2 Synopsis

Trial Registration ID-number: NCT00127283	**IND Number:** 2004-004202-24 **EudraCT number**: 2004-004202-24
Title of Trial Randomised, Double-Blind, Placebo Controlled, Multi-Centre, Parallel Groups Confirmatory Efficacy and Safety Trial of Activated Recombinant Factor VII (NovoSeven®/Niastase®) in Acute Intracerebral Haemorrhage	
Investigators There was one principal investigator for each of the trial centres.	
Trial Sites Of a total of 164 initiated trial sites, there were 122 sites that randomised and dosed at least one patient. The country distribution was as follows (number of actively recruiting sites per country in parenthesis): Australia (3), Austria (2), Belgium (3), Brazil (2), Canada (12), China (3), Croatia (1), Denmark (3), Finland (4), France (4), Germany (8), Hong Kong (1), Israel (2), Italy (3), Netherlands (5), Norway (2), Singapore (2), Spain (5), Sweden (6), Taiwan (3), Thailand (1) and USA (47). In addition, 4 sites in USA randomised at least one patient, but trial drug was not administered.	
Publications None	
Trial Period 10 May 2005 to 30 January 2007	**Development Phase** 3a
Objectives *Primary Objective*: To evaluate the efficacy of rFVIIa (NovoSeven®/Niastase®) in reducing disability and improving clinical outcome by preventing early haematoma growth in patients with acute intracerebral haemorrhage (ICH). *Secondary Objective*: To evaluate the safety of rFVIIa (NovoSeven®/Niastase®) in reducing disability and improving clinical outcome by preventing early haematoma growth in patients with acute intracerebral haemorrhage (ICH).	
Methodology This was a randomised, double-blind, multi-centre, multi-national, placebo-controlled trial with 816 patients planned to be equally randomised to receive either 20 or 80 µg/kg rFVIIa or placebo. A baseline CT scan was to be performed within 3 hours after symptom onset to confirm the diagnosis of ICH, and trial product was to be administered as soon as possible and no later than 1 hour after this baseline scan. CT scans were repeated at 24 hours and 72 hours post-dose, and examinations and assessments of clinical outcome and neurological status were performed daily until Day 3. Follow-up examinations were conducted at discharge or at Day 15 after trial drug administration (whichever came first) as well as at Day 90. Adverse events were reported daily from the time of admission to hospital until discharge or until Day 90 (whichever came first), while serious adverse events were reported from the time of trial product administration until the End of Trial Form was completed. In addition to the internal Novo Nordisk Safety Committee, an external, independent Data Monitoring Committee (DMC) was constituted for the trial.	
Number of Subjects Planned and Analysed Planned: 816 patients (272 in each treatment group); Randomised: 841 patients (ITT analysis set); Dosed: 821 patients (safety analysis set). The PP analysis set comprised 778 patients.	
Diagnosis and Main Criteria for Inclusion Patients aged > 18 years of age (≥ 20 years of age in Taiwan) with spontaneous ICH diagnosed by a head CT scan performed within 3 hours of symptom onset.	
Test Product, Dose and Mode of Administration 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 dose was to be administered as soon as possible and no later than 1 hour after the baseline CT scan, which	

was to be recorded within 3 hours of symptom onset.

Reference Therapy, Dose and Mode of Administration

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

The primary efficacy variable was the modified Rankin Scale (mRS) for assessment of disability. Additional prioritised efficacy parameters comprised the Barthel Index for assessment of functional independence, changes in lesion volumes and mortality. National Institute of Health Stroke Scale (NIHSS), extended Glasgow Outcome Scale (eGOS), Quality of Life and hospitalisation parameters were included as parameters of secondary importance.

Criteria for Evaluation – Safety

Key safety criteria comprised adverse events until discharge or until Day 90, whichever came first, serious adverse events until the End of Trial Form was completed, and changes in coagulation-related parameters.

Statistical Methods

All analyses were pre-specified in the statistical analysis plan except where otherwise stated. For the primary efficacy analysis a one-sided test with a significance level of 2.5% was used. For all other efficacy endpoints, statistical tests were two-sided and the significance level was 5%.

Efficacy: The primary endpoint was poor outcome, which was defined as dead or severe disability (scores of 5-6) on the modified Rankin Scale (mRS) at Day 90. Parametric models applied for the clinical outcome endpoints included treatment group, age, gender, ICH volume at baseline and location of haemorrhage at baseline (infra-tentorial vs. supra-tentorial) and baseline clinical status as covariates. Modified Rankin scale and mortality endpoints were analysed by logistic regression models, whereas the Barthel Index, GCS, NIHSS and Quality of Life endpoints were analysed by analysis of variance (ANOVA). Hospitalisation parameters were analysed using the Wilcoxon rank sum test.

Parametric models applied for the haemorrhagic endpoints included treatment group, ICH volume at baseline, time from stroke to baseline CT scan and time from baseline CT to dosing as covariates. Haemorrhagic endpoints were analysed using a generalised linear mixed model. In addition to the above fixed effects, subject and reader were included as random effects.

Safety: A logistic regression analysis on thromboembolic events was performed to evaluate the effect of treatment and the following well established risk factors: age, gender, race (grouped as Asian, Black or African-American, and Other ethnicity), history of thromboembolism, and baseline NIHSS. In addition, the following exploratory covariates were considered: history of hypertension, history of diabetes, use of platelet aggregation inhibitors (incl NSAIDs) and baseline cholesterol level. Analyses for arterial and venous events were performed separately. To evaluate whether there was a temporal relationship between dosing and onset of thromboembolic adverse events, a time to event analysis was performed applying the Cox-regression model and evaluating the same covariates as above in a similar manner. Changes in coagulation parameters were compared between active dose groups and placebo using an ANOVA with treatment group as a factor and baseline measurement as a covariate. Exacerbation of brain oedema (oedema/ICH-volume ratio > 2.5) at 72 hours post-dose was analysed using the Fischer's Exact test.

Demography of Trial Population

Patient demographics were comparable across treatment groups. The mean age was 65.0 years, and 62% of patients were male. The majority (69%) of patients were white, while 9% were black or African American and 19% were Asian. No differences in disease characteristics were noted between treatment groups except that the proportion of patients presenting with intraventricular haemorrhage (IVH) appeared higher in the rFVIIa treatment groups relative to placebo (35% and 41% of patients receiving 20 and 80µg/kg rFVIIa, respectively, versus 29% of patients receiving placebo). Mean ICH volume was 23.3 mL. Haemorrhage was located in the deep gray matter for the majority (78%) of patients, and oedema was present at baseline in 95% of patients. The mean interval from ICH onset to baseline CT scan was 109.2 ± 38.6 minutes, the mean interval from baseline CT scan to treatment was 51.1 ± 17.4 minutes, and the mean time from ICH onset to dosing was 160.3 ± 36.6 minutes, with no noticeable differences between dose groups for these intervals.

Efficacy Results

A total of 841 patients were included in the intention-to-treat analysis set, of which 20 patients were randomised but withdrawn from the study before receiving trial drug. Results below pertain to the ITT analysis set.

- No effect of rFVIIa dosing was observed for the primary endpoint of poor outcome at Day 90, defined as dead or severe disability (scores of 5-6) on the modified Rankin Scale (mRS). Estimated odds ratios for the primary analysis were not in favour of active treatment (20 µg/kg rFVIIa group: 1.01; 80 µg/kg rFVIIa group: 1.40). Since the statistical test was one-sided and the trend was not in favour of active treatment, p-values were not applicable.
- Statistically significant improvements on the National Institute of Health Stroke Scale (NIHSS) were observed for the 80 µg/kg treatment group relative to placebo at Day 15 (p=0.0028) and at Day 90 (p=0.0234).
- No effect of rFVIIa dosing was evident for the remaining endpoints related to clinical outcome, quality of life or hospitalisation parameters.
- The estimated mean percent change in ICH volume from baseline to 24 hours was reduced from 25.8% in the placebo group to 11.3% in the 80 µg/kg rFVIIa group, which was highly statistically significant (p=0.0004). Analysis results on mean absolute change in ICH volume from baseline to 24 hours reflected the results obtained on the corresponding percent change endpoint. Dosing with 80 µg/kg rFVIIa limited haematoma expansion within 24 hours by 3.82 mL relative to placebo (mean model estimate), which was highly statistically significant (p=0.0091).
- The effect of 80 µg/kg rFVIIa on limiting ICH expansion within 24 hours translated into a borderline statistically significant reduction of percent change in total lesion volume (the sum of ICH, intraventricular haemorrhage (IVH) and oedema volumes) within 72 hours, with mean changes being 62.2% for placebo and 54.9% for 80 µg/kg rFVIIa (p=0.0523). When considering the corresponding absolute change, dosing with 80 µg/kg rFVIIa limited total lesion volume expansion within 72 hours by 6.66 mL relative to placebo (mean model estimate), which was borderline statistically significant (p=0.0621).
- As expected, ICH volumes tended to decrease across all treatment groups between 24 and 72 hours, as the haematoma will have started to dissolve to some extent within this time period. The effect of treatment on the tertiary endpoints of percent and absolute ICH volume change from baseline to 72 hours was consequently less prominent, but similar trends were observed as for the corresponding 24-hour endpoint.
- Trends on ICH volume and total lesion volume endpoints for the 20 µg/kg rFVIIa treatment group were towards reduced haematoma volumes, suggesting a dose-related effect of rFVIIa.
- A subset of patients was identified *post hoc*, excluding patients in whom trial drug intervention would be unlikely to succeed due to poor prognosis at baseline. Selection criteria for the identified sub-population comprised age ≤ 70 years, baseline ICH volume < 60 mL, baseline IVH volume < 5 mL and time from symptom onset to trial drug administration ≤ 2.5 hours. This limited the analysis set to a total of 160 patients. The estimated odds ratio for suffering a poor outcome, defined as dead or severe disability (scores of 5-6) on the mRS, was reduced to 0.28 in the 80 µg/kg rFVIIa group relative to placebo (p=0.0309; one-sided test). The identified sub-population was analysed with respect to the Barthel Index, the NIHSS and good outcome on mRS as well, which showed similar trends of improved clinical outcome with 80 µg/kg rFVIIa, with statistically significant improvements observed for the NIHSS at both Day 15 and Day 90 in the 80 µg/kg rFVIIa group. The improved clinical outcome with 80 µg/kg rFVIIa relative to placebo corresponded with a more pronounced haemostatic effect in the identified sub-population. The model-estimated absolute 24-hour ICH volume change relative to placebo went from a reduction of 3.82 mL in the 80 µg/kg rFVIIa group of the ITT analysis population to a corresponding reduction of 7.32 mL in the identified sub-population.

Safety Results

A total of 821 patients received trial drug and thus constitute the safety analysis set.

- A total of 117 thromboembolic events were recorded in 97 patients. Events were recorded in 11%, 11% and 13% of patients receiving placebo, 20 and 80 µg/kg rFVIIa, respectively, of which serious events accounted for 8%, 9% and 11% of events.
- Arterial thromboembolic events were reported for 5% of patients receiving placebo versus 6% and 10% of patients receiving 20 and 80 µg/kg rFVIIa, respectively. Logistic regression analysis indicated a statistically significantly increased risk of arterial thromboembolism with 80 µg/kg rFVIIa relative to placebo (OR=2.08; p=0.0363). With the exception of one event of retinal artery embolism, one event of renal artery thrombosis and one event of

intracardiac thrombus (all three events occurring in the 80 µg/kg rFVIIa treatment group), arterial thromboembolic events comprised myocardial infarctions (40 events in 39 patients) and cerebral infarctions (21 events in 20 patients).

- The incidence of adverse events of myocardial infarction was higher in the rFVIIa treatment groups (5% and 6% of patients receiving 20 and 80 µg/kg rFVIIa, respectively) relative to the placebo group (3% of patients), which was in accordance with ECG and troponin-I findings. The majority of patients recovered from the myocardial infarctions. Fatal myocardial infarctions occurred in one patient of the placebo group, two patients of the 20 µg/kg rFVIIa group and two patients of the 80 µg/kg rFVIIa group.
- A minor trend towards an increase in incidence of cerebral infarction was noted with rFVIIa dosing (2.3%, 1.5% and 3.4% of patients receiving placebo, 20 µg/kg rFVIIa and 80 µg/kg rFVIIa, respectively).
- A total of 53 venous thromboembolic events were recorded in 44 patients. Events were reported for 6% of patients receiving placebo versus 5% and 5% of patients receiving 20 and 80 µg/kg rFVIIa, respectively, with no differences between treatment groups.
- A total of 164 died. The ninety-day mortality rate was 19% with placebo versus 19% and 21% with 20 and 80 µg/kg rFVIIa, respectively.
- Except for the increase of arterial thromboembolic adverse events in patients receiving rFVIIa, no treatment-dependent patterns in the type and frequency of adverse events were apparent. Specifically, no increase in risk of hydrocephalus with rFVIIa dosing was observed.
- 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.
- An efficacy sub-population was identified *post hoc* with the aim of identifying a patient population in which trial drug intervention would be expected to contribute to an improved outcome. The incidences of the individual thromboembolic event types in this sub-group of patients were similar to those observed in the total safety analysis set, and the overall safety profile in this sub-group of patients may therefore be anticipated to be similar to the safety profile determined for the total safety set of 821 patients.

Conclusions

- Although statistically highly significant effects of rFVIIa on limiting haematoma expansion were demonstrated, this did not translate into overall improvements in clinical outcome for the total efficacy analysis set. Thus, estimated odds ratios for the primary endpoint analysis of poor outcome on the mRS at Day 90 were not in favour of active treatment.
- The incidence of arterial thromboembolic adverse events (primarily myocardial infarctions and ischaemic strokes) was statistically significantly higher with rFVIIa treatment compared with placebo. The difference was primarily accounted for by an increased incidence of myocardial infarctions in patients receiving rFVIIa, with a similar albeit minor trend observed for cerebral infarctions. No other safety issues were identified.
- A subset of 160 patients was identified *post hoc*, excluding patients in whom trial drug intervention would be unlikely to succeed due to poor prognosis at baseline. The estimated odds ratio for suffering a poor outcome on the mRS was reduced to 0.28 in the 80 µg/kg rFVIIa group relative to placebo (p=0.0309; one-sided test), and improvements were shown for the Barthel Index, the NIHSS and good outcome on mRS as well. The improved clinical outcome with 80 µg/kg rFVIIa relative to placebo corresponded with a more pronounced haemostatic effect in the identified sub-population. The safety profile in this subset of patients appeared similar to that of the total safety analysis set.

The trial was conducted in accordance with ICH Good Clinical Practice and the Declaration of Helsinki