2 Synopsis

Trial Registration ID-number: NCT00154427	**IND Number:** BB IND 12931 **EudraCT number:** 2004-000100-40
Title of Trial A multi-centre, randomised, double-blind, placebo-controlled, dose escalation trial on safety and efficacy of activated recombinant factor VII (rFVIIa/NovoSeven®) in the treatment of post-operative bleeding in patients following cardiac surgery requiring cardiopulmonary bypass	
Investigators There was one principal investigator for each trial site. Signatory investigator: Dr. [redacted]	
Trial Sites Of a total of 64 initiated trial sites, 30 sites randomised and dosed at least one patient. The country distribution was as follows (number of actively recruiting sites per country in parenthesis): Argentina (2), Brazil (1), Denmark (1), France (1), Germany (4), India (5), Italy (2), Malaysia (1), South Africa (2), Spain (3), Sweden (1), United Kingdom (4) and the United States (3).	
Publications None	
Trial Period 11 August 2004 to 29 November 2007	**Development Phase** 2
Objectives **Primary Objective:** To evaluate the safety of activated recombinant factor VII (rFVIIa) in the treatment of post-operative bleeding in patients following cardiac surgery requiring cardiopulmonary bypass (CPB). **Secondary Objective:** To evaluate the efficacy of rFVIIa in the treatment of post-operative bleeding in patients following cardiac surgery requiring CPB.	
Methodology This was a multi-centre, multi-national, randomised, double-blind, placebo-controlled, dose escalation trial of the safety and efficacy of rFVIIa in cardiac surgery. Eligible patients had undergone cardiac surgery requiring cardiopulmonary bypass (CPB) and had been admitted to post-operative care environment (e.g. Intensive Care Unit) for at least 30 minutes (stabilization period). Patients were randomised upon reaching a pre-specified bleeding rate, which was estimated based on drainage volume from drains placed in the cardio-thoracic cavity. Trial product was administrated as a single i.v. bolus injection as soon as possible after the subject became eligible. The first cohort (40 µg/kg rFVIIa) comprised 70 patients randomised 1:1 to active treatment or placebo. After completion of the original second cohort (80 µg/kg rFVIIa, 51 patients, randomisation ratio 2:1 active drug vs. placebo), the independent DMC recommended to duplicate cohort 2 by adding an additional 51 patients into cohort 2 to enable a more thorough safety evaluation at this dose level. The protocol was amended accordingly by adding an additional cohort, 2b, comprising 51 patients. The pre-specified randomisation ratio of 2:1 was retained, resulting in 68 patients receiving 80 µg/kg rFVIIa and 34 patients receiving placebo in cohort 2a and 2b combined. Due to evolution of medical practice during the nearly four-year period of patient enrolment, and at the recommendation of the Steering Committee, it was then decided not to initiate the originally planned third cohort (160 µg/kg rFVIIa). The patients were closely monitored for 5 days after trial product administration with an additional telephone follow-up approximately 30 days after trial product administration. An external, independent Data Monitoring Committee (DMC) was constituted for the trial.	
Number of Subjects Planned and Analysed Originally, 70 patients were planned in each of dose tiers 40, 80 and 160 µg/kg rFVIIa, but the protocol was subsequently amended to plan for 172 patients (70 in the first cohort and 51 in each of cohorts 2a and 2b). Randomised and dosed: 172 patients; safety and ITT analysis sets: 172 patients; PP analysis set: 84 patients; modified PP analysis set: 123 patients.	

Diagnosis and Main Criteria for Inclusion

Eligible patients had undergone cardiac surgery requiring cardiopulmonary bypass (CPB) and had been admitted to post-operative care environment (e.g. Intensive Care Unit) for at least 30 minutes (stabilization period). Patients were randomised upon reaching a pre-specified bleeding rate, which was estimated based on drainage volume from drains placed in the cardio-thoracic cavity

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. Batch numbers: NR40202, RR40249 and RR40386

Duration of Treatment

Single dose

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. Batch numbers: NR40041, RR40033 and RR40420

Criteria for Evaluation – Efficacy

Transfusion requirements, number of patients requiring transfusions, cardio-thoracic cavity drainage, time until drains placed in the cardio-thoracic cavity were removed, number of patients undergoing re-operation due to bleeding, and hospitalisation parameters (ventilator-free days, ICU-free days and hospital-free days).

Criteria for Evaluation – Safety

Incidence of critical serious adverse events (death, acute myocardial infarction (AMI), cerebral infarction, clinically symptomatic pulmonary embolism (PE), and other clinically symptomatic thrombotic events) within c30 days (primary endpoint), adverse events, mortality, laboratory parameters and vital signs.

Statistical Methods

The frequency of cSAEs (primary endpoint) was analyzed by logistic regression adjusting for the pre-specified variables of prior cardiac surgery, use of antifibrinolytic medication and treatment. Re-operation due to bleeding was analyzed using chi-square tests. Continuous efficacy endpoints (drainage rates, drainage volumes, transfusion volumes) were analyzed by analysis of covariance on ranks adjusting for the pre-specified variables of prior cardiac surgery, cardiopulmonary bypass time, use of antifibrinolytic medication, country and treatment. Analyses of drainage volumes and rates were also adjusted for pre-dosing drainage rate or pre-dosing volume, as appropriate. Data were transformed to ranks since they were not normally distributed and were substantially skewed. Categorical efficacy outcomes (percentage of subjects having transfusion, combined and by type) were analyzed by logistic regression adjusting for pre-specified variables of prior cardiac surgery, use of antifibrinolytics and treatment.

Demography of Trial Population

The mean age was 63.6 years, and 82% of patients were white. Patients were on average somewhat older and heavier in the 40 µg/kg rFVIIa group when comparing across treatment groups, and there was a higher proportion of females in the active dose groups relative to placebo. Consistent with the clinical setting, patients were on average hypothermic (mean temperature 35.6°C) and hypotensive (mean systolic and diastolic blood pressure 108.9 and 58.6 mmHg, respectively). A total of 31% of surgeries were urgent or emergency surgeries in the 40 µg/kg rFVIIa group, whereas such procedures comprised 18% and 13% of surgeries in the placebo group and 80 µg/kg rFVIIa group, respectively. Also, there was a trend towards more allogeneic transfusions prior to trial product administration being administered to patients of the 40 µg/kg rFVIIa dose group as compared with patients of the placebo group.

Efficacy Results

A total of 172 patients were included in the intention-to-treat analysis set to which the below results pertain.

- Median total transfusion volume after trial product administration as well as the proportion of patients requiring transfusion after trial product administration was significantly reduced with rFVIIa relative to placebo (see Table). Similar results were obtained for requirement for red blood cell transfusion. A minority of patients received platelets and fresh frozen plasma, for which trends towards a reduction of requirements in rFVIIa-dosed patients were noted as well.

- For cardio-thoracic cavity drainage, a statistically significant reduction across endpoints, which comprised drain rate (see Table), drain volume and drain ratio (ratio between the average drainage rate during the 4-hour period after versus before trial product administration), were observed for the 80 µg/kg rFVIIa group relative to placebo. Notably, the median drain rate within 4 hours of trial product administration was reduced by approximately 50% from 56.0 mL/hour in the placebo group to 26.7 mL/hour in the 80 µg/kg rFVIIa group, which was highly statistically significant (p=0.0005). Evaluation of the cumulative drainage volumes at 24 hours and 5 days post-dose indicated that the statistically significant difference for the 80 µg/kg rFVIIa treatment group was sustained in comparison to placebo treatment, implying duration of treatment benefit. No effect of 40 µg/kg rFVIIa was demonstrated.
- The proportion of patients who required re-operation due to bleeding was 25% with placebo versus 14.3% and 11.6% with 40 and 80 µg/kg rFVIIa, respectively, the comparison of 80 µg/kg rFVIIa versus placebo being statistically significant (p=0.0422).
- The time until drains placed in the cardio-thoracic cavity were removed was on average 2.6 days and did not differ noticeably between dose groups.
- No differences between treatment groups were noted for hospitalisation parameters comprising ventilator-free days within 5 days after dosing and ICU-free days and hospital-free days within 30 days after dosing.

Table: Key Efficacy Results

	Placebo	40 ug/kg rFVIIa	80 ug/kg rFVIIa
Median volume of Total Transfusions (mL)			
Within 4 Hours after dosing	211.0	0.0	0.0
P-value vs. Placebo		0.0688	0.6968
Within 24 Hours after dosing	600.0	552.0	280.0
P-value vs. Placebo		0.0280	0.0471
Within 5 days after dosing	825.0	640.6	500.0
P-value vs. Placebo		0.0442	0.0156
Patients Requiring any Transfusion (%)			
Within 4 Hours after dosing	51.5%	40.0%	39.1%
P-value vs. Placebo		0.2663	0.1902
Within 24 Hours after dosing	72.1%	60.0%	55.1%
P-value vs. Placebo		0.1479	0.0729
Within 5 days after dosing	89.7%	68.6%	73.9%
P-value vs. Placebo		0.0072	0.0351
Median Drain rate within 4 hours after dosing (mL/hour)			
Median	56.0	53.3	26.7
P-value vs. Placebo		0.1342	0.0005
Patients Requiring Re-operation due to Bleeding (%)			
Within 30 days after dosing	25.0%	14.3%	11.6%
P-value vs. Placebo		0.2089	0.0422

Safety Results

A total of 172 patients were randomised and received trial drug and thus constitute the safety analysis set.

- The primary endpoint of the trial was the incidence of critical serious adverse events (death, acute myocardial infarction (AMI), cerebral infarction, clinically symptomatic pulmonary embolism (PE), and other clinically symptomatic thrombotic events). Critical SAEs were reported for 7.4% of patients receiving placebo versus 14.3% and 11.6% of patients receiving 40 and 80 µg/kg rFVIIa, respectively. The critical SAEs of death, cerebral infarction and "other clinically symptomatic thrombotic events" occurred more frequently in patients receiving rFVIIa relative to placebo, whereas no events of acute myocardial infarction or clinically symptomatic pulmonary embolism were reported in the active treatment groups. The apparent increase in critical SAEs in the active dose

groups relative to placebo did however not reach statistical significance (40 µg/kg vs. placebo: p=0.2525; 80 µg/kg vs. placebo: p= 0.4269), although it should be noted that the lower than anticipated event rate did not provide adequate statistical power to detect such differences. Details of critical SAEs are tabulated below.

- A total of 8 thromboembolic events were reported. All of these events were serious adverse events and were categorised as critical SAEs. Thromboembolic adverse events were reported for 1.5% of patients receiving placebo versus 8.6% and 5.8% of patients receiving 40 and 80 µg/kg rFVIIa, respectively. Events deemed possibly or probably related to trial product by the investigator were recorded in the 40 µg/kg rFVIIa group (intestinal infarction and lacunar infarction, both possibly related) and in the 80 µg/kg rFVIIa group (cerebral infarction and ischaemic stroke, both possibly related).
- Fatal adverse events were reported for 5.9% of patients receiving placebo versus 11.4% and 8.7% of patients receiving 40 and 80 µg/kg rFVIIa, respectively. When considering the distribution of events across system organ classes and preferred terms, no major differences between treatment groups were noted. All fatal adverse events were judged by the investigator to be unlikely related to trial product, except for a fatal event of intestinal infarction recorded for a patient of the 40 µg/kg rFVIIa group, which was judged by the investigator to be possibly related to trial product.
- 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.

Table: Treatment Emergent Critical, Serious Adverse Events - Safety Analysis Set

Patient No.	Treatment	Age (Yrs)	Preferred Term	Latency (Days)*	Severity	Relation to Trial Product	Action	Outcome
[redacted]								

* Latency=time from trial product administration to onset of event.
** The event of myocardial infarction was upgraded by the sponsor from a non-serious to a serious adverse event. This occurred after unblinding of treatment allocation.
Recover.: Recovered

Conclusions

In this safety trial of rFVIIa in patients undergoing cardiac surgery requiring cardiopulmonary bypass, a numerical increase in the overall incidence of pre-defined critical, serious adverse events (death, acute myocardial infarction, cerebral infarction, clinically symptomatic pulmonary embolism, and other clinically symptomatic thrombotic events) was observed in the rFVIIa treatment groups relative to placebo. The odds ratio for the incidence of these events in either of the active dose groups (40 and 80 µg/kg rFVIIa) did not differ statistically significantly from placebo, although it should be noted that the lower than anticipated event rate did not provide adequate statistical power to detect such differences.

The trial was underpowered for demonstration of efficacy. Nevertheless, statistically significant reductions in transfusion requirement, in volume and rate of drainage from drains placed in the cardio-thoracic cavity and in the need for re-operation due to bleeding were observed after trial product administration for patients receiving rFVIIa relative to those receiving placebo.

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