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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

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Abstract

Objectives: Somatrogon is a long-acting recombinant human growth hormone (GH) employed as a once-weekly treatment for children with GH deficiency (GHD). A 12-month, phase 2 study of once-weekly somatrogon vs. once-daily GH (Genotropin®) was initiated, after which participants could enroll into an open-label extension (OLE) evaluating the safety and efficacy of long-term somatrogon treatment.

Methods: There were five study periods, Periods I and II were 6 months each while Periods III, IV, and V were 12 months each. In the main study (Periods I and II), 53 prepubertal children with GHD were randomized to once-weekly somatrogon (0.25, 0.48, or 0.66 mg/kg/week) or once-daily Genotropin (0.034 mg/kg/day); 48 continued into the OLE, consisting of Period III (original somatrogon dose; Genotropin recipients randomized to one of three somatrogon doses), Period IV (somatrogon 0.66 mg/kg/week), and Period V (prefilled somatrogon pen [0.66 mg/kg/week]).

Results: At the end of Period III, the mean ± SD annual height velocity (HV) for 0.25, 0.48, and 0.66 mg/kg/week somatrogon groups was 7.73 ± 1.89, 7.54 ± 1.28, and 8.81 ± 1.12 cm/year, respectively; HV was sustained during Periods IV/V. Height SD scores (SDS) showed progressive improvement throughout the OLE, regardless of initial cohort assignment, approaching the normal range (−0.69 ± SD 0.87) at the end of Period V Year 1. Mild or moderate treatment-emergent adverse events were reported in 81.3% of participants, most unrelated to study drug.

Conclusions: Up to 5 years of once-weekly somatrogon was well tolerated and resulted in sustained improvement in height SDS and delta height SDS in prepubertal short children with GHD. Clinicaltrials.gov:NCT01592500.

Keywords: children; Genotropin; growth hormone; growth hormone deficiency; height velocity; IGF-1; long-acting growth hormone; pediatric; somatrogon; somatropin.

Introduction

Human growth hormone (hGH) is critical for linear growth and for accrual of lean body mass. Growth hormone (GH) deficiency (GHD) in children results in impaired linear growth. Recombinant hGH (rhGH) is a well-established, effective treatment for children with short stature due to multiple growth disorders, including GHD [1]. Most of the currently available rhGH products require daily subcutaneous (SC) injections, due to the short half-life of rhGH. However, poor treatment compliance has been identified as one of the main issues with daily SC rhGH injections [2–4] that, if sustained, can result in significantly slower linear growth, with consequently shorter adult height potential [2]. Long-acting forms of GH that require less-frequent injections are particularly attractive and could potentially improve treatment adherence and response to treatment, compared with daily injections of rhGH [5].

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Somatrogon (MOD-4023) is a long-acting rhGH currently approved in Canada, Australia, Japan, the United Kingdom, and the European Union as a once-weekly treatment for children with GHD. Somatrogon consists of the amino acid sequence of hGH fused to three copies of the C-terminal peptide (CTP) from the β-chain of human chorionic gonadotropin. Animal studies showed that fusion of hGH to CTP significantly increased the serum half-life of the molecule relative to hGH [6] and a study in healthy adults showed that somatrogon had a pharmacokinetic and pharmacodynamic profile that supported once-weekly dosing [7]. Studies in adults with GHD showed somatrogon could be administered as a once-weekly injection, which resulted in similar efficacy to once-daily rhGH (Genotropin®) [8].

Zelinska and coauthors reported results of a phase 2 study in prepubertal children with GHD that compared the safety, tolerability, and efficacy of three dose levels of once-weekly somatrogon (0.25, 0.48, or 0.66 mg/kg/week) with once-daily Genotropin (0.24 mg/kg/week) [9]. The estimated half-life of somatrogon was ~18.3–36.1 h, which was approximately 5- to 10-fold longer than that of once-daily Genotropin. All three somatrogon-treated cohorts demonstrated adequate catch-up growth with dose-dependent responses. The cohort that received the highest dose of somatrogon (0.66 mg/kg/week) achieved the highest annualized mean (±standard deviation [SD]) height velocity (HV), which was closest to that of children who received once-daily Genotropin (somatrogon: 11.9 ± 3.5 cm/year vs. Genotropin: 12.5 ± 2.1 cm/year).

Participants who completed 12 months of somatrogon treatment in this main study were eligible to be enrolled into an open-label extension (OLE) study, the data of which are reported here. Participants received somatrogon for up to an additional 5 years following completion of the main study. The principal objective of this OLE study was to evaluate the safety and efficacy of long-term exposure to somatrogon in children with GHD.

Methods

Study design and treatment

This was a phase 2, open-label, randomized, dose-finding, safety study (NCT01592500) of three different once-weekly somatrogon doses (0.25, 0.48, or 0.66 mg/kg/week) in initially prepubertal children with GHD. This study comprised five treatment periods (Supplementary Figure 1) and was sponsored by OPKO Health. The main study consisted of two active treatment periods (Periods I and II), each lasting 6 months. During Period I, all three somatrogon cohorts received once-weekly somatrogon at 0.25 mg/kg/week for the first 2 weeks, with doses increased in a stepwise manner every 2 weeks up to the maximum allocated dose, which was then maintained for the remainder of Period I. In Period II, participants continued their originally allocated Period I dose. Participants who completed the main study and provided written consent were enrolled into the OLE study, which followed participants for up to 5 additional years of exposure to once-weekly somatrogon.

The OLE study consisted of three periods (Periods III, IV, and V) (Supplementary Figure 1). Period III consisted of an additional 12 months at the original somatrogon dose level; participants who received Genotropin in the main study were re-randomized to one of the three somatrogon dose regimens. Period IV consisted of Years 2–4 of the OLE, during which time all participants transitioned to receive once-weekly somatrogon at 0.66 mg/kg/week. Participants in Period V (PEN) transitioned from single-use vials of somatrogon (SC injection via needle and syringe) to a prefilled pen device at the same somatrogon dose (0.66 mg/kg/week). Period V is still ongoing (until marketing approval). Data up to August 2019 (including 1 year of Period V) are reported herein.

The secondary objective of this study was to evaluate growth outcomes with long-term treatment with once-weekly somatrogon (i.e., beyond the initial 12-month main study). The research related to human use complied with all the relevant national regulations and institutional policies, was in accordance with the tenets of the Helsinki Declaration and International Conference on Harmonisation Good Clinical Practice guidelines, and has been approved by the authors' institutional review board or independent ethics committee of the participating institutions. The Data Safety Monitoring Board met approximately every 6 months to review any safety concerns. Signed consent was obtained from each participant's parents/legal guardian(s) prior to commencement of the main study; where appropriate, the child's assent was also obtained. Participants who chose to continue into the OLE study provided signed consent forms.

Participants

As described previously ([9]), participants were enrolled in the main study if they met the following inclusion criteria: (1) prepubertal children (boys aged 3–11 years and girls 3–10 years) with isolated GHD or GHD as part of multiple pituitary hormone deficiency; (2) diagnosis of GHD confirmed by two different GH provocation tests (peak plasma GH level of ≤10 ng/mL) using a validated assay (insulin tolerance/arginine/clonidine/glucagon (with or without propranolol)/L-dopa plus propranolol); (3) bone age not older than chronological age (≤9 years for girls and ≤10 years for boys); (4) no previous exposure to rhGH therapy; (5) impaired height and HV (height standard deviation score (SDS) ≤−2.0 for chronological age and sex, and annualized HV <25th percentile (HV<−0.7 SDS) for chronological age and sex, according to standard growth charts of Prader et al. [10]; (6) body mass index (BMI) within ±2 SD of mean BMI for chronological age and sex according to the 2,000 Centers for Disease Control and Prevention standards [11]; (7) baseline IGF-I SDS level ≤−1.0 for chronological age and sex; (8) no signs/symptoms of intracranial hypertension; (9) children with multiple hormonal deficiencies were required to be on stable replacement therapy for at least 3 months (or 6 months for thyroid replacement therapy) prior to the first dose of study

drug; (10) for girls, normal 46 XX karyotype; and (11) written informed consent provided by parent or legal guardian of the patient and assent provided by the patient.

Participants who had completed 12 months of treatment in the main study period were eligible to continue to receive once-weekly somatrogon treatment in the OLE study.

Study assessments

Anthropometric assessments

Annual HV was assessed at every 12-month interval and change in height SDS and bone maturation (based on bone age X-ray) were assessed every 12 months. Height was measured using a calibrated, wall-mounted (Harpenden or similar) stadiometer, and weight was measured using a digital scale, with children wearing minimal clothing. Participants were defined to have achieved final height if the HV for the previous 6-month interval was <1 cm/year.

Study assays

IGF-1

As described previously [9], IGF-1 concentrations were measured by chemiluminescent immunoassay (IDS-iSYS IGF-1 kits) with an intra-assay coefficient of variation that was equal to or less than 10%. The SDS of the value was calculated per sample. Study participants with persistent IGF-1 SDS >2 had their treatment dose reduced by 15%.

Immunogenicity assessments

Assessment of antidrug antibodies (ADAs) and neutralizing antibodies (NAbs) against somatrogon were performed at Months 6 and 12 of Period III and every 12 months thereafter. As previously described [9], ADA-positive samples were confirmed for somatrogon specificity, and somatrogon-binding antibodies were analyzed for CTP- and hGH specificity. Samples with anti-somatrogon antibodies were also analyzed for anti-somatrogon and anti-hGH neutralizing activity by mean of a cell-based assay.

Safety

Safety evaluations included monitoring of all adverse events (AEs), including serious AEs (SAEs) and local injection site reactions, vital signs, electrocardiograms, physical examination, and laboratory assessments (thyroid status, hematology, blood biochemistry, glucose and lipid metabolism, insulin-like growth factor-1 [IGF-1] levels, immunogenicity, and urinalysis). Analyses of routine hematology and serum biochemistry parameters, and glucose and lipid parameters, as well as hormonal (thyroid) status were performed at a central laboratory. AEs were coded using the Medical Dictionary for Regulatory Activities, version 20.1. Treatment-emergent AEs (TEAEs) for each 12-month period were defined as those that started in each 12-month period and separately for Period V. TEAEs of special interest were reported under the system organ classes for immunogenicity and hypersensitivity, thyroid function impairment, arthralgia, injection site reactions, glucose metabolism impairment, scoliosis, myalgia, and edema.

Adherence

Adherence to somatrogon treatment was assessed by comparing the expected vs. actual number of doses administered. Patients' diaries and injection vials were returned for accountability (split doses were excluded).

Statistical analyses

All participants were included in the full analysis set. Statistical analyses were descriptive, and no formal hypothesis testing was performed. The primary safety endpoints included the incidence of AEs and ADA formation, assessment of local site injections, IGF-1 levels, and IGF-1 SDS, as well as laboratory assessments. The secondary endpoints included annual HV, change in height SDS, and annual bone maturation.

Results

Patients and treatment

Of the 53 participants who completed the main study, 48 participants from seven countries were randomized and entered Period III of the OLE study (Figure 1). At the beginning of Period III, approximately half the participants were <7 years old. The majority of participants were male (66.7%) and almost all the participants were White (93.8%) (Supplementary Table 1). All participants, except for one, were prepubertal Tanner stage I at the beginning of the OLE study (Supplementary Table 1).

There were only two discontinuations during Period III, with 46 (95.8%) participants completing this period; none of the discontinuations during Period III were due to an AE

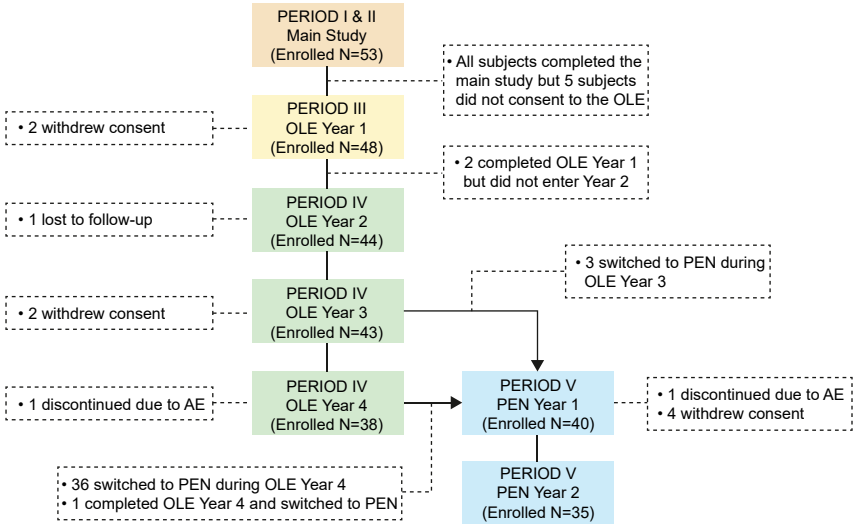

Figure 1: Participant disposition.
AE, adverse event; OLE, open-label extension; PEN, somatrogon delivery via pen device.

(Supplementary Table 2). Four discontinuations occurred during Period IV, one of which was due to an AE (scoliosis; Supplementary Table 3). During Period V (PEN), there were eight discontinuations: seven participants withdrew from the study and one discontinued treatment due to an AE (osteochondrosis; Supplementary Table 3). The completion rates for each OLE period (Periods III, IV, and Year 1 of Period V) ranged from 87.5 to 97.7% (Supplementary Tables 2 and 3). The total duration of treatment is shown in Supplementary Table 4. Across the OLE study (Periods III to V), participants had a mean compliance rate of 98%.

Efficacy

At the end of Period III, the somatrogon 0.25 and 0.48 mg/kg/week cohorts had similar mean (SD) annual HVs of 7.73 (1.89) cm/year and 7.54 (1.28) cm/year, respectively. The mean (SD) annual HV in the 0.66 mg/kg/week cohort (8.81 [1.12] cm/year) was higher than in the lower dose cohorts, consistent with the results reported at 12 months in the main study [9]. The mean annual HV observed in Periods IV and V (Figure 2) indicated a sustained growth response, irrespective of whether participants had been assigned to receive somatrogon or Genotropin in the main study. Following the transition to the pen device (Period V), the mean annual HV was similar to that in the previous 6- and 12-month timepoints during which single-use vials were employed.

Mean height SDS progressively increased from the main study baseline (–3.98 [SD 1.22]) throughout the OLE and was within the normal range (–0.69 [SD 0.87]) by the end of the first year of Period V (Table 1, Figure 3). There were no clinically meaningful differences in mean height SDS, regardless of whether somatrogon or Genotropin was administered in the main study (Figure 4). The cohorts that received somatrogon 0.25 and 0.48 mg/kg/week had similar

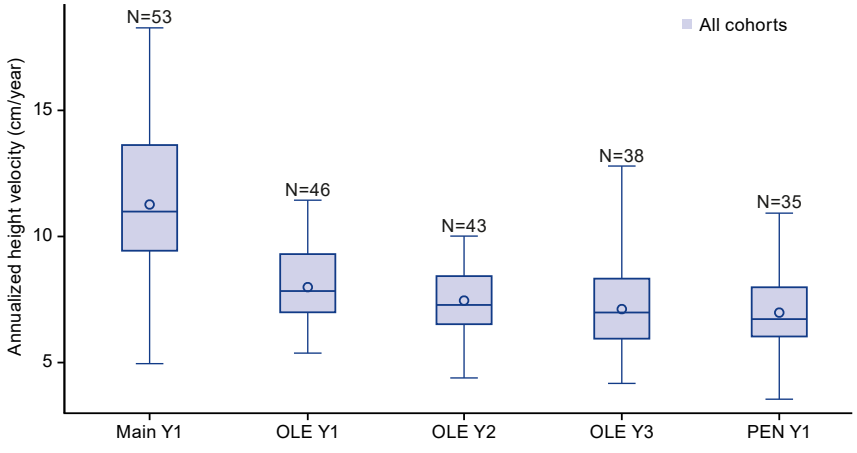

Figure 2: Annualized height velocity for all cohorts combined at each year of study. The upper whisker represents maximum, and the lower whisker represents minimum. Box is first and third quartiles; the circle is the mean, and the horizontal line is the median. Number of participants is shown above the whiskers.
OLE, open-label extension; PEN, somatrogon delivery via pen device; Y, Year.

Table 1: Height SDS at the end of Periods III (Year 1 of OLE), IV (Years 2–4 of OLE), and V (PEN): full analysis set.

	Year 1 (N=48)	Year 2 (N=44)	Year 3 (N=43)	PEN (N=40)
Height SDS (Z) at end of year				
n	46	43	38	35
Mean, SD	−2.06	−1.59	−1.27	−0.69
	(0.85)	(0.80)	(0.93)	(0.87)
Median	−1.93	−1.39	−1.19	−0.66
Minimum, maximum	−4.51,	−4.06,	−3.90,	−2.86,
	−0.61	−0.18	0.27	1.50

N, participants who entered the study period; n, participants with Height SDS for the study period; PEN, somatrogon delivery via prefilled pen device; SDS, standard deviation score.

cumulative changes in height SDS at the end of each year. The changes in height SDS observed for the 0.66 mg/kg/week cohort were consistently higher than for the lower dose cohorts at the end of the main study and each year of Periods III to V. None of the participants in the study had achieved final adult height at the time of this analysis.

Participants in all three somatrogon dose cohorts exhibited a similar increase in bone maturation at the end of Period III (Supplementary Table 5); these findings were consistent with the results of the main study. Consistent increases in bone maturation were also observed across Periods IV and V, showing continued bone maturation over time. The pace of bone age maturation was congruent with chronologic age advancement.

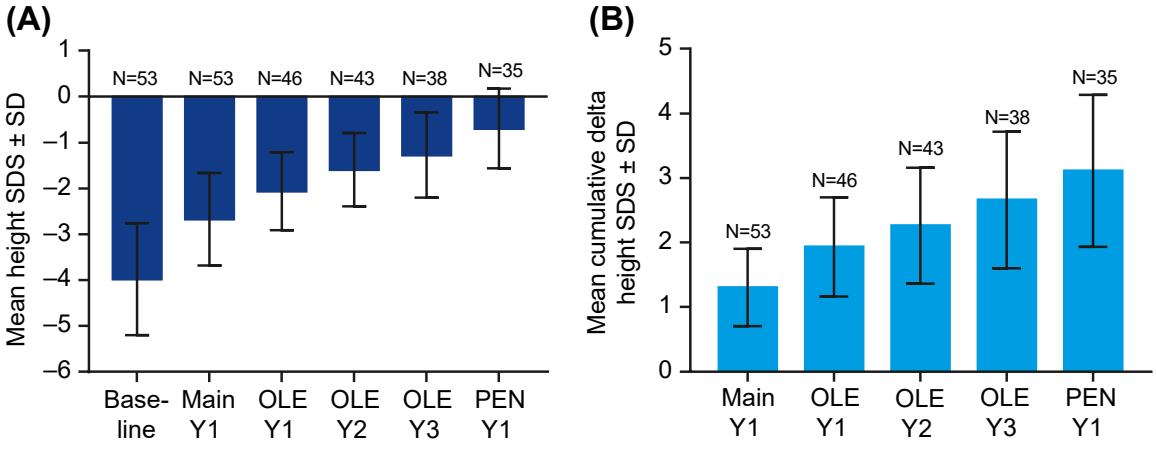

Figure 3: Mean height SDS (A) and mean cumulative delta height SDS (B) for each year of the study (all cohorts combined). Number of participants is shown above the bars. OLE, open-label extension; PEN, somatrogon delivery via pen device; SDS, standard deviation score; Y, Year.

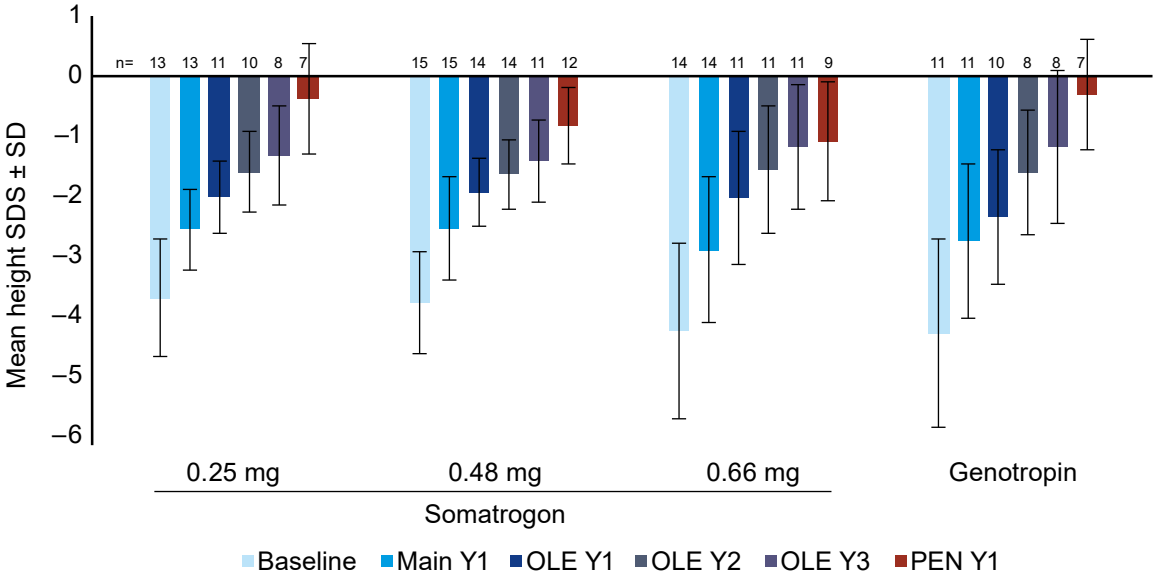

Figure 4: Summary of height SDS by year of study and initial cohort assignment: full analysis set. OLE, open-label extension; PEN, somatrogon delivery via pen device; SDS, standard deviation score; Y, Year.

Table 2: Summary of participants with TEAEs during the OLE study: full analysis set.

n, % [No. of AEs]	Overall (N=48)	Year 1 (N=48)	Year 2 (N=44)	Year 3 (N=43)	Year 4 (N=38)	PEN (N=40)
TEAE	39 (81.3) [257]	25 (52.1) [78]	22 (50.0) [48]	18 (41.9) [39]	15 (39.5) [25]	24 (60.0) [67]
Serious TEAE	3 (6.3) [4]	2 (4.2) [2]	1 (2.3) [1]	0	1 (2.6) [1]	0
TEAE, study-drug-related	7 (14.6) [14]	0	1 (2.3) [1]	1 (2.3) [4]	2 (5.3) [6]	3 (7.5) [3]
TEAE leading to study drug withdrawal	2 (4.2) [2]	0	0	0	1 (2.6) [1]	1 (2.5) [1]
TEAE leading to study drug reduction or interruption	4 (8.3) [4]	0	1 (2.3) [1]	0	2 (5.3) [2]	1 (2.5) [1]
TEAE leading to study discontinuation	2 (4.2) [2]	0	0	0	1 (2.6) [1]	1 (2.5) [1]
Deaths	0	0	0	0	0	0

AE, adverse event; N, number of participants who entered the study period; n, number of participants with event; OLE, open-label extension; PEN, somatrogon delivery via prefilled pen device; TEAEs, treatment-emergent adverse event.

Safety

A total of 39 (81.3%) participants reported at least one TEAE during the OLE study (Table 2). Most TEAEs were mild or moderate in intensity and the majority was considered unrelated to study treatment (Table 2, Supplementary Table 6). The most commonly reported TEAEs were upper respiratory tract infections (27.1%) and bronchitis (22.9%) (Supplementary Table 6). Three (6.3%) participants reported at least one SAE. All SAEs were considered unrelated to study treatment, except for one instance of scoliosis, which the investigator considered unexpected and probably related to study treatment. No deaths occurred during the OLE. No injection site reactions were reported while somatrogon was administered using single-use vials and syringes in Periods III and IV. During Period V, when a pen device was used for administration, three participants reported injection site reactions (bruising in two participants and erythema in one participant), which were mild to moderate in intensity. Most TEAEs of special interest were considered unrelated or unlikely to be related to study treatment. The four TEAEs of special interest that were considered possibly or probably related to study treatment were two instances of scoliosis (one mild and one severe) during Period IV and one instance of mild hypercholesterolemia and one instance of mild injection site bruising during Period V. Two participants discontinued the OLE study due to TEAEs. As indicated previously, one participant had a severe instance of scoliosis that occurred during Period IV Year 4 and was considered probably related to study treatment. The second TEAE leading to participant discontinuation was osteochondrosis of moderate severity in PEN Year 1; this TEAE was considered unlikely to be related to study treatment.

Measurements of glucose metabolism, thyroid status, cortisol levels, lipid parameters, and hematology/chemistry were within normal limits, similar to the findings from the main study (Supplementary Table 7). Although there were isolated, individual observations of IGF-1 SDS >2, none were persistent. The mean (SD) IGF-1 SDS for all participants were similar at the end of OLE Year 1 (Period III) and Year 2 (Period IV), with values of 0.64 (0.96) and 0.65 (1.08), respectively (Table 3). Mean (SD) IGF-1 SDS increased by the end of OLE Year 3 (Period IV) and the first year of Period V, with values of 1.05 (0.82) and 1.29 (0.81), respectively. Mean IGF-1 SDS was <2 across all time points in Periods III to V.

Table 3: IGF-1 SDS at the end of Period III (Year 1 of OLE), Period IV (Years 2–4 of OLE), and Period V (PEN): full analysis set.

	Total year 1 (N=48)	Year 2 (N=44)	Year 3 (N=43)	Year 4 (N=38)	PEN (N=40)
IGF-1 SDS (Z) at end of year					
n	43	41	38	1	35
Mean, SD	0.64	0.65	1.05	0.29	1.29
	(0.96)	(1.08)	(0.82)	(–)	(0.81)
Median	0.58	0.68	1.09	0.29	1.25
Minimum, maximum	−1.66, 2.64	−2.23, 2.69	−0.96, 2.92	0.29, 0.29	−0.34, 2.71

N, participants who entered the study period; n, participants with IGF-1 SDS at end of period; IGF-1, insulin-like growth factor 1; OLE, open-label extension; PEN, somatrogon delivery via prefilled pen device; SD, standard deviation; SDS, standard deviation score.

Immunogenicity

A total of 18 (37.5%) of 48 participants tested positive for ADAs during the OLE study. Of these 18 participants, 10 also had ADAs in the main study and five had received Genotropin. Among the participants who tested positive for ADAs, specificity for hGH (anti-hGH) and CTP (anti-CTP) was observed in 16/18 and 3/18 participants, respectively. No clinically meaningful differences in annual HV or TEAEs were observed between ADA-positive and ADA-negative participants. None of the participants tested positive to NAbs during the OLE study.

Discussion

This is the first long-term study to describe the efficacy and safety of somatrogon in participants with GHD. Participants treated with once-weekly somatrogon for up to 5 years in the OLE study demonstrated sustained improvement in growth parameters, including annual HV, height SDS, and change in height SDS. This improvement in linear growth was observed with somatrogon administration using either single-use vials or pen devices during Periods III to V. Height SDS approached normal (zero) during the OLE study (Periods III to V), indicating mean height for age and gender was achieved following once-weekly somatrogon treatment, consistent with findings from the main study period [9]. Sustained growth response was preserved in participants who originally received daily Genotropin for 12 months in the main study and were subsequently switched to somatrogon. Progressive gains in height SDS and change in height SDS were observed at the end of Periods IV to V for all treatment groups, regardless of initial cohort assignment. The two cohorts that received the lowest doses (0.25 and 0.48 mg/kg/week) showed similar increases in mean height SDS and change in height SDS across the OLE (Periods III, IV, and V), though these increases were not as large as those observed in the 0.66 mg/kg/week cohort.

Once-weekly dosing of somatrogon for up to 5 years in the OLE, including the transition to the pen device, was well tolerated in children with pediatric GHD. The incidence and types of TEAEs reported in the OLE were consistent with what was reported in the main study [9]. There were no new or unexpected safety signals identified in the OLE, which included Period V when participants were switched to the pen device.

The high level of adherence observed (>90%) throughout the 5 years of the OLE period suggests participants are able to maintain long-term treatment with once-weekly somatrogon. Given that the mean duration of rhGH treatment may be as long as 10 years [12], long-term adherence to treatment is essential to maximize treatment efficacy, as poor compliance [2, 13] or early cessation [3] in patients with GHD have been associated with reductions in linear growth and treatment response. Given the challenges of adhering to once-daily GH injections and the fact that patients and caregivers have shown a preference for a less-frequent injection schedule [14], the results from this long-term study (acknowledging the relatively small number of patients) indicate that once-weekly somatrogon may be a valuable treatment option for patients with GHD, with the potential to improve treatment adherence. Despite requiring less-frequent injections compared with daily Genotropin, once-weekly somatrogon has a similar efficacy and safety profile as Genotropin.

An important consideration during treatment is the timing of IGF-1 sampling, given that the sampling results are used to guide dose adjustments. For rhGH products that require daily administration, most sampling times provide reasonable estimates of the average IGF-1 SDS, due to the fact that fluctuations over the 24-h dosing interval are modest. However, for long-acting GH treatments that are administered weekly, fluctuations in the IGF-1 profile over the dosing interval are likely to be larger compared with daily GH treatments. Whether the wider variation (relative to daily GH) in IGF-I concentration post dosing is secondary to inherent differences in metabolism related to adiposity or other factors, the mechanisms underlying these observations are not well understood. Given the larger fluctuations, to obtain an accurate estimate of the mean IGF-1 SDS over the longer dosing interval of long-acting GH products such as somatrogon and somapacitan [15], the timing of IGF-1 sampling relative to dose administration is critical. IGF-1 concentration data from the main part (Period I/II) of this study were analyzed using pharmacokinetic/pharmacodynamic analytical methods, as previously reported by Fisher et al. [16]. This analysis showed mean IGF-1 SDS over the 1-week dosing interval following somatrogon administration was best approximated by IGF-1 assessments 4 days (96 h) after dose administration. IGF-1 assessments made 2–3 days after drug administration represent peak IGF-1 SDS levels. These elevated IGF-1 levels are transient and decrease over the dosing interval; there is presently little evidence that such intermittent elevations in IGF-1 are detrimental [17, 18]. Further, IGF-1 elevations are observed in normal growth, with high IGF-1 levels contributing to the longitudinal growth spurt during puberty. With the goal of maintaining IGF-1 SDS within the normal range where possible during the GH treatment period, we would suggest that mean/average IGF-1 levels (measured at 4 days post somatrogon administration) are a more useful measure of safety as they represent the overall systemic exposure to IGF-1 levels.

A key strength of this study is that it provides safety and efficacy data on patients receiving somatrogon over an extended (5-year) period. An additional strength of this study is that data were collected from participants who originally received once-daily Genotropin and were subsequently switched to once-weekly somatrogon, allowing comparison of participants who were switched vs. those who received somatrogon continuously. One limitation of this OLE study was that somatrogon was the only drug evaluated over the extended treatment period.

Conclusions

In this long-term study of once-weekly somatrogon for up to 5 years, participants showed improvement in annual HV, height SDS, and change in height SDS. Sustained growth response during the OLE period was demonstrated in treated participants, regardless of whether they received once-weekly somatrogon or once-daily Genotropin during the main study. The safety and tolerability profile of once-weekly somatrogon during the OLE was excellent and similar to that observed during the main study. These findings, coupled with the high level of adherence observed, suggest that once-weekly somatrogon is an effective, long-term treatment option for children with GHD.

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Informed consent: Signed consent was obtained from each participant's parents/legal guardian(s) prior to commencement of the main study; where appropriate, the child's assent was also obtained. Participants who chose to continue into the OLE study provided signed consent forms.

Ethical approval: The research related to human use complied with all the relevant national regulations and institutional policies, was in accordance with the tenets of the Helsinki Declaration and International Conference on Harmonisation Good Clinical Practice guidelines, and has been approved by the authors' institutional review board or independent ethics committee of the participating institutions.

Data sharing statement: Upon request, and subject to review, Pfizer will provide the data that support the findings of this study. Subject to certain criteria, conditions, and exceptions, Pfizer may also provide access to the related individual de-identified participant data. See https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information.

References

1. Collett-Solberg PF, Jorge AAL, Boguszewski MCS, Miller BS, Choong CSY, Cohen P, et al. Growth hormone therapy in children; research and practice – a review. Growth Hormone IGF Res 2019;44:20–32.
2. Cutfield WS, Derraik JG, Gunn AJ, Reid K, Delany T, Robinson E, et al. Non-compliance with growth hormone treatment in children is common and impairs linear growth. PLoS One 2011;6:e16223.
3. Hughes IP, Choong C, Rath S, Atkinson H, Cotterill A, Cutfield W, et al. Early cessation and non-response are important and possibly related problems in growth hormone therapy: an OZGROW analysis. Growth Hormone IGF Res 2016;29:63–70.
4. Rosenfeld RG, Bakker B. Compliance and persistence in pediatric and adult patients receiving growth hormone therapy. Endocr Pract 2008; 14:143–54.
5. 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;25:267–73.
6. Hershkovitz O, Bar-Ilan A, Guy R, Felikman Y, Moschcovich L, Hwa V, et al. In Vitro and in vivo characterization of MOD-4023, a long-acting carboxy-terminal peptide (CTP)-modified human growth hormone. Mol Pharm 2016;13:631–9.
7. Kramer WG, Jaron-Mendelson M, Koren R, Hershkovitz O, Hart G. Pharmacokinetics, Pharmacodynamics, and safety of a long-acting human growth hormone (MOD-4023) in healthy Japanese and Caucasian adults. Clin Pharmacol Drug Dev 2018;7:554–63.
8. Strasburger CJ, Vanuga P, Payer J, Pfeifer M, Popovic V, Bajnok L, et al. MOD-4023, a long-acting carboxy-terminal peptide-modified human growth hormone: results of a phase 2 study in growth hormone-deficient adults. Eur J Endocrinol 2017;176:283–94.

9. Zelinska N, Iotova V, Skorodok J, Malievsky O, Peterkova V, Samsonova L, et al. Long-acting C-terminal peptide-modified hGH (MOD-4023): results of a safety and dose-finding study in GHD children. J Clin Endocrinol Metab 2017;102:1578–87.
10. Prader A, Largo RH, Molinari L, Issler C. Physical growth of swiss children from birth to 20 years of age. First Zurich Longitudinal Study of Growth and Development. Helv Paediatr Acta Suppl 1989;52:1–125.
11. Kuczmarski RJ, Ogden CL, Grummer-Strawn LM, Flegal KM, Guo SS, Wei R, et al. CDC growth charts: United States. Adv Data 2000:1–27.
12. Straetemans S, De Schepper J, Thomas M, Tenoutasse S, Beauloye V, Rooman R. Criteria for first-year growth response to growth hormone treatment in prepubertal children with growth hormone deficiency: do they predict poor adult height outcome? Front Endocrinol 2019;10:792.
13. Kapoor RR, Burke SA, Sparrow SE, Hughes IA, Dunger DB, Ong KK, et al. Monitoring of concordance in growth hormone therapy. Arch Dis Child 2008;93:147–8.
14. McNamara M, Turner-Bowker DM, Westhead H, Yaworsky A, Palladino A, Gross H, et al. Factors driving patient preferences for growth hormone deficiency (GHD) injection regimen and injection device features: a discrete choice experiment. Patient Prefer Adherence 2020;14:781–93.
15. Juul Kildemoes R, Hojby Rasmussen M, Agerso H, Overgaard RV. Optimal monitoring of weekly IGF-I levels during growth hormone therapy with once-weekly somapacitan. J Clin Endocrinol Metab 2021; 106:567–76.
16. Fisher DM, Rosenfeld RG, Jaron-Mendelson M, Amitzi L, Koren R, Hart G. Pharmacokinetic and pharmacodynamic modeling of MOD-4023, a long-acting human growth hormone, in growth hormone deficiency children. Horm Res Paediatr 2017;87:324–32.
17. Allen DB, Backeljauw P, Bidlingmaier M, Biller BM, Boguszewski M, Burman P, et al. GH safety workshop position paper: a critical appraisal of recombinant human GH therapy in children and adults. Eur J Endocrinol 2016;174:1–9.
18. Johannsson G, Bidlingmaier M, Biller BMK, Boguszewski M, Casanueva FF, Chanson P, et al. Growth hormone research society perspective on biomarkers of GH action in children and adults. Endocr Connect 2018;7:R126–r34.

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