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Original Article

Efficacy and safety of GH treatment in Japanese children with short stature due to *SHOX* deficiency: a randomized phase 3 study

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Highlights

- GH was effective and safe for 1–2 yr in 19 patients with *SHOX* deficiency.
- GH significantly improved Δheight SDS for chronological age.
- GH did not cause excessive bone maturation.

Abstract. We conducted a randomized phase 3 study to investigate the efficacy and safety of GH treatment in prepubertal Japanese patients with short stature due to *SHOX* deficiency. The patients were randomly allocated to the GH-GH group (n = 10), in which the patients were treated with GH (0.35 mg/kg/wk) subcutaneously once daily for 24 mo, or the no-treatment (NT)-GH group (n = 9), in which the patients were untreated for the first 12 mo and then administered the same dosage of GH for the next 12 mo. At month 12, the Δheight standard deviation score (SDS) for chronological age (CA) and serum IGF-1 level were significantly higher in the GH-GH group than those in the NT-GH group. In contrast, bone age (BA) and ΔBA/ΔCA were numerically higher in the GH-GH group but were not statistically significant. At month 24, these parameters were comparable between the two groups. The height velocity was significantly larger in the GH-GH group during the first year and in the NT-GH group during the second year. No serious adverse drug reactions were observed; however, one patient in the GH-GH group exhibited increased insulin resistance at month 24. These results indicated that GH is a promising treatment option for short stature in patients with *SHOX* deficiency.

Key words: *SHOX* deficiency, phase 3 clinical trial, GH, short stature

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Introduction

SHOX is a DNA-binding transcription factor cloned from the short arm pseudoautosomal region (PAR1) of the human sex chromosomes (1). Since PAR1 is shared by the X and Y chromosomes, *SHOX* escapes X inactivation and is present in two active copies in both males and females (2). The *SHOX* coding region spans approximately 40 kb and is located 500–600 kb from the Xp/Yp telomere (GRCh37/hg19) (2). *SHOX* is associated with at least three enhancers in the upstream region and six in the downstream region (2, 3). *SHOX* deficiency (loss-of-function abnormality) is caused by pathogenic sequence variants (SVs), such as nonsense, missense, and indel variants in the coding exons, and pathogenic copy number variants (CNVs), such as microdeletions and microduplications that disrupt the integrity of the *SHOX* coding/enhancer regions in subjects with an apparent normal karyotype (2). Because unequal crossover frequently occurs in PAR1 due to the abundance of repeat segments (4), CNVs rather than SVs account for the majority (~80%) of *SHOX* deficiencies (2).

Heterozygous *SHOX* deficiency (haploinsufficiency) causes diverse clinical features, including the apparent idiopathic short stature (ISS) phenotype and Léri–Weill dyschondrosteosis (LWD), characterized by Madelung deformity and severe short stature (2, 5). Since LWD predominantly manifests in pubertal and adult females, it has been suggested that gonadal estrogens exert a maturational effect on skeletal tissues that are susceptible to the unbalanced premature fusion of growth plates due to *SHOX* deficiency, facilitating the development of LWD in a female-dominant and pubertal tempo-dependent fashion (2, 6). To date, heterozygous *SHOX* deficiency has been identified in ~10% (1.1–22.2%) of patients with an apparent ISS phenotype and 70–90% of patients with LWD (2). In Japan, Shima *et al*. performed SV analysis for coding exons and enhancers and CNV analysis for coding and enhancer regions in 312 children with an apparent ISS phenotype and 16 children with LWD, revealing *SHOX* deficiency in 12 children with an apparent ISS phenotype (3.8%) and eight children with LWD (50%) (7).

Recombinant human GH has been utilized to treat short stature caused by *SHOX* deficiency in several countries other than Japan, successfully promoting statural growth (8–10). Hence, we conducted a multicenter, open-label, randomized, parallel-group, phase 3 study to investigate whether GH is effective and safe in Japanese patients with short stature due to *SHOX* deficiency (iRCT2080223889).

Patients and Methods

Patient enrollment

We enrolled Japanese patients eligible for this study using the following selection criteria: [1] demonstration of heterozygous *SHOX* deficiency via genetic analyses, such as fluorescence *in situ* hybridization, multiplex ligation-dependent probe amplification, array comparative genomic hybridization, Sanger sequencing, or next-generation sequencing, and confirmation of a normal karyotype to rule out Turner syndrome; [2] short stature with a height standard deviation score (SDS) for chronological age (CA) of ≤ –2.0; [3] of prepubertal age, *i.e.*, 3.0–10.5 yr in boys and 3.0–9.0 yr in girls; [4] no physical signs of puberty; [5] height data obtained at 9–15 mo before the screening for enrollment; [6] normal GH secretion in provocation tests performed at or within 12 mo before screening; [7] no medications that could affect growth within 24 mo before screening (except for topical corticosteroids and oral corticosteroids for ≤ 7 d); [8] lack of other clinically discernible diseases that could affect stature, such as diabetes mellitus, malignancy, and heart, kidney, or liver disease; and [9] no history of radiotherapy or chemotherapy. Patients were excluded from the study if they met any of the following criteria: [1] diagnosed with Langer mesomelic dysplasia; [2] diagnosed with other diseases responsible for short stature (except small for gestational age); [3] treated within 24 mo before screening with regular GH therapy or other medications that could affect growth, including corticosteroids (except topical corticosteroids and oral corticosteroids for ≤ 7 d), anabolic steroids, thyroid hormones, sex hormones, progesterone, gonadotropin-releasing hormone analogs, and IGF-1; [4] had a history of radiotherapy or chemotherapy; [5] diagnosed with diabetes mellitus, malignancy, or diseases of the heart, kidney, or liver; [6] were allergic to GH treatment; [7] received other study drugs within 6 mo before screening; and [8] judged ineligible by investigators.

Study design

Patients were randomly allocated to the GH-GH and no-treatment (NT)-GH groups. The GH-GH group received subcutaneous injections of GH (Growject®) at a dose of 0.35 mg/kg/wk once daily for 24 mo, while the NT-GH group received no treatment for the first 12 mo and was then treated with the same dose of GH for the next 12 mo. The efficacy and safety of GH treatment were assessed at months 12 and 24. Based on a previous study in non-Japanese patients (11), we hypothesized that the difference in Δheight SDS for CA at month 12 (the primary endpoint in this study) would be 0.54 between the GH-GH group and the NT-GH group at month 12. To obtain an effect size of 0.54 with a power of 80% at a 5% level of significance, this study required the enrollment of 13 patients in each group. Thus, the total sample size at the time of enrollment was assumed to be 32, considering the possible discontinuation and withdrawal of several patients.

Assessment of efficacy

We assessed the difference in Δheight SDS for CA between the GH-GH and NT-GH groups at month 12 as

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the primary endpoint and the change in Δheight SDS for CA during the study period. We evaluated the height velocity, Δbone age (BA), ΔBA/ΔCA, and serum IGF-1 SDS levels. Height SDS was calculated using age- and sex-matched growth references for Japanese children (12). Height velocity was obtained as the increment in height during the first and second years. BA was evaluated by a single expert (Dr. Mari Sato, Pediatrics Center, Toho University Omori Medical Center) using the Tanner–Whitehouse 2 method, standardized for Japanese children (13). Serum IGF-1 SDS levels were calculated using Japanese reference data (14).

Assessment of safety

We evaluated the incidence of adverse events (AEs), serious AEs, AEs of special interest, and adverse drug reactions (ADRs) as safety endpoints. The AEs were classified as mild (not interfering with daily activities), moderate (interfering with daily activities and requiring therapeutic interventions), or severe (seriously disrupting daily activities). The AEs of special interest include decreased glucose tolerance, nephrotic syndrome, hyperthyroidism, seizures, and other laboratory abnormalities or events requiring drug discontinuation or additional treatment measures. ADRs were defined as AEs considered related to the study drug by the investigators. We examined biochemical data, including HbA1c and thyroid hormone levels, and performed an oral glucose tolerance test (OGTT) with 1.75 g/kg glucose (maximum of 75 g) at months 12 and 24.

Statistical analysis

Since the Shapiro–Wilk test showed both normality and non-normality in the raw variables (samples) for most items obtained at different visits, we expressed the data as the mean ± SE, which shows the distribution of the mean and can be utilized irrespective of the normality or non-normality of the raw variables. For variables following normality, we employed Student's *t*-test and Welch's *t*-test for two groups with similar and different variances, respectively, after comparing variances using the F-test. For variables not following normality, we used the Mann–Whitney U-test. The statistical significance of the frequencies was analyzed using Fisher's exact probability test. All statistical analyses were performed using the SAS version 9.4 statistical software package (SAS Institute, Cary, NC, USA). $P < 0.05$ was considered significant.

Ethics

This study was approved by the Institutional Review Board Committee of each investigator who participated in the study, and written informed consent was obtained from the parents and informed assent from the patients. This study was conducted following the principles of the Declaration of Helsinki.

Results

Patient enrollment

We identified 7 boys and 12 girls aged 4–9 yr in 13 hospitals, including two pairs of siblings who satisfied the inclusion criteria. Medical experts at each hospital determined and approved eligibility to participate in this study. We utilized the age at participation in this study as a stratification factor (boys aged < 7 yr and girls aged < 6 yr; and boys aged ≥ 7 yr and girls aged ≥ 6 yr) and randomly allocated the 19 patients using an electronic data capture to the GH-GH group (n = 10) and the NT-GH group (n = 9), with a ratio of ~1:1 in each group. Thus, the number of patients did not reach the initially planned number (13 in each group), primarily because of the rarity of *SHOX* abnormalities.

The baseline characteristics of the patients are shown in **Table 1**. The values were comparable between the two groups, except for maternal height, which was significantly lower in the GH-GH group than that in the NT-GH group. While all 19 patients completed the 24-mo study period, two patients in the GH-GH group entered puberty between months 15 and 18 after the initiation of this study, and three patients in the NT-GH group entered puberty between months 3 and 6, 15, and 18, and 21 and 24, respectively, after the initiation of this study. The data of these five patients who entered puberty were treated as missing.

Assessment of efficacy

The results are shown in **Table 2** and **Fig. 1**, and the growth patterns of the enrolled patients are shown in Supplementary Fig. 1. The Δheight SDS for CA steadily increased after the start of GH treatment in both groups (from the first year in the GH-GH group and the second year in the NT-GH group). Moreover, it was significantly higher in the GH-GH group than that in the NT-GH group at month 12 (the primary endpoint). In contrast, there was no significant difference between the two groups at month 24. Furthermore, the height velocity increased during the first year of GH treatment. Although it became somewhat smaller during the second year of GH treatment in the GH-GH group; in the NT-GH group, it was similar to the baseline level during the first year of non-treatment and was clearly increased after GH treatment in the second year to a degree similar to that observed during the first year of GH treatment in the GH-GH group. Thus, the height velocity was significantly higher in the GH-GH group than that in the NT-GH group in the first year and significantly lower in the GH-GH group than that in the NT-GH group in the second year. The BA progressed faster than the CA during GH treatment. However, while ΔBA and ΔBA/ΔCA were numerically higher in the GH-GH group than those in the NT-GH group, they were not statistically significant. Serum IGF-1 SDS levels increased during the first three months of GH treatment and plateaued

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Table 1. Baseline characteristics of the Japanese patients enrolled in this study

	GH-GH group	NT-GH group	*P*-value
Male:Female	3:7	4:5	0.65
Age, yr	6.2 ± 0.5	6.6 ± 0.6	0.67
Height SDS for CA	−2.70 ± 0.14	−2.57 ± 0.16	0.71
Height SDS ≤ −2.5	7	4	0.37
Height SDS > −2.5	3	5	
Weight, kg	18.7 ± 1.4	18.4 ± 1.4	0.90
BMI, kg/m^2	17.2 ± 0.6	16.2 ± 0.7	0.27
Bone age, yr	6.0 ± 0.6	6.3 ± 0.7	0.74
Maternal height, cm	146.1 ± 1.9	153.3 ± 2.4	0.03
Paternal height, cm	168.2 ± 1.2	166.4 ± 2.1	0.44

Values are expressed as the mean ± SE. CA, chronological age; BMI, body mass index; NT, no treatment.

Table 2. Effects of GH treatment on various parameters

	GH-GH group	NT-GH group	*P*-value
ΔHeight SDS for CA			
At month 12	0.92 ± 0.07	0.13 ± 0.04	< 0.01
At month 24	1.39 ± 0.16	1.04 ± 0.09	0.10
Height velocity, cm/yr			
Baseline	5.0 ± 0.3	4.7 ± 0.2	0.43
During the first year	9.8 ± 0.4	5.6 ± 0.2	< 0.01
During the second year	7.5 ± 0.5	9.8 ± 0.4	< 0.01
ΔBA			
At month 12	1.5 ± 0.3	0.9 ± 0.2	0.15
At month 24	2.8 ± 0.5	2.3 ± 0.4	0.48
ΔBA/ΔCA			
At month 12	1.51 ± 0.30	0.94 ± 0.19	0.15
At month 24	1.40 ± 0.24	1.19 ± 0.19	0.52
Serum IGF-1 SDS			
Baseline	−1.02 ± 0.26	−0.86 ± 0.25	0.68
At month 12	1.25 ± 0.43	−0.81 ± 0.26	< 0.01
At month 24	1.15 ± 0.51	1.11 ± 0.30	0.95

Values are expressed as the mean ± SE. NT, no treatment; CA, chronological age; BA, bone age.

after that in both groups. Serum IGF-1 values remained < +2 SD in most patients, while three patients in the GH-GH group and one patient in the NT-GH group transiently had serum IGF-1 values ≥ +2.5 SD.

Assessment of safety

AEs occurred in 100% of patients in the GH-GH group (10/10, 61 events) and in the NT-GH group (9/9, 65 events) over two years (Supplementary Table 2). AEs of special interest occurred in 60% of patients in the GH-GH group (6/10, 10 events) over two years and in 11% of patients in the NT-GH group (1/9, 1 event) during the second year (Supplementary Table 3). No serious ADRs were observed; however, one patient in the GH-GH group showed signs of insulin resistance at month 24 because of a high baseline serum insulin concentration, although the blood HbA1c level and the OGTT results yielded normal findings (Supplementary Table 2). In addition, although *SHOX* abnormalities are often associated with scoliosis, compromising statural growth (15), scoliosis was not reported at the start of GH treatment or during the study period in any of the enrolled patients.

Laboratory tests revealed elevated levels of serum liver enzymes (n = 1) and triglycerides (n = 1), which were considered unrelated to GH treatment. All patients had normal HbA1c levels throughout the study, while borderline OGTT patterns were observed in two patients at screening (GH-GH group, n = 1; NT-GH group, n = 1), in five patients at month 12 (GH-GH group, n = 2; NT-GH group, n = 3), and in seven patients at month 24 (GH-GH group, n = 2; NT-GH group, n = 5).

Discussion

We conducted a randomized phase 3 study on GH treatment in 19 Japanese patients with short stature due to *SHOX* deficiency. Several important findings were obtained. First, the Δheight SDS for CA at month 12 (the

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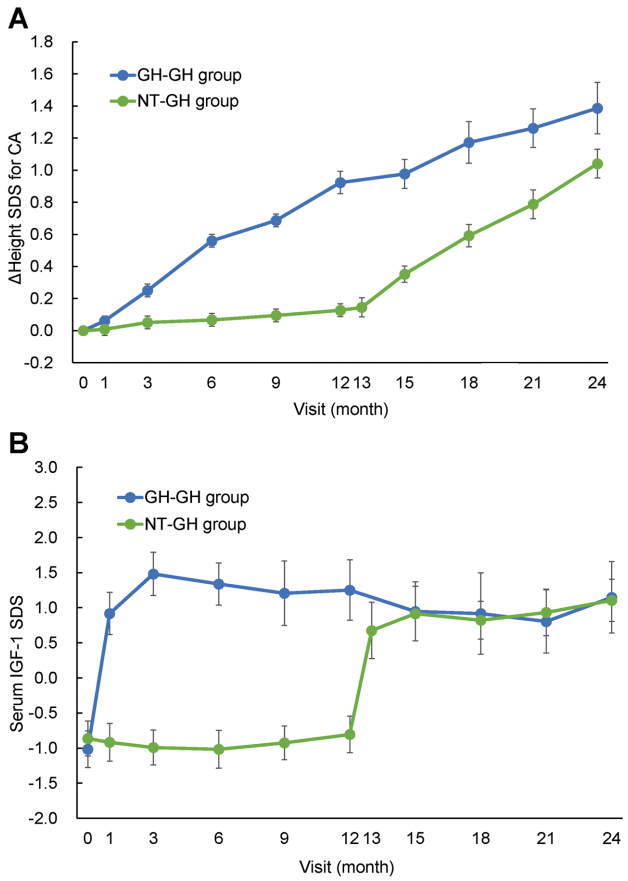

Fig. 1. The effects of GH treatment. A: Change in Δheight standard deviation score (SDS) for chronological age (CA). B: Change in serum IGF-1 SDS.

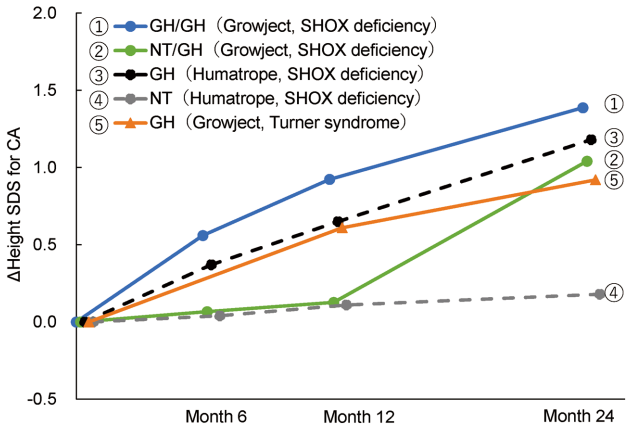

Fig. 2. Changes in Δheight SDS for chronological age in this study (Growject®) and previous studies in *SHOX* deficiency (Humatrope®) and Turner syndrome (Growject®).

primary endpoint in this study) was significantly higher in the GH-GH group than that in the NT-GH group and steadily increased with GH therapy. Consistent with this, the height velocity significantly increased with GH treatment in both groups. These results indicate that GH treatment promotes statural growth in patients with *SHOX* deficiency, at least in the first two years of treatment. Second, BA progressed faster than CA during GH treatment, while the ΔBA and ΔBA/ΔCA were not significantly different between the GH-GH and NT-GH groups. This may pose a question that GH treatment may not increase the final adult height. However, a previous study revealed that 57% of patients with *SHOX* deficiency and 32% of those with Turner syndrome achieved final adult heights higher than –2 SDS after GH treatment (9). Furthermore, the final adult height of patients with *SHOX* deficiency is 6.3 cm higher in GH-treated patients than in non-treated patients (10). Thus, GH treatment is expected to increase the final adult height of Japanese patients with *SHOX* deficiency. Third, the mean serum IGF-1 SDS levels increased rapidly and remained in the high-normal range throughout the study period. This would be consistent with the increased Δheight SDS for CA and height velocity during the GH treatment. Since the serum IGF-1 SDS levels remained within the normal range in most patients, there were no significant safety concerns regarding increased IGF-1 levels in this study. Finally, no serious ADRs were observed in our study, except for a single patient in the GH-GH group who exhibited increased insulin resistance at month 24. In addition, scoliosis, which can affect height data, was not reported in this study. This indicates the safety of GH treatment in patients with *SHOX* deficiency. These findings argue for the efficacy and safety of GH treatment in this study.

Similar studies have been performed in non-Japanese patients with *SHOX* deficiency and Japanese patients with Turner syndrome accompanied by *SHOX* haploinsufficiency. In *SHOX* deficiency, treatment with 0.35 mg/kg/wk of GH (Humatrope®) yielded a mean Δheight SDS for CA of 0.65 at month 12 and 1.18 at month 24 and a mean height velocity of 8.7 cm/yr in the first year and 7.3 cm/yr in the second year in patients aged 7.3 yr with a height SDS for CA of –3.27 at the initiation of GH treatment (**Fig. 2**) (8, 11). In Turner syndrome, treatment with GH (JR-8810) at a dose of 1.0 IU/kg/wk (equivalent to 0.35 mg/kg/wk) yielded a mean Δheight SDS for CA of 0.61 at month 12 and 0.92 at month 24 and the mean height velocity of 7.3 cm/yr in the first year and 5.3 cm/yr in the second year in patients who were aged 9.9 yr and had a height SDS for CA of –3.69 at the start of GH treatment (**Fig. 2**) (16 and unpublished data). Thus, the mean Δheight SDS for CA and the mean height velocity after initiating GH treatment are higher in this study than in these two studies. However, the patients in this study are younger and taller and had a higher height SDS at the initiation of GH treatment than those in the previous two studies. Considering that the height velocity gradually decreases with age in childhood and that the height SDS reflects the individual growth potential, a younger age and a higher-height SDS could have contributed to the apparently higher Δheight SDS for CA and height velocity in this study. Thus, the effects of GH treatment on Δheight SDS for CA and height velocity would be similar between

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this study and the previous two studies. However, the GH effect may be more or less compromised in patients with Turner syndrome. Furthermore, the data on BA, IGF-1, and the AEs were similar among the three studies (8, 9, 11, 16 and unpublished data). Collectively, these results suggest that GH therapy is an effective and safe treatment option for *SHOX* deficiency as well as for Turner syndrome with *SHOX* haploinsufficiency.

Conclusion

This randomized phase 3 study of Japanese patients with *SHOX* deficiency revealed the efficacy and safety of GH treatment over a 1- or 2-yr period. These results, in conjunction with previous data (8–11, 16 and unpublished data), indicate that GH is a promising treatment option for patients with short stature due to *SHOX* deficiency. However, the number of patients enrolled (n = 19) was small and did not reach the originally planned number (n = 32), primarily because of the rarity of *SHOX* deficiency. Thus, further studies are necessary to arrive at a more definitive conclusion regarding the efficacy and safety of GH treatment for *SHOX* deficiency.

Conflict of interests: K.T., T.Y., Y.S., H.H., N.T., R.I., and M.N. are employees and/or stockholders of the Development Division of JCR Pharmaceuticals, Ashiya, Japan. This study was funded by JCR Pharmaceuticals Co., Ltd. M.F. received a research grant from JCR Pharmaceuticals.

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