The Journal of Clinical Endocrinology & Metabolism, 2023, **108**, 3090–3099
https://doi.org/10.1210/clinem/dgad394
Advance access publication 5 July 2023
Clinical Research Article

Effective GH Replacement With Somapacitan in Children With GHD: REAL4 2-year Results and After Switch From Daily GH

Bradley S. Miller,[1] Joanne C. Blair,[2] Michael Højby Rasmussen,[3] Aristides Maniatis,[4] Jun Mori,[5] Volker Böttcher,[6] Ho-Seong Kim,[7] Rikke Beck Bang,[8] Michel Polak,[9] and Reiko Horikawa[10]

[1]Division of Pediatric Endocrinology, University of Minnesota Medical School, MHealth Fairview Masonic Children's Hospital, Minneapolis, MN 55454, USA
[2]Department of Endocrinology, Alder Hey Children's NHS Foundation Trust, Liverpool, L14 5AB, UK
[3]Clinical Drug Development, Novo Nordisk A/S, Søborg 2860, Denmark
[4]Rocky Mountain Pediatric Endocrinology, Centennial, 80112 CO, USA
[5]Division of Pediatric Endocrinology and Metabolism, Children's Medical Center, Osaka City General Hospital, Osaka 534-0021, Japan
[6]Division of Pediatric Endocrinology and Metabolism, MVZ Endokrinologikum Frankfurt am Main, Frankfurt 60596, Germany
[7]Department of Pediatrics, Severance Children's Hospital, Institute of Endocrinology, Yonsei University College of Medicine, Seoul 03722, Republic of Korea
[8]Biostatistics Rare Disease and Advanced Therapies, Novo Nordisk A/S, Aalborg 9220, Denmark
[9]Service d'Endocrinologie, Gynécologie et Diabétologie Pédiatriques, Hôpital Universitaire Necker Enfants Malades Paris, Assistance Publique-Hôpitaux de Paris, Paris 75015, France
[10]Division of Endocrinology and Metabolism, National Center for Child Health and Development, Tokyo 157-0074, Japan

Correspondence: Bradley S. Miller, MD, PhD, Division of Pediatric Endocrinology, University of Minnesota Medical School, MHealth Fairview Masonic Children's Hospital, Pediatric Endocrinology Academic Office Building, 2450 Riverside Ave S AO-201, Minneapolis, MN 55454, USA. Email: mille685@umn.edu; or Michael Højby Rasmussen, MD, Clinical Drug Development, Novo Nordisk A/S, Vandtårnsvej 108-1102860, Søborg 2860, Denmark. Email: mhr@novonordisk.com.

Abstract

Context: Somapacitan is a long-acting GH derivative for treatment of GH deficiency (GHD).

Objective: Evaluate the efficacy and tolerability of somapacitan in children with GHD after 2 years of treatment and after the switch from daily GH.

Design: A randomized, multinational, open-labelled, controlled parallel group phase 3 trial, comprising a 52-week main phase and 3-year safety extension (NCT03811535).

Setting: Eighty-five sites across 20 countries.

Patients: A total of 200 treatment-naïve prepubertal patients were randomized and exposed; 194 completed the 2-year period.

Interventions: Patients were randomized 2:1 to somapacitan (0.16 mg/kg/wk) or daily GH (0.034 mg/kg/d) during the first year, after which all patients received somapacitan 0.16 mg/kg/wk.

Main outcome measures: Height velocity (HV; cm/year) at week 104. Additional assessments included HV SD score (SDS), height SDS, IGF-I SDS, and observer-reported outcomes.

Results: HV was sustained in both groups between 52 and 104 weeks. At week 104, mean (SD) for HV between weeks 52 and 104 was 8.4 (1.5) cm/year after continuous somapacitan treatment and 8.7 (1.8) cm/year after 1 year of somapacitan treatment following switch from daily GH. Secondary height-related endpoints also supported sustained growth. Mean IGF-I SDS during year 2 was similar between groups and within normal range (−2 to +2). Somapacitan was well tolerated, with no safety or tolerability issues identified. GH patient preference questionnaire results show that most patients and their caregivers (90%) who switched treatment at year 2 preferred once-weekly somapacitan over daily GH treatment.

Conclusions: Somapacitan in children with GHD showed sustained efficacy and tolerability for 2 years, and after switching from daily GH. Patients/caregivers switching from daily GH expressed a preference for somapacitan.

Clinical Trial Registration: NCT03811535

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

Abbreviations: AE, adverse event; GHD, GH deficiency; GH-PPQ, GH patient preference questionnaire; HSDS, height SD score; HV, height velocity; HVSDS, height velocity SD score; IGF-I SDS, IGF-I SD score; LAGH, long-acting growth hormone; SC, subcutaneous.

Received: 18 April 2023. **Editorial Decision:** 29 June 2023. **Corrected and Typeset:** 18 July 2023

GH deficiency (GHD) in children is characterized by the inadequate production or secretion of GH, resulting in reduced longitudinal growth and adult height. Moreover, the condition can negatively impact quality of life, affect social and emotional well-being, and lessen functionality in adulthood (1, 2). Replacement therapy has for decades been able to restore normal growth with daily subcutaneous (SC) injections of recombinant GH, having an excellent efficacy and safety profile (3). However, daily injections represent a treatment burden disrupting the daily lives and routines of families, which can result in low adherence (4, 5) and consequently poor growth outcomes (6).

Somapacitan (Novo Nordisk A/S) is a reversible albumin-binding GH derivative (99% similarity to endogenous human GH) suitable for once-weekly SC administration to treat GHD (7). The addition of a short fatty acid linker to facilitate somapacitan binding to albumin prolongs its half-life, a technology that has been successfully used to prolong the half-life in other commercially available peptide drugs (8-11). Somapacitan is approved by the US Food and Drug Administration for the treatment of GHD in children (12-15) and in development for treatment of short stature in children born small for gestational age (16). The recently initiated phase 3, 4-way basket studies, REAL8 and REAL9 (Clinicaltrials.gov: NCT05330325 and NCT05723835, respectively) will also look at the use of somapacitan to treat short stature in Turner syndrome, Noonan syndrome, small for gestational age, and idiopathic short stature. Results from the phase 2 REAL3 study in prepubertal, GH treatment-naïve children with GHD (Clinicaltrials.gov: NCT02616562) suggest 0.16 mg/kg/wk somapacitan has the same efficacy and safety profile as 0.034 mg/kg/d daily GH (Norditropin, Novo Nordisk) treatment for up to 4 years of treatment (13-15). Recent pivotal phase 3 results from the REAL4 study (Clinicaltrials.gov: NCT03811535) demonstrated noninferiority in height velocity (HV) for 0.16 mg/kg/wk somapacitan compared with 0.034 mg/kg/d daily GH (Norditropin) with similar safety and tolerability in prepubertal, GH treatment-naïve children with GHD after 1 year of treatment (12). Additionally, somapacitan has been shown to reduce the treatment burden associated with daily SC injections of GH for both patients and their caregivers (12-14). Reduced treatment burden is proposed to lessen the distress associated with daily injections, decrease interference with daily life, and potentially improve treatment adherence and clinical outcomes. Indeed, there was a clear preference for once-weekly somapacitan over daily GH after switching from daily GH treatment in year 4 of the REAL3 trial (15).

Here, we present novel efficacy, safety, and patient preference results from the REAL4 study after 2 years of once-weekly somapacitan treatment, as well as after 1 year of once-weekly somapacitan treatment following the switch from daily GH in children with GHD.

Materials and Methods

Study Design

The REAL4 trial was conducted as a randomized, multinational, open-labeled, and active-controlled parallel-group phase 3 trial at 85 sites in 20 countries in Asia, Europe, and North America (ClinicalTrials.gov: NCT03811535). The sponsor (Novo Nordisk A/S) designed the trial and oversaw its conduct. The main phase lasted 52 weeks and investigated the efficacy and safety of 0.16 mg/kg/wk somapacitan treatment for GHD in children compared with a control group receiving daily GH (Norditropin; 0.034 mg/kg/d) (Fig. 1A). This is being followed by an ongoing 3-year single-group extension period. During the extension period all patients receive 0.16 mg/kg/wk somapacitan, either continuing somapacitan treatment ("soma/soma" group) or switching from daily GH treatment in year 1 to once-weekly somapacitan in year 2 ("switch" group). Two-year data reported here were collected between May 2019 and December 2022.

The somapacitan dose is supported by results from a phase 2 dose-finding trial (NCT03878446) demonstrating similar efficacy and safety matching that of daily treatment with 0.034 mg/kg/d Norditropin (13). 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 SC, the approved administration route for Norditropin and the 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.

Patients were seen at weeks 4, 13, 26, 39, 52, 65, 78, 91, and 104; 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.

Patients

Two hundred prepubertal children (Tanner stage 1) 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. A description of key inclusion and exclusion criteria, as well as how eligible subjects were randomized, were previously published (12). 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

Efficacy endpoints

Longitudinal growth in children with GHD was assessed by annualized HV (cm/year) and measured as standing height with a stadiometer at week −2, 0 (baseline), 13, 26, 39, 52, 65, 78, 91, and 104 with HV calculated as change from week 0 in the first year and as change from week 52 in the second year. Other efficacy endpoints included change from baseline in HV SD score (HVSDS), height SDS (HSDS), and bone age vs chronological ratio. Bone age (radiograph of left hand and wrist) was centrally assessed as previously described (17).

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 week −2, 0, 4, 13,

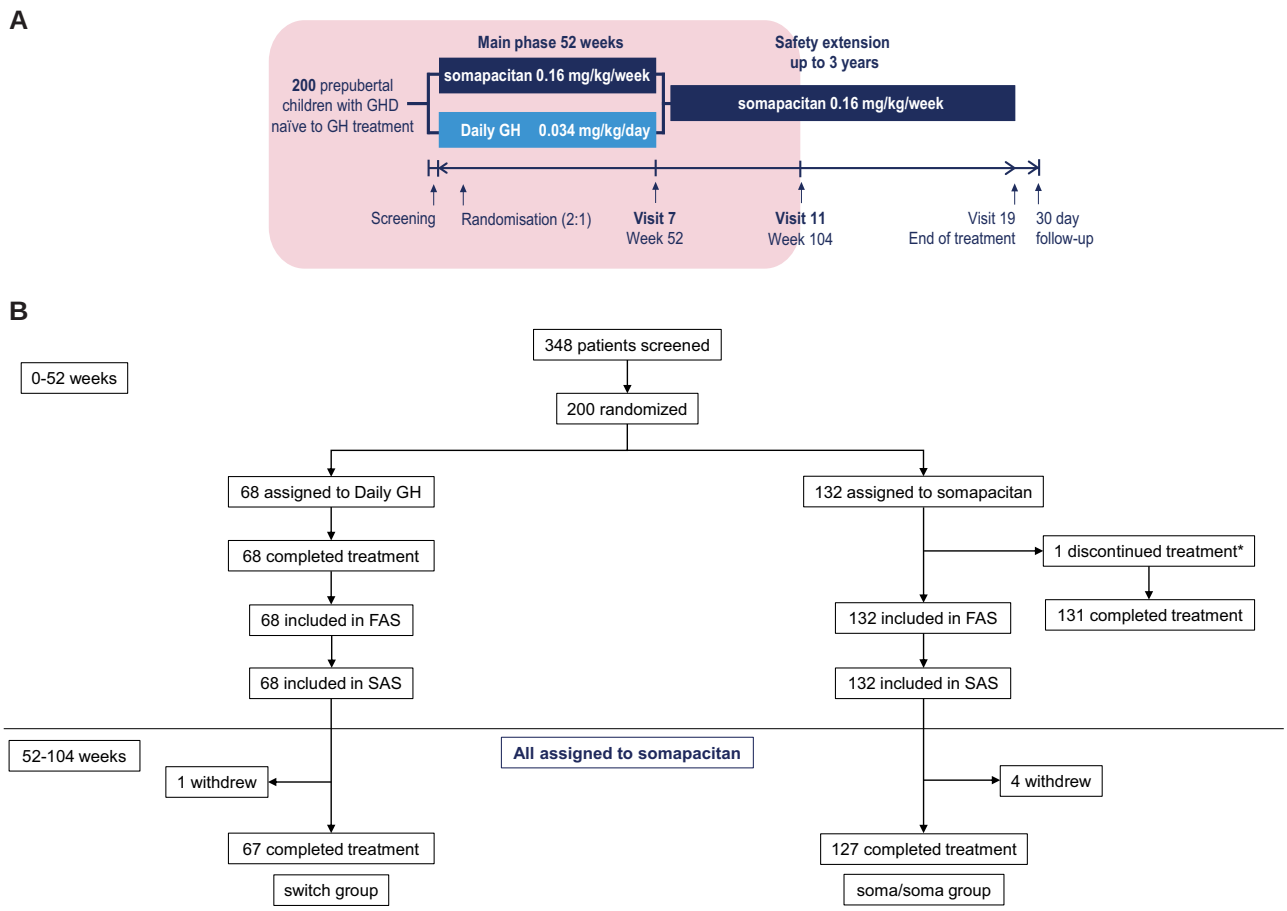

Figure 1. Trial overview and profile. (A) Design of the REAL4 trial and safety extension. Results from the main phase and first year of safety extension (104 weeks total) are reported in this study. Time axis is not to scale. (B) Population disposition of trial participants during the main trial period (weeks 0-52) and the first year of the extension period (weeks 52-104). 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. A total of 127 and 67 children completed 104 weeks in soma/soma and switch groups, respectively; 132 and 68 were included in the FAS and SAS, respectively. *1 participant discontinued treatment in the main phase. Abbreviations: GHD, GH deficiency; SAS, safety analysis set.

26, 39, 52, 78, and 104. Blood samples for IGF-I measurements in subjects treated with somapacitan up to week 104 were taken at the following timepoints after dosing: week 4, week 26, and week 78 (days 1-4 after dosing; around peak level), week 13, week 39, and week 104 (day 7 after dosing; trough level) and at week 52 (days 4-6 after dosing; expected weekly average IGF-I SDS). Weekly average IGF-I SDS were estimated by population pharmacokinetic/pharmacodynamic modelling as previously described (12).

Observer-reported Outcomes

To understand patient/caregiver preference for either daily GH or somapacitan, a GH patient preference questionnaire (GH-PPQ) was completed by the parents/caregivers of patients in the switch group 4 weeks after the child switched from daily GH to once-weekly somapacitan treatment (week 56).

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. Safety evaluation 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 secondary safety endpoints including 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 (18).

Statistical Analysis

Two analysis populations were defined: the full analysis set included all randomly assigned patients (used for efficacy outcome analyses) and the safety analysis set included all patients exposed to 1 or more doses of the trial product (used for safety outcome analyses). Observation periods included on-treatment (the time from first administration and up until last trial contact, visit 11 or 14 days after last administration, whichever comes first) and in-trial (the time from first administration and up until visit 11 or last trial contact, whichever comes first).

As per the trial protocol, statistical analyses of data were performed after 52 weeks of treatment, and no statistical analyses of data were performed after 104 weeks of treatment. Descriptive statistics for HV, HVSDS, HSDS and bone age up to week 104 (including change from baseline) are presented here.

Safety endpoint changes from baseline to week 104 in glucose metabolism parameters were analyzed using descriptive statistics. All adverse events with onset after the first administration of treatment and with a start date up until 14 days after last dose or until visit 11 (week 104), whichever comes first, were included and analyzed using descriptive statistics.

Role of the Funding Source

The study was sponsored by Novo Nordisk A/S. The sponsor was involved in the study design, collection, analysis, interpretation, and presentation of data.

Results

Study Population

Of the 200 randomly assigned patients to receive once-weekly somapacitan (132) or daily GH (Norditropin; 68), only 1 did not complete 52 weeks of treatment. The remaining 199 rolled over into the 3-year safety extension where all patients receive 0.16 mg/kg/wk somapacitan (Fig. 1B). In total, 127 children completed 104 weeks of somapacitan treatment (soma/soma group) and 67 completed 1 year of somapacitan treatment after switching from daily GH (switch group) (Fig. 1B). Four subjects in the soma/soma group and 1 in the switch group were discontinued and withdrawn from the trial during the 52- to 104-week period. None were discontinued because of AEs. In the soma/soma group, 1 participant was lost to follow up, 2 were described as other reasons not related to AEs, and 1 was withdrawn by the parent/guardian. The 1 switch group patient was discontinued at the discretion of the investigator because of protocol noncompliance.

Demographics and baseline characteristics were largely similar across both treatment groups and previously published (12), with slightly lower numerical mean HV, HSDS, HVSDS, IGF-I SDS, and GH peak in the daily GH group at baseline (Table 1). Adherence during year 2 was high for both treatments. Mean adherence for the soma/soma group and the switch group between weeks 52 and 104 was 90.3% and 88.8%, respectively, with the median for both groups being 94.3%.

At baseline (week 0), all children were Tanner stage I. After 104 weeks of treatment, of children treated with somapacitan, 118 (92.9%) remained at stage I, 7 (5.5%) were stage II, and 2 (1.6%) were stage III. Similarly, for children who switched treatment from daily GH to somapacitan at week 52, 57 (86.4%) remained at stage I, 6 (9.1%) were stage II, and 3 (4.5%) were stage III at week 104.

Table 1. Study demographics and baseline characteristics

	soma/soma (somapacitan weeks 0-104) n = 132	Switch (daily GH weeks 0-52 somapacitan weeks 52-104) n = 68	Total n = 200
Mean age, y (SD)	6.4 (2.2)	6.4 (2.4)	6.4 (2.3)
< 6 y, n (%)	64 (48.5)	33 (48.5)	97 (48.5)
Male, n (%)	99 (75.0)	50 (73.5)	149 (74.5)
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 (4.6)	16.0 (5.0)	16.5 (4.7)
Mean BMI, kg/m^2 (SD)	15.7 (1.6)	15.6 (1.4)	15.7 (1.5)
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 HVSDS (SD)	−2.35 (1.5)	−2.52 (1.6)	−2.41 (1.5)
Mean HSDS (SD)	−2.99 (1.0)	−3.47 (1.5)	−3.15 (1.2)
Mean IGF-I SDS (SD)	−2.03 (1.0)	−2.33 (1.0)	−2.13 (1.0)
GH peak, µg/L (SD)	4.93 (2.5)	4.10 (2.8)	4.65 (2.6)
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; HSDS, height SD score; HV, height velocity; HVSDS, height velocity SD score; SDS, SD score.

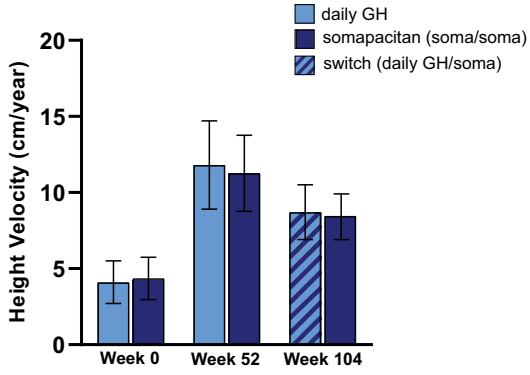

Figure 2. Observed height velocity from baseline to week 104. Mean (SD) observed HV (cm/year) at baseline (week 0), week 52, and week 104 for the soma/soma and switch groups. Data are presented as mean with error bars representing SD. Abbreviations: HV, height velocity; soma, somapacitan.

Efficacy Results

Height velocity

Observed HV increased from baseline to week 104 in a similar manner for both treatment groups (Fig. 2), demonstrating sustained efficacy after 2 years of somapacitan treatment (soma/soma group) and after 1 year of somapacitan treatment following the switch from daily GH to somapacitan treatment (switch group). Annualized observed mean (SD) HV during weeks 52 to 104, in which week 52 was used as "baseline," was 8.4 (1.5) cm/y for soma/soma group and 8.7 (1.8) cm/y for switch group (Table 2).

Other growth-related assessments

HSDS and HVSDS increased from baseline (week 0) to week 104 for both groups, with change differences similar between treatment groups (Table 2). Observed mean HSDS progressed similarly for both treatment arms, with measurements for the soma/soma and switch groups being −2.99 and −3.47 at week 0, −1.78 and −2.09 at week 52, and −1.23 and −1.47 at week 104, respectively (Fig. 3A). Mean change in HSDS calculated to baseline (week 0) also progressed similarly in both treatment groups to be within the normal range, demonstrating sustained efficacy (Fig. 3B). This included after switching from daily GH to once-weekly somapacitan, indicating small numerical differences in mean HV are due to inherent baseline differences between the groups (Table 1) rather than the treatment effect. For example, these might be due to small numerical differences in means at baseline seen between the groups for HV, HSDS, HVSDS, and IGF-I SDS (Table 1). Observed mean body mass index SDS remained within the normal range in year 2, with 0.44 seen for the soma/soma group and 0.29 for the switch group at week 104, respectively. Bone age to chronological age ratio advanced similarly in both groups (**Table 2**), with no changes in skeletal proportions reported.

IGF-I SDS

IGF-I release is stimulated by GH and represents the most widely used biomarker for monitoring GH treatment response (19). Change in mean IGF-I SDS from baseline to week 104 was similar between treatment groups (Table 2). In year 2, weekly average IGF-I SDS calculated from pharmacokinetic/pharmacodynamic modelling suggests similar mean average IGF-I levels over the weekly dosing interval within normal range (−2 to +2 SDS) for both treatment groups (+0.72 and +0.75 for the soma/soma and switch groups, respectively) (Fig. 4).

Safety Results

Adverse events

The number of patients with AEs in year 2 was 82 (62.6%) and 39 (57.4%) for soma/soma and switch groups, respectively (Table 3). Most AEs were mild or moderate in severity and judged as unlikely related to the trial product. In total, 3 (2.3%) patients in the soma/soma group reported 4 serious AEs, whereas none was reported in the switch group. All serious AEs were reported recovered/resolved and deemed unlikely to be related to trial product. The most common AEs observed in ≥ 5% of the patients in both groups during year 2 were mostly events commonly observed in children such as nasopharyngitis and pyrexia, as well as cases of COVID-19, of which there were 6 (4.6%) and 5 (7.4%) in the soma/soma and switch groups, respectively. There were no deaths, and no patients discontinued the study from AEs.

Table 2. Observed efficacy and PD endpoints at week 104

	soma/soma Mean (SD)	Switch Mean (SD)
Annualized HV, cm/y at week 104	8.4 (1.5)	8.7 (1.8)
Change in HSDS from baseline to week 104	1.8 (0.7)	2.0 (1.0)
Change in HVSDS from baseline to week 104	5.2 (2.6)	5.6 (3.2)
Change in IGF-I SDS from observed baseline to week 104	1.8 (1.0)	2.1 (1.3)
Change in BA vs CA from baseline to week 104	2.5 (1.2)	2.5 (1.1)

Abbreviations: BA, bone age; CA, chronological age; HSDS, height SDS; HV, height velocity; HVSDS, HV SD score; SDS, SD score.

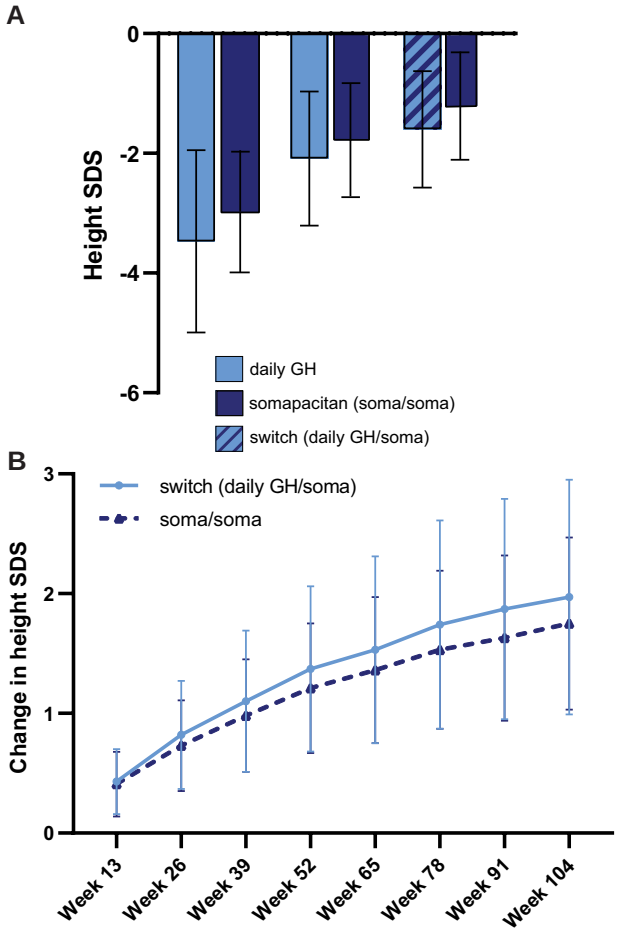

Figure 3. Sustained increase in HSDS from baseline to week 104 for continued somapacitan treatment (soma/soma) and switch from daily GH to somapacitan treatment. (A) Observed mean HSDS at baseline (week 0), week 52, and week 104 for the soma/soma and switch groups. (B) Mean change in HSDS from baseline. Data are presented as mean with error bars representing SD. Abbreviations: HSDS, height SD score; soma, somapacitan.

IGF-I SDS

The vast majority of observed IGF-I SDS values were within normal range (−2 to +2) regardless of time of measurement after dosing. Overall, IGF-I levels greater than +2 SDS were measured in 28 (21.7%) and 10 (14.7%) patients in the soma/soma and switch groups, respectively, during weeks 52 to 104. This surpassing of +2 SDS occurred on 2 consecutive visits in 1 (0.8%) and 2 (3.1%) of the patients in the soma/soma and switch groups, respectively. The number of patients that at some time during the second year had an IGF-I SDS value exceeding +2.5 was 15 (11.6%) and 4 (5.9%) in the soma/soma and switch groups, respectively. None of these patients had a IGF-I value exceeding +2.5 SDS at 2 consecutive visits. No trend was seen in the amount or type of AEs reported in patients with IGF-I levels greater than +2 SDS.

Other safety assessments

There were few reports of children experiencing injection site reactions during year 2: 3 (2.3%) and 2 (2.9%) in the soma/soma and switch groups, respectively (Table 4). No children reported injection site pain in either group during year 2 (Table 4).

There were no clinically relevant findings related to hematology, biochemistry, hormones, fasting lipids, or glucose metabolism (ie, change in fasting plasma glucose and glycated hemoglobin) in either treatment group. Between weeks 52 and 104, nonneutralizing antidrug antibodies were detected in 9 (6.8%) and 5 (7.4%) patients for the soma/soma and switch groups, respectively. No neutralizing antidrug antibodies were detected in either treatment group.

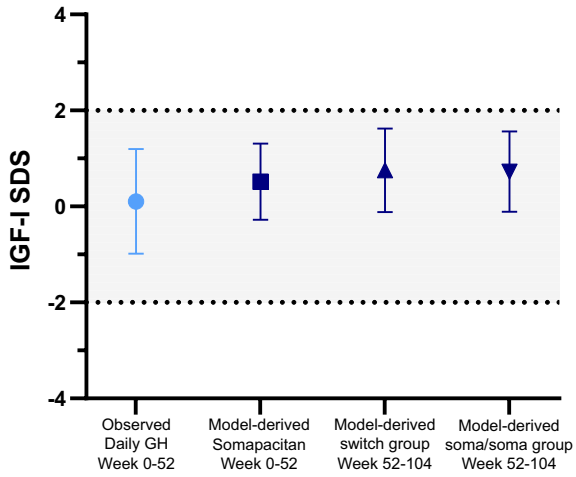

Figure 4. IGF-I SDS remained in normal range in year 2. Model-derived means for weekly average IGF-I SDS in somapacitan-treated patients after 52 weeks of treatment (+0.52), between 52 and 104 weeks of treatment (+0.72) or following switch from daily GH to somapacitan in year 2 (+0.75) are compared with observed IGF – I SDS for daily GH at week 52 (+0.10). Data are presented as mean with error bars representing SD. Abbreviations: SDS, SD score; soma, somapacitan.

Observer-reported Outcomes

The GH-PPQ was completed in week 56 by 50 parents/caregivers of patients who switched treatment from daily GH to somapacitan at week 52. The results show that most parents/caregivers of patients who switched treatment preferred once-weekly somapacitan over daily GH treatment (45/50; 90%), of which the vast majority (38/45; 84.5%) reported a "strong" or "very strong" preference for somapacitan (Fig. 5). Of the few (5/50; 10%) who did not report preference for somapacitan treatment, they indicated no preference between treatments, with none favoring daily GH over somapacitan. When asking the 45 respondents who preferred somapacitan over daily GH, high-scoring reasons for this preference included: number of times needing to perform injections (27/45; 60%); less worried about remembering to perform injections (21/45; 46.7%); as well as child less worried about getting injections and child less annoyed about getting injections (both 15/45; 33.3%). Other responses included: less need to change own plans because of injections (14/45; 31.1%); less need to change the child's plans (12/45; 26.7%); and less pain from the injections (7/45; 15.6%). Of those who preferred somapacitan, most (35/45; 77.8%) answered that they would be more adherent to once-weekly somapacitan compared with the daily GH treatment regime.

Discussion

The current study represents a continuation of the phase 3 REAL4 trial, beyond the main phase period (52 weeks) and

Table 3. Adverse events

	Weeks 0-52 Somapacitan n = 132			Weeks 0-52 Daily GH n = 68			Weeks 52-104 soma/soma n = 131			Weeks 52-104 Switch n = 68		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
All events	96 (72.7)	327	243.4	41 (60.3)	150	217.0	82 (62.6)	210	166.5	39 (57.4)	84	125.3
Serious events	6 (4.5)	8	6.0	2 (2.9)	3	4.3	3 (2.3)	4	3.2	0		
Severity												
Mild	89 (67.4)	270	201.0	35 (51.5)	122	176.5	77 (58.8)	174	137.9	34 (50.0)	64	95.4
Moderate	27 (20.5)	50	37.2	12 (17.6)	27	39.1	23 (17.6)	35	27.7	9 (13.2)	18	26.8
Severe	4 (3.0)	7	5.2	1 (1.5)	1	1.4	1 (0.8)	1	0.8	2 (2.9)	2	3.0
Relation to trial product												
Probably	12 (9.1)	17	12.7	4 (5.9)	5	7.2	6 (4.6)	11	8.7	1 (1.5)	1	1.5
Possibly	22 (16.7)	47	35.0	9 (13.2)	21	30.4	6 (4.6)	8	6.3	9 (13.2)	12	17.9
Unlikely	91 (68.9)	263	195.8	38 (55.9)	124	179.4	81 (61.8)	191	151.4	38 (55.9)	71	105.9

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

Table 4. Injection site reactions

	Weeks 0-52 somapacitan n = 132			Weeks 0-52 daily GH n = 68			Weeks 52-104 soma/soma n = 131			Weeks 52-104 switch n = 68		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
General disorders and administration site conditions	7 (5.3)	9	6.7	4 (5.9)	4	5.8	3 (2.3)	6	4.8	2 (2.9)	2	3.0
Bruising	2 (1.5)	2	1.5	2 (2.9)	2	2.9	1 (0.8)	3	2.4	0		
Hematoma	2 (1.5)	4	3.0	0			0			0		
Pain	2 (1.5)	2	1.5	1 (1.5)	1	1.4	0			0		
Hemorrhage	0			0			1 (0.8)	1	0.8	0		
Mass	0			0			1 (0.8)	1	0.8	0		
Reaction	0			0			1 (0.8)	1	0.8	0		
Swelling	1 (0.8)	1	0.7	0			0			0		
Hypersensitivity	0			1 (1.5)	1	1.4	0			1 (1.5)	1	1.5
Macule	0			0			0			1 (1.5)	1	1.5

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

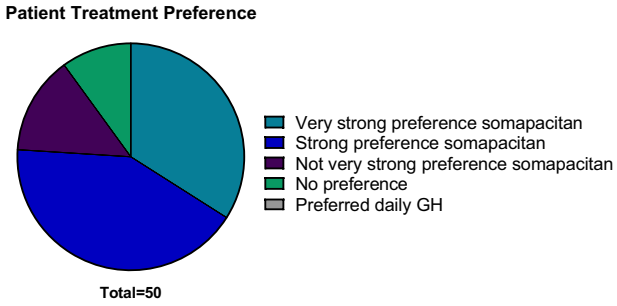

Figure 5. Patient preference for once-weekly somapacitan over daily GH. Observer-reported outcome assessments performed at week 56 using GH-PPQ for patients switching from daily GH to once-weekly somapacitan treatment at week 52. Abbreviations: PPQ, patient preference questionnaire.

into the first year of the 3-year safety extension period. During the main phase, we demonstrated noninferiority and comparable safety between patients receiving either 0.16 mg/kg/wk somapacitan or 0.034 mg/kg/d daily GH (12). Here, we show that there is a sustained efficacy and safety profile consistent with daily GH treatment after 2 years of treatment with somapacitan, as well as after 1 year of somapacitan treatment following the switch from daily GH. Nearly all parents/caregivers have a strong or very strong preference for once-weekly somapacitan treatment over daily GH, with none favoring daily GH over once-weekly somapacitan. Most of those who prefer somapacitan responded that they would be more adherent to once-weekly somapacitan administration compared with daily injections of GH.

Similar efficacy results were observed in this study for both treatment arms: 2 years of treatment with 0.16 mg/kg/wk somapacitan (soma/soma group) and 1 year of treatment with 0.16 mg/kg/wk somapacitan following the switch from daily GH (switch group). A small, numerical difference was observed in the first year for mean HV between daily GH and somapacitan (11.7 vs 11.2 cm/y, respectively; noninferiority confirmed), and this difference was sustained into year 2 (8.7 vs 8.4 cm/y for the switch and soma/soma groups, respectively) (12). This indicates that both groups are following their growth potential based on their baseline characteristics, rather than a difference in treatment per se. Indeed, the switch group had slightly lower mean values for several key baseline parameters, including HV, HVSDS, HSDS, IGF-I SDS, and GH peak. This view is also supported by a continuous trend toward increased HSDS in each group regardless of treatment. The results presented in the current study, therefore, demonstrate the efficacy profile of somapacitan is sustained after 2 years of treatment and following the switch of patients from daily GH to once-weekly somapacitan.

Somapacitan was well tolerated and not associated with an increased number of AEs, immunogenicity, metabolic complications, neutralizing antibodies, tolerability issues, or injection site reactions, including no reports of injection site pain. These are encouraging findings because discomfort/pain associated with daily GH injections has been associated with poor treatment adherence in both children and adults (20-22). Poor adherence to GH treatment has been shown to be linked with significantly lower growth velocity in children (23, 24). Thus, improved adherence to treatment may lead to improved growth outcomes in a real-world setting. Taken together, safety and efficacy results presented in the current study support somapacitan as having a similar safety and efficacy profile to daily GH, consistent with 52-week results from REAL4 (12) and 4 years of results from phase 2 REAL3 (15). This continuity in efficacy and safety beyond 1 year of treatment is similar to that reported for other long-acting growth hormones (LAGHs) (25, 26).

To monitor the effects of GH therapy, IGF-I SDS is commonly used as a surrogate marker for efficacy, adherence, and safety in long-term GH treatment (27). Here, we find that in both treatment groups, the observed mean IGF-I SDS increased from low baseline values to week 104 and there was no marked change from year 1 to year 2. All mean IGF-I SDS values remained within the normal range (−2 to +2) through year 2 whether patients remained on once-weekly somapacitan treatment or switched from daily GH to once-weekly somapacitan treatment. A marginal difference in the number of patients in the soma/soma (11.6%) and switch (5.9%) groups that have an IGF-I SDS >+2.5 was observed. A possible explanation is that this may be due to a discrepancy in the actual timing of IGF-I SDS sampling between the groups or, because of the relatively low number of patients, it may be from random chance. Nonetheless, no safety issues were observed in subjects with IGF-I levels above +2 SDS.

One of the main objectives for developing a LAGH to treat GHD in children is to establish a less burdensome dosing regimen that is as efficacious and safe as existing daily GH replacement therapy. As described previously, several randomized clinical studies in children show that once-weekly somapacitan has an efficacy and safety profile similar to the profiles for daily GH (12-16). Although adherence in controlled clinical trials is high, reducing the number of injections required with somapacitan will potentially improve adherence and decrease barriers to initiating and maintaining replacement therapy in a real-world setting and thereby improve treatment outcomes. Although challenges often related to injection site reactions were encountered in early attempts to develop LAGHs (28-31), multiple studies have demonstrated that both adults and children treated with once-weekly somapacitan experience a very low proportion of injection site reactions ranging from 0% to 6.7% (12-14, 16, 32-34). Consistent with these observations, a low proportion of injection site reactions was observed in REAL4 from weeks 52 to 104 for both groups (2.3% and 2.9% in the soma/soma and switch groups, respectively). Notably, no patients in this study reported injection site pain in year 2. A desirable efficacy and safety profile, including a low proportion of injection site reactions associated with somapacitan treatment coupled with a device for administering somapacitan that has previously been demonstrated to be easy to use and easy to learn (12) might, taken together, make somapacitan an attractive alternative to daily GH treatment for patients and their caregivers. Consistent with this, GH-PPQ results presented here demonstrate the majority of patients and their caregivers prefer once-weekly somapacitan to daily GH. These findings align well with GH-PPQ results observed after switching from daily GH to once-weekly somapacitan in year 4 of the REAL3 trial where most (9/11; 81.2%) strongly or very strongly preferred once-weekly somapacitan over daily GH, and none preferred daily GH over somapacitan (15).

The preference for once-weekly somapacitan over daily GH reported here by caregivers is due to a variety of different reasons. These include the child being less worried or less annoyed by injections as well as experiencing less pain and once-weekly injections infringing less on the plans of the patient and/or parents/caregivers. These reasons are supported by treatment burden questionnaires reported at 52 weeks in REAL4 and in REAL3 where patient/caregiver responses favored 0.16 mg/kg/wk somapacitan over daily GH treatment in terms of the impact on emotional well-being, physical functioning, and social well-being (12, 13, 35). Importantly, the 2 highest scoring reasons for preferring once-weekly somapacitan over daily GH in the current study were the number of times needing to do injections and being less worried about remembering to perform injections. Both of these reasons might, similar to reduced injection site pain, be linked to possibly improved adherence and subsequent improved clinical outcomes. However, long-term surveillance studies in a real-world setting are required to best demonstrate improved adherence and clinical outcomes with once-weekly somapacitan (35). Nonetheless, these results are encouraging.

In conclusion, these novel data support efficacy and safety results previously published for somapacitan in the treatment of prepubertal children with GHD (12-15). In year 2 of the REAL4 study, height-related outcomes and safety profiles were similar for patients who continued once-weekly somapacitan treatment and those who switched from daily GH to somapacitan. Most patients and their caregivers preferred treatment with once-weekly somapacitan over treatment with daily GH and indicated that they would be more adherent to the weekly, rather than daily treatment regimen. The plain language summary of this work is available at Miller et al (36).

Acknowledgments

The authors thank the patients and their families, nurses and study coordinators, and all investigators involved in this study, including members of the REAL4 Study Group*, without whom the study would not have been possible. The sponsor was involved in the study design, collection, analysis, and interpretation of data, as well as data checking of information provided in the manuscript. The authors thank Lasse de Fries Jensen and Sebastian Roehrich of Novo Nordisk for critically assessing the manuscript. The authors also thank Rasmus Juul Kildemoes and Julie Desrochers of Novo Nordisk for their help with pharmacokinetic/pharmacodynamic modelling. Medical writing and editorial support were provided by Greg Markby, PhD, and Ryan Ard, PhD, of Novo Nordisk.

Disclosures

B.S.M.: Consultant: Abbvie, Ascendis Pharma, BioMarin, Bristol Myers Squibb, EMD Serono, Endo Pharmaceuticals, Novo Nordisk, Orchard Therapeutics, Pfizer, Provention Bio, and Tolmar; Research support: Alexion, Abbvie, Aeterna Zentaris, Amgen, Amicus, Lumos Pharma, Lysogene, Novo Nordisk, OPKO Health Pfizer, Prevail Therapeutics, and Sangamo Therapeutics. J.C.B.: Advisory board: Novo Nordisk; Speaker fees from Novo Nordisk and Ipsen; Financial support to attend scientific meetings: Novo Nordisk. M.H.R.: Employee, stockholder: Novo Nordisk. A.M.: Principal Investigator: Novo Nordisk, Ascendis, OPKO, and Pfizer. J.M.: Advisory boards: Novo Nordisk; Consultant: J.C.R.; Speaker fees: Novo Nordisk, Pfizer, and JCR. V.B.: Advisory boards: Merck; Speaker fees: Novo Nordisk and Merck; Financial support to attend scientific meetings: Ferring, Lilly, Merck, and Novo Nordisk. R.B.B.: Employee, stockholder: Novo Nordisk. M.P.: Advisory boards: Ipsen, Novo Nordisk, Pfizer; Speaker fees: Novo Nordisk and Ipsen; Research support: Ipsen, Novo Nordisk, Pfizer, Sandoz, Merck and Sanofi, as well as French institutional grants (PHRC and ANR). R.H.: Advisory boards: Novo Nordisk, Pfizer, Ascendis, and Lumos Pharma; Speaker fees: Novo

Nordisk, Pfizer, and JCR; Research support: Sandoz. H.S.K. has nothing to disclose.

Data Availability

Available from the corresponding author on reasonable request. *Members of the REAL4 Study Group:

Austria: Dieter Furthner, Pamina Sonnleitner, Thomas Pixner, Angelika Geyrhofer, Dominika Cizmarova, Karl Zwiauer.

Canada: Rose Girgis.

Denmark: Anders Juul, Rikke Beck Jensen.

France: Michel Polak, Emeline Roy, Peter Jones, Romain Berthaud, Michaela Semeraro, Regis Coutant, Natacha Bouhours-Nouet, Aurélie Donzeau, Jessica Amsellem-Jager, Stéphanie Rouleau, Pascal Barat, Agnès Linglart, Cecile Teinturier, Anne Sophie Lambert.

Germany: Volker Böttcher, Alexander Mann, Gerhard Binder, Roland Schweizer, Sabine Heger, Nicolin Datz.

Hungary: Agota Muzsnai, Borbála Tobisch.

India: Rajesh Khadgawat, Viveka Jyotsna, Vaman Khadilkar, Madhura Karguppikar, Nikhil Shah, Praveen Valliyaparambil, Nithya Abraham.

Israel: Nehama Zuckerman Levin, Adi Miller Barmak, Ameer Elemy, Christopher Fady Farah, Liat Etshtein, Suha Rizik, Wasim Said, Naim Shehadeh, Alon Eliakim, Eyal Zifman, Liat Pearl, Rachel Shatzman Steuerman, Nitzan Dror, Ruby Haviv, Moshe Phillip, Ariel Tenenbaum, Sari Karpel, Marianna Rachmiel, Galia Barashi, Maor Leibzon, Yossef Schon, Larica Naugolny.

Italy: Maura Arosio, Claudia Giavoli, Eriselda Profka, Giulia Rodari, Stefano Stagi, Anna Madera, Valerio Maniscalco, Gaia Varriale, Franco Ricci, Maria Parpagnoli, Marco Cappa, Carla Bizzarri, Danilo Fintini, Giuseppe Pontrelli, Laura Chioma, Laura Paone.

Japan: Kenichi Kashimada, Maki Gau, Yoko Saito, Kei Takasawa, Ryuichi Nakagawa, Reiko Horikawa, Erika Uehara, Keisuke Yoshii, Masaaki Matsumoto, Rieko Minegishi, Shintaro Terashita, Tomoe Ogawa, Tomohiro Nagata, Tomoko Ota, Yasuhiro Naiki, Takashi Hamajima, Masako Izawa, Takamasa Kano, Jun Mori, Hidechika Morimoto, Hisakazu Nakajima, Mihoko Yamaguchi, Nozomi Nishida, Satoshi Miyagaki, Takeshi Ota, Yasuhiro Kawabe, Yasuhisa Ohata, Taichi Kitaoka, Takuo Kubota, Masanobu Kawai, Shinobu Ida, Takatoshi Maeyama, Yasuko Shoji, Yuri Etani, Tohru Yorifuji, Kana Kitayama, Maki Oyachi, Rie Kawakita, Shinji Higuchi, Yoh Watanabe, Yuki Yamada, Kayo Ozaki, Akari Mitsuboshi, Masaaki Matsumoto, Masashi Nagai, Toshihide Kubo, Kana Fukuda, Mahoko Furujo, Yousuke Higuchi, Yuki Ebuchi, Hitoshi Tobiume, Kazuhiro Sekimoto, Masanori Ikeda, Masato Yasui, Michiko Muraoka, Mitsuru Tsuge, Osamu Mitani, Saori Hioki, Yosuke Fujii, Kenichi Miyako, Mika Makimura, Miwa Furuzono, Noriko Oyama, Terumichi Matsuo, Satoko Umino, Junko Nishioka, Kikumi Ushijima, Reo Saiki, Shuichi Yatsuga, Yasutoshi Koga, Yukari Tanaka, Yuko Koga, Miyuki Kitamura, Takako Matsumoto, Tooru Araki, Aya Kodera, Kenji Urayama, Kunimi Kitada, Michimasa Fujiwara, Mizue Iwase, Motohiro Inotani, Sadanori Yamashita, Tomoko Sakamoto, Isho Izumi, Atsuko Ogasawara, Atsushi Iwabuchi, Hiroto Idesawa, Yasuko Fujisawa, Hiroyuki Ono, Tsutomu Ogata, Sayaka Yoshida, Atsuko Nishiyama, Atsushi Inagaki, Emi Wakita, Hiroki Nishikawa, Masayuki Onaka, Naohiro Yamamoto, Rika Suzuki, Soshi Hachisuka, Takahiro Mori, Takumi Okamura, Yuri Kamatani, Yuya Yamada, Shun Soneda. Korea: Ho-Seong Kim, Ah Reum Kwon, Jung hwan Suh, Hanwook Yoo, Jin-Ho Choi, Mi-Seon Lee, Cheol Woo Ko, Gi Min Lee, Jeong Eun Moon, Rosie Lee, Su Jeong Lee, Yun Jeong Lee, Jin Soon Hwang, Chang Dae Kum, Junggi Rho, Woo Yeong Chung, Jae Hyun Kim, Jaewon Choe, Minseung Kim, Yo Han Ahn, Dongkyu Jin, Hyo Jung Park, Min-Sun Kim, Sung Yoon Cho, Sujin Kim, Jieun Lee.

Latvia: Iveta Dzivite-Krisane, Inara Kirillova, Una Lauga-Tunina.

Poland: Mieczyslaw Szalecki, Elzbieta Moszczynska, Karolina Kot, Urszula Watrobinska.

Russia: Elena Borisovna Bashnina, Maria Turkunova, Olga Sergeevna Berseneva, Galina Alexandrovna Galkina, Natalia Morozova, Marina Komkova, Evgeniia Gennadievna Mikhailova, Irina Shevkulenko, Alisa Vitebskaya, Elena Pisareva, Lubov Nikolaevna Samsonova, Elena Kiseleva, Goar Okminyan, Oleg Latyshev, Tatyana Kovalenko, Lyaisan Malikovna Mullahmetova, Olga Kunaeva, Margarita Kovarenko, Anna Episheva, Oxana Pilipenko, Ekaterina Gushchina, Yulia Samoilova, Nargiz Diraeva, Oxana Oleynik, Tatiana Filippova, Tatiana Sivolobova, Marina Koshmeleva.

Serbia: Tatjana Milenkovic, Katarina Mitrovic, Rade Vukovic, Sladjana Todorovic, Vera Zdravkovic, Maja Jesic, Smiljka Kovacevic, Vladislav Bojic, Silvija Sajic, Sasa Zivic, Sandra Stankovic, Ljiljana Saranac, Martin Novak, Vesna Cvetkovic, Ivana Vorgucin, Slavica Dautovic.

Slovenia: Tadej Battelino, Mojca Zerjav-Tansek.

Spain: Marta Ramón-Krauel, Lourdes Ibañez, Montserrat Amat Bou, Paula Casano Sancho, Jesús Barreiro, Lidia Castro, Paloma Cabanas.

Switzerland: Christa Flueck, Claudia Böttcher.

Thailand: Vichit Supornsilchai, Khomsak Srilanchakon, Nawaporn Numbenjapon, Piriya Chantrathammachart.

Ukraine: Olga Vyshnnevska, Olena Bolshova, Mykola Tronko, Tatyana Malinovskaya, Oksana Fishchuk, Iryna Trompinska, Maryna Vlasenko, Nataliya Shulha, Oleksandr Onikiienko.

United Kingdom: Joanne Blair, Julie Park, Philip Murray, Ajay Thankamony, Emile Hendriks, Verghese Mathew, Assunta Albanese, Elena Monti.

United States: Bradley Miller, Arpana Rayannavar, Kyriakie Sarafoglou, Alisha Olson, Jensina Ericksen, Kristin Boxwell, Lawrence Silverman, Harold Starkman, Melisa Woo, Barbara Cerame, Kristin Sabanosh, Laurie Ebner-Lyon, Marie Fox, Sunita Cheruvu, Iris Gutmark-Little, Gajanthan Muthuvel, Jacob Redel, Philippe Backeljauw, Leah Tyzinski, Tammy Weis, Judith L. Ross, Evan Graber, Aristides Maniatis, Mako Sather, Donna Campbell, Bhuvana Sunil, Barbara Thompson, Britney Frazier, Gad Kletter, Georgia Goldberg, Sophie Schmitter, Jennifer Abuzzahab, Ewa Oberdorfer, Jennifer Kyllo, Melinda Pierce, Paul H. Saenger, Jorge E. Mejia-Corletto, Anita Farhi, Marilyn Richardson, Melissa Allman, Oscar Escobar, Luigi Garibaldi, Wayne V. Moore, Terri Luetjen, Michael Stalvey, Gail Mick, Giovanna Beauchamp, Jake Orr, Hannah Tucker, Paul Thornton, Alejandro de la Torre, Joel W Steelman, Susan Hsieh, Larry Rodriguez, Tiffany Skrodzki, John Fuqua, Nadine Haddad, Monica Marin, Kruti Shah, Steven D. Chernausek, Linda Weber, Mitchell

E. Geffner, Clement Cheung, Norma Martinez, Eva Tsalikian, Michael Tansey, Julie Coffey, Asheesh Dewan, Carron Schweiger, Milagros Huerta, Wanda Tong, Timothy Flannery, Daina Dreimane, Francoise Sutton, Quentin Lee Van Meter, Mary A Bertossi, Toni Kim, Gnanagurudasan Prakasam, Ulas Nadgir, William Lagarde, Hillary Lockemer, Mark D. Henin, Kendra Marr, Sunil Nayak, Alicia G. Marks, Alexandria Jenkins, Judy Bonnett, Rebecca Somershoe.

References

1. 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.
2. 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. Doi: 10.1016/j.ghir.2021.101392
3. 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.
4. 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.
5. 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. Doi: 10.3389/fendo.2018.00688
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. Thygesen P, Andersen HS, Behrens C, *et al.* Nonclinical pharmacokinetic and pharmacodynamic characterisation of somapacitan: a reversible non-covalent albumin-binding growth hormone. *Growth Horm IGF Res*. 2017;35:8-16. Doi: 10.1016/j.ghir.2017.05.006
8. 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.
9. Deacon CF. Potential of liraglutide in the treatment of patients with type 2 diabetes. *Vasc Health Risk Manag*. 2009;5(1):199-211.
10. 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.
11. Kurtzhals P, Østergaard S, Nishimura E, Kjeldsen T. Derivatization with fatty acids in peptide and protein drug discovery. *Nat Rev Drug Discov*. 2023;22(1):59-80.
12. Miller BS, Blair JC, Rasmussen MH, *et al.* Weekly somapacitan is effective and well tolerated in children with GH deficiency: the randomized phase 3 REAL4 Trial. *J Clin Endocrinol Metab*. 2022;107(12):3378-3388.
13. Sävendahl L, Battelino T, Brod M, *et al.* REAL 3 study group. 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.
14. 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*. 2021;107(5):1357-1367.
15. Sävendahl L, Battelino T, Rasmussen MH, *et al.* Weekly somapacitan in GH deficiency: 4-year efficacy, safety and treatment/disease burden results from REAL 3. *J Clin Endocrinol Metab*. 2023; 108(10):2569-2578.
16. Juul A, Backeljauw P, Højby M, *et al.* Somapacitan in children born small for gestational age: a multi-centre, open-label, controlled phase 2 study. *Eur J Endocrinol*. 2023;188(1):lvac008.
17. Greulich WW, Pyle SJ. *Radiographic Atlas of Skeletal Development of the Hand and Wrist*. Stanford University Press; 1959.
18. 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.
19. Melmed S. Pathogenesis and diagnosis of growth hormone deficiency in adults. *N Engl J Med*. 2019;380(26):2551-2562.
20. Graham S, Weinman J, Auyeung V. Identifying potentially modifiable factors associated with treatment non-adherence in paediatric growth hormone deficiency: a systematic review. *Horm Res Paediatr*. 2018;90(4):221-227.
21. Mohseni S, Heydari Z, Qorbani M, Radfar M. Adherence to growth hormone therapy in children and its potential barriers. *J Pediatr Endocrinol Metab*. 2018;31(1):13-20.
22. Rosenfeld RG, Bakker B. Compliance and persistence in pediatric and adult patients receiving growth hormone therapy. *Endocr Pract*. 2008;14(2):143-154.
23. Kapoor RR, Burke SA, Sparrow SE, *et al.* Monitoring of concordance in growth hormone therapy. *Arch Dis Child*. 2008;93(2): 147-148.
24. 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.
25. Maniatis AK, Casella SJ, Nadgir UM, *et al.* Safety and efficacy of lonapegsomatropin in children with growth hormone deficiency: enliGHten trial 2-year results. *J Clin Endocrinol Metab*. 2022;107(7):e2680-e2689.
26. Zadik Z, Zelinska N, Iotova V, *et al.* An open-label extension of a phase 2 dose-finding study of once-weekly somatrogon vs. once-daily Genotropin in children with short stature due to growth hormone deficiency: results following 5 years of treatment. *J Pediatr Endocrinol Metab*. 2023;36(3):261-269.
27. Blum WF, Alherbish A, Alsagheir A, *et al.* The growth hormone-insulin-like growth factor-I axis in the diagnosis and treatment of growth disorders. *Endocr Connect*. 2018;7(6): R212-r222.
28. 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.
29. Reiter EO, Attie KM, Moshang T, Jr., *et al.* Genentech Inc Alkermes inc collaborative study group. 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.
30. Touraine P, D'Souza GA, *et al.* G. H. Lipoatrophy Study Group. Lipoatrophy in GH deficient patients treated with a long-acting pegylated GH. *Eur J Endocrinol*. 2009; 161(4):533-540.
31. 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.
32. 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.
33. 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.
34. 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.
35. Miller BS. What do we do now that the long-acting growth hormone is here? *Front Endocrinol (Lausanne)*. 2022;13:980979.
36. Miller BS, Blair J, Højby Rasmussen M, *et al.* Plain language summary for "Effective GH Replacement with Somapacitan in Children with GHD: REAL4 2-year Results and after Switch from Daily GH." 2023. *figshare*. Journal contribution. Doi: 10.6084/m9.figshare.23591865.v1