2 Synopsis

Trial Registration ID-number NCT00486278	**IND Number** – BB-IND#13,317 **EudraCT number** – 2006-004879-35 **Japanese Registration number** – JapicCTI-080612

Title of Trial

A multi-centre, randomised, double-blinded, controlled, dose-escalation trial on safety and efficacy of activated recombinant FVII analogue (NN1731) in the treatment of joint bleeds in congenital haemophilia patients with inhibitors

Investigator(s)

A primary investigator was appointed for each of the 40 sites initiated. Dr [redacted] was appointed signatory investigator and approved the clinical trial report on behalf on all investigators.

Trial Site(s)

A total of 40 sites were initiated in 18 countries. The patients randomised and exposed to trial product(s) were recruited from 28 sites in 13 countries (Brazil, Croatia, Hungary, Italy, Japan, Malaysia, Poland, South Africa, Turkey, Taiwan, Thailand, the U.K. and the U.S.).

Publications

None.

Trial Period	**Development Phase**
12 June 2007 to 18 June 2010 (prematurely terminated)	2

Objectives

The overall objective of the trial was to evaluate the safety and efficacy of the rFVIIa analogue for treatment of joint bleeds in patients with congenital haemophilia A or B with inhibitors.

Primary Objective

- to evaluate the safety of five escalating doses of the rFVIIa analogue in patients with haemophilia and inhibitors being treated for acute joint bleeds

Secondary Objectives

- to evaluate the efficacy of the rFVIIa analogue for treatment of acute joint bleeds in patients with haemophilia and inhibitors
- to evaluate the immunogenicity of the rFVIIa analogue
- to evaluate the pharmacokinetics of the rFVIIa analogue

Methodology

– This trial was designed as a global multi-centre, randomised, double-blinded, controlled, dose-escalation trial on safety and preliminary efficacy of the rFVIIa analogue in the treatment of acute joint bleeds in adolescent and adult patients with congenital haemophilia complicated by high responding inhibitors performed in a hospital setting.

– Patient eligibility was assessed after signing informed consent at a screening visit (Visit 1). Eligible patients received a patient number. When experiencing a qualifying joint bleed, the patient had to attend the clinic and receive the initial dose of trial product within 3 hours (+30 mins) of onset of bleed.

– Qualifying bleeds were randomised to receive either the rFVIIa analogue at the current lowest available dose level or rFVIIa as the active comparator. The randomisation ratio was 4:1 (rFVIIa analogue: rFVIIa) in all dose tiers. Patients stayed at the clinic 12 hours post–initial dose in order to monitor and evaluate the clinical response. After treatment in a dose tier, patients were to attend a follow-up visit at Day 7 at the investigator clinic to evaluate general safety parameters and to screen for the formation of antibodies towards trial product. The screening for formation of antibodies was repeated 4 weeks (28 days) following trial product administration. Finally, blood samples were obtained for antibody testing immediately prior to the first dose in each subsequent dose tier. Further, blood samples were obtained for safety analyses and evaluation of pharmacokinetic (PK) parameters (dose tiers 3, 4 and 5 only) immediately prior to and after administration of trial product.

– Sequential dose escalation followed an external independent data monitoring committee (DMC) review. The dose-escalation design allowed each patient to be randomised for more than one qualifying joint bleed, up to a maximum

of 5 qualifying joint bleeds. In such cases, the patient was to be randomised into different escalating dose tiers of the rFVIIa analogue. If a bleeding episode was controlled successfully with a single dose of trial product and no additional haemostatic treatment was administered 24 hours after that dose, the patient was eligible for treatment in a higher dose tier only if subsequent bleeds occurred in a different joint.
– A total of 25 bleeds were planned in each dose tier. Each dose tier initially included 10 bleeds to form the basis for a DMC safety evaluation before dose escalation. The dose tier was expanded to include an additional 15 bleeds in parallel with dose escalation: Hence, several dose tiers were open simultaneously for randomisation.

Number of Subjects Planned and Analysed

Patients
– A total of 75 patients were planned to be screened and enrolled into the trial.
– A total of 92 patients were screened.
– A total of 51 patients were randomised in the trial and exposed to trial products; including 46 patients exposed to the rFVIIa analogue.
– A total of 9 patients withdrew from the trial after randomisation. Hence, 42 randomised patients completed the trial.
- A total of 30 patients had assessment(s) of pharmacokinetic data.
A total of 11 adolescent patients (from 12 to 17 years of age) were exposed in the trial.

Bleeds
- A total of 25 bleeds were planned in each dose tier. After DMC evaluation of the first 20 bleeds in the first dose tier, it was decided to discontinue dose tier 1 as the data indicated that more than one dose was required in order to successfully control the bleeds (main efficacy endpoint). Hence, the number of bleeds included in dose tier 1 was 20. Dose tier 2 included the planned 25 bleeds. Because of slow recruitment of patients into the trial, dose tiers 3 and 4 were reduced from 25 to 20 bleeds each. The trial was discontinued prematurely; hence, 12 bleeds were included in dose tier 5.
In summary:
– A total of 97 bleeds were randomised in the trial.
– A total of 96 bleeds were treated in the trial and comprised the Safety Analysis Set.
– A total of 95 bleeds comprised the Full Analysis Set; 1 bleed was excluded due to nonfulfilment of criteria for qualifying bleed.
– Total of 42 bleeds treated in dose tiers 3, 4 or 5 were included in the PK Analysis Set.

Diagnosis and Main Criteria for Inclusion
Patients with haemophilia A or B with high-responding inhibitors (defined as current or historical titre>5 Bethesda units [BU]/mL and known antihuman FVIII or >IX anamnestic response) were eligible for inclusion in the trial. Adolescent patients (12–17 years of age) and adult patients (above 18 years of age) were eligible for inclusion.

Test Product, Dose and Mode of Administration, Batch Number
– A total of 5 dose levels/tiers of the rFVIIa analogue (5, 10, 20, 40 and 80 µg/kg body weight [bw]) were included. rFVIIa analogue was provided as a sterile freeze-dried powder in single-use vials of 1.2 mg (batch nos. SLDP015, TLDP007, VLDP032) to be reconstituted with 2.2 mL of sterile water for injection (batch nos. VR40201, VR40320, XR40135, SR40234, VR40026 [Japan], VR40212 [Japan], 404039 [U.S.]).
– The visual appearance of the freeze-dried rFVIIa analogue powder differs slightly from the powder of rFVIIa and placebo. Reconstitution of the trial product was thus to be handled by a third party not involved in any other trial activities in order to keep the blind towards patients, caregivers, investigators and trial personnel. The reconstituted preparation of the rFVIIa analogue is a colourless and clear/almost clear solution with pH = 6.0.
– The rFVIIa analogue was to be administered as a slow (at a rate not to exceed 1–2 mL per minute) i.v. bolus injection. Based on the different dose levels of the rFVIIa analogue, different volumes of the rFVIIa analogue were to be administered.
- The volume to be injected in the rFVIIa treatment arm was larger than the volume to be injected of the rFVIIa

analogue. To blind the treatment allocation, an injection of placebo was added in the rFVIIa analogue dose arm to attain equal volumes as used in the rFVIIa dose arm. Thus, for the rFVIIa analogue treatment arm two volumes were administered, of which one was the rFVIIa analogue trial product and the other placebo. After injection of the first volume/injection, the line was to be flushed.

Duration of Treatment

– Up to 3 doses of trial product were to be administered every 3 hours (+30 minutes) until bleeding was controlled. The initial dose of trial product was to be administered within 3 hours (+30 minutes) from the onset of the joint bleeding. The patient received up to three doses of trial product, separated by a dosing interval of 3 hours (+30 minutes). If haemostasis had not been achieved after three doses, the patient was to be treated with other haemostatic agents according to local standard of care. The trial product was administered in a hospital setting under direct supervision of medically qualified trial personnel at the clinic.

– Patients presenting with several qualifying joint bleeds during the trial period could be treated with the rFVIIa analogue in different dose tiers (for a maximum of five bleeding episodes) or with the active control (90 μg/kg rFVIIa). The patient was randomised in the lowest available dose tier and could only be treated once in each dose tier.

– The duration of patient participation in the trial was from 6 to 36 months, depending on the actual frequency of joint bleeds experienced in the entire trial population.

Reference Therapy, Dose and Mode of Administration, Batch Number

– The trial included an active comparator: rFVIIa at a standard dose regimen of 90 μg/kg bw administered every 3 hours.

– Activated recombinant FVII (rFVIIa) (batch nos. SR40453, TR40068, TR40294, TR40380, VR40250, VR40266, XR40104) and placebo (batch nos. RR40275, VR40623, VR40326) were provided as a sterile, freeze-dried powder in single-use vials of 1.2 mg to be reconstituted with 2.2 mL of sterile water for injection (batch nos. VR40201, VR40320, XR40135, SR40234, VR40026 [Japan], VR40212 [Japan], 404039 [U.S.]). The reconstituted preparation of rFVIIa is a colourless and clear/almost clear solution with pH = 5.5.

– The rFVIIa dose was split into two volumes matching the volumes of the rFVIIa analogue volume and placebo volume in the respective dose tiers. The product was to be administered as a slow (rate not to exceed 1–2 mL per minute) i.v. bolus injection. After injection of the first volume/injection, the line was to be flushed.

Criteria for Evaluation – Efficacy

Secondary Endpoints – Efficacy

- bleeding episode successfully controlled with one single dose of trial product (main efficacy endpoint)
- number of doses needed to control bleeding within 9 hours after first trial product administration or need of additional haemostatic medication within 9 hours after first trial product administration
- time to control of bleed after first trial product administration
- joint status/symptoms including pain, swelling and mobility
- time to pain relief after first trial product administration
- need for additional haemostatic agents within 24 hours after successful control of bleeding episode with trial product
- effective bleeding control at 9 hours and no additional haemostatic agents within 24 hours after successful control of bleeding episode

Secondary Endpoint – Pharmacokinetics

- Pharmacokinetic parameters based on FVIIa activity: AUC_{0-t}, AUC, MRT, $t_{½}$, CL and V_{ss}

Criteria for Evaluation – Safety

Primary Endpoints

- adverse events (AEs):
  - Non-serious AEs occurring from the first administration of trial product until 7 days after first trial product administration (treatment-emergent events) *and*

– treatment-emergent serious adverse events (SAEs) collected from the first administration of trial product to the end of patients' participation in the trial.

Secondary Endpoints

- immunogenicity:
  - rFVIIa analogue and/or rFVIIa antibody development *and*
  - rFVIIa analogue and/or rFVII inhibitor (i.e., neutralising antibodies) development
- biochemistry, haematology and coagulation-related parameters
- urinalysis, vital signs, physical examination and body measurements

Statistical Methods

Analysis Sets

- All 51 patients exposed to at least one dose of trial product were included in the Safety Analysis Set.
- The Full Analysis Set included 50 treated patients with available data (on efficacy variables) after administration of trial product.
- The PK Analysis Set included all randomised patients with pharmacokinetic assessments in tiers 3–5 and who completed the trial without violating the protocol in a manner judged to affect the pharmacokinetic endpoints.

Primary Endpoint – Safety

- Treatment-emergent events were presented in total and by category (serious/non-serious), severity (mild, moderate and severe), and causality (possibly or probably related as judged by the investigator), and were summarised by treatment group, displaying the number of events and the number and percent of patients experiencing the event, within system organ class, and MedDRA preferred term. In addition, MESIs and thromboembolic events were summarised separately.
- A total of adverse events including and bleeds treated with the rFVIIa analogue was presented, based on the total number of bleeding episodes treated with the rFVIIa analogue. For each individual dose of the rFVIIa analogue, the number of patients is equal to the number of bleeding episodes, but it is possible that the same patient received rFVIIa more than once. For that reason the calculation of rates for the rFVIIa group are based on number of treated bleeding episodes.

Secondary Endpoints – Safety

- Immunogenicity: In cases of any antibodies or inhibitors development in patients included in the Safety Analysis Set, a point estimate of the frequency of antibody development and of inhibitor development were to be presented for each rFVIIa analogue dose level and for rFVIIa, respectively, together with a corresponding 95% confidence interval. In cases of no antibody/inhibitor development, point estimates and confidence intervals for each dose were not to be provided.
- Biochemistry, haematology, Troponin I, coagulation factors and coagulation-related parameters: Quantitative laboratory parameters were summarised by treatment and time-point. Baseline was defined as the last measurement before the initial administration of the trial product. For assessments after baseline where repeated assessments of laboratory data were performed, the original value was used for summary statistics except in cases where a decision was made (based on a reasonable rationale) to exclude the original value from the calculations. Qualitative parameters were summarised by treatment and time-point. All laboratory parameters were listed individually by treatment, patient ID and time-point. Quantitative parameters outside the reference range were flagged.
- Urinalysis: Urinalysis parameters were summarised by treatment and time-point and listed individually by treatment, patient ID and time-point.
- Vital signs: Vital sign parameters were summarised by treatment and time-point. The parameters were listed individually by dose level, patient ID and time-point. Quantitative parameters outside reference range were flagged.
- Physical Examination and Body Measurements: Physical examination findings were summarised by treatment, body system and time-point. Furthermore, data listing of individual abnormal physical examination findings were made. Body measurements were individually listed and summarised by treatment and time-point.

Secondary Endpoints – Pharmacokinetics

- Blood samples for assessment of pharmacokinetic endpoints were drawn in a bleeding state pre-dose and at regular intervals up to 12 hours post-dose. Start time of administration of initial dose was set as time-point = 0.
- The derived pharmacokinetic parameters were based on available rFVIIa activity data up to and including the 3 hour sample post-dose. Standard pharmacokinetic parameters (AUC_{0-t}, $t_{½}$, AUC, CL, MRT and V_{ss}) were calculated using non-compartmental methods.
- All pharmacokinetic parameters were listed individually and summarised for the three rFVIIa analogue dose-level groups and the rFVIIa treatment group.
- Dose linearity over dose tiers was evaluated by regression analyses of log-transformed AUC_{0-t} and $t_{½}$ using log dose as a covariate. For AUC_{0-t} dose linearity means a slope of 1, while for $t_{½}$ dose linearity means a slope of 0. Dose linearity was also evaluated based on log dose of di-sialylated rFVIIa analogue.

Secondary Endpoints – Efficacy

- All efficacy endpoints were summarised and listed by dose.
- The effect of rFVIIa was summarised by dose tier, in order to evaluate any dose-tier effect. Any possible dose tier effect apart from a linear trend over time was evaluated.
- The primary model was a logistic regression of success after one dose of trial product with treatment (90 µg/kg rFVIIa, 5 µg/kg rFVIIa analogue, 10 µg/kg rFVIIa analogue, 20 µg/kg rFVIIa analogue, 40 µg/kg rFVIIa analogue, 80 µg/kg rFVIIa analogue,) as a factor and with target joint (yes/no) and time since trial start (i.e., first patient first visit [FPFV]) as covariates.
- The treatment differences between each dose of the rFVIIa analogue and rFVIIa dose were estimated and presented with p-values and 95% confidence intervals. Logistic regression analysis would not be able to estimate differences between groups where one or both had 100% response rate. For that reason only p-values were presented for endpoints where it was expected that some treatment groups would achieve 100% success and they were derived from a simpler and more robust Fishers exact test. This applies to all other endpoints than 'success with 1 dose', 'time to control of bleeding episode' and 'time to pain relief'..
- The main efficacy endpoint was examined for trends over dose tiers (for bleeds treated with the rFVIIa analogue) with respect to age, bleeding site and severity; cause of bleed;, time from onset of bleed to initial dose; and historical FVIII/IX inhibitor level.
- All efficacy endpoints, except endpoints relating to pain, swelling or range of motion, were also analysed and summarised for the subgroup of target joint bleeds.

Demography of Trial Population

- Fifty-one (51) male patients with haemophilia A or B and inhibitors from 13 countries were exposed to trial product.
- Overall, no clinically relevant differences (i.e., differences judged to have an impact on the results and conclusions of the trial) in demography and baseline characteristics between the rFVIIa analogue and rFVIIa or between dose levels of the rFVIIa analogue were apparent.
- All patients were male; the age at screening ranged from 12 to 69 years of age. A total of 11 adolescent patients (below age 18) were included in the trial.
- The majority of patients had haemophilia A, with 3 of 46 patients treated with the rFVIIa analogue having haemophilia B. None of the bleeds treated with rFVIIa occurred in patients with haemophilia B.
- During the trial, a total of 96 bleeds were dosed with trial product, 77 bleeds were treated with the rFVIIa analogue, and 19 bleeds were treated with rFVIIa. Nine of 46 patients (19.6%) treated with the rFVIIa analogue were adolescent patients, and 3 of 17 patients (17.6%) treated with rFVIIa were adolescents.
- The pre-dose bleeding symptoms including swelling, pain and loss of range of motion were more severe for bleeds treated with rFVIIa as compared with rFVIIa analogue–treated bleeds. Consequently, more patients had bleeds with higher total baseline scores in the rFVIIa treatment group as compared with bleeds treated in the rFVIIa analogue groups.
- The proportion of target joint bleeds (defined as joints with 3 or more bleeds in the past 6 months) appeared to be higher in bleeds treated with the rFVIIa analogue (49.4%) as compared with rFVIIa-treated bleeds (31.6%).

Pharmacokinetic and Efficacy Results

Pharmacokinetic Profile

- The single-dose pharmacokinetic profile of 20–80 µg/kg rFVIIa analogue observed in actively bleeding patients with haemophilia confirmed the pharmacokinetic profile of the rFVIIa analogue seen in healthy subjects.
- After the end of the rFVIIa analogue infusion, the FVII activity declined in an exponential way with a tendency to a bi-exponential decay pattern.
- A 3–4 times higher peak activity was seen for 80 µg/kg rFVIIa analogue as compared with 90 µg/kg rFVIIa.
- At 1 hour post-injection of trial product the mean plasma activities of the rFVIIa analogue were below the levels obtained after rFVIIa administration.
- Dose–proportionality was confirmed (i.e., no statistical significant deviation from proportionality was observed) in the dose interval 20–80 µg/kg of the rFVIIa analogue.

Efficacy

- The efficacy of rFVIIa was similar to that observed and reported in clinical trials and in practice.
- The majority of joint bleeds were treated successfully with 1–3 doses of 5–80 µg/kg rFVIIa analogue.
- The efficacy of doses of 20–80 µg/kg of the rFVIIa analogue were numerically better than 90 µg/kg rFVIIa. Overall, 98% (41/42) of the joint bleeds were controlled successfully with the rFVIIa analogue in a combined evaluation of 20–80 µg/kg dose groups compared with 90% (17/19) of bleeds treated with rFVIIa (90 µg/kg). This corresponds to a 5–fold reduction in frequency of treatment failures with the rFVIIa analogue (20–80 µg/kg) as compared with rFVIIa (90 µg/kg). The dose regimen of 1–3 doses of 80 µg/kg of the rFVIIa analogue appeared to have the highest efficacy as evaluated by efficacy of a single or 2 doses, number of treatment failures and sustained control and supported by a high frequency of patients with a normalisation of aPTT levels post-dose.
- Please note that due to the small sample size, the efficacy of the rFVIIa analogue would need to be verified in a larger confirmatory trial.

Treatment Efficacy as Evaluated by Number of Doses and Need of Additional Haemostatic Medication Administered to Control Bleeding Episode within 9 Hours from Start of Treatment– Full Analysis Set

	rFVIIa analogue					rFVIIa
	5 µg/kg	10 µg/kg	20 µg/kg	40 µg/kg	80 µg/kg	
Total bleeds	15	19	16	16	10	19
Treatment successes[a]	12 (80%)	16 (84.2%)	16 (100%)	15 (93.8%)	10 (100%)	17 (89.5%)
Treatment failures[b]	3 (20%)	3 (15.8%)	0 (0.0%)	1 (6.3%)	0 (0.0%)	2 (10.5%)
Bleeds controlled with a single dose	3 (20%)	3 (15.8%)	2 (12.5%)	5 (31.3%)	4 (40.0%)	6 (31.6%)
Bleeds controlled with 2 doses	5 (33.3%)	9 (47.4%)	7 (43.8%)	6 (37.5%)	4 (40.0%)	4 (21.1%)
Bleeds controlled with 3 doses	4 (26.7%)	4 (21.1%)	7 (43.8%)	4 (25.0%)	2 (20.0%)	7 (36.8%)

a: bleeds successfully controlled with 1–3 doses of trial product
b: additional haemostatic medication administered to obtain bleeding control

Safety Results

Exposure

- A total of 51 patients received at least one dose of trial product(s); including 46 patients exposed to the rFVIIa analogue.
- Approximately half of the patients (47.1%) were treated for one qualifying bleed (i.e., in one dose tier during the trial). A total of 15 patients (29.4%) were included in 2 dose tiers, 7 (13.7%) in 3 dose tiers, 4 (7.8%) in 4 dose tiers, and 1 patient (2%) was treated in all dose tiers. The mean number of doses received was 4.02, ranging from 1 dose to 15 doses.

- A total of 17 patients were randomised to receive 90 µg/kg rFVIIa during the trial. The majority of patients randomised to 90 µg/kg rFVIIa received rFVIIa in one dose tier; 2 patients were randomised to rFVIIa in 2 dose tiers. The total number of rFVIIa doses administered during the trial ranged from 1 to 6, with a mean of 2.4 doses (excluding rFVIIa administered as additional haemostatic medication). Total exposure to rFVIIa (excluding rFVIIa administered as additional haemostatic medication) ranged from 85 µg/kg bw to 528 µg/kg bw with a mean of 215 µg/kg bw.
- A total of 46 patients were randomised to receive the rFVIIa analogue. Approximately half (54.3%) of the patients exposed to the rFVIIa analogue received the rFVIIa analogue in one dose tier; 13 (28.3%) received the rFVIIa analogue in 2 dose tiers; 7 (15.2%) in 3 dose tiers, and 1 patient received the rFVIIa analogue in all dose tiers. The mean total number of rFVIIa analogue doses received during the trial was 3.6, ranging from 1 dose to 15 doses. The mean total rFVIIa analogue dose received during the trial was 86 µg/kg ranging from 5 µg/kg bw to 459 µg/kg bw.

Safety Profile

- Overall, the rFVIIa analogue was safe and well tolerated, with a low frequency of adverse events in all dose groups (5–80 µg/kg).

Overview of All Treatment-emergent Adverse Events – Safety Analysis Set

	rFVIIa analogue, N (%) E						rFVIIa N (%) E
	5 µg/kg	10 µg/kg	20 µg/kg	40 µg/kg	80 µg/kg	Total	
Total bleeds	16	19	16	16	10	77	19
Adverse events	5 (50 %) 10	5 (26.3%) 8	5 (25 %) 5	3 (18.8%) 5	0 (0%) 0	20 (26 %) 28	10 (52.6%) 11
Serious adverse events	2 (12.5%) 3	3 (15.8%) 5	2 (12.5%) 2	2 (12,5%) 2	0 (0%) 0	9 (11.7%) 12	2 (10.5%) 3
Adverse events with onset within 7 days post-dose	6 (37.5%) 7	3 (15.8%) 3	3 (18.8%) 3	1 (6.3%) 3	0 (0%) 0	13 (16.9%) 16	8 (42.1%) 8
Possibly/probably related adverse events	3 (18.8%) 3	0 (0%) 0	0 (0%) 0	0 (0%) 0	0 (0%) 0	3 (3.9%) 3	1 (5.3%) 1
Adverse events leading to withdrawal	3 (18.8%) 3	1 (5.3%) 1	0 (0%) 0	0 (0%) 0	0 (0%) 0	4 (5.2%) 4	1 (5.3%) 1

N = number of bleeds with adverse event, % = proportion of bleeds with adverse event, E = number of adverse events.
Treatment-emergent non-serious adverse events were defined as events occurring from initial dose of trial product (for treatment of bleed) until 7 days after initial dose.
Treatment-emergent serious adverse events were defined as all events collected from the first administration of trial product to the end of patients' participation in the trial.

- The reported frequency of adverse events in the rFVIIa analogue–treatment groups was lower than the frequency in the rFVIIa group(s).
- A few serious adverse events were reported in patients exposed to trial product. All serious adverse events had an onset more than 2 weeks after treatment with trial product, and were evaluated as not related to the trial product as judged by the investigator and sponsor.
- No antibody formation was detected in any patient exposed to trial product.
- No safety signals were revealed by any of the laboratory safety parameters.
- Post-dose levels of coagulation-related parameters showed a strong and rapid effect of the rFVIIa analogue on the coagulation system. When evaluating the effect of rFVIIa analogue and rFVIIa on reducing the clotting time in an aPTT assay, a dose-dependent reduction of the aPTT was observed with increasing doses of the rFVIIa analogue. In addition, the frequency of bleeds where a normalisation of aPTT values were obtained post-dose appear to increase with increasing dose level of the rFVIIa analogue (20 µg/kg rFVIIa analogue: 4/16 bleeds; 40 µg/kg rFVIIa analogue: 9/16 bleeds; 80 µg/kg rFVIIa analogue: 8/10 bleeds). No normalisation of aPTT values were recorded in bleeds treated with 5 and 10 µg/kg rFVIIa analogue or 90 µg/kg rFVIIa.

Conclusions

- This trial is the largest prospective, randomised, double-blind actively controlled clinical trial of recombinant bypassing agents ever conducted in actively bleeding haemophilia patients with inhibitors.
- The rFVIIa analogue was well tolerated, with no safety issues observed at any dose levels. In particular, no antibodies were detected in any exposed patient.
- The results confirm the pharmacokinetic profile of the rFVIIa analogue seen in healthy subjects.
- The trial showed clinical proof-of-concept by demonstrating that the rFVIIa analogue was safe and effective in treating joint bleeds and providing sustaining bleed control in patients with haemophilia and inhibitors.
- A high efficacy rate of 1–3 doses of 5–80 µg/kg rFVIIa analogue in controlling acute joint bleeds in patients with haemophilia A or B and inhibitors was seen. The efficacy of dose regimens of 1–3 doses of 20–80 µg/kg of the rFVIIa analogue were generally numerically better than the dose regimen of 1–3 doses of 90 µg/kg rFVIIa. The dose regimen of 1–3 doses of 80 µg/kg of the rFVIIa analogue appeared to have the highest efficacy as evaluated by efficacy of a single or 2 doses, number of treatment failures and sustained control. The efficacy of the rFVIIa analogue would need to be verified in a larger confirmatory trial. The efficacy of the 80 µg/kg rFVIIa analogue dose regimen observed in this trial was high. The high efficacy was furthermore supported by a post-dose normalisation of aPTT in 8 of 10 patients treated with 80 µg/kg rFVIIa analogue.

The trial was conducted in accordance with the Declaration of Helsinki (World Medical Association. Declaration of Helsinki. Ethical Principles for Medical Research Involving Human Subjects. 52nd WMA General Assembly, Edinburgh, Scotland, October 2000. Last amended with Note of Clarification on Paragraph 29 by the WMA General Assembly, Washington 2002, and Note of Clarification on Paragraph 30 by the WMA General assembly, Tokyo 2004) and ICH Good Clinical Practice (refer to applicable edition).

The results presented reflect data available in the clinical database as of 4-Aug-2010 *(date of database lock)*.