2 Synopsis

Trial Registration ID-number	**EudraCT number**
NCT00936403	2008-008240-25

Title of Trial

A randomised, open-labelled, single dose, dose-escalation trial investigating safety, tolerability, pharmacokinetics and pharmacodynamics of pegylated long-acting human growth hormone (NNC126-0083) compared to Norditropin NordiFlex® in growth hormone deficient (GHD) children

Investigator

Prof. [redacted]

Trial Sites

The trial was conducted at 17 sites in 9 countries; 10 sites in Europe (Belgium: 2, Denmark: 1, France: 2, Macedonia: 1, Slovenia: 1, Spain: 2, Turkey: 3 sites, UK: 1) and 4 sites outside Europe (Israel: 4). The sites in Turkey did not initiate the screening and thus no subjects were participating at these sites.

Publications

N/A

Trial Period	**Development Phase**
First patient first visit: 03 Aug 2009 Last patient last visit: 18 July 2010	Phase 2

Objectives

Primary Objective

- To determine safety and tolerability of single subcutaneous (s.c.) doses of NNC126-0083 compared to 7 days treatment with s.c. doses of Norditropin NordiFlex® in children with GHD

Secondary Objectives

- To determine pharmacokinetics (PK) and pharmacodynamics (PD) of single s.c. doses of NNC126-0083 compared to 7 days treatment with s.c. doses of Norditropin NordiFlex® in children with GHD
- To compare local tolerability (i.e. injection-site reactions) of single s.c. doses of NNC126-0083 compared to 7 days treatment with s.c. doses of Norditropin NordiFlex® in children with GHD

Methodology

This was a randomised, open-labelled, single-dose, dose-escalation trial. Four dose levels (0.01, 0.02, 0.04 and 0.06 mg protein/kg) were investigated. In each cohort, the subjects were randomised to receive either a single dose of NNC126-0083 (n=6) or 7 once-daily doses of 0.035 mg/kg per day of Norditropin NordiFlex® (Norditropin®) (n=2).

Blood samples were collected for assessment of the PK and PD and clinical laboratory safety. Progression to the next cohort (i.e., next dose level) took place only after evaluation of the interim data on safety, PK and anti-NNC126-0083 antibody development, by an internal safety assessment group.

The trial consisted of eight visits: a screening visit (Visit 1) followed by a GH wash-out period of 7 (+2) days; a treatment period (Visits 2–7); and a follow-up visit (Visit 8). The treatment period comprised randomisation and dosing on Day 1, a 4-day in-house period at the hospital (Days 1–4; Visit 2), and an ex-house surveillance period (Visits 3–7) where the subject attended the site for blood sampling and safety assessments. Each subject received only one type of treatment at one specific dose level. The trial products were administered in the morning as s.c. injections.

Number of Subjects Planned and Analysed

Planned:	32 subjects with GHD (8 subjects per cohort)
Screened:	34 subjects
Randomised:	31 subjects
Exposed:	30 subjects
Withdrawn:	1 subject was withdrawn prior to exposure

Completed: 30 subjects
Analysed: 30 subjects
Because of two events of [redacted], a withdrawn consent before randomisation, and a withdrawal after randomisation but before exposure, the number of subjects exposed to NNC126-0083 at each dose cohort of 0.01, 0.02, 0.04 and 0.06 mg protein/kg was 3, 8, 5 and 6, respectively. The Norditropin® cohort held 8 subjects.

Diagnosis and Main Criteria for Inclusion

- Confirmed diagnosis of growth hormone insufficiency as defined by two different GH provocation tests, defined as a peak of GH level < 7 ng/mL. For subjects with three or more pituitary hormone deficiencies, only one GH provocation test was needed. If in accordance with country-specific practice, GH insufficiency could be defined by only one GH provocation test, defined as a peak of GH level < 7 ng/mL.
- Pre-pubertal subjects
- Boys: age ≥ 6 years and ≤ 12 years (France: Boys: Age ≥ 9 years and ≤ 12 years)
  Girls: age ≥ 6 years and ≤ 12 years (France: Girls: Age ≥ 9 years and ≤ 12 years)
- GH replacement treatment ≥ 3 months

All subjects were required to discontinue GH replacement treatment 7 (+2) days prior to treatment with NNC126-0083 or Norditropin®.

Test Product, Dose and Mode of Administration, Batch Numbers

Single doses of NNC126-0083 were administered as s.c. injections during the morning, at escalated doses of 0.01, 0.02, 0.04 and 0.06 mg protein/kg. Only one dose level of NNC126-0083 was administered within one cohort. Batch numbers: TLDS005 (NNC126-0083) and TLDS004 (placebo used only for dilution of NNC126-0083).

Duration of Treatment

The subjects were dosed once with NNC126-0083 or once daily for 7 days with Norditropin®.

Reference Therapy, Dose and Mode of Administration, Batch Numbers

Norditropin® was administered daily for 7 days, at a dose of 0.035 mg/kg in all cohorts. Norditropin® was administered as s.c. injections during the morning, in the right thigh on uneven days and in the left thigh on even days. Batch numbers: VY50074, XY50102, XY50125 and XY50149.

Criteria for Evaluation – Efficacy

The PK endpoints were based on plasma concentrations of NNC126-0083 determined after one dose of NNC126-0083 and serum concentrations Norditropin® after the first administration of Norditropin®.
The PD endpoints were based on serum concentrations of IGF-I and IGFBP-3 up to 168 hours after trial product administration. The parameters were determined after one dose of NNC126-0083 or after once-daily administration of Norditropin® for 7 days.

Criteria for Evaluation – Safety

- Adverse events
- Clinical laboratory safety (haematology, biochemistry, urinalysis)
- Fasting glucose
- Fasting insulin
- Physical examination
- Local tolerability
- Vital signs
- Body weight
- ECG
- Antibodies against NNC126-0083 and GH

All safety assessments were based on data collected up to 10 days (240 hours) after a single dose of NNC126-0083 and 3 days after last dose (240 hours after the first dose) of Norditropin®.

Statistical Methods

Pharmacokinetic Endpoints

$AUC_{0\text{-}24h}$, $AUC_{0\text{-}168h}$, AUC, C_{max}, t_{max}, λ_z, $t_{½}$, V_z/F, CL/F, MRT and steady-state

Pharmacodynamic Endpoints

- For IGF-I, IGF-I SDS, IGFBP-3 and IGFBP-3 SDS: $AUC_{0\text{-}168h}$, $AUC_{0\text{-}168h}$/168 hours, $\Delta AUC_{0\text{-}168h}$/168 hours, C_{max},

and ΔC_{max}
- For IGF-I: steady-state

AUC = area under the plasma/serum concentration curve versus time; AUC_{0-168h}/168 hours = the average concentration (or SDS), defined as the area under the profile in the interval 0–168 hours after first trial product administration, divided by 168 hours; CL/F = systemic clearance from plasma/serum, divided by the bioavailability after s.c. administration; C_{max} = maximum plasma/serum concentration; ΔAUC_{0-168h}/168 hours = baseline-adjusted AUC_{0-168h}/168 hours, defined as the ratio between AUC_{0-168h}/168 hours and the baseline concentration. For SDS, ΔAUC_{0-168h}/168 hours is defined as the difference between AUC_{0-168h}/168 hours SDS and the baseline SDS; ΔC_{max} = baseline-adjusted C_{max}, defined as the ratio between C_{max} and the baseline concentration. For SDS, ΔC_{max} is defined as the difference between C_{max} SDS and the baseline SDS; λ_z = terminal rate constant; MRT = mean residence time; t½ = apparent terminal half-life; t_{max} = time to maximum plasma/serum concentration; V_z/F = the volume of distribution, based on the terminal phase and divided by the bioavailability after s.c. administration

Standard deviation scores (SDS) are data normalised with respect to gender and age-related mean, and the standard deviation estimates provided by the laboratory. Norditropin® AUC_{0-168h} was calculated as $7 \times AUC_{0-24h}$. Steady-state was evaluated by visual inspection of the individual and the estimated mean plots for ratios between the 24 hours post-dose plasma concentrations after every two consecutive injections. A significance level of 5% was used throughout the statistical analyses. The full analysis set (FAS; i.e., all randomised and exposed subjects) was used for analysis of PK/PD endpoints, whereas the safety analysis set was used for analysis of safety endpoints. The term 'treatment' was considered as a factor with five levels.

Pharmacokinetic Endpoints

All PK endpoints were summarised by dose and treatment using descriptive statistics. All individual values were listed. For NNC126-0083, the dose proportionality of AUC, AUC_{0-168h}, and C_{max} was investigated by estimating the slope in the linear regression models of log(AUC), log(AUC_{0-168h}) and log(C_{max}), respectively, versus log(dose), where dose is in mg protein/kg. A slope β of 1 meant that the pharmacokinetics was dose proportional. The estimated quantity was described with 95% confidence intervals.

For all PK endpoints, scatter plots vs. dose were made with both axes on original scale. For AUC, AUC_{0-168h}, and C_{max} of NNC126-0083, scatter plots vs. dose were supplemented with the curves estimated from the linear estimated regression model and a similar curve (line) estimated from the model, where β=1 was set as restriction, corresponding to dose-proportionality. For AUC, AUC_{0-168h}, and C_{max} of NNC126-0083 the above described scatter plots vs. dose were also made with both axes on logarithmic scale.

Pharmacodynamic Endpoints

All PD endpoints were summarised by dose and treatment using descriptive statistics.

For AUC_{0-168h}/168 hours and C_{max}, a comparison between each of the NNC126-0083 doses and Norditropin® was performed using an analysis of variance model with treatment as factor and the pre-dose value (first dose) as a covariate. AUC_{0-168h}/168 hours and C_{max} were log-transformed in the analysis, and so was the pre-dose value. For each NNC126-0083 dose, mean ratios (mean differences for SDS) vs. Norditropin® were estimated from the model together with 95% confidence intervals.

The comparison of IGF-I profiles obtained for NNC126-0083 and Norditropin® was supplemented with an estimate of AUC_{0-168h}/168 hours in steady-state, performed by the Department for Quantitative Clinical Pharmacology and reported separately.

Safety

All data were listed and summarised by descriptive statistics. For fasting blood glucose and insulin, the delta-values, defined as the baseline-subtracted maximum value were calculated and summarised. The delta-values were evaluated in the time interval 0–240 hours for both NNC126-0083 and Norditropin®.

Demography of Trial Population

A total of 30 subjects (22 boys and 8 girls) were investigated. The majority of the subjects were [redacted] (at least [redacted] out of 30), at least [redacted] subject was [redacted], and [redacted] subjects were of unknown race (due to prohibited recording in France). The mean age at baseline ranged from 8.2 to 9.9 years (min [redacted] years; max [redacted] years). The

subjects had a mean baseline height from 120 to 135 cm. Standardised height scores were not calculated. The mean weight ranged from 24.1 to 34.9 kg. The span in weight was due to differences in age at inclusion. The estimated mean IGF-I SDS at baseline (i.e., pre-dose Day 1) was in the lower end of the reference range at baseline (NNC126-0083: -3.7, -1.4, -1.4 and -3.6; Norditropin®: -1.2). All subjects were assessed as pre-pubertal at baseline. The subjects were considered representative for children with GHD.

Efficacy Results

Pharmacokinetics

NNC126-0083 and Norditropin® mean profiles are presented in Figure 1.

- The systemic exposure of NNC126-0083, as measured by the estimated mean AUC and C_{max}, increased with the dose. A more than dose-proportional exposure was observed for the highest dose levels 0.04 and 0.06 mg protein/kg, although this deviation from dose proportionality was not statistically significant
- Following treatment with NNC126-0083, the estimated mean time to reach maximal plasma concentration (t_{max}) ranged from 8.8 to 22.7 hours. Following treatment with Norditropin®, t_{max} was 5.3 hours
- Diurnal variations in PK concentrations, and considerable individual variation in exposure was observed

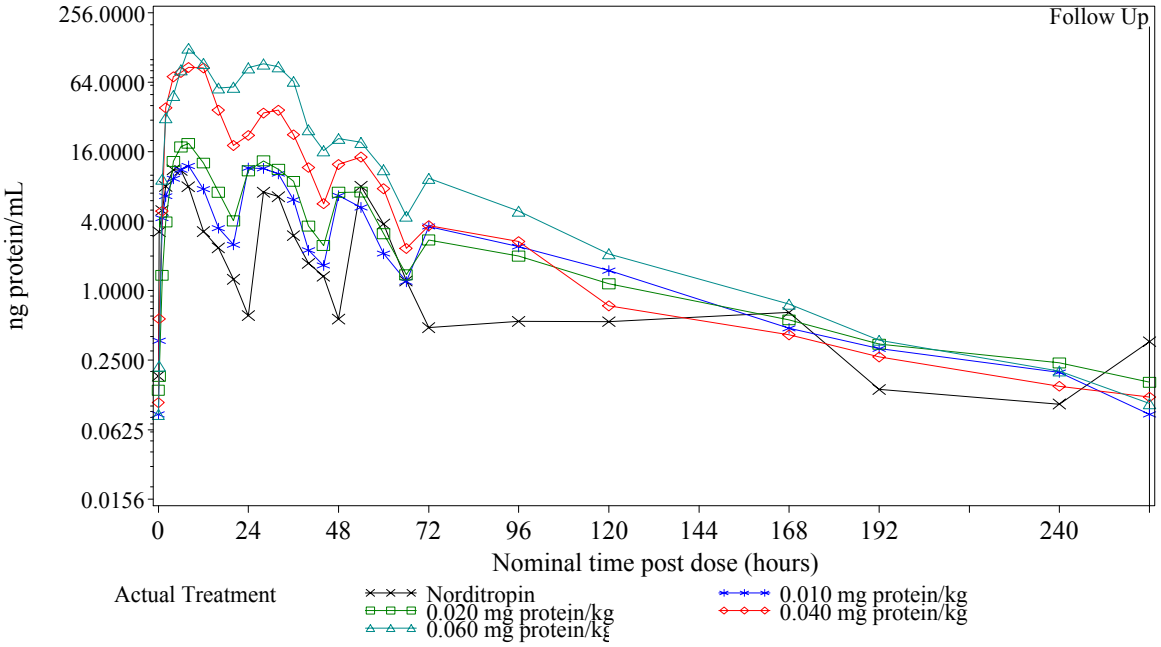

Figure 1 Estimated Mean Profiles of NNC126-0083 and Norditropin® (ng protein/mL) on Logarithmic Scale – Full Analysis Set

Pharmacodynamics

Estimated mean IGF-I profiles are presented in Figure 2 (ng/mL), Figure 3 (ng/mL; change from baseline) and Figure 4 (SDS).

- Increases in IGF-I and IGFBP-3 levels were observed for all NNC126-0083 and Norditropin® dose groups
- After NNC126-0083 administration, the highest mean values for IGF-I $AUC_{0\text{-}168h}$/168 hours and IGF-I C_{max} (191.4 and 252.2 ng/mL, respectively), were observed for cohort 0.04 mg protein/kg. The mean values for IGF-I $AUC_{0\text{-}168h}$/168 hours and C_{max} for Norditropin® (261.1 and 338.1 ng/mL, respectively) were higher than for any of the NNC126-0083 cohorts, although the difference was not statistically significant for the NNC126-0083 cohorts 0.06 mg protein/kg ($AUC_{0\text{-}168h}$/168 hours and C_{max}) or 0.04 mg protein/kg (C_{max})
- The increase in the baseline-adjusted IGF-I $AUC_{0\text{-}168h}$/168 hours and C_{max} for the NNC126-0083 0.06 mg protein/kg cohort was 3.0 (SD: 1.6) and 5.4 (SD: 3.3), respectively. The Norditropin® cohort had a higher increase in the baseline-adjusted $AUC_{0\text{-}168h}$/168 hours (3.2; SD: 2.3), but a lower increase for the baseline-adjusted C_{max}

(4.2; SD: 3.1), when compared with the NNC126-0083 cohorts

- The greatest increase from baseline in the mean IGF-I SDS $AUC_{0\text{-}168h}$/168 hours was observed for the Norditropin® cohort (2.1 SDS; SD: 1.6), followed by the NNC126-0083 0.06 mg protein/kg cohort (1.9 SDS; SD:1.5). The greatest increase from baseline in the estimated mean IGF-I SDS C_{max} was observed for the NNC126-0083 0.06 mg protein/kg cohort (3.6 SDS; SD: 1.7), followed by the Norditropin® cohort (2.8 SDS; SD: 1.8)
- Increases in IGF-I levels (ng/mL and SDS) were dose-dependent for C_{max}, but not for $AUC_{0\text{-}168h}$, after NNC126-0083 administration
- For the three highest NNC126-0083 dose levels 0.02, 0.04 and 0.06 mg protein/kg, the mean IGF-I C_{max} values (ng/mL and SDS) were similar to those recorded prior to the wash-out of recombinant human GH
- The mean values for IGFBP-3 $AUC_{0\text{-}168h}$/168 hours and IGFBP-3 C_{max} for Norditropin® and NNC126-0083 were comparable, with the exception of $AUC_{0\text{-}168h}$/168 hours and C_{max} for the NNC126-0083 0.01 mg protein/kg cohort which were significantly different from the Norditropin® cohort
- The increases in the mean baseline-adjusted IGFBP-3 $AUC_{0\text{-}168h}$/168 hours and C_{max} (both in ng/mL and SDS) were greatest for the NNC126-0083 0.06 mg protein/kg cohort, followed by the Norditropin® cohort
- After administration of NNC126-0083, no dose-response relationship was evident for the estimated mean IGFBP-3 $AUC_{0\text{-}168h}$/168 hours, IGFBP-3 SDS $AUC_{0\text{-}168h}$/168 hours or IGFBP-3 C_{max}. A dose-response relationship was apparent for the estimated mean IGFBP-3 SDS C_{max}

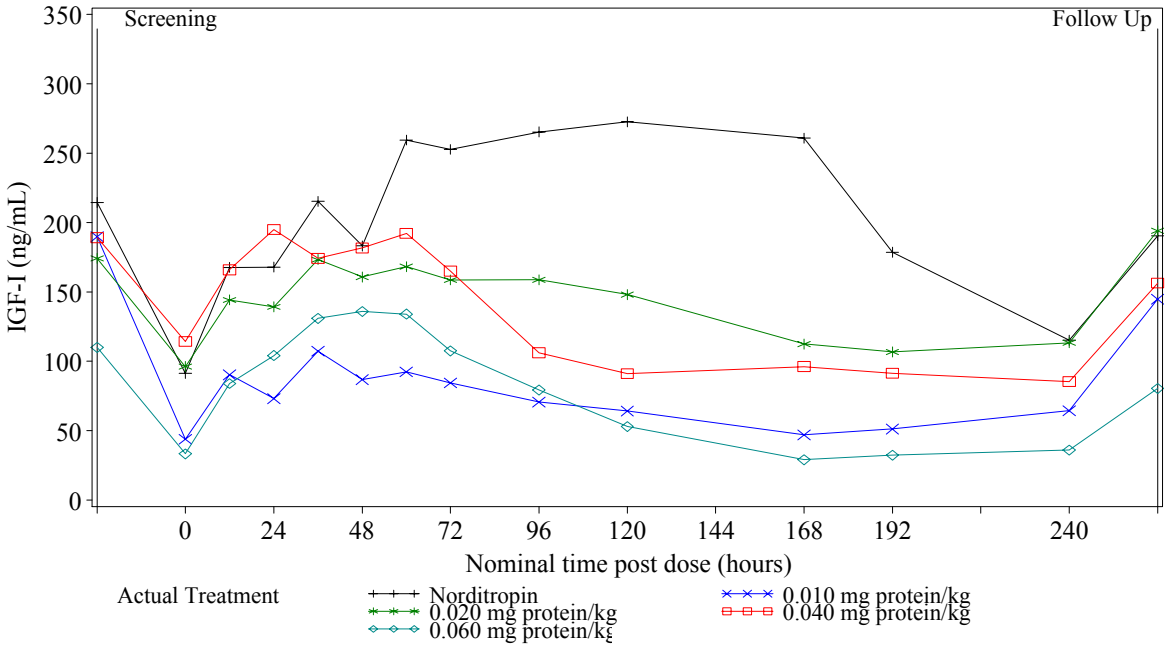

Figure 2 Estimated Mean Profiles of IGF-I (ng/mL) – Full Analysis Set

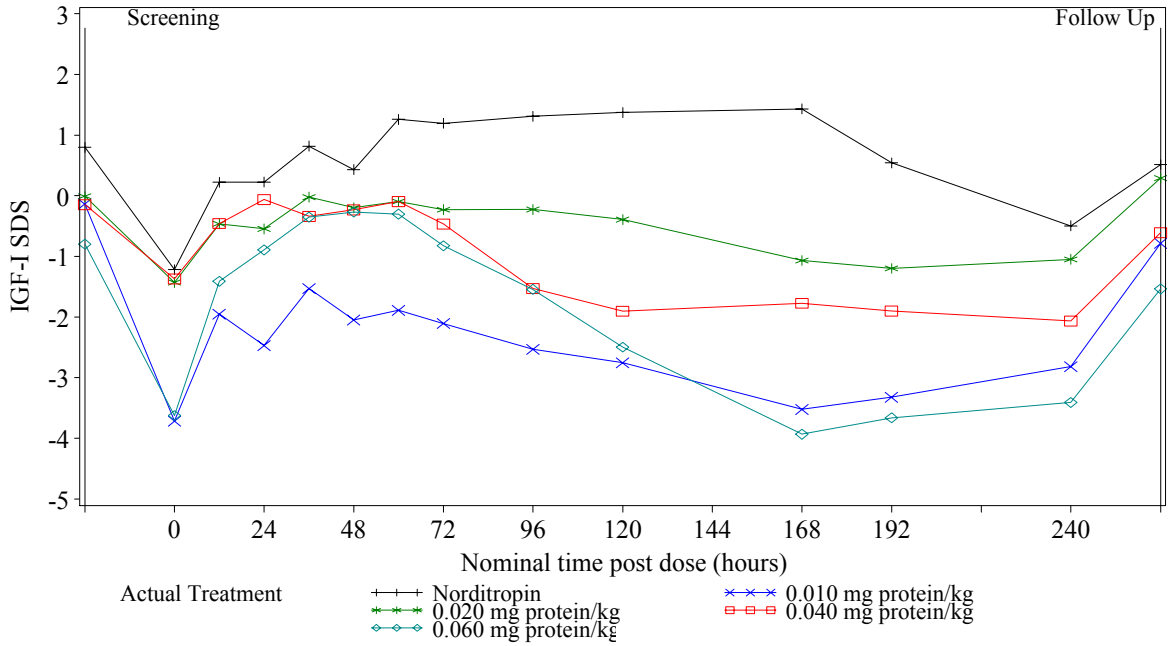

Figure 3 Estimated Mean Profiles of IGF-I SDS – Full Analysis Set

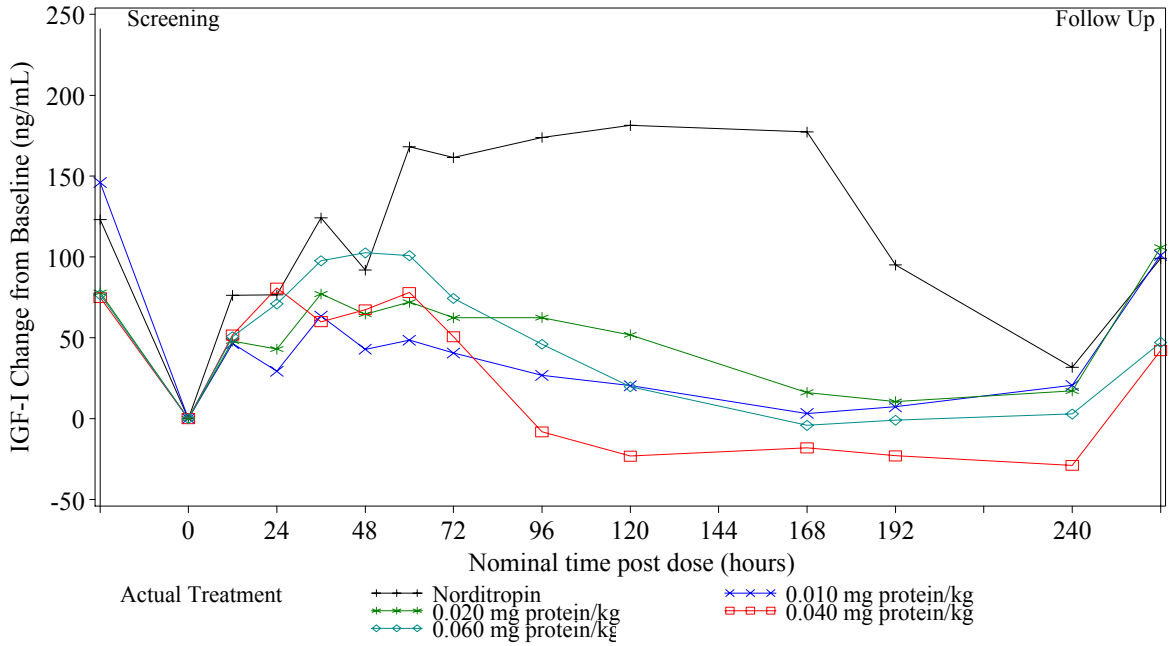

Figure 4 Estimated Mean Profiles of Change in IGF-I (ng/mL) from Baseline – Full Analysis Set

Safety Results

- NNC126-0083 was well tolerated at all dose levels investigated
- Relatively few adverse events were reported during the trial: a total of 22 adverse events in 15 of 30 subjects, including 2 events of 'wrong technique in drug usage process' that were not associated with adverse events, in the

0.02 mg protein/kg cohort. There were no apparent differences in the number and type of adverse events between NNC126-0083 and Norditropin®, or between the NNC126-0083 cohorts.

- All adverse events reported were mild or moderate in severity, and had resolved at the end of the trial.
- There were no deaths or serious adverse events reported during the trial. No subjects were withdrawn due to adverse events
- In all, 2 adverse events were evaluated as possibly or probably related to NNC126-0083: 1 injection-site reaction (mild redness and induration) in the 0.04 mg protein/kg cohort and 1 event of mild and transient pancytopenia in the 0.06 mg protein/kg cohort.
- There were few, transient, and clinically insignificant reports of local tolerability-reactions in the NNC126-0083 cohorts. The reactions were comparable to the clinical experience with daily hGH treatment. No signs of lipoatrophy were observed
- No clinically relevant changes from screening in the assessments of the vital signs, physical examinations or ECG recordings were observed
- The fasting serum glucose and insulin levels were moderately and transiently increased in the NNC126-0083 (0.06 mg protein/kg) and Norditropin® groups; a well-known effect of GH treatment
- Decreases in blood levels of uric acid and urea were observed for all treatment groups between approximately 0 and 3 days post-dose. Both mean and individual levels did not fall below the normal range
- One finding of transient, [redacted] antibodies against NNC126-0083 was recorded for one sample from cohort 0.01 mg protein/kg. The tests results for neutralising and cross-reactive antibodies were negative. There was no apparent influence on the PK or PD parameters.

Conclusions

- No clinical safety concerns were raised in relation to single-dose treatment with NNC126-0083 in children with GHD, at dose levels up to (and including) 0.06 mg protein/kg
- No significant local tolerability issues were identified
- The systemic exposure of NNC126-0083 increased with the dose. A more than dose-proportional exposure was observed for the highest dose levels 0.04 and 0.06 mg protein/kg, although this deviation from dose proportionality was not statistically significant
- Following treatment with NNC126-0083, dose-dependent increases in IGF-I levels (ng/mL and SDS) were evident for C_{max}, but not for $AUC_{0\text{-}168h}$. The mean values for IGF-I $AUC_{0\text{-}168h}$/168 hours and IGF-I C_{max} were higher for Norditropin® than for NNC126-0083, although the difference was not statistically significant for the NNC126-0083 cohorts 0.06 mg protein/kg ($AUC_{0\text{-}168h}$/168 hours and C_{max}) or 0.04 mg protein/kg (C_{max}). The Norditropin® cohort had a higher increase in the baseline-adjusted IGF-I $AUC_{0\text{-}168h}$/168 hours but lower increase for baseline-adjusted IGF-I C_{max}, when compared with the NNC126-0083 cohorts

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 15-Nov-2010 (date of database freeze).