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ORIGINAL ARTICLE

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Somapacitan, a once-weekly reversible albumin-binding GH derivative, in children with GH deficiency: A randomized dose-escalation trial

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Summary

Objective: To evaluate the safety, local tolerability, pharmacodynamics and pharmacokinetics of escalating single doses of once-weekly somapacitan, a reversible, albumin-binding GH derivative, vs once-daily GH in children with GH deficiency (GHD).

Design: Phase 1, randomized, open-label, active-controlled, dose-escalation trial (NCT01973244).

Patients: Thirty-two prepubertal GH-treated children with GHD were sequentially randomized 3:1 within each of four cohorts to a single dose of somapacitan (0.02, 0.04, 0.08 and 0.16 mg/kg; n=6 each), or once-daily Norditropin® SimpleXx® (0.03 mg/kg; n=2 each) for 7 days.

Measurements: Pharmacokinetic and pharmacodynamic profiles were assessed.

Results: Adverse events were all mild, and there were no apparent treatment-dependent patterns in type or frequency. Four mild transient injection site reactions were reported in three of 24 children treated with somapacitan. No antisomapacitan/anti-human growth hormone (hGH) antibodies were detected. Mean serum concentrations of somapacitan increased in a dose-dependent but nonlinear manner: maximum concentration ranged from 21.8 ng/mL (0.02 mg/kg dose) to 458.4 ng/mL (0.16 mg/kg dose). IGF-I and IGFBP-3, and change from baseline in IGF-I standard deviation score (SDS) and IGFBP-3 SDS, increased dose dependently; greatest changes in SDS values were seen for 0.16 mg/kg. IGF-I SDS values were between −2 and +2 SDS, except for peak IGF-I SDS with 0.08 mg/kg somapacitan. Postdosing, IGF-I SDS remained above baseline levels for at least 1 week.

Conclusions: Single doses of once-weekly somapacitan (0.02-0.16 mg/kg) were well tolerated in children with GHD, with IGF-I profiles supporting a once-weekly treatment profile. No clinically significant safety/tolerability signals or immunogenicity concerns were identified.

The members of NN8640-4042 Study Group are listed in Appendix 1

Clinical trial registration no. (ClinicalTrials.gov): NCT01973244

KEYWORDS
growth hormone, growth hormone deficiency, IGF-I, long-acting growth hormone

1 | INTRODUCTION

In healthy subjects, endogenous GH is synthesized by the somatotrophic cells in the pituitary gland under hypothalamic control, and a complex regulatory system controls the pulsatile release of fine-tuned GH bursts into the peripheral circulation. None of the previously or currently recommended GH therapies to treat children with GH deficiency (GHD) or adult GHD (AGHD) have been able to mimic this complex, endogenous, physiologically regulated system. Nevertheless, these nonphysiological replacement therapies have been used for several decades—in particular, daily recombinant human GH has been used since 1985—and have been shown to promote linear growth without safety concerns.[1] However, clinical studies have shown poor compliance by children with a once-daily injection regimen of GH,[2,3] attributed in part to difficulties with injections.[4] In addition, it has been reported that GH compliance positively affects growth velocity.[5,6] It is possible that longer-acting GH preparations allowing for reduced injection frequency could improve treatment adherence, although this has not been demonstrated. If treatment adherence is greater with reduced injection frequency, this could potentially result in improved long-term treatment outcomes.[7]

Somapacitan is a novel, reversible, albumin-binding GH derivative in which fatty acids with noncovalent albumin-binding properties have been conjugated by alkylation to GH in order to bind endogenous albumin, resulting in an extended half-life of the molecule, such that once-weekly subcutaneous (s.c.) administration is possible. The addition of fatty acids to therapeutic proteins through acylation is used to facilitate binding of these molecules to circulating albumin. In humans, noncovalent binding of the molecules to albumin in the blood results in a reduced clearance and significantly prolongs the in vivo half-life. This method of prolonging the plasma half-life—and thus, the therapeutic action—of peptide drugs has been used successfully in the development of insulin detemir, a long-acting insulin analogue,[8] and liraglutide, a long-acting glucagon-like peptide-1 (GLP-1) derivative.[9] This technology of using a conjugated linker was not associated with any significant tolerability issues with insulin or GLP-1.[9,10]

The safety, pharmacokinetics (PK) and IGF-I profiles generated by once-weekly dosing of somapacitan have been studied in healthy adult male subjects[11] and patients with AGHD.[12] The results showed that a once-weekly dosing regimen for somapacitan was feasible.[11,12] The current study was a single-dose trial of somapacitan in children with GHD.

2 | SUBJECTS AND METHODS

2.1 | Patients

The study enrolled prepubertal boys and girls (Tanner stage 1; boys aged ≥6-<13 years; girls aged ≥6-<12 years) with body weight ≥16.0-≤50.0 kg and a confirmed diagnosis of GHD based on two different GH stimulation tests (peak GH ≤7.0 ng/mL). For children with three or more pituitary hormone deficiencies, only a single provocation test result was required. Patients with known additional pituitary hormone deficiencies received a minimum of 3 months of effective treatment prior to trial drug administration. The patients received stable GH replacement treatment for at least 3 months prior to inclusion in the trial, and discontinued their GH treatment between 7 and 10 days before receiving the trial product. Patients were excluded if they had presence of significant clinical illness, confirmed diagnosis of medical syndromes (eg Turner, Noonan, Russell-Silver, skeletal dysplasias or absence of GH receptors), history or presence of malignancy or overt diabetes mellitus.

2.2 | Trial design and procedures

This was a phase 1, randomized, open-label, active-controlled, single-dose, dose-escalation trial (NCT01973244), conducted in 14 paediatric endocrinology clinics in eight countries. The protocol was approved by the local and national ethics committees as appropriate and conducted in accordance with the ICH guidelines for Good Clinical Practice[13] and the Declaration of Helsinki.[14] Before any study activity, parents or guardians provided written informed consent and patients provided signed assent, where required.

The primary objective of the trial was to evaluate the safety and tolerability of a single s.c. dose of somapacitan vs once-daily GH (Norditropin® SimpleXx®, somatropin; Novo Nordisk A/S, Gentofte, Denmark) given for 7 days in children with GHD. Secondary objectives were to evaluate the pharmacokinetics (PK) and pharmacodynamics (PD) of a single s.c. dose of somapacitan and to compare local tolerability with once-daily GH given for 7 days in children with GHD. PD were assessed using serum concentrations of IGF-I and IGF-binding protein-3 (IGFBP-3). Four cohorts, each including eight children with GHD, were investigated. Within each cohort, subjects were randomized 3:1, using a telephone-based interactive voice/web response system, to treatment with either a single dose of somapacitan or 7 days of once-daily injections of GH. Somapacitan use was investigated at four sequential dose levels: 0.02, 0.04, 0.08 and 0.16 mg/kg, and GH was given at 0.030 mg/kg/d.

The patients attended a screening visit, followed by a GH washout period of 7-10 days immediately before the first injection with trial product. The study protocol involved a 3-day in-house stay, followed by a 7-day ex-house period and a final follow-up visit scheduled 28-35 days after the first injection with trial product. Somapacitan was administered as a single s.c. dose in the thigh, using a standard syringe. GH (somatropin; Norditropin® SimpleXx®) was administered once daily for 7 days, using single-use prefilled pens (NordiPen®; Novo Nordisk A/S, Hillerød, Denmark). Progress to the next dose level in a new cohort of patients took place after evaluation by an internal safety assessment group; progress to the next planned dose level was mandated if ≤1 not-acceptable adverse events (AEs) were reported and/or detected by laboratory measurements, and no concerns were

raised based on the PK and PD properties. All children with GHD were recruited from paediatric endocrine units (please refer to the Acknowledgements). Previous human growth hormone (hGH) replacement therapy was resumed from day 10.

2.3 | Safety assessments

The safety of somapacitan and GH was assessed on the basis of data on AEs, clinical laboratory measurements (haematology, biochemistry, urinalysis, fasting blood glucose, fasting blood insulin and antibodies), physical examinations, vital signs, body weight, electrocardiogram (ECG) and injection site tolerability. The latter was evaluated by manual, visual inspection of injection sites, assessing the occurrence of pain, tenderness, itching, rash, redness, induration and any other signs of injection site reactions.

2.4 | Trial procedures and assay methods

Blood samples for PK and PD assessments were taken just prior to the first treatment injection; 1, 4, 8, 12, 16, 24, 28, 36, 48, 72, 96, 168 and 240 hours postdose; and at the follow-up visit. Serum concentrations of somapacitan were analysed using a validated somapacitan-specific luminescent oxygen channelling immunoassay with no cross-activity with hGH (for details, see Rasmussen et al.[12]). The sensitivity of the somapacitan immunoassay was 0.50 ng/mL. The concentration of GH in serum from patients treated with Norditropin® was assessed at a central laboratory using a commercially available kit (Siemens IMMULITE® 2000; Siemens Medical Solutions Diagnostics GmbH, Fernwald, Germany). Analysis of serum IGF-I and IGFBP-3 concentrations was performed using commercially available assay kits (Immuno Diagnostic Systems immunoassay ISYS assay, Boldon, UK) at the analytical central laboratory (Laboratorium für Klinische Forschung GmbH, Schwentinental, Germany). GH, IGF-I and IGFBP-3 assay performance was in accordance with the assay information provided by the manufacturer. IGF-I standard deviation scores (SDS) were calculated according to Bidlingmaier et al.[15] and IGFBP-3 SDS were calculated using reference data supplied by the kit manufacturer (Immuno Diagnostic Systems).

Serum samples for determination of antibodies against somapacitan or hGH were collected at baseline (prior to treatment start), end of treatment (168 hours after the last dose) and at the follow-up visit. Antibodies against somapacitan or against hGH were evaluated in patients treated with the respective drugs using a bridging ELISA in each case. Both assays were developed and validated by Novo Nordisk A/S (Maaloev, Denmark) (for details see Rasmussen et al.[12]). Laboratory safety assessments were performed as follows: haematological (white blood cell count, red blood cell count, haemoglobin, haematocrit, mean corpuscular volume [MCV], mean corpuscular haemoglobin concentration [MCHC], platelets), biochemistry (sodium, potassium, chloride, calcium [total], inorganic phosphate, creatinine, urea, uric acid, total protein, albumin, bilirubin [total], creatinine kinase [CK], alkaline phosphatase, gamma-glutamyl transferase [GGT], aspartate transaminase [AST], alkaline phosphatase [ALT], C-reactive protein [CRP]), urinalysis (protein, glucose, erythrocytes, leucocytes, bilirubin), glycated haemoglobin (HbA_{1c}), glucose and insulin. These were all analysed at Laboratorium für Klinische Forschung GmbH.

2.5 | Statistical analysis

A significance level of 5% was used without adjustment for multiple testing. All tests were two-sided superiority tests. Dose proportionality was investigated using a linear regression model with the log-transformed end-point as the dependent variable and log-transformed dose as covariate. Other end-points were evaluated using descriptive statistics. Sample size was not based on formal calculations but was determined to expose the lowest possible number of patients to somapacitan while enabling adequate assessment of safety, PK and PD data to continue to the next dose level.

2.6 | Pharmacokinetics

The following PK parameters were determined using standard non-compartmental methods: the somapacitan peak plasma concentration (C_{max}), time to C_{max} (t_{max}), area under the curve (AUC) from 0-168 hours after dosing ($AUC_{(0\text{-}168\ h)}$; somapacitan only) and terminal half-life ($t_{½}$). AUC for 0-24 hours ($AUC_{(0\text{-}24\ h)}$) was determined for Norditropin® only. All evaluations for somapacitan were based on evaluation of data collected for up to 7 days (168 hours) and at end of trial. All PK parameters were analysed using descriptive statistics. Dose proportionality was investigated using a linear regression model with the log-transformed end-point ($AUC_{(0\text{-}168\ h)}$ or C_{max}) as the dependent variable and the log-transformed dose as covariate. In descriptive statistics and all formal statistical testing, all patients receiving Norditropin® (n=8) were pooled into one dose group, irrespective of the allocated dose cohort.

2.7 | Pharmacodynamics

The following PD end-points were calculated for IGF-I and IGFBP-3: $AUC_{(0\text{-}168\ h)}$, C_{max} and t_{max} derived from serum concentration vs time profiles. AUC end-points were approximated by a linear trapezoidal technique. Changes in IGF-I and in IGFBP-3 were compared between dose levels of somapacitan, and between somapacitan doses and Norditropin®, using an analysis of covariance (ANCOVA) model with treatment as a factor and the predose value as covariate. $AUC_{(0\text{-}168\ h)}$ and C_{max} values were log-transformed before analysis. Mean ratios/differences for somapacitan doses and mean ratios/differences for somapacitan vs Norditropin® were estimated with corresponding 95% confidence intervals (CIs) and *P*-values.

3 | RESULTS

3.1 | Patient disposition and characteristics

A total of 32 children with GHD (23 with idiopathic GHD and nine with organic GHD) were randomized, exposed and completed the trial (somapacitan: 24 children; Norditropin®: 8 children). No children withdrew from the trial. Race and ethnicity were as follows:

28 children were Caucasian, one was reported as "other" and details were not reported for three patients in France due to local regulations. The proportion of boys (n=23) was greater than girls (n=9), except in the somapacitan 0.04 mg/kg group (one boy, five girls). In the Norditropin® group, all eight children were boys. The pretrial hGH dose was approximately 0.03 mg/kg (min: 0.013; max: 0.045 mg/kg). Patients' baseline characteristics are summarized in Table 1.

3.2 | Safety

Somapacitan administered s.c. to children with GHD was well tolerated at all doses investigated (0.02-0.16 mg/kg), with no clinically significant safety or local tolerability issues identified. No serious AEs were reported, and there were no AEs leading to withdrawal.

A total of 19 AEs were reported in 11 children (46%) treated with somapacitan, and two AEs (nausea and vomiting) were reported in one child (13%) following once-daily Norditropin® SimpleXx® treatment. The majority of events were single events reported in one or two children. AEs occurring in ≥5% of children are listed in Table 2. With somapacitan, the AEs reported in at least two children were nasopharyngitis, headache and vomiting; AEs reported in one child each were general disorders and administration site conditions (n=3), infections and infestations (n=4), and myalgia, dizziness, haematuria, epistaxis and pruritus (all n=1). All AEs were reported as mild. All AEs except one were reported as unlikely to be related to trial products; haematuria (somapacitan 0.02 mg/kg) was reported as possibly trial product related. There were no apparent treatment-dependent patterns in the type and frequency of AEs reported either within or among system organ classes.

Mean fasting plasma glucose levels (4.5-4.9 mmol/L) were within normal ranges for all dose groups, and no clinically relevant changes were observed during the trial period. The mean fasting insulin level was within the lower part of the normal ranges for all dose groups. In the somapacitan 0.04, 0.08 and 0.16 mg/kg dose groups, the fasting blood glucose and fasting insulin increased initially from baseline to day 2, to decrease again towards baseline levels from days 2-7; all values were within the normal range. There were no changes towards abnormal clinically significant findings from screening in vital signs, physical examination or ECG in any of the treatment groups. No positive test results for antisomapacitan antibodies or anti-hGH antibodies were reported in the trial.

3.3 | Local tolerability

Four mild and transient injection site reactions were reported in three of 24 children treated with somapacitan (12.5%). The three patients with injection site reactions all received 0.16 mg/kg (two events of injection site pain, both judged as clinically significant; one event of small bruise and one event of haematoma, both judged as not clinically significant by the investigators). In the current trial, where only one strength of somapacitan was available, two sequential injections was allowed in the 0.16 mg/kg group to reduce the volume if required, and the three patients with mild and transient injection site reactions all received two injections. No injection site reactions were reported following somapacitan 0.02, 0.04 or 0.08 mg/kg or Norditropin® injections.

3.4 | Pharmacokinetics

The mean serum concentration of somapacitan increased with dose following single-dose administration of children with GHD (Figure 1). Mean somapacitan $AUC_{(0-168\ h)}$, C_{max} and t_{max} increased with dose (Table 3). Somapacitan $AUC_{(0-168\ h)}$ and C_{max} increased with increasing dose to a greater extent than would have been expected with dose proportionality. The effect of doubling a dose was estimated to be 3.47 and 2.86 for $AUC_{(0-168\ h)}$ and C_{max}, respectively.

3.5 | Pharmacodynamics

A dose-dependent IGF-I response was induced, with increased IGF-I levels at all dose levels of somapacitan investigated (somapacitan single dose 0.02, 0.04, 0.08 and 0.16 mg/kg). The mean IGF-I responses after one single dose of somapacitan, and once-daily Norditropin® for

TABLE 1 Summary of patients' baseline characteristics

	Norditropin® (mg/kg)	Somapacitan dose (mg/kg)				
	0.03	0.02	0.04	0.08	0.16	Total (all groups)
Subjects, n	8	6	6	6	6	32
Age, years	8.5 (6.0-11.0)	8.0 (6.0-11.0)	7.5 (6.0-11.0)	8.0 (7.0-11.0)	9.0 (6.0-11.0)	9.0 (6.0-11.0)
Male, n	8	4	1	5	5	23
Female, n	0	2	5	1	1	9
Height, m	1.29 (1.04-1.45)	1.15 (1.09-1.5)	1.28 (1.10-1.39)	1.25 (1.15-1.39)	1.33 (1.12-1.48)	1.22 (1.04-1.48)
Body weight, kg	27.1 (17.0-39.8)	19.4 (18.5-41.2)	28.7 (18.8-34.7)	25.6 (20.1-35.3)	26.4 (18.6-38.5)	25.5 (17.0-41.2)
BMI, kg/m^2	15.7 (14.5-18.9)	15.6 (12.6-19.6)	17.0 (13.5-22.1)	16.8 (14.2-18.8)	15.7 (12.9-17.6)	15.7 (12.6-22.1)
Idiopathic GHD, n	6	6	2	5	4	23
Organic GHD, n	2	0	4	1	2	9

Data are presented as median (range).
BMI, body mass index; GHD, growth hormone deficiency.

TABLE 2 Adverse events occurring in ≥5% of patients exposed to somapacitan, by system organ class and preferred term

	Norditropin® (mg/kg)		Somapacitan dose (mg/kg)								Total somapacitan	
	0.03		0.02		0.04		0.08		0.16			
Dose (mg/kg)	N (%)	E	N (%)	E	N (%)	E	N (%)	E	N (%)	E	N (%)	E
Subjects exposed, n	8		6		6		6		6		24	
All AEs	1 (13%)	2	2 (33%)	3	4 (67%)	9	2 (33%)	3	3 (50%)	4	11 (46%)	19
Occurring in ≥5% of patients by MedDRA SOC/PT												
Infections/ Infestations												
Nasopharyngitis	0		1 (17%)	1	1 (17%)	1	0		0		2 (8%)	2
Nervous system disorders												
Headache	0		0		0		1 (17%)	1	1 (17%)	1	2 (8%)	2
Gastrointestinal disorders												
Vomiting	1 (13%)	1	0		1 (17%)	1	0		1 (17%)	1	2 (8%)	2
Nausea	1 (13%)	1	0		0		0		0		0	

%, percentage of exposed subjects having the event; AE, adverse event; E, number of AEs reported; N, number of subjects having the event at least once; MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term; SOC, system organ class.

7 days, were within the reference ranges (82–269 ng/mL), except for an initially greater C_{max} above the upper reference range for IGF-I in the somapacitan 0.08 mg/kg dose group (this group had the highest IGF-I level at baseline; Figure 2A).

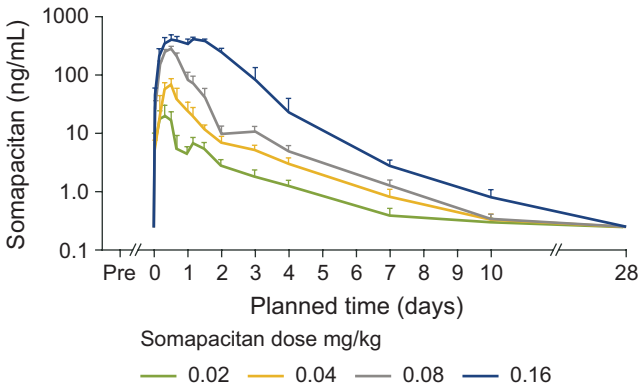

FIGURE 1 Pharmacokinetic mean profiles (+SEM; log-scale) after a single-dose administration of somapacitan. SEM, standard error of the mean

The mean IGF-I SDS during a week ranged from −2 to +2 SDS following one single dose of somapacitan and once-daily Norditropin®. A peak slightly above +2 SDS was observed for somapacitan 0.08 mg/kg (Figure 2B) which, as mentioned above, had the highest IGF-I level at baseline, whereas the 0.16 mg/kg group had the lowest baseline level (Figure 2B). When correcting for baseline IGF-I levels, the highest IGF-I response was seen with 0.16 mg/kg (Figure 2C).

A clear dose response was observed in the mean change in IGF-I SDS when adjusted for baseline (Figure 2C). The greatest change in IGF-I SDS was observed for somapacitan 0.16 mg/kg (from −2.5 at baseline to +1 at day 3; Figure 2B). A clear dose response was observed for IGF-I $AUC_{(0\text{-}168\ h)}$ within the somapacitan dose levels after adjustment for baseline levels. The IGF-I $AUC_{(0\text{-}168\ h)}$ in the somapacitan 0.04, 0.08 and 0.16 dose mg/kg groups was not significantly different compared to the IGF-I $AUC_{(0\text{-}168\ h)}$ of Norditropin® (data not shown).

A dose-dependent increase was observed in IGFBP-3 following somapacitan single-dose administration (Figure 3A). The reference range for IGFBP-3 is 2576-5777 ng/mL; baseline values of IGFBP-3

Somapacitan, mg/kg	N	$AUC_{(0\text{-}168\ h)}$, ng·h/mL	C_{max}, ng/mL	t_{max}, h (SD)	$t_{1/2}$, h
0.02	6	606 (72.5)	21.8 (122.2)	7.3 (1.6)	45.1 (34.6)
0.04	6	1840 (61.7)	71.9 (68.1)	10.6 (2.0)	41.1 (10.4)
0.08	6	6288 (39.5)	278.0 (30.7)	11.3 (1.7)	36.6 (17.1)
0.16	6[a]	25512 (23.2)	458.4 (30.7)	25.9 (15.0)	34.1 (21.4)

[a]Four subjects receiving somapacitan 0.16 mg/kg were evaluated for $t_{1/2}$; two subjects did not have three measurements above the lower limit of quantification in the terminal phase.
AUC, area under the curve; C_{max}, maximum concentration; CV, coefficient of variation; SD, standard deviation; $t_{½}$, terminal half-life; t_{max}, time to maximum concentration.

TABLE 3 Summary of pharmacokinetic end-points following a single dose of somapacitan. Data are geometric mean (CV, %) except for t_{max} (mean [SD])

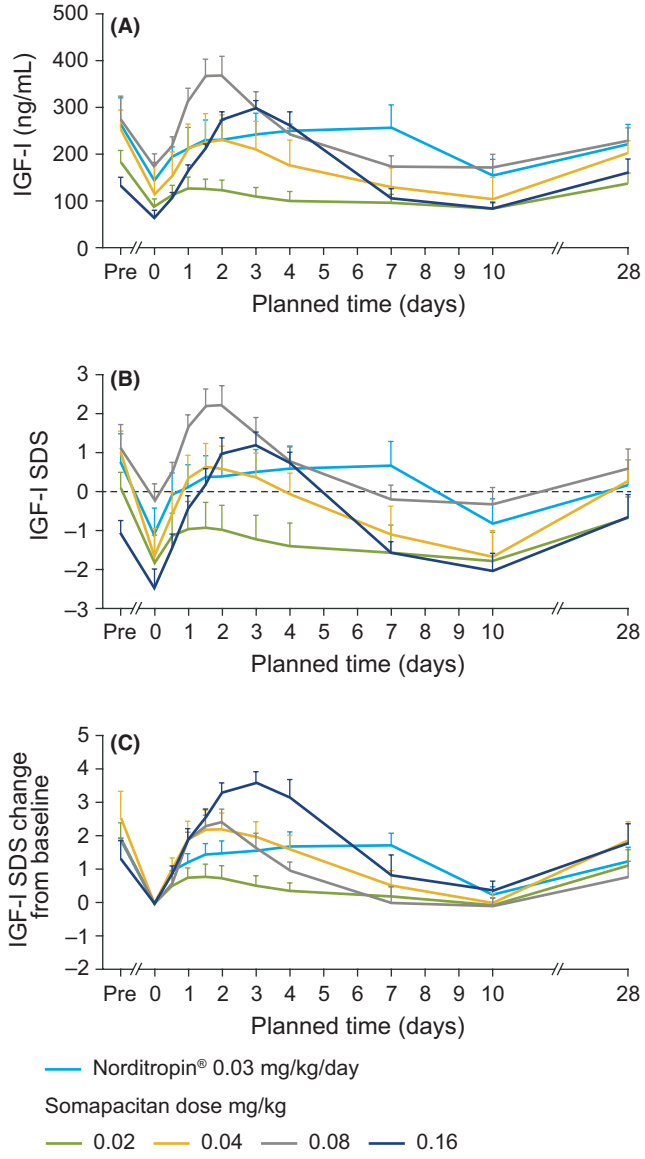

FIGURE 2 Mean (+SEM) levels of IGF-I and IGF-I SDS vs time after treatment with somapacitan or Norditropin® in children with GHD. (A) IGF-I (ng/mL); (B) IGF-I SDS; (C) change from baseline in IGF-I SDS. GHD, growth hormone deficiency; SDS, standard deviation score; SEM, standard error of the mean

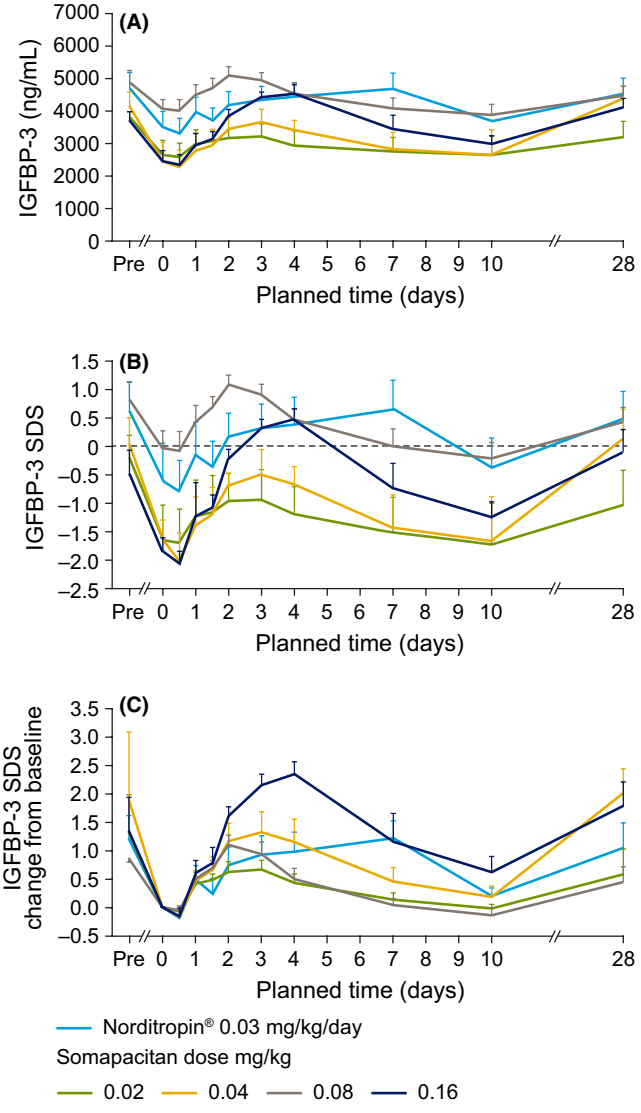

FIGURE 3 Mean (SEM) levels of IGFBP-3 and IGFBP-3 SDS vs time after treatment with somapacitan or Norditropin® in children with GHD. (A) IGFBP-3 (ng/mL); (B) IGFBP-3 SDS; (C) change from baseline in IGFBP-3 SDS. GHD, growth hormone deficiency; SDS, standard deviation score; SEM, standard error of the mean

for the somapacitan 0.02, 0.04 and 0.16 mg/kg doses were just at the lower border of this range, whereas the baseline value of the 0.08 mg/kg dose fell well within it. Mean IGFBP-3 increased initially after trial drug administration to stabilize at levels within the reference range. There was some variation in the pretrial and baseline IGFBP-3 SDS values across dose groups. A dose-dependent increase was observed in the mean IGFBP-3 SDS after once-weekly somapacitan and once-daily Norditropin® (Figure 3B). The mean IGFBP-3 SDS increased from values in the lower reference range (from −2 to 0) to values within the middle of the reference range (−1 to +1). The greatest change in IGFBP-3 SDS was observed in the somapacitan 0.16 mg/kg dose group.

4 | DISCUSSION

In this dose-escalation trial of somapacitan, a reversible albumin-binding GH derivative, the doses tested (0.02, 0.04, 0.08 and 0.16 mg/kg) were well tolerated in children with GHD, with no clinically significant safety or local tolerability issues identified. All AEs except one were reported as unlikely to be related to trial products; only haematuria (somapacitan 0.02 mg/kg) was reported as possibly trial product related, but the investigator did not provide a hypothesis for this judgement. No antisomapacitan antibodies or anti-hGH antibodies were detected in the trial. Similar findings were reported in previous trials of somapacitan in healthy adult males (no antisomapacitan antibodies; hGH was not used)[11] and in AGHD patients (no antisomapacitan or anti-hGH antibodies).[12]

The half-life of somapacitan has been extended through non-covalent binding to endogenous albumin. A similar mechanism has been successfully employed to extend the half-life of insulin and GLP-1,[8,9] with no associated significant tolerability issues.[9,10] Several previous attempts have been made to develop a GH preparation that can be administered less frequently than once daily (summarized in Christiansen et al.[7]). However, safety and tolerability issues have been associated with some long-acting GH formulations. For example, a pegylated GH formulation administered as once-weekly s.c. injections in children with GHD or AGHD was associated with significant lipoatrophy at the injection site in 12.4% of patients,[16] and a relatively high frequency of injection site reactions (30% in a single-dose study[17] and typically 39-50% in 6- to 12-month studies) has been observed in studies of long-acting formulations of GH,[18-20] although reactions are usually described as mild to moderate and/or transient.[18-22] One sustained-release GH injected once or twice monthly for 6 months or 2 years was accompanied by nodules (56%-60%), erythema (49%-54%) and postinjection pain (36%-37%).[23,24]

Treatment adherence may improve with longer-acting GH preparations compared with daily injections. Improved adherence has not been proven and should ideally be compared in a randomized controlled trial. However, as the differences in adherence between long-acting GH and daily GH under the controlled conditions of a trial are likely to be small, it would require very large numbers and a long, less controlled trial extension period to demonstrate significant differences. However, adherence does not depend only on administration frequency, but also on other factors such as injected volume, effectiveness and safety. Injection site reactions could be a major tolerability issue and would probably limit treatment adherence. It is therefore essential to check the local tolerability and safety of new long-acting GH preparations as well as ensuring that new preparations require similar volumes to be injected as for daily GH. In the current study, four injection site reactions were reported in the somapacitan group. No injection site reactions were observed in the daily GH group; however, the number of subjects receiving once-weekly somapacitan was three times the number in the daily hGH group. The four injection site reactions were all mild and transient, with short duration, similar to injection site reactions observed with daily GH administration. The injection site reactions reported only occurred in the three subjects requiring two sequential injections. Of note, in a 26-week trial in patients with adult GHD, more than 1500 somapacitan injections were administered to 61 patients and only two mild and transient injection site reactions were observed.[25]

For the somapacitan dosing range tested in this trial (0.02-0.16 mg/kg), drug exposure parameters (C_{max} and AUC) were dose dependent, although not dose proportional. In contrast, when somapacitan doses of 0.02-012 mg/kg were tested in adult patients with GHD, dose-proportional increases in PK parameters were observed,[12] and the increase in PK parameters appears to be influenced by body weight. The shape of the somapacitan profiles in children with GHD indicated nonlinear PK.

There was some variation in the baseline IGF-I SDS values across dose groups. The different IGF-1 baseline values after 7-10 days' washout may be due to the period of washout being too short for some of the children with GHD. When correcting for baseline IGF-I levels, the PD responses were dose dependent, with mean IGF-I SDS elevated for at least 7 days but remaining within the normal range, and thus supporting once-weekly dosing of somapacitan for the treatment of children with GHD. In a previous multiple-dose trial of somapacitan in adults with GHD, no IGF-I accumulation was observed;[12] however, in the current single-dose trial in children, accumulation was not addressed, and in some patients, IGF-I levels did not completely return to baseline after 7 days; this will therefore need to be addressed in a multiple-dose trial. As the IGF-I response to the somapacitan doses of 0.04, 0.08 and 0.16 mg/kg was comparable to the IGF-I response to Norditropin®, these doses seem relevant for such a phase 2 dose finding study.

The C_{max} of somapacitan after a single dose in this trial was between 22 and 458 ng/mL (0.94-19.7 nmol/L). Human serum albumin is present in human serum at a concentration of 530 000-758 000 nmol/L.[26] The albumin/somapacitan molar ratio at highest concentration and lowest normal albumin concentration is approximately 26 900, suggesting albumin occupancy of approximately 0.004%. Thus, binding of somapacitan is very unlikely to affect other medications that rely on binding to albumin.

It could be speculated that the use of a long-acting GH is less physiological than that of daily growth hormone injections and that permanently high GH concentrations could lead to downregulation and potentially less growth, affecting adult height. In the current study, the PK profile of once-weekly somapacitan revealed levels that were not permanently high, but varied throughout the week with a peak after approximately 2 days and a trough value after 7 days. Future clinical trials of longer duration need to determine whether long-term administration with somapacitan is as efficacious and safe as daily GH in children with GHD. A limitation of this trial was the small number of patients; however, childhood GHD is relatively uncommon, and a large sample size is not feasible. An unequal gender distribution between treatment groups could have affected the IGF-I results, and it has been suggested that response to GH with respect to IGF-I differs in prepubertal boys and girls;[27] however, the small sample sizes in the current trial did not permit analysis by gender. Further, the relatively low number of subjects limited the statistical interpretation of the data, and variations of the IGF-I baseline levels also made interpretation difficult. It is also worth noting that this was a single-dose trial resulting in short-term exposure to somapacitan on which the reported safety, PK and PD data are based; the long-term effects of somapacitan on IGF-I levels and adverse event profile are more likely to be observed in future long-term trials.

In conclusion, single doses of somapacitan within the dose range 0.02-0.16 mg/kg were well tolerated when administered to prepubertal children with GHD. No clinically significant safety signals causally related to somapacitan were identified, nor were any immunogenicity concerns revealed. The IGF-I profile indicates that somapacitan is suitable for once-weekly dosing in children with GHD.

DECLARATION OF INTEREST

TB is a board member of Novo Nordisk, Sanofi, Eli Lilly Medtronic and Bayer Health Care, and a consultant for Spring. His institution received research grant support, with receipt of travel and accommodation expenses in some cases, from Abbott, Medtronic, Novo Nordisk, GluSense, Sanofi, Sandoz and Diamyd. He has received honoraria for participating on the speaker's bureaux of Eli Lilly, Bayer, Novo Nordisk, Medtronic, Sanofi and Roche, and owns stocks of DreamMed. MHR is an employee of Novo Nordisk A/S. JDS has received consultation fees from Ferring, Novo Nordisk and Pfizer. NZ-L and ZG have received consultation fees from Novo Nordisk. LS has received consultation fees from Ferring, Novo Nordisk, Merck, Pfizer and Sandoz, and research grants from Merck, Novo Nordisk and Pfizer.

AUTHOR CONTRIBUTIONS

All authors provided (i) substantial contributions to the conception and design, or the acquisition, analysis or interpretation of the data; (ii) the drafting of the article or critical revision for important intellectual content; (iii) final approval of the version to be published; and (iv) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the article are appropriately investigated and resolved, and therefore fulfil the authorship criteria of the International Committee of Medical Journal Editors (ICMJE). All authors, external and internal, had full access to all the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

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APPENDIX 1 NN8640-4042 Study Group

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