2 Synopsis

Trial registration ID-number: NCT01365520	**EudraCT number**: **2010-023921-39**
Title of trial Multi-Centre, Open-Label, Randomised Trial Investigating the Pharmacokinetics of a Single Dose of turoctocog alfa in Patients with Haemophilia A *The trial product, turoctocog alfa, was previously named N8. The name was changed after finalisation of the protocol for this trial.*	
Investigators Professor [redacted] Dr [redacted]	
Trial sites [redacted], United Kingdom [redacted], Malaysia	
Publications None	
Trial period Initiation date: 13 June 2011 Completion date: 25 September 2011	**Development phase** Phase 1
Objectives **Primary objective:** • To evaluate the pharmacokinetics (PK) of two different lots of turoctocog alfa after a single intravenous administration in patients with haemophilia A. **Secondary objective:** • To evaluate the safety of turoctocog alfa after intravenous administration in patients with haemophilia A.	
Methodology This is a multi-centre, open-label, randomised trial investigating the pharmacokinetics of two different lots of turoctocog alfa after a single, intravenous dose in patients with haemophilia A. Following a screening visit (Visit 1), a PK assessment visit (Visit 2) was to take place at least 4 days after the preceding turoctocog alfa administration and when the results from Visit 1 had been evaluated. In the period between Visit 1 and Visit 2 the patients were given prophylactic treatment with turoctocog alfa as in the pivotal NN7008-3543 phase 3 trial, except during the above-mentioned washout period of at least 4 days. Prior to dosing at Visit 2, patients were randomised 1:1 to receive a single dose of 50 ± 5 IU/kg turoctocog alfa from one of two production lots. Blood samples for PK analyses and safety parameters were drawn prior to dosing and at frequent intervals up until 48 hours after trial drug administration. An end-of-trial visit (Visit 3) was held after completion of the PK assessment period. In addition to recording of adverse events, laboratory parameters and vital signs at all three scheduled visits, all patients were examined for development of FVIII inhibitors at Visit 1 and at 48 hours after the turoctocog alfa PK assessment dose. In case of confirmation of FVIII inhibitor development, the patient was to attend additional follow-up visits for assessment of adverse events and inhibitor status. Such follow-up visits were to take place up until 3 months after initial confirmation of FVIII inhibitors as deemed relevant. Otherwise, the duration of trial participation for each patient was expected to be 1 week to 2 months depending on the timing of the PK assessment visit in relation to the screening visit. During the entire trial period, all bleeding episodes requiring treatment with turoctocog alfa or other FVIII-containing products were recorded.	
Number of patients planned and analysed A total of four patients – two allocated to each of two turoctocog alfa production lots - were planned and analysed.	

Diagnosis and main criteria for inclusion

Patients who had completed the pivotal NN7008-3543 phase 3 trial were eligible for inclusion. According to the inclusion criteria for trial NN7008-3543 these were male patients with the diagnosis of severe haemophilia A (FVIII less than or equal to 1%) of 12 to 65 years of age and weighing 10 to 120 kg at the time of inclusion into NN7008-3543.

Investigational medicinal product and/or investigational medical device, dose and mode of administration, batch number

The turoctocog alfa trial product was supplied by Novo Nordisk A/S, Denmark, as freeze-dried powder in single use vials (two different production lots of trial product) of 2000 IU/vial. Each trial product vial was to be reconstituted with 4.3 mL of isotonic 0.9% sodium chloride solution for injection (also provided in single use vials), resulting in a concentration of 500 IU/mL turoctocog alfa when reconstituted. Batch numbers: XR40383 (lot A) and YR40140 (lot B).

Duration of treatment

In the period between the screening visit and the PK session, patients were to be treated with turoctocog alfa for prevention of bleeds (prophylaxis) using the same turoctocog alfa regimen as applied in the NN7008-3543 (pivotal phase 3) trial. Prior to the PK session, a washout period of at least 4 days for turoctocog alfa was required.

At the PK session, patients received turoctocog alfa at a dose of 50 ± 5 IU/kg bw, administered i.v. as a single bolus injection using a syringe.

Reference therapy, dose and mode of administration, batch number

Not applicable

Criteria for evaluation – efficacy

Pharmacokinetic assessment was based on the chromogenic substrate assay (chromogenic assay) and the one-stage clotting assay (clotting assay). The primary PK endpoints were incremental recovery at 30 minutes post-dose (IR30min)(defined as the dose-normalised level recorded 30 min after infusion divided by dose and reported as [IU/mL]/[IU/kg]), terminal half-life (t½), clearance (CL) and area under the curve (AUC) as recommended in the EMA guidelines for clinical investigation with recombinant FVIII products.

Criteria for evaluation – safety

Adverse events, vital signs and clinical laboratory tests (haematology, biochemistry and FVIII inhibitors).

Statistical methods

All four screened and exposed patients completed the trial and thus constitute the full analysis set for pharmacokinetic, safety and efficacy evaluation. No data were excluded from analysis.

Separate sets of pharmacokinetic parameters were calculated based on data from the chromogenic assay as well as the clotting assay. The pharmacokinetic parameters were derived according to non-compartmental methods normalised to planned dose. The actual time points for sampling (relative to the time of end of injection) were used for the calculation of pharmacokinetic parameters.

No hypothesis testing of differences between lots was done due to the low number of observations. Instead, results are summarised descriptively. Endpoints analysed after log-transformation are also presented using geometric means and coefficients of variation.

Demography of trial population

[redacted] were enrolled in the United Kingdom, and [redacted] were enrolled in Malaysia. [redacted] racial origin. The age of patients ranged from 25 to 41 years, and body mass index ranged from 19.1 to 27.8. As per protocol, all patients had haemophilia A.

Efficacy results

Four patients were enrolled and received trial drug and thus constitute the full analysis set.

- There were no apparent pharmacokinetic differences between lots A and B. Due to the low number of observations (two PK profiles for each lot), no statistically valid conclusions can be drawn with respect to the pharmacokinetic similarity of the two lots.
- Two bleeding episodes were recorded. Both were spontaneous bleeds rated as mild/moderate in severity, and both occurred during the late phase of an attempted washout period prior to the pharmacokinetic assessment visit. Response to turoctocog alfa treatment was rated as "good" and "excellent" for the respective bleeds.

Safety results

Four patients were enrolled and received trial drug and thus constitute the full analysis set.

- Two adverse events (events of abdominal discomfort and hyperglycaemia) were recorded for the trial. Both were non-serious adverse events of mild severity, and both were evaluated by the investigator as unlikely related to trial product.
- None of the patients tested positive for FVIII inhibitors, and no safety issues were raised from examination of the remaining safety laboratory parameters or vital signs.

Conclusions

- There were no apparent pharmacokinetic differences between lots A and B. The pharmacokinetic data of the current trial add to the pool of pharmacokinetic data generated from the turoctocog alfa development programme but are in themselves too limited to draw any statistically valid conclusions on pharmacokinetics or lot variability with respect to pharmacokinetics.
- No safety issues were raised.

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