Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

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eMethods

The following clinical events were assessed through review of the patient medical records/chart, and reported in the eCRF from the start of the index cardiac surgery until hospital discharge or postoperative day 28, whichever came first.

Major bleeding

Bleeding categories according to the modified Universal Definition of Perioperative Bleeding (UDPB) in adult cardiac surgery (if different categories indicate mixed definitions of bleeding, the worst definition applies):

Bleeding definition class	Postop chest tube blood loss in first 12 hours (mL)	RBC (units)	Plasma (units)	PLT (units)	PCC	rFVIIa	Re-exploration /tamponade
0 – insignificant	<600	0	0	0	No	No	No
1 – mild	601–800	1	0	0	No	No	No
2 – moderate	801–1000	2–4	2–4	Yes	Yes	No	No
3 – severe	1001–2000	5–10	5–10	NA	NA	No	Yes
4 – massive	>2000	>10	>10	NA	NA	Yes	NA

For this study the following components of the UDPB score were not used: delay in chest closure and use of cryoprecipitate or fibrinogen concentrate. NA = not applicable; PCC = prothrombin complex concentrate; PLT = platelets; rFVIIa = recombinant activated factor VII; UDPB = Universal Definition of Perioperative Bleeding.

Adverse event (AE)

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

Adverse drug reaction (ADR)

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

Other significant AEs

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

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

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

Serious AE (SAE)
Any untoward medical occurrence that at any dose:

- results in death,
- is life-threatening,
- requires hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity,
- is another important medical event.

New York Heart Association classification

Class	Patient symptoms
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea (shortness of breath).
II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea (shortness of breath).
III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea.
IV	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.

Canadian Cardiovascular Society Class IV angina
Inability to carry on any physical activity without discomfort; anginal syndrome may be present at rest.

Complex surgery
Procedures other than isolated aortocoronary bypass (ACB), isolated single valve repair/replacement, or isolated repair of atrial septal defect (ASD).

Critical preoperative state
Determined by blinded adjudication on patients who underwent emergency surgery and had any of the following conditions: (1) ventricular tachycardia or fibrillation or cardiac arrest; (2) preoperative cardiac massage; (3) preoperative ventilation before anesthetic room; (4) hemodynamic support requiring preoperative inotropes or ventricular assist devices; (5) preoperative acute renal failure (anuria or oliguria <10mL/hour); (6) acute aortic dissection.

Myocardial infarction
Diagnosis supported by elevated troponin and ischemic ECG changes or positive imaging studies (angiographic evidence of new thrombosis or occlusion of graft or native coronary; new wall motion abnormalities by echocardiography)). The diagnosis of myocardial infarction requires any ONE of the following criterion: (1) a typical rise of troponin or a typical fall of an elevated troponin detected at its peak post-surgery in a patient without a documented alternative explanation for an elevated troponin (e.g., pulmonary embolism) OR a rapid rise and fall of creatine kinase-muscle/brain (CK-MB). This criterion also requires that 1 of the following must also exist: A. ischemic signs or symptoms (i.e., chest, arm, neck or jaw discomfort; shortness of breath; pulmonary edema); B. development of pathologic Q waves present in any two contiguous leads that are ≥ 30 milliseconds; C. ECG changes indicative of ischemia (i.e., ST segment elevation [≥ 2 mm in leads V 1 , V 2 , or V 3 OR ≥1 mm in the other leads], ST segment depression [≥ 1 mm], or symmetric inversion of T waves ≥1 mm) in at least two contiguous leads; D. coronary artery intervention (i.e., percutaneous coronary intervention [PCI] or coronary artery bypass graft [CABG] surgery); E. new or presumed new cardiac wall motion abnormality on echocardiography or new or presumed new fixed defect on radionuclide imaging; (2) Pathologic findings of an acute or healing myocardial infarction; (3) development of new pathological Q waves on an ECG if troponin levels were not obtained or were obtained at times that could have missed the clinical event (SAE).

Stroke
Cerebrovascular accident: includes a physician diagnosis of stroke or CT/MRI evidence of a prior stroke. Transient ischemic attack: a transient focal neurological deficit.

Acute kidney injury
Greater than a 2-fold rise in creatinine or new initiation of dialysis.

Thromboembolic events
Thromboembolic spinal cord ischemia resulting in leg weakness or paralysis (SAE). The diagnosis of peripheral arterial thrombosis required clear evidence of abrupt occlusion of a peripheral artery (i.e., not a stroke, myocardial infarction, or pulmonary embolism) consistent with either an acute local thrombotic event or a peripheral arterial embolism. To fulfill this definition we required at least one of the following objective findings of peripheral arterial thrombosis: (1) surgical report indicating evidence of arterial thrombosis/peripheral arterial embolism; (2) pathological specimen demonstrating arterial thrombosis/peripheral arterial embolism; (3) imaging evidence consistent with arterial thrombosis/peripheral arterial embolism; (4) autopsy reports documenting arterial thrombosis/peripheral arterial embolism.

FIBRES Inclusion/Exclusion Criteria

Inclusion criteria
Patients undergoing index cardiac surgery with cardiopulmonary bypass (CPB) in whom fibrinogen supplementation is ordered in accordance with accepted clinical standards (significant hemorrhage and known or presumed hypofibrinogenemia).

Exclusion criteria
Patients who meet any of the following criteria are *not* eligible for the study:
1. Receipt of fibrinogen-rich products (fibrinogen concentrate or cryoprecipitate) within 24 hours before surgery
2. History of severe allergic reaction to cryoprecipitate or fibrinogen concentrate
3. Refusal of ABPs, fibrinogen concentrate or cryoprecipitate due to religious or other reasons
4. Fibrinogen level known to be >3.0 g/L within 30 minutes of IMP order (to eliminate the risk of raising patients' fibrinogen levels to >4.0 g/L with supplementation)
5. Known pregnancy

FIBRES Outcome Definitions

Primary outcomes
The primary endpoint, which is of efficacy, is the comparison of the total number of units of allogeneic blood components (red blood cells [RBCs], pooled or apheresis platelets, and plasma) administered during the first 24 hours after termination of CPB.
Note: In Canada, the vast majority of platelets are supplied to hospitals as buffy-coat pools of 4 units resuspended in male plasma. The buffy-coat production method results in greater yield of platelets compared to standard random donor platelet production methods (usually supplied in other countries as pools of 5-6 units).

Secondary efficacy endpoints
Comparison of the total number of units of allogeneic blood components (RBCs, pooled or apheresis platelets, and plasma) administered from the beginning of surgery until 7 days after surgery or discharge, if earlier.

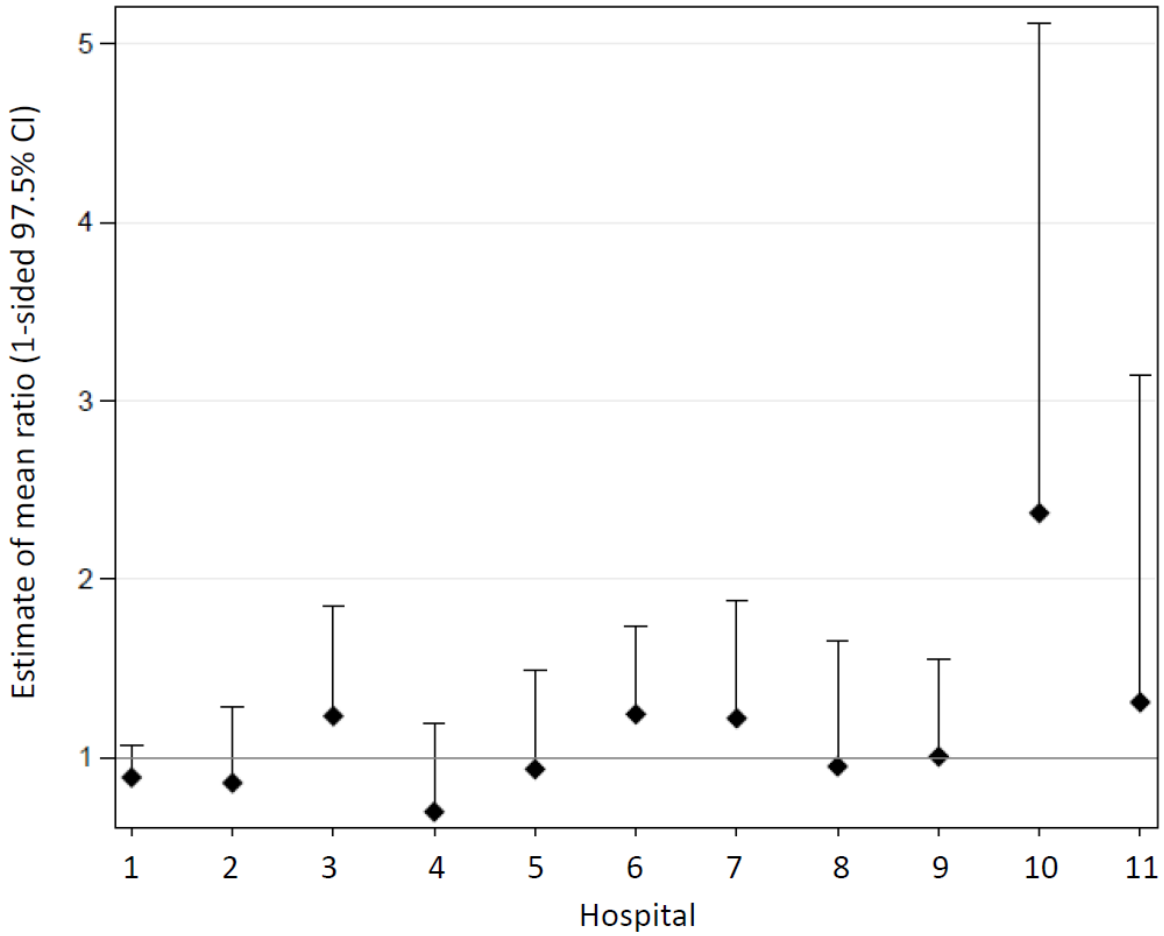
Comparison of major bleeding, using the validated UDPB in cardiac surgery during the first 24 hours after termination of CPB.

Comparison of the effect on fibrinogen levels measured by the change in plasma fibrinogen levels (as measured using the Clauss assay) before and after the first dose of fibrinogen supplementation (limit of 75 minutes before and after the start of the IMP infusion).

Adverse events and other secondary endpoints
Detailed list of AEs and SAEs, will be collected up to postoperative day 28 and compared numerically between the two groups.

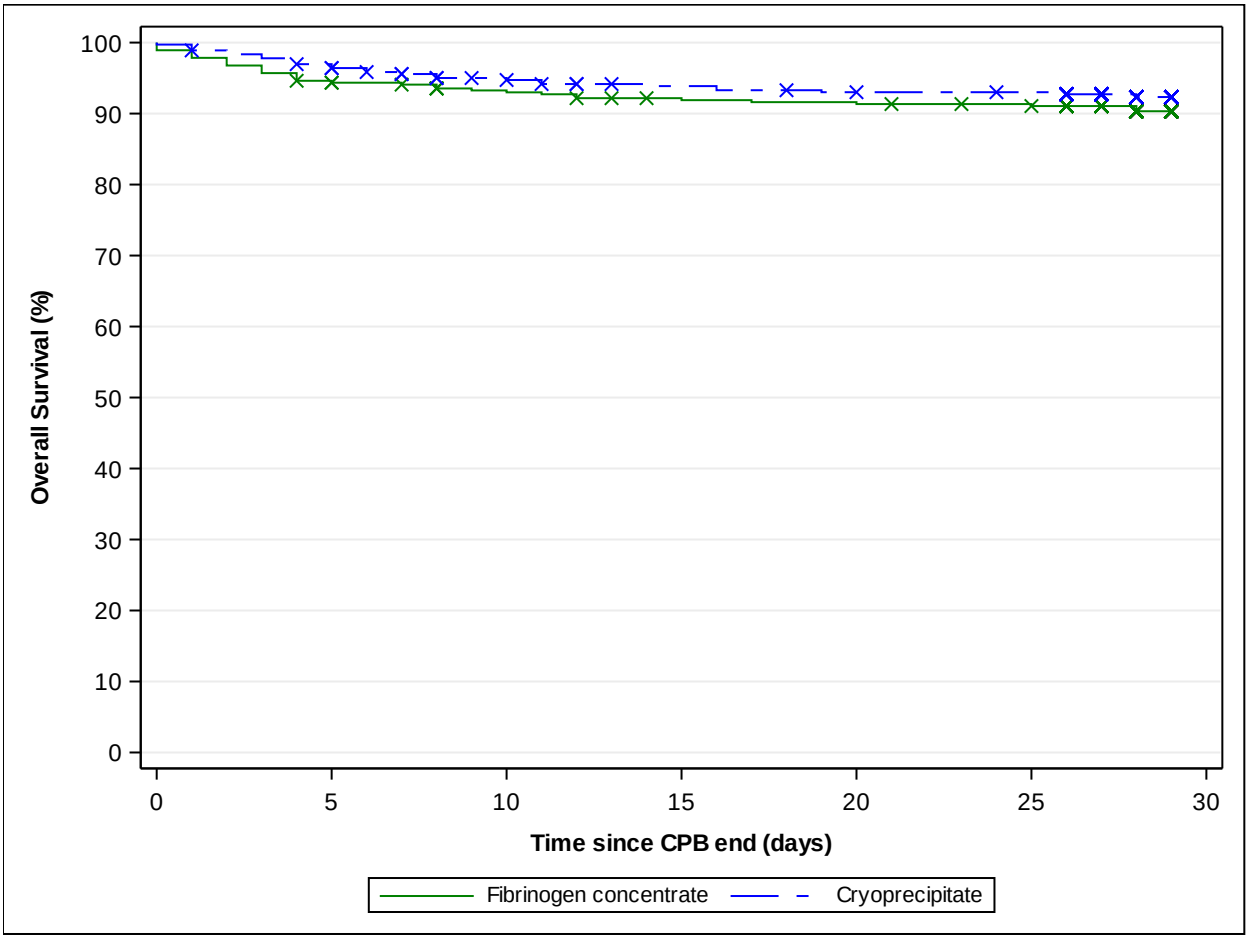
Other secondary endpoints that will also be compared between groups are:
- Duration of mechanical ventilation (measured as duration of ventilation and ventilator-free days up to postoperative day 28)
- Duration of intensive care unit (ICU) stay up to postoperative day 28
- Duration of hospitalization up to postoperative day 28

eFigure 1. Estimate of Site-Specific Mean Ratio (1-Sided 97.5% CI) of the Number of Allogeneic Blood Component Units Transfused within 24-hours Post Bypass in the Fibrinogen Concentrate to Cryoprecipitate Treatment Groups*



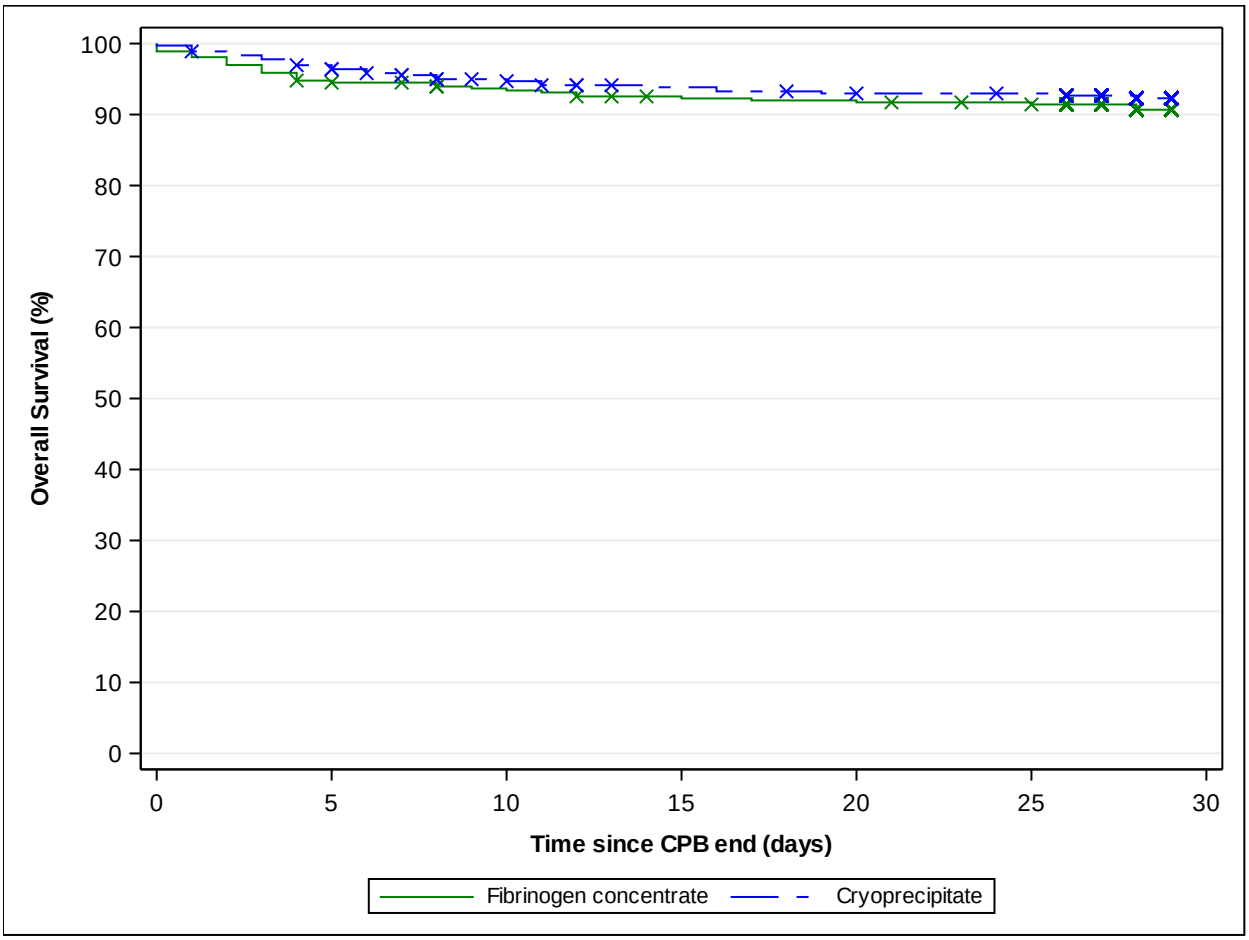
* This is a post-hoc analysis. Treatment by site interaction was significant (P<0.001) for the primary outcome when site was included in the model as a fixed-effect variable. The two sites that were relative outliers (hospitals 10 and 11) included 26 patients in total. When sites were included individually (11 categories), the non-inferiority criterion was met, with a 1-sided 97.5% CI of -∞ to 1.15. However, the model deviance was high. A second model was therefore constructed in which sites were pooled into three categories based on the number of patients enrolled (n <40; 41-99; >99). Deviance was diminished in this model and the non-inferiority criterion was also met, with a 1-sided 97.5% CI of -∞ to 1.13.

eFigure 2. Kaplan–Meier Curve for Overall Survival (Primary Analysis Set)



CPB = cardiopulmonary bypass

eFigure 3. Kaplan–Meier Curve for Overall Survival (Per-Protocol Set)



CPB = cardiopulmonary bypass

eTable 1. Details of Intervention, Laboratory Values and Fibrinogen levels, and Bleeding Categories in the Per-Protocol Population

Outcome	Fibrinogen Concentrate (N=364)	Cryoprecipitate (N=361)
Intervention details		
Dosage of investigational product		
Mean (SD)	4.8 (2.1) g	12.8 (8.5) units
Median (IQR)	4 (4–4) g	10 (10–10) units
Doses of investigational product – No. (%)		
1	304 (83.5)	295 (81.7)
2	47 (12.9)	48 (13.3)
3	9 (2.5)	10 (2.8)
4 or more	4 (1.1)	8 (2.2)
Time from start of surgery to order of 1st dose, median (IQR), hours	5.8 (4.6–7.3)	5.7 (4.6–7.1)
Time from order of 1st dose to administration, median (IQR), min	45 (31–62)	47 (37–61)
Plasma fibrinogen, median (IQR), g/L		
Pre-transfusion	1.6 (1.3–1.9) (n=344)	1.6 (1.3–1.9) (n=344)
Post-transfusion	2.5 (2.1–2.9) (n=317)	2.3 (2.0–2.6) (n=294)
Change from pre-transfusion	0.9 (0.6–1.2) (n=299)	0.7 (0.5–1.0) (n=278)
Bleeding categories according to modified UDPB classification		
≥2 (moderate to massive) – No. (%)	172 (47.3)	168 (46.5)
<2 (insignificant to mild) – No. (%)	192 (52.7)	193 (53.5)
24-hour chest tube drainage, median (IQR), mL	790 (500–1330)	830 (540–1350)
Prothrombin complex concentrate – No. (%)	108 (29.7)	97 (26.9)
Recombinant factor VII – No. (%)	35 (9.6)	28 (7.8)

IQR = interquartile range; SD = standard deviation; RBC = red blood cells; UDPB = Universal Definition of Perioperative Bleeding, 1 intraoperative death included in the moderate to massive group in the fibrinogen concentrate group

eTable 2. Allogeneic Transfusion Components Within 24 hours After Cardiopulmonary Bypass in Assessed Subgroups

Population and Outcome	Fibrinogen Concentrate			Cryoprecipitate			Fibrinogen Concentrate - Cryoprecipitate	Fibrinogen Concentrate/ Cryoprecipitate	Non-inferiority P value	p-value for interaction between planned treatment and subgroup[a]
	N	Median (IQR) – units	LSMean (CI) – units	N	Median (IQR) – units	LSMean (CI) – units	Mean difference (CI) – units	Ratio (1-sided 97.5% CI) of LSMeans		
	A priori defined subgroups									
Excluding patients who were in critical state before surgery	309	10.0 (4.0 – 20.0)	13.6 (12.2 to 15.1)	325	13.0 (6.0 – 22.0)	16.2 (14.8 to 17.8)	-2.65 (-5.00 to 0.28)	0.84 (-∞ to 0.96)	<0.001	
Elective surgery	231	9.0 (4.0 – 17.0)	11.7 (10.4 to 13.3)	235	11.0 (5.0 – 20.0)	14.4 (12.9 to 16.1)	-2.67 (-5.00 to 0.34)	0.81 (-∞ to 0.96)	<0.001	0.02[b]
Non-elective surgery	141	20.0 (10.0 – 33.0)	23.8 (21.0 to 26.9)	128	19.0 (12.0 – 27.0)	21.8 (19.1 to 25.0)	1.922 (-2.81 to 6.65)	1.09 (0 to 1.31)	0.15	
Complex surgery	267	14.0 (8.0 – 24.0)	18.5 (16.7to 20.4)	260	16.0 (8.0 – 24.0)	18.8 (17.0 to 20.8)	-0.35 (-3.36 to 2.66)	0.98 (-∞ to 1.13)	0.003	0.41
Non-complex surgery	105	7.0 (2.0 – 16.0)	10.7 (8.9 to 13.0)	103	11.0 (4.0 – 18.0)	12.5 (10.4 to 14.9)	-1.74 (-4.86 to 1.38)	0.86 (-∞ to 1.12)	0.006	
	Post-hoc defined subgroups									
Non-elective surgery adjusted	141			128			NA	1.04 (0 to 1.24)	0.06	NA

Population and Outcome	Fibrinogen Concentrate			Cryoprecipitate			Fibrinogen Concentrate - Cryoprecipitate	Fibrinogen Concentrate/ Cryoprecipitate	Non-inferiority P value	p-value for interaction between planned treatment and subgroup[a]
	N	Median (IQR) – units	LSMean (CI) – units	N	Median (IQR) – units	LSMean (CI) – units	Mean difference (CI) – units	Ratio (1-sided 97.5% CI) of LSMeans		
for critical state before surgery										
Non-elective surgery excluding patients who were in critical state before surgery	78	16.0 (8.0 – 25.0)	19.1 (15.8 to 23.0)	90	17.0 (11.0 – 27.0)	21.0 (17.8 to 24.8)	-1.92 (-7.88 to 4.03)	0.91 (-∞ to 1.17)	0.01	
Excluding patients without fibrinogen / FIBTEM measurement prior to first dose	361	12.0 (5.0 – 22.0)	16.4 (15.0 to 18.0)	351	14.0 (6.0 – 23.0)	17.0 (15.5 to 18.7)	-0.62 (-3.06 to 1.82)	0.96 (-∞ to 1.10)	<0.001	NA
Excluding patients with fibrinogen >2.0 g/L or FIBTEM A10 > 10 mm prior to first dose	297	10.0 (4.0 – 20.0)	15.3 (13.7 to 17.0)	283	13.0 (6.0 – 22.0)	16.7 (15.1 to 18.6)	-1.44 (-4.20 to 1.32)	0.91 (-∞ to 1.06)	<0.001	NA
Excluding patients with UDPB <2 prior to first dose	337	13.0 (8.0 – 24.0)	18.0 (16.5 to 19.5)	340	15.0 (8.0 – 23.0)	18.2 (16.7 to 19.8)	-0.22 (-2.68 to 2.25)	0.99 (-∞ to 1.11)	<0.001	NA

[a] After the applicable interaction terms (subgroup/treatment) were included in the generalized linear model for counting data, the p-values were derived from the corresponding Chi-Square test statistic. [b]The non-elective group included all patients in critical state before surgery, which was a prognostically important variable for which there was between-group imbalance in the primary analysis set. [c]Interaction between non-elective patients excluding critical state patients and elective patients. CI = confidence interval; IQR = interquartile range; LSMean = least square mean; NA = not applicable; UDPB = Universal Definition of Perioperative Bleeding

eTable 3. Adverse Events Occurring in More Than One Patient for the Primary Analysis Set

	Fibrinogen Concentrate (N=372)	Cryoprecipitate (N=363)
	No. patients[a] (%) [no. events]	**No. patients[a] (%) [no. events]**
All AEs	**248 (66.7) [623]**	**264 (72.7) [673]**
Infections and infestations	*51 (13.7) [55]*	*56 (15.4) [61]*
Bacteremia	1 (0.3) [1]	1 (0.3) [1]
Clostridium difficile colitis	1 (0.3) [1]	1 (0.3) [1]
Infection of a hematoma	1 (0.3) [1]	1 (0.3) [1]
Infection	0 (0.0) [0]	2 (0.6) [2]
Pneumonia	18 (4.8) [18]	19 (5.2) [20]
Postoperative wound infection	6 (1.6) [6]	9 (2.5) [9]
Sepsis	13 (3.5) [13]	15 (4.1) [15]
Septic shock	0 (0.0) [0]	3 (0.8) [3]
Urinary tract infection	7 (1.9) [7]	3 (0.8) [3]
Neoplasms benign, malignant and unspecified	*1 (0.3) [1]*	*0 (0.0) [0]*
Blood and lymphatic system disorders	*68 (18.3) [80]*	*62 (17.1) [74]*
Anemia	58 (15.6) [58]	52 (14.3) [53]
Heparin-induced thrombocytopenia	3 (0.8) [3]	0 (0.0) [0]
Thrombocytopenia	15 (4.0) [15]	20 (5.5) [20]
Immune system disorders	*2 (0.5) [2]*	*0 (0.0) [0]*
Metabolism and nutrition disorders	*7 (1.9) [7]*	*4 (1.1) [6]*
Fluid overload	2 (0.5) [2]	1 (0.3) [1]
Hypervolemia	1 (0.3) [1]	1 (0.3) [1]
Hypokalemia	1 (0.3) [1]	1 (0.3) [2]
Psychiatric disorders	*57 (15.3) [57]*	*54 (14.9) [54]*
Delirium	56 (15.1) [56]	54 (14.9) [54]
Nervous system disorders	*26 (7.0) [28]*	*26 (7.2) [31]*
Brain injury	0 (0.0) [0]	2 (0.6) [2]
Cerebrovascular accident	16 (4.3) [16]	17 (4.7) [17]
Depressed level of consciousness	0 (0.0) [0]	2 (0.6) [2]
Hypoesthesia	2 (0.5) [2]	0 (0.0) [0]
Seizure	1 (0.3) [1]	5 (1.4) [5]
Spinal cord ischemia	2 (0.5) [2]	1 (0.3) [1]
Vocal cord paralysis	4 (1.1) [4]	0 (0.0) [0]
Transient ischemic attack	1 (0.3) [1]	1 (0.3) [1]
Eye disorders	*0 (0.0) [0]*	*3 (0.8) [3]*
Ear and labyrinth disorders	*0 (0.0) [0]*	*1 (0.3) [1]*
Cardiac disorders	*143 (38.4) [173]*	*164 (45.2) [201]*
Atrial fibrillation	108 (29.0) [109]	122 (33.6) [122]
Atrial flutter	3 (0.8) [3]	2 (0.6) [2]
Atrioventricular block	16 (4.3) [16]	16 (4.4) [16]
Cardiac arrest	5 (1.3) [5]	7 (1.9) [7]
Cardiac failure congestive	4 (1.1) [4]	6 (1.7) [6]

	Fibrinogen Concentrate (N=372)	Cryoprecipitate (N=363)
	No. patients[a] (%) [no. events]	**No. patients[a] (%) [no. events]**
Cardiac tamponade	18 (4.8) [19]	16 (4.4) [18]
Cardiogenic shock	4 (1.1) [4]	6 (1.7) [6]
Myocardial infarction	3 (0.8) [3]	4 (1.1) [4]
Pericarditis	0 (0.0) [0]	2 (0.6) [2]
Pericardial effusion	3 (0.8) [3]	6 (1.7) [6]
Right ventricular failure	0 (0.0) [0]	2 (0.6) [2]
Ventricular tachycardia	1 (0.3) [1]	1 (0.3) [1]
Vascular disorders	*23 (6.2) [28]*	*38 (10.5) [39]*
Deep vein thrombosis	3 (0.8) [3]	9 (2.5) [9]
Hemorrhage	14 (3.8) [16]	13 (3.6) [13]
Peripheral ischemia	3 (0.8) [3]	3 (0.8) [3]
Shock	1 (0.3) [1]	1 (0.3) [1]
Shock hemorrhage	1 (0.3) [1]	1 (0.3) [1]
Respiratory, thoracic and mediastinal disorders	*39 (10.5) [45]*	*48 (13.2) [53]*
Acute respiratory distress syndrome	1 (0.3) [1]	1 (0.3) [1]
Aspiration	1 (0.3) [1]	1 (0.3) [1]
Atelectasis	1 (0.3) [1]	2 (0.6) [2]
Dyspnea	1 (0.3) [1]	1 (0.3) [1]
Hypoxia	0 (0.0) [0]	3 (0.8) [3]
Pleural effusion	10 (2.7) [11]	16 (4.4) [16]
Pneumothorax	5 (1.3) [5]	8 (2.2) [8]
Pulmonary embolism	2 (0.5) [2]	0 (0.0) [0]
Pulmonary edema	2 (0.5) [2]	1 (0.3) [1]
Respiratory failure	16 (4.3) [16]	17 (4.7) [17]
Gastrointestinal disorders	*24 (6.5) [28]*	*29 (8.0) [31]*
Dysphagia	7 (1.9) [7]	11 (3.0) [11]
Gastrointestinal hemorrhage	7 (1.9) [7]	10 (2.8) [10]
Intestinal ischemia	5 (1.3) [6]	3 (0.8) [3]
Pancreatitis	1 (0.3) [1]	2 (0.6) [2]
Hepatobiliary disorders	*32 (8.6) [32]*	*37 (10.2) [37]*
Hepatic failure	3 (0.8) [3]	7 (1.9) [7]
Hepatic function abnormal	27 (7.3) [27]	26 (7.2) [26]
Ischemic hepatitis	1 (0.3) [1]	3 (0.8) [3]
Skin and subcutaneous tissue disorders	*3 (0.8) [3]*	*3 (0.8) [3]*
Rash	2 (0.5) [2]	0 (0.0) [0]
Blister	0 (0.0) [0]	2 (0.6) [2]
Musculoskeletal and connective tissue disorders	*0 (0.0) [0]*	*1 (0.3) [1]*
Renal and urinary disorders	*51 (13.7) [52]*	*48 (13.2) [50]*
Acute kidney injury	29 (7.8) [29]	29 (8.0) [29]
Renal failure	19 (5.1) [20]	19 (5.2) [19]

	Fibrinogen Concentrate (N=372)	Cryoprecipitate (N=363)
	No. patients[a] (%) [no. events]	**No. patients[a] (%) [no. events]**
Urinary retention	2 (0.5) [2]	2 (0.6) [2]
Congenital, familial and genetic disorders	*1 (0.3) [1]*	*0 (0.0) [0]*
General disorders and administration site conditions	*6 (1.6) [6]*	*5 (1.4) [5]*
Multiple organ dysfunction syndrome	3 (0.8) [3]	5 (1.4) [5]
Injury, poisoning and procedural complications	*9 (2.4) [10]*	*12 (3.3) [12]*
Cardiac procedure complication	2 (0.5) [2]	0 (0.0) [0]
Laryngeal nerve dysfunction	1 (0.3) [1]	1 (0.3) [1]
Subarachnoid hemorrhage	0 (0.0) [0]	2 (0.6) [2]
Transfusion reaction	1 (0.3) [1]	1 (0.3) [1]
Vasoplegia syndrome	3 (0.8) [3]	1 (0.3) [1]
Surgical and medical procedures	*4 (1.1) [4]*	*1 (0.3) [1]*
Hospitalization	1 (0.3) [1]	1 (0.3) [1]

[a]Patients who experienced more than one event are counted only once in the total for each SOC (*italics*) and overall. All SOC categories are included. Only PTs for events that occurred in more than one patient are listed, i.e., events that occurred in a single patient in one group but in no patients in the other group are not listed, though they are counted in the totals rows.
AE = adverse event; PT = preferred term; SOC = system organ class.
Adverse events were categorized according to MedDRA version 21.1.

eTable 4. Survival Stratified by Preoperative Critical State (Primary Analysis Set)

Treatment Group	Survival to 28 days	Death before 28 days
	No. (%)	No. (%)
Not in critical state before surgery (N=634)		
Fibrinogen concentrate (N=309)	293 (94.8)	16 (5.2)
Cryoprecipitate (N=325)	310 (95.4)	15 (4.6)
In critical state before surgery (N=101)		
Fibrinogen concentrate (N=63)	44 (69.8)	19 (30.2)
Cryoprecipitate (N=38)	26 (68.4)	12 (31.6)
All (N=735)		
Fibrinogen concentrate (N=372)	337 (90.6)	35 (9.4)
Cryoprecipitate (N=363)	336 (92.6)	27 (7.4)

eTable 5. Survival Stratified by Preoperative Critical State (Per-Protocol Set)

Treatment Group	Survival to 28 days	Death before 28 days
	No. (%)	No. (%)
Not in critical state before surgery (N=625)		
Fibrinogen concentrate (N=302)	287 (95.0)	15 (5.0)
Cryoprecipitate (N=323)	308 (95.4)	15 (4.6)
In critical state before surgery (N=100)		
Fibrinogen concentrate (N=62)	44 (71.0)	18 (29.0)
Cryoprecipitate (N=38)	26 (68.4)	12 (31.6)
All (N=725)		
Fibrinogen concentrate (N=364)	331 (90.9)	33 (9.1)
Cryoprecipitate (N=361)	334 (92.5)	27 (7.5)