Pegylated Long-Acting Human Growth Hormone Is Well-Tolerated in Healthy Subjects and Possesses a Potential Once-Weekly Pharmacokinetic and Pharmacodynamic Treatment Profile

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Background: Recombinant human GH (rhGH) is usually administered as a daily sc injection, which may be both inconvenient and distressing for patients. NNC126-0083 is a pegylated rhGH developed with the aim of reducing serum clearance and thereby prolonging the exposure leading to once-weekly sc administration.

Objectives: In this first human dose trial, the safety, tolerability, pharmacokinetics, and pharmacodynamic parameters of a single administration of NNC126-0083 were evaluated.

Subjects and Methods: Seven groups of eight healthy male volunteers were dosed once with a single sc administration of NNC126-0083 (n = 6) or placebo (n = 2). The doses were escalated between the cohorts in a sequential mode. Blood samples for assessment of safety, pharmacokinetics, and pharmacodynamic response (IGF-I, IGF binding protein-3, free IGF-I) as well as GH binding protein were taken up to 240 h after dosing.

Results: Seven doses of NNC126-0083 were administered. After NNC126-0083 administration, a significant deviation from pharmacokinetic dose proportionality was observed for the highest doses. A strong dose-dependent pharmacodynamic response was seen with elevated levels of IGF-I and IGF binding protein-3 for all doses administered. The elevation was maintained for more than 1 wk for the highest doses. All doses of NNC126-0083 were well tolerated. No local tolerability issues were identified.

Conclusion: After a single sc administration of NNC126-0083 in healthy male volunteers, a sustained dose-dependent pharmacodynamic response was induced. These results indicate that NNC126-0083 has the potential for an efficacious, well-tolerated, once-weekly rhGH compound in the treatment of GH deficiency in adults. (J Clin Endocrinol Metab 95: 3411–3417, 2010)
glycol (PEG) residue at glutamine 141 of the hGH molecule. The pegylation prolongs the in vivo mean residence time, mainly through reduced clearance by filtration in the kidneys (prolonged elimination phase) (3). Given current information, pegylation of proteins does not in itself seem to represent a safety risk to humans (4–8).

We present the results from the first human dose trial with NNC126-0083. The trial was performed to assess the short-term safety, local tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of NNC126-0083 compared with placebo after ascending single sc doses in healthy male subjects. Also, injection site reactions for NNC126-0083 were compared with those of a single dose of Norditropin SimpleXx (Novo Nordisk A/S, Denmark). Furthermore, the PD of ascending single sc doses of NNC126-0083 was compared with that of a single dose of Norditropin SimpleXx.

Harmonization Good Clinical Practice (10). The trial was approved by the Danish Medicines Agency and by an independent local ethics committee.

Subjects and Methods

Subjects

Healthy, nonsmoking, male subjects aged 20–40 yr (weight <100 kg; body mass index, 19–28 kg/m²) were recruited in the trial. Institutional Review Board approval was obtained, and all subjects signed informed consent forms. In total, 58 subjects were randomized and exposed to trial product. Two subjects withdrew after dose, up to 24 h after treatment with Norditropin SimpleXx, before dosing with NNC126-0083, and against hGH were collected: before dosing and up to 48 h after treatment with Norditropin SimpleXx, (0, 1, 2, 4, 6, 8, 12, 16, 20, and 24 h) and up to 10 d (240 h) after treatment with NNC126-0083 (0, 1, 2, 4, 6, 8, 12, 16, 20, and 24 h on d 1, and less frequently thereafter).

Analysis of plasma concentrations of NNC126-0083 were conducted at York Bioanalytical Solutions Ltd. (York, UK) using a validated NNC126-0083-specific ELISA developed by Novo Nordisk A/S. The assay was a sandwich ELISA where monoclonal anti-NNC126-0083 antibodies were used as capturing antibodies and biotin-labeled hGH-specific monoclonal antibodies were used as detection antibodies. All samples from subjects receiving active treatment were analyzed for NNC126-0083. From subjects receiving placebo, only the samples taken before dose and 48 h after dose were analyzed to verify placebo.

In the ELISA, the capturing antibody specifically binds to the PEG moiety of NNC126-0083 and hence, is specific to NNC126-0083. Therefore, only NNC126-0083 is measured because GH without PEG is not captured and does not interfere in the assay. Analysis of recombinant hGH (rhGH) in plasma was conducted at Capio Diagnostic A/S (Copenhagen, Denmark) using a commercially available immunoradiometric assay (Biocode; Hycel, Liège, Belgium) measuring rhGH as well as endogenous GH.

PD

Blood samples for PK assessment were collected 30 min before dose and up to 24 h after treatment with Norditropin SimpleXx (0, 1, 2, 4, 6, 8, 12, 16, 20, and 24 h) and up to 10 d (240 h) after treatment with NNC126-0083 (0, 1, 2, 4, 6, 8, 12, 16, 20, and 24 h on d 1, and less frequently thereafter).

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Antibodies

Blood samples for measurement of antibodies against NNC126-0083 and against hGH were collected: before dosing with Norditropin SimpleXx, before dosing with NNC126-0083,
10 d after dosing with NNC126-0083, and at the follow-up visit 28–40 d after dosing with NNC126-0083. Determination of antibodies toward NNC126-0083 in serum was performed by screening samples with a bridging ELISA developed by Novo Nordisk A/S that detects antibodies that bind to NNC126-0083. Antibody specificity to either NNC126-0083 or hGH was analyzed by a competitive inhibition test in which samples that were positive in the screening assay were analyzed with and without preincubation with either NNC126-0083 or hGH. Antibody responses were furthermore characterized for in vitro neutralizing effect using a BAF-3 cell-based proliferation assay. The BAF-3 cells were stably transfected with hGH receptor, resulting in dependence on either NNC126-0083 or hGH for growth and survival. The cell line shows a dose-related stimulation of proliferation by adding increasing concentrations of hGH or hGH analogs. An antibody response would be characterized as in vitro neutralizing if it inhibits cell proliferation. The analysis was carried out at Novo Nordisk A/S (Maaloev, Denmark).

Safety

The safety of NNC126-0083 was assessed from adverse events, clinical laboratory assessments, physical examinations, vital signs, electrocardiogram, and injection site tolerability.

Statistical analysis

PK

Derived PK endpoints included peak plasma concentration ($C_{\text{max}}$), time to maximum plasma concentration ($t_{\text{max}}$), area under the curve (AUC) (NNC126-0083: AUC$_{0–168\ h}$; Norditropin SimpleXx: AUC$_{0–6\ h}$, AUC$_{0–24\ h}$), and terminal half-life, which were calculated using standard noncompartmental methods. For NNC126-0083, dose-linearity of AUC and $C_{\text{max}}$ were investigated by testing the unity of the slope in linear regression models of log (AUC) and log($C_{\text{max}}$), respectively, on log(dose) where dose is in milligrams of protein per kilogram.

PD

IGF-I, free IGF-I, IGFBP-3, GHBP, $C_{\text{max}}$, and AUC were calculated using standard noncompartmental methods. Statistical comparison of the NNC126-0083 dose groups vs. placebo for $C_{\text{max}}$ and AUC$_{0–168\ h}$ was conducted by an ANOVA model. The endpoints were log-transformed and analyzed with a fixed effect and with the log-transformed baseline value as a covariate. The estimated mean differences of the logarithmic endpoints of each dose level of NNC126-0083 compared with placebo were transformed back to the original scale and presented as ratios of means including 95% confidence interval (CI). Furthermore, for each dose level, a $P$ value for test of the hypothesis of no difference compared with placebo is presented. A significance level of 5% was used throughout the statistical analyses. All tests were two-sided.

A total of 56 subjects were included in the PK/PD analysis set (all completers) and 58 subjects were included in the safety analysis set (all exposed).

Results

Baseline characteristics

Baseline characteristics were similar across treatment groups. The mean (sd) age was 28.2 (6.1) yr. The mean (sd) weight was 78.9 (9.2) kg, and the mean (sd) body mass index was 24.5 (2.3) kg/m$^2$. The majority of subjects (51 of 58) were Caucasians, two were African-Americans, and five were of other ethnic origin.

PK

The PK mean profiles after single-dose administration of NNC126-0083 are presented in Fig. 2. Systemic exposure to NNC126-0083, as measured by AUC$_{0–168\ h}$ and $C_{\text{max}}$, increased with increasing dose (Table 1). An overall significant deviation from dose-linearity was observed ($P < 0.0001$), most pronounced at high doses ($\geq 0.08$ mg NNC126-0083/kg). At these doses, $C_{\text{max}}$ and AUC$_{0–168\ h}$ increased more than proportionally with dose. The PK of NNC126-0083 is nonlinear, in the sense that clearance of the drug becomes saturated. This is reflected in $C_{\text{max}}$ and AUC, which at higher doses are more than proportionally increased. The estimated relative increases for $C_{\text{max}}$ and AUC$_{0–168\ h}$ were 3.5 and 4.5, respectively, for a doubling in dose. Nonlinear elimination after $C_{\text{max}}$ was also indicated at the high doses. A diurnal variation in the PK profiles was observed. The diurnal variations were present in all dose groups. On the relative scale (i.e. log scale), the fluctuations were most pronounced in the low-dose groups, whereas on the absolute scale the fluctuations increased with dose. The PK properties of Norditropin SimpleXx after a single sc injection were as expected.

PD

A strong dose-dependent PD response was observed with elevated IGF-I levels at all doses administered compared with placebo (Fig. 3A and Table 2). The dose-dependent increase in IGF-I was statistically significant, ex-
except for IGF-I \(C_{\text{max}}\) at the lowest dose. Mean IGF-I \(t_{\text{max}}\) ranged between 62 and 97 h after dosing and reached an average peak of 1113 ng/ml at the highest dose. The baseline mean level was 204 ng/ml. The IGF-I elevation was maintained for more than 1 wk at the highest doses. The estimated mean IGF-I \(C_{\text{max}}\) increased up to 4.3 times (95% CI, 3.7; 5.0) compared with placebo. The estimated mean IGF-I AUC\(_{0–168}\) h increased up to 3.5 times (95% CI, 3.1; 3.9) compared with placebo. A similar response pattern was seen for free IGF-I as for IGF-I (Fig. 3). Diurnal fluctuations were also observed to some degree in free IGF-I (Fig. 3B). No marked diurnal fluctuations were observed with placebo (Fig. 3).

A statistically significant dose-response was also observed in the IGFBP-3 profiles, except at the two lowest dose levels. Mean IGFBP-3 \(t_{\text{max}}\) ranged from 88 to 130 h after dosing and reached an average peak of 7980 ng/ml. The baseline mean level was 4397 ng/ml. The estimated mean IGFBP-3 \(C_{\text{max}}\) increased up to 1.6 times (95% CI, 1.4; 1.7) compared with placebo. The estimated mean IGFBP-3 AUC\(_{0–168}\) h increased up to 1.4 times (95% CI, 1.3; 1.5) compared with placebo. No apparent dose-response or systemic variation was observed for GHBP after treatment with NNC126-0083.

After administration of Norditropin SimpleXx, a clear PD response was observed with elevated IGF-I levels at both dose levels (Fig. 3A). Mean IGF-I \(t_{\text{max}}\) was 27 and 30 h after dosing and reached an average peak of 344 ng/ml with a dose of 0.04 mg/kg (baseline mean IGF-I, 182.9 ng/ml). No marked difference between doses was observed. Similar diurnal fluctuations were observed in free IGF-I as observed with NNC126-0083 (Fig. 3B).

Under the conditions of this trial, the IGF-I response for NNC126-0083 at 0.01–0.04 mg protein/kg was comparable to the response observed for Norditropin SimpleXx at 0.02–0.04 mg/kg (Fig. 3A).

### Safety

NNC126-0083 was well tolerated at all doses. No serious adverse events were reported. In the NNC126-0083 group, 92 events were reported in 31 subjects. The most frequent adverse events were considered to be typical for this class of compounds and included headaches (21 events in 15 subjects) and edema (seven events in three subjects). Headaches were reported from 1 to 11 d after dosing and lasted in most

<table>
<thead>
<tr>
<th>Dose of NNC126-0083 mg protein/kg</th>
<th>n</th>
<th>AUC(_{0–168}) h ((h \times \text{ng protein/ml}))</th>
<th>(C_{\text{max}}) ((\text{ng protein/ml}))</th>
<th>(t_{\text{max}}) (h)</th>
<th>nt</th>
<th>(t_{1/2}) (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.005</td>
<td>6</td>
<td>130 (45)</td>
<td>6.4 (5.4)</td>
<td>16.3 (14.0)</td>
<td>1</td>
<td>187.4 (.)</td>
</tr>
<tr>
<td>0.01</td>
<td>6</td>
<td>174 (106)</td>
<td>11.1 (9.8)</td>
<td>9.0 (2.5)</td>
<td>0</td>
<td>N.C.</td>
</tr>
<tr>
<td>0.02</td>
<td>6</td>
<td>518 (194)</td>
<td>25.2 (19.3)</td>
<td>9.0 (3.5)</td>
<td>1</td>
<td>27.3 (.)</td>
</tr>
<tr>
<td>0.04</td>
<td>6</td>
<td>1,324 (819)</td>
<td>62.6 (58.6)</td>
<td>22.0 (20.2)</td>
<td>4</td>
<td>36.2 (18.5)</td>
</tr>
<tr>
<td>0.08</td>
<td>6</td>
<td>7,977 (6,043)</td>
<td>268 (171)</td>
<td>20.7 (7.3)</td>
<td>5</td>
<td>32.5 (7.4)</td>
</tr>
<tr>
<td>0.16</td>
<td>5</td>
<td>31,428 (16,190)</td>
<td>1,031 (346)</td>
<td>24.8 (10.4)</td>
<td>5</td>
<td>42.4 (11.6)</td>
</tr>
<tr>
<td>0.33</td>
<td>6</td>
<td>123,485 (30,231)</td>
<td>2,983 (1,547)</td>
<td>47.6 (8.0)</td>
<td>6</td>
<td>59.7 (33.7)</td>
</tr>
</tbody>
</table>

Data are presented as mean (SD). The terminal half-life \(t_{1/2}\) for the lowest dose is disregarded (187.4 h). Several profiles were not found suitable for estimation of the terminal elimination phase by noncompartmental methods, primarily due to the diurnal variation. Estimates were therefore only available for one profile at the 0.005 and 0.02 mg protein/kg doses, whereas no value could be estimated for the 0.01 mg protein/kg group for \(t_{1/2}\). N.C., Not calculated.
Most cases were of mild severity. Edema was reported from 2 to 4 d after dosing and lasted from 1 to 4 d. Edema was also graded mild in most cases. No local tolerability issues were identified.

Ten of 58 subjects (17%) experienced 30 possibly/probably treatment-related adverse events. For the highest doses of NNC126-0083, 0.16 and 0.33 mg protein/kg, an increased frequency of headaches was observed compared with placebo. At 0.33 mg protein/kg, adverse events primarily related to peripheral fluid retention were observed (a well-known effect of hGH). One event of mild tenderness at the injection site was reported 6 h after dose in one subject dosed with 0.33 mg protein/kg. No other injection site reactions after NNC126-0083 treatment were reported. All adverse events classified as possibly or probably related to NNC126-0083 treatment were graded mild (29 of 30) or moderate (one of 30), and all had resolved by the end of the trial. There were no clinically significant changes in physical examination, blood pressure, or electrocardiogram during exposure to NNC126-0083.

Initial increased levels of fasting blood glucose (peak 6.6 mmol/liter for 0.33 mg protein/kg) and insulin (peak 150 pmol/liter for 0.33 mg protein/kg) were observed up to 6 d after dosing at doses of at least 0.08 mg protein/kg. The increases were most pronounced at the two highest doses. An increase in glucose and insulin was also observed after daily Norditropin SimpleXx administration. It is not possible to make a valid statistical comparison between a once-weekly exposure to a single dose once-daily exposure. Transient and mild changes in clinical chemistry parameters were observed, including increases in serum alanine aminotransferase, serum glutamic oxaloacetic transaminase, and inorganic phosphate levels at doses at least 0.16 mg protein/kg, and decreased levels of potassium (≥0.08 mg protein/kg) and urea (≥0.16 mg protein/kg). The increases in serum alanine aminotransferase and serum glutamic oxaloacetic transaminase levels were observed on d 8–11 at dose levels of at least 0.48 mg/kg. The mean values were all within the reference range, and the individually increased values had returned to normal at the follow-up visit in the majority of subjects.

Antibodies

One sample positive for NNC126-0083 antibodies was seen 10 d after dosing of 0.01 mg protein/kg. No cross-reactivity to GH was demonstrated. The sample was negative for in vitro neutralizing antibodies against NNC126-0083. The follow-up assessment 29 d after dosing was negative. There was no apparent influence on PK and PD parameters.

**Discussion**

NNC126-0083 was well tolerated at all doses administered. The maximum tolerated dose was therefore considered to be at least 0.33 mg protein/kg, the highest dose
administered. The GH products currently marketed in the European Union and the United States are all short-acting (i.e., the treatment regimen usually follows daily injections). Although GH treatment has proved both efficacious and safe, one major drawback of the treatment has been the need for daily sc injections, which represents a burden for the children and their parents, resulting in very low compliance in some cases (11). In a recent trial, approximately 25% missed three injections or more per month using needle and syringe administration, and 13% missed over one half of the prescribed dose (12). Furthermore, it has been recently reported that children as well as adolescents and adults receiving GH treatment had a low compliance after 2 yr of treatment and that difficulties with injections play a significant role (13). Development of liquid GH and convenient pen devices has simplified the administration process. However, these advancements still necessitate daily GH treatment. Thus, there is a need for a treatment with less frequency of injections when administering GH.

Because the safety of Norditropin SimpleXx as a once-daily GH treatment is well established, the primary focus of safety of NNC126-0083 was local tolerability (injection site reactions). Hence, a secondary objective of the trial was to compare injection site reactions of single doses of NNC126-0083 with those of a single dose of Norditropin SimpleXx. No significant local tolerability issues were identified. The subject who experienced mild pain/tenderness at the injection site after NNC126-0083 administration was in the highest dose group (0.33 mg protein/kg), which received the highest dose volume per kilogram (48 µl/kg). Other subjects in this group received similar or higher total dose volumes without developing injection site reactions. The highest dose in the current trial is outside the planned therapeutic doses in future trials in GHD and AGHD subjects. Dose levels planned for future trials in GHD and AGHD subjects will range from 0.01 to 0.08 mg protein/kg, and same doses are planned for a trial in GHD children. Mild tenderness at the injection site was also reported in one subject dosed with Norditropin SimpleXx at 0.02 mg/kg (6 µl/kg). The same subject received NNC126-0083 at 0.02 mg protein/kg (3 µl/kg) without any injection site reactions. Based on these observations, dosing with NNC126-0083 at anticipated therapeutic doses is not expected to cause any different local tolerability issues with regard to injection site reactions compared with daily hGH administration. Thus, the long-acting preparation of GH (NNC126-0083) reported in the present trial was well tolerated in healthy male subjects. It should be emphasized that the current trial only provides short-term data on local tolerability given the single administration, and longer term trials with other long-acting GH formulations have caused lipoatrophy. In a recent publication, lipoatrophy was reported when administering a pegylated GH compound after single as well as after multiple administration (14). In another trial lasting up to 24 moths, Nutropin Depot, a rhGH encapsulated in microspheres, was associated with injection site reactions in the vast majority of patients, and in 11% lipoatrophy was observed (15, 16).

The PK profiles after administration of NNC126-0083 showed significant deviation from dose linearity. Cmax and AUC0–168 h increased more than proportionally with dose, but this was primarily seen at high doses (≥0.08 mg protein/kg), that is at doses higher than expected normal therapeutic doses. A diurnal fluctuation in the PK profiles was observed. The diurnal variations were present in all dose groups. On the relative scale (i.e., log scale), the fluctuations were most pronounced in the low-dose groups, whereas on the absolute scale the fluctuations increased with dose. Several activities were performed to elucidate the reason for these fluctuations—for example, if it could be explained by sample handling procedures or the assay applied for quantification of NNC126-0083.

However, handling procedure was according to instructions, and assay applied is specific toward NNC126-0083. One explanation could be diurnal variation in lymphatic drainage in the sc tissue (17). Subcutaneous absorption can take place via the blood vessels or via the lymph. The main determinant for absorption via blood vessels or lymph is molecular size. Furthermore, lymph flow rate shows significant diurnal variation with a very low flow during the night. Thus, the observed diurnal variation in NNC126-0083 having a much larger molecular weight than GH may be attributed to diurnal variation in lymphatic drainage in the sc tissue, although this needs to be further explored. Fluctuations in the PK profiles were observed when four different assays were used [two ELISA methods (NNC126-0083 ELISA and immunoradiometric assay), one method based on GHBP, and one cell-based assay]. Because the assay for NNC126-0083 is specific toward NNC126-0083 (see Subjects and Methods), and hence does not measure endogenous GH, it can be excluded that endogenous GH explains the observed diurnal fluctuations in NNC126-0083. A minor degree of fluctuation in free IGF-I was observed after NNC126-0083 administration as well as after rhGH administration in the present study. Diurnal fluctuations in free IGF-I have previously been observed and have been suggested to be parallel to variations in insulin (through its impact on IGFBP-1) (18).

Comparing the PD of NNC126-0083 and Norditropin SimpleXx was a secondary objective of the trial. NNC126-0083 is a long-acting compound compared with the once-daily Norditropin SimpleXx, and this should be kept in
mind when comparing the PD response of the two compounds after a single dose. Plasma samples were collected and analyzed up to 48 h after dosing for Norditropin SimplexX and up to 240 h after dosing for NNC126-0083. Considering the above-mentioned differences, it is not possible to make a valid comparison between once-daily and long-acting compounds at a time when steady state is not yet reached. As a rough comparison, the PD response based on $C_{\text{max}}$ rather than AUC was considered most appropriate. The mean IGF-I $C_{\text{max}}$ for Norditropin SimplexX increased by factors 1.62 (0.02 mg/kg) and 1.94 (0.04 mg/kg) from baseline values. In comparison, the levels increased by factors 1.36 (0.01 mg protein/kg), 1.89 (0.02 mg protein/kg), and 2.28 (0.04 mg protein/kg) after treatment with NNC126-0083. Thus, the IGF-I response for once-weekly NNC126-0083 at 0.01–0.04 mg protein/kg was comparable to the response observed for once-daily Norditropin SimplexX.

In conclusion, single doses of NNC126-0083 administered subcutaneously to healthy male subjects were tolerated at all doses (that is up to 0.33 mg protein/kg), with no serious safety issues or significant local tolerability issues identified. A significant dose-dependent IGF-I response was induced at all dose levels, with elevated IGF-I levels at all doses of NNC126-0083. The IGF-I response after a single dose of NNC126-0083 at 0.01–0.04 mg protein/kg was comparable to the response after a single dose of Norditropin SimplexX at 0.02–0.04 mg/kg under the conditions of this trial. Future clinical trials need to determine whether long-term administration with NNC126-0083 is efficacious and safe in GHD adults and children. The present trial indicates that NNC126-0083 has the potential for an efficacious, well-tolerated, once-weekly GH treatment of GHD in adults.

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