2 Synopsis

Trial Registration ID-number: NCT00123591	**EudraCT number:** 2004-000088-92
Title of Trial A Randomised, Double-Blind, Placebo-Controlled, Multi-centre, Dose Escalation Study to Evaluate the Safety and Preliminary Efficacy of Recombinant Factor VIIa (NovoSeven®/NiaStase®) in Subjects with Brain Contusions	
Investigators There was one principal investigator for each of the trial centres.	
Trial Sites Of a total of 38 initiated trial sites, there were 25 actively recruiting trial sites in the following countries (number of sites per country in parenthesis): Canada (4), Finland (1), Germany (5), India (2), Israel (3), Italy (4), Singapore (2), Spain (2), Switzerland (1), and Taiwan (1).	
Publications None.	
Trial Period 6 January 2005 to 12 May 2006.	**Development Phase** 2
Primary Objective: • To evaluate the safety of NovoSeven®/NiaStase® in patients with brain contusions. **Secondary Objective:** • To evaluate the preliminary efficacy of NovoSeven®/NiaStase® in preventing early haemorrhagic progression in contusive brain injury.	
Methodology This was a randomised, double-blind, multi-centre, placebo-controlled, dose escalation trial with five dose tiers (40, 80, 120, 160 and 200 µg/kg rFVIIa). In addition to standard therapy, patients with contusive brain injury admitted to hospital received a single intravenous injection of either active drug or placebo as soon as possible following the baseline CT scan, which was to be recorded no later than 6 hours after injury (no later than 4 hours after injury for the eight patients recruited before the implementation of protocol amendment no. 3). For patients recruited following implementation of protocol amendment no. 4, a repeat CT scan was obtained to serve as baseline CT scan in case of a delay of more than 2.5 hours from initial CT scan to trial drug administration, and trial drug was to be administered as soon as possible and no later than 30 minutes thereafter (except for German and Dutch trial sites, where patients were to be withdrawn from the trial when exceeding this 2.5-hour time window). In no case was trial drug to be administered later than 7 hours after injury (no later than 5 hours after injury for the eight patients recruited before the implementation of protocol amendment no. 3). A total of 24 patients were evenly randomised to either active drug or placebo in the first dose tier, while the subsequent dose tiers consisted of 18 patients randomised 2:1 to active drug versus placebo. Patients were monitored closely for 5 days to evaluate the safety and preliminary efficacy of the treatment regimen. CT scans were performed at baseline and at 24 and 72 hours after dosing. A follow-up consultation was conducted on Day 15 after trial product administration.	
Number of Subjects Planned and Analysed Planned: 96 patients (24 in the lowest dose tier and 18 in each of the following 4 dose tiers); Randomised and dosed: 97 patients; ITT and safety analysis sets: 97 patients; PP analysis set: 74 patients.	
Diagnosis and Main Criteria for Inclusion Adult patients with contusive brain injury confirmed by a CT scan within 4 hours of onset (within 6 hours of onset for patients recruited after the implementation of protocol amendment no. 3), which was to show intraparenchymal haemorrhage (one or more contusions) with a total minimum volume of ≥ 5 mL and at least one single intraparenchymal haemorrhage of ≥ 1 mL (for patients recruited after implementation of protocol amendment no. 3, the requirement was a total minimum volume of ≥ 2 mL).	
Test Product, Dose and Mode of Administration, Batch Number Activated recombinant human FVII (rFVIIa; NovoSeven®) was supplied by Novo Nordisk A/S, Denmark, as sterile, freeze-dried powder in single-use vials of 4.8 mg of rFVIIa to be reconstituted with sterile water for injection. The	

trial product was administered as a single intravenous bolus injection over 2 minutes.

Duration of Treatment

A single bolus dose was administered as soon as possible following the baseline computed tomography scan and no later than 7 hours after injury (no later than 5 hours after injury for patients recruited before the implementation of protocol amendment no. 3).

Reference Therapy, Dose and Mode of Administration, Batch Number

Trial product (placebo) was supplied by Novo Nordisk A/S, as sterile, freeze-dried powder in single-use vials of 4.8 mg to be reconstituted with sterile water for injection. The trial product was administered as a single intravenous bolus injection over 2 minutes.

Criteria for Evaluation – Efficacy

Haemorrhagic endpoints comprised change in intracerebral, subdural, epidural and oedema volumes from baseline to 24 and 72 hours after dosing. Clinical outcome endpoints comprised Barthel Index (BI) and the extended Glasgow Outcome Score (eGOS) at Day 15; changes in scores on the Glasgow Coma Scale and Neuroworsening endpoint measured over the duration of the trial; the proportion of patients with no or minimal deficit (Barthel Index = 95-100 and Extended Glasgow Outcome Score $\geq$ 7) at Day 15; the proportion of patients who were functionally independent (BI = 60-100 and eGOS $\geq$ 5) at Day 15; and hospitalisation parameters.

Criteria for Evaluation – Safety

Adverse events during the 15-day trial period, vital signs, electrocardiogram (ECG) findings, coagulation-related laboratory parameters (prothrombin time (PT)/international normalised ratio (INR), activated partial thromboplastin time (aPTT), prothrombin fragment 1+2 (F1+2), fibrinogen, D-dimer, antithrombin), troponin-I, plasmin α2-antiplasmin complex, glucose, and haematology parameters.

Statistical Methods

The primary safety endpoint of occurrence of SAEs within 15 days of dosing was analysed using Fisher's exact test. Cochran-Armitage test for trend was applied to evaluate whether there was an increasing risk of incurring SAEs with increasing dose. Mortality, non-serious adverse events as well as thromboembolic adverse events were analysed as for the primary endpoint. Results for the remaining safety endpoints were summarised descriptively.

The changes in haemorrhage volumes were explored separately for each type of haemorrhage by a generalised linear mixed model with subject and reader as random effects. Covariates included as fixed effects in the model comprised treatment group, baseline haemorrhage volume, time from injury to baseline CT scan, and time from CT scan to dosing. Barthel Index and changes in GCS score were analysed using the Wilcoxon rank sum test. Dead patients were assigned the worst possible score. The overall rating for eGOS was calculated according to the lowest outcome category indicated on the scale and summarised by treatment. Composite outcome categories were analysed by Fisher's exact test and Cochran-Armitage test for trend as appropriate.

The significance level was set to 5% and all tests were two-sided.

Demography of Trial Population

Pending

Efficacy Results

- Trends towards a reduction of change in ICH volume were observed with rFVIIa dosing at 24 and 72 hours after baseline (test for trend for percent change; p=0.0948 and p=0.0437, respectively). No consistent effect of rFVIIa treatment was demonstrated for the remaining haemorrhagic endpoints or for clinical outcome endpoints. Thus, no definite efficacy conclusions can be drawn from this trial.
- It should be noted that the primary objective of this trial was to evaluate safety of rFVIIa, and the trial was vastly underpowered with respect to demonstration of efficacy.

Safety Results

A total of 97 patients were included in the safety evaluation.

- The proportion of patients with SAEs occurring within the 15-day trial period (the primary endpoint) was identical when comparing rFVIIa dose groups combined against placebo. When considering individual dose groups, the highest incidence was observed in the highest dose level of 200 µg/kg rFVIIa, where 7 of 12 patients (58%) had an SAE. However, there were no noticeable differences between dose groups with respect to the distribution of SAEs or AEs within the different system organ classes and preferred terms.

- Twelve thromboembolic adverse events were recorded during the trial. Overall, thromboembolic events occurred in 13% of rFVIIa-dosed patients versus 6% of patients receiving placebo. No differences in the incidence of arterial thromboembolism were noted. Venous thromboembolic events occurred in 11% of patients receiving rFVIIa versus 3% of patients receiving placebo, of which clinically asymptomatic DVTs (only detected by protocol mandated ultrasound examination of lower extremities, a procedure that is not routinely performed in TBI patients) accounted for 6 of the 9 reported venous events reported for the total study population. DVTs were reported in 8% of patients receiving rFVIIa and in 3% of patients receiving placebo.
- Mortality rates were similar when comparing rFVIIa dose groups combined against placebo, although the highest mortality rate was observed in the highest dose tier of 200 µg/kg rFVIIa.
- No clinically significant changes in coagulation-related parameters were observed with rFVIIa dosing, and there were no indications of systemic activation of the coagulation cascade in the patients treated with rFVIIa. Furthermore, vital signs and haematological and blood biochemistry parameters including troponin-I did not raise safety concerns.
- In conclusion, no safety concerns were identified for the entire cohort of rFVIIa-dosed patients or for the individual dose tiers compared with placebo. A similar conclusion was reached by the independent data monitoring committee.

Conclusions

- No safety concerns were identified for the entire cohort of rFVIIa-dosed patients or for the individual dose tiers compared with placebo. A similar conclusion was reached by the independent data monitoring committee.
- Trends towards a reduction of change in ICH volume were observed with rFVIIa dosing at 24 and 72 hours after baseline. No consistent effect of rFVIIa treatment was demonstrated for the remaining haemorrhagic endpoints or for clinical outcome endpoints. Thus, no definite efficacy conclusions could be drawn from this safety trial, which was vastly underpowered with respect to demonstration of efficacy.

The trial was conducted in accordance with ICH Good Clinical Practice (May, 1996) and the Declaration of Helsinki (2002).