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Original Research

Efficacy, safety, and insulin-like growth factor I of weekly somapacitan in children with growth hormone deficiency: 3-year results from REAL4

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Abstract

Objective: Somapacitan is a long-acting GH approved for once-weekly treatment of GH deficiency (GHD). This study aims to evaluate the efficacy and tolerability of somapacitan after 3 years of treatment and 2 years after switch from daily GH in children with GHD.

Design: Randomized, multi-national, open-labelled, active-controlled parallel-group phase 3 trial, with a 52-week main phase and 3-year safety extension (NCT03811535).

Methods: Treatment-naïve children with GHD were randomized (2:1) to continuous somapacitan (0.16 mg/kg/week; "soma/soma" group) or daily GH (Norditropin®; 0.034 mg/kg/day) followed by somapacitan (0.16 mg/kg/week; "switch" group).

Results: Of 200 participants, 188 completed 3 years of treatment. Sustained growth was observed in both groups. At week 156, mean (SD) height velocity (HV) between weeks 104 and 156 was 7.4 (1.5) cm/year in the soma/soma group and 7.8 (1.4) cm/year in the switch group. At week 156, the soma/soma and switch groups had reached a mean (SD) height SD score (HSDS) of −0.95 (0.98) and −1.08 (0.93), respectively, and were approaching the mean mid-parental HSDS of −0.74 (for both groups). Mean total insulin-like growth factor I (IGF-I) SDS during year 3 was similar between groups and within normal range (−2.0 to +2.0). Bioactive IGF-I and bioactive IGF-I to IGF-I ratio were similar between groups. Somapacitan was well tolerated, with low proportions reporting injection-site reactions.

Conclusions: Sustained efficacy and tolerability were observed for continuous somapacitan treatment for 3 years, and for 2 years after the switching from daily GH treatment. HSDS in both groups was approaching mean mid-parental HSDS.

Clinical trial registration: NCT03811535

Keywords: growth hormone, growth hormone deficiency, growth hormone replacement therapy, long-acting growth hormone, somapacitan

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Significance

Growth hormone deficiency (GHD) in children leads to reduced growth velocity and adult height and impacts quality of life. Traditional treatment involves daily GH injections, which can be burdensome and lead to poor adherence, which is associated with poor growth outcomes. This study evaluates the long-term efficacy and safety of weekly somapacitan, a long-acting GH, in children with GHD. Over 3 years, somapacitan demonstrated sustained growth and was well-tolerated. Importantly, the study also showed that mean total insulin-like growth factor I (IGF-I) levels remained within the normal range, and bioactive IGF-I levels were similar between treatment groups. The findings highlight the potential of weekly somapacitan as an effective and less burdensome alternative to daily GH.

Introduction

Children with GH deficiency (GHD) experience reduced growth velocity and adult height,[1] impacting their quality of life.[2,3] Traditionally, GHD treatment involves daily subcutaneous (s.c.) GH injections,[1,4] which can be burdensome[5] and often result in poor adherence,[6,7] negatively impacting growth outcomes.[8] Long-acting GH (LAGH) formulations for once-weekly administration offer a less burdensome alternative,[9] and are expected to improve adherence and clinical outcomes. However, long-term efficacy and safety monitoring is required.[9]

Somapacitan (Sogroya®, Novo Nordisk A/S) is a LAGH approved for once-weekly s.c. administration to treat GHD in children and adults, and its efficacy and tolerability have been demonstrated in multiple randomized controlled trials.[10-19] The pivotal phase 3 REAL4 study (NCT03811535) demonstrated non-inferiority in height velocity (HV) for somapacitan compared with daily GH (Norditropin®, Novo Nordisk A/S) with similar safety and tolerability after 52 weeks in prepubertal, GH treatment-naïve children with GHD.[16] Mean levels of insulin-like growth factor I (IGF-I), a biomarker for monitoring GH treatment response,[20] were similar between groups and within normal range [−2.0 to +2.0 standard deviation score (SDS)].[16] In the second year, all participants were receiving somapacitan, and sustained efficacy and tolerability were demonstrated in both groups ("soma/soma" group, receiving somapacitan only, and "switch" group, receiving daily GH the first year then switch to somapacitan).[17]

Treatment with LAGHs, like somapacitan, shows different IGF-I profiles compared with daily GH over the weekly dosing interval with a serum IGF-I peak roughly 1-4 days after dosing that declines to trough values on day 7 before the next dose.[9] Modest and transient increases in IGF-I above +2.0 SDS have not been associated with adverse events (AEs) and may be acceptable during GH treatment. The true bioactive fraction of IGF-I circulating unbound to binding proteins, such as IGF binding protein-3 (IGFBP-3), typically accounts for less than 1% of total IGF-I in serum.[21] Thus, measuring total IGF-I levels might not reflect the true amount of bioactive IGF-I circulating in patients treated with GH. While the IGF-I/IGFBP-3 molar ratio can be used as a rough surrogate marker of circulating free IGF-I,[22] directly measuring IGF-I bioactivity is possible with an IGF-I kinase receptor activation (KIRA) assay to assess the IGF-I fraction able to bind the IGF-I receptor.[23,24] The impact of treatment with daily GH vs LAGH on bioactive IGF-I response in children with GHD has not yet been investigated.

Here, we present novel efficacy and safety results for year 3 of the phase 3 REAL4 study, exploring the sustained long-term efficacy and safety of 0.16 mg/kg/week somapacitan in children with GHD.

Methods

Study design

REAL4 is a randomized, multi-national, open-label, active-controlled parallel-group phase 3 trial (NCT03811535). The main phase was 52 weeks and investigated the efficacy and safety of 0.16 mg/kg/week somapacitan treatment for GHD compared with daily GH (Norditropin®; 0.034 mg/kg/day; control) (Figure 1A). Somapacitan was provided as pre-filled pen-injectors of the FlexPro® family (Novo Nordisk A/S) and daily GH (0.034 mg/kg/day Norditropin®) was provided using Norditropin FlexPro® 10 mg/1.5 mL. The main phase was followed by an ongoing 3-year extension period (weeks 52 to 208) where all participants received somapacitan 0.16 mg/kg/week. Three-year (week 156) data reported here were collected between May 2019 and December 2023. The trial protocol was approved by local and national ethics committees, as appropriate, and conducted in accordance with the International Conference on Harmonisation Guidelines for Good Clinical Practice[25] and the Declaration of Helsinki. Further details on the study design were reported previously.[16]

Participants

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

Objectives and endpoints

Efficacy endpoints

Longitudinal growth was assessed by annualized HV and measured as standing height with a stadiometer. Other efficacy endpoints included change from baseline in HV SD score (HVSDS), height SDS (HSDS), and bone age.

Pharmacodynamic endpoints

IGF-I analyses were performed by a central laboratory using a commercially available assay kit (Immunodiagnostic Systems Immunoassay), and estimated weekly average IGF-I SDS was calculated. Blood samples for IGF-I measurements in participants treated with somapacitan were taken at the following timepoints after dosing to estimate peak, average, and trough levels: week 4, 26, 78, and 130 (day 1-4 after dosing; around peak level), week 13, 39, 104, and 156 (day 7 after dosing; trough level) and at week 52 (day 4-6 after dosing; expected weekly average level). Other pharmacodynamic endpoints included IGFBP-3 SDS, IGF-I/IGFBP-3 molar ratio and bioactive IGF-I. IGFBP-3 was measured in a similar manner as

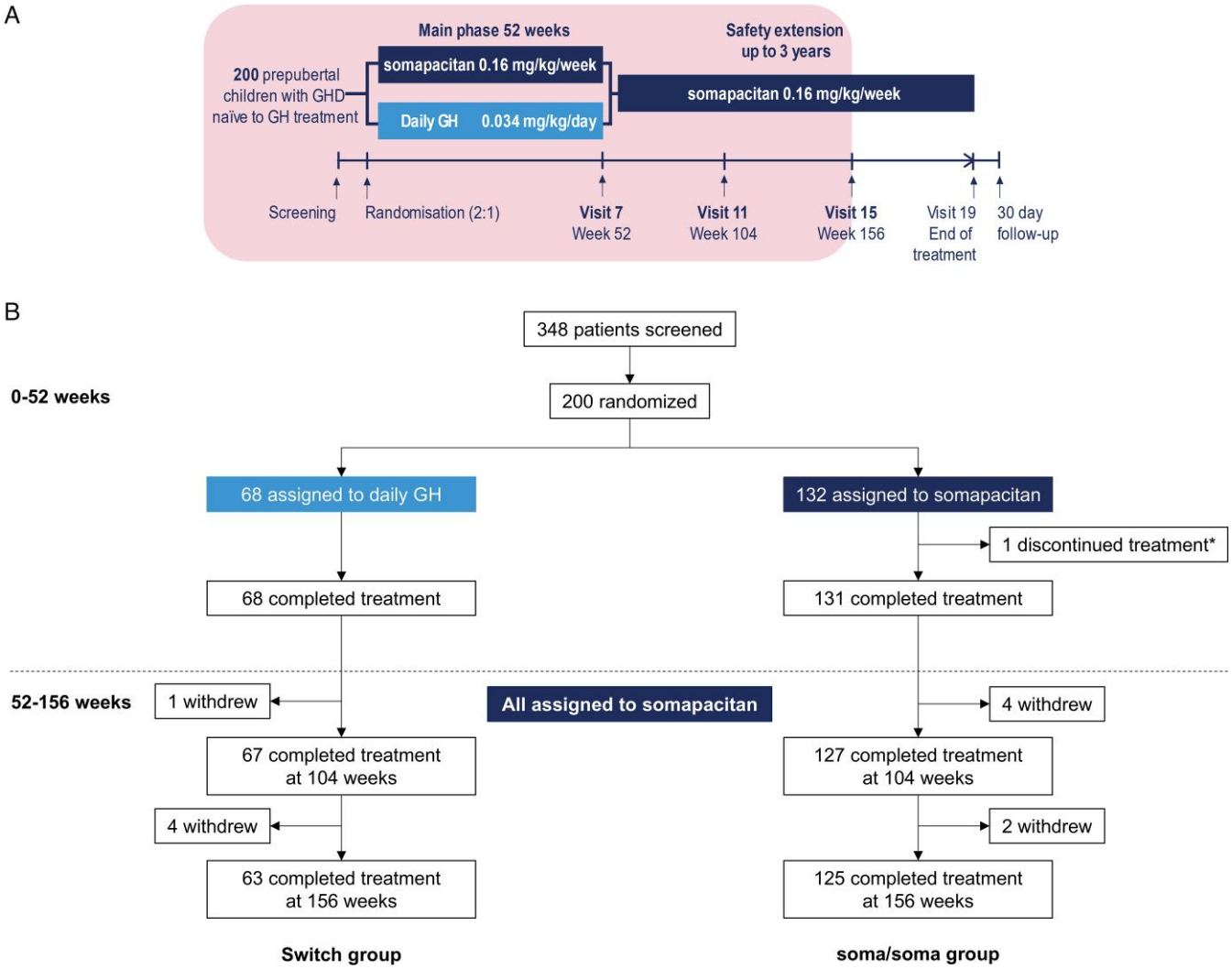

Figure 1. Trial overview and profile. (A) Design of the REAL4 study and safety extension. Results from the main phase and first 2 years of the safety extension (156 weeks total) are reported in this study. Time axis is not to scale. (B) Population disposition of trial participants during the main trial period (weeks 0-52) and the first 2 years of the extension period (weeks 52-156). The full analysis set includes all randomly assigned children in the trial to either weekly somapacitan or daily GH (Norditropin®). The safety analysis set includes all randomly assigned children who received at least 1 dose of randomized treatment. 125 and 63 children completed 156 weeks in soma/soma and switch groups, respectively. Modified from Miller BS, J Clin Endocrinol Metab. 2022;107(12):3378-3388. *1 participant discontinued treatment in the main phase. GHD, GH deficiency; soma, somapacitan.

IGF-I, and IGF-I/IGFBP-3 molar ratio was calculated as described by Friedrich et al.[26] Bioactive IGF-I was measured at baseline and week 13, 26, 78, and 104, using an in-house IGF-I kinase receptor activation assay as previously described.[23,24]

Safety assessments

Safety was assessed as the incidence of AEs, summarized by Medical Dictionary for Regulatory Activities (MedDRA) system organ class, and MedDRA preferred term, as well as injection site reactions, occurrence of anti-drug antibodies, among others.

Statistical analysis

Statistical analyses of data were previously performed for 52 weeks of treatment (main phase), and no statistical testing was performed thereafter (as per trial protocol). Data are presented using descriptive statistics for the efficacy and safety endpoints up to week 156. All AEs with onset after the first administration of treatment and with a start date up until 14 days after last dose or until visit 15 (week 156), whichever comes first, were included.

Role of the funding source

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

Results

Study population

Two-hundred randomly assigned participants received either once-weekly somapacitan ($n = 132$) or daily GH (Norditropin®; $n = 68$) in the first year (main phase) of the REAL4 study.[16] 199 completed treatment and rolled over into the 3-year safety extension where all participants receive 0.16 mg/kg/week somapacitan (Figure 1B). For year 2 (the first year of the safety extension), 127 children completed

Table 1. Study demographics and baseline characteristics.

	soma/soma group ($n = 132$)	Switch group ($n = 68$)	Total ($n = 200$)
Age, years	6.4 (2.2)	6.4 (2.4)	6.4 (2.3)
<6 years, *n* (%)	64 (48.5%)	33 (48.5%)	97 (48.5%)
Sex:			
Male, *n* (%)	99 (75.0%)	50 (73.5%)	149 (74.5%)
Female, *n* (%)	33 (25.0%)	18 (26.5%)	51 (25.5%)
Race:			
White, *n* (%)	78 (59.1%)	36 (52.9%)	114 (57.0%)
Asian, *n* (%)	46 (34.8%)	28 (41.2%)	74 (37.0%)
Black or African American, *n* (%)	0 (0%)	1 (1.5%)	1 (0.5%)
Not reported, *n* (%)	7 (5.3%)	3 (4.4%)	10 (5.0%)
Other, *n* (%)	1 (0.8%)	0 (0%)	1 (0.5%)
Weight, kg	16.7 (4.6)	16.0 (5.0)	16.5 (4.7)
BMI, kg/m^2	15.7 (1.6)	15.6 (1.4)	15.7 (1.5)
BMI SDS	−0.17 (0.97)	−0.25 (1.05)	−0.19 (1.00)
Height, cm	102.3 (12.5)	100.2 (15.0)	101.6 (13.4)
HV, cm/year	4.3 (1.4)	4.1 (1.4)	4.2 (1.4)
HVSDS	−2.35 (1.51)	−2.52 (1.55)	−2.41 (1.52)
HSDS	−2.99 (1.02)	−3.47 (1.52)	−3.15 (1.23)
IGF-I SDS	−2.03 (0.97)	−2.33 (1.03)	−2.13 (1.00)
IGFBP-3 SDS	−1.89 (1.12)	−2.18 (1.27)	−1.99 (1.18)
IGF-I/IGFBP-3 molar ratio, %	10.03 (2.91)	9.42 (3.28)	9.82 (3.05)
Bioactive IGF-I, ng/mL, geometric mean (CV%)[a]	0.36 (51.2%)	0.36 (52.5%)	0.36 (51.5%)
Bioactive IGF-I to total IGF-I ratio, %[a]	1.00 (0.97)	1.36 (1.71)	1.12 (1.28)
GH peak, µg/L	4.9 (2.5)	4.1 (2.8)	4.7 (2.6)
Etiology:			
Idiopathic, *n* (%)	115 (87.1%)	61 (89.7%)	176 (88.0%)
Organic, *n* (%)	17 (12.9%)	7 (10.3%)	24 (12.0%)

Values are reported as mean (SD) unless otherwise stated. The values are based on the full analysis set.
[a]Data on bioactive IGF-I and bioactive IGF-I to total IGF-I ratio at baseline were available for 130 participants in the soma/soma group and 67 participants in the switch group. Modified from Miller BS, J Clin Endocrinol Metab. 2022;107(12):3378-3388.
Abbreviations: BMI, body mass index; CV%, coefficient of variation percent; GHD, GH deficiency; HSDS, height SD score; HV, height velocity; HVSDS, height velocity SD score; IGF-I SDS, IGF-I SD score; IGFBP-3, IGF-binding protein 3; SDS, SD score; soma, somapacitan.

2 years of continuous somapacitan treatment (the "soma/soma" group), while 67 children completed 1 year of somapacitan treatment after switching from daily GH (the "switch" group).[17] For year 3 (the second year of the safety extension), 125 children in the soma/soma group completed 3 years of continuous somapacitan treatment and 63 children in the switch group completed 2 years of somapacitan treatment after switching from daily GH (Figure 1B). None discontinued treatment due to AEs. In the safety extension (week 52-156), withdrawals were due to lost to follow-up, physician decision, withdrawal by parent/guardian, and other reasons.

Demographics and baseline characteristics were largely similar across both treatment groups, although the switch group showed slightly lower numerical mean values for HV, HSDS, HVSDS, IGF-I SDS, and GH peak at baseline (Table 1). The mean (SD) mid-parental height for the participants was 158.9 (8.9) cm for females and 171.3 (6.0) cm for males, and the mean (SD) mid-parental HSDS was −0.74 (0.99). Adherence during the safety extension was high for both treatments. Mean adherence for the soma/soma group and the switch group between week 52 and 156 was 89.0% and 86.0%, respectively, with medians of 96.2% and 95.2%, respectively.

At baseline (week 0), all children were tanner stage I. After 156 weeks in the soma/soma group, 105 (84.7%) remained stage I, 14 (11.3%) were stage II and 5 (4.0%) were stage III. Similarly, after 156 weeks in the switch group, 50 (79.4%) remained stage I, 7 (11.1%) were stage II and 3 (4.8%) were stage III, 1 (1.6%) was stage IV, and 2 (3.2%) were stage V.

Efficacy results

Height velocity

At week 156, observed mean (SD) annualized HV during weeks 104 to 156 was 7.4 (1.5) cm/year for the soma/soma group and 7.8 (1.4) cm/year for the switch group (Table 2), indicating sustained efficacy in both groups (Figure 2).

Other growth-related assessments

Secondary growth assessments confirmed sustained growth for both groups. HSDS and HVSDS increased from baseline to week 156 in both groups (Table 2). Mean HSDS progressed similarly in both groups, with means moving more into normal reference range (−2.0 to +2.0 SDS). At week 156, mean (SD) HSDS was −0.95 (0.98) in the soma/soma group and −1.08 (0.93) in the switch group (Figure 3). Notably, both groups approached the mean mid-parental HSDS of −0.74. Observed mean (SD) body mass index (BMI) SDS remained within normal range in year 3, with +0.33 (0.91) for the soma/soma group and +0.24 (0.93) for the switch group. Mean (SD) change from baseline in BMI SDS were 0.51 (0.63) and 0.50 (0.72) for the soma/soma group and switch group, respectively. Bone age advanced similarly in both groups (Table 2). The mean (SD) bone age to chronological age ratio improved from 0.65 (0.14) at baseline to 0.85 (0.15) at week 156 [mean change of 0.20 (0.18)] in the soma/soma group, and from 0.65 (0.15) to 0.85 (0.16) [mean change of 0.19 (0.14)] in the switch group.

Table 2. Observed efficacy and pharmacodynamic endpoints at week 156.

	Soma/soma group ($n = 124$)	Switch group ($n = 63$)
Annualised HV, cm/year[a]	7.4 (1.5)	7.8 (1.4)
Change in HSDS from baseline	2.04 (0.85)	2.38 (1.14)
Change in HVSDS from baseline	4.07 (2.50)	4.57 (2.75)
Change in IGF-I SDS from baseline[b,c]	1.79 (1.12)	1.96 (1.02)
Change in bone age, years[d]	3.88 (1.39)	3.81 (1.17)

Values are reported as mean (SD) and are based on the in-trial observation period [ie, the time from first administration and up until visit 15 (week 156) or last trial contact, whichever comes first].
[a]Annualised HV was calculated as change from week 104 to 156 in the third year.
[b]Blood samples for IGF-I measurements at week 156 were taken on day 7 after dosing (ie, around trough level).
[c]Data are missing for 2 participants in the soma/soma group and 3 participants in the switch group.
[d]Data are missing for 5 participants in the soma/soma group.
Abbreviations: HSDS, height SD score; HV, height velocity; HVSDS, height velocity SD score; IGF-I SDS, IGF-I SD score; soma, somapacitan.

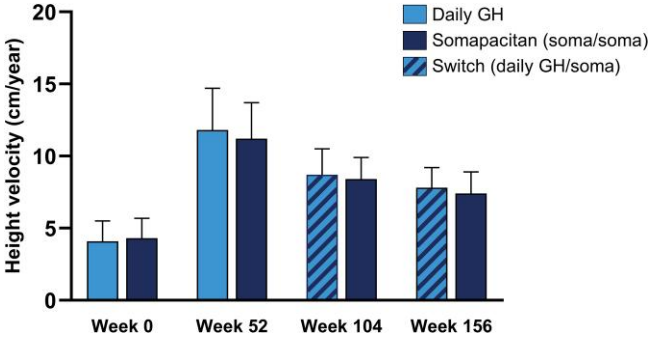

Figure 2. Observed HV from baseline to week 156. Observed mean HV (cm/year) at baseline (week 0), week 52, week 104, and week 156 for the soma/soma and switch groups. Data are presented as mean with error bars representing SD and are based on the in-trial observation period [ie, the time from first administration and up until visit 15 (week 156) or last trial contact, whichever comes first]. HV, height velocity; soma, somapacitan.

Total IGF-I

Change in mean IGF-I SDS from baseline to week 156 was similar between the groups (Table 2). During the safety extension (week 52 to 156), the IGF-I SDS and IGFBP-3 SDS peak and trough levels remained stable in both groups (Figure 4A, B). After 156 weeks, weekly average IGF-I SDS calculated from pharmacokinetic/pharmacodynamic modelling suggests similar mean values that are within the intended normal range (−2.0 to +2.0 SDS) for both treatment groups: +0.76 and +0.88 for the soma/soma and switch groups, respectively (Figure 5).

Total IGF-I/IGFBP-3 molar ratio

Mean IGF-I/IGFBP-3 molar ratios were similar for both treatment groups and fluctuated around 20% depending on sampling time (ie, peak, average, or trough level samples). In the soma/soma group, mean (SD) IGF-I/IGFBP-3 molar ratios at baseline, week 52 (average), and 156 (trough) were 10.0% (2.9), 19.8% (6.5), and 19.4% (6.7), respectively. In the switch group, mean (SD) IGF-I/IGFBP-3 molar ratios at baseline, week 52 (average), and 156 (trough) were 9.4% (3.3), 19.3% (5.8), and 19.8% (8.0), respectively.

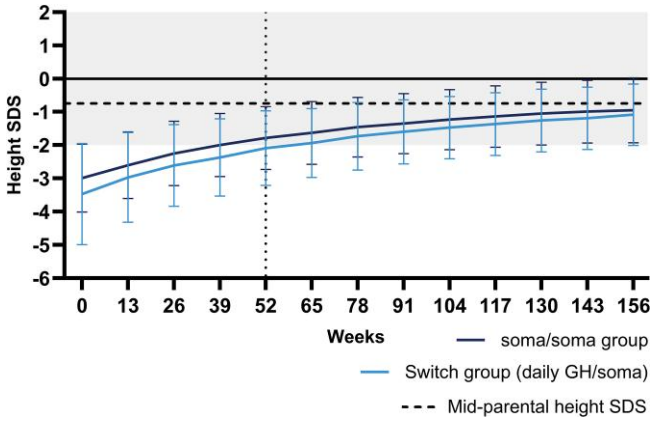

Figure 3. Sustained increase in HSDS from baseline to week 156 for both treatment groups. Observed mean HSDS from baseline to week 156. The gray area indicates normal range (−2.0 to 2.0 SDS), and the horizontal dashed line indicates the mean mid-parental height SDS of −0.74 across the groups. In the individual groups, the mean mid-parental height SDS is −0.68 and −0.86 in the soma/soma group and switch group, respectively. The vertical dotted line indicates when all participants were assigned to somapacitan at week 52. During the first 52 weeks, the soma/soma group received somapacitan, and the switch group received daily GH. Data are presented as mean with error bars representing SD and are based on the in-trial observation period [ie, the time from first administration and up until visit 15 (week 156) or last trial contact, whichever comes first]. HSDS, height SD score; soma, somapacitan.

Bioactive IGF-I concentrations

During the first 52 weeks of treatment, bioactive IGF-I increased from baseline and reached similar levels at week 13 (trough sampling) in the groups. At week 26 (peak sampling), the soma/soma group (receiving somapacitan) had numerically higher levels compared with the switch group (receiving daily GH until week 52) with geometric means [coefficient of variation percent (CV%)] of 0.93 ng/mL (48.9%) and 0.77 ng/mL (42.3%), respectively (Figure 4C). At week 78 (peak sampling), where both groups received somapacitan, the bioactive IGF-I levels geometric means (CV%) were 0.95 ng/mL (46.0%) ng/mL and 0.90 ng/mL (52.2%) in the soma/soma group and switch group, respectively, and 0.66 ng/mL (53.5%) and 0.75 ng/mL (58.5%), respectively at week 104 (trough sampling). Mean change (SD) from baseline were 0.64 (0.41) ng/mL and 0.61 (0.41) ng/mL at week 78 (peak sampling) and 0.35 (0.34) ng/mL and 0.45 (0.39) ng/mL at week 104 (trough sampling) in the soma/soma group and switch group, respectively. The trajectories for bioactive IGF-I over time varied by sampling time, especially for the soma/soma group (Figure 4C), while the trajectories for the bioactive IGF-I to IGF-I ratio kept more stable after baseline and were more similar between the groups (Figure 4D). The mean (SD) bioactive IGF-I to IGF-I ratio decreased from baseline [baseline value of 1.12 (1.28) % across groups], reaching a level of 0.48 (0.23) % and 0.55 (0.27) % in the soma/soma group and switch group, respectively, at week 104.

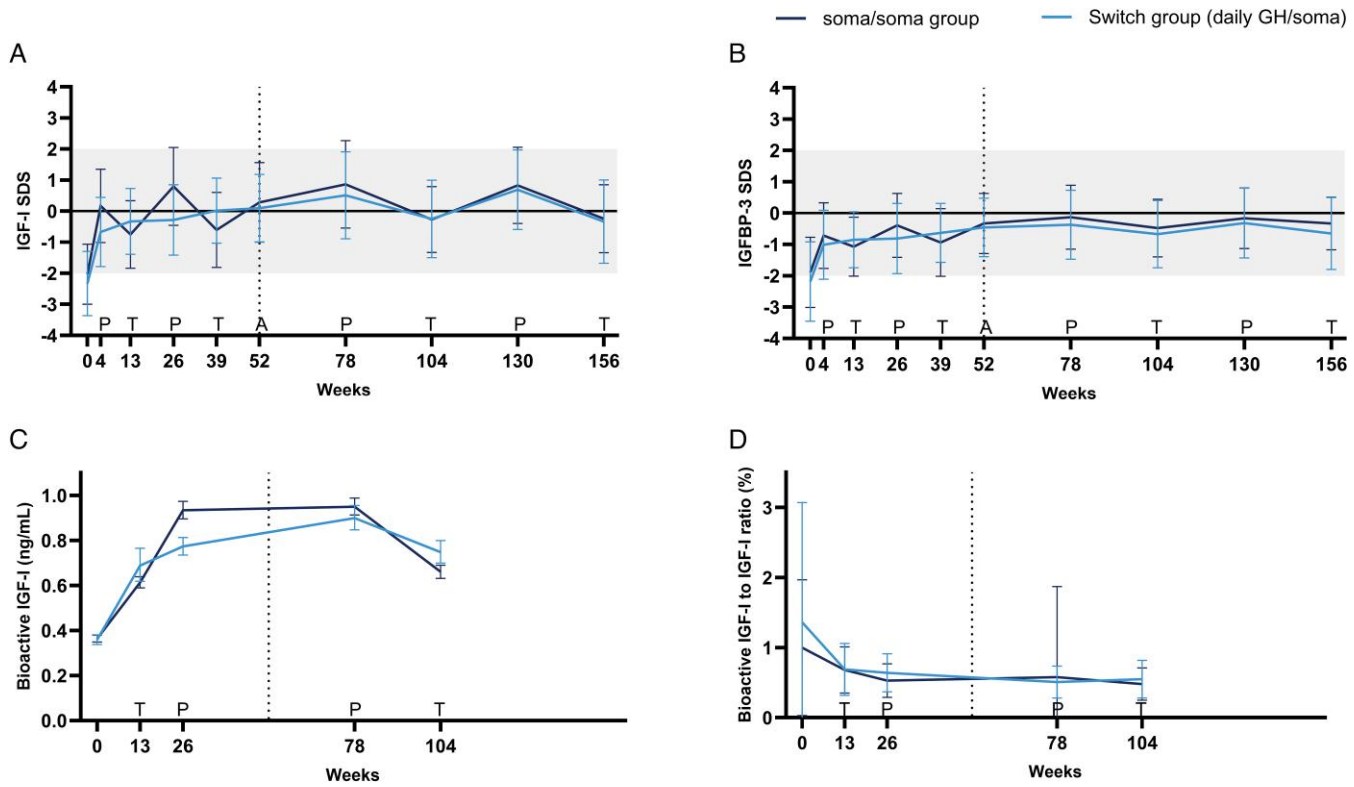

Figure 4. Observed pharmacodynamic endpoints from baseline to week 156. Observed values from baseline to 156 weeks for (A) IGF-I SDS, (B) IGFBP-3 SDS, (C) bioactive IGF-I, and (D) bioactive IGF-I to total IGF-I ratio. Blood samples for IGF-I, IGFBP-3 and bioactive IGF-I measurements in participants treated with somapacitan were taken at day 1-4 after dosing ('P", around peak level), day 4-6 after dosing ('A", around average level), and day 7 after dosing ('T", around trough level). The gray area indicates normal range (−2.0 to 2.0 SDS). The vertical dotted line indicates when all were assigned to somapacitan at week 52. During the first 52 weeks, the soma/soma group received somapacitan, and the switch group received daily GH. Data are presented as mean with error bars representing SD and are based on the in-trial observation period for panel (A, B, and D), and as geometric means with mean ± standard error to the mean on log-scale back transformed (error bars) for panel (C). Data on bioactive IGF-I was available for a total of 197 participants at baseline and 192 participants at week 104. IGFBP-3, IGF-binding protein 3; SDS, SD score; soma, somapacitan.

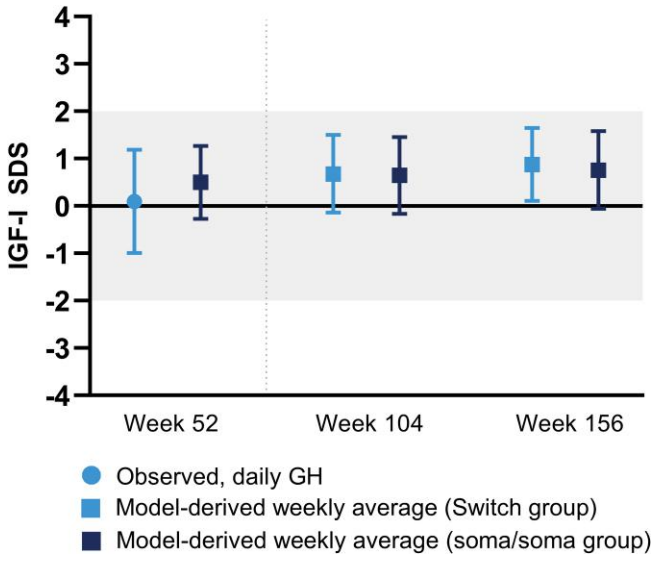

Figure 5. IGF-I SDS remained within normal range. Model-derived weekly average IGF-I SDS for somapacitan treatment and observed IGF-I SDS for daily GH. The vertical dotted line indicates when all were assigned to somapacitan at week 52. During the first 52 weeks, the soma/soma group received somapacitan, and the switch group received daily GH. Data are presented as mean with error bars representing SD. SDS, SD score; soma, somapacitan.

Safety results

Adverse events

The number of participants with AEs in year 3 (weeks 104-156) was 82 (64.6%) and 45 (67.2%) for soma/soma and switch groups, respectively (Table 3). Most AEs were mild or moderate in severity and judged unlikely related to the trial product. In total, 7 (5.5%) of the participants in the soma/soma group reported 10 serious AEs, while 2 were reported in the switch group by 2 (3.0%). One of the serious AEs (lipoatrophy) in the soma/soma group was not resolved and was deemed probably related to trial product. The lipoatrophy was in the left upper arm, and it was not clear whether this was the primary injection site and proper rotation between different body parts could have been lacking. Two other serious AEs reported by a participant in the soma/soma group were deemed possibly related to trial product (lipoma and pharyngotonsillitis). The remaining serious AEs were all reported recovered/resolved and deemed unlikely to be related to trial product.

The most common AEs, observed in ≥5% of the participants in both groups during year 3, were mostly events commonly observed in children such a viral infection, nasopharyngitis, influenza, vomiting, and pyrexia, as well as cases of COVID-19. There were no deaths, and no participants discontinued the treatment due to AEs. The treatment

Table 3. Adverse events week 104-156.

	Soma/soma group ($n = 127$)			Switch group ($n = 67$)		
	N (%)	*E*	*R*	*N* (%)	*E*	*R*
All adverse events	82 (64.6)	239	190.0	45 (67.2)	111	171.3
Serious adverse events	7 (5.5)	10	8.0	2 (3.0)	2	3.1
Severity						
Mild	73 (57.5)	191	151.8	41 (61.2)	95	146.6
Moderate	28 (22.0)	43	34.2	14 (20.9)	15	23.1
Severe	3 (2.4)	5	4.0	1 (1.5)	1	1.5
Relation to trial product						
Probable	5 (3.9)	7	5.6	1 (1.5)	2	3.1
Possible	12 (9.4)	18	14.3	2 (3.0)	2	3.1
Unlikely	78 (61.4)	214	170.1	45 (67.2)	107	165.1

On-treatment observation period [ie, the time from first administration and up until last trial contact, visit 15 (week 156) or 14 days after last administration, whichever comes first].
Abbreviations: %, percentage of participants; E, number of events; *N*, number of participants; R, event rate per 100 patient-years at risk; soma, somapacitan.

changes due to AEs included reducing the dose in 2 (3.0%) participants in the switch group and interrupting the treatment temporarily in 1 (1.5%) participant in the switch group and 2 (1.6%) participants in the soma/soma group.

IGF-I SDS

Consistent with observations from year 1 and 2 of the REAL4 study, the vast majority of children receiving somapacitan in year 3 had observed IGF-I values within normal range (−2.0 to +2.0 SDS). During weeks 104 to 156, IGF-I levels >+2.0 SDS were measured at some point in 24 (19.1%) and 8 (12.3%) participants in the soma/soma and switch groups, respectively. Values above +2.0 SDS reported at 2 consecutive visits during this period occurred in 2 (1.7%) and 1 (1.7%) of the participants in the soma/soma and switch groups, respectively. The number of participants that at some time during year 3 had an IGF-I value exceeding +2.5 SDS was 14 (11.1%) and 3 (4.6%) in the soma/soma and switch groups, respectively, with participants exceeding +3.0 SDS were 4 (3.2%) and 1 (1.5%), respectively. One participant (0.8%) in the soma/soma group had an IGF-I value exceeding +2.5 SDS at 2 consecutive visits during year 3. No AEs were reported for this participant, and a very small dose reduction was performed. No trend was seen in the amount or type of AEs reported in participants with IGF-I levels >+2.0 SDS at 2 consecutive visits during the extension period (week 52-156).

Other safety assessments

Consistent with observations in year 1 and 2 of the REAL4 study, there were few reports of children experiencing injection site reactions during year 3 (Table 4). One participant in the soma/soma group (0.8%) reported injection site pain (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 HbA_{1c}) in either treatment group. No neutralizing anti-drug antibodies were detected in either treatment group. Antibodies did not appear to affect pharmacokinetic or pharmacodynamic profiles or annualized HV.

Table 4. Injection site reactions week 104-156.

	Soma/soma group ($n = 127$)			Switch group ($n = 67$)		
	N (%)	*E*	*R*	*N* (%)	*E*	*R*
All injection site reactions	4 (3.1)	6	4.8	1 (1.5)	1	1.5
Bruising	0			0		
Haematoma	0			0		
Pain	1 (0.8)	1	0.8	0		
Haemorrhage	0			0		
Mass	0			0		
Reaction	1 (0.8)	1	0.8	0		
Erythema	2 (1.6)	4	3.2	0		
Swelling	0			1 (1.5)	1	1.5
Hypersensitivity	0			0		
Macule	0			0		

On-treatment observation period [ie, the time from first administration and up until last trial contact, visit 15 (week 156) or 14 days after last administration, whichever comes first].
Abbreviations: %, percentage of participants; E, number of events; *N*, number of participants; R, event rate per 100 patient-years at risk; soma, somapacitan.

Discussion

The current study presents novel efficacy and safety data for children with GHD treated with once-weekly somapacitan in the third year of the REAL4 study. Previously, in the main phase (52 weeks), non-inferiority in HV was demonstrated for 0.16 mg/kg/week somapacitan compared with 0.034 mg/kg/day daily GH.[16] These findings accompanied similar safety and weekly average IGF-I levels between treatment groups for children with GHD.[16] The current study period shows that somapacitan continues to be well tolerated and shares a similar safety profile to the well-known profile for daily GH with sustained efficacy after 3 years of treatment with somapacitan (soma/soma group), as well as after 2 years of somapacitan treatment following the switch from daily GH at week 52 (switch group). Finally, in addition to total IGF-I analyses, novel IGF-I/IGFBP-3 molar ratio and bioactive IGF-I data presented here suggest similar IGF-I response between somapacitan and daily GH treatments at both the level of total IGF-I and the bioactive fraction of IGF-I.

It is noteworthy that the small numerical difference observed in HV between the groups during the first and second year of treatment also persists after 3 years: mean HV at week 52 for somapacitan ("soma/soma" group) and daily GH ("switch" group) was 11.2 and 11.7 cm/year, respectively;[16] mean HV at week 104 for soma/soma and switch groups was 8.4 and 8.7 cm/year, respectively;[17] while mean HV at week 156 reported here for soma/soma and switch groups was 7.4 and 7.8 cm/year, respectively. This suggests that the 2 groups are following their growth potential, rather than a difference in treatment (once-weekly somapacitan vs daily GH) per se. This aligns with recent findings indicating that baseline gene expression patterns in blood samples can predict responses to both once-weekly somapacitan and daily GH treatment.[27]

The small numerical differences observed for HSDS between treatment groups at baseline have gradually become smaller as the children grow. After 3 years of replacement

treatment in the REAL4 study, the vast majority of the children have reached a height within normal range (−2.0 to +2.0 SDS). We note for the first time that in the REAL4 study, observed height increases in both groups begin to approach mean mid-parental HSDS at week 156. Taken together with improvements in HVSDS, these results confirm sustained efficacy for somapacitan in both groups.

During the course of the study, pharmacodynamic endpoints were largely within normal range with few participants having elevated IGF-I SDS values defined as >+2.0 SDS. Our findings for IGF-I/IGFBP-3 molar ratio seem consistent with a previous study. Gaddas et al.[28] assessed the IGF-I/IGFBP-3 molar ratio in 92 children with growth deficiency (majority with GHD) before and after initiating GH treatment and compared their levels with those of healthy children of same age/sex and observed an initial increase in IGF-I/IGFBP-3 molar ratio, after which the ratio stayed within normal range for most children.[28] In our study, we observed a similar pattern, with mean values largely within the ranges observed in healthy age/sex-matched children.[28]

While the total IGF-I SDS and bioactive IGF-I levels increased, the proportion of bioactive IGF-I decreased from around 1% at baseline and stabilized around 0.5% after baseline. A similar pattern was seen for the REAL5 study, where children born small for gestational age were treated with different doses of daily GH or somapacitan.[29] In that study, geometric mean bioactive IGF-I of nearly 1 ng/mL and mean bioactive IGF-I to total IGF-I ratio of around 0.5% were reached at week 8 (peak sampling), which is similar to what was observed in the present study at week 26 and 78 (peak samplings). Another study of children born small for gestational age showed that when total IGF-I concentrations vary, bioactive IGF-I SDS tend to stay within the normal reference ranges.[30]

In previous studies it has been shown that participants/caregivers experienced with both daily GH and once-weekly somapacitan treatments (eg, switching from daily GH treatment in year 4 of the REAL3 study and year 2 of the REAL4 study) report a strong or very strong preference for once-weekly somapacitan over daily GH with none reporting a preference for the daily GH treatment regimen.[17,19] Consistently, a reduced treatment burden has also been reported for once-weekly somapacitan compared with daily GH.[15,16,18] Adherence to once-weekly somapacitan in the REAL4 study continues to be high as is expected in a controlled trial. In a real-world setting, it is possible that this could translate into higher adherence to once-weekly somapacitan when compared with daily GH and, therefore, potentially better growth and health outcomes for treated children with GHD.

The potential benefits of LAGHs could also be relevant in other disorders commonly treated with daily GH. Somapacitan is currently in phase 3 clinical development for the treatment of short stature in children born small for gestational age, Turner syndrome, Noonan syndrome, and idiopathic short stature (REAL8, NCT05330325; REAL9, NCT05723835). Results from the phase 2 randomized controlled global REAL5 study suggest somapacitan 0.24 mg/kg/week offers the same efficacy and safety profile as daily GH for treatment of short stature in children born small for gestational age.[29]

This trial had some limitations. Blinding of the participants was not possible during the main phase,[16] since this would require a placebo ("double dummy treatment"), which is not considered ethical in this population. The blood samples for assessing IGF-I, IGFBP-3 and bioactive IGF-I were taken at various time points after somapacitan dosing (either around peak, average, or trough level). This was done in order to enable pharmacokinetic/pharmacodynamic modelling but challenges the interpretation of the measured values slightly. This trial had several strengths. Overall, few participants withdrew from the study and adherence to treatment was high.

In conclusion, this study confirmed sustained efficacy with similar safety, tolerability, and IGF-I response for both groups: continuous somapacitan for 3 years (soma/soma) and somapacitan for 2 years following the switching from daily GH treatment at week 52 (switch group). Reassuringly, in year 3 (the second year of the REAL4 safety extension), growth-related outcomes and safety profiles were similar in both treatment groups. Bioactive IGF-I and bioactive IGF-I to IGF-I ratio were similar between both groups, including during the first 52 weeks of treatment when the switch group was receiving daily GH. Longer-term safety and efficacy monitoring in REAL4 is currently ongoing into the fourth and final year of the study. A plain language summary of this work is available at Miller et al.[31]

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Data availability

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