2 Synopsis

Trial Registration ID-number	**EudraCT number**
NCT00715689	2008-001061-29

Title of Trial

A randomised, double blind, placebo-controlled, multiple dose, dose-escalating, sequential dose group trial investigating safety, tolerability, pharmacokinetics and pharmacodynamics of pegylated long-acting human growth hormone (NNC126-0083) in growth hormone deficient adults (AGHD).

Investigators

Dr. [redacted]

Trial Sites

Three trial sites in Denmark ([redacted], [redacted] and [redacted]).

Publications

NA

Trial Period	**Development Phase**
2 July 2008 to 31 March 2009	Phase 2

Objectives

Primary Objective:

- To determine safety and tolerability of ascending multiple subcutaneous (s.c.) doses of NNC126-0083 in AGHD male and female subjects compared to placebo.

Secondary Objective:

- To determine pharmacokinetics (PK) and pharmacodynamics (PD) of ascending multiple s.c. doses of NNC126-0083 in AGHD male and female subjects.

Methodology

This was a randomised, double-blind, placebo-controlled, multiple-dose, dose-escalating, sequential-dose group trial including 4 dose levels with 8 AGHD subjects in each cohort.

Within each dose level subjects were randomised to receive multiple doses of NNC126-0083 (n=6) or placebo (n=2). The doses were administered three times at 1-week intervals. The dose levels were 0.01, 0.02, 0.04 and 0.08 mg protein/kg. After the first and third dose administration, blood sampling was done for 7 and 10 days (168 and 240 hours), respectively, to assess laboratory safety parameters, PK and PD. Progress to the next higher dose level took place following evaluation of interim safety, PK and antibody data from the prior dose level by an internal safety assessment group.

The subjects attended a screening visit (Visit 1), a growth hormone (GH)-washout period of at least 14 days, a treatment period (Visits 2 to 14) and a follow-up visit 20–27 days after the last dosing (Visit 15). The treatment period comprised three dosing days: Visit 2 (first dosing followed by a 4-day in-house stay), Visit 6 (second dosing) and Visit 7 (third dosing followed by a 4-day in-house stay).

Number of Subjects Planned and Analysed

AGHD subjects (male and female) on GH replacement therapy.

Planned: 32 subjects (4 cohorts of 8 subjects each)
Screened: 43 subjects
Enrolled/treated: 33 subjects
Withdrawn: 1 subject was withdrawn due to other reasons ([redacted] reasons)
Completed: 32 subjects

Subjects were stratified into two groups to minimise the age- and sex-related difference in response to GH:

Group 1: Females ≥ 20 years ≤ 65 and males ≥ 20 years < 35

Group 2: Males ≥ 35 years ≤ 65

Diagnosis and Main Criteria for Inclusion

Eligible subjects included AGHD male or female subjects as defined in the consensus guidelines for the diagnosis and treatment of adults with GH deficiency II. Subjects should have received GH replacement therapy for more than 3 months. BMI should be from 18.5 to 35.0 kg/m^2, both inclusive, and age ≥ 20 and ≤ 65 years. Subjects with malignant disease, proliferative retinopathy, heart insufficiency (NYHA class >2), poorly controlled diabetes mellitus with HbA_{1c} > 8.0% or receiving insulin treatment were not allowed in the trial.

All subjects were required to discontinue GH replacement treatment 2 weeks before first dose.

Test Product, Dose and Mode of Administration, Batch Number

NNC126-0083 drug product: 6.8 mg protein/mL (20 mg NNC126-0083/mL). Batch no.: TLDS005.

NNC126-0083 was delivered as a lyophilised powder in vials, to be reconstituted in sterile water. The dose levels were 0.01, 0.02, 0.04 and 0.08 mg protein/kg, and the injection volume was 1.47, 2.92, 5.88 and 11.76 µL/kg, respectively. All dose administrations were given in the morning (fasting) as s.c. injections into a lifted skin-fold of the thighs; the first and third dose in the right thigh and the second dose in the left thigh.

Duration of Treatment

The subjects were dosed once weekly for 3 subsequent weeks.

Reference Therapy, Dose and Mode of Administration, Batch Number

NNC126-0083 placebo: 0 mg/mL. Batch no.: TLDS004.

Placebo was comparable to the NNC126-0083 drug product except for the active ingredient. Placebo treatment was given at volumes equivalent to NNC126-0083 drug product.

Criteria for Evaluation – Efficacy

Pharmacokinetics:

- NNC126-0083 plasma concentrations after first and third dose.

Pharmacodynamics:

- Insulin-like growth factor I (IGF-I) serum concentrations after first and third dose.
- IGF protein binding 3 (IGFBP-3) serum concentrations after first and third dose.

Other:

- GH binding protein (GHBP) serum concentrations after first and third dose.

All assessments were based on evaluation of data collected up to 7 days (168 hours) after first dose and up to 10 days (240 hours) after the third dose.

Criteria for Evaluation – Safety

Safety parameters were assessed after first and third dose administration and included vital signs, physical examination, body weight, clinical laboratory examinations (haematology, biochemistry, urinalysis, fasting insulin and fasting glucose), NNC126-0083 antibodies, ECG and adverse events including injection site reactions.

All assessments were made up to 7 days after first and up to 10 days after the third dose administration.

Statistical Methods

A significance level of 5% was used throughout the statistical analyses, and no adjustment for multiple testing was applied. Unless otherwise stated all placebo subjects were pooled assuming no cohort effect for these subjects.

PK endpoints included AUC, $AUC_{0\text{-}168h}$, C_{max}, t_{max}, $t_{½}$, λ_z, V_z/f, CL/f, MRT and duration of appearance, all derived from NNC126-0083 plasma profiles. Further, in order to investigate steady-state PK and accumulation, the ratios of $AUC_{0\text{-}168h}$ after third dosing versus AUC and $AUC_{0\text{-}168h}$ after first dosing, respectively, were calculated.

All PK endpoints were analysed using descriptive statistics. Furthermore, dose-proportionality of AUC after first dosing, $AUC_{0\text{-}168h}$ after third dosing, and C_{max} after first and third dosing, respectively, were investigated by estimating the slope in the linear regression model of the log-transformed PK endpoint versus log(dose). The estimated slope including a 95% confidence interval (CI) was reported. Steady-state investigations were done by estimating the ratio of $AUC_{0\text{-}168h}$ after third dosing versus AUC and $AUC_{0\text{-}168h}$ after first dosing using an ANOVA model with the log-transformed ratio as dependent variable and dose as a factor. The mean ratios were estimated and 95% CIs were calculated.

PD endpoints included $AUC_{0\text{-}168h}$, $AUC_{0\text{-}240h}$, incremental (baseline-adjusted) AUCs ($iAUC_{0\text{-}168h}$ and $iAUC_{0\text{-}240h}$), C_{max}, and ΔC_{max} (baseline-adjusted) derived from IGF-I and IGFBP-3 serum profiles. All endpoints were calculated in two versions using the measured concentrations (ng/mL) as well as age-adjusted standard deviation scores (SDS). Further, the ratios between the 168h post-third and post-second (or post-first) dose concentrations were calculated. The ΔC_{max}, was defined as the ratio between C_{max} and the corresponding baseline (i.e., pre-dose) value, whereas for SDS, it was the baseline-subtracted C_{max}. All AUCs (and iAUCs) were divided by 168h or 240h (the dosing interval) in order for these quantities to be interpreted as mean concentrations (for iAUC change in means) during the dosing interval.

Other endpoints included $AUC_{0\text{-}168}$, $AUC_{0\text{-}240h}$, $iAUC_{0\text{-}168}$, $iAUC_{0\text{-}240t}$, C_{max} and ΔC_{max} derived from GHBP serum profiles.

All PD and GHBP endpoints were analysed using descriptive statistics. Furthermore, the endpoints were analysed using an ANOVA model with dose level and stratum as factors and the pre-dose value corresponding to first dosing as a covariate. Endpoints (except iAUC and all SDS endpoints) and the corresponding pre-dose values were log-transformed. Mean ratios (differences for iAUC and SDS endpoints) between the doses of NNC126-0083 and placebo were estimated and 95% CIs were calculated. Furthermore for each dose level, the hypothesis of no difference compared to placebo was tested. Steady-state investigations of IGF-I and IGFBP-3 were done by estimating the mean ratios of the 168h post-third and post-second (or post-first) dose concentration using an ANOVA model with the log-transformed ratio as dependent variable and dose as a factor. The mean ratios were estimated and 95% CIs were calculated. Furthermore, the overall mean ratio of the ratio versus placebo was estimated using a similar ANOVA model with NNC126-0083/placebo as a factor with two levels only.

Safety endpoints: All safety endpoints were analysed using descriptive statistics.

Demography of Trial Population

A total of 33 AGHD subjects were investigated: 22 men and 11 women. The mean age at baseline was 48.8 (range 26 to 63) years. All subjects were white, except 1 subject of other ethnic origin. The mean BMI was 26.7 (range 19.6 to 34.8) kg/m^2. Stratification Group 1 (males < 35 years and females) comprised 17 subjects and Group 2 (males ≥ 35) 16 subjects.

Efficacy Results

Pharmacokinetics

Mean NNC126-0083 concentration–time profiles are presented in Figure 1.

- Following three once-weekly s.c. injections of NNC126-0083 mean time to reach maximum concentration (t_{max}) ranged from 6.9 to 27.5 hours and mean terminal half-life ($t_{½}$) ranged from 46.3 to78.7 hours (geometric means).
- Deviation from dose-proportionality was apparent at the highest dose (0.08 mg protein/kg), where more than dose-proportional exposure was observed, although not statistically significant.
- Diurnal variations were observed.
- PK steady-state appeared to have been reached at third dose.
- No accumulation was observed.

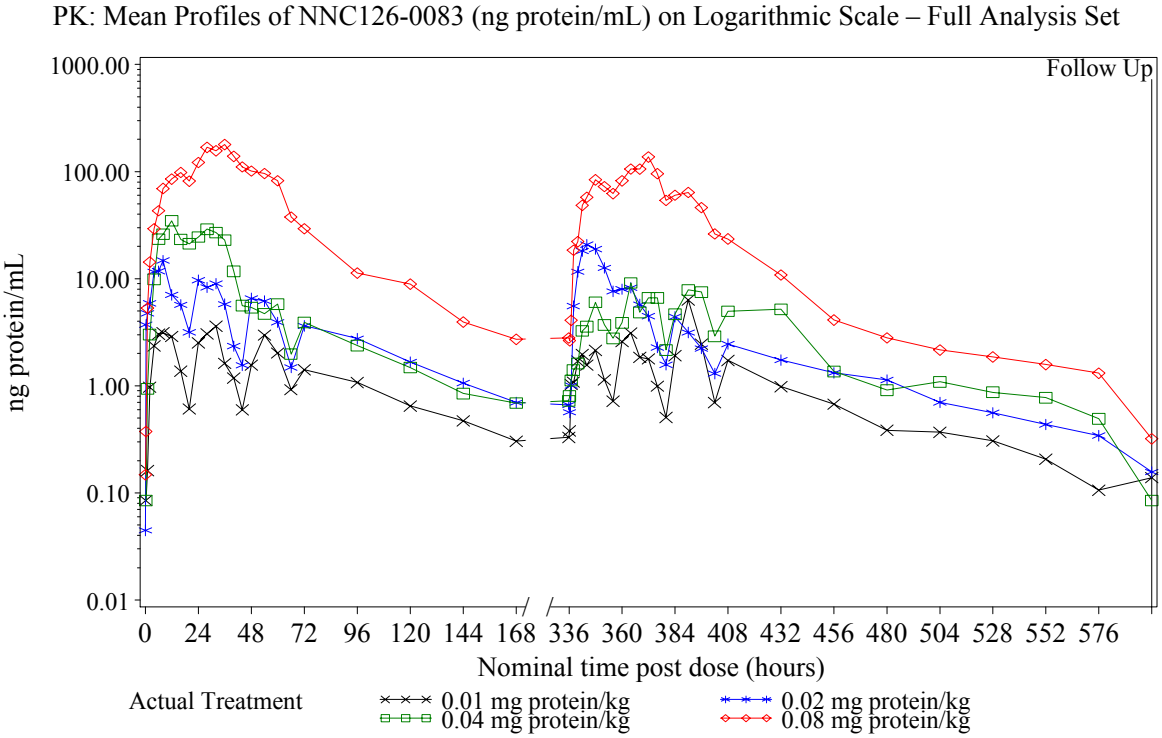

Figure 1 NNC126-0083: Mean Plasma Concentration–Time Profiles (ng protein/mL)

Pharmacodynamics

- After NNC126-0083 administration a clear dose-dependent increase in IGF-I levels was observed at all doses administered (Figures 2 and 3).
- Statistically significant increases in the estimated mean IGF-I SDS C_{max} and IGF-I SDS $AUC_{0\text{-}168h}$ were seen at all dose levels when compared to placebo.
  - The estimated mean IGF-I SDS C_{max} and IGF-I SDS $AUC_{0\text{-}168h}$ during third dosing increased up to 6.7 SDS [95% CI: 5.5; 7.8] and up to 6.1 SDS [95% CI: 5.2; 7.1], respectively, compared to placebo when adjusting for baseline values (Table 1).
- Steady-state IGF-I appeared to have been reached at second dose.
- A clear dose-dependent increase was also observed in the IGFBP-3 levels.
- Statistically significant increases in the estimated mean IGFBP-3 SDS C_{max} and IGFBP-3 SDS $AUC_{0\text{-}168h}$ were seen at all dose levels, except the lowest dose, when compared to placebo.
  - The estimated mean IGFBP-3 SDS C_{max} and IGFBP-3 SDS $AUC_{0\text{-}168h}$ during third dosing increased up to 3.0 SDS [95% CI: 2.0; 3.9] and up to 2.8 SDS [95% CI: 1.9; 3.7], respectively, compared to placebo when adjusting for baseline values.
- For GHBP, no apparent dose–response was observed.

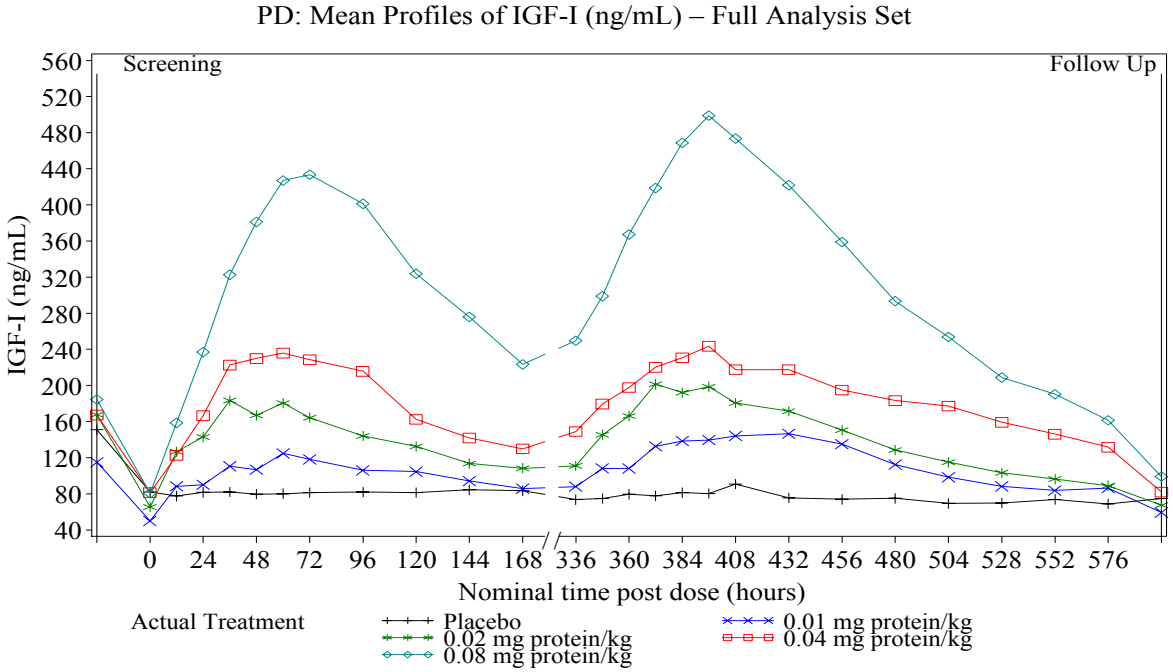

Figure 2 IGF-I Mean Profiles (ng/mL)

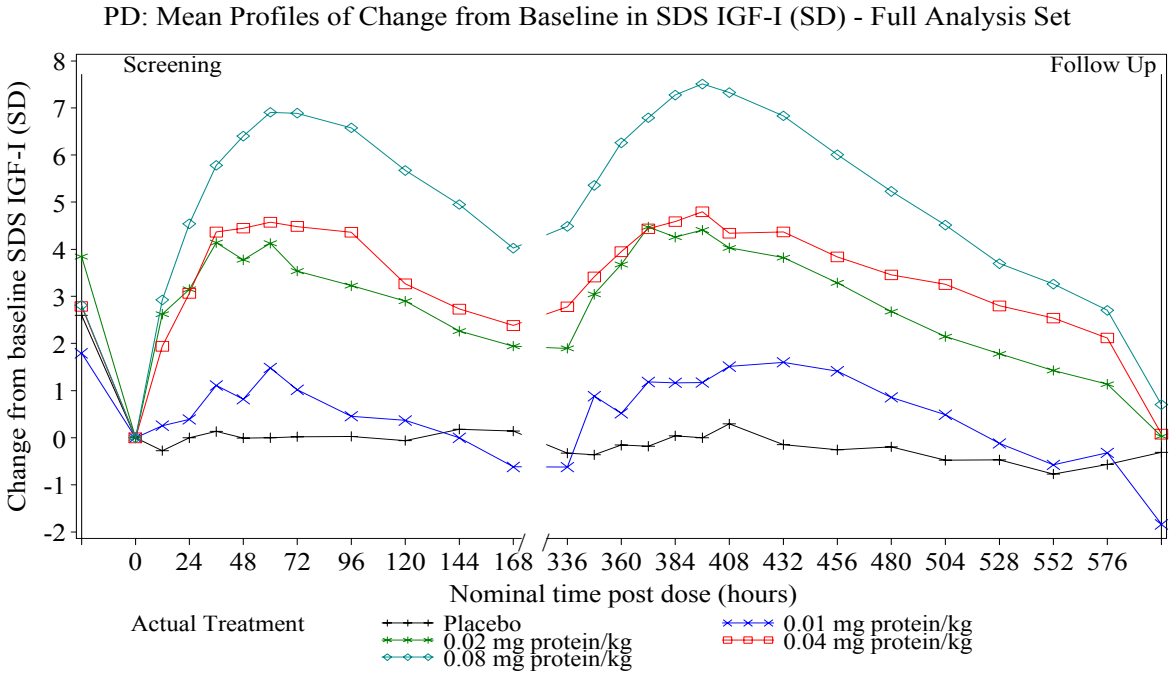

Figure 3 IGF-I Mean Profiles (SDS)

Table 1 IGF-I SDS C_{max} and IGF-I SDS AUC_{0-168h} after Third Dose, Adjusted for Baseline Values

	IGF-I SDS C_{max}		IGF-I SDS AUC_{0-168h}	
Dose (mg protein/kg)	Estimated mean difference (SDS)	95 % CI	Estimated mean difference (SDS)	95 % CI
0.01 versus placebo	1.6	[0.1; 3.0]	1.8	[0.5; 3.0]
0.02 versus placebo	3.6	[2.4; 4.7]	3.3	[2.4; 4.3]
0.04 versus placebo	4.6	[3.3; 5.8]	3.8	[2.8; 4.8]
0.08 versus placebo	6.7	[5.5; 7.8]	6.1	[5.2; 7.1]

Safety Results

- NNC126-0083 was well tolerated at all dose levels.
- A total of 43 adverse events were recorded in 21 subjects. There were no apparent differences in adverse events possibly or probably related to trial drug between NNC126-0083 and placebo.
- Four serious adverse events were recorded, all unlikely to be trial drug related (gastroenteritis in 3 subjects [0.04 mg protein/kg]) and urinary tract infection in 1 subject [placebo]).
- No significant difference in local tolerability between NNC126-0083 and placebo was observed. The local tolerability reactions recorded were comparable to clinical experience with daily hGH treatment in both placebo and NNC126-0083 groups. There were no signs of lipoatrophy.
- No findings considered to be related to NNC126-0083 were observed in vital signs, physical examinations or ECG recordings.
- Fasting plasma glucose and insulin levels were moderately increased at 0.04 and 0.08 mg protein/kg, mainly during the first dosing (a well-known effect of GH treatment).
- A decrease in urea levels during the first and third dosing was observed, most pronounced at the highest dose (a well-known effect of GH treatment)
- No positive findings of antibodies against NNC126-0083 were observed.

Conclusions

- Three once-weekly doses of NNC126-0083 administered to AGHD subjects were well tolerated at all doses, that is up to 0.08 mg protein/kg, with no serious safety issues identified.
- No significant local tolerability issues were identified.
- No positive findings of antibodies against NNC126-0083 were observed.
- The PK profiles after administration of NNC126-0083 showed deviations from dose-proportionality at the highest dose, where more than dose-proportional exposure was observed. No accumulation of NNC126-0083 was observed at any dose level.
- A clear dose-dependent PD response was observed with elevated IGF-I levels at all doses. Steady-state IGF-I appeared to have been reached at second dose.
- The present study strongly indicates that NNC126-0083 has the potential for an efficacious, well-tolerated, once-weekly compound in the treatment of AGHD.

The trial was conducted in accordance with the Declaration of Helsinki (2004) and ICH Good Clinical Practice (1996).