clearly identified as a drug interaction.

e) Medication error

A 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 or instructions for use/labelling. The reaction must be clearly identified as a medication error.

7.4 Appropriateness of Measurements

Since the ultimate goal of the study is the measure the need for post-therapy haemostatic interventions following cardiac surgery in adults, the clinical assessment of haemostatic effectiveness provides the key clinical information on treatment efficacy. Haemostatic effectiveness will be based on the haemostatic efficacy scale developed by Sarode and colleagues [69] (in discussion with the Food and Drug Administration), modified to reflect the special considerations of haemorrhage during cardiac surgery. The secondary and exploratory endpoints will provide further information on the clinical efficacy and safety of *Octaplex* in this clinical setting.

8 DATA HANDLING AND RECORD KEEPING

8.1 Documentation of Data

8.1.1 Source Data and Records

Source data are defined as all information related to clinical findings, observations or other activities in the study, written down 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 as required by local regulations.

For each patient enrolled, the Investigator will indicate in the source record(s) that the patient participates in this study.

For data capture, a validated Electronic Data Capture (EDC) system providing an electronic CRF (eCRF) application will be used.

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

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

The Investigator may authorise site staff (e.g., sub-investigators, clinical research coordinators/assistants, nurses) to enter study data into the eCRF. This must be documented in the Delegation of Authority Log signed by the Investigator.

8.1.2 Case Report Forms

Authorised study site staff (e.g., blood bank/pharmacy technologist, research coordinator/assistant) will be responsible for completing an eCRF record for each patient enrolled. All site personnel will be trained on completion of a patient's eCRF. The site is also provided with the approved eCRF Completion Guidelines which will assist in data entry and data issues/questions. Additional site training may be provided as refreshers throughout the study, if needed. All persons allowed to enter or to change eCRF data must be listed in the Delegation of Authority Log.

For each patient enrolled, an eCRF record will be completed within the EDC system and finally approved by the Investigator or an authorised sub-investigator.

Prior to operational use, the eCRF application will be validated. All site personnel will be trained on the EDC system and study specific eCRFs prior to receiving access to the live system for data entry.

8.1.3 Changes to Case Report Form (CRF) Data

Monitors will perform source data verification (SDV) as defined for the study and described in the study Monitoring Plan.

If any errors or discrepancies in the eCRFs are found during data entry or review, discrepancies will be generated programmatically within the EDC system, and 'manual' queries will be generated by either a monitor or Data Management.

Discrepancies and queries can only be corrected by the Investigator(s) or other authorised site personnel. An audit trail documents all changes to the data over the entire study period. If the reason for a change is not obvious, a comment must be supplied in the query's response, stating the reason for the change, prior to closing. The study monitor should provide guidance to Investigator(s) and the Investigator(s)' designated representatives on making such corrections.

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 to Investigators

An Investigator's Brochure (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 *Octaplex* under evaluation and the respective benefit-risk ratio.

An updated IB will be provided by the Sponsor at regular intervals and if important new safety-relevant information concerning *Octaplex* becomes available.

The Investigators will be informed about the methods for rating relevant study outcomes and for completing CRFs.

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

For FP, which is the standard-of-care blood product, the corresponding label per local regulations will apply.

8.3 Responsibilities

Coordinating Investigator

[redacted]
Department of Anaesthesia and Pain Management
Toronto General Hospital
200 Elizabeth Street, 3EN-460
Toronto, ON, M5G 2C4
Canada

Phone: [redacted]
Fax: [redacted]
Email: [redacted]

Central laboratory

Not applicable.

Data management

ERGOMED CDS GmbH
Im Mediapark 2
D-50670 Cologne, Germany

Study statistician

[redacted]
ERGOMED plc
8045 Arco Corporate Drive, Suite 310
Raleigh, NC 27617
United States

[redacted]

Contract research organisation (CRO)

OZMOSIS RESEARCH INC.
700 University Ave, Suite 217-2N
Toronto, ON, M5G 1Z5, Canada

Monitoring

For US:

Octapharma USA Inc.
117 West Century Road
Paramus, New Jersey 07652, United States

For Canada:

OZMOSIS RESEARCH INC.
700 University Ave, Suite 217-2N
Toronto, ON, M5G 1Z5, Canada

Investigators

At each study site the 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 authorised 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. 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

If errors in data transcription are encountered, a query should be raised which needs to be answered by appropriately delegated site staff. Provision of additional patient data should be avoided (except if needed for SAE reporting). 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 and Safety Monitoring Committee

An IDSMC will be established by the Sponsor. The IDSMC will be composed of recognised experts in the field of statistics, perioperative medicine and haematology who are not actively recruiting patients.

The IDSMC will review accumulating safety, endpoint and other study data (recruitment, retention and compliance, data quality and timeliness, risk versus benefit, summary statistics of outcomes) every time 100 patients have completed the study.

The IDSMC will provide recommendations about continuing, modifying and/or stopping the study based on considerations of treatment efficacy, patient safety and trial futility as appropriate. In addition, the IDSMC may make observations or recommendations to the sponsor about, but not limited to, the following:

- Efficacy of the study intervention;
- Definitions of and responses to AEs and patterns in AEs;
- Benefit/risk ratio of procedures and participant burden;
- Selection, recruitment and retention of participants;
- Adherence to protocol requirements;
- Completeness, quality and analysis of measurements;
- Amendments to the study protocol and consent forms;
- Performance of individual centres and core labs; and
- Patient safety.

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

9 STATISTICAL METHODS AND SAMPLE SIZE

The statistical analysis will be delegated under an agreement of transfer of responsibilities to an external statistician. Details on planned descriptive and exploratory analyses will be provided in a separate Statistical Analysis Plan (SAP).

9.1 Determination of Sample Size

The analysis of the primary efficacy endpoint will involve comparison of haemostatic treatment response to IMP, defined as 'effective' if no additional haemostatic intervention, such as administration of any systemic haemostatic agents (including platelets, cryoprecipitate, fibrinogen concentrate, activated recombinant factor VII, other coagulation factor products or a second dose of IMP) or any haemostatic interventions (including surgical re-opening for bleeding) is required from 60 minutes to 24 hours after initiation of the first dose of IMP.

Patients categorised as having an 'ineffective' haemostatic treatment response to IMP, due to requiring administration of any haemostatic intervention, including a second dose of IMP, in the time window from 60 minutes to 24 hours after initiation of the first IMP dose, will be considered as treatment failures.

Of the more than 100 patients studied in the FARES pilot study, approximately 75% of patients in the PCC group and 65% in the FP group demonstrated haemostatic treatment response from 60 minutes to 24 hours after initiation of the first IMP dose [58]. Using a more conservative estimate of 70% versus 65%, it is estimated that 410 patients will be required to demonstrate non-inferiority with a one-sided α of 0.025, power of ≥90% and non-inferiority margin of 0.10 when using a Farrington-Manning score test.

It is anticipated that up to 20% of randomised patients may not meet administration criteria (based on objective Bleeding Severity Scale and INR) due to cessation of haemorrhage between randomisation and delivery of IMP to the operating room and therefore will not receive the therapy.

An administrative unblinded interim analysis will be carried out after 200 evaluable patients have been randomised and treated and will be used to re-estimate the sample size or stop for futility (non-binding) (**Section 9.4**). Patient recruitment will continue during the conduct of the interim analysis. The sample size in the second stage is limited to 210–800 evaluable patients. Accounting for drop-outs as described above, the total sample size will range between 513–1250 if the study is not stopped for futility at the interim (see table below).

	Stage 1	**Stage 2 – Minimum**	**Stage 2 – Maximum**	**Total - Maximum**
Evaluable patients	200	210	800	1000
Sample size including 20% dropouts	250	263	1000	1250

9.2 Statistical Analysis

A formal SAP describing all details of the analyses to be performed will be prepared by the study statistician and approved by the Sponsor prior to study initiation.

The non-inferiority of the primary endpoint 'haemostatic response' will be tested between the treatment groups by means of a Farrington-Manning score test with a non-inferiority margin of 0.10 at a one-sided significance level alpha of 2.5%, testing the null hypothesis as follows:

H_0: $p(PCC) \leq p(FP) - 0.10$

will be tested against the alternative

H_1: $p(PCC) > p(FP) - 0.10$

where p(PCC) and p(FP) denote the haemostatic response proportions in the PCC and FP treatment groups, respectively.

At the end of the trial, the inverse normal test statistic with equal weights given by

$$(\Phi^{-1}(1 - p_1) + \Phi^{-1}(1 - p_2))/\sqrt{2}$$

is calculated, where p_1 and p_2 denote the p-values for testing the non-inferiority null hypothesis for the first and the second stage of the trial, respectively. If the test statistic exceeds the value 1.96, non-inferiority is demonstrated (see [94]).

Only in case that non-inferiority is demonstrated at the second stage of the study, i.e., the null hypothesis is rejected at the one-sided 2.5% level of significance, superiority of PCC with regard to the primary endpoint will be investigated:

H_0: $p(PCC) \leq p(FP)$

will be tested against the alternative

H_1: $p(PCC) > p(FP)$

The Farrington-Manning score test will be used to calculate a two-sided 95% confidence interval based on the inverse normal test statistic as given above. This confidence interval corresponds with the test decision for showing non-inferiority and/or superiority [95]. This hierarchical test procedure allows to perform the superiority test at the full alpha of 2.5%.

9.2.1 Populations for Analysis

The full analysis set (FAS) will consist of all consented and randomised patients who receive any amount of the intervention, which will serve as the primary analysis set. A supporting efficacy analysis will be performed for the per-protocol set (PPS), which will exclude all patients with major deviations (e.g., patients who receive an IMP different to the IMP assigned by randomisation; patients who receive <50% of the planned dose; and patients who significantly violate inclusion/exclusion criteria). Randomised but untreated patients will not be included in the efficacy or safety analyses, but will be followed for 30 days to determine between-group comparability in baseline characteristics and outcomes.

A final decision about the classification of protocol deviations and their consequences regarding assignment of patients to analysis populations will be made during the data review meeting prior to the final analyses. All protocol deviations documented during the conduct of the study or identified at the data review process prior to database lock will be reviewed and classified as minor or major and with respect to their significance for the

planned analyses. This classification of protocol deviations is the joint responsibility of the clinical project manager, the study statistician, and Octapharma's responsible medical expert, and will be agreed and documented before the database is locked and the statistical analyses are performed.

The safety analysis population (SAF) will be identical to the FAS. In addition, to ensure that the safety reporting is complete, all haemostatic therapy and SAE data will be collected in cases where consent for remaining in the study cannot be obtained from Canadian sites due to logistical issues (e.g., patient died and a legally authorised representative could not be reached) and REB approval is obtained to collect the information. For Canadian patients who refuse consent, only treatment allocation data will be collected, and patients will not be included in any analyses.

The following subgroups will be analysed: sex (male/female); urgency (elective/non-elective surgery); and complexity (simple/complex surgery [procedures other than isolated ACB, single valve or repair of atrial septal defect]). Moreover, the impact of CPB duration on effectiveness will be evaluated by assessing treatment effect based on CPB duration increments.

Details on the subgroup analyses will be given in a Statistical Analysis Plan.

9.2.2 Efficacy Analysis Plan

Descriptive statistics or frequency tables will be presented for all efficacy data in addition to the inferences performed. Simple tests of comparison will be used to compare endpoints between the two groups. The summary tables and exploratory inferences will be chosen according to the scaling level of the measurements. Frequency tables will be provided for categorical responses and summary statistics for continuous data. The SAP will detail all analyses, including exploratory analyses (e.g., *p*-values and confidence intervals) to be undertaken.

9.2.3 Safety Analysis Plan

Secondary safety endpoints will be analysed analogously to the primary endpoint, presenting point estimates and two-sided 95% CIs in addition to descriptive statistics. Prior to study initiation, the SAP will detail all analyses to be undertaken.

9.2.3.1 Adverse events, including thromboembolic and other events of special interest

AEs will be coded according to the latest Medical Dictionary for Regulatory Activities (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 unlikely, probably or possibly related to the IMP) and serious TEAEs will be summarised and tabulated according to primary system organ class and preferred term. TEAEs leading to death and TEAEs resulting in withdrawal from the study will be tabulated using frequency tables if a reasonable number of events of this type are observed.

Analogous frequency tables for TEEs (identified using MedDRA SMQs) and composite events will be provided separately.

Patient listings will be provided for patients with SAEs, TEEs, AEs leading to withdrawal from the study and AEs leading to death. Listings for non-treatment-emergent AEs, e.g., for patients enrolled but not randomised will be provided separately.

9.2.3.2 Mortality

The number of patients who died will be summarised. A possible difference between treatment groups will be estimated by a risk ratio with 95% CI. Kaplan-Meier estimates for the time to death distribution will be calculated and graphically presented if a sufficient number of cases have been registered.

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 scheduled time point and changes from baseline to each scheduled time point. Mean concentration versus time profiles will be plotted for quantitative data
- 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 scheduled time point. Scatterplots between scheduled time points of lab values with normal ranges will be used for visual illustration.
- Number and frequency of patients with clinically significant laboratory values. A separate patient listing will be provided

9.2.4 Handling of Missing Data

In general, missing data will not be imputed. Due to the nature of the study, important variables are expected to have few missing data. In addition to presentation of the primary and secondary endpoints for different analysis sets, further multiple imputation methods may be used to impute missing values. Technical details will be described in the Statistical Analysis Plan.

9.3 Randomisation, Stratification and Code Release

Eligible patients will be randomly assigned to receive either *Octaplex* or FP. Randomisation lists using a permuted-block, randomisation scheme (stratified by site) will be prepared by the biostatistician. Sealed randomisation envelopes based on the randomisation lists will then be provided to the blood banks/pharmacies of the participating centres who will be responsible for providing the IMP.

Patients will be identified using a sequential numbering system within the centre. Randomisation will then be performed in sequential order of the patient IDs.

9.4 Interim Analysis

An administrative unblinded interim analysis will be carried out by an independent statistician when approximately 200 patients have been randomised and treated. Unblinded information will be communicated only to the IDSMC. Possible outcomes of this analysis and recommendations to the sponsor are:

- The study will be stopped for futility. The decision to stop for futility is non-binding.
- The sample size will be re-estimated by the independent statistician.

Patient recruitment will continue during the conduct of the interim analysis. The study cannot be stopped for efficacy at the interim analysis.

The sample size re-estimation will be based on the evaluation of the conditional power, calculated as described in section 7.3 of [94] making use of the observed response rates at the time of the interim analysis and inverse normal combination test statistic with equal weights given by

$$(\Phi^{-1}(1 - p_1) + \Phi^{-1}(1 - p_2))/\sqrt{2},$$

where p_1 and p_2 denote the p-values for testing the non-inferiority null hypothesis for the first and the second stage of the trial, respectively. The aspired conditional power used for the new intended sample size will be 90%.

A 20% drop-out rate will be added to the re-estimated sample size of evaluable patients to receive the number of patients to be enrolled in the second stage.

The minimum number of patients for the second stage is 210 evaluable subjects (even if the re-estimated sample size is below this number) or 263 including the possible dropouts (+20%). The sample size for the second stage cannot exceed 1250 patients (dropouts included). If the drop-out adjusted re-estimated sample size exceeds this threshold, the IDSMC may recommend to either stop the trial for futility or to enrol the maximum number of 1250 patients.

In addition, the IDSMC will review selected unblinded summary statistics every time 100 patients have completed the study (**Section 8.6**).

10 ETHICAL/REGULATORY, LEGAL AND ADMINISTRATIVE ASPECTS

10.1 Ethical/Regulatory Framework

This study will be conducted under 21 CFR Part 312, the FDA's investigational new drug application (IND) requirements and the FDA's human subject protection requirements at 21 CFR Parts 50 and 56. In addition, we are seeking a waiver to allow informed consent to be obtained after randomisation at the Canadian sites, in accordance with Article 3.7A of the 2018 Tri-Council Policy Statement on the Ethical Conduct for Research Involving Humans. The study will also 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 the applicable IRBs and relevant regulatory authorities. The study will be conducted in compliance with the protocol, GCP guidelines and applicable regulatory requirements.

The regulatory application or submission for regulatory approval will be made by the Sponsor or designated third party (e.g., CRO).

10.2 Approval of Study Documents

The study protocol, informed consent form, and any other materials provided to the patients and further requested information will be submitted by the Sponsor or the Site Investigator to the appropriate IRB. The study must be approved by the IRB before the patient is exposed to a study-related procedure.

The Sponsor, the Site Investigator and any third party (e.g., CRO) 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 Subject/Patient Information and Informed Consent

This is a pragmatic trial that compares two coagulation factor replacement therapies that are currently routinely used for the study indication in multiple regions globally and in various settings.

The Investigator will obtain freely given written consent from each patient after an appropriate explanation of the aims, methods, anticipated benefits, potential hazards, and any other aspect of the study which is relevant to the patient's decision to participate. The informed consent form must be signed, with name and date and time noted by the patient before they are exposed to any study-related procedure, including screening tests for eligibility.[4] Should consent be later withdrawn by the patient, no additional data will be collected.

The study coordinator or assistant will explain that the patients are completely free to refuse to enter or withdraw from the study at any time, without any consequences to their future care and without the need to justify. Each patient will be informed that his/her medical (source) records may be reviewed by the study monitor, a quality assurance auditor or a health authority inspector, in accordance with applicable regulations, and that

[4] In Canada, informed consent will be obtained after randomisation, in accordance with Article 3.7A of the 2018 Tri-Council Policy Statement on the Ethical Conduct for Research Involving Humans.

these persons are bound by confidentiality obligations. In addition to the study protocol, study hospitals will also follow their institutional guidelines and approvals when consenting and collecting data. Their process will be documented in their SOPs.

10.3.1 Evidence for the prospect of direct benefit to patients because of participation in the study

Cardiac surgery can be complicated by coagulopathic bleeding that often leads to excessive blood loss, blood product transfusion and bleeding-related complications [1-4]. Bleeding and transfusions are associated with increased morbidity, mortality and risk of adverse outcomes (e.g., infection, heart failure) [2, 5-17].

The current standard of care for this complication in North America is FP, which is administered in around 15% of all cardiac surgeries in the United States [29]. However, FP can cause SAEs including allergic reactions [30]; TRALI, which is a leading cause of transfusion-related death [30, 40]; and TACO, which occurs in approximately 5% of transfusions [41]. FP transfusion can also lead to transmission of infectious diseases, as FP is not usually filtered or treated with solvent/detergent [42]. FP use also requires ABO blood group compatibility matching and thawing, which can delay therapy. The large volumes of FP needed to achieve therapeutic effect can further delay time to haemostatic control and lead to substantial haemodilution, resulting in additional RBC transfusions [47].

PCCs, such as *Octaplex*, have several potential advantages over FP. PCCs are associated with a substantially lower risk of TRALI (due to pooling of the source donor plasma), and also a lower risk of TACO [38] as substantially lower volumes of PCC are required than with FP to achieve dose-equivalence for increasing thrombin generation [47]. The production of PCCs includes numerous pathogen-inactivation steps using solvents, detergents, pasteurisation, nanofiltration and vapor-heated treatment [1, 48], which is beneficial to patients because of the reduction in the risk of transmission of infectious agents. Unlike FP, PCCs do not require ABO compatibility matching or thawing, and can therefore be prepared and administered more quickly.

The potential benefits of *Octaplex*, compared with FP, were investigated in FARES, a multicentre, randomised, active-control, pragmatic, Phase 2 pilot study [58]. Efficacy data obtained from the FARES study showed significantly lower chest tube drainage in the PCC group ($P<0.001$); a numerically higher percentage of treatment response in the PCC group; and a significantly lower number of transfused units of ABP in the PCC group versus the FP group ($P<0.001$) [58]. The significantly lower blood loss and, consequently, reduced exposure to ABP transfusions and their associated risks demonstrates how PCC use can directly benefit patients in this context, as both bleeding and transfusions during cardiac surgery have been associated with increased morbidity and mortality [2, 11, 14, 15, 17]. LEX-211 will expand the supporting scientific evidence for use of PCCs to treat bleeding in cardiac surgical patients requiring coagulation factor replacement.

10.4 Protocol Amendments

Any amendments will be submitted to the institutional IRB and any authority as required by applicable regulations.

IRB approval will, at a minimum, be requested for any change to this protocol which could affect the safety of the patients, the objective or 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 Subject/Patient 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 identifier. Documents not intended 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 co-operate 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. All enrolled patients will be monitored, with 100% source data verification for the data relevant for the primary and safety endpoints.

The monitor must be given direct access to source documents (original documents, data and records). Direct access includes permission to examine, analyse, 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.

Monitoring will take place as per the study Monitoring Plan.

11.2 Audit and Inspection

The Investigator will make all study-related source data and records available to a qualified quality assurance auditor, IRB or 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 efficacy of the IMP have been captured.

12 REPORTING AND PUBLICATION

12.1 Clinical Study Report

A clinical study report (in accordance with relevant guidelines) will be prepared by the Sponsor after completion of the study.

12.2 Publication Policy

The results of this study will be published and may be presented at scientific meetings.

In accordance with standard editorial and ethical practice, the Sponsor will publish the multicentre data only in their entirety and not as individual centre data. Authorship will be determined by mutual agreement. Any subsequent publications based on subsets of the data will require approval from the Sponsor.

13 LIABILITIES AND INSURANCE

In order to cover any potential damage or injury occurring to a patient in association with the IMP or participation in the study, the Investigators and/or their institutions 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

15.1 Appendix 1: Bleeding Score

Grade	*Visual presentation*	*Anatomic appearance*	*Qualitative description*	*Visually estimated rate of blood loss (mL/min)*
0	No bleeding	No bleeding	No bleeding	≤1.0
1	Ooze or intermittent flow	Capillary-like bleeding	Mild	>1.0–5.0
2	Continuous flow	Venule and arteriolar-like bleeding	Moderate	>5.0–10.0
3	Controllable spurting and/or overwhelming flow	Noncentral venous- and arterial-like bleeding	Severe	>10.0–50.0
4	Unidentified or inaccessible spurting or gush	Central arterial- or venous-like bleeding	Life threatening*	>50.0