

Safety and Feasibility of Recombinant Factor VIIa for Acute Intracerebral Hemorrhage

Stephan A. Mayer, MD; Nikolai C. Brun MD, PhD; Joseph Broderick, MD; Stephen Davis, MD; Michael N. Diringer, MD; Brett E. Skolnick, PhD; Thorsten Steiner, MD; for the Europe/AustralAsia NovoSeven ICH Trial Investigators

Background and Purpose—Hematoma growth occurs in 38% of intracerebral hemorrhage (ICH) patients scanned by computed tomography (CT) within 3 hours of onset. Activated recombinant factor VII (rFVIIa) promotes hemostasis at sites of vascular injury and may minimize hematoma growth after ICH.

Methods—In this randomized, double-blind, placebo-controlled, dose-escalation trial, 48 subjects with ICH diagnosed within 3 hours of onset were treated with placebo (n=12) or rFVIIa (10, 20, 40, 80, 120, or 160 $\mu\text{g}/\text{kg}$; n=6 per group). The primary endpoint was the frequency of adverse events (AEs). Safety assessments included serial electrocardiography (ECG), troponin I and coagulation testing, lower extremity Doppler ultrasonography, and calculation of edema:ICH volume ratios.

Results—Mean age was 61 years (range, 30 to 93) and 57% were male. At admission, mean National Institutes of Health Stroke Scale (NIHSS) score was 14 (range, 1 to 26), median Glasgow Coma Scale score was 14 (range, 6 to 15), and mean ICH volume was 21 mL (range, 1 to 151). Mean time from onset to treatment was 181 minutes (range, 120 to 265). Twelve serious AEs occurred, including 5 deaths (mortality 11%). Six AEs were considered possibly treatment-related, including rash, vomiting, fever, ECG T-wave inversion, and 2 cases of deep vein thrombosis (placebo and 20- $\mu\text{g}/\text{kg}$ groups). No myocardial ischemia, consumption coagulopathy, or dose-related increase in edema:ICH volume occurred.

Conclusion—This small phase II trial evaluated a wide range of rFVIIa doses in acute ICH and raised no major safety concerns. Larger studies are justified to determine whether rFVIIa can safely and effectively limit ICH growth. (*Stroke*. 2005;36:74-79.)

Key Words: cerebral hemorrhage ■ coagulation ■ emergency medical services ■ fibrinolysis ■ stroke

Intracerebral hemorrhage (ICH) is the deadliest, most disabling, and least treatable form of stroke. Approximately 40% of patients die within 1 month of ICH onset, and two-thirds of survivors never regain functional independence.¹ Although guidelines for supportive care exist,¹ there is currently no treatment that has been shown in a randomized controlled trial to improve outcome after ICH.

Hematoma volume is a critical determinant of mortality and functional outcome after ICH,^{2,3} and early hematoma growth may be an important cause of early neurological deterioration. Prospective and retrospective studies indicate that substantial hematoma enlargement occurs in up to 38% of ICH patients initially scanned within 3 hours of onset, and

in 16% of those scanned between 3 and 6 hours, even in the absence of coagulopathy.⁴⁻⁷ The only prospective study of this phenomenon revealed a >33% increase in ICH volume in 26% of patients at 1 hour, and in an additional 12% between 1 and 20 hours.⁴ Early hematoma growth appears to be a dynamic process, with continued bleeding or rebleeding occurring at multiple sites over several hours.⁸

Intervention with ultra-early hemostatic therapy in the emergency setting could potentially improve outcome after ICH by arresting ongoing bleeding and minimizing hematoma growth. Recombinant factor VIIa (rFVIIa) is currently approved to treat bleeding in hemophilia patients with inhibitors to factors VIII or IX, and is approved in Europe for the

Received July 6, 2004; accepted July 22, 2004.

From the Departments of Neurology and Neurosurgery (S.M.), Columbia University College of Physicians and Surgeons, New York, NY; Novo Nordisk A/S (N.B.), Bagsvaerd, Denmark; the University of Cincinnati Medical Center (J.B.), Cincinnati, Ohio; Royal Melbourne Hospital (S.D.), University of Melbourne, Melbourne, Australia; Washington University School of Medicine (M.D.), St. Louis, Mo; Novo Nordisk (B.S.), Princeton, NY; and the University of Heidelberg (T.S.), Heidelberg, Germany.

S.M. developed the original concept for this study and wrote the trial protocol, with input from the authors, who comprise the trial steering committee (SC). The SC was responsible for scientific supervision of the trial, had full access to the data, and takes responsibility for the integrity of the data and data analysis. The SC was responsible for the data analysis and interpretation and for drafting the manuscript. Before trial initiation, the sponsor (Novo Nordisk) agreed to present and publish the results regardless of outcome. All members of the SC received consulting fees as compensation for time devoted to the project, except N.B. and B.S., who are employees of Novo Nordisk. S.M., M.D., and T.S. have received speaking honoraria from Novo Nordisk.

Correspondence to Dr Stephan A. Mayer, Neurological Institute, 710 West 168th Street, Box 39, New York, NY 10032. E-mail sam14@columbia.edu
© 2004 American Heart Association, Inc.

Stroke is available at <http://www.strokeaha.org>

DOI: 10.1161/01.STR.0000149628.80251.b8

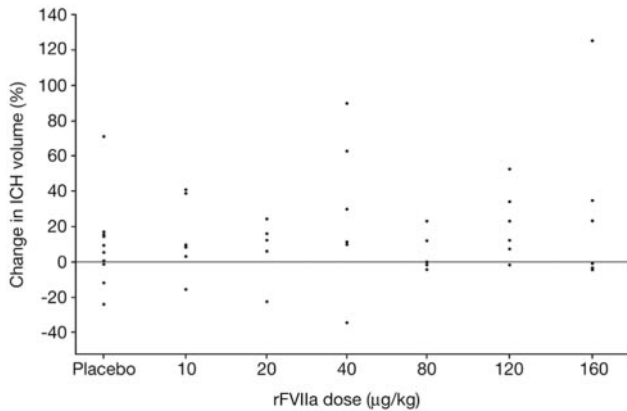


Figure 1. Percent change in ICH volume from baseline to 24 hours in individual patients, by treatment group. A dose-related treatment effect is not evident.

treatment of factor VII deficiency and Glanzmann thrombasthenia. After vascular damage and local initiation of the coagulation cascade, rFVIIa enhances thrombin generation on the surface of activated platelets, leading to the formation of a stable, lysis-resistant plug at the site of vessel injury.⁹ rFVIIa has been successfully used to control intracranial hemorrhage in patients with hemophilia or other coagulation disorders,^{10,11} and can arrest intraoperative bleeding and reverse coagulopathies in patients undergoing neurosurgical procedures.¹² rFVIIa has also been reported to prevent or minimize refractory bleeding in noncoagulopathic patients.^{13,14} Although thromboembolic complications related to rFVIIa administration have occurred, with >400 000 doses administered for a growing number of clinical uses, the frequency of serious adverse events (SAEs) remains <1%.¹⁵

We report data from a randomized, double-blind, placebo-controlled, dose-escalation study designed to evaluate the safety and feasibility of rFVIIa treatment for acute ICH.

Subjects and Methods

Subjects

Adult patients (18 years and older) with spontaneous ICH documented by computed tomography (CT) scan within 3 hours of

symptom onset were eligible for enrollment. Exclusion criteria included: deep coma (Glasgow Coma Scale [GCS] 3 to 5) at time of admission; surgical hematoma evacuation planned or performed within 24 hours of admission; secondary ICH related to aneurysm, arteriovenous malformations, trauma, tumor, infarction, dural sinus thrombosis, known oral anticoagulant use, coagulopathy, or thrombocytopenia; any history or acute evidence of thrombotic, hypercoagulable, or vaso-occlusive disease; acute sepsis or crush injury; pregnancy; known malignant disease or alcohol abuse; previous disability (baseline modified Rankin Scale [mRS] score >2); known or suspected allergy to the trial product; and participation in another trial.

Informed Consent

The study protocol was approved by local ethics committees in participating countries. Informed consent was obtained before any study-related activity. In accordance with local regulations, consent could be waived or obtained from a legally acceptable representative if the patient lacked capacity to provide consent. Patients were required to provide consent on regaining consciousness; those declining were withdrawn.

Study Design and Procedures

The study was conducted between August 2001 and October 2002 at 14 trial centers in Australia,² Germany,¹ Italy,¹ Singapore,³ Spain,⁴ Taiwan,² and the United Kingdom.¹ Forty-eight patients were enrolled in 6 sequential dose tiers (n=8 per tier) and randomly allocated to receive placebo or rFVIIa (NovoSeven; Novo Nordisk A/S, Bagsvaerd, Denmark). A randomization schedule was generated and as patients were recruited, they were allocated to the next available randomization number within the dose tier, which indicated whether the patient was to receive placebo or rFVIIa. Within each dose tier, 2 subjects received placebo and 6 received rFVIIa (10, 20, 40, 80, 120, or 160 µg/kg). On completion of each dose tier, enrollment was stopped until an independent data and safety monitoring board reviewed all SAEs, CT images, and other clinical and laboratory data, and approved progression to the next dose.

rFVIIa or placebo (a freeze-dried powder in single-use vials) was reconstituted with sterile water and administered as a single intravenous slow bolus injection within 1 hour of the baseline CT scan, and not later than 4 hours after symptom onset. Follow-up CT scans were performed 1 hour after the baseline scan, and 24 and 72 hours after dosing. Blood samples drawn at admission and 1 and 24 hours after dosing were centrally analyzed for coagulation parameters (International Normalized Ratio [INR], activated partial thromboplastin time [aPTT], D-dimers, antithrombin III [AT-III], fibrinogen, prothrombin fragments 1+2, and factor VII coagulant activity [FVII:C]) and standard hematology and blood chemistry measurements. Clinical

TABLE 1. Overview of Adverse Events

Dose (µg/kg)	No. of Pts	AEs	SAEs	DVT*	ECG Changes*	Excessive Brain Edema†	Deaths
Placebo	11	64	3	1	0	1	2
10	6	24	0	0	0	2	0
20	6	15	1	1	1	0	0
40	6	51	2	0	2	1	1
80	6	30	1	0	0	0	0
120	6	29	1	0	0	0	1
160	6	39	4	0	0	0	1
Total	47	252	12	2	3	4	5

AEs indicates adverse events; DVT, deep vein thrombosis; ECG, electrocardiography; SAEs, serious adverse events; No. of Pts, number of patients.

*Detected by routine screening at 24 or 72 hours (ECG) or 72 hours (lower extremity Doppler). ECG changes refers to abnormal and clinically significant findings.

†Defined as an edema:ICH volume ratio >2.5 at 72 hours.

TABLE 2. Thrombotic or Possibly Treatment-Related Adverse Events

Subject No.	Dose Group, $\mu\text{g}/\text{kg}$	Complication	Severity	Relationship to Trial Drug
102	Placebo	Popliteal vein DVT at 72 hours	Serious	Possible
1503	10	Pruritic rash	Mild	Possible
1103	20	Vomiting	Mild	Possible
2301	20	Fever	Mild	Possible
2501	20	ECG T wave inversion detected at 24 hours, CK-MB-negative	Moderate	Possible
2501	20	Peroneal vein DVT at 72 hours	Mild	Possible
1506	40	ECG T wave inversion detected at 24 and 72 hours, troponin I-negative	Moderate	Unlikely
2302	40	Rehospitalized for unstable angina 29 days after treatment	Serious	Unlikely

CK-MB indicates creatine kinase MB fraction; DVT, deep vein thrombosis; ECG, electrocardiogram; LBBB, left bundle branch block; LAD, left axis deviation; NR, not rated as an adverse event.

assessments were performed daily until day 5, at day 15 (or discharge if earlier), and at day 90. Neurological deterioration was assessed using the GCS and National Institute of Health Stroke Scale; day 15 and day 90 assessments included the mRS, Extended Glasgow Outcome Scale, and Barthel Index.

CT Image Analysis

CT data were transmitted to a centralized imaging laboratory (Bio-Imaging Technologies Inc) and analyzed in random sequence using Analyze software (Mayo Clinic) by 2 independent, neuroradiologists blinded to treatment. ICH, intraventricular hemorrhage (IVH), and edema volumes were calculated using a semi-automated process by tracing the perimeter of appropriate high- and low-attenuation zones and calculating lesion areas for each slice multiplied by slice thickness to yield lesion volumes. Edema volumes were calculated by subtracting ICH volume from the combined ICH plus edema volume.

Endpoints

The primary endpoint was the frequency of adverse events (AEs) that were possibly or probably related to treatment. AEs were assessed until day 15 or discharge if earlier, and SAEs until completion of the trial (day 90). Predefined safety endpoints included evidence of: (1) myocardial ischemia; (2) deep vein thrombosis (DVT) or pulmonary embolism (PE); (3) cerebral artery or vein thrombosis; (4) consumption coagulopathy; and (5) excessive or unusual perihematomal brain

edema (edema:ICH volume ratio >2.5 at 72 hours). Planned safety assessments included electrocardiography and measurements of serum troponin I levels at baseline and 24 hours, coagulation testing at baseline, 1 hour, and 24 hours, and lower extremity Doppler ultrasonography at 72 hours.

Secondary endpoints included percent and absolute changes in ICH, IVH, and total hemorrhage (ICH+IVH) volume between baseline and 24 hours; the proportion of patients with ICH growth ($>33\%$ or 12.5 mL increase from baseline); in-hospital neurological deterioration (decrease of ≥ 2 points in the GCS, or increase of ≥ 4 points in the National Institute of Health Stroke Scale) between day 0 and 5; and the proportion of patients who were dead, alive with minimal or no disability (Barthel Index, 95 to 100; Extended Glasgow Outcome Scale, 8; mRS, 0 to 2), or alive and functionally independent (Barthel Index, 60 to 100; Extended Glasgow Outcome Scale, 5 to 8; mRS, 0 to 3) at 90 days.

Statistical Analysis

Statistical analyses were performed according to the principle of intention-to-treat. The safety evaluation included all patients who received the trial product and did not withdraw consent. Interobserver reliability of ICH and edema volume measurements was assessed by calculating mean differences and intraclass correlation coefficients between the 2 blinded readers. Differences in ICH volume and coagulation parameters were compared between different rFVIIa dose groups and placebo using analysis of covariance (ANCOVA). Point estimates and 2-sided 95% confidence intervals for mean differences between the dose groups were calculated as appropriate. Significance was set at $P < 0.05$ for all analyses.

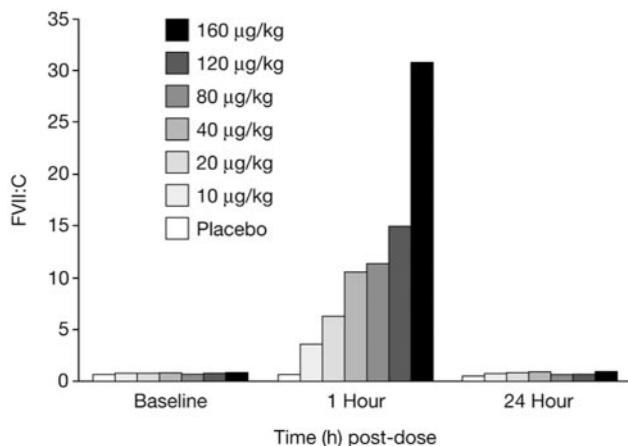


Figure 2. Mean factor VII:C activity at baseline, 1 and 24 hours after dosing, by treatment group. A dose-response relationship is evident ($P < 0.0005$ at 1 hour compared with placebo, ANCOVA). At 1 hour, between-group differences (U/mL) from placebo and were significant for the 80 (11.3; 95% CI, 4.1 to 18.5), 120 (12.5; 95% CI, 5.3 to 19.7), and 160 (30.5; 95% CI, 23.6 to 37.3) $\mu\text{g}/\text{kg}$ doses.

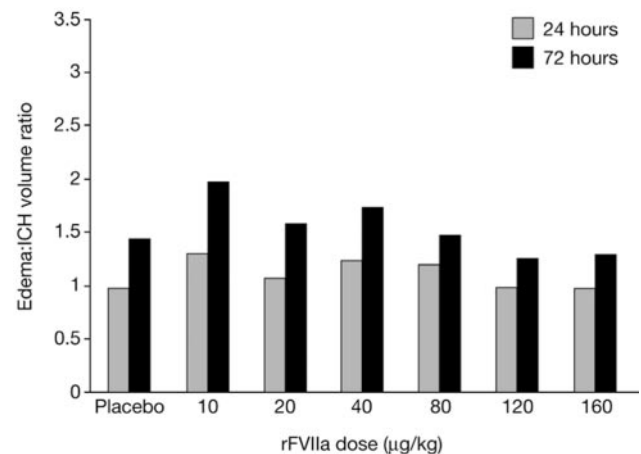


Figure 3. Edema-ICH volume ratios, by treatment group. No dose-response relationship is evident ($P = 0.90$ at 24 hours and $P = 0.79$ at 72 hours, compared with placebo, ANCOVA).

Results

Forty-eight patients were randomized to treatment. One patient originally included with waiver of informed consent subsequently withdrew and was excluded from the analysis. Mean age was 61 ± 15 years (range, 30 to 93); 57% were male; 60% were white; and 40% were Asian. At admission, mean National Institute of Health Stroke Scale score was 14 ± 7 (range, 1 to 26), median GCS score was 14 (range, 6 to 15), and mean blood pressure was 175/95 mm Hg.

Mean time from symptom onset to baseline CT was 112 ± 32 minutes (range, 57 to 173); in 57% (27/47) the baseline CT was performed within 2 hours of onset. Mean time from baseline CT to trial product administration was 69 ± 28 minutes (range, 17 to 166); the target interval of CT-to-treatment of <1 hour was attained in 49% (23/47) of cases. Mean time from ICH onset to treatment was 181 ± 36 minutes (range, 120 to 265); the target interval of treatment within 4 hours of onset was attained in 96% (45/47) of cases.

Mean ICH volume at baseline was 21 ± 24 mL (range, 1 to 151). Hemorrhages were located in the putamen (40% of patients), thalamus (32%), lobar regions (19%), pons or midbrain (6%), and cerebellum (2%). Twenty-one patients (45%) had IVH. Although there was considerable variability in baseline ICH volume between the treatment groups, these differences were not significant (Table I, available online only at <http://www.strokeaha.org>).

The overall frequency of ICH growth was 17% at 1 hour and 19% at 24 hours (Table II, available online only at <http://www.strokeaha.org>). Percent changes in ICH volume between baseline and 24 hours did not differ between groups (Figure 1). Analysis of total hemorrhage volumes (ICH+IVH) yielded similar results (data not shown). Overall, the neurological scales showed nonsignificant trends toward improvement between baseline and 90 days, with no significant differences between groups (Table II). Mean difference (and SD) of paired reader measurements was -1.57 mL (3.83) for all measurements (intraclass correlation coefficient, 0.99).

Forty-seven patients experienced 252 AEs, of which 12 were SAEs (Table 1). No noticeable differences in the types, frequency, or severity of AEs were observed between dose groups. The most common AEs were fever ($n=19$), headache ($n=14$), urinary tract infection ($n=12$), hypertension ($n=11$), and constipation ($n=11$). There were 5 thromboembolic or ischemic and 6 potentially treatment-related AEs (Table 2). Among the prespecified safety endpoints, there were 2 cases of DVT detected at 72 hours, and 2 instances of clinically significant new-onset electrocardiography changes without troponin I elevation; there were no instances of PE, cerebral infarction, venous thrombosis, consumption coagulopathy, or clinical deterioration caused by unusual or excessive brain edema.

Ten patients experienced 12 SAEs, including ICH-related neurological deterioration ($n=6$), subsequent detection of an arteriovenous malformation that required surgery, delayed unstable angina, pneumonia, urosepsis, dyspnea, and aforementioned DVT (each $n=1$). Two of the 11 placebo-treated patients and 3 of 36 rFVIIa-treated patients died during the 90-day trial period (11% mortality). All deaths occurred

within 7 days of admission; in each case, ICH was identified as the primary cause of death.

No significant differences in coagulation parameters were observed in patients given rFVIIa compared with placebo (data not shown), with 2 exceptions: at 1 hour, INR values were suppressed <0.6 at all doses ($P=0.003$, ANCOVA), and FVII:C activity showed an appropriate dose-related increase ($P<0.0005$, ANCOVA; Figure 2). These changes had fully resolved at 24 hours. There was no significant dose-related effect of rFVIIa on edema:ICH volume ratio (Figure 3). Four patients were rated as having excessive brain edema (edema:ICH ratio >2.5) at 72 hours; none of these cases was associated with symptomatic deterioration.

Discussion

In this study, we administered a wide range of doses of rFVIIa to 48 patients with acute ICH. Although rFVIIa has a good safety profile in patients with hemophilia and other bleeding disorders, experience with this agent in older, noncoagulopathic patients with risk factors for cardiovascular disease has been limited. Accordingly, our main concern was detection of treatment-related thromboembolic or coagulation-related AEs. rFVIIa was generally well-tolerated, and only 6 possible treatment-related AEs occurred, including 2 cases of DVT (in the placebo and 20- $\mu\text{g}/\text{kg}$ groups). A parallel study of 40 ICH patients that tested a lower range of doses has demonstrated a similar safety profile.¹⁶

For hemostatic therapy to effectively inhibit ongoing bleeding, early treatment is essential.⁸ In the prospective study by Brott et al that demonstrated a 38% frequency of ICH growth in patients initially scanned within 3 hours, enlargement had already occurred 1 hour after the baseline scan in two-thirds of cases.⁴ By extrapolating Brott's data, even if a hemostatic agent works perfectly, one might expect a growth rate as high as 26% with a mean CT-to-needle time of 60 minutes, or 17% if this interval is 30 minutes.⁸ In the current study, mean time from symptom onset to treatment was 181 minutes, and the mean "CT-to-needle" time was 69 minutes. In ongoing studies, we have modified the trial protocol to minimize unnecessary treatment delays related to the baseline assessment and randomization process.

A wide range of rFVIIa doses have been found to effectively inhibit bleeding in a variety of conditions, emphasizing the need for dose-finding studies in ICH.¹⁷ In this study, patients were enrolled in dose tiers in an ascending manner. The lowest dose in this study of 10 $\mu\text{g}/\text{kg}$ was used because the first signs of effect of rFVIIa on measured laboratory parameters occur at this dose in healthy volunteers.¹⁸ The highest dose used was 160 $\mu\text{g}/\text{kg}$ because this dose has been shown to be safe in healthy volunteers and hemophilic patients.^{17,18}

Only 6 of 252 AEs (2.4%) were considered possibly or probably treatment-related by the local investigator. Of these, 3 were potentially thromboembolic: 2 instances of DVT detected at 72 hours (placebo, 20 $\mu\text{g}/\text{kg}$), and 1 instance of T-wave inversion on electrocardiography at 24 hours, which did not meet enzyme criteria for myocardial infarction. There were 12 SAEs overall, including one of the aforementioned cases of DVT, and a patient in the 20- $\mu\text{g}/\text{kg}$ dose group in

whom unstable angina developed 29 days after randomization, which was judged as unlikely to be related to treatment. The other 10 SAEs were nonthromboembolic in nature, consistent with the natural history of ICH, and deemed unlikely to be related to treatment.

Thrombin has been hypothesized as edema-generating.¹⁹ To evaluate whether rFVIIa exacerbated perihematoma edema, edema-to-ICH volume ratios were compared between dose groups. Although visual inspection suggests a trend toward lower edema-to-ICH ratios at higher doses, we found no significant differences (Figure 3). We also found no evidence of subclinical activation of systemic coagulation, which is in accordance with findings in patients with hemophilia^{15,20} and in warfarin-treated normal volunteers.¹⁸

FVII:C activity, which measures in vivo biological activity of rFVIIa, showed a dose-response effect at 1 hour that completely resolved by 24 hours, consistent with the 2.6-hour half-life of rFVIIa.²¹ The magnitude of these elevations were equivalent to those observed in patients with hemophilia²⁰ and anticoagulated normal subjects¹⁸ given similar doses.

The overall frequency of ICH growth in our study, defined as a >33% or 12.5-mL increase from baseline, was 20% at 24 hours, which is lower than the 38% frequency found in Brott's prospective study. Two retrospective studies of ICH patients scanned within 3 hours of onset reported frequencies of ICH growth of 18% and 36%.^{5,7} The comparatively low rate of ICH growth observed in our study might be related to random sample variation, as suggested by the fact that ICH growth occurred in only 1 of 11 placebo-treated patients. There were no significant differences in percent change in ICH volume between placebo and the dose groups tested, but the number of patients in each group was too small to allow meaningful comparisons.

In summary, acute treatment of ICH patients with rFVIIa is feasible and in this small phase II study was safe across a wide range of doses. A large (n=400) multicenter trial of similar design comparing 40, 80, and 160 $\mu\text{g}/\text{kg}$ rFVIIa with placebo is currently underway to determine whether this treatment can effectively limit ICH growth. Given the current lack of effective medical and surgical therapies for ICH, our findings indicate that larger studies investigating the potential efficacy of rFVIIa for limiting early expansion are justified.

Appendix: Trial Personnel

Steering Committee

Stephan A. Mayer, MD, New York, NY (Chairman); Joseph Broderick, MD, Cincinnati, Ohio; Nikolai C. Brun, MD, PhD, Bagsvaerd, Denmark (non-voting); Steven Davis, MD, Melbourne, Australia; Michael N. Diringer, MD, St Louis, Mo; Brett E. Skolnick, PhD, Princeton, NJ (non-voting); Thorsten Steiner, MD, Heidelberg, Germany.

Sponsor

Novo Nordisk, A/S, Bagsvaerd, Denmark.

Statistician

Kamilla Begtrup, PhD, Bagsvaerd, Denmark.

Data and Safety Monitoring Board

Thomas G. Brott, MD, Jacksonville, Fla (Chairman); Kjell Asplund, Stockholm, Sweden; Thomas P. Bleck, MD, Charlottesville, Va; Miguel Escobar, Houston, Tex; Inge Scharer, Frankfurt, Germany.

Neuroradiologists

Robert Zimmerman, New York, NY; Joseph Maldjian, MD, Winston-Salem, NC.

Contract Research Organization

Quintiles Transnational, Inc, Arancha Lopez, Global Project Manager.

Site Investigators (number of subjects enrolled)

Dr Thorsten Steiner, Heidelberg, Germany (9); Dr Angel Chamorro, Barcelona, Spain (7); Dr Puay-Yong Ng, Singapore (6); Dr Timothy Lee, Singapore (6); Dr James Barrett, Merseyside, UK (3); Dr Shinn-Zong Lin, Taipei, Taiwan (3); Dr Geoffrey Donnan, Heidelberg West, Australia (3); Dr José Alvarez Sabin, Barcelona, Spain (2); Dr Stephen Davis, Melbourne, Australia (2); Dr Giuseppe Miceli, Pavila, Italy (1); Dr Antoni Davalos, Girona, Spain (1); Dr Yung-Kwang Tu, Taipei, Taiwan (1); Dr John Thomas, Singapore (1).

Acknowledgments

The authors thank Drs Ulla Hedner and Elisabeth Erhardtson for critical early input regarding trial design; Drs Robert Zimmerman and Joseph A. Maldjian for performing the radiological assessment; and Drs Thomas Brott and Thomas Bleck for providing key input at the inception of this trial. Funding for this trial was provided by Novo Nordisk A/S, Bagsvaerd, Denmark.

References

1. Broderick JP, Adams HP, Jr, Barsan W, Feinberg W, Feldmann E, Grotta J, Kase C, Krieger D, Mayberg M, Tilley B, Zabramski JM, Zuccarello M. Guidelines for the management of spontaneous intracerebral hemorrhage: a statement for healthcare professionals from a special writing group of the Stroke Council, Am Heart Association. *Stroke*. 1999;30:905-915.
2. Broderick JP, Brott TG, Duldner JE, Tomsick T, Huster G. Volume of intracerebral hemorrhage. A powerful and easy-to-use predictor of 30-day mortality. *Stroke*. 1993;24:987-993.
3. Hemphill JC 3rd, Bonovich DC, Besmertis L, Manley GT, Johnston SC. The ICH score: a simple, reliable grading scale for intracerebral hemorrhage. *Stroke*. 2001;32:891-897.
4. Brott T, Broderick J, Kothari R, Barsan W, Tomsick T, Sauerbeck L, Spilker J, Duldner J, Khoury J. Early hemorrhage growth in patients with intracerebral hemorrhage. *Stroke*. 1997;28:1-5.
5. Fujii Y, Tanaka R, Takeuchi S, Koike T, Minakawa T, Sasaki O. Hematoma enlargement in spontaneous intracerebral hemorrhage. *J Neurosurg*. 1994;80:51-57.
6. Fujitsu K, Muramoto M, Ikeda Y, Inada Y, Kim I, Kuwabara T. Indications for surgical treatment of putaminal hemorrhage. Comparative study based on serial CT and time-course analysis. *J Neurosurg*. 1990;73:518-525.
7. Kazui S, Naritomi H, Yamamoto H, Sawada T, Yamaguchi T. Enlargement of spontaneous intracerebral hemorrhage. Incidence and time course. *Stroke*. 1996;27:1783-1787.
8. Mayer SA. Ultra-early hemostatic therapy for intracerebral hemorrhage. *Stroke*. 2003;34:224-229.
9. Monroe DM, Hoffman M, Oliver JA, Roberts HR. Platelet activity of high-dose factor VIIa is independent of tissue factor. *Br J Haematol*. 1997;99:542-547.
10. Fewel ME, Park P. The emerging role of recombinant-activated factor VII in neurocritical care. *Neurocrit Care*. 2004;1:19-30.
11. Arkin S, Cooper HA, Hutter JJ, Miller S, Schmidt ML, Seibel NL, Shapiro A, Warrier I. Activated recombinant human coagulation factor VII therapy for intracranial hemorrhage in patients with hemophilia A or B with inhibitors. Results of the NovoSeven emergency-use program. *Haemostasis*. 1998;28:93-98.
12. Park P, Fewel ME, Garton HJ, Thompson BG, Hoff JT. Recombinant activated factor VII for the rapid correction of coagulopathy in nonhemophilic neurosurgical patients. *Neurosurgery*. 2003;53:34-39.
13. Friederich PW, Henny CP, Messelink EJ, Geerdink MG, Keller T, Kurth KH, Buller HR, Levi M. Effect of recombinant activated factor VII on perioperative blood loss in patients undergoing retropubic prostatectomy:

- a double-blind placebo-controlled randomised trial. *Lancet*. 2003;361:201–205.
14. O'Neill PA, Bluth M, Gloster ES, Wali D, Priovolos S, DiMaio TM, Essex DW, Catanese CA, Strauss RA. Successful use of recombinant activated factor VII for trauma-associated hemorrhage in a patient without preexisting coagulopathy. *J Trauma*. 2002;52:400–405.
 15. Roberts HR, Monroe DM 3rd, Hoffman M. Safety profile of recombinant factor VIIa. *Semin Hematol*. 2004;41(Suppl 1):101–108.
 16. Mayer SA, Brun N, Davis S, Broderick J, Diringer MN, Steiner T, for the US NovoSeven ICH Trial Investigators. Safety and preliminary efficacy of recombinant coagulation factor VIIa in acute intracerebral hemorrhage: US Phase 2A Study. *Stroke*. 2004;35:332 [Abstract].
 17. Hedner U. Dosing and monitoring NovoSeven treatment. *Haemostasis*. 1996;26(suppl 1):102–108.
 18. Erhardtsen E, Nony P, Dechavanne M, Ffrench P, Boissel JP, Hedner U. The effect of recombinant factor VIIa (NovoSeven) in healthy volunteers receiving acenocoumarol to an International Normalized Ratio above 2.0. *Blood Coagul Fibrinolysis*. 1998;9:741–748.
 19. Lee KR, Colon GP, Betz AL, Keep RF, Kim S, Hoff JT. Edema from intracerebral hemorrhage: the role of thrombin. *J Neurosurg*. 1996;84:91–96.
 20. Macik BG, Lindley CM, Lusher J, Sawyer WT, Bloom AL, Harrison JF, Baird-Cox K, Birch K, Glazer S, Roberts HR. Safety and initial clinical efficacy of three dose levels of recombinant activated factor VII (rFVIIa): results of a phase I study. *Blood Coagul Fibrinolysis*. 1993;4:521–527.
 21. Lindley CM, Sawyer WT, Macik BG, Lusher J, Harrison JF, Baird-Cox K, Birch K, Glazer S, Roberts HR. Pharmacokinetics and pharmacodynamics of recombinant factor VIIa. *Clin Pharmacol Ther*. 1994;55:638–648.