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ORIGINAL RESEARCH ARTICLE

Population Pharmacokinetics and Pharmacodynamics of Once-Daily Growth Hormone Norditropin® in Children and Adults

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Abstract

Background and Objective Once-daily injectable recombinant human growth hormone (GH) formulations (e.g. Norditropin®; Novo Nordisk A/S) are used to treat GH deficiency in children and adults, with much of the therapeutic effect mediated via the insulin-like growth factor-I (IGF-I) response. Despite a long history of use, there are few data on the pharmacokinetics and pharmacodynamics (serum IGF-I response) of this therapy, or of potential differences in the relationship of GH pharmacokinetic/pharmacodynamic (PK/PD) effects between children and adults. This study aimed to characterise the GH pharmacokinetics and IGF-I profile following daily subcutaneous GH in adults and children with GH deficiency.

Methods A model was developed based on a population PK/PD modelling meta-analysis of data from three phase I clinical trials (two using Norditropin® as a comparator with somapacitan, and one as a comparator with a pegylated GH product). Sequential model building was performed, first developing a model that could describe GH pharmacokinetics. A PD model of IGF-I data was then developed using PK and PD data, and where all PK parameters were kept fixed to those estimated in the PK model.

Results The model developed accurately describes and predicts GH pharmacokinetics and IGF-I response. Body weight was shown to have an important inversely correlated influence on GH exposure (and IGF-I standard deviation score), and this largely explained differences between adults and children.

Conclusions The pharmacokinetics/pharmacodynamics developed here can inform expectations about the PD effects of different doses of GH in patients with GH deficiency of different body weights, regardless of their age.

Clinical Trial Registration Pooled modelling analysis of data from ClinicalTrials.gov identifiers NCT01973244, NCT00936403 and NCT01706783.

Dates of registration NCT01973244: 22 October, 2013; NCT00936403: 9 July, 2009; NCT01706783: 11 October, 2012.

1 Introduction

Growth hormone deficiency (GHD) affects both children and adults, with the clinical manifestations varying depending on the age of onset [1–3]. In children, GHD is characterised by growth failure [3]. In adults, the characteristic features of GHD include central obesity, loss of lean muscle mass, decreased bone mass and possibly reduced quality of life [1, 2]. Replacement therapy

Key Points

This is the first model-based meta-analysis of the pharmacokinetics and pharmacodynamics of the insulin-like growth factor-I (IGF-I) response during clinical use of growth hormone in children and adults with growth hormone deficiency.

Body weight was found to explain the differences in pharmacokinetics and part of the difference in the pharmacokinetic/pharmacodynamic relationship (to IGF-I) between children and adults.

Exposure–response data were used to identify the doses and exposures needed to provide matching IGF-I results in children and adults.

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with exogenous human growth hormone (GH) has been used successfully to treat short stature in children with GHD for many years [4]. Growth hormone is also of benefit for the treatment of adults with GHD [5–7], in whom clinical features, such as central obesity and osteoporosis, may be ameliorated or reversed following sustained daily GH replacement therapy.

Physiological GH secretory patterns are pulsatile. Growth hormone secretion is regulated by a number of neurotransmitter pathways and peripheral feedback signals that act directly on the anterior pituitary gland and/or modulate the secretion of GH-releasing hormone or somatostatin, from the hypothalamus [8]. Age, nutritional status and sex also affect GH secretion [8]. Growth hormone pulses, which account for most (85%) of the daily GH production, occur mainly at night, while nadir GH levels occur mainly during the daytime [9]. Exogenous GH administration, given once daily or at more prolonged intervals, however, does not mimic the endogenous pulsatile pattern of hormone secretion. Nevertheless, in clinical trials, only minor differences have been observed between daily subcutaneous injections and continuous infusions of GH in terms of producing insulin-like growth factor-I (IGF-I) and promoting linear growth [10, 11]. Changes in serum IGF-I levels are considered to be a good predictor of the treatment response to GH [12]. Clinical guidelines recommend measuring serum IGF-I levels in GH-treated children to monitor compliance and the production of IGF-I after GH dose changes. They suggest that the GH dose should be decreased if serum IGF-I levels rise above the laboratory-defined upper limit of the normal range for the age or stage of puberty of the patient [3] (although, in children born short for gestational age, higher than normal IGF-I levels may be therapeutically appropriate). In adults, serum levels of IGF-I are similarly used to guide GH dose adjustments [13].

Data on the pharmacokinetic (PK) and pharmacodynamic (PD) (as assessed by serum IGF-I levels) profile following daily subcutaneous injection of recombinant human GH are sparse both for children [14–16] and for adults [17, 18], and are typically based on small ($n \leq 20$) numbers of patients. Additionally, the potential differences in the relationship of GH pharmacokinetics and pharmacodynamics between children and adults have not been clearly established. Thus, the aim of this study was to characterise the pharmacokinetics and IGF-I profile of daily subcutaneous injections of GH (Norditropin® [somatropin]; Novo Nordisk A/S, Søborg, Denmark) in adults and children with GHD based on a population PK/PD modelling meta-analysis of data from three phase I clinical trials. In addition, we aimed to explore potential covariates that explain observed differences in GH pharmacokinetics and pharmacodynamics between children and adults with GHD.

2 Methods

2.1 Data Description

We conducted a pooled modelling analysis of data from three phase I trials, in which GH was used as a comparator arm: two randomised studies of children with GHD (Trial 1, ClinicalTrials.gov identifier NCT01973244 [19] and Trial 2, NCT00936403 [20]), and one randomised study of subjects with adult GHD (Trial 3, NCT01706783) [21]. Details of the study designs and inclusion/exclusion criteria for these three trials have previously been published in full [19–21].

In brief, Trial 1 was a phase I, randomised, open-label, active-controlled, dose-escalation trial involving 32 prepubertal GH-treated children with GHD, in which Nordtropin® was used as an active comparator to somapacitan (a once-weekly GH in development) [19]. Subjects were sequentially randomised 3:1 within each of four cohorts to a single subcutaneous dose of somapacitan or once-daily subcutaneous injection of GH (Norditropin® NordiPen®; Novo Nordisk A/S; 0.03 mg/kg; $n = 8$) for 7 days. After a GH wash-out period of 7–10 days, blood samples for PK assessments were taken before the first treatment injection, then at 1, 4, 8, 12, 16, 24, 28, 36, 48, 72, 96, 168 and 240 h following the first dose, and at the follow-up visit scheduled at 28–35 days after the first injection. Pharmacodynamic parameters were also assessed using some of these samples.

Trial 2 was a single-dose, dose-escalation trial designed to investigate the safety, tolerability, pharmacokinetics and pharmacodynamics of NNC126-0083, a pegylated long-acting GH, in prepubertal children with GHD, with Norditropin® as the active comparator [20]. The subjects were randomised (3:1) to treatment with either a single dose of NNC126-0083 or 7 days of once-daily subcutaneous injections of GH (Norditropin® NordiFlex®; Novo Nordisk A/S; 0.035 mg/kg; $n = 8$). Previous GH treatment was stopped 7–9 days before the first injection with the trial product. At each dose level, blood samples for PK assessments were taken before the first treatment injection, at the time of the first injection, then 15 min, 1, 2, 4, 6 and 8 h post-dose, and then every fourth hour until 48 h post-injection. Thereafter, sampling was done every 6 h until 72 h post-injection, and once during each following visit up to the final follow-up visit at 27–31 days after the first injection. Pharmacodynamic parameters were also assessed using some of these samples.

Trial 3 was a phase I, randomised, open-label, active-controlled, multiple-dose, dose-escalation trial involving 34 GH-treated adult subjects with GHD, in which Nordtropin® was used as an active comparator to somapacitan [21].

Adult subjects were sequentially assigned into four cohorts, each comprising eight subjects, randomised within each cohort (3:1) to once-weekly somapacitan or daily subcutaneous injections of GH (Norditropin® NordiFlex®; mean 0.0042 mg/kg; $n = 8$) for 4 weeks at a dose that replicated the pre-trial dose of GH. Daily GH treatment was discontinued 14 days before the trial start. After the first and fourth doses of somapacitan, blood samples for PK assessments were collected at baseline, and 7 days after the first and fourth somapacitan dose (0, 12, 24, 48, 72, 96, 120, 144 and 168 h). Pharmacodynamic parameters were also assessed using some of these samples.

2.2 PK/PD Modelling Strategy

Structural model development was performed using a sequential model building approach. Initially, a PK model for GH was developed. When an adequate description of the PK data was achieved, a PD model of IGF-I data was developed using PK and PD data, and where all PK parameters were kept fixed to those estimated in the PK model.

2.3 Assays and Data Handling

The concentration of GH in serum from subjects treated with Norditropin® NordiPen® (Trial 1) and Norditropin® NordiFlex® (Trials 2 and 3) was assessed at the central laboratory using a commercially available kit (Siemens IMMULITE® 2000; Siemens Medical Solutions Diagnostics GmbH, Fernwald, Germany). Analysis of serum IGF-I concentrations was performed using commercially available assay kits (Siemens IMMULITE® [Trial 2]; Immuno Diagnostic Systems immunoassay ISYS assay, Boldon, UK [Trials 1 and 3]) at the analytical central laboratory Laboratorium für Klinische Forschung GmbH, Schwentinental, Germany. Growth hormone and IGF-I assay performance were in accordance with the assay information provided by the manufacturers.

Pharmacokinetic data below the lower limit of quantification were excluded from the analysis, these values being 0.10 ng/mL in Trials 1 and 3, and 0.010 ng/mL in Trial 2. Additive, proportional and combined additive and proportional error models were tested during model development. For the final PK model, the residual error of GH PK data (ng/mL) was assumed to follow a proportional distribution, and separate residual distributions were estimated for adult and child data. For the final PK/PD model, the residual error of IGF-I (ng/mL) was assumed to follow a proportional distribution, and separate residual distributions were estimated for each trial to account for potential differences resulting from the assays.

2.4 Structural PK/PD Model

Several structural PK models were tested to describe the GH pharmacokinetics. These included one- and two-compartment disposition models, with combinations of linear and transit-compartment absorption models, and linear or saturable elimination models. To describe the baseline GH levels observed prior to initial dosing, a zero-order GH rate constant was used.

Indirect response PK/PD models with either additive or proportional effects of GH on the input rate of IGF-I were tested to describe the concentration–response relationship and delay observed between time to maximum concentration for GH and time to maximum concentration for IGF-I. E_{max} models were used, as the relationship between GH pharmacokinetics and IGF-I production following GH analogs has previously been well characterised by such models in both adults and children [22, 23]. In addition to an estimate of the IGF-I production rate at zero GH concentration (K_{in}), an estimate was derived for the endogenous GH level ($K_{in,\,endo}$) based on the estimated E_{max} relationships for children and adults.

It was realised during model development that the E_{max} parameter was not identifiable in the adult population in this study, as only one dose concentration was administered and the PK levels were well below the GH concentration corresponding to half-maximum stimulation of IGF-I production rate (EC_{50}) levels estimated (see Table 2 for the final model). Therefore, model development was conducted with the typical estimate for E_{max} for adults fixed to that obtained for somapacitan in a meta-analysis also including Trials 1 and 3 [23]. This was done under the assumption that the maximum possible stimulation of IGF-I production would be similar between Norditropin® and somapacitan. In children, the E_{max} parameter was identifiable in this study, as higher PK levels were obtained in the range of the EC_{50} for somapacitan.

2.5 Model Variability

Base PK and PK/PD models were constructed with inter-individual variability (IIV) and without covariates. Inter-individual variabilities for PK and PK/PD parameters were assumed to follow log-normal distributions. A systematic stepwise search for IIVs on PK and PD parameters was conducted using maximum likelihood of models with IIV. Parameter IIVs were included in the model when they led to a significant drop in the objective function value (< -10.83, $p < 0.001$).

2.6 Covariate Analysis

Final PK and PK/PD models including covariates were identified by including a prespecified set of covariates on

all model parameters identified with IIV. Body weight (kg) and age group (children/adults) were the only tested covariates, and were selected to investigate to what degree body weight could explain differences in PK and PD parameters in children and adults. Sex was not tested because of the small number of female individuals in the data ($n = 4$).

Body weight was included as a continuous covariate and implemented as follows:

$$P_i = P_{\text{typ}} \cdot \left(\frac{\text{BW}}{70\ \text{kg}}\right)^{\theta_{\text{BW}_P}} \cdot e^{\eta_{P_i}}$$

where P_i is the individual parameter for subject i, P_{typ} is the typical (population) parameter, BW is body weight, θ_{BW_P} is the covariate relationship and η_{P_i} is a normally distributed value describing the unexplained IIV for subject i. For adults, as $E_{\max}$ was not identifiable in these data, the typical $E_{\max}$ relationship to body weight was fixed to that estimated for somapacitan [15].

$$E\max i_{\text{adult}} = E\max\ \text{typ}_{\text{adult}} \cdot \left(\frac{\text{BW}}{85\ \text{kg}}\right)^{\theta_{\text{BW}_{E_{\max}\text{adult}}}} \cdot e^{\eta_{E_{\max} i}}$$

$$E\max i_{\text{child}} = E\max\ \text{typ}_{\text{child}} \cdot \left(\frac{\text{BW}}{25\ \text{kg}}\right)^{\theta_{\text{BW}_{E_{\max}\text{child}}}} \cdot e^{\eta_{E_{\max} i}}$$

The age group (child/adult) covariate was implemented as follows:

$$P_i = \left(P_{\text{typ}_{\text{adult}}}{}^{\text{adult}} + P_{\text{typ}_{\text{child}}}{}^{1-\text{adult}}\right) \cdot e^{\eta_{P_i}}$$

where adult is a discrete value taking 1 or 0 given the covariate and $P_{\text{typ}_{\text{adult}}}$ and $P_{\text{typ}_{\text{child}}}$ are the typical parameters (adult and child, respectively).

2.7 Model Evaluation and Model Selection

Model development and model selection were guided by comparison of the objective function value between nested models, model stability and precision of parameter estimates. Standard goodness-of-fit plots were generated while developing both PK and PK/PD models to evaluate the fit of the candidate models to the data. These included plots of the observed GH and IGF-I concentrations compared with population and individual predicted concentrations, and plots of conditional weighted residuals.

2.8 Model Simulations

Model simulations were performed using the individual post hoc Bayes estimates for each subject. Insulin-like growth factor-I simulations were performed on a ng/mL scale and values were transformed to an age- and sex-specific IGF-I standard deviation score (SDS) according to Bidlingmaier et al. [24].

2.9 Software Implementation

Population PK/PD analysis was performed using non-linear mixed-effects modelling with NONMEM® (Version 7.3; ICON Development Solutions, Hanover, MD, USA). Model parameters were estimated using the first-order conditional estimation with interaction method. The precision of model parameters was derived from the variance–covariance matrix produced by NONMEM®.

3 Results

3.1 Data and Demographics

A total of 23 subjects were eligible for the analysis: 15 children and eight adults with GHD. One adult subject was excluded from the analysis because of a potential dosing error indicated by a significantly higher PK profile following the first dose compared to subsequent doses (peak ratio of first:second dose, 4.05). These data were excluded, as this single outlier could potentially bias PK/PD interpretation across the population. The population baseline characteristics are presented in Table 1. A total of 614 PK data points were above the lower limit of quantification (0.5 ng/mL) and were included in the analysis. Conversely, 39 data points (5.4%) were below the lower limit of quantification and were excluded from the analysis. A total of 334 IGF-I data points were included in the analysis.

3.2 Pharmacokinetics of GH

3.2.1 Population PK Model

The structural model that best described the GH concentration–time profiles following daily subcutaneous GH administration is presented in Fig. 1. The final PK model was a one-compartment model with first-order absorption, linear elimination and a component of endogenous GH production. Parameters of the structural PK model were K_a (linear absorption rate constant), V/F (apparent volume of distribution), CL/F (apparent clearance) and PK_{Base} (GH concentrations attributed to endogenous production). Inter-individual variabilities were estimated for K_a, V/F, CL/F, and PK_{Base}, and IIV correlations were identified between K_a and V/F and between K_a and CL/F (Table S1 of the Electronic Supplementary Material [ESM]). The parameter estimates of the final PK model are presented in Table 2.

Figure 2 presents the observed and model-predicted GH concentration–time profiles following daily subcutaneous

GH administration. Time to maximum concentration occurred after approximately 5.4 h for children and approximately 2.1 h for adults. The observed and model-predicted GH concentration–time profiles for the fourth week of GH treatment in adults with GHD are presented in Fig. S1 of the ESM. As seen from the model predictions, the final population PK model provided an adequate description of the geometric mean of the PK data, with the model closely replicating the GH trajectories over time for children and adults with GHD. The individual baseline GH levels attributed to endogenous GH production ranged from below the limit of quantification up to 6.8 ng/mL (Table 1). Standard goodness-of-fit plots for the final PK model confirmed the qualification of the model and are available in Fig. S2 of the ESM. Flip-flop pharmacokinetics was present in the model and the apparent half-life of approximately 6 h was determined by the absorption rate (Table 2).

3.2.2 Effect of Body Weight on Pharmacokinetics

Body weight was a significant explanatory factor for the IIV of K_a, CL/F and PK_{Base}, with a positive correlation between body weight and CL/F and an inverse correlation between body weight, K_a and PK_{Base} (Table S1 and Fig. S3 of the ESM). Overall, body weight was found to have a clear and relevant influence on GH exposure. Figure 3 presents the relationship between body weight and dose-normalised GH exposure, with increased body weight being associated with decreased exposure. When accounting for the influence of body weight, no additional differences in pharmacokinetics were found between children and adults.

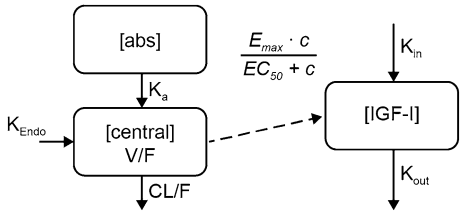

Fig. 1 Schematic of the structural pharmacokinetic/pharmacodynamic (PK/PD) model for growth hormone (GH). The PK model included a single pathway from the absorption compartment (abs) to the central compartment (central) through first-order absorption. The baseline GH levels observed prior to initial dosing were described via a zero-GH production rate. The PK/PD model included an indirect response relationship (dashed line) between the central compartment and the insulin-like growth factor-I (IGF-I) compartment. c growth hormone concentration in the central compartment, CL growth hormone systemic clearance, E_{max} maximum increase in IGF-I production rate, EC_{50} GH concentration corresponding to half-maximum stimulation of IGF-I production rate, F bioavailability, K_a linear absorption rate constant, K_{endo} zero-order process for endogenous growth hormone production, K_{in} zero order production rate of IGF-I, K_{out} first-order elimination rate of IGF-I, V volume of distribution

3.3 Pharmacodynamics of GH

3.3.1 Population PK/PD Model

The structural model that best described the IGF-I concentration–time profiles following daily subcutaneous GH administration is presented in Fig. 1. The final PK/PD model was an indirect response model, with a saturable effect relationship between the GH pharmacokinetics and IGF-I rate of production used to describe the IGF-I concentration–time

Table 1 Demographic characteristics of patients included in the analysis

Category	Group	Trial 1 [19]	Trial 2 [20]	Trial 3 [21]	Total
All	*N*	8	8	7	23
Sex	Male	8	6	5	19
	Female	0	2	2	4
Age (years)	Mean (SD)	8.2 (1.6)	8.2 (1.8)	58.0 (15.8)	23.4 (24.9)
	Range	6–11	6–11	23–68	6–68
Body weight (kg)	Mean (SD)	26.1 (7.5)	29.7 (7.9)	80.8 (18.2)	44.0 (27.4)
	Range	17–39.8	18–40.5	59.1–102.2	17–102.2
Baseline GH[a] (ng/mL)	Mean (SD)	1.4 (2.4)	0.5 (0.4)	0.7 (1.4)	0.9 (1.6)
	Range	0–6.8	0.1–1.1	0–3.8	0–6.8
Dose (mg)	Mean (SD)	0.8 (0.2)	1.0 (0.3)	0.3 (0.1)	0.7 (0.4)
	Range	0.5–1.2	0.6–1.4	0.2–0.5	0.2–1.4

Data are mean (SD)

GH growth hormone, *SD* standard deviation

[a]Baseline GH level indicates the mean of the baseline and follow-up sample. In total, eight subjects were treated with Norditropin® in Trial 3 and one subject was excluded from the analysis because of inconsistent pharmacokinetics

Table 2 Parameter estimates: final pharmacokinetic model

Parameter	Description	Estimate (95% CI)	RSE (%)	IIV CV (%)	Shrinkage (%)
K_a (1/h)	Absorption rate constant	0.122 (0.07–0.17)	21.6	89.7	29.5
V/F (L)	Apparent volume of distribution	28.2 (17.1–39.3)	20.1	77.5	21.2
CL/*F* (L/h)	Apparent clearance	24.7 (16.2–33.2)	17.6	33.2	10.7
GH_{Base} (ng/mL)	Baseline GH level	0.188 (0.03–0.35)	43.0	177	3.61
$\theta_{BW_{CL/F}}$	Body weight covariate on the apparent clearance	0.982 (0.62–1.34)	18.7	–	–
$\theta_{BW_{Ka}}$	Body weight covariate on the absorption rate constant	− 0.687 (− 1.17 to − 0.20)	35.8	–	–
$\theta_{BW_{GH_{Base}}}$	Body weight covariate on the baseline GH level	−0.991 (− 1.96 to − 0.02)	50.0	–	–
Proportional error AGHD (%)	–	41.4	–	–	2.45
Proportional error GHD (%)	–	56.1	–	–	4.31

The estimated half-life is 5.6 h and is determined by the absorption rate ($t_{½}$ = ln(2)/0.122) because of flip-flop pharmacokinetics

AGHD adults with growth hormone deficiency, *BW* body weight, *CI* confidence interval, *CL/F* apparent clearance, *CV* coefficient of variation, *GH* growth hormone, *GHD* children with growth hormone deficiency, *h* hours, *IIV* inter-individual variability, *Ka* linear absorption rate constant, *RSE* relative standard error, *V/F* apparent volume of distribution

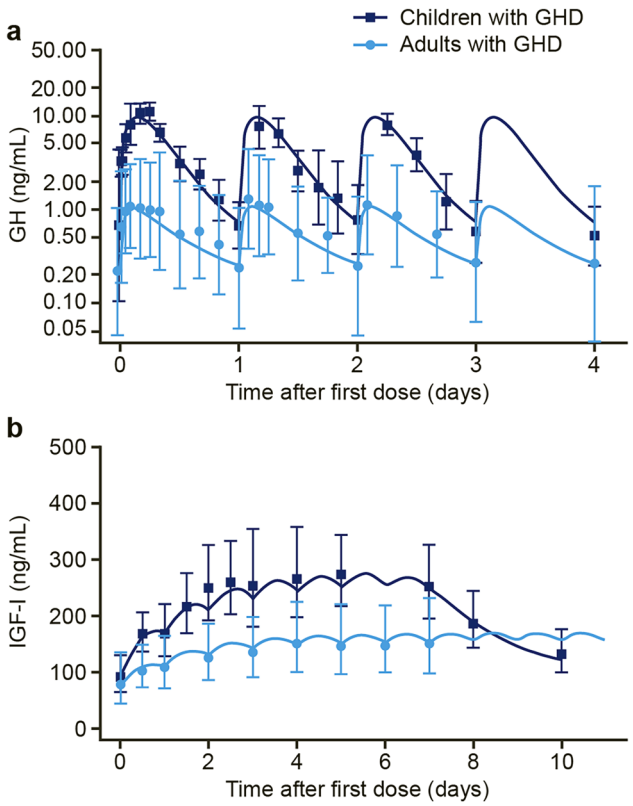

Fig. 2 Growth hormone (GH) pharmacokinetic (PK) profile (**a**) and pharmacodynamic (PD) profile (**b**) with final model fit for multiple doses in children (dark blue) and adults (light blue) with GH deficiency (GHD). Data are presented as geometric mean, with 95% confidence intervals. Lines represent the geometric mean of the population model predictions. Only full PK profiles up to 4 days after the first dose are presented for clarity. The observed and model-predicted GH concentration–time profiles for the fourth week of GH treatment in adults with GHD are presented in Fig. S1 of the ESM. *IGF-I* insulin-like growth factor-I

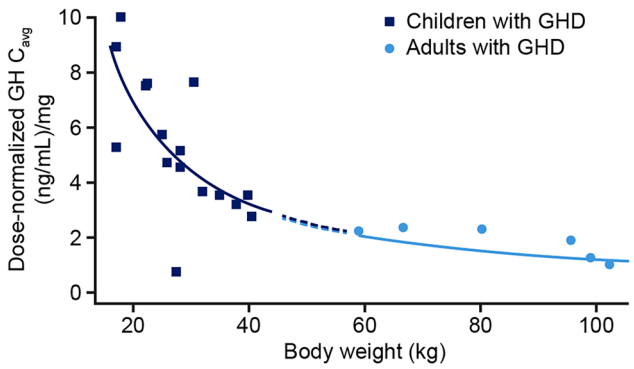

Fig. 3 Relationship between steady-state dose-normalized growth hormone (GH) concentration in children (light blue) and adults (dark blue) with GH deficiency (GHD) and body weight. Body weight is adequate for explaining the difference in GH pharmacokinetics between children and adults with GHD. C_{avg} average concentration at steady state, *PK* pharmacokinetic

profile. The stimulatory effect of GH on the IGF-I production rate was best described as additive, as in the previously published analyses for somapacitan (27). Parameters of the structural PK/PD model were K_{in} (zero-order IGF-I production rate), K_{out} (first-order IGF-I elimination rate), E_{max} (maximum increase in IGF-I production rate) and EC_{50}. Inter-individual variabilities were estimated for K_{in}, K_{out} and E_{max}, with no IIV correlations (Table S2 of the ESM). The parameter estimates of the final PK/PD model are presented in Table 3.

Figure 2 presents the observed and model-predicted IGF-I concentration–time profiles following daily subcutaneous GH administration. The observed and model-predicted IGF-I concentration–time profiles for the fourth week of

GH treatment in adults with GHD are presented in Fig. S1 of the ESM. The indirect response PK/PD model provided a good fit of the observed data, as shown by the close fit of the model population predictions to the observed IGF-I concentrations. Standard goodness-of-fit plots for the final PK/PD model are available in Fig. S4 of the ESM.

3.3.2 Effect of Body Weight on Pharmacodynamics

Body weight was an explanatory factor for E_{max} with a significant correlation with IGF-I response in children, and a fixed relationship that was consistent with post hoc estimates in adults (Fig. S5 of the ESM).

3.4 Simulation of Pharmacokinetics and IGF-I

Figure 4 presents the simulated steady-state exposure–response between steady-state average GH pharmacokinetics and IGF-I average SDS for once-daily subcutaneous administration of GH in children and adults with GHD, together with the steady-state GH concentration and IGF-I SDS time-course profiles. Based on the simulations, dose concentrations of 3 µg/kg/day for adults with adult GHD and 30 µg/kg/day for children with GHD are adequate for providing an IGF-I average SDS of approximately 1.1.

4 Discussion

This was the first meta-analysis of both GH pharmacokinetics and IGF-I response in children and adults, and was used to develop a population PK/PD model incorporating data from three phase I clinical trials of human GH. This model is also the first to characterise the exposure and effect of daily GH (Norditropin®) to be published, despite the product being available for many years. We aimed to quantify the effect of daily GH on IGF-I in both children and adults with GHD, and our model accurately described both the PK and PD data following repeated GH administrations. This suggests that the model would adequately predict the GH and IGF-I profiles resulting from steady-state dosing in children and adults with GHD. Our model identified body weight as an important covariate influencing both GH pharmacokinetics and pharmacodynamics. Indeed, body weight was

Table 3 Parameter estimates. Final pharmacodynamic model

Parameter	Description	Estimate (95% CI)	RSE (%)	IIV CV (%)	Shrinkage (%)
K_{in} (ng/mL/h)	Zero-order production rate of IGF-I at zero GH levels (estimated)	0.949 (0.411–1.49)	28.9	117	15.1
$K_{in,endo_{adult}}$ (ng/mL/h)	Zero-order production rate of IGF-I at endogenous GH levels for 85-kg adults with GHD (derived)	1.97	–	–	–
$K_{in,endo_{child}}$ (ng/mL/h)	Zero-order production rate of IGF-I at endogenous GH levels for 25-kg children with GHD (derived)	2.22	–	–	–
K_{out} (1/h)	First-order elimination rate of IGF-I	0.0262 (0.0218–0.0306)	8.6	17.4	31.3
EC_{50} (ng/mL)	Somatropin concentration corresponding to half-maximum stimulation of IGF-I production rate	2.13 (1.39–2.88)	17.9		
$E\max_{adult}$ (ng/mL/h)	Maximum increase in IGF-I production rate for adults with GHD	15.1 (fixed)	–	33.1	13.3
$\theta_{BW_{E_{max_{adult}}}}$	Body weight covariate on the maximum increase in IGF-I production rate for adults with GHD	0.46 (fixed)	–	–	–
$E\max_{child}$ (ng/mL/h)	Maximum increase in IGF-I production rate for children with GHD	6.48 (4.75–8.70)	14.0	33.1	13.3
$\theta_{BW_{E_{max_{child}}}}$	Body weight covariate on the maximum increase in IGF-I production rate for children with GHD	1.94 (1.05–2.84)	23.5	–	–
Proportional error Trial 1 (%)	–	14.6	–	–	9.4
Proportional error Trial 2 (%)	–	8.7	–	–	5.5
Proportional error Trial 3 (%)	–	11.4	–	–	12.0

BW body weight, *CI* confidence interval, *CV* coefficient of variation, E_{max} maximum increase in IGF-I production rate, EC_{50} GH concentration corresponding to half-maximum stimulation of IGF-I production rate, *GH* growth hormone, *GHD* growth hormone deficiency, *IGF-I* insulin-like growth factor-I, *IIV* inter-individual variability, K_{endo} zero-order process for endogenous growth hormone production, K_{in} zero order production rate of IGF-I, K_{out} first-order elimination rate of IGF-I, *RSE* relative standard error

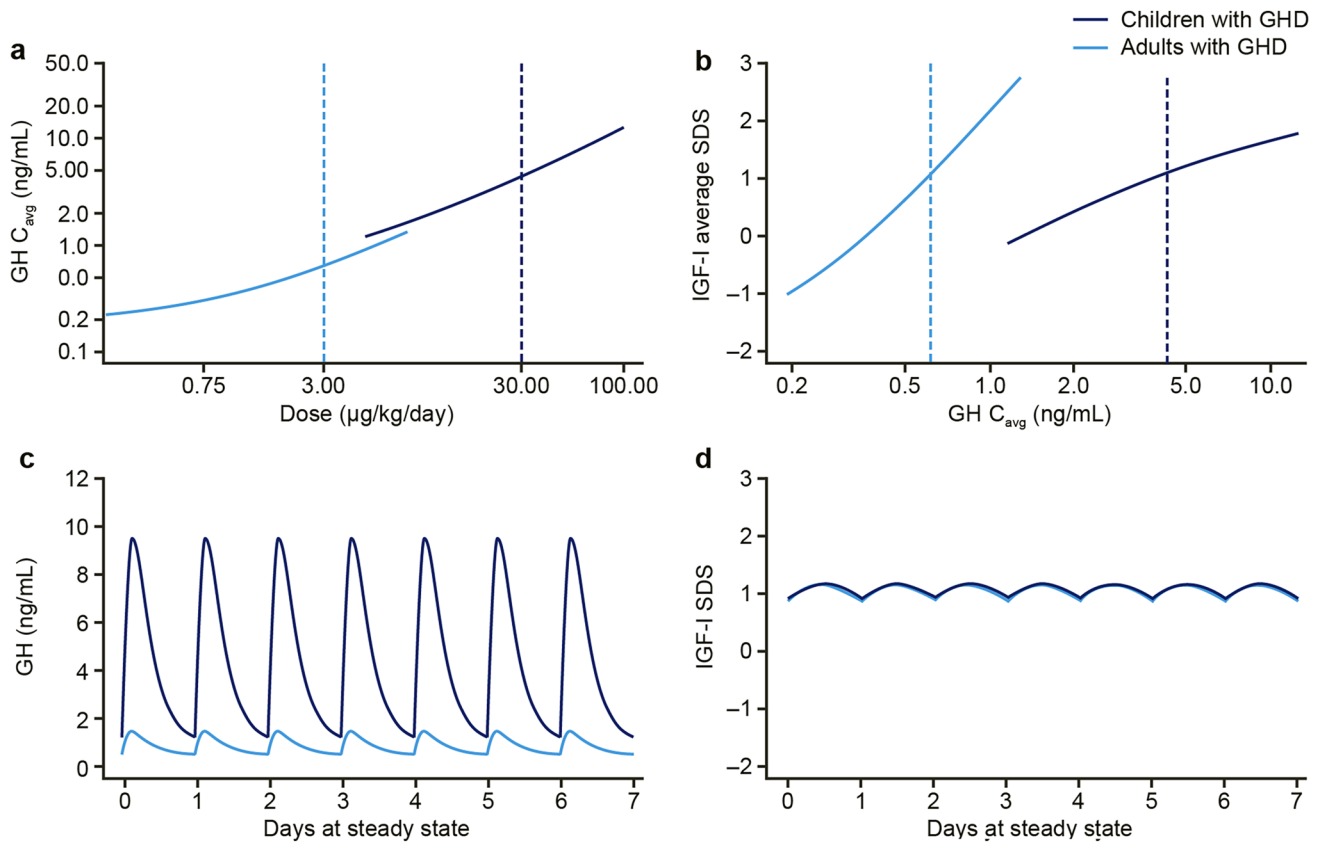

Fig. 4 Simulated steady-state dose-exposure (**a**) and steady-state exposure–response (**b**) between growth hormone (GH) pharmacokinetics and insulin-like growth factor-I (IGF-I) standard deviation score (SDS) for once-daily subcutaneous administration of GH, and GH concentration (**c**) and IGF-I SDS profiles (**d**) at dose concentrations giving a matching response in children (dark blue) and adults (light blue) with GH deficiency (GHD). In (**a**) and (**b**), lines are means of individual predictions across the dose and exposure range. Vertical dotted lines denote the dose and exposure giving an average IGF-I response of approximately 1.1 SDS. In (**c**) and (**d**), lines are means of individual prediction at dose levels of 3 µg/kg/day for adults and 30 µg/kg/day for children, both providing an IGF-I average SDS of approximately 1.1. *PK* pharmacokinetic

sufficient to explain the difference in GH exposure between adults and children.

The GH PK profile was characterised by a pronounced peak approximately 5.4 h and 2.1 h after dosing in children and adults, respectively, declining to a trough value within 24 h, with little accumulation. An endogenous GH level was identified in both children and adults, and was implemented in the model. The parameter estimates indicated flip-flop pharmacokinetics, where the approximate 6-h apparent half-life of GH is determined by the absorption rate. This is consistent with previous knowledge that circulating GH has a short apparent half-life, whether endogenously produced [25] or administered intravenously [26].

The IGF-I profile was well characterised and, despite the fluctuating PK profile of GH, IGF-I remained relatively stable over time in both children and adults. The exposure–response data were used to identify the doses and exposures needed to provide matching IGF-I results in children and adults. While body weight appeared to influence IGF-I levels and the effect of GH on IGF-I production, a significantly lower exposure–response relationship was seen for children than adults (Fig. 4) when observing IGF-I SDS and adjusting for body weight, meaning that children need higher GH exposures to induce the same IGF-I response. It is important to remember that IGF-I levels are generally naturally higher in children than in adults [24], which means that children need higher absolute IGF-I concentrations (ng/mL) than adults to achieve a desired therapeutic IGF-I SDS response.

Our analysis showed good agreement between the drug-independent constants, k_{in} and k_{out}, estimated here for Norditropin®, and those previously modelled for somapacitan [23]. This similarity indicates a consistency in understanding of the production and turnover of IGF-I, and provides a basis for evaluating the relative effects of short- and long-acting GH using parameters such as EC_{50} and E_{max}. EC_{50} is expected to differ between these molecules as a result of differences in receptor binding potency, but the

maximum stimulation of the GH receptor is expected to be the same. Because E_{max} in children was estimated to be similar for Norditropin® and somapacitan, the assumption was made here that E_{max} for adults could also be fixed to that reported for somapacitan.

The limitations of our study include the fact that the data were obtained from a relatively small number of patients (especially adults) in three different trials in which Norditropin® was included only as a one-dose-level control group. Necessarily, this Norditropin® dose was nearly an order of magnitude lower in the adult study than in the two child studies. Nevertheless, by pooling the data, we were able to construct an accurate model based on, respectively, more than 600 and more than 300 PK and PD data points.

5 Conclusions

Our study has enabled a PK/PD model to be constructed that accurately describes and predicts the pharmacokinetics and IGF-I response of once-daily GH in both GHD adults and children, although it should be noted that the model is an experimental tool not approved by regulatory authorities. While the pharmacokinetics of GH fluctuate across a 24-h period with a high peak:trough ratio, this effect is less pronounced in the IGF-I response, where the profile is relatively stable across 24 h, owing to the delay between pharmacokinetics and IGF-I response. Body weight was shown to have an important inversely correlated influence on GH exposure (and IGF-I–SDS response), and this largely explained the differences between the adult and child groups. We believe that our model will help provide a better understanding of the GH dosing regimens currently applied, and that it gives an understanding of why different dose concentrations are needed in the paediatric setting as compared with adults. The model can also inform expectations about PD effects with different GH doses and patient body weights.

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Declarations

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Conflicts of Interest/Competing Interests Theodoros Papathanasiou and Birgitte Bentz Damholt were employees/shareholders of Novo Nordisk A/S at the time of writing. Henrik Agersø, Michael Højby Rasmussen and Rasmus Juul Kildemoes are employees/shareholders of Novo Nordisk A/S.

Ethics Approval All trials were approved from the local and national ethics committees and were conducted in accordance with the International Conference on Harmonisation guidelines for Good Clinical Practice [27] and the Declaration of Helsinki [28]. For children with growth hormone deficiency, parent or guardian signed informed consent was required before the initiation of any trial activity.

Consent to Participate Not applicable.

Consent for Publication Not applicable.

Availability of Data and Material The datasets generated during and/or analysed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

Code Availability Not applicable.

Authors' Contributions All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by TP and RJK. The first draft of the manuscript was written by TP and RJK, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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