2 Synopsis

Trial Registration ID-number: NCT00951405	**IND Number:** 13990 **EudraCT number:** 2008-006424-54 **Japanese Registration number:** 090860

Title of Trial

An Exploratory Multi-Centre, Multi-National, Randomised, Double Blinded, Parallel Arm Trial Evaluating Safety, Pharmacokinetics and Dose-finding of Prophylactic Administration of Long Acting rFVIIa (LA-rFVIIa)* in Haemophilia A or B Patients with Inhibitors.

*Presently named N7-GP.

Investigators

There was one principal investigator for each trial site.

Professor [redacted], was designated signatory investigator for the trial.

Trial Sites

A total of 21 sites were initiated for this trial. The country distribution was as follows (number of actively recruiting sites per country in parenthesis): France (1), Japan (3), Malaysia (1), Serbia (1), South Africa (2), Sweden (1), Turkey (2), United Kingdom (2) and United States (5).

Publications

None

Trial Period	**Development Phase**
The trial had first patient's first visit 1 September 2009. Last patient's last visit was 29 March 2011	Phase 2

Objectives

Primary Objective:

- To determine the safety including the potential immunogenicity of N7-GP i.v. administered to haemophilia patients with inhibitors every second day for 12 weeks at three dose levels 25 µg/kg, 100 µg/kg and 200 µg/kg.

Secondary Objectives:

- To evaluate the preliminary efficacy of N7-GP in reducing the bleeding frequency in haemophilia A and B patients with inhibitors, and to identify the dose(s) suitable for further development.
- To investigate the pharmacokinetic properties of multiple i.v. doses of three dose levels of N7-GP.
- To investigate the effect of N7-GP on health economic and patient reported outcome parameters.

Methodology

Patients aged 12 – 65 years (both inclusive) were evenly randomised to receive repeated doses of 25 µg/kg, 100 µg/kg or 200 µg/kg N7-GP. The trial was divided into three time periods: an observation period (at least 3 months), a treatment period (3 months) and a follow-up period (at least 4 weeks). After the screening visit, the patient entered the *observation period*. During this period, no prophylactic treatment was allowed. The prophylactic *treatment period* comprised approximately 41 doses of N7-GP administered as i.v. bolus injections every second day at one of three dose levels (25 µg/kg, 100 µg/kg or 200 µg/kg). No prophylactic treatment was allowed in the *follow-up period*.

Throughout the trial the patients were in contact with the treatment centre on a weekly basis either by visits or by telephone. All bleeding episodes were treated with rFVIIa and recorded in the patient diary. Treatment with N7-GP was continued during the treatment of bleeding episodes. Mild to moderate joint bleeds, muscle bleeds or mucocutaneous bleeds were treated with rFVIIa according to the NovoSeven®/NovoSeven RT®/NiaStase® package insert or consistent with current clinical practice. Treatment of serious bleeds (e.g. intracranial bleeds, intra-abdominal bleeds) was to be decided by the responsible physician. Serious bleeding episodes requiring prolonged treatment would have caused withdrawal from the trial.

Number of Subjects Planned and Analysed

Planned:	24 patients
Randomised and dosed:	23 patients (full analysis set)
Completed:	20 patients (6 or more patients in each treatment group).

Diagnosis and Main Criteria for Inclusion

Male haemophilia A or B patients with inhibitors aged 12 – 65 years (both inclusive) were included in the trial. Patients were required to have historical or ongoing high-titre inhibitors (≥ 5 Bethesda units [BU]), based on medical records, laboratory report reviews or patient/care provider interviews and to have at least 2 bleeding episodes requiring bypassing haemostatic-drug-based treatment within the last month or 12 bleeding episodes within the last 6 months prior to the observation period.

Test Product, Dose and Mode of Administration, Batch Number

N7-GP (PEGylated rFVIIa), previously named long acting rFVIIa, and placebo was supplied by Novo Nordisk A/S, Denmark, as sterile, freeze-dried powder in single use vials of 4.0 mg. Each vial was to be reconstituted in 2.2 mL sterile water for injection, resulting in a N7-GP concentration of 2 mg/mL when reconstituted. Treatment with N7-GP (25 µg/kg, 100 µg/kg or 200 µg/kg) was administered as single i.v. bolus injections over 2-10 minutes every second day. N7-GP batch numbers: XLDP003 and XLDP004.

Duration of Treatment

Treatment with N7-GP (25 µg/kg, 100 µg/kg or 200 µg/kg) was administered as single i.v. bolus injections over 2-10 minutes every second day, resulting in approximately 41 N7-GP administrations during 12 weeks treatment period.

Reference Therapy, Dose and Mode of Administration, Batch Number

Blinding of the investigator, the designated staff and the patient was maintained through administration of a combination of active trial product and placebo. Placebo was used for this purpose only. Placebo was supplied as sterile freeze-dried powder in single use vials. Placebo batch number: VR40326.

Criteria for Evaluation – Efficacy

- The efficacy endpoint of main interest was reduction in annualised bleeding frequency investigated using the total number of bleeds in each period.
- Additional secondary efficacy endpoints included amount of haemostatic drug used for treatment of bleeding episodes (on-demand), changes in number of specific bleedings (e.g., target joint bleeds, muscle bleeds, joint bleeds and others) during each period and bleeding episodes by cause (spontaneous, traumatic, other), change in FVIII or FIX inhibitor titre level during treatment compared to entry.
- The pharmacokinetic endpoint of main interest was area under the FVIIa activity-time profile in the given time period ($AUC_{0\text{-}48h}$ and $AUC_{0\text{-}\infty}$)

Criteria for Evaluation – Safety

- The primary endpoints were: frequency of adverse events, serious adverse events and medical events of special interest, neutralising antibodies towards FVII and/or N7-GP, coagulation-related parameters (D-dimers, prothrombin fragment 1+2, fibrinogen, prothrombin time [PT], activated partial thromboplastin time [aPTT]) and antithrombin [AT]), haematology, biochemistry, urinalysis, ECG, troponin T, vital signs, physical examination and injection site inspection.

Statistical Methods

Safety endpoints were evaluated by descriptive statistics. The efficacy endpoint of main interest was analysed using a Poisson regression model adjusting for subject, age group (12-17 years or 18-65 years) and treatment (25 µg/kg, 100 µg/kg, 200 µg/kg or 'observation period') allowing for over-dispersion and with an offset for duration of period. The annualised bleeding frequency was compared between and within dose levels. The primary test compared the 200 µg/kg group with the 25 µg/kg group. If that test was statistically significant, the 100 µg/kg group would be compared with the 25 µg/kg group. Furthermore, change from observation period to treatment period was tested for each dose. The total amount of haemostatic drug used for treatment of bleeding episodes (on-demand) during each treatment period and the change in FVIII or FIX inhibitor titre levels from the observation period to the treatment period were analysed by analysis of covariance (ANCOVA). Number of specific bleedings and number of bleeding episodes by cause during each period were analysed by the same Poisson regression model as for total number of bleeding episodes. All pharmacokinetic endpoints were calculated using standard non-compartmental methods.

Demography of Trial Population

The demographics of the trial population at baseline are presented below. Of the included patients, 82.6% had haemophila A and 17.4% had haemophila B. All patients were males and had historical or ongoing high titre inhibitors (≥ 5 BU). The mean age was 24.7 years. Whites, Black or African Americans, and Asians were included at all three dose tiers with a slight overrepresentation of Whites in the 25 µg/kg dose tier. None of the differences in baseline characteristics among dose tiers were considered to influence the conclusions drawn from the trial.

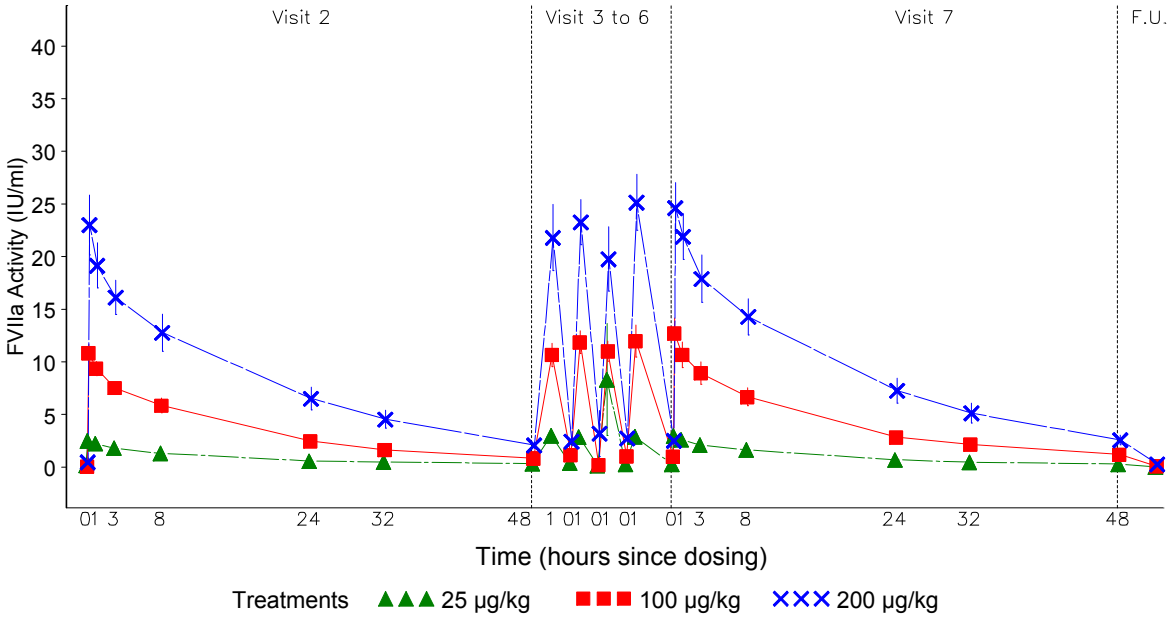
Baseline Demographics - Full Analysis Set

	N7-GP 25 µg/Kg	N7-GP 100 µg/Kg	N7-GP 200 µg/Kg	N7-GP Total
Number of Subjects	8	7	8	23
Age (years)				
N	8	7	8	23
Mean (SD)	25.1 (13.9)	25.1 (10.9)	23.8 (10.9)	24.7 (11.5)
Median	19.0	20.0	19.0	20.0
Min , Max	16.0 , 54.0	13.0 , 42.0	13.0 , 44.0	13.0 , 54.0
Sex, N(%)				
N	8 (100.0)	7 (100.0)	8 (100.0)	23 (100.0)
Male	8 (100.0)	7 (100.0)	8 (100.0)	23 (100.0)
Race, N(%)				
N	8 (100.0)	7 (100.0)	8 (100.0)	23 (100.0)
White	[redacted]			
Black or African American				
Asian				
Other				
Haemophilia Type* N(%)				
N	8 (100.0)	7 (100.0)	8 (100.0)	23 (100.0)
Haemophilia A	[redacted]			19 (82.6)
Haemophilia B				4 (17.4)

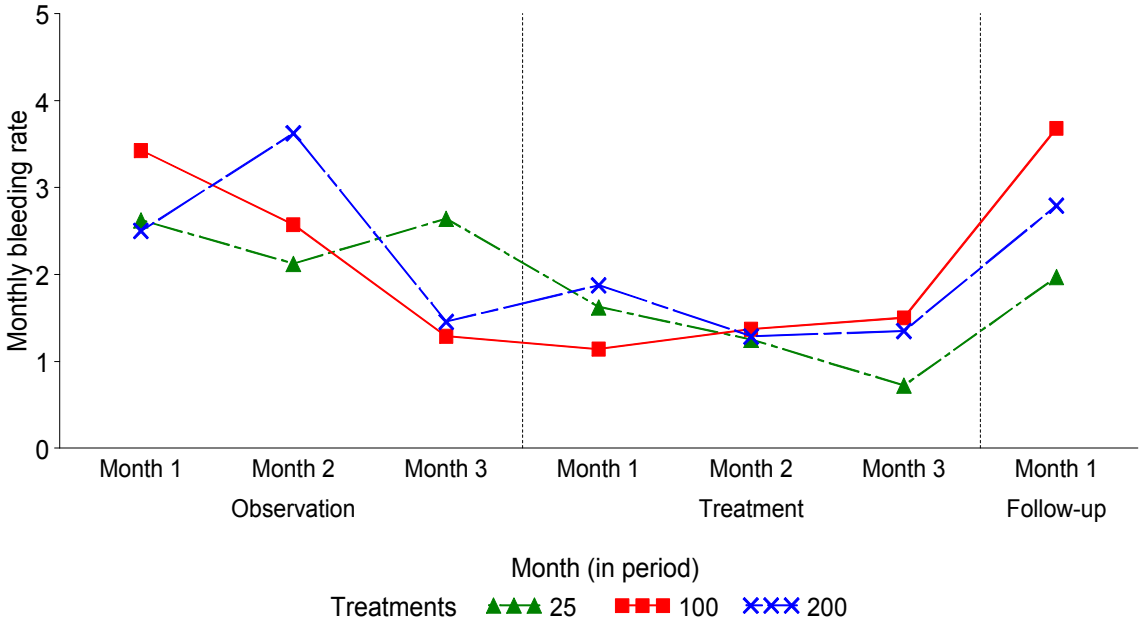
Efficacy Results

- There was no indication of deviation from pharmacokinetic dose-response proportionality. The half-life of N7-GP was approximately 15 hours.
- Reductions in annualised bleeding rates of 52%, 45% and 36% compared to the observation period were estimated for dose levels 25 µg/kg, 100 µg/kg and 200 µg/kg, respectively, but no dose-response relationship was found.
- At all dose levels, annualised bleeding rates were lower in the treatment period compared to the observation period ($p<0.10$).
- Analyses of efficacy, in subgroups of patients with specific bleeding episodes, were consistent with the overall efficacy findings. Thus, no dose-response relationship was observed in reduction of annualised bleeding rates of specific bleedings (target joint bleeds, joint bleeds, muscle bleeds and others) or related to specific causes of bleeding (spontaneous, post-traumatic, other).
- No dose-response relationship was observed in reduction of the total amount of on-demand haemostatic medication used.
- No treatment-related change in health-related quality of life was observed.

Mean PK Profiles of FVIIa activity



Bleeding Rates by Month - Full Analysis Set



Only the rate from the first month in the follow-up period is displayed.
The duration of one month is defined as a period of 30 days.

Safety Results

- In total, 37 treatment-emergent adverse events were reported for 16 patients. The most commonly reported events were medication errors (5 events in 3 patients). No noteworthy differences in the frequency of any adverse event were apparent among the three dose levels. Four events were evaluated by the investigator as possibly or probably related to trial product (two events of overdosing, malaise and increased gamma-glutamyl-transferase).
- No anti-N7-GP antibodies were detected.
- No thromboembolic events, serious adverse events or adverse events leading to withdrawal were reported.
- Results on safety laboratory parameters and other safety-related examinations did not indicate clinically significant changes as a result of N7-GP administration.

Conclusions

- N7-GP was well tolerated and no safety concerns were identified. No anti-N7-GP antibodies were detected.
- At all dose levels, reduced annualised bleeding rates were observed in the treatment period as compared to the observation period but no dose-response relationship was found.
- No dose-response relationship was observed in reduction of the total amount of on-demand haemostatic medication used.
- There was no indication of deviation from pharmacokinetic dose proportionality. The half-life of N7-GP was approximately 15 hours.
- No treatment-related changes in health economic or patient reported outcome parameters were observed.

The trial was conducted in accordance with the Declaration of Helsinki (2008) and ICH Good Clinical Practice (1996).

The results presented reflect data available in the clinical database as of 12 April 2011.