SUPPLEMENTAL MATERIAL

Supplemental table 1. Details of the EAB, DSMB and SAB

Board	Details
Endpoint Adjudication Board	The EAB consisted of 9 Adjudicators (4 hematologists, 2 emergency medicine physicians, 2 trauma surgeons, and 1 gastroenterologist). A lack of conflict of interest was ascertained.
Safety Adjudication Board	The SAB consisted of 3 voting members and 1 physician/moderator (non-voting member). The 3 voting members had experience in coagulation, anticoagulation treatments and their reversal, and cardiology. The physician moderator had experience in pharmacovigilance and risk management. A lack of conflict of interest was ascertained.
Data Safety Monitoring Board	The DSMB consisted of 4 voting expert members (3 physicians/1 biostatistician). The 3 physician members had experience in anticoagulant therapy and their reversal; the independent biostatistician had experience in clinical trials. All of them had prior DSMB experience. A lack of conflict of interest was ascertained.

Supplemental table 2. Secondary endpoints

Endpoint	Timeframe
Plasma levels of factors II, VII, IX, X and of proteins C and S	24 hours from start of infusion
Hemostatic efficacy of 4F-PCC and plasma for visible and musculoskeletal non-visible bleeding	3 and 6 hours from start of infusion
Time from start of infusion until INR correction	-
Time from randomization until INR correction	-
Total number of packed red blood cell transfusions and the proportion of patients with 1 or more PRBC transfusions	24 hours from start of infusion
Use of non-study-prescribed blood products and/or hemostatic agents	From randomization until 24 hours after infusion start
All-cause mortality	45 days after treatment
Safety and tolerability of 4F-PCC and plasma	-

Supplemental table 3**.** Primary rating of hemostatic efficacy: definitions for assessment

Rating	**Definition**	
	Visible bleeding	**Non-visible bleeding**
Excellent* (Effective)	Cessation of bleeding ≤1 hour after the end of infusion and no additional coagulation intervention required	1. Musculoskeletal bleeding: pain relief or no increase in swelling or unequivocal improvement in objective signs of bleeding ≤1 hour after the end of infusion; and the condition has not deteriorated during the 24-hour period 2. ICH: ≤20% increase in hematoma volume compared to baseline on repeat CT scan performed at the 3- and 24-hour time point 3. Non-visible bleeding that is not described above (e.g. GI bleeding): ≤10% decrease in both Hb/Hct† at 24 hours‡ compared to baseline (initial correction of decrease in Hb with PRBCs, with a transfusion trigger of a Hb ≤8 ±1 g/dL [i.e. transfuse PRBCs if the Hb ≤8 ±1 g/dL])
Good§ (Effective)	Cessation of bleeding >1 and ≤4 hours after end of infusion and no additional coagulation intervention required	1. Musculoskeletal bleeding: Pain relief or no increase in swelling or unequivocal improvement in objective signs of bleeding >1 and ≤4 hours after the end of infusion; and the condition has not deteriorated during the 24-hour period 2. ICH: >20%, but ≤35% increase in hematoma volume compared to baseline on a repeat CT scan performed at the 24-hour time point 3. Non-visible bleeding that is not described above: >10 to ≤20% decrease in both Hb/Hct† at 24 hours‡ compared with baseline (initial correction of decrease in Hb with PRBCs, with a transfusion trigger of a Hb ≤8 ±1 g/dL [i.e. transfuse PRBCs if the Hb ≤8 ±1 g/dL])

Poor/None‖ (Non-effective)	Cessation of bleeding >4 hours after end of the infusion, and/or additional coagulation intervention required (e.g. plasma, whole blood cell pack, or coagulation factor products)	1. Musculoskeletal bleeding: no improvement by 4 hours after the end of infusion and/or the condition has deteriorated during the 24-hour period 2. ICH: >35% increase in hematoma volume compared to baseline on repeat CT scan performed at the 24 hour time point 3. Non-visible bleeding that is not listed above: >20% decrease in both Hb/Hct at 24 hours‡ compared to baseline (initial correction of decrease in hemoglobin with PRBCs, with a transfusion trigger of a Hb ≤8 ±1 g/dL [i.e. transfuse PRBCs if the Hb ≤8 ±1 g/dL])

Any additional diagnostic data for a particular bleeding site, e.g. nasogastric tube, ultrasound, GI endoscope, or CT scans, were taken into account for the overall assessment. Pain, swelling and signs of bleeding were considered to be typical symptoms in cases of musculoskeletal bleeding and were expected to be present at baseline. Any uncontrolled bleeding that did not respond to 4F-PCC or plasma and was related to the underlying disease was taken into account for the overall assessment.

CT, computed tomography; GI, gastrointestinal; Hb, hemoglobin; Hct, hematocrit; ICH, intracranial hemorrhage; PRBCs, packed red blood cells

*For all types of bleeding: no additional plasma, blood products (whole blood products not including PRBCs) and/or coagulation factor products required after initial treatment with study drug; †The smallest percentage decrease in Hb or Hct should be used to determine the efficacy rating of excellent, good or poor/none; ‡Assumption for the 24-hour adjusted Hb/Hct calculation: for each unit of PRBC transfusion there is generally an increase of 1 g/dL in Hb or 3% increase in Hct; §For all types of bleeding: no more than two additional units of plasma or blood products and/or coagulation factor products required after initial treatment with study drug; ‖For all types of bleeding: more than two additional units of plasma, blood products and/or coagulation factor products required after initial treatment with study drug

Supplemental table 4. Patients meeting each of the three acute major bleeding eligibility criteria (ITT-E population)

Definition	4F-PCC (N=98)		Plasma (N=104)	
	n	%	n	%
1. Life-threatening or potentially life-threatening bleeding	73	74.4	73	70.1
2. Acute bleeding associated with a fall in hemoglobin level ≥2 g/dL	36	36.7	34	29.8
3. Bleeding requiring blood product transfusion (blood products include plasma, red blood cells and other coagulation factor products)	71	72.4	82	78.8

Supplemental table 5. Length of hospital stay (ITT-E population)

Parameter	4F-PCC (N=98)		Plasma (N=104)	
	Median	IQR	Median	IQR
Inpatient time (hours)	107.9	71.6-151.3	101.4	67.4-146.9
Emergency department time (hours)	4.9	0-8.7	5.0	0-9.4
Intensive care unit / critical care unit (hours)	0	0-44.7	0	0-40.0
General floor time (hours)	71.1	31.1-146.5	67.9	21.0-136.5

Supplemental table 6. Primary rating of hemostatic efficacy by type of major bleeding (ITT-E population)

Type of bleeding	Hemostatic efficacy rating	4F-PCC (N=98) n	4F-PCC (N=98) %	Plasma (N=104) n	Plasma (N=104) %	2-sided p-value*
Gastrointestinal	Excellent or good	41	74.5	44	75.9	0.8718
	Poor or none	14	25.5	14	24.1	
Visible	Excellent or good	12	75.0	12	57.1	0.2662
	Poor or none	4	25.0	9	42.9	
ICH	Excellent or good	5	41.7	7	58.3	0.4241
	Poor or none	7	58.3	5	41.7	
Musculoskeletal	Excellent or good	7	100	2	28.6	0.0072
	Poor or none	0	0	5	71.4	
Other non-visible	Excellent or good	6	75.0	3	50.0	0.3519
	Poor or none	2	25.0	3	50.0	

*Cochran-Mantel-Haenszel

Note: due to the small numbers of patients involved in some categories, it is probable that there was insufficient power to detect differences between groups; 4F-PCC, four-factor prothrombin complex concentrate; ICH, intracranial hemorrhage; N, total number of patients; n, number of patients within subtype group

Supplemental table 7. Hemostatic efficacy by country/region (ITT-E population)

		4F-PCC (N=98)		Plasma (N=104)		Two-sided p-value
		n	%	n	%	(Cochran-Mantel-Haenszel)
Europe	Excellent or good	20	66.7	22	68.8	0.86
	Poor/none	10	33.3	10	31.3	
United States	Excellent or good	51	75.0	46	63.9	0.16
	Poor/none	17	25.0	26	36.1	

Breslow Day test for 3-way interaction of region by treatment by outcome was 0.343. Results for both regions are not significantly different.

Supplemental table 8. Rapid reduction of INR (≤1.3 at 0.5 hours after the end of infusion) by country/region (ITT-E population)

		4F-PCC (N=98)		Plasma (N=104)		Two-sided p-value
		n	%	n	%	(Cochran-Mantel-Haenszel)
Europe	Rapid reduction	15	50.0	1	3.1	<0.0001
	No rapid reduction	15	50.0	31	96.9	
United States	Rapid reduction	46	67.6	9	12.5	<0.0001
	No rapid reduction	22	32.4	63	87.5	

Breslow Day test for 3-way interaction of region by treatment by outcome was 0.510. Results for both regions are not significantly different.

Supplemental table 9. Hemostatic efficacy (ITT population)

Primary rating	**Number (%) of patients [95% CI]**		**Difference 4F-PCC – plasma (%) [95% CI]**
	4F-PCC (N=107)	**Plasma (N=109)**	
Hemostatic efficacy rating by category*			
Excellent	46† (43.0)	46† (42.2)	
Good	28 (26.2)	26 (23.9)	
Poor/none	33 (30.8)	37 (33.9)	
Non-effective	*26 (24.3)*	*33 (30.3)*	
Missing primary rating	*7 (6.5)*	*4 (3.7)*	
'Effective' hemostasis	**74 (69.2) [60.4; 77.9]**	**72 (66.1) [57.2; 74.9]**	**3.1‡ [–9.4; 15.6]**

*Hemostatic efficacy assessed by a blinded independent board; †p-value=0.75 by Cochran-Mantel-Haenszel test; ‡4F-PCC non-inferior to plasma; Effective hemostasis, hemostatic efficacy rated as excellent or good; 4F-PCC, four-factor prothrombin complex concentrate; CI, confidence interval

Supplemental table 10. Rapid INR reduction (ITT population)

	Number (%) of patients [95% CI]		**Difference 4F-PCC – plasma (%) [95% CI]†**
	4F-PCC (N=107)	**Plasma (N=109)**	
Rapid decrease of INR*	64 (59.8) [50.5; 69.1]	10 (9.2) [3.8; 14.6]	**50.6 [37.9; 63.4]**

*INR ≤1.3 at 0.5 h after the end of infusion; †4F-PCC non-inferior to plasma: lower limit of 95% CI >–10%; 4F-PCC superior to plasma: lower limit of 95% CI >0; 4F-PCC, four-factor prothrombin complex concentrate; CI, confidence interval; N, total number of patients

Supplemental table 11. Number of patients with SAEs by preferred term to Day 45 visit (ITT-S population)

Preferred term*	**Number (%) of patients**	
	4F-PCC (N=103)	**Plasma (N=109)**
Any SAE†	**32 (31.1)**	**26 (23.9)**
Ischemic stroke	3 (2.9)	0
Pneumonia	2 (1.9)	1 (0.9)
Respiratory failure	2 (1.9)	1 (0.9)
Hemorrhage intracranial	2 (1.9)	0
Atrial flutter	2 (1.9)	0
Cardiac failure congestive	1 (1.0)	4 (3.7)
Encephalopathy	0	2 (1.8)
Subarachnoid hemorrhage	0	2 (1.8)
Myocardial ischemia	0	2 (1.8)
Anemia	0	2 (1.8)
Related SAE‡	**2 (1.9)**	**4 (3.7)**
Deep vein thrombosis	1 (1.0) (Onset day: 13)	0
Ischemic stroke	1 (1.0) (Onset day: 43)	0
Myocardial ischemia	0	2 (1.8) (Onset day: 1, both patients)
Fluid overload	0	1 (0.9) (Onset day: 3)
Respiratory failure	0	1 (0.9) (Onset day: 1)

*Listed in descending order based on frequency in 4F-PCC group and coded according to MedDRA 12.0; multiple SAE entries per patient possible. †SAEs reported for >1 patient per group; ‡Defined as events whose relationship to study treatment was related in the opinion of the investigator

Supplemental table 12. Number of patients with fluid overload or cardiac events (ITT-S population)

Parameter	4F-PCC (N=103)		Plasma (N=109)	
	n	%	n	%
Any fluid overload or similar cardiac events	5	4.9	14	12.8
Fluid overload	0	0	4	3.7
Pulmonary edema	2	1.9	4	3.7
Cardiac failure				
Cardiac failure congestive	2	1.9	5	4.6
Cardiac failure	1	1.0	1	0.9
Cardiac failure chronic	0	0	1	0.9

Supplemental table 13. Listing of patients who died up to Day 45 (ITT-S population)

Cause of death (reported term)	Study day	Age (years)	Comfort care	Relationship to treatment (as adjudicated by the SAB)
4F-PCC group (N=10)				
Increased size of intracranial hemorrhage	3	82	Yes	Not related
Gradual worsening of cardiogenic heart failure	5	75	Yes	Not related
Sudden death	7	56	No	Possibly related
Sepsis (staph infection uncertain etiology)	26	66	Yes	Not related
Acute renal failure	19	71	Yes	Not related
Pancreatic cancer	30	84	Yes	Not related
Cardiopulmonary arrest	31	54	No	Not related
Respiratory failure	33	79	Yes	Not related
Stage IV lung cancer	34	73	Yes	Not related
Myocardial infarction	38	88	Yes	Not related
Plasma group (N=5)				
Systemic infection	4	89	Yes	Not related
Worsening metastatic lung cancer	7	85	Yes	Not related
Progression of hemorrhagic anemia	7	80	No	Not related
Sepsis shock	14	80	Yes	Not related
Worsening hepatic failure	24	72	Yes	Not related

Supplemental table 14. Definitions of non-serious AEs and SAEs

Event type	Definition
Serious adverse event (SAE)	Any untoward medical occurrence that at any dose: resulted in death; was life-threatening; required in-patient hospitalization or prolongation of existing hospitalization; resulted in persistent or significant disability/incapacity; was a congenital anomaly/birth defect; was according to investigator's judgment another medically important condition. Important medical events that did not result in death, were not life-threatening, or did not require hospitalization could have been considered an SAE when, based upon appropriate medical judgment, they had jeopardized the patient and required medical or surgical intervention to prevent one of the outcomes listed in the definition. Examples of such medical events include allergic bronchospasms requiring intensive treatment in an emergency department (ED) or at home, convulsions that do not result in in-patient hospitalization, or the development of drug dependency or drug abuse. "Life-threatening" meant that the patient was at immediate risk of death from the AE as it occurred. It did not include an AE that, had it occurred in a more severe form, might have caused death. "Requires in-patient hospitalization" was to be defined as hospital admission required for treatment of the AE. Hospital admission for scheduled elective surgery was not an SAE.
Non-serious adverse event	AEs which did not fulfil the criteria for an SAE were defined as non-serious AEs