Research Article

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Comparing Daily GH with Once-Weekly Somapacitan for Effective GH Replacement in Children With GHD: Three-Year Results From REAL 3.

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ABSTRACT

Context : The daily injections required for current GH therapy can be taxing. A long-acting GH derivative called somapacitan is being developed to treat GH deficit (GHD).
Goal : After three years of treatment, assess the safety, effectiveness, and tolerability of once-weekly somapacitan.
Design : A multicenter, randomized, controlled, phase 2 research (NCT02616562) comparing once-daily GH with somapacitan lasted 156 weeks.
Location : 29 locations throughout 11 nations.
Patients : A total of fifty-nine GHD children were randomly assigned (1:1:1:1) and given therapy. After three years, fifty-three youngsters were done.
Interventions : During the first year of treatment, patients received subcutaneous injections of somapacitan (0.04 [n = 14], 0.08 [n = 15], or 0.16 [n = 14] mg/kg/wk) or daily GH (n = 14) (0.034 mg/kg/d, or 0.238 mg/kg/wk). After that, all somapacitan patients received 0.16 mg/kg/wk.
Key Outcome Measures : Changes from baseline in height SD score (HSDS), height velocity (HV) at year three, and IGF-I SDS.
Findings : In comparison to daily GH, the estimated treatment difference (95% CI) in HV for somapacitan at year three was 0.8 cm/y (−0.4 to 2.1). The difference in HVSDS between the daily GH, the pooled somapacitan groups, and somapacitan 0.16/0.16 mg/kg/wk was similar from baseline to year 3. All groups showed a progressive rise in HSDS from baseline. The mean HSDS at year three was comparable for daily GH and the pooled somapacitan groups. Treatment differences in mean IGF-I SDS from baseline to year three were comparable.
Conclusions : In children with GHD, once-weekly somapacitan demonstrated maintained efficacy over three years in all evaluated height-based outcomes, while also being comparably safe and tolerable to daily GH. For this study, there is a simple language summary (1) accessible.

Keywords : growth hormone, growth hormone deficiency, childhood growth hormone deficiency, growth hormone replacement therapy, somapacitan, longacting growth hormone

INTRODUCTION

Children with reduced growth velocity and adult height below the normal range are diagnosed with GH deficit (GHD) (2). The illness may have detrimental effects on children's quality of life, interfere with social and emotional development, and reduce an adult's capacity for function (3, 4).
In the majority of cases, GH replacement therapy can restore normal growth, enabling patients to reach an adult height within the normal range (2). The approved GH therapeutic alternatives available today require daily subcutaneous injections due to their short in vivo half-lives (5)Patients and caregivers may find this regimen taxing, which may lower treatment adherence (6, 7) and result in less than ideal clinical outcomes (8, 9). In fact, up to 25% of kids might skip more than two shots every week (8–12).
Somapacitan, a once-weekly treatment for GHD in children, is in clinical research (16) to lessen the burden of once-daily injections (13–15). It has been licensed for the treatment of adults in Europe, the US, and Japan(17–19). There are more long-acting GH drugs that are either in clinical trials or have just received approval (20, 21).
A 1.2 kDa side chain with noncovalent albumin-binding characteristics is attached by alkylation to GH with a single amino acid change, resulting in a 23 kDa molecule, in somapacitan, a reversible albumin-binding GH derivative (22–23). In the field of endocrinology, the addition of a fatty acid linker to aid somapacitan's binding to albumin and extend its half-life (23) has been effectively applied to extend half-lives in other commercially available drugs (24–26).It has been demonstrated that somapacitan directly promotes longitudinal development in animal models by activating GH

receptors on the peripheral tibia growth plate (23). In earlier phase 3 clinical trials, somapacitan was demonstrated to have a safety and tolerability profile consistent with daily GH's known evidence, as well as an efficacy comparable to that of daily GH for the treatment of adult GHD (27–29).

The phase 2 REAL 3 experiment (ClinicalTrials.gov identifier: NCT02616562) examines the safety, tolerability, and effectiveness of weekly somapacitan in comparison to daily administration of daily GH (Norditropin) in prepubertal children with GHD. The 26-week and 1-year data, which we previously reported, demonstrated that somapacitan 0.16 mg/kg/wk significantly increased height velocity (HV) (estimated treatment difference [95% CI]: 1.8 cm/y [0.5-3.1]) and height SD scores (SDS) (0.35 [0.05-0.65]) compared to daily GH (30).In contrast to once-daily GH, we report on the unique efficacy and safety outcomes of once-weekly somapacitan treatment after three years.

MATERIALS AND METHODS

Design of Study

REAL 3 is a 4-arm parallel group trial that is randomized, international, active-controlled, double-blinded, open-label (in comparison to daily GH), dose-finding, and naïve to GH medication for prepubertal children with GHD. The study examined the safety and effectiveness of three distinct dosages of once-weekly somapacitan medication (0.04, 0.08, or 0.16 mg/kg/wk) in contrast to an active, open-labelled control arm that received daily GH (0.034 mg/kg/d, or 0.238 mg/kg/wk).A 26-week extension (through year 1) followed the initial 26-week trial period. In order to assess the long-term safety of somapacitan 0.16 mg/kg/wk (30), there was also a 104-week safety extension (up to year 3) and a further ongoing 208-week safety extension trial period. We provide statistics from the conclusion of the 104-week (up to year 3) extension period in this paper.The clinical height assessments were carried out by assessors blinded to the somapacitan dosing; the experiment was double-blind with regard to the initial somapacitan dose.The sponsor was unblinded following the main trial period's double-blinding, while the participants and site personnel continued to be blinded to the somapacitan dose level allocation until week 52, the end of the extension trial period.

The procedure was carried out in compliance with the Helsinki Declaration and the International Conference on Harmonization Guidelines for Good Clinical Practice, and it was approved by the relevant local and national ethics committees. Before the initial study procedure, the parents (or the child's legally recognized agent) provided written informed consent, and the child's agreement was gained when the time was right.

Patients

Prior reports have been made about trial eligibility, key inclusion, and exclusion criteria (30). In summary, the patients who qualified for the screening were prepubertal adolescents who had been diagnosed with GHD during the 12 months before to the test, as established by two distinct GH stimulation tests (defined as a peak GH level of ≤7.0 ng/mL without prior exposure to GH therapy and/or IGF-I treatment). All children who had three or more pituitary hormone deficiencies simply needed to take one GH stimulation test. There were sixty patients in all scheduled for enrollment.

Treatment and Randomization

During the 26-week main trial phase and the 26-week extension trial period, patients were randomized (1:1:1:1) to receive either daily GH (0.034 mg/kg/d, equal to 0.238 mg/kg/wk) subcutaneously, or once-weekly somapacitan therapy (0.04, 0.08, or 0.16 mg/kg/wk). The GH dosage was calculated using body weight, which was measured at each visit during the course of the medication. Researchers at the study sites used an interactive response system that was web-based and trial-specific to randomly assign the children.Within the rest-of-the-world region, the randomization was stratified by sex, age (<6 and ≥6 years), and region (Japan and the rest of the world).

All participants who were given somapacitan throughout the trial's first year were given the option to continue using somapacitan (0.16 mg/kg/wk) or to switch to somapacitan (0.16 mg/kg/wk) for the 104-week safety extension. During the 104-week safety extension, patients who received daily GH during the first year continued to receive the same medication at the same dose. The two experimental products were injected subcutaneously.Prefilled pen injectors of the FlexPro group, created by Novo Nordisk A/S, were supplied with somapacitan dosages of 5 mg/1.5 mL, 10 mg/1.5 mL, and 15 mg/1.5 mL. The dosage of GH was 10 mg/1.5 mL per day using Norditropin FlexPro.

Results

Every 13 weeks, patients were examined for safety laboratory measurements, adverse event (AE) monitoring, and efficacy assessments.

Effectiveness

The main goal of the experiment is to compare the effectiveness of daily GH with three different dosages of once-weekly somapacitan medication in prepubertal children with GHD who have not yet received GH treatment after 26 weeks of treatment (30). This report focuses on the secondary results that were gathered throughout the extension period, which are as follows: The third year's HV (cm/y) and changes from baseline to the end of the third year for height SDS, HVSDS, IGF-I

SDS, and insulin-like binding protein-3 (IGFBP-3) SDS were included in the efficacy investigation. The recommendations set forth by the European Medicines Agency (31) were adhered to while measuring standing height.

Safety

Safety outcomes included bone age (X-ray of left hand and wrist), which was centrally assessed in accordance with Greulich and Pyle's (32) progression in comparison with chronological age at year three, incidence of adverse events (AEs), including injection site reactions at year three, and the occurrence of anti-somapacitan and anti-GH antibodies at year three.Using a validated antibody binding assay, anti-GH and anti-somapacitan antibodies were measured. If planned on a sampling day, blood samples were obtained for antibodies and IGF-I and IGFBP-3 biomarkers prior to trial medication administration.

Pharmacokinetics

A central laboratory used commercially available test kits (Immunodiagnostic Systems Immunoassay) to perform pharmacokinetics analyses of IGF-I and IGFBP-3 (33). Day 7 after dosage saw the collection of trough samples, while Days 1 through 4 following dosage saw the collection of peak samples. The samples were gathered in order to provide data on fluctuations from peak to bottom and to calculate the average through population pharmacokinetic/pharmacodynamic modeling. The modified least mean squares model, as described by Friedrich et al. (33) was used to determine IGF-I SDS.

Results as recorded by observers

In accordance with US Food and Drug Administration guidelines (34) the Growth Hormone Deficiency–Child Impact Measure (GHD-CIM) was created to evaluate the effects of GHD on children's physical functioning as well as their social and emotional well-being. For the parents and guardians of children between the ages of 4 and under 13 years old, the GHD-CIM observer report (GHD-CIM ObsRO) was created (35). As reported by their parents or a legally recognized representative, the effect of somapacitan in relation to daily GH on children's emotional well-being, physical functioning, and social well-being was examined using changes from baseline in scores on the GHD-CIM ObsRO (35), an observer-reported outcome questionnaire.An indicator of the importance that observers place on the ObsRO is provided by the least significant difference (36). The least significant difference for GHDCIM ObsRO was measured at five points for physical functioning, social well-being, and overall score; it was seven points for emotional well-being (35).

Compliance

By documenting dosages (including the date, time, and content of each dose as well as any missed doses), treatment adherence was evaluated. All doses exceeding 0 that were entered into the diary and delivered between 3 am and 3 am the next day (daily GH) or within 2 days prior to or following the scheduled date of dosing (somapacitan) were included in the count of doses in adherence.

Analytical Statistics

The analyses of the pharmacokinetic, efficacy, and health-related quality of life (HRQoL) outcomes using the full analysis set (FAS). All children who were assigned at random and received at least one dose of randomized therapy were to be included in the FAS. Children were only excluded from the FAS in extraordinary circumstances. All randomly assigned children who received at least one dose of randomized therapy were included in the safety analysis set (SAS), which was used for analyses of the safety outcomes.

Effectiveness and Observer-Reported Results

HV was computed for the primary trial period prior to year 1. HV = (height at visit – height at baseline)/(time from baseline to visit in years) is used to calculate the baseline height (weeks 0-26) and the extension trial period (weeks 26–year 1). Following year 1, HV was computed as HV = (height at visit – height at year 1)/(time from year 1 to visit in years) for the first year of the safety extension trial period (year 1-2) and HV = (height at visit – height at year 2) for the second year of the safety extension trial period (year 2-3)2)/(the number of years from year 2 to visit). A mixed model for repeated measurements was used to calculate and analyze HV at year three. Treatment, age group, sex, region, and sex by age group interaction term were the variables, while height at baseline was the covariate. All of these factors were nested within the week as a factor. For the child's repeated measurements, the variability was described using an unstructured covariance matrix. The treatment differences between the somapacitan and daily GH therapy arms were estimated with the accompanying 95% confidence intervals using the mixed model for repeated measurements. Descriptive statistics were utilized to assess the variations in height SDS, HVSDS, and IGF-I SDS from the baseline to the third year (33) and to quantify the changes.

Descriptive statistics were used to examine the bone age progression as compared to chronological age up to year 3, the IGFBP-3 SDS and GHD-CIM ObsRO scores at that year, and the data. The treatment arm and the pooled somapacitan groups (somapacitan 0.04/0.16 mg/kg/wk, somapacitan 0.08/0.16 mg/kg/wk, and somapacitan 0.16/0.16 mg/kg/wk combined) were examined for height-based outcomes. GHD-CIM ObsRO scores at year three and the estimated treatment difference

between somapacitan and daily GH in HV were subjected to post hoc-defined statistical analysis.

Security and Compliance

Descriptive statistics were used to examine the adverse events, and the results were summarized according to the treatment, system organ class, and preferred word included in the Medical Dictionary for Regulatory Activities. The number and proportion of patients who had adverse events (AEs) as well as the quantity and frequency of occurrences were included in the descriptive statistics. Adverse events were categorized by patient, treatment (combined somapacitan groups and daily GH), and severity, together with information about demographics and the trial product.Descriptive statistics were used to examine the prevalence of anti-somapacitan and anti-GH antibodies, technical complaints, injection site responses, and changes in physical signs and vital signs from baseline to year three. The statistical significance of the differences in treatment adherence across the arms was not examined.

RESULTS

Patient Disposition and Characteristics

The SAS was made up of the 59 GHD children who were randomly assigned to receive treatment. Of the 57 children in the FAS, two were removed due to early treatment discontinuation following to incorrect randomization. There were 14, 15, 14, and 14 patients in the FAS for the daily GH and the mg/kg/wk and 0.04/0.16, 0.08/0.16, and 0.16/0.16 mg/kg/wk groups, respectively (Fig. 1). Before the conclusion of year 3, eight patients stopped their treatment—two due to adverse events, two because they withdrew from the trial, and four because they broke protocol (Fig. 1).51 (86.4%) of the 53 (89.8%) youngsters who finished the trial's three years without stopping their treatment too soon.

There were no clinically significant differences between the four treatment groups at baseline, and patient characteristics were similar in each group (Table 1). All treatment arms had baseline levels of IGF-I SDS that were below the normal reference range, which is between −2 and +2. The mean (SD) for the combined somapacitan groups was −2.35 (0.93), while the daily GH group had −2.07 (0.74).

Compliance

With a mean adherence rate of 92.2% for somapacitan (somapacitan pooled) and 87.2% for daily GH (for the 57 children included in the FAS), the majority of children received their treatment as scheduled.

Effectiveness Outcomes

Results based on height

First-year HV data were previously published (30). Fig. 2 shows the observed mean HV at years 1, 2, and 3 for each of the four groups as well as the pooled somapacin groups. In years two and three, there were no statistically significant differences in HV between the daily GH therapy and the 0.08/0.16 and 0.16/0.16 mg/kg/wk dosages of somapacitan.The estimated treatment difference (95% CI) in HV for the 0.16/0.16 mg/kg/wk somapacitan group at year 3 when compared with daily GH was 0.8 cm/y (−0.4 to 2.1) in the post hoc analysis. In comparison to the HVSDS values for the other three treatment arms, the baseline HVSDS value for the somapacitan 0.08/0.16 mg/kg/wk treatment arm was greater (Table 1).

Up until year 1, a dosage-related response in HVSDS was observed among the somapacitan dose groups. When comparing the daily GH group with the somapacitan treatment arms by year 3, the mean (SD) HVSDS was statistically greater (Fig. 3). Between the 0.16/0.16 mg/kg/wk somapacitan group, the pooled somapacitan groups, and daily GH, the change in HVSDS from baseline to year 3 was comparable (Table 2).

Fig. 4 shows the height SDS at years 1, 2, and 3. For the three somapacitan dosage groups and daily GH, the mean height SDS was minimal and comparable at baseline (Table 1). From baseline to year three, there was a progressive rise in height SDS for both daily GH and all somapacitan therapy arms. The mean (SD) height SDS and daily GH for the combined somapacitan groups were comparable at year 3 (Fig. 4). All treatment arms had comparable mean (SD) changes in height SDS from baseline to year 3 (Table 2).

IGF-I Standard Deviation

The somapacitan and daily GH treatment arms' mean (SD) IGF-I SDS values increased from baseline to within the normal range after three years of treatment: 1.30 (0.94) for daily GH and 0.97 (1.13), 1.03 (1.32), 1.63 (0.89), and 1.22 (1.14) for somapacitan mg/kg/wk, 0.08/0.16, and 0.16/0.16 mg/kg/wk, and pooled groups, respectively. For each treatment arm, the observed decrease in mean (SD) IGF-I SDS from baseline to year three was 3.26 (1.04), 3.52 (1.43), 3.66 (1.29), 3.49 (1.25), and 3.40 (1.58), respectively. Figure 5 displays the average IGF-I SDS values for each treatment arm calculated from the model, as well as the observed IGF-I SDS values at weeks 143 (peak) and 156 (trough) for all treatment arms.IGF-I SDS values > 2 were sporadically observed during the trial's three years in 17 children (39.5%) receiving somapacitan treatment (somapacitan 0.04/0.16 mg/kg/wk, n = 3 [21.4%]; somapacitan 0.08/0.16 mg/kg/wk, n = 6 [40%]; somapacitan 0.16/0.16 mg/kg/wk, n = 8 [57.1%]), and 4 children (28.6%) receiving daily GH.

IGFBP-3 Standard Deviation

Overall trial changes for IGFBP-3 SDS were similar to those

noted for IGF-I SDS. In the third year, the mean (SD) of the IGFBP-3 SDS increased from low baseline levels (below the normal range; Table 1) to levels within the normal range (somapacitan 0.04/0.16 mg/kg/wk: −0.39 [0.96]; somapacitan 0.08/0.16 mg/kg/wk: from −0.08 [0.71]; somapacitan 0.16/0.16 mg/kg/wk: 0.02 [0.90]; daily GH: 0.29 [0.79]. IGFBP-3 SDS rose for the pooled somapacitan groups from −2.08 (1.35) to −0.14 (0.86).

Age of the bones

In both treatment arms, the ratio of bone age to chronological age at baseline was less than unity (Table 1). This ratio rose over the course of the trial's three years in every treatment arm, although it never fell below one (Fig. 6). For somapacitan 0.04/0.16, 0.08/0.16, 0.16/0.16 mg/kg/wk, and pooled groups, respectively, and 3.06 (1.76) for daily GH, the observed change in mean (SD) bone age from baseline to year 3 was 3.98 (1.51), 4.09 (1.42), 4.9 (1.78), and 4.34 (1.59).

Results as recorded by observers

Fig. 7 displays a post hoc analysis of the estimated treatment difference in the change in GHD-CIM ObsRO scores between somapacitan and daily GH for the FAS from baseline to years 1 and 3. After three years of treatment, the total score and the estimated treatment difference for all three GHD-CIM ObsRO domains favored the somapacitan treatment arms over daily GH, but they were not statistically significant.

Safety Outcomes

During the course of the three years of treatment, somapacitan was well tolerated, and no new concerns related to local tolerability or clinically significant safety were found. In general, the treatment arms' overall adverse event rates per 100 patient-years in years two and three were comparable: daily GH was 224.9 and the pooled somapacitan groups had 237.7. Table 3 shows that most adverse events (AEs) were classified as moderate (89.5%) and considered unlikely to be related to therapy (92.5%). Similar percentages of individuals treated with somapacitan and those treated with daily GH reported experiencing the two most prevalent adverse events (AEs), nasopharyngitis and influenza (Fig. 8).In all, 6 (10.2%) kids experienced 11 significant adverse events (SAEs) in the 3 years of treatment (30). During the first year of treatment, three children had SAEs. The SAE event rates for the daily GH treatment arm (8.5 SAEs/100 patient-years of exposure) and pooled somapacitan groups (6.5 SAEs/100 patient-years of exposure) were comparable (Table 4). One kid receiving somapacitan 0.16/0.16 mg/kg/wk experienced two SAEs (generalized edema and vomiting), which were assessed as likely connected to the trial product and recorded as unanticipated serious adverse events.Due to the child's edema, the hospital was consulted, and IV fluids and antibiotics (ceftriaxone) were used to treat the suspected infection. After six days, the child's condition improved, allowing the trial product to be reintroduced without any further episodes. During the first year of the experiment, one child receiving somapacitan 0.08/0.16 mg/kg/wk was reported to have one SAE (hypopituitarism). From visit 4 to visit 16 (the follow-up visit for the current study period), the treatment arm with anti-human GH antibodies of low titer persisted, and the event was deemed to be minor in severity. For in vitro neutralizing antibodies, every sample that tested positive for antibodies was negative. The pharmacokinetic and pharmacodynamic characteristics of somapacitan or annualized HV did not seem to be impacted by antibodies.

From baseline to year three, there was an increase in fasting insulin levels in all therapy groups.For children with GHD receiving GH medication, the change from baseline was within predicted ranges and comparable between the somapacitan and daily GH treatment groups. From baseline to year three, there were no discernible clinically significant changes in mean glycated haemoglobin or fasting glucose in any of the therapy groups.One child receiving daily GH experienced two instances of abnormal glucose metabolism in year two. The investigator classified these events as mild and possibly connected to the trial product; no further action was thought to be required in response to the AE, and the abnormalities were reversible.

DISCUSSION

The information offered here is the first record of a long-acting growth hormone that shows consistent effectiveness over a three-year period across all evaluated height-based outcomes. The 3-year data demonstrated the safety and effectiveness of somapacitan in treatment-naïve prepubertal children with GHD; the data were comparable to those of daily GH, indicating that somapacitan may be a useful treatment substitute for daily GH, especially given that it requires fewer injections than daily GH.After a year, we have previously documented a dose-dependent response with somapacitan for HV in children with GHD, where therapy with 0.16 mg/kg/wk of somapacitan led to a statistically significant increase in HV when compared with daily GH (30).

We now offer new 3-year data for the three height-based outcomes, which, with the exception of a change from baseline in HVSDS for somapacitan 0.08/0.16 mg/kg/wk compared with daily GH, show higher or equivalent values for all three somapacitan treatment arms. Due to the fact that all children who were initially randomized to receive somapacitan were given the same dose (0.16 mg/kg/wk) following year 1, at year3. For at least two years, all children receiving somapacitan had been given the same dose of 0.16 mg/kg/wk.

The most frequently used and recognized biomarker for GH response is IGF-I, which is tracked in children to guarantee GH treatment compliance and long-term safety (37). IGF-I SDS and IGFBP-3 SDS were found to increase in the somapacitan treatment arms in a dose-dependent manner up until the first year. Following three years of therapy, there was a comparable mean rise in IGF-I SDS from baseline in both the daily GH and somapacitan-treated groups, indicating that both treatments had a similar impact on IGF-I (and IGFBP-3) in children with GHD. Crucially, by year three, the mean IGF-I SDS for every treatment arm was still within the normal range. The IGF-I profile linked to long-acting GH is not the same as the one seen after daily GH administration.Stable IGF-I levels can be reached with daily GH in a matter of days to weeks after beginning a new dosage (38).

IGF-I concentrations rise after long-acting GH injection over a few days, peaking at a level that may surpass the standard specified normal reference range before falling to trough concentrations before the next injection (39). Because long-acting GH has greater maximum levels and lower trough values than daily GH, the reported IGF-I SDS value is consequently dependent on the sample time. Because there is less weekly fluctuation, observed IGF-I SDS values for daily GH are less sensitive to the time of sampling.Sampacitan samples were collected in years 1 and 3 close to the IGF-I SDS maximum value. When comparing the levels of IGF-I SDS caused by somapacitan with daily GH at various time points, this should be taken into account.

When children with GHD receive GH treatment, their bone age increases, usually in a way that is suitable for their height (40). After three years of replacement therapy, the ratio of bone age to chronological age neared 1 in all treatment groups, demonstrating a normalization of the ratio.

The influence of somapacitan compared to daily GH on emotional, physical, and social well-being was examined using the validated and trustworthy GHD-CIM ObsRO tool to assess disease-specific functioning (35). Point estimates for each of the three somapacitan arms over daily GH after three years of treatment, as well as for the individual GHD-CIM ObsRO domains and total scores, favored somapacitan 0.16 mg/kg/wk over daily GH after one year of treatment. These variations, though, did not become statistically significant.Given that somapacitan was tested against an active comparator, significant differences between the comparator arms were not anticipated, which makes these positive scores all the more encouraging. Less injections is anticipated to result in a decreased treatment burden as well. Additionally, these results could point to a connection between increased HRQoL and growing height, which is consistent with earlier research showing that children and adolescents with GHD who received GH therapy had better HRQoL (41, 42). Therefore, in order to attain improved height during childhood, it may be beneficial to start therapy early and at an adequate dose. This is consistent with earlier research that has shown how important it is to start treatment as soon as feasible for this problem (43, 44).

When somapacitan 0.16 mg/kg/wk was given to prepubertal children with GHD, there were no new, clinically relevant safety or local tolerability concerns found. The medication was well tolerated. The somapacitan treatment arms and the daily GH therapy arm had comparable AE rates (event rate per 100 patient-years at risk). After the first year, all injection site-related adverse events were deemed to be of minor severity. In the third year of somapacitan treatment, two injection site reactions were recorded in one child; these were deemed non-serious and went away after the injection site was rotated Overall, third-year findings show that the safety profile and effectiveness of once-weekly somapacitan are comparable to those of daily GH. For children with GHD, somapacitan may offer a less intensive form of treatment as an alternative to daily GH administration load due to a decrease in injections from daily GH (from 365 to 52 injections annually). The current study's observed safety profiles aligned with results from a phase 1 trial involving somapacitan (16, 30), the study's initial year (30), and established safety profiles for growth hormone products generally (45). There were extremely few withdrawals from the trial—two due to adverse events, two due to study withdrawals, and four due to protocol violations—and comparable adherence rates across the groups. However, the small number of patients included in each trial arm limits the study's findings. Studies are still being conducted to evaluate somapacitan's long-term safety.

In summary, these findings showed that somapacitan medication administered once a week for three years produced a sustained efficacy in all measured height-based outcomes in children with GHD. During the third year, the somapacitan groups' height-based results were comparable to those of the daily GH group. Between somapacitan and daily GH, the mean change in IGF-I SDS during treatment was comparable. Although positive, HRQoL statistics did not become statistically significant during this period. Less injections are also anticipated, which will lessen the therapeutic load. There were no additional safety or tolerability issues found in the safety profile of once-weekly somapacitan, which was comparable to the safety profile observed for daily GH.

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REFERENCES

1. Sävendahl L. Plain language summary - Effective growth hormone replacement with once-weekly somapacitan versus daily growth hormone in children with growth hormone deficiency: 3-year results from REAL 3. figshare. 2022. https://doi.org/10.6084/m9.figshare.17086649.v1

2. 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 Paed. 2016;86(6):361-397.

3. Brod M, Alolga SL, Beck JF, Wilkinson L, Højbjerre L, Rasmussen MH. Understanding burden of illness for child growth hormone deficiency. Qual Life Res. 2017;26(7):1673-1686.

4. Backeljauw P, Cappa M, Kiess W, et al. Impact of short stature on quality of life: a systematic literature review. Growth Horm IGF Res. 2021;57-58:101392.

5. Høybye C, Cohen P, Hoffman AR, et al. Status of long-actinggrowth hormone preparations--2015. Growth Horm IGF Res. 2015;25(5):201-206.

6. 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.

7. 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.

8. Cutfield WS, Derraik JG, Gunn AJ, et al. Non-compliance with growth hormone treatment in children is common and impairs linear growth. PloS one. 2011;6(1):e16223.

9. Kapoor RR, Burke SA, Sparrow SE, et al. Monitoring of concordance in growth hormone therapy. Arch Dis Child. 2008;93(2):147-8.

10. Rosenfeld RG, Bakker B. Compliance and persistence in pediatric and adult patients receiving growth hormone therapy. Endocr Pract. 2008;14(2):143-154.

11. van Dommelen P, Koledova E, Wit JM. Effect of adherence to growth hormone treatment on 0-2 year catch-up growth in children with growth hormone deficiency. PloS one. 2018;13(10):e0206009.

12. Farfel A, Shalitin S, Morag N, Meyerovitch J. Long-term adherence to growth hormone therapy in a large health maintenance organization cohort. Growth Horm IGF Res. 2019;44:1-5.

13. Brod M, Højbjerre L, Alolga SL, Beck JF, Wilkinson L, Rasmussen MH. Understanding treatment burden for children treated for growth hormone deficiency. Patient. 2017;10(5):653-666.

14. Kremidas D, Wisniewski T, Divino VM, et al. Administration burden associated with recombinant human growth hormone treatment: perspectives of patients and caregivers. J Pediatr Nurs. 2013;28(1):55-63.

15. Tanaka T, Sato T, Yuasa Mhwm A, Akiyama T, Tawseef A. Patient preferences for growth hormone treatment in Japanese children. Pediatr Int. 2021;63(10):1185-1191.

16. Battelino T, Rasmussen MH, De Schepper J, Zuckerman-Levin N, Gucev Z, Savendahl L. Somapacitan, a once-weekly reversible albumin-binding GH derivative, in children with GH deficiency: a randomized dose-escalation trial. Clin. Endocrinol.2017;87(4):350-358.

17. Novo Nordisk A/S. Sogroya 10 mg/1.5 mL solution for injection in pre-filled pen summary of product characteristics. 2021. https://www.ema.europa.eu/en/documents/product-information/sogroyaepar-product-information_en.pdf. Accessed 3 September 2021.

18. Novo Nordisk Inc. Sogroya, somapacitan-beco injection prescribing information. 2020. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/761156s000lbl.pdf. Accessed 3 September 2021.

19. Novo Nordisk Pharma Ltd. Sogroya, somapacitan-beco injection prescribing Information. 2021. https://www.pmda.go.jp/PmdaSearch/iyakuDetail/

ResultDataSetPDF/620023_24124A1G1024_1_02. Accessed 3 September 2021.

20. Ascendis Pharma. SKYTROFA™ (lonapegsomatropin-tcgd) for injection, for subcutaneous use prescribing information. 2021. https://ascendispharma.us/products/pi/skytrofa/skytrofa_pi.pdf. Accessed 3 September 2021.

21. Pfizer Inc. Press release: EMA accepts marketing application for somatrogon to treat pediatric patients with growth hormone deficiency. 2021. https://www.pfizer.com/news/press-release/press-release-detail/ema-accepts-marketingapplication-somatrogon-treat. Accessed 3 September 2021.

22. Thygesen P, Andersen HS, Behrens C, et al. Nonclinical pharmacokinetic and pharmacodynamic characterisation of somapacitan: a reversible non-covalent albumin-binding growth hormone. Growth Hormone IGF Res. 2017;35:8-16.

23. Johansson E, Nielsen AD, Demuth H, et al. Identification of binding sites on human serum albumin for somapacitan, a long-acting growth hormone derivative. Biochemistry. 2020;59(14):1410-1419.

24. 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.

25. Deacon CF. Potential of liraglutide in the treatment of patients with type 2 diabetes. Vasc Health Risk Manag. 2009;5(1):199-211.

26. Lau J, Bloch P, Schaffer L, et al. Discovery of the once-weekly glucagon-like peptide-1 (GLP-1) analogue semaglutide. J Med Chem. 2015;58(18):7370-7380.

27. 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.

28. 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. Clinic. Endocrinol.2020;93(5):620-628.

29. Johannsson G, Gordon MB, Højby Rasmussen M, et al. Onceweekly somapacitan is effective and well tolerated in adults with GH deficiency: a randomized phase 3 trial. J Clin Endocrinol Metab. 2020;105(4):e1358-1376.

30. Sävendahl L, Battelino T, Brod M, Højby Rasmussen M, Horikawa R, Juul RV, Saenger P. 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):e1847-1861.

31. CHMP CfMPfHU. Executive Summary. EMEA/CHMP/BMWP. 2005;94528. https://www.ema.europa.eu/en/documents/scientificguideline/annex-guideline-similar-biological-medicinal-productscontaining-biotechnology-derived-proteins_en-2.pdf. Accessed 19 September 2021.

32. Greulich WW, Pyle SI. Radiographic atlas of skeletal development of the hand and wrist. 2nd edition. Stanford, CA: Stanford University Press; 1959.

33. Friedrich N, Wolthers OD, Arafat AM, et al. Age- and sex-specific reference intervals across life span for insulin-like growth factor binding protein 3 (IGFBP-3) and the IGF-I to IGFBP-3 ratio measured by new automated chemiluminescence assays. J Clin Endocrinol Metab. 2014;99(5):1675-1686.

34. Food and Drug Administration. Guidance for industry: patientreported outcome measures: use in medical product development to support labeling claims. 2009. https://www.fda.gov/media/77832/download. Accessed 19 July 2021.

35. Brod M, Højby Rasmussen M, Vad K, et al. Psychometric validation of the growth hormone deficiency-child impact measure (GHD-CIM). PharmacoEconomics - open. 2021.

36. Johnston BC, Ebrahim S, Carrasco-Labra A, et al. Minimally important difference estimates and methods: a protocol. BMJ Open. 2015;5(10):e007953.

37. Blum WF, Alherbish A, Alsagheir A, et al. The growth hormoneinsulin-like growth factor-I axis in the diagnosis and treatment of growth disorders. Endocr Connect. 2018;7(6):R212-r222.

38. Yuen KC, Cook DM, Rumbaugh EE, Cook MB, Dunger DB. Individual igf-I responsiveness to a fixed regimen of low-dose growth hormone replacement is increased with less variability in obese compared to non-obese

adults with severe growth hormone deficiency. Horm Res. 2006;65(1):6-13.

39. Bidlingmaier M, Schilbach K. The use of IGF-I to monitor long-acting growth hormone therapy—timing is an art.... J Clin Endocrinol Metab. 2021;106(5):e2367-e2369.

40. Martin DD, Wit JM, Hochberg Z, et al. The use of bone age in clinical practice - part 1. Hormone Res Paediatr. 2011;76(1):1-9.

41. Geisler A, Lass N, Reinsch N, et al. Quality of life in children and adolescents with growth hormone deficiency: association with growth hormone treatment. Hormone Res. Paediatr. 2012;78(2):94-99.

42. Tanaka T, Hasegawa T, Ozono K, et al. Effect of growth hormone treatment on quality of life in Japanese children with growth hormone deficiency: an analysis from a prospective observational study. Clin Pediatr Endocrinol. 2014;23(3):83-92.

43. Rogol AD, Hayden GF. Etiologies and early diagnosis of short stature and growth failure in children and adolescents. J Pediatr.. 2014;164(5 Suppl):S1-14.e16.

44. Haymond M, Kappelgaard AM, Czernichow P, Biller BM, Takano K, Kiess W. Early recognition of growth abnormalities permitting early intervention. Acta paediatrica (Oslo, Norway: 1992). 2013;102(8):787-796.

45. Bell J, Parker KL, Swinford RD, Hoffman AR, Maneatis T, Lippe B. Long-term safety of recombinant human growth hormone in children. J Clin Endocrinol Metab. 2010;95(1):167-177.