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Clinical Research Article

Weekly Somapacitan is Effective and Well Tolerated in Children With GH Deficiency: The Randomized Phase 3 REAL4 Trial

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Abstract

Context: Somapacitan, a once-weekly reversible albumin-binding GH derivative, is evaluated in children with GH deficiency (GHD).

Objective: To demonstrate efficacy and safety of somapacitan vs daily GH.

Methods: REAL4 is a randomised, multinational, open-labeled, active-controlled parallel group phase 3 trial, comprising a 52-week main trial and 3-year extension (NCT03811535).

Setting: Eighty-six sites across 20 countries.

Patients: 200 treatment-naïve patients were randomized and exposed.

Interventions: Patients were randomized 2:1 to somapacitan (0.16 mg/kg/wk) or daily GH (Norditropin; 0.034 mg/kg/d), administered subcutaneously.

Main outcome measures: The primary endpoint was annualized height velocity (HV; cm/y) at week 52. Additional assessments included HV SD score (SDS), height SDS, bone age, IGF-I SDS, patient-reported outcomes, and safety measures.

Results: Estimated mean HV at week 52 was 11.2 and 11.7 cm/y for somapacitan and daily GH, respectively. Noninferiority was confirmed. Changes in HV SDS, height SDS, bone age, and IGF-I SDS from baseline to week 52 were similar between treatment groups. At week 52, mean IGF-I SDS values were similar between treatment groups and within normal range (–2 to +2). Safety of somapacitan was consistent with the well-known daily GH profile. Low proportions of injection-site reactions were reported for somapacitan (5.3%) and daily GH (5.9%). Both treatments similarly reduced disease burden from baseline to week 52, whereas a greater treatment burden reduction was observed for somapacitan.

Conclusions: Similar efficacy for somapacitan compared to daily GH was demonstrated over 52 weeks of treatment with comparable safety and mean IGF-I SDS levels in treatment-naïve children with GHD.

Key Words: growth hormone, growth hormone deficiency, growth hormone replacement therapy, long-acting growth hormone, somapacitan, treatment burden

Abbreviations: AE, adverse event; CA, chronological age; GHD, GH deficiency; GHD-CIM, Growth Hormone Deficiency—Child Impact Measure; GHD-CTB, Growth Hormone Deficiency—Child Treatment Burden; GHD-PTB, Growth Hormone Deficiency—Parent Treatment Burden; HSDS, height SD score; HV, height velocity; LAGH, long-acting GH; PD, pharmacodynamic; PK, pharmacokinetic.

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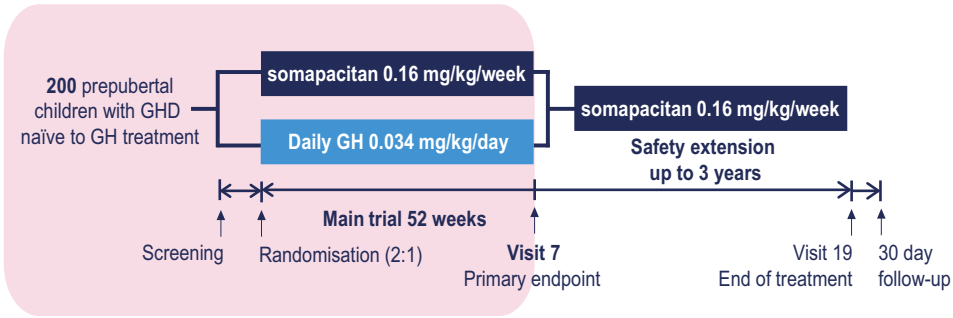

Figure 1. Trial overview. Design of the REAL4 trial and extension. Results from main trial (52 weeks) are reported in this paper. Time axis is not to scale. Abbreviation: GHD, GH deficiency.

GH is essential for longitudinal growth in children. GH deficiency (GHD) is characterized by the inadequate production or secretion of GH. Treatment with GH replacement therapy improves overall health and final adult height for children with GHD (1, 2). Normal growth can often be restored, but the short half-life of GH necessitates daily subcutaneous injections, which can be a burden for children and their caregivers, disrupting the daily lives and routines of families and resulting in low adherence (3, 4). In 1 study, one-quarter of children treated with daily GH therapy reported missing 2 or more injections per week (5). Low adherence negatively affects growth outcomes (6) and is partly attributed to injection pain and frequency of injections (5, 7).

A long-acting GH (LAGH) should, at minimum, have the same excellent efficacy and safety profile as GH administered daily while also reducing the number of injections (8). Somapacitan (Novo Nordisk A/S), a once-weekly treatment for GHD, is in clinical phase 3 development for GHD in children. It reduces injection frequency from 365 injections per year required for daily GH replacement to 52 injections per year (9, 10). This is expected to reduce distress associated with daily injections, decrease interference with daily life, and thereby potentially improve treatment adherence and, consequently, clinical outcomes.

Somapacitan is a 23.3-kDa human GH derivative (99% similarity to endogenous GH) linked to a small noncovalent albumin-binding moiety that facilitates reversible endogenous albumin binding to delay somapacitan elimination. Similar technologies enhance the half-life of other peptide drugs, such as long-acting insulin detemir (11), glucagon-like peptide-1 molecules liraglutide (12), and semaglutide (13). In previous trials, somapacitan has been shown to be well tolerated in adults and children with GHD (9, 10, 14–16) and effective in adults with GHD (17, 18). A phase 2 dose-finding and safety trial in prepubertal children with GHD suggests 0.16 mg/kg/wk somapacitan has the same efficacy and safety profile as daily GH treatment (0.034 mg/kg/d Norditropin, Novo Nordisk A/S) for up to 3 years of treatment (10, 16).

The primary objective of the phase 3 REAL4 trial was to evaluate the efficacy, safety, and tolerability of once-weekly somapacitan compared with daily GH in prepubertal, treatment-naïve children with GHD.

Methods

Study Design

The current trial was conducted as a randomized, multinational, open labeled, and active-controlled parallel group phase 3 trial at 86 sites in 20 countries in Asia, Europe, and North America (ClinicalTrials.gov: NCT03811535). The study was conducted in Austria, Canada, France, Germany, India, Israel, Italy, Japan, Korea, Latvia, Poland, Russia, Serbia, Slovenia, Spain, Switzerland, Thailand, Ukraine, United Kingdom, and United States. The sponsor (Novo Nordisk A/S) designed the trial and oversaw its conduct. The trial investigated the efficacy and safety of once-weekly somapacitan treatment (0.16 mg/kg/wk) for GHD in children compared with a control group receiving daily GH (Norditropin, Novo Nordisk; 0.034 mg/kg/d) (Fig. 1). The main trial period was 52 weeks, followed by an ongoing 3-year single-group extension period. The 52-week data reported here were collected between May 2019 and November 2021.

The somapacitan dose is supported by results from a phase 2 dose-finding trial (NCT03878446) demonstrating the efficacy and safety of 0.16 mg/kg/wk somapacitan matches that of daily treatment with 0.034 mg/kg/d Norditropin (10). The daily GH dose of 0.034 mg/kg/d was chosen based on the maximum dose according to the product label for children with GHD (0.034 or 0.035 mg/kg/d in participating countries). Both treatments were administered subcutaneously, the approved administration route for Norditropin and intended route of somapacitan administration. The 0.16 mg/kg/wk dose of somapacitan was provided as 5 mg/1.5 mL, 10 mg/1.5 mL, and 15 mg/1.5 mL prefilled pen injectors of the FlexPro family (Novo Nordisk A/S). Daily GH (0.034 mg/kg/d Norditropin) was provided using Norditropin FlexPro 10 mg/1.5 mL.

Participants were seen at weeks 4, 13, 26, 39, and 52; dosing was calculated based on the participant's body weight at each of these visits. Efficacy measurements, adverse event recording, and safety laboratory measurements took place at these time points.

The trial protocol was approved by local and national ethics committees, as appropriate, and conducted in accordance with the International Conference on Harmonisation Guidelines for Good Clinical Practice (19) and the Declaration of Helsinki (20).

Patients

Two hundred prepubertal children with a confirmed diagnosis of GHD and no prior exposure to GH therapy and/or IGF-I treatment were enrolled. Informed consent was obtained in writing from the parents and/or the child's legally acceptable representative, and child assent was obtained as age appropriate.

Key inclusion criteria included: for girls—Tanner stage 1 for breast development (no palpable glandular breast tissue) and age between 2.5 years and 10 years at screening; for

boys—testes volume <4 mL and age between 2.5 years and 11 years at screening. For all children: impaired height (at least 2.0 SD below mean) for chronological age (CA) and sex; impaired height velocity (HV) (annualized HV below the 25th percentile) for CA and sex; and IGF-I <−1.0 SDS at screening.

Children with any clinically significant abnormality likely to affect growth or the ability to evaluate growth with standing measurements were excluded. Other exclusion criteria included: children born small for gestational age; diabetes mellitus diagnosis; attention deficit hyperactivity disorder diagnosis; concomitant administration of treatments that may affect growth, such as methylphenidate for treatment of attention deficit hyperactivity disorder; and history or presence of malignancy and/or intracranial tumour.

Eligible subjects were randomly assigned using a trial-specific, interactive web-based response system. Participants were randomized 2:1 to receive either once-weekly somapacitan or daily GH (Norditropin), respectively. The randomization was stratified by region (Japan; rest-of-the-world) as well as by age (<6; ≥6 years), sex (boys; girls), and GH peak level (< 7.0; ≥7.0 ng/mL).

Treatment adherence during the trial was monitored by electronic diaries. The date, time, and injection dose of the trial drug as well as any missed doses were recorded.

Objectives and Endpoints

Primary endpoint

The primary objective of the trial was to evaluate the effect of once-weekly somapacitan vs daily GH on longitudinal growth in children with GHD. This was assessed by annualized HV (cm/y) and measured as standing height with a stadiometer at baseline and at week 52. Although the study was open-labeled, assessors performing height measurements were blinded to treatment allocation.

Other efficacy endpoints

Supportive secondary efficacy endpoints included change from baseline to week 52 in HV SD score (HV SDS), height SDS (HSDS), and bone age vs CA ratio. Bone age (radiograph of left hand and wrist) was centrally assessed as previously described (21).

Pharmacodynamic endpoint

The main pharmacodynamic endpoint was IGF-I SDS. IGF-I analyses were performed by a central laboratory using a commercially available assay kit (Immunodiagnostic Systems Immunoassay) on samples collected at weeks 13 and 39 (day 7 after somapacitan dosing for assessing trough levels), weeks 4 and 26 (in a window of 1-4 days after somapacitan dosing designed to characterize the peak), and week 52 (4-6 days after somapacitan dosing to capture expected weekly average levels). This was done to provide information on peak-to-trough IGF-I fluctuations for somapacitan treatment and derive a weekly IGF-I average using population pharmacokinetic/pharmacodynamic (PK/PD) modeling.

Patient-reported Outcomes

Patient-reported outcome questionnaires were completed by the parent or caregiver to evaluate the full spectrum of impacts and burden of GHD treatment as well as overall improvements in these aspects in children with GHD. First, the Growth Hormone Deficiency—Child Impact Measure (GHD-CIM) is a disease-specific questionnaire developed in line with US Food and Drug Administration guidance (22) to assess the impact of GHD on physical functioning and social and emotional well-being of children with GHD (23). Two additional disease-specific questionnaires, also developed in line with US Food and Drug Administration guidance (22), were the Growth Hormone Deficiency—Child Treatment Burden (GHD-CTB) and Growth Hormone Deficiency—Parent Treatment Burden (GHD-PTB) (24, 25). GHD-CTB measures the physical burden of GH treatment as well as the burden of GH treatment on emotional well-being and interference in daily life activities of children with GHD, whereas GHD-PTB measures the burden of GH treatment on the emotional well-being of the parent/caregiver as well as the interference in daily life activities of the parent/caregiver. The Growth Hormone Device Assessment Tool was applied to evaluate the ease of use of the somapacitan and Norditropin in devices of the FlexPro family.

Safety Assessments

Safety was assessed by the incidence of adverse events (AEs), which were summarized by treatment, Medical Dictionary for Regulatory Activities system organ class, and Medical Dictionary for Regulatory Activities preferred term. Supportive secondary safety included incidence of AEs evaluated from visit 1 (week −2), and injection site reactions evaluated at every visit from visit 2 (week 0); occurrence of anti-somapacitan and anti-GH antibodies; incidence of technical complaints; and changes from baseline in clinical safety laboratory parameters, including hematology, biochemistry, hormones (including morning cortisol, thyroid function test), fasting lipids, fasting glucose, fasting insulin, and glycated hemoglobin levels. Assessment of antibodies against somapacitan or daily GH were performed by the study sponsor using a validated anti-somapacitan or anti-human GH antibody-binding assay (14).

Statistical Analysis

Two analysis populations were defined: the full analysis set included all randomly assigned participants (used for efficacy outcome analyses) and the safety analysis set included all participants exposed to 1 or more doses of trial product (used for safety outcome analyses). Observation periods included on-treatment (the time from first administration and up until last trial contact or visit 7 or 14 days after last administration, whichever comes first) and in-trial (the time from first administration and up until visit 7 or last trial contact, whichever comes first).

Two distinct estimand strategies were defined to evaluate treatment effect from different scientific perspectives. The treatment policy strategy recommended by the Food and Drug Administration and Pharmaceuticals and Medical Devices Agency evaluates data collected up to and including week 52, regardless of treatment discontinuation, or use of ancillary therapy. The hypothetical strategy recommended by the European Medicines Agency evaluates data collected up to and including week 52, excluding data assessed after discontinuation of randomized treatment.

HV was analyzed based on both the treatment policy strategy and the hypothetical strategy. HV at week 52 was analyzed using an analysis of covariance model with treatment,

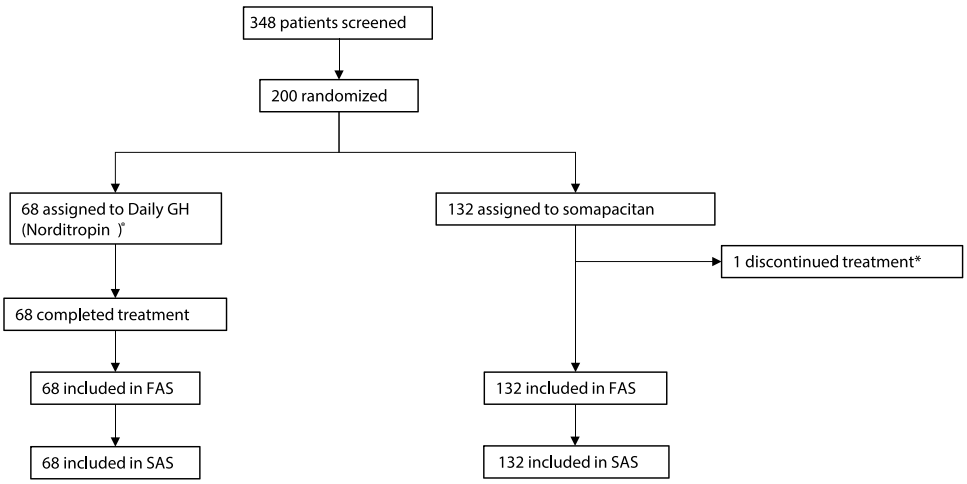

Figure 2. Trial profile. The full analysis set (FAS) represents all randomly assigned children in the trial to either weekly somapacitan or daily GH (Norditropin). The safety analysis set (SAS) contains all randomly assigned children who received at least 1 dose of randomized treatment. *One patient receiving somapacitan discontinued treatment because of violation of inclusion/exclusion criteria but was included in the FAS and SAS.

sex, age group, region, GH peak group and sex by age group by region interaction term as factors, and baseline height as covariate. The prespecified noninferiority threshold was −1.8 cm/y. Changes in height SDS and HV SDS were analyzed using the same analysis model as was used for analyzing the primary endpoint for the treatment policy estimand with the exception that baseline height SDS and baseline HV SDS were used, respectively, as covariates in the model instead of baseline height. Change in bone age was analyzed using an analysis of covariance model on change in bone age/chronological age assessed at week 52 and the model included treatment, sex, age group, region, GH peak group, and sex by age group by region interaction term as factors and bone age/chronological age at screening as a covariate. Patient-reported outcomes (exploratory endpoints) were analyzed based on the "on-treatment" observation period using a mixed model for repeated measurements, including the same factors as the primary analysis as well as the baseline assessment for GHD-CIM.

Safety endpoint changes from baseline to week 52 in glucose metabolism parameters were analyzed using descriptive statistics. All AEs with onset after the first administration of treatment and with start date up until 14 days after last dose or until week 52 (whichever comes first) were included and analyzed using descriptive statistics.

PK/PD Modeling

IGF-I SDS profiles and weekly IGF-I average SDS at steady-state week 52 were estimated by population PK/PD modeling. Models were fitted to PK and IGF-I data from this study and previous phase 1 and 2 data in children with GHD (9, 10) using models developed from full PK and IGF-I profiles obtained in phase 1 healthy adults, and adults and children with GHD (26, 27). Weekly average IGF-I levels were calculated from the estimated IGF-I area under the curve in a dosing interval for each individual treated with somapacitan.

Role of the Funding Source

The sponsor was involved in the study design, collection, analysis, interpretation, and presentation of data.

Results

Study Population

Two hundred treatment-naïve participants were randomly assigned to receive once-weekly somapacitan (132) or daily GH Norditropin (68) (Fig. 2). In total, 199 completed the 52 weeks of treatment. One patient with GHD receiving somapacitan discontinued treatment because of a violation of other inclusion/exclusion criteria, and thus was randomized in error, but was included in the final analysis set and safety analysis set.

Demographics and baseline characteristics were largely similar in both treatment groups (Table 1). Mean HSDS at baseline was slightly lower in the control daily GH group (−3.47) compared with the somapacitan treatment group (−2.99). Similarly, mean GH peak levels were slightly lower in the control daily GH group (4.10) compared with the somapacitan treatment group (4.93).

Adherence was high for both treatments. The mean and median adherence for somapacitan treatment were 95.8% and 100%, respectively. The mean and median adherence for the daily GH group were 88.3% and 96.9%, respectively.

Efficacy Results

Primary endpoint: height velocity

Observed HV increased from baseline to week 52 in a similar manner for both treatment groups (Fig. 3). Estimated mean HV after 52 weeks of treatment (the primary endpoint) was 11.2 cm/y for somapacitan and 11.7 cm/y for daily GH (Table 2), regardless of which estimate was used. The estimated treatment difference was −0.5 cm/y (95% confidence interval, −1.1 to 0.2). Noninferiority was confirmed (noninferiority threshold: −1.8 cm/y) and differences in HV between treatment groups were not statistically significant.

Other growth-related assessments

As with the primary endpoint, secondary height-related endpoints HVSDS and HSDS increased from baseline to week 52 for somapacitan and daily GH, with change differences between treatment groups not statistically significant (Table 2).

Table 1. Study demographics and baseline characteristics (week 0 of REAL4)

	Somapacitan 0.16 mg/kg/wk n = 132	Daily GH 0.034 mg/kg/d n = 68	Total n = 200
Mean age, (SD), y	6.4 (2.2)	6.4 (2.4)	6.4 (2.3)
<6 y, n (%)	64 (48.5)	33 (48.5)	97 (48.5)
Female, n (%)	33 (25.0)	18 (26.5)	51 (25.5)
Race, n (%)			
White	78 (59.1)	36 (52.9)	114 (57.0)
Asian	46 (34.8)	28 (41.2)	74 (37.0)
Black or African American	0 (0)	1 (1.5)	1 (0.5)
Not reported	7 (5.3)	3 (4.4)	10 (5.0)
Other	1 (0.8)	0 (0)	1 (0.5)
Mean weight, kg (SD)	16.7 (4.60)	16.0 (4.95)	16.5 (4.72)
Mean BMI, kg/m^2 (SD)	15.7 (1.59)	15.6 (1.38)	15.7 (1.52)
Mean height, cm (SD)	102.3 (12.5)	100.2 (15.0)	101.6 (13.4)
Mean HV, cm/y (SD)	4.3 (1.4)	4.1 (1.4)	4.2 (1.4)
Mean HV SDS (SD)	−2.35 (1.51)	−2.52 (1.55)	−2.41 (1.52)
Mean height SDS (SD)	−2.99 (1.02)	−3.47 (1.52)	−3.15 (1.23)
Mean IGF-I SDS (SD)	−2.03 (0.97)	−2.33 (1.03)	−2.13 (1.00)
GH peak, µg/L (SD)	4.93 (2.50)	4.10 (2.77)	4.65 (2.62)
GHD etiology, n (%)			
Idiopathic	115 (87.1)	61 (89.7)	176 (88.0)
Organic	17 (12.9)	7 (10.3)	24 (12.0)

Full analysis set.
Abbreviations: BMI, body mass index; GHD, GH deficiency; HV, height velocity; SDS, SD score.

A steady and similar increase in body weight was observed over the 52 weeks for both treatment groups, as expected in growing children. Observed mean body mass index SDS remained within the normal range, with an increase from −0.17 to +0.39 in the somapacitan group and a decrease from −0.25 to −0.49 in the daily GH group. Bone age to CA ratio advanced similarly in both groups (Table 2), with no changes in skeletal proportions reported.

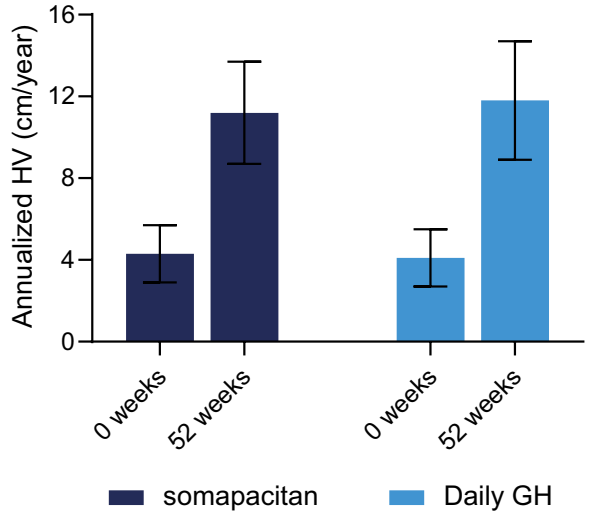

Figure 3. Observed height velocity from baseline to week 52. Mean observed HV (cm/year) at baseline and week 52 for 0.16 mg/kg/wk somapacitan and 0.034 mg/kg/d daily GH (Norditropin) treatment groups. Error bars represent SD. Abbreviation: HV, height velocity.

Table 2. Statistical analyses of in-trial efficacy endpoints at week 52

	Somapacitan 0.16 mg/kg/wk estimated mean	Daily GH 0.034 mg/kg/d estimated mean	ETD (95% CI)
Annualized HV, cm/y	11.2	11.7	−0.5 (−1.1 to 0.2)
Change in HSDS from baseline	1.25	1.30	−0.05 (−0.18 to 0.08)
Change in HVSDS from baseline	8.05	8.82	−0.78 (−1.63 to 0.08)
Change in IGF-I SDS from baseline	2.36	2.33	0.03 (−0.30 to 0.36)
Change in BA vs CA	0.06	0.08	−0.02 (−0.06 to 0.01)

Full analysis set.
Abbreviations: BA, bone age; CA, chronological age; CI, confidence interval; ETD, estimated treatment difference; HSDS, height SD score; HV, height velocity; HVSDS, height velocity SD score; SDS, SD score.

IGF-I SDS

GH stimulates IGF-I release, which is the mostly widely used biomarker for GH treatment response (28). To characterize the weekly IGF-I profile in response to weekly somapacitan treatment, samples were collected at different timepoints of the dosing interval. The observed IGF-I SDS for somapacitan based on samples collected at week 52 corresponded well with the model-derived weekly average IGF-I SDS for somapacitan (Fig. 4A). Observed mean IGF-I SDS values were similar between treatment groups at week 52 (+0.28 vs +0.10 for somapacitan and Norditropin, respectively) and within normal range (−2 to +2) (Fig. 4A). Change in mean IGF-I SDS from baseline to week 52 was also similar with no statistically significant differences between treatment groups ($P = 0.8544$) (Table 2). The IGF-I SDS profile increased after an injection of somapacitan to an estimated mean (SD) peak of +1.66 (0.90), which occurred after an average time (SD) of 57.6 (7.9) hours (Fig. 4B). After this, the profile declined to a mean (SD) predose IGF-I SDS of −0.83 (0.78).

Safety Results

The number of participants with adverse events (AEs) was 94 (71.2%) and 41 (60.3%) for somapacitan and daily GH treatment groups, respectively (Table 3). Most AEs were mild or moderate in severity (98%) and judged unlikely related to trial product. In total, 6 (4.5%) participants reported 8 serious AEs in the somapacitan group, whereas 2 (2.9%) participants reported 3 serious AEs in the daily GH group. All serious AEs were reported recovered/resolved by the end of the trial and deemed unlikely to be related to trial product. The most common AEs observed in ≥5% of the participants were events commonly observed in children, including headache, nasopharyngitis, pyrexia, pain in extremity, bronchitis, and vomiting. There were no deaths, and no participants discontinued the study because of AEs.

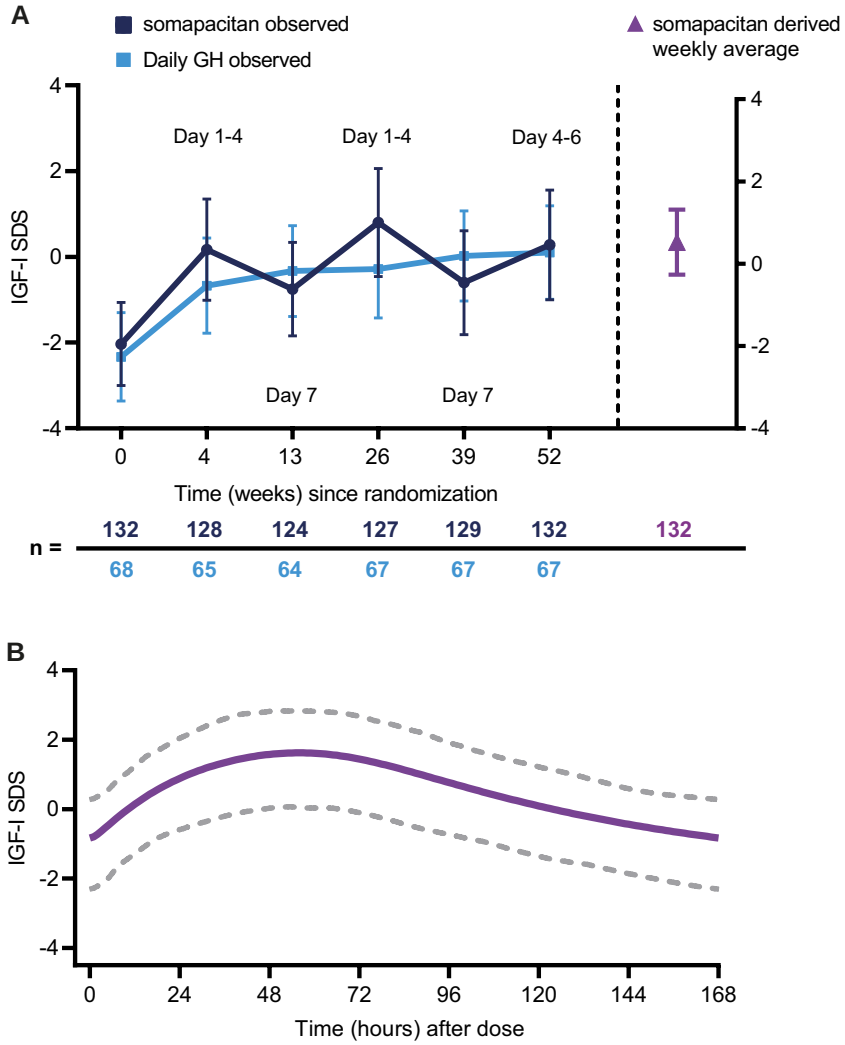

Figure 4. IGF-I SDS profiles following somapacitan administration. (A) Observed mean IGF-I SDS for 0.16 mg/kg/wk somapacitan and 0.034 mg/kg/d daily GH (Norditropin). Samples collected at week 0 were taken prior to first dose. To characterize the weekly IGF-I profile, week 4 and 26 samples were collected in a window designed to characterize the peak between 1 and 4 days after dosing: mean sampling times after dosing were 45 and 44 hours (1.9 and 1.8 days), respectively. Trough samples at weeks 13 and 39 were taken on day 7. Week 52 samples taken 4 to 6 days after dosing captured expected weekly averages: mean sampling time after dosing was 113 hours (4.7 days). Error bars represent SD. Time axis is not to scale. (B) Estimated IGF-I SDS profile over the week were derived by population PK/PD modeling. The solid line represents mean profiles based on population PK/PD modeling. Dotted gray lines represent 5th to 95th percentile. Abbreviations: PK/PD, pharmacokinetic/pharmacodynamic; SDS, SD score.

Overall, IGF-I levels above +2.0 SDS were measured at sometime during the study by 36 (27.3%) and 3 (4.4%) participants in the somapacitan and daily GH treatment groups, respectively. In the somapacitan group, 33 participants had IGF-I measurements above +2.0 SDS only at peak IGF-I levels. No participants receiving somapacitan had IGF-I values exceeding +2.0 SDS at trough levels. The number of participants with an IGF-I SDS above +2.0 at 2 or more consecutive visits during the 52-week treatment period was 5 (3.8%) and 2 (2.9%) for the somapacitan and daily GH treatment groups, respectively. No trend was seen in the amount or type of AEs reported in these participants. One participant in each treatment group (0.8% for somapacitan and 1.4% for daily GH) had dose reductions because of IGF-I SDS exceeding +2.5 at 2 consecutive visits. No safety issues were observed in relation to the IGF-I SDS levels above +2.5 in these 2 participants.

There were few reports of participants experiencing injection site reactions: 7 (5.3%) and 4 (5.9%) in the somapacitan and daily GH treatment groups, respectively (Table 4). In both treatment groups, the same proportion (1.5%) reported mild and transient injection site pain.

There were no clinically relevant findings related to glucose metabolism (ie, change in fasting plasma glucose and glycated hemoglobin) in either treatment group.

Before the start of dosing (baseline sample), four participants tested positive for low titer nonneutralizing anti-somapacitan antibodies that did not cross react with human GH, suggesting a potential for false positives. All 4 participants tested negative for anti-somapacitan antibodies during the remainder of the trial, indicating that these baseline findings were indeed false positives. The vast majority of antibodies detected in this study were single transient low titer. Two (1.5%) participants in the somapacitan group and one (1.5%) in the daily GH group had 2 or more consecutive positive nonneutralizing antibody samples. No neutralizing antibodies were detected in either group.

Table 3. Adverse events

	Somapacitan 0.16 mg/kg/wk n = 132			Daily GH 0.034 mg/kg/d n = 68		
	N (%)	E	R	N (%)	E	R
All events	94 (71.2)	310	232.3	41 (60.3)	147	212.8
Serious events	6 (4.5)	8	6.0	2 (2.9)	3	4.3
Severity						
Mild events	87 (65.9)	253	189.6	35 (51.5)	119	172.2
Moderate events	27 (20.5)	50	37.5	12 (17.6)	27	39.1
Severe events	4 (3.0)	7	5.2	1 (1.5)	1	1.4
Relation to trial product						
Probably related	12 (9.1)	16	12.0	4 (5.9)	5	7.2
Possibly related	20 (15.2)	45	33.7	9 (13.2)	21	30.4
Unlikely related	90 (68.2)	249	186.6	38 (55.9)	121	175.1

Safety analysis set.
Abbreviations: E, number of events; R, event rate per 100 patient-years at risk.

Patient-reported Outcomes

The change in GHD-CIM scores from baseline to week 52 demonstrates high overall similarity in reduced disease burden between treatment groups (Fig. 5A and B). Treatment burden was not collected at baseline as enrolled patients were treatment-naïve at baseline. Thus, treatment burden (GHD-CTB and GHD-PTB) was assessed between treatments groups at week 52. Results from these treatment burden assessments favor somapacitan over daily GH across all domains (Fig. 5C and D), with the difference being statistically significant for GHD-PTB. The Growth Hormone Device Assessment Tool scores indicate the same high proportion of respondents (96%) found somapacitan and Norditropin in devices of the FlexPro family to be easy or very easy to use, and a similarly high proportion of respondents in both groups (>90%) found the devices easy or very easy to learn to use.

Discussion

The primary objective of this phase 3 trial was met demonstrating noninferiority in HV of once-weekly somapacitan compared with daily GH (Norditropin) in treatment-naïve children with GHD.

GH replacement therapy is approved for treating GHD in children and is demonstrated to restore longitudinal growth with relatively few side effects (2). Despite ongoing improvements in injection device design, daily GH injections can be burdensome for patients and their caregivers, disrupting and interfering with daily life. This treatment burden is at least partly responsible for observed nonadherence to prescribed replacement therapy and suboptimal clinical outcomes (8, 29). The overall objectives for developing a LAGH are therefore to establish a less burdensome dosing regimen that interferes less with daily life and is as safe and efficacious as daily GH to potentially improve adherence and clinical outcomes.

Several technologies have been used to prolong GH action, including GH with noncovalent albumin-binding properties (eg, somapacitan), covalent or transient pegylation (eg, lonapegsomatropin), as well as GH-fusion proteins (eg, somatrogon) (29). Earlier attempts to develop LAGHs encountered setbacks, which were often related to injection site reactions (30–33). One pegylated LAGH formulation administered as once-weekly subcutaneous injections in children or adults with GHD was associated with significant lipoatrophy at the injection site in 12.4% of participants (32). In a more recent study involving the LAGH lonapegsomatropin, a transiently pegylated prodrug, injection site reactions were observed in 47.5% of participants receiving lonapegsomatropin, including pain in 40% of participants (34). Fewer injection site reactions were reported in another study with lonapegsomatropin (35). For the once-weekly GH-fusion protein somatrogon, injection site pain was reported for 39.4% of participants in 1 phase 3 study (36) and 72.7% in a phase 3 study conducted in Japanese patients (37). Previous studies of somapacitan in both adults and children with GHD have consistently demonstrated infrequent injection site reactions that were both mild and transient (1.8%-6.7% of participants) (10, 15–18). In line with these findings, few injection site reactions for somapacitan were reported in the current study (5.3%), including a very low proportion reporting pain (1.5%). Additionally, reported data from this trial indicate that somapacitan in a device of the FlexPro family is easy to learn to use and easy to use and is therefore expected to contribute to an overall positive treatment experience. Together, device-related treatment experience parameters in combination with a low proportion of injection site reactions (including pain) may facilitate patient and caregiver acceptability in addition to the desirable therapeutic profile.

Serum IGF-I levels are typically higher the first days after LAGH dosing before decreasing until the next injection (29). A clinical guidance recommended goal for any GH treatment used to treat GHD is to maintain mean IGF-I SDS levels in the physiological range between −2 to +2 and avoid persistent values above this normal range (38). Note, transient IGF-I SDS above +2 have not been shown to be a safety concern (38). As is a typical characteristic across LAGHs, the IGF-I profile during somapacitan treatment, with peaks and troughs over the weekly dosing interval, differs from the profile seen with daily GH. Observed mean peak and trough IGF-I SDS levels (+1.66 and −0.83, respectively) during the somapacitan weekly dosing interval were within normal range. For participants receiving somapacitan in this study, IGF-I SDS reached a maximum around day 3 after somapacitan administration before declining to trough level on day 7. In a small subgroup, transient IGF-I SDS values above +2 can be expected around

Table 4. Injection site reactions

	Somapacitan 0.16 mg/kg/wk n = 132			Daily GH 0.034 mg/kg/d n = 68		
	N (%)	E	R	N (%)	E	R
Bruising	2 (1.5)	2	1.5	2 (2.9)	2	2.9
Pain	2 (1.5)	2	1.5	1 (1.5)	1	1.4
Haematoma	2 (1.5)	4	3.0	0 (0)	—	—
Hypersensitivity	0 (0)	—	—	1 (1.5)	1	1.4
Swelling	1 (0.8)	1	0.7	0 (0)	—	—

Safety analysis set.
Abbreviations: %, percentage of patients; E, number of events; R, event rate per 100 patient-years at risk.

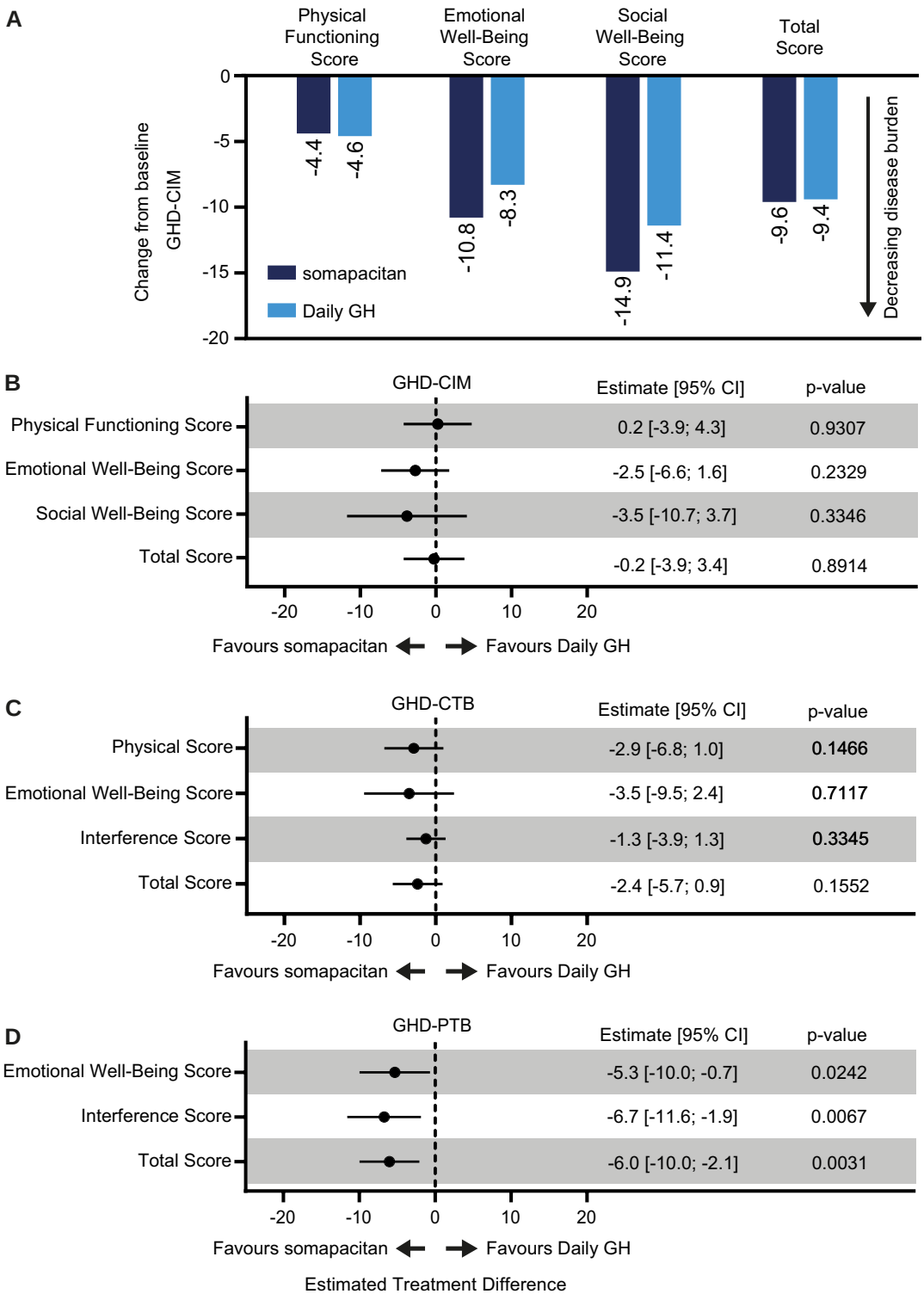

Figure 5. Patient reported outcomes at week 52. (A) Change from baseline to week 52 between somapacitan and daily GH (Norditropin) in disease burden (GHD-CIM) domain scores and total score (FAS). A lower number indicates a greater burden reduction. (B) Estimated treatment differences from baseline to week 52 between somapacitan and daily GH (Norditropin) in disease burden (GHD-CIM) domain scores and total score (FAS). Estimated treatment difference at week 52 between somapacitan and daily GH (Norditropin®) in treatment burden domain scores and total score (FAS) for (C) child (GHD-CTB) and (D) parent/caregiver (GHD-PTB). Abbreviations: CI, confidence interval; CIM, Child Impact Measure; CTB, Child Treatment Burden; FAS, full analysis set; GHD, GH deficiency; PTB, Parent Treatment Burden.

day 3 after somapacitan dosing before returning to predose levels. This is relevant to consider when sampling IGF-I levels. Average IGFI-SDS is expected around day 4 or 5 after dosing, a timeframe that allows the clinician to monitor IGF-I values with a close approximation of the average weekly exposure.

Similar efficacy results obtained in this study for 0.16 mg/kg/wk somapacitan and 0.034 mg/kg/d daily GH (Norditropin) were accompanied by results showing similar mean change in IGF-I SDS from baseline to week 52 (2.36 vs 2.33, respectively) and similar mean IGF-I SDS within the normal range at week

52 (+0.28 vs +0.10, respectively). Because of the known dose-response relationship between GH and IGF-I SDS, achieving similar IGF-I SDS and clinical outcomes in this noninferiority trial confirms comparable titration of treatment groups and underlines the clinical relevance of the results. Although there are various limitations hampering comparisons of data across different clinical trials, putting recently available phase 3 results for different LAGHs into context may be clinically informative. The mean annualized HV of 11.2 cm/y reported for 0.16 mg/kg/wk somapacitan in this study aligns with published results from a phase 3 study with 0.24 mg/kg/wk lonapegsomatropin (reported mean HV of 11.2 cm/y) (35) as well as a phase 3 study with 0.66 mg/kg/wk somatrogon (reported mean HV of 10.1 cm/y) (36). In the current study, clinically relevant improvements similar to daily GH treatment (Norditropin) were observed for all height measures at week 52 following somapacitan treatment (ie, mean annualized HV of 11.2 cm/y, mean change in HVSDS of 8.05, and mean change in HSDS of 1.25), indicating that the efficacy profile of somapacitan is similar to daily GH.

Disease and treatment burden of once-weekly somapacitan and daily GH treatment along with overall improvements for participants were also evaluated in this trial. GHD-CIM is a validated and reliable measure used to investigate the impact of GHD on physical functioning, emotional well-being, and social well-being (23). Results from baseline to week 52 indicate that both somapacitan and daily GH reduce disease burden to a similar degree, consistent with similar efficacy results between treatment groups. On top of similar reductions in disease burden for both treatments, decreasing the number of required injections with once-weekly somapacitan treatment (52 vs 365 injections per year for daily GH) is expected to reduce the treatment burden on patients and their caregivers. When assessing treatment burden between groups, the estimated treatment difference showed a consistent trend favoring once-weekly somapacitan over daily GH, with statistically significant results observed for GHD-PTB scores. These results suggest lower treatment burden for patients and caregivers with somapacitan compared with daily GH.

Somapacitan was well tolerated and not associated with increased number of AEs, immunogenicity, metabolic complications, tolerability issues, or injection site reactions compared with daily GH. Overall, somapacitan shared a similar safety profile to the well-known profile for daily GH. These findings are consistent with the 3-year extension period results from a phase 2 trial in somapacitan-treated children with GHD observing similar safety and efficacy for somapacitan compared with daily GH (16).

This trial had some limitations. Blinding was not possible for once-weekly vs daily treatment doses because this would require a "dummy treatment," which is not considered ethical in pediatric populations. A strength of this study was that height assessments were performed in an observer-blinded manner to limit bias, a precaution not taken for other recent phase 3 studies investigating LAGHs. In addition, adherence in this study was high in both treatment groups, which is to be expected in a controlled clinical trial. However, reducing injection number by 313 injections each year is expected to reduce the overall treatment burden and thus improve adherence in a real-world setting.

In conclusion, noninferiority in HV for somapacitan compared with daily GH was demonstrated with similar safety and mean IGF-I SDS in treatment-naïve children with GHD. These results therefore fulfill expectations from medical and research societies for the development of LAGH replacement therapies (8). We expect the observed reduction in treatment burden with once-weekly somapacitan will lead to improved adherence and treatment outcomes, while potentially also decreasing the barrier to initiating and/or maintaining replacement therapy.

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Data Availability

Available from corresponding author on reasonable request.

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References

1. Grimberg A, DiVall SA, Polychronakos C, *et al.* Guidelines for growth hormone and insulin-like growth factor-I treatment in children and adolescents: growth hormone deficiency, idiopathic short stature, and primary insulin-like growth factor-I deficiency. *Horm Res Paediatr*. 2016;86(6):361-397.
2. Polak M, Blair J, Kotnik P, Pournara E, Pedersen BT, Rohrer TR. Early growth hormone treatment start in childhood growth hormone deficiency improves near adult height: analysis from

NordiNet® International Outcome Study. *Eur J Endocrinol*. 2017;177(5):421-429.
3. Yuen KCJ, Miller BS, Biller BMK. The current state of long-acting growth hormone preparations for growth hormone therapy. *Curr Opin Endocrinol Diabetes Obes*. 2018;25(4):267-273.
4. Acerini CL, Segal D, Criseno S, *et al*. Shared decision-making in growth hormone therapy-implications for patient care. *Front Endocrinol (Lausanne)*. 2018;9:688.
5. Kapoor RR, Burke SA, Sparrow SE, *et al*. Monitoring of concordance in growth hormone therapy. *Arch Dis Child*. 2008;93(2):147-148.
6. Loftus J, Miller BS, Parzynski CS, *et al*. Association of daily growth hormone injection adherence and height among children with growth hormone deficiency. *Endocr Pract*. 2022;28(6):565-571.
7. Cutfield WS, Derraik JGB, Gunn AJ, *et al*. Non-compliance with growth hormone treatment in children is common and impairs linear growth. *PLoS One*. 2011;6(1):e16223.
8. Christiansen JS, Backeljauw PF, Bidlingmaier M, *et al*. Growth hormone research society perspective on the development of long-acting growth hormone preparations. *Eur J Endocrinol*. 2016;174(6):C1-C8.
9. Battelino T, Rasmussen MH, De Schepper J, Zuckerman-Levin N, Gucev Z, Sävendahl L, NN8640-4042 Study Group. Somapacitan, a once-weekly reversible albumin-binding GH derivative, in children with GH deficiency: a randomized dose-escalation trial. *Clin Endocrinol (Oxf)*. 2017;87(4):350-358.
10. Sävendahl L, Battelino T, Brod M, *et al*. group Rs. Once-weekly somapacitan vs daily GH in children with GH deficiency: results from a randomized phase 2 trial. *J Clin Endocrinol Metab*. 2020;105(4):e1847-e1861.
11. Havelund S, Plum A, Ribel U, *et al*. The mechanism of protraction of insulin detemir, a long-acting, acylated analog of human insulin. *Pharm Res*. 2004;21(8):1498-1504.
12. Deacon CF. Potential of liraglutide in the treatment of patients with type 2 diabetes. *Vasc Health Risk Manag*. 2009;5(1):199-211.
13. Lau J, Bloch P, Schäffer L, *et al*. Discovery of the once-weekly glucagon-like peptide-1 (GLP-1) analogue semaglutide. *J Med Chem*. 2015;58(18):7370-7380.
14. Rasmussen MH, Janukonyté J, Klose M, *et al*. Reversible albumin-binding GH possesses a potential once-weekly treatment profile in adult growth hormone deficiency. *J Clin Endocrinol Metab*. 2016;101(3):988-998.
15. Johannsson G, Feldt-Rasmussen U, Håkonsson IH, *et al*. Safety and convenience of once-weekly somapacitan in adult GH deficiency: a 26-week randomized, controlled trial. *Eur J Endocrinol*. 2018;178(5):491-499.
16. Sävendahl L, Battelino T, Rasmussen MH, Brod M, Saenger P, Horikawa R. Effective GH replacement with once-weekly somapacitan vs daily GH in children with GHD: 3-year results from REAL 3. *J Clin Endocrinol Metab*. 2022;107(5):1357-1367.
17. Johannsson G, Gordon MB, Rasmussen MH, *et al*. Once-weekly somapacitan is effective and well tolerated in adults with GH deficiency: a randomized phase 3 trial. *J Clin Endocrinol Metab*. 2020;105(4):e1358-e1376.
18. Otsuka F, Takahashi Y, Tahara S, Ogawa Y, Højby Rasmussen M, Takano K. Similar safety and efficacy in previously treated adults with growth hormone deficiency randomized to once-weekly somapacitan or daily growth hormone. *Clin Endocrinol (Oxf)*. 2020;93(5):620-628.
19. ICH Harmonised Tripartite Guideline. *Guideline for Good Cinical Practice E6*. Geneva, Switzerland: ICH. Published November 2016. https://database.ich.org/sites/default/files/E6_R2_Addendum.pdf. Accessed June 2021.
20. *WMA Declaration of Helsinki—Ethical Principles for Medical Research Involving Human Subjects*. Fortaleza, Brazil: WMA. Published October 2013. https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/. Accessed June 2021.
21. Greulich WW, Pyle SJ. *Radiographic Atlas of Skeletal Development of the Hand and Wrist*. Stanford University Press. 1973.
22. Food and Drug Administration. Guidance for Industry. Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. 2009. http://www.fda.gov/downloads/Drugs/Guidances/UCM193282.pdf.
23. Brod M, Højby Rasmussen M, Vad K, *et al*. Psychometric validation of the growth hormone deficiency-child impact measure (GHD-CIM). *Pharmacoecon Open*. 2021;5(3):505-518.
24. Brod M, Rasmussen MH, Vad K, Alolga S, Bodoin J. Growth hormone deficiency (GHD): assessing parent burden for child growth hormone deficiency treatment: the Growth Hormone Deficiency—Parent Treatment Burden measure (GHD-PTB). ESPE ABSTRACT. 2019.
25. Brod M, Rasmussen MH, Vad K, Alolga S, Bedoin J. SUN-248 growth hormone deficiency (GHD): assessing burden of treatment in children and adolescents ABSTRACT. *J Endocr Soc*. 2019;3-(suppl 1). SUN-248.
26. Juul RV, Rasmussen MH, Agersø H, Overgaard RV. Pharmacokinetics and pharmacodynamics of once-weekly somapacitan in children and adults: supporting dosing rationales with a model-based analysis of three phase I trials. *Clin Pharmacokinet*. 2018;58(1):63-75.
27. Papathanasiou T, Agersø H, Damholt BB, Højby Rasmussen M, Kildemoes RJ. Population pharmacokinetics and pharmacodynamics of once-daily growth hormone Norditropin® in children and adults. *Clin Pharmacokinet*. 2021;60(9):1217-1226.
28. Melmed S. Pathogenesis and diagnosis of growth hormone deficiency in adults. *N Engl J Med*. 2019;380(26):2551-2562.
29. Miller BS, Velazquez E, Yuen KCJ. Long-acting growth hormone preparations—current status and future considerations. *J Clin Endocrinol Metab*. 2019;105(6):e2121-e2133.
30. Khadilkar V, Radjuk KA, Bolshova E, *et al*. 24-month Use of once-weekly GH, LB03002, in prepubertal children with GH deficiency. *J Clin Endocrinol Metab*. 2014;99(1):126-132.
31. Reiter EO, Attie KM, Moshang T Jr, *et al*. A multicenter study of the efficacy and safety of sustained release GH in the treatment of naive pediatric patients with GH deficiency. *J Clin Endocrinol Metab*. 2001;86(10):4700-4706.
32. Touraine P, D'Souza GA, *et al*. Lipoatrophy in GH deficient patients treated with a long-acting pegylated GH. *Eur J Endocrinol*. 2009;161(4):533-540.
33. Biller BM, Ji HJ, Ahn H, *et al*. Effects of once-weekly sustained-release growth hormone: a double-blind, placebo-controlled study in adult growth hormone deficiency. *J Clin Endocrinol Metab*. 2011;96(6):1718-1726.
34. Chatelain P, Malievskiy O, Radziuk K, *et al*. A randomized phase 2 study of long-acting TransCon GH vs daily GH in childhood GH deficiency. *J Clin Endocrinol Metab*. 2017;102(5):1673-1682.
35. Thornton PS, Maniatis AK, Aghajanova E, *et al*. Weekly lonapegsomatropin in treatment-naïve children with growth hormone deficiency: the phase 3 height trial. *J Clin Endocrinol Metab*. 2021;106(11):3184-3195.
36. Deal C, Steelman J, Vlachopapadopoulou E, *et al*. Efficacy and safety of weekly somatrogon vs daily somatropin in children with growth hormone deficiency: a phase 3 study. *J Clin Endocrinol Metab*. 2022;107(7):e2717-e2728.
37. Horikawa R, Tanaka T, Hasegawa Y, *et al*. Efficacy and safety of once-weekly somatrogon compared with once-daily somatropin (Genotropin®) in Japanese children with pediatric growth hormone deficiency: results from a randomized phase 3 study. *Horm Res Paediatr*. 2022;95(3):275-285.
38. Johannsson G, Bidlingmaier M, Biller BMK, *et al*. Growth hormone research society perspective on biomarkers of GH action in children and adults. *Endocr Connect*. 2018;7(3):R126-R134.