2 Synopsis

Trial Registration ID-number NCT00323570	**IND Number – BB-IND 9864** **EudraCT number – 2005-002059-41**

Title of Trial
A multi-centre, randomised, double-blind, parallel group, placebo controlled trial to evaluate the efficacy and safety of activated recombinant factor VII (rFVIIa/NovoSeven®/NiaStase®) in severely injured trauma patients with bleeding refractory to standard treatment

Investigators
There was one principal investigator for each trial site. The signatory investigator was [redacted],M.D.

Trial Sites
150 trial sites were initiated, of which 100 had at least one randomised patient and at least one patient who was dosed with trial product (rFVIIa or placebo). The distribution of sites that actively recruited in the participating countries was: Australia (5), Austria (3), Belgium (1), Brazil (4), Canada (11), Czech Republic (3), Finland (1), France (1), Germany (12), Greece (1), Hong Kong (1), Hungary (2), Israel (2), Italy (6), Netherlands (1), New Zealand (1), Norway (1), Portugal (1), Singapore (3), South Africa (3), Spain (7), Sweden (1), Switzerland (2), Taiwan (2), United Kingdom (2), United States (23).

Publications
None

Trial Period	**Development Phase**
8 August 2005 to 4 September 2008	Phase 3

Objectives
Primary Objective:
- To evaluate the efficacy and safety of rFVIIa (NovoSeven®/NiaStase®) compared to placebo as an adjunct to standard treatment of trauma patients with active haemorrhage refractory to blood component therapy and surgical haemostatic procedures.

Methodology
This was a multi-centre, randomised, double-blinded, parallel group, placebo-controlled trial to evaluate the efficacy and safety of rFVIIa (NovoSeven®/NiaStase®) in patients with blunt and/or penetrating trauma injuries. Patients who met entry criteria were randomised and received trial drug (rFVIIa or placebo) as an adjunct to standard treatment. The estimated time from injury to admission at hospital (investigative site) was limited to a maximum of 4 hours. Patients with confirmed clinical indicators for active haemorrhage refractory to standard treatment were randomised equally to one of two treatment groups:
- Three single doses of rFVIIa (200 mcg/kg + 100 mcg/kg + 100 mcg/kg); or
- Three single doses of placebo (in identical volumes to active treatment)

Randomised patients were to be administered the first dose of trial drug (rFVIIa or placebo) intravenously as a slow-bolus injection, no earlier than upon the completion of the 4th unit of RBC and no later than by the completion of the 8th unit of RBC. The estimated time from injury to administration of first dose was limited to a maximum of 12 hours. A second dose was to be administered one hour after the initial dose, and a third dose was to be administered three hours after the initial dose. Safety and efficacy endpoints were evaluated at different timepoints from randomisation through Day 30. Serious Adverse Events (SAEs), mortality, and patient status were followed through Day 90. Specific procedures including physical examination, measurement of vital signs, and laboratory assessments were conducted at defined intervals throughout the trial. Several endpoints were monitored throughout the trial at defined intervals, including but not limited to mortality, transfusion requirements, organ function and adverse events.

Number of Subjects Planned and Analysed
The protocol for the F7Trauma-1648 trial was merged into the protocol for the F7Trauma-1711 trial, and the analysis of patients presented in this report was based on patients pooled from both trials. A total of 1502 patients were planned to be randomised and dosed with trial drug. A planned interim analysis for futility was performed by the

independent Data Monitoring Committee (DMC) using mortality data for 467 blunt trauma patients (220 [rFVIIa] and 247 [placebo]) and morbidity data for 38 blunt trauma patients (17 [rFVIIa] and 21 [placebo]). The total conditional power for showing superiority was 11.2%. As this number was smaller than the predefined threshold of 50%, the recommendation was made to stop the trial for futility. The final sample size of patients described in this report is smaller than the planned sample size of 1276 patients with blunt trauma (638 per treatment arm) that had an estimated overall power of 80.1% for the primary endpoint. Therefore, the results presented in this report should be interpreted within this context. Among patients with blunt trauma, the ITT analysis set for baseline analyses included 468 patients (247 placebo, 221 rFVIIa) of whom 5 were withdrawn (3 placebo, 2 rFVIIa), and 3 were lost to follow-up (2 placebo, 1 rFVIIa). The ITT analysis set for efficacy analyses included the 460 patients who completed the trial (242 placebo, 218 rFVIIa). The PP analysis set included 399 patients (214 placebo, 185 rFVIIa). Among patients with penetrating trauma, the ITT analysis set for baseline analyses included 86 patients (40 placebo, 46 rFVIIa), of whom 3 were withdrawn (2 placebo, 1 rFVIIa), and 1 (rFVIIa) was lost to follow-up. The ITT analysis set for efficacy analyses included the 82 patients who completed the trial (38 placebo, 44 rFVIIa). The PP analysis set included 77 patients (36 placebo, 41 rFVIIa).
Diagnosis and Main Criteria for Inclusion Patients between the ages of 18 and 70 years (inclusive) with blunt and/or penetrating trauma injuries, meeting the inclusion and exclusion criteria and having received a minimum of 4 units and a maximum of 8 units of red blood cells (RBC) were eligible to be randomised in the trial. Patients who were moribund or had severe traumatic brain injury were excluded from the trial. The inclusion and exclusion criteria limited the study population to patients with evidence of active and continuing haemorrhage in the torso or proximal lower extremities at the time of randomisation.
Test Product, Dose and Mode of Administration, Batch Number Activated recombinant human FVII (NovoSeven®/NiaStase®) was to be supplied by Novo Nordisk A/S, Denmark as sterile, freeze-dried powder in single use vials to be reconstituted with sterile water for injection. Batch numbers were RR 40069, PR 40213, SR 40360 and TR 40097.
Duration of Treatment Dosing was to be initiated no later than 30 minutes after randomisation (randomisation was defined as the breaking the seal of drug box). Trial drug was to be administered at Hour 0 (Time at first dose), Hour 1 (± 15 minutes) and Hour 3 (± 15 minutes).
Reference Therapy, Dose and Mode of Administration, Batch Number Matching placebo was to be supplied by Novo Nordisk A/S, Denmark as sterile, freeze-dried powder in single use vials to be reconstituted with sterile water for injection. Batch numbers were RR 40032, PR 40229, RR 40391 and TR 40409.
Criteria for Evaluation – Efficacy All cause 30-day mortality, durable morbidity (defined as pulmonary and/or renal dysfunction requiring ongoing medical intervention), assessment of tissue bleeding, multi-organ failure, single organ failure, ICU-free days, hosptial-free days and allogeneic transfusion requirements
Criteria for Evaluation – Safety Incidence of critical serious adverse events (death, thromboembolic events and other medical events of special interest [MESI]), adverse events, laboratory parameters (including troponin I) and vital signs.
Statistical Methods The mortality rates were to be compared between treatment groups using a logistic regression including relevant baseline covariates, such as: Age, ISS, GCS, INR and ALI. The null hypothesis was that the two treatment groups had the same mortalities, i.e., that the odds ratio between the rFVIIa group and the placebo group was 1. The alternative hypothesis was that the mortality in the rFVIIa group was lower than the mortality in the placebo group, i.e., that the odds ratio between the rFVIIa group and the placebo group was lower than 1. A two-sided test with a significance level of 5% was to be used. If superior mortality could not be demonstrated, it was a prerequisite for the use of the next primary endpoint of durable morbidity that the mortality in the rFVIIa treatment group in the blunt stratum was non-inferior. The test for non-inferiority of mortality was to compare the upper limit of the one-sided

95% confidence interval for the log relative risk with log(1.05), which was the value corresponding to a relative non-inferiority margin of Delta = 5%. The morbidity rates were to be compared between treatment groups using a logistic regression including the same baseline covariates as those in the mortality analysis. The mean number of days alive and free from both ventilator and renal replacement, was to be compared between treatment groups using an analysis of variance model with treatment as factor and the same baseline covariates as those in the mortality analysis. Time to death from time of first dose through Day 30 was to be described with Kaplan-Meier curves and the two treatment groups were to be compared using a Cox Proportional Hazards model with treatment as factor and adjusting for the same covariates as above. Number of RBCs from time of first dose through Hour 24 was to be compared between the two treatment groups using a Wilcoxon-Mann-Whitney test. Number of patients receiving 10 units or more of red blood cells (RBC) from time of injury through Hour 24 was to be compared between the two treatment groups using a logistic regression model with treatment as factor. Total number of all allogeneic transfusions from time of first dose through Hour 24 was to be compared between the two treatment groups using a Wilcoxon-Mann-Whitney test. The clinical assessments of tissue bleeding were to be compared between treatment groups using a Chi-Square test. The amounts of RBC, FFP, platelets, cryoprecipitate/fibrinogen concentrate, and all allogeneic units transfused through Hour 24 and Hour 48 were to be compared between treatment groups using a Wilcoxon-Mann-Whitney test. Repeated assessments of organ function (pulmonary, renal, cardiovascular and hepatic) were to be compared between treatment groups using a random effects model for normally distributed data. The number of ICU-free days and hospital-free days were to be calculated for each patient and compared between the two treatment groups using the same analysis of variance model as used for the number of days alive and free from both ventilator and renal replacement therapy. Summary tables of the safety endpoints, adverse events and serious adverse events, displaying both the numbers of events and numbers of subjects experiencing the event, were to be presented.

Demography of Trial Population

Patients with Blunt Trauma

The baseline clinical profiles were consistent with that of patients having suffered severe trauma. The overall profile of demographics and baseline characteristics appeared to be comparable between treatment groups (Table 1). Mean base deficit scores were 6.1 mEq/L in the rFVIIa-treated patients and 8.7 mEq/L for placebo-treated patients. The mean ages were 39 years (rFVIIa) and 40 years (placebo), and the majority of patients were White (82% [rFVIIa] and 85% [placebo]) or male (73% [rFVIIa] and 74% [placebo]). pH values were low within 30 minutes prior to randomisation, indicating acidosis from haemorrhagic shock.

Patients with Penetrating Trauma

The baseline clinical profiles were consistent with that of patients having suffered severe trauma. The overall profile of demographics and baseline characteristics appeared to be comparable between treatment groups (Table 2). The mean lactate level was 5.4 mmol/L for rFVIIa-treated patients and 4.5 mmol/L for placebo-treated patients. The patients were younger (mean age of 34 years [rFVIIa] and 29 years [placebo]), and had a higher proportion who were male (94% [rFVIIa] and 93% [placebo]) or black or African American (28% [rFVIIa] and 43% [placebo]), compared with patients with blunt trauma. pH values were low within 30 minutes prior to randomisation, indicating acidosis from haemorrhagic shock.

Table 1. Baseline Characteristics of Patients with Blunt Trauma – ITT Analysis Set

	Placebo	rFVIIa
No. of Subjects	247	221
Age (Years), N	247	221
Mean (SD)	39.9 (14.16)	39.2 (14.35)
Median	39.0	37.0
Min - Max	17 - 71	18 - 79
Ethnic Origin, n (%), N	247 (100)	221 (100)
White	211 (85.4)	182 (82.4)
Asian	24 (9.7)	21 (9.5)
Black or African American	5 (2.0)	9 (4.1)
Other	6 (2.4)	8 (3.6)
Native Hawaiian or Other Pacific Islander	1 (0.4)	1 (0.5)
Sex, n (%), N	247 (100)	221 (100)
Male	182 (73.7)	162 (73.3)
Height (cm), N	245	218
Mean (SD)	175.0 (8.97)	173.9 (9.64)
Min - Max	150 - 198	146 - 200
Estimated Weight (kg), N	246	221
Mean (SD)	79.3 (13.94)	77.9 (16.49)
Median	80.0	77.0
Min - Max	48 - 130	45 - 160
Base Deficit (mEq/L), N	50	41
Mean (SD)	8.7 (4.13)	6.1 (3.04)
Median	8.6	5.9
Min - Max	0.1 - 16.0	0.2 - 12.0
Temperature (C), N	223	192
Mean (SD)	35.6 (1.18)	35.7 (1.18)
Median	35.8	36.0
Min - Max	31.5 - 38.6	29.4 - 38.3
Systolic Blood Pressure (mmHg), N	247	221
Mean (SD)	96.6 (26.29)	100.9 (27.17)
Median	92.0	100.0
Min - Max	48.0 - 181.0	49.0 - 216.0
Lactate (mmol/L), N	173	166
Mean (SD)	3.7 (2.18)	3.7 (2.28)
Min - Max	0.2 - 10.6	0.3 - 19.0
pH, N	210	182
Mean (SD)	7.3 (0.09)	7.3 (0.09)
Median	7.3	7.3
Min - Max	7.0 - 7.4	7.0 - 7.5
Pulse (beats/min), N	247	221
Mean (SD)	107.9 (24.22)	109.3 (24.55)
Median	106.0	110.0
Min - Max	30.0 - 176.0	53.0 - 176.0

N: total number of patients

Table 2. Baseline Characteristics of Patients with Penetrating Trauma – ITT Analysis Set

	Placebo	rFVIIa
No. of Subjects	40	46
Age (Years), N	40	46
Mean (SD)	29.4 (10.32)	33.8 (11.86)
Median	27.0	30.0
Min - Max	18 - 56	18 - 67
Ethnic Origin, n (%), N	40 (100)	46 (100)
White	15 (37.5)	29 (63.0)
Black or African American	17 (42.5)	13 (28.3)
Asian	5 (12.5)	2 (4.3)
Other	3 (7.5)	2 (4.3)
Native Hawaiian or Other Pacific Islander	0 (0.0)	0 (0.0)
Sex, n (%), N	40 (100)	46 (100)
Male	37 (92.5)	43 (93.5)
Height (cm), N	40	46
Mean (SD)	176.4 (7.37)	175.3 (6.92)
Median	177.8	175.0
Min - Max	165 - 200	153 - 190
Estimated Weight (kg), N	40	46
Mean (SD)	75.7 (11.50)	75.1 (11.73)
Median	74.5	75.0
Min - Max	50 - 105	50 - 110
Base Deficit (mEq/L), N	8	14
Mean (SD)	6.5 (4.01)	7.2 (4.10)
Median	6.3	7.8
Min - Max	0.3 - 14.0	1.6 - 14.5
Temperature (C), N	37	42
Mean (SD)	35.8 (0.84)	35.6 (1.38)
Median	35.8	35.8
Min - Max	33.9 - 37.0	31.5 - 38.2
Systolic Blood Pressure (mmHg), N	40	46
Mean (SD)	107.1 (24.13)	105.6 (26.95)
Median	109.0	102.0
Min - Max	56.0 - 170.0	54.0 - 160.0
Lactate (mmol/L), N	25	36
Mean (SD)	4.5 (2.18)	5.4 (3.22)
Median	4.0	5.1
Min - Max	1.5 - 9.7	0.7 - 12.4
pH, N	30	40
Mean (SD)	7.3 (0.09)	7.3 (0.11)
Median	7.3	7.3
Min - Max	7.1 - 7.5	7.0 - 7.6
Pulse (beats/min), N	40	45
Mean (SD)	104.8 (22.14)	108.3 (23.13)
Median	103.0	105.0
Min - Max	66.0 - 158.0	61.0 - 158.0

N: total number of patients

Efficacy Results

- Based on the recommendation by the DMC to stop the trial for futility, the final sample size of patients described in this report (460 patients with blunt trauma in the ITT efficacy analysis set) was smaller than the planned sample size of 1276 patients with blunt trauma (638 per treatment arm) that had an estimated overall power of 80.1% for the primary endpoint. Therefore, the results presented in this report should be interpreted within this context.
- The ITT analysis set for efficacy analyses included the 460 patients with blunt trauma who completed the trial (242 placebo, 218 rFVIIa) and the 82 patients with penetrating trauma who completed the trial (38 placebo, 44 rFVIIa).
- ITT and PP analysis sets showed comparable results. The results in this conclusion section are presented only for the ITT analysis set. For some parameters, the sample size of patients with penetrating trauma was too small for meaningful comparison.
- Baseline demographic and clinical profiles of the patients in this trial were consistent with that of patients with severe blunt or penetrating trauma. The overall baseline profiles of patients with blunt trauma appeared to be comparable between treatment groups. Similarly, the overall baseline profiles of patients with penetrating trauma were comparable between treatment groups. Patients with blunt trauma had more affected ISS regions and a higher mean ISS score, compared with patients with penetrating trauma.
- All-cause 30-day mortality rates were comparable between treatment groups (24 out of 218 patients, 11.0% [rFVIIa] and 26 out of 242 patients, 10.7% [placebo]) in patients with blunt trauma. Superiority and non-inferiority of rFVIIa, compared with placebo, were not demonstrated ($p = 0.934$ and $p = 0.372$, respectively). Superiority of rFVIIa to placebo in 30-day morbidity was not demonstrated ($p = 0.752$). Similarly, superiority of rFVIIa in 30-day mortality was not demonstrated among patients with penetrating trauma ($p = 0.402$). Morbidity on Day 30 in the ITT analysis set was too low for meaningful comparison among patients with penetrating trauma.
- Among patients with blunt trauma or penetrating trauma, the mean number of days alive and free of pulmonary and/or renal dysfunction, and the time to death were comparable between the rFVIIa and placebo treatment groups ($p \geq 0.05$).
- Among patients with blunt trauma, significantly fewer units of transfused RBC, FFP and all allogeneic transfusions were required through Hours 24 and 48 by rFVIIa-treated patients, compared with placebo-treated patients ($p < 0.05$). By Hour 24, the mean ± SD units of RBC transfused were 6.9 ± 10.42 U (rFVIIa) and 8.1 ± 10.87 U (placebo) ($p = 0.038$), and by Hour 48, they were 7.8 ± 10.60 U (rFVIIa) and 9.1 ± 11.27 U (placebo) ($p = 0.040$). By Hour 24, the mean ± SD units of FFP transfused were 4.7 ± 6.38 U (rFVIIa) and 6.9 ± 8.62 U (placebo) ($p < 0.001$), and by Hour 48, they were 5.3 ± 6.69 U (rFVIIa) and 8.0 ± 10.13 U (placebo) ($p = 0.001$). Similarly, the mean ± SD units of total allogeneic transfusions were 17.1 ± 26.78 U (rFVIIa) and 20.7 ± 25.68 U (placebo) ($p = 0.030$) and by Hour 48, they were 19.0 ± 27.11 U (rFVIIa) and 23.5 ± 27.98 U (placebo) ($p = 0.036$). Platelet and cryoprecipitate administration from dosing to Hours 24 and 48 was comparable between treatment groups.
- Among patients with penetrating trauma, significantly fewer units of FFP were required through Hours 24 and 48 by rFVIIa-treated patients (mean ± SD) (3.8 ± 6.01 U and 4.0 ± 6.18 U), compared with placebo-treated patients (5.7 ± 6.40 U and 6.5 ± 7.43 U; $p = 0.035$ through Hour 24, $p = 0.021$ through Hour 48). A significantly smaller proportion of patients required transfusion of 10 or more units of red blood cells from the time of injury until Hour 24 after injury in the rFVIIa-treated group (30.4%), compared with the placebo-treated group (52.5%) ($p = 0.040$).
- No significant difference in the number of transfusion units of fibrinogen concentrate was observed between treatment groups among patients with blunt or penetrating trauma.
- Among patients with blunt trauma, there was a significant difference between rFVIIa and placebo treatment groups in bleeding response after the third dose of trial drug, with bleeding decreased in 19% of patients (rFVIIa) and 17.% (placebo), and bleeding stopped in 25% of patients (rFVIIa) and 11% (placebo) ($p < 0.001$).
- Among patients with blunt trauma, there was a trend towards a smaller proportion of patients with MOF from time of first dose through Day 30 among rFVIIa-treated patients (53.7%), compared with placebo-treated patients (62.0%) ($p = 0.089$).
- The mean numbers of ICU-free and hospital-free days were comparable between rFVIIa and placebo for all comparisons.

Table 3. Mortality through Day 30 and Morbidity on Day 30 in Patients with Blunt or Penetrating Trauma – ITT Analysis Set

	Placebo	rFVIIa	
Blunt Trauma			
N	242	218	
Mortality			
# Dead through Day 30 (%)	26 (10.7)	24 (11.0)	
p-value for superiority			0.934
p-value for non-inferiority			0.372
OR (95% CI)			0.97 (0.53 - 1.80)
Morbidity			
# Morbidity on Day 30 (%)	23 (9.5)	19 (8.7)	
p-value for superiority			0.752
OR (95% CI)			0.90 (0.47 - 1.72)
Penetrating Trauma			
N	38	44	
Mortality			
# Dead through Day 30 (%)	5 (13.2)	8 (18.2)	
p-value for superiority			0.402
OR (95% CI)			1.76 (0.47 - 6.65)
Morbidity			
N	38	44	
# Morbidity on Day 30 (%)	0 (0.0)	1 (2.3)	
p-value for superiority			1.000
OR (95% CI)			NA

Odds ratio greater than 1.0 favors Placebo.
p-values are from logistic regression.
Patients without assessments at day 30 and not recorded as dead will be assumed alive at day 30.

Table 4. Total Number of Units of Blood Products Transfused from Time of First Dose through Hours 24 and 48 for Patients with Blunt Trauma – ITT Analysis Set

	Placebo	rFVIIa	p-value	(95% CI)
N	247	221		
Fresh Frozen Plasma				
Hour 24				
Number of transfused patients, N(%)	188 (76.1)	160 (72.4)		
Mean number of tranfusions(SD)	6.9 (8.62)	4.7 (6.38)	0.001	0 - 2
Hour 48				
Number of transfused patients, N(%)	195 (78.9)	166 (75.1)		
Mean number of tranfusions(SD)	8.0 (10.13)	5.3 (6.69)	0.001	0 - 2
Platelets				
Hour 24				
Number of transfused patients, N(%)	117 (47.4)	112 (50.7)		
Mean number of tranfusions(SD)	3.4 (6.99)	3.3 (8.38)	0.842	0 - 0
Hour 48				
Number of transfused patients, N(%)	124 (50.2)	117 (52.9)		
Mean number of tranfusions(SD)	3.9 (7.83)	3.7 (8.59)	0.948	0 - 0
Cryoprecipitate				
Hour 24				
Number of transfused patients, N(%)	41 (16.6)	34 (15.4)		
Mean number of tranfusions(SD)	1.3 (4.30)	0.9 (3.32)	0.661	0 - 0
Hour 48				
Number of transfused patients, N(%)	41 (16.6)	34 (15.4)		
Mean number of tranfusions(SD)	1.4 (4.54)	0.9 (3.32)	0.638	0 - 0
Red Blood Cells				
Hour 24				
Number of transfused patients, N(%)	222 (89.9)	184 (83.3)		
Mean number of tranfusions(SD)	8.1 (10.87)	6.9 (10.42)	0.038	0 - 2
Hour 48				
Number of transfused patients, N(%)	228 (92.3)	191 (86.4)		
Mean number of tranfusions(SD)	9.1 (11.27)	7.8 (10.60)	0.040	0 - 2
All Allogeneic transfusions				
Hour 24				
Number of transfused patients, N(%)	228 (92.3)	198 (89.6)		
Mean number of tranfusions(SD)	20.7 (25.68)	17.1 (26.78)	0.030	0 - 4
Hour 48				
Number of transfused patients, N(%)	231 (93.5)	201 (91.0)		
Mean number of tranfusions(SD)	23.5 (27.98)	19.0 (27.11)	0.036	0 - 5

p value based on Wilcoxon-Mann-Whitney test. 95% CI is based on the Hodges-Lehmann test.

Table 5. Total Number of Units of Blood Products Transfused from Time of First Dose through Hours 24 and 48 for Patients with Penetrating Trauma – ITT Analysis Set

	Placebo	rFVIIa	p-value	(95% CI)
N	40	46		
Fresh Frozen Plasma				
Hour 24				
Number of transfused patients, N(%)	33 (82.5)	29 (63.0)		
Mean number of tranfusions(SD)	5.7 (6.40)	3.8 (6.01)	0.035	0 - 3
Hour 48				
Number of transfused patients, N(%)	33 (82.5)	29 (63.0)		
Mean number of tranfusions(SD)	6.5 (7.63)	4.0 (6.18)	0.021	0 - 4
Platelets				
Hour 24				
Number of transfused patients, N(%)	21 (52.5)	15 (32.6)		
Mean number of tranfusions(SD)	2.5 (4.08)	1.6 (3.68)	0.076	0 - 1
Hour 48				
Number of transfused patients, N(%)	21 (52.5)	16 (34.8)		
Mean number of tranfusions(SD)	2.7 (4.10)	1.9 (3.93)	0.115	0 - 1
Cryoprecipitate				
Hour 24				
Number of transfused patients, N(%)	11 (27.5)	8 (17.4)		
Mean number of tranfusions(SD)	2.0 (4.75)	1.6 (4.08)	0.331	0 - 0
Hour 48				
Number of transfused patients, N(%)	11 (27.5)	8 (17.4)		
Mean number of tranfusions(SD)	2.0 (4.75)	1.6 (4.08)	0.331	0 - 0
Red Blood Cells				
Hour 24				
Number of transfused patients, N(%)	33 (82.5)	37 (80.4)		
Mean (SD)	6.2 (6.54)	4.5 (7.34)	0.109	0 – 4
Hour 48				
Number of transfused patients, N(%)	35 (87.5)	39 (84.8)		
Mean (SD)	6.8 (6.90)	5.0 (7.45)	0.107	0 - 4
All Allogeneic Transfusions				
Hour 24				
Number of transfused patients, N(%)	35 (87.5)	39 (84.8)		
Mean (SD)	16.8 (19.28)	11.2 (15.01)	0.088	0 - 9
Hour 48				
Number of transfused patients, N(%)	37 (92.5)	39 (84.8)		
Mean (SD)	18.4 (20.67)	12.2 (15.68)	0.062	0 - 10

p value based on Wilcoxon-Mann-Whitney test. 95% CI is based on the Hodges-Lehmann test.

Safety Results

- The safety analysis set comprised all randomised patients who received trial drug: 224 (rFVIIa) and 250 (placebo) among patients with blunt trauma, and 46 (rFVIIa) and 40 (placebo) among patients with penetrating trauma.
- Among patients with blunt trauma, the overall distribution of AEs and SAEs by organ class through Hour 48 were comparable between treatment groups. A total of 536 AEs were recorded in 78.6% of rFVIIa-treated patients and 678 AEs in 76.4% of placebo-treated patients. Serious adverse events were recorded in a slightly smaller proportion of rFVIIa-treated patients (65.6% [348 events]), compared with placebo-treated patients (70.8% [390 events]). The most frequently occurring SAEs were infections and infestations, respiratory, thoracic and mediastinal disorders and vascular disorders.
- Among patients with blunt trauma, MESIs occurred in a comparable proportion of rFVIIa-treated patients (39.7%

[133 events]) and placebo-treated patients (40.0% [160 events]). The most frequent MESIs were sepsis and all fatalities. Thromboembolic (TE) events occurred in a slightly larger proportion of rFVIIa-treated patients (16.1% patients, 16 arterial events, 29 venous events), compared with placebo-treated patients (13.2%, 11 arterial events, 24 venous events). Cerebral or cerebellar infarctions were the most frequent arterial events (4 [rFVIIa]) and 5 [placebo]). Apart from this, the distribution of arterial events was slightly different between groups. Deep vein thrombosis (DVT) was the most frequent venous events (14 [rFVIIa] and 14 [placebo]). Among rFVIIa-treated patients, five TE events were considered by the investigator to be probably related to the trial product, 24 events possibly related and 16 events unlikely related. All patients recovered from the five events probably related to trial product. Among placebo-treated patients, four events were considered to be probably related to the trial product, 22 events possibly related and nine events unlikely related. All patients recovered from the three events probably related to trial product.

- Among patients with penetrating trauma, the overall profile of AEs through Hour 48 was comparable between treatment groups.The numbers of patients who experienced SAEs or MESIs in this trauma category were too small for meaningful comparison. A total of 101 AEs were recorded through Hour 48 in 78.3% of rFVIIa-treated patients and 94 AEs in 77.5% placebo-treated patients. A total of 35 SAEs occurred in 39.1% of rFVIIa-treated, and 44 events in 50.0% of placebo-treated patients. Thromboembolic events occurred in a small proportion of patients in both treatment groups: 4.3% of patients (one arterial and one mixed event) (rFVIIa) and 10.0% (one arterial and four venous events) (placebo). Among rFVIIa-treated patients, the two TE events that occurred (arterial thrombosis limb and cerebral infarction) were considered to be possibly related to the trial product. Both patients recovered. Among placebo-treated patients, three events (2 deep vein thrombosis events and one pulmonary embolism event) were considered to be possibly related to the trial product. The patient who had the pulmonary embolism had a fatal outcome. The other patients recovered.
- Patients with blunt trauma had a similar 90-day mortality rate in both treatment groups: 13.4% (30 patients) in the rFVIIa group and 13.2% (33 patients) in the placebo group. Mortality among patients with penetrating trauma was too small for meaningful comparison: nine out of 46 patients in the rFVIIa group and five out of 40 patients in the placebo group.
- The proportions of patients with blunt or penetrating trauma who had Troponin I levels of > 1 (at Hours 24 and 48) or > 2 mcg/L (at Hour 48) were significantly higher in the rFVIIa-treated patients, compared with the placebo-treated patients ($p < 0.05$), although by 72 hours the proportions of patients with elevated Troponin I were again comparable in between rFVIIa and placebo. There appeared to be no clinical significance of elevated Troponin I levels.
- Mean baseline PT, aPTT and INR values in both rFVIIa and placebo treatment groups were comparable but elevated above the normal range among patients with blunt or penetrating trauma. Mean baseline fibrinogen levels in both treatment groups were comparable and within the normal range among patients with blunt or penetrating trauma.
- Mean FVII:a and FVII:C levels were elevated after rFVIIa administration among patients with blunt or penetrating trauma. Mean platelet counts were within normal range at baseline, but decreased to below normal range after dosing among patients with patients with blunt or penetrating trauma.

Conclusions

The haemostatic effect of rFVIIa in trauma patients was supported by a statistically significant reduction in the average transfusion requirements for RBC, FFP and total allogeneic blood. No benefit of rFVIIa was observed on mortality endpoints. There was a trend towards less MOF among patients with blunt trauma. Thromboembolic events occurred in a slightly larger group of rFVIIa-treated patients. There was a benefit-risk ratio consistent with the known properties of rFVIIa in critical bleeding.

The trial was conducted in accordance with the Declaration of Helsinki(2000) and ICH Good Clinical Practice (1996).