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Efficacy and Safety of Once-Weekly Somatrogon Compared with Once-Daily Somatropin (Genotropin®) in Japanese Children with Pediatric Growth Hormone Deficiency: Results from a Randomized Phase 3 Study

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Keywords
Growth hormone · Growth hormone deficiency · Long-acting growth hormone · Somatrogon · Genotropin

Abstract

Introduction: Somatrogon is a long-acting recombinant human growth hormone being developed as a once-weekly treatment for children with growth hormone deficiency (GHD). The objective of this phase 3 study (NCT03874013) was to compare the efficacy and safety of once-weekly somatrogon with once-daily Genotropin in Japanese children with GHD. ***Methods:*** In this open-label, randomized, active-controlled study, 44 prepubertal Japanese children with GHD (boys: 3 to <11 years; girls: 3 to <10 years) were randomized 1:1 to receive once-weekly somatrogon or once-daily Genotropin (0.025 mg/kg/day) for 12 months. Dose escalation for somatrogon-treated subjects occurred in the first 6 weeks (0.25, 0.48, and 0.66 mg/kg/week; 2 weeks each) with the remaining 46 weeks at a dose of 0.66 mg/kg/week. The study's primary endpoint was annualized height velocity (HV) at 12 months. ***Results:*** Baseline characteristics were similar between treatment groups. Compared with Genotropin-treated subjects, somatrogon-treated subjects had higher least-squares mean HV at 12 months (9.65 cm/year vs. 7.87 cm/year). Once-weekly somatrogon was concluded as being comparable to once-daily Genotropin as the mean treatment difference (somatrogon-Genotropin) in HV was +1.79 cm/year (95% confidence interval, 0.97–2.61), which was greater than the preestablished margin (−1.8 cm/year). For both treatment groups, most adverse events were mild to moderate in severity and a similar proportion of subjects reported injection-site pain, although the somatrogon group reported more painful injections. ***Conclusion:*** In prepubertal Japanese children with GHD, once-weekly somatrogon was comparable to once-daily Genotropin in terms of annualized (12-month) HV. Both treatments had similar safety and tolerability profiles.

This study is registered at ClinicalTrials.gov (NCT03874013).

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Introduction

Growth hormone deficiency (GHD) in children is associated with abnormal linear growth, manifesting as short stature and reduced age-related height velocity (HV) [1]. GHD is also associated with metabolic alterations, resulting in dyslipidemia and insulin resistance as well as an increased risk of cardiovascular disease [2]. Recombinant human growth hormone (rhGH) is a well-established treatment for children with GHD, and its safety and effectiveness have been demonstrated in more than 30 years of clinical use. The primary goal of rhGH therapy in children is to increase growth velocity and enable attainment of an adequate adult height [3]. In addition to normalizing adult height, rhGH also enables early "catch-up growth" in children [4], which has been demonstrated to have positive effects on the physiology and psychology of children with GHD [5, 6].

The majority of rhGH products that are currently available require daily subcutaneous (SC) injections, due to their short half-life [7]. Daily treatment for GHD can constitute a significant burden for both children and their caregivers [8]. Injection pain/discomfort [9], storage and reconstitution of medication, and interruption to daily activities are some of the factors that have been identified as treatment-related burdens. These factors make it difficult to adhere to daily SC injections, as has been observed in several studies, resulting in missed doses [10] and poor persistence with treatment [11]. Nonadherence can lead to poor treatment response, with treated children demonstrating suboptimal longitudinal and "catch-up" growth [4, 10, 11]. A long-acting form of rhGH that requires less frequent administration may reduce the discomfort and distress of daily injections, leading to improved adherence and treatment efficacy [12]. A recent study of Japanese children with GHD showed a clear preference for a once-weekly injection schedule over a once-daily injection schedule [13].

Somatrogon (MOD-4023) is a long-acting rhGH currently being developed for the treatment of children with GHD. Somatrogon consists of the amino acid sequence of hGH fused to 3 copies of the C-terminal peptide from the β-chain of human chorionic gonadotropin. Previous studies have shown that fusion of C-terminal peptide to target proteins results in increased stability of the target, thereby improving half-life and bioavailability [14, 15]. In studies in healthy Japanese adult volunteers, somatrogon had a half-life of approximately 22 h and was well tolerated [16].

A randomized, dose-finding phase 2 study in European children with GHD evaluated the safety, tolerability, and efficacy of 3 different doses (0.25, 0.48, or 0.66 mg/kg/week) of somatrogon administered once weekly in comparison with daily injections of rhGH (Genotropin; 0.24 mg/kg/week) [17]. Somatrogon was observed to have a half-life of approximately 18–36 h compared with Genotropin's 3.5 h. Children in all somatrogon dose cohorts achieved adequate catch-up growth after 12 months of treatment [17]. Children who received the highest dose of somatrogon (0.66 mg/kg/week) had a mean annualized HV (11.9 ± 3.5 cm/year) that was closest to that of children who received daily Genotropin (12.5 ± 2.1 cm/year).

Following the dose-finding study, a global, randomized phase 3 study (NCT02968004) in prepubertal children with GHD conducted in 21 countries (not including Japan) demonstrated the noninferiority of once-weekly somatrogon (0.66 mg/kg/week) compared with daily Genotropin (0.24 mg/kg/week) [18]. Given that ethnicity has been shown to affect exposure and responses to certain drugs [19], including growth hormone (GH) therapy [20], it was important to assess the efficacy and safety of somatrogon across a broad range of ethnicities. Based on this rationale, a phase 3, open-label, randomized, multicenter study (NCT03874013) was initiated to evaluate the efficacy and safety of somatrogon administered once weekly compared with Genotropin administered once daily in prepubertal Japanese children with GHD.

Materials and Methods

Study Design and Treatment

This phase 3 study was a 12-month, open-label, randomized, active-controlled, parallel-group study of the efficacy and safety of once-weekly somatrogon compared with once-daily Genotropin in Japanese prepubertal children with GHD; this study was sponsored by OPKO and Pfizer (NCT03874013). Following a 4-week screening period, subjects were randomized 1:1 to receive once-weekly somatrogon or once-daily Genotropin for 12 months via SC injection using a pen device. Subjects in the somatrogon group received once-weekly SC injections of somatrogon in 3 escalating doses (0.25, 0.48, and 0.66 mg/kg/week; 2 weeks at each dose) for 6 weeks. After this period, subjects continued to receive somatrogon once weekly at a dose of 0.66 mg/kg/week for 46 weeks. Subjects in the Genotropin group received once-daily SC injections of Genotropin at 0.025 mg/kg/day or 0.175 mg/kg/week, which is the approved Genotropin dose in Japan. Subjects who completed the 12-month main study were eligible to participate in a single-arm, long-term, open-label extension involving once-weekly administration of somatrogon. During the study, doses of somatrogon and Genotropin were adjusted every 3 months, based on the subject's body weight. Doses were decreased if required, based on predefined dose-adjustment criteria, which included treatment-related severe adverse events (AEs) and repeated elevated levels of insulin-like growth factor-1 (IGF-1; >+2 standard deviation scores [SDS]).

The primary objective of this study was to demonstrate that the annual (12-month) HV from once-weekly somatrogon administration is comparable to once-daily Genotropin administration in Japanese children with GHD. The secondary objectives were to evaluate the safety and tolerability of somatrogon administered once weekly in Japanese children with GHD, to characterize other growth parameters (change in height SDS and bone age/maturation) and biochemical markers (IGF-1 and insulin-like growth factor-binding protein 3 [IGFBP-3]) associated with GH therapy, and to evaluate the pharmacokinetic (PK) and pharmacodynamic (PD) profiles of 3 different doses of once-weekly somatrogon.

Subjects

Prepubertal children (boys: 3 to <11 years; girls: 3 to <10 years) with a confirmed diagnosis of GHD were eligible for enrollment in this study if they had a height SDS ≤−2, an impaired HV (below the 25th percentile for chronological age), and a baseline IGF-1 level that was at least 1 SD below the age- and sex-standardized mean IGF-1 levels (SDS ≤−1) [21] and had not received prior rhGH therapy. Diagnosis of GHD had to be confirmed by 2 different GH provocation tests (peak serum GH level of ≤6.0 ng/mL or ≤16 ng/mL for a GH-releasing peptide-2 provocation test). Subjects were excluded if they had any prior history of cancer or had received radiation therapy or chemotherapy. Subjects who were malnourished (body mass index <−2 SDS [age and sex standardized]), were born small for their gestational age, or had anti-hGH antibodies at screening, diabetes mellitus, psychosocial dwarfism, or known or suspected chromosomal abnormalities or genetic/epigenetic variants (including Turner syndrome, Laron syndrome, Noonan syndrome, Prader-Willi syndrome, Silver-Russell syndrome, SHOX mutations/deletions, and skeletal dysplasias) were also excluded from the study.

Study Assessments

Efficacy

Height measurements were performed at screening, baseline, and months 3, 6, 9, and 12 (end of treatment) using a calibrated stadiometer; 3 independent readings were recorded for each visit and the mean was calculated. Height SDS was derived from age and gender according to the local primary care provider standard (national survey data from 2000) [22]. Annualized HV was calculated as the change in height from visit 2 (baseline) to visit 9 (month 12). Bone age was determined via X-ray according to the Tanner-Whitehouse 2 protocol using a central bone age reader at screening or baseline, and week 52.

PK and PD Assessments

For subjects in the somatrogon group, blood samples were collected 12–120 h post dose for the analysis of serum somatrogon and IGF-1 in accordance with sampling subblocks (online suppl. Table 1; see www.karger.com/doi/10.1159/000524600 for all online suppl. material). For each subject, 2 samples were collected during each of the 3 dosing periods (0.25, 0.48, and 0.66 mg/kg/week), with a total of 6 samples collected for each subject. The timing of the sample collection varied according to (i) the subblock subjects were assigned to and (ii) the current dosing period (online suppl. Table 1). Median concentrations were calculated for each dose using a naïve pooled estimate at each time point. Subjects who received Genotropin had blood samples collected regularly over the study period. IGF-1 concentrations were monitored to help assess compliance and response to treatment. With daily rhGH, there is no concern about the time after dose for the collection of samples because the peak:trough ratios are small and any observations are reflective of what would be observed over the dosing interval. Following once-weekly treatment with somatrogon, there may be significant peak:trough variability throughout the dosing interval. A recent PK/PD analysis by Fisher et al. [23] showed that the mean IGF-1 SDS over the 1-week dosing interval was best approximated by IGF-1 assessments 4 days (96 h) after dose administration. For this reason, blood samples for IGF-1 measurement for the somatrogon group were taken on day 4 post dose. Patients who had IGF-1 SDS >+2 on consecutive assessments (post-baseline) had their dose of study treatment reduced. Assessment of antidrug antibodies (ADAs) against somatrogon and Genotropin was performed at protocol-specified time points by Eurofins Pharma Bioanalytics Services US Inc. The development of binding and/or neutralizing antibodies (nAbs) against somatrogon was assessed using qualitative, validated methods as described by Zelinska et al. [17].

Safety

Safety evaluations included all AEs, concomitant medication use, treatment compliance, vital signs, electrocardiogram, physical examination, and laboratory assessments (hematology, blood chemistry, glucose metabolism, endocrinology, IGF-1 levels, immunogenicity, and urinalysis). An AE was defined as any adverse change from the subject's condition at baseline, regardless of whether it was considered related to the investigational product. AEs (including injection-site reactions) were assessed at all study visits; however, injection-site reactions were not assessed at predose visits 7 (month 6) and 9 (month 12). AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA, v22.1). The intensity or severity of an AE was characterized as mild, moderate, or severe. Subjects recorded data on AEs, concomitant medications, and injection-site reactions at home using a patient diary.

Any injection-site reactions that met the criteria for "abnormal" were assessed as AEs. An abnormal injection-site reaction was defined as a reaction that was moderate to severe in intensity, required medical attention, was deemed abnormal by the investigator, or had a pain score ≥4, based on the protocol-specified Pain Assessment Scale (ranging from 0 ["no hurt"] to 5 ["hurts worse"]). In the somatrogon group, the severity of injection-site pain after each weekly injection was recorded. In contrast, in the Genotropin group, only the most severe pain for the week was recorded (i.e., once a week), rather than after each daily injection. Where a Genotropin subject experienced multiple events of pain score ≥4, only 1 occurrence was recorded in the diary; hence, only 1 AE would be recorded.

Statistical Analyses

The full analysis set included all subjects who were randomized and received at least 1 dose of study treatment, and the safety set included all subjects who received at least 1 dose of study treatment. The primary efficacy endpoint was annual HV (cm/year) after 12 months of treatment. The goal of the primary efficacy analysis was to demonstrate that in terms of the primary efficacy endpoint (annual HV at 12 months), somatrogon administered once weekly is comparable to Genotropin administered once daily. Comparability of once-weekly somatrogon and once-daily Ge-

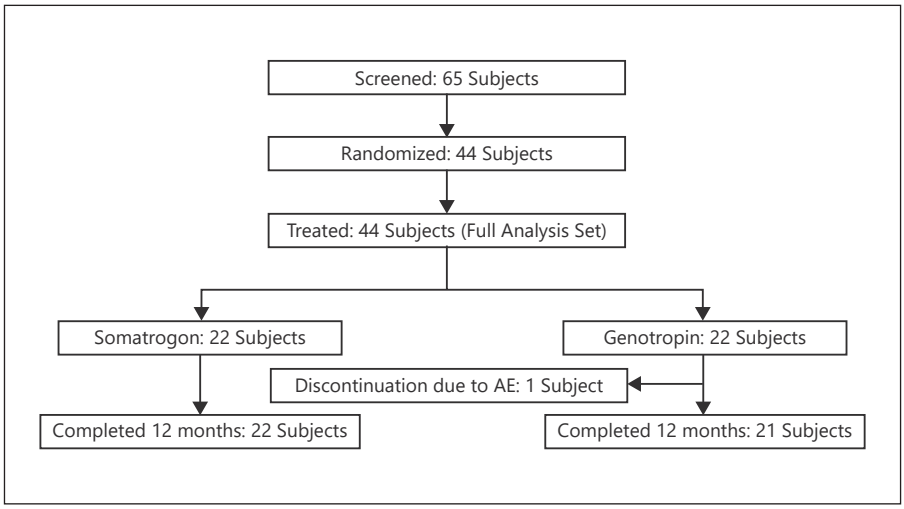

Fig. 1. Subject disposition. AE, adverse event.

Table 1. Subject demographics and baseline characteristics (safety analysis set)

	Somatrogon (n = 22)	Genotropin (n = 22)	Total (N = 44)
Mean (SD) age, years	5.28 (1.84)	6.78 (2.34)	6.03 (2.21)
Age group, *n* (%)			
≥3 to ≤7 years	19 (86.4)	12 (54.5)	31 (70.5)
>7 years	3 (13.6)	10 (45.5)	13 (29.5)
Sex, *n* (%)			
Male	9 (40.9)	12 (54.5)	21 (47.7)
Female	13 (59.1)	10 (45.5)	23 (52.3)
Peak GH level group,[a] *n* (%)			
Low	1 (4.5)	1 (4.5)	2 (4.5)
High	21 (95.5)	21 (95.5)	42 (95.5)
IGF-1 SDS (*Z*-score)			
Mean (SD)	−1.39 (0.90)	−1.62 (0.84)	−1.50 (0.87)
Median	−1.46	−1.42	−1.42
Range (min, max)	−3.48, 0.64	−3.74, −0.52	−3.74, 0.64
Mean IGF-1 (SD), µg/L	72.9 (33.5)	80.5 (30.7)	76.7 (32.0)
Height SDS (*Z*-score)			
Mean (SD)	−2.61 (0.44)	−2.53 (0.40)	−2.57 (0.42)
Median	−2.70	−2.48	−2.59
Range (min, max)	−3.38, −1.83	−3.45, −1.83	−3.45, −1.83

GH, growth hormone; GHRP-2, growth hormone-releasing peptide 2; IGF, insulin-like growth factor; max, maximum; min, minimum; SDS, standard deviation score. [a] Based on: ≤3 ng/mL or >3 to ≤6 ng/mL; or if GHRP-2 provocation test is used, ≤10 ng/mL or >10 to ≤16 ng/mL.

notropin was concluded for the primary efficacy endpoint if the point estimate of the mean treatment difference (somatrogon-Genotropin) was ≥−1.8 cm/year. The preestablished mean treatment difference of −1.8 cm/year was the noninferiority margin used in the phase 3 global study comparing once-weekly somatrogon with once-daily Genotropin. The mean and 95% confidence interval (CI) for HV at 12 months and the point estimate of the treatment difference were calculated using the least square (LS) means from an analysis of covariance model. The analysis of covariance model included terms for treatment and gender as factors and peak hGH value and baseline height SDS as covariates. The secondary efficacy endpoints were annualized HV following 6 months of treatment, change in height SDS at 6 and 12 months (compared with baseline), and change in bone maturation (defined as the ratio of bone age to chronological age) after 12 months (compared with bone maturation at screening).

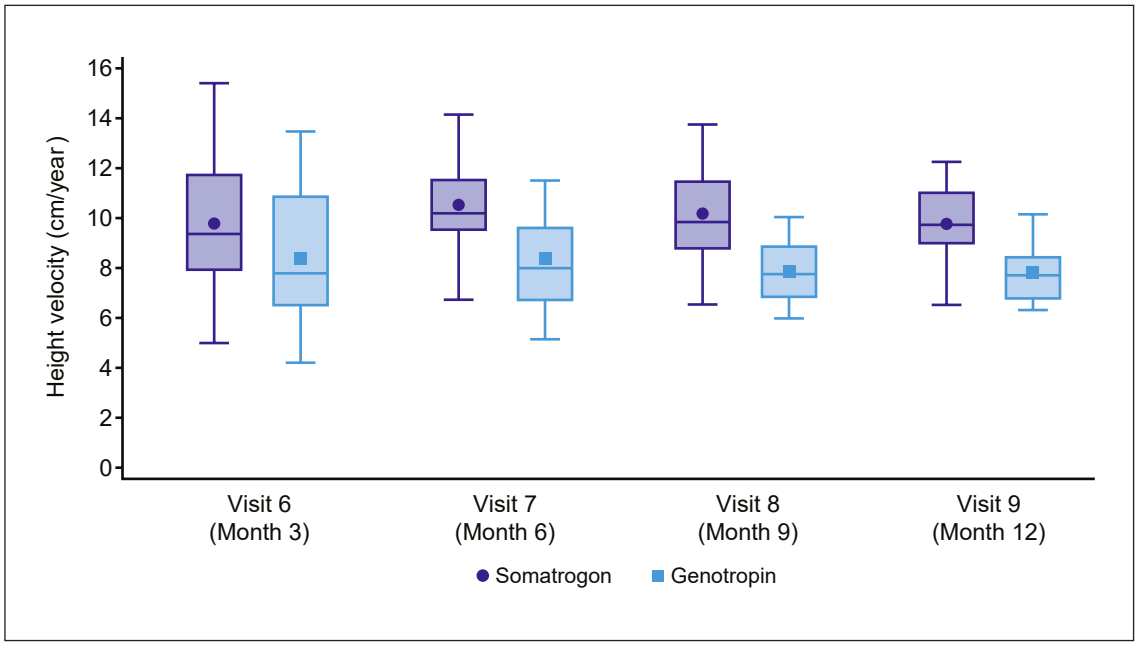

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Fig. 2. Box plot of height velocity over time (full analysis set). Baseline defined as the last nonmissing measurement prior to the start of study drug. Missing values are not imputed.

Results

Patients and Treatment

A total of 65 subjects were screened, and 44 subjects were randomized; all randomized subjects received at least 1 dose of study treatment (Fig. 1). Of the 44 subjects who received treatment, 43 completed the 12-month study. Most of the demographic and baseline characteristics were similar between the 2 treatment groups (Table 1). Approximately half (47.7%) of the subjects were male, and the majority of subjects (70.5%) were between 3 and 7 years of age. Due to the high proportion of subjects aged >7 years in the Genotropin group (10 [45.5%] subjects compared with 3 [13.6%] subjects in the somatrogon group), some baseline demographic characteristics (height and weight) were slightly higher in the Genotropin group.

Efficacy

At month 12, the LS mean for HV was 9.65 cm/year for the somatrogon group and 7.87 cm/year for the Genotropin group (online suppl. Table 2). The mean treatment difference (somatrogon-Genotropin) in HV was +1.79 cm/year (95% CI, 0.97–2.61), which was greater than the preestablished margin of −1.8 cm/year. Thus, once-weekly somatrogon was concluded as being comparable with once-daily Genotropin. The LS mean for HV at month 6 in the somatrogon group (10.35 cm/year) was also higher than in the Genotropin group (8.47 cm/year) (online suppl. Table 2). The resulting treatment difference for the LS mean HV was +1.88 cm/year (95% CI, 0.74–3.03). Mean HV values for the somatrogon group were higher than for the Genotropin group at months 3, 6, 9, and 12 of the study (Fig. 2). The LS mean change in height SDS from baseline to 12 months in the somatrogon group (0.94) was higher than in the Genotropin group (0.52) (online suppl. Table 2). The mean treatment difference for the change in height SDS was +0.42 (95% CI, 0.23–0.61). A similar trend was observed for the change in height SDS from baseline to 6 months, with a mean treatment difference of +0.26 (95% CI, 0.12–0.41).

The mean (SD) change in bone maturation at 12 months was 0.052 (0.065) and 0.035 (0.062) for the somatrogon and Genotropin groups, respectively. Mean bone maturation was <1.0 in both treatment groups at 12 months (somatrogon: 0.80; Genotropin: 0.80), and advancement in bone age did not exceed advancement in chronological age. The mean IGF-1 SDS (relative to baseline) increased across all post-baseline visits for the somatrogon treatment group (Fig. 3). In the Genotropin treatment group, mean IGF-1 SDS increased until month 6 and decreased at months 9 and 12. From week 2, mean

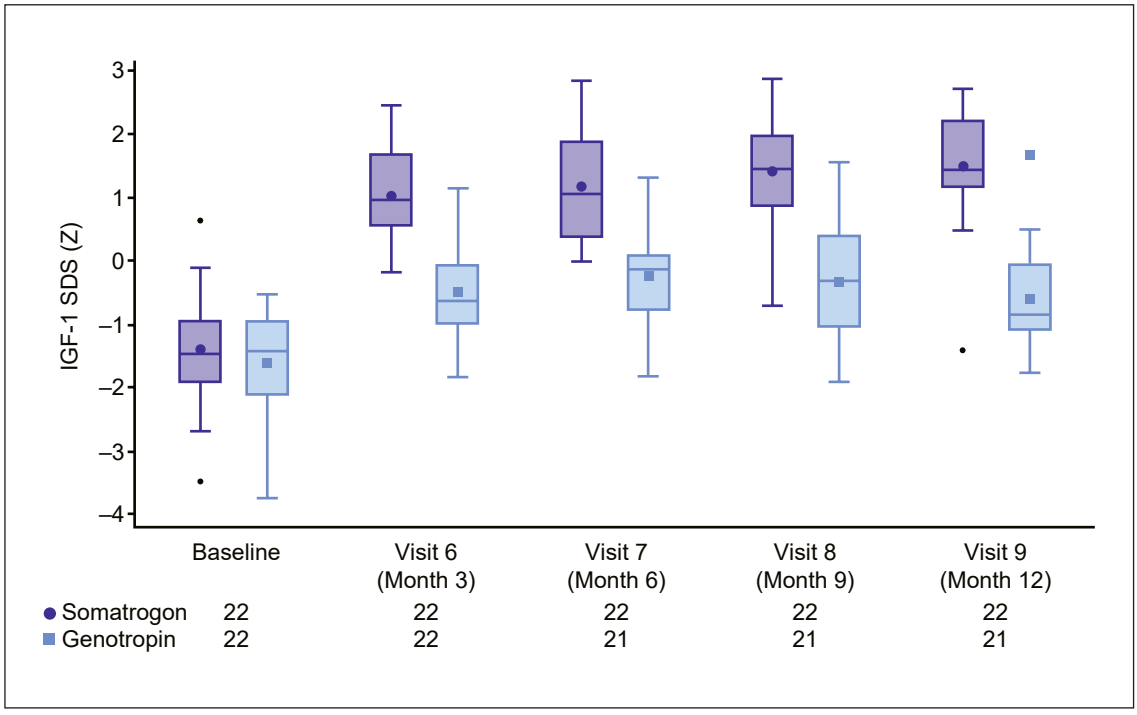

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Fig. 3. Box plot of IGF-1 SDS over time (full analysis set). SDS, standard deviation score.

Table 2. TEAEs (all causalities) – safety analysis set

	Somatrogon, *n* (%)	Genotropin, *n* (%)	Total, *N* (%)
Subjects evaluable for AEs	22	22	44
AEs, *n*	359	106	465
Subjects with AEs	22 (100.0)	19 (86.4)	41 (93.2)
Subjects with SAEs	2 (9.1)	2 (9.1)	4 (9.1)
Subjects with severe AEs	2 (9.1)	2 (9.1)	4 (9.1)
Subjects discontinued from the study due to AE[a]	0	1 (4.5)	1 (2.3)
Subjects discontinued the study drug due to AE and continued the study[b]	0	0	0
Subjects with dose reduced or temporary discontinuation due to AEs	0	0	0

SAEs are based on the investigator's assessment. AE, adverse event; SAE, serious adverse event. [a] Subjects who have an AE record that indicates that the AE caused the subject to be discontinued from the study. [b] Subjects who have an AE record that indicates that action taken with study treatment was drug withdrawn, but AE did not cause the subject to be discontinued from the study.

IGF-1 SDS values in the somatrogon group approached 0 SDS and remained above 0 SDS through month 12. Mean IGF-1 SDS values in the Genotropin group ranged from −0.59 to −0.25 SDS at all post-baseline visits.

Pharmacokinetics/Pharmacodynamics

Peak serum concentrations of somatrogon were achieved at 12–18 h after dosing, and the maximum concentration of somatrogon increased with increasing dosage (Fig. 4). The calculated median concentrations of IGF-1, IGF-1 SDS, and IGFBP-3 based on sparse sampling showed that somatrogon treatment resulted in an IGF-1 and IGFBP-3 response. Median IGF-1 SDS values did not exceed +2 SDS through the course of the week or at regular study visits over 12 months (Fig. 3).

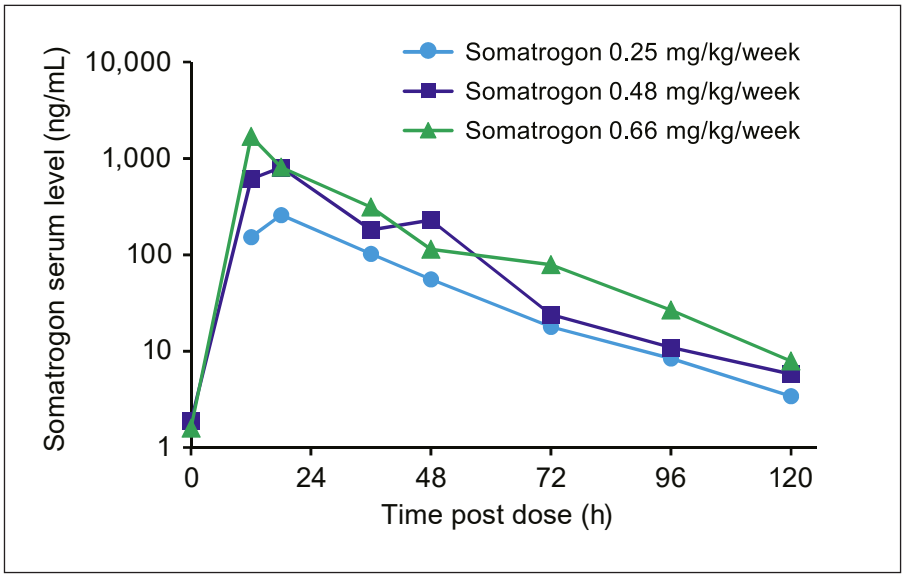

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Fig. 4. Median somatrogon serum concentration following once-weekly administration.

Safety

The mean duration of treatment was 367.6 days in the somatrogon group and 344.6 days in the Genotropin group. A total of 22/22 (100.0%) and 19/22 (86.4%) subjects reported all-causality AEs in the somatrogon and Genotropin groups, respectively (Table 2). Although the number of subjects reporting treatment-emergent AEs (TEAEs) was similar between the treatment groups, the incidence of TEAEs was higher in the somatrogon group (somatrogon: 359 events; Genotropin: 106 events). The primary cause for the difference in the incidence of TEAEs was the greater number of events of injection-site pain reported in the somatrogon group (somatrogon: 205 events; Genotropin: 8 events). The majority of the TEAEs in both treatment groups were mild to moderate in severity (somatrogon: 90.9%, Genotropin: 77.3%).

The incidence of serious AEs (SAEs) was low in both treatment groups (Table 2). Treatment-emergent SAEs were reported by 2 (9.1%) subjects in the somatrogon group (hypoparathyroidism, influenza, traumatic fracture, and febrile convulsion) and 2 (9.1%) subjects in the Genotropin group (craniopharyngioma and asthma). The event of craniopharyngioma reported in the Genotropin group was classified by the investigator as a treatment-related SAE and resulted in the subject being discontinued from the study. The most frequently reported all-causality AEs were nasopharyngitis (somatrogon: 54.5%; Genotropin: 50.0%), injection-site pain (somatrogon: 72.7%; Genotropin: 13.6%), influenza (somatrogon: 27.3%; Genotropin: 27.3%), pyrexia (somatrogon: 18.2%; Genotropin: 13.6%), and pharyngitis (somatrogon: 13.6%; Genotropin: 18.2%) (Table 3).

Table 3. All-causality treatment-related AEs reported in ≥10% of subjects in either treatment group

Subjects, *n* (%)	Somatrogon (*n* = 22)	Genotropin (*n* = 22)	Total (*N* = 44)
With any AE	22 (100.0)	17 (77.3)	39 (88.6)
Nasopharyngitis	12 (54.5)	11 (50.0)	23 (52.3)
Injection-site pain	16 (72.7)	3 (13.6)	19 (43.2)
Influenza	6 (27.3)	6 (27.3)	12 (27.3)
Pyrexia	4 (18.2)	3 (13.6)	7 (15.9)
Pharyngitis	3 (13.6)	4 (18.2)	7 (15.9)
Conjunctivitis	1 (4.5)	5 (22.7)	6 (13.6)
Gastroenteritis	4 (18.2)	2 (9.1)	6 (13.6)
Bronchitis	4 (18.2)	1 (4.5)	5 (11.4)
Vomiting	3 (13.6)	1 (4.5)	4 (9.1)
Eczema asteatotic	0	3 (13.6)	3 (6.8)

Subjects counted once per treatment per event. AE, adverse event.

The most commonly reported treatment-related AE was injection-site pain (pain score ≥4), which was reported by 72.7% and 13.6% of subjects in the somatrogon and Genotropin groups, respectively. Although the somatrogon group had a higher proportion of subjects with injection-site pain scores ≥4, the proportion of subjects who reported any injection-site pain (pain scores: 1–5) was similar between the somatrogon (100%) and Genotropin

groups (91%). The proportion of subjects reporting lower pain scores (1–3) was higher in the Genotropin group (77.3%) compared with the somatrogon group (27.3%). The severity of all reported AEs of injection-site pain in the somatrogon group was mild (15 subjects), with the exception of 1 subject who reported moderate injection-site pain. None of the subjects reported severe injection-site pain. Most events of injection-site pain were reported during the first 6 months of the study.

No deaths occurred during the study, and no subjects had a dose reduction due to an AE. A total of 5 subjects in the somatrogon group had IGF-1 SDS >+2 on consecutive assessments (post-baseline), which necessitated dose reductions for all 5 subjects. For the majority of subjects in both treatment groups, blood glucose and HbA1c (%) levels remained in the normal range for the following post-baseline visits: months 1, 3, 6, 9, and 12 for blood glucose and months 6 and 12 for HbA1c. Similarly, levels of thyrotropin and free thyroxine remained within the normal range for most post-baseline visits (months 3, 6, 9, and 12) for the majority of subjects in both treatment groups. Overall, there were no clinically meaningful differences observed between treatment groups in terms of glucose metabolism, hematology, chemistry, thyroid function, lipid profiles, and urinalysis parameters. The number of subjects in the somatrogon group who reported IGF-1 SDS >+2 at each visit was as follows: month 3: 3 (13.6%) subjects; month 6: 4 (18.2%) subjects; month 9: 5 (22.7%) subjects; and month 12: 6 (27.3%) subjects. None of the subjects in the Genotropin group reported IGF-1 SDS >+2.

Immunogenicity

A total of 18/22 subjects in the somatrogon group and 4/22 subjects in the Genotropin group tested positive for ADAs during the 12-month treatment period. Most subjects in the somatrogon group who tested positive for ADAs had ADAs that were specific for the hGH component of somatrogon. Two subjects in the somatrogon group tested positive for nAbs against somatrogon at a single visit but were negative for all subsequent visits. None of the subjects in the Genotropin group tested positive for nAbs.

In terms of clinical endpoints, there were no differences between somatrogon recipients who were ADA-positive compared with those who were ADA-negative, suggesting that the presence of ADAs to somatrogon did not have an effect on the efficacy or safety of the treatment during the 12-month study. However, these findings should be interpreted with caution given the small number of subjects and the imbalance between the number of ADA-positive and ADA-negative subjects. The ongoing open-label extension of the study is actively monitoring immunogenicity, safety, and efficacy of all subjects.

Discussion

This study was the first clinical trial to assess the efficacy and safety of somatrogon administered once weekly compared with Genotropin administered once daily in Japanese children. This study met its primary objective, showing that once-weekly somatrogon was comparable to once-daily Genotropin in terms of annual HV after 12 months of treatment. Somatrogon administered once weekly was well tolerated in prepubertal Japanese children with GHD, with most TEAEs being mild to moderate in severity and a similarly low incidence of SAEs observed in both treatment groups. With efficacy comparable to once-daily Genotropin but requiring fewer injections, once-weekly somatrogon has the potential to improve treatment adherence and resulting growth outcomes, making it a valuable treatment option for prepubertal Japanese children with GHD.

Somatrogon administered once weekly was concluded as being comparable to Genotropin administered once daily as the mean treatment difference (somatrogon-Genotropin) in HV was +1.79 cm/year (95% CI, 0.97–2.61), which was greater than the preestablished margin of −1.8 cm/year. Compared with the Genotropin group, the somatrogon group had higher HV at 12 months (9.65 cm/year vs. 7.87 cm/year) and showed a greater improvement in height SDS from baseline to 12 months (0.94 vs. 0.52). In the phase 3 global study, the 12-month HV and improvements in height SDS were similar between the somatrogon (HV: 10.10 cm/year; height SDS change: 0.92) and Genotropin (HV: 9.78 cm/year; height SDS change: 0.87) treatment groups [18], noting that the dose of Genotropin was greater than that used in this study.

In this study, both treatment groups had similar proportions of subjects reporting all-causality TEAEs (somatrogon: 100%; Genotropin: 86.4%). These proportions are consistent with the results reported in the phase 3 global study (somatrogon: 87.2%; Genotropin: 84.3%). Both studies also reported a low incidence (<10%) of SAEs and severe AEs. The somatrogon group in this study had a higher incidence of TEAEs compared with the Genotropin group, due primarily to the higher incidence of injection-site pain in the somatrogon group (somatrogon: 205 events; Genotropin: 8 events). Per protocol, in-

jection-site pain was recorded as an AE if it was reported as having a pain score ≥4. Subjects from both treatment groups reported events of injection-site pain with pain scores <4, which were not recorded as AEs. Both groups had a similar proportion of subjects reporting injection-site pain (pain scores: 1–5), with more subjects reporting higher pain scores (pain scores: ≥4) in the somatrogon group. Except for 1 subject, all AEs of injection-site pain in the somatrogon group were assessed as mild; most events of injection-site pain occurred within the first 6 months of the study.

The pain and discomfort of daily GH injections have been identified by patients and caregivers as some of the key burdens associated with daily GH treatment [8, 9, 24]. Other treatment burdens identified included a fear of injections, the requirement to store/reconstitute medication, and life interference associated with daily injections. These burdens are likely to influence adherence to treatment, which is critical for treatment efficacy. A recent systematic review reported that nonadherence to rhGH treatments may be as high as 71% [25]. Nonadherence may reduce the efficacy of GH treatment, resulting in suboptimal growth responses and reduced HV and final adult height [9]. Reducing the number of rhGH injections required is likely to significantly lower the treatment burden associated with GH treatment, which may encourage greater adherence in patients and caregivers. As such, somatrogon administered once weekly may alleviate many of the issues associated with compliance with once-daily Genotropin. Although the somatrogon group had a higher incidence of injection-site pain compared with the Genotropin group, subjects may prefer to receive 1 injection of somatrogon compared with 7 injections of Genotropin during the course of a week. This is supported by a discrete choice experiment conducted in Japanese children with GHD, which found a clear preference for a once-weekly injection schedule instead of a once-daily injection schedule [13]. Although the use of once-weekly somatrogon may improve adherence among patients with GHD, it is possible that some patients with poor adherence to daily GH treatment (e.g., adolescents) will also show poor adherence to long-acting treatments such as once-weekly somatrogon.

A key strength of this study is the fact that it is the first clinical study of once-weekly somatrogon in Japanese children. Another strength of this study is that it enabled a direct comparison of the efficacy and safety of somatrogon administered once weekly with Genotropin (somatropin) administered once daily; somatropin is currently the most widely used treatment for GHD. The main weakness of the study was the use of a single somatrogon treatment arm, which meant that dose dependence could not be fully determined. However, the phase 2 dose-finding study showed that children who received once-weekly somatrogon at 0.66 mg/kg/week had a similar mean annualized HV to children who received once-daily Genotropin at 0.24 mg/kg/week [17]. Further, the phase 3 global study in non-Japanese subjects demonstrated that the somatrogon dose of 0.66 mg/kg/week was noninferior to Genotropin at 0.24 mg/kg/week. The results observed in this study, comparing a somatrogon dose of 0.66 mg/kg/week and a Genotropin dose of 0.175 mg/kg/week in Japanese subjects, were consistent with the findings reported in the global study and the phase 2 dose-finding study [17].

Conclusion

This study showed that somatrogon administered once weekly was comparable to Genotropin administered once daily with respect to annual HV following 12 months of treatment in prepubertal Japanese children with GHD. Once-weekly somatrogon also had a similar safety and tolerability profile to once-daily Genotropin. Compared with once-daily Genotropin, the reduced number of injections required by once-weekly somatrogon treatment has the potential to lessen the treatment burden experienced by pediatric patients with GHD and their caregivers, potentially resulting in improved adherence and treatment response.

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Statement of Ethics

This study was approved by the Institutional Review Board or Independent Ethics Committee of the participating institutions and followed the Declaration of Helsinki and International Conference on Harmonisation Good Clinical Practice guidelines. All 32 participating institutions/centers are listed on ClinicalTrials.gov (identifier: NCT03874013). Written informed consent was obtained from each subject's parents/legal guardians prior to commencement of the study.

Conflict of Interest Statement

R. Horikawa: advisory boards of Novo Nordisk, Pfizer, Lumos Pharma, and OPKO; consulting fees from Novo Nordisk, Pfizer, Lumos Pharma, Sandoz, and Ascendis Pharma; recipient of grants from Novo Nordisk and Sandoz; speakers bureau for Novo Nordisk, Pfizer, Eli Lilly & Company, and Sandoz. T. Tanaka: advisory board of OPKO and an Editorial Board Member of Hormone Research in Paediatrics. T. Yorifuji: advisory boards of Novo Nordisk and Pfizer; consulting fees from Novo Nordisk and Pfizer. R.G. Rosenfeld: advisory boards of Lumos, DNARx, and BioMarin; consulting fee from OPKO. Y. Hoshino, A. Okayama, D. Shima, and R. Gomez: employees and stockholders of Pfizer. A. Pastrak and O. Castellanos: employees and stockholders of OPKO. Y. Hasegawa and D. Ng: no conflicts of interest to declare.

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Author Contributions

All authors participated in the interpretation and analysis of the study data, and in the drafting, critical revision, and approval of the final version of the manuscript. Y. Hoshino and R. Gomez conceived the study and R. Horikawa, D. Ng, Y. Hoshino, R. Gomez, and A. Pastrak designed the study. Y. Hasegawa collected the data and A. Okayama and A. Pastrak conducted statistical analyses. O. Castellanos was the medical monitor.

Data Availability 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 deidentified participant data. See https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information.

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