

Original Article

Onset of puberty and near adult height in short children born small for gestational age and treated with GH: Interim analysis of up to 10 years of treatment in Japan

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Abstract. The safety and effectiveness of long-term (10-yr) GH treatment in short Japanese children born small for gestational age (SGA) were evaluated based on interim data analysis from a clinical study, including the findings concerning the influence on the onset of puberty and subjects who achieved near adult height (NAH). Sixty-one subjects were analyzed at baseline in this study. Eleven subjects (6 boys and 5 girls) achieved NAH (mean 157.4 cm and 145.5 cm, respectively), and the Δ height SDS from the start of GH treatment was +1.6 in boys and +1.8 in girls. The median age (yr) at onset of puberty was 11.4 in boys and 9.9 in girls, comparable to healthy children. However, the mean height (cm) at onset of puberty (137.0 in boys; 125.5 in girls) was shorter than that of healthy children. Treatment-related adverse events were generally mild to moderate in severity; however, adenoidal hypertrophy was observed in two subjects as a serious adverse event. One subject had jaw malformation related to GH treatment at a dose of 0.067 mg/kg/d. No notable changes in HbA1c levels were observed, and the levels remained within the reference range. We have confirmed the safety and effectiveness of long-term GH treatment through this ongoing clinical study.

Key words: small for gestational age (SGA), short stature, long-term GH treatment, pubertal onset, adult height

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Introduction

GH treatment for short children with small for gestational age (SGA) short stature was approved in 2008 in Japan. A study of GH (Genotropin[®]) treatment for SGA short stature commenced in 2001 prior to the publication of the Japanese guidelines for GH treatment of SGA short stature (1); we initially used a height SD

score (SDS) ≤ -2.0 as the criterion for initiating GH treatment, which is the same approved criterion used in other disorders causing growth failure. However, the criterion in the Japanese guidelines for GH treatment of SGA short stature is a height SDS < -2.5 , based on the assumption that short children may possibly achieve a catch-up height of approximately 0.5 SD during puberty (by adulthood) even without GH treatment (2).

We have previously reported the efficacy and safety of GH treatment in this population via a dose-response study (3) and a follow-up study reporting outcomes of long-term GH treatment (4–8 yr) in a subpopulation of Japanese short children born SGA (4–6), who met all criteria for GH treatment according to the Japanese guidelines (1).

Here, we report an interim data analysis from the ongoing study started in 2001 that examined the long-term (10 yr) safety and effectiveness of GH treatment for children with SGA short stature, including data from a subpopulation of subjects with a height SDS at baseline of ≥ -2.5 to ≤ -2.0 . In addition, we assessed the onset of puberty and adult height in these children, which may be influenced by GH treatment. This study is a Pfizer-sponsored ongoing post-marketing clinical study following the approval of GH treatment for SGA short stature in 2008 (clinicaltrials.gov: NCT 01859949).

Subjects and Methods

Subjects and data source

Sixty-two subjects from 20 sites were enrolled in a subsequent long-term study (study number: GENASG-0021-007 [hereinafter, referred to as “Study 007”]) of subjects who had completed a multicenter, open-label, randomized parallel-group comparative study involving two different dose groups of GH treatment in short children born SGA (study number: 307-MET-0021-002 [hereinafter, referred to as “Study 002”]).

We report an interim analysis of data collected as of the cutoff date of June 21, 2012.

Study design and statistical methods

In Study 002 (3), the subjects were randomly assigned to two groups and received different doses of GH (Genotropin®, 0.033 mg/kg/d or 0.067 mg/kg/d). After treatment for 1 yr, Study 002 was completed, and then the subjects who had completed Study 002 were enrolled in Study 007. In Study 007, the dose was increased to 0.067 mg/kg/d in the group receiving 0.033 mg/kg/d GH (0.033/0.067 mg group), while the children assigned to the group that received 0.067 mg/kg/d remained on the same dose (0.067/0.067 mg group). If any adverse event occurred during Study 002 and the investigator judged that the dose increase was not appropriate, the 0.033 mg/kg/d dose could be maintained in Study 007, and those subjects were analyzed in the 0.033/0.067 mg group. Study 007 contains two phases consisting of the period from study start to the date of obtaining manufacture and sales approval and the period after the approval date (post-marketing phase). The dose can be decreased to 0.033 mg/kg/d during the post-marketing phase if it is judged to be appropriate from the viewpoint of age, puberty, growth rate and safety.

The treatment termination criteria defined in the protocol are “reaching a height SDS of 0 SD for chronological age”, “reaching a bone age of 17 yr in boys or 15 yr in girls”, “annual height velocity < 2 cm after achieving peak velocity at puberty” and “height velocity for chronological age < 1.0 cm/yr.” When a subject met any of these criteria, GH treatment was terminated.

Auxological data, bone age and methodology were collected or calculated as previously reported (4). In addition, body mass index (BMI)-SDS was calculated using the formula reported by Kato *et al.* (7). All adverse events recorded with a Case Report Form were coded with the preferred terms of the World Health Organization-Adverse Reaction Terminology (WHO-ART) and categorized by system organ class.

Ethical considerations

This study was conducted in accordance

Table 1 Clinical characteristics at birth and start of GH treatment

	0.033/0.067 mg group		0.067/0.067 mg group	
At birth				
Boy/girl	15/14		18/14	
Birth length (cm)	40.34 ± 5.26	(29)	40.18 ± 5.34	(32)
Birth weight (g)	1694.8 ± 556.7		1757.3 ± 612.0	
Gestational age (wk)	36.4 ± 3.1		36.9 ± 3.2	
At start of GH treatment				
Chronological age (yr)	5.2 ± 1.6	(29)	5.4 ± 1.3	(32)
Bone age (yr)	4.55 ± 1.88	(28)	4.80 ± 1.62	(31)
Height (cm)	93.97 ± 9.88	(29)	95.42 ± 8.32	(32)
Height SDS	-3.14 ± 0.76	(29)	-3.09 ± 0.83	(32)
Patient-adjusted height SDS	-2.90 ± 1.13	(29)	-2.68 ± 1.10	(32)
Height velocity (cm/yr)	5.36 ± 0.99	(29)	5.45 ± 1.21	(32)
Height velocity SDS	-1.87 ± 1.22	(29)	-1.45 ± 1.60	(32)
Weight (kg)	12.27 ± 2.87	(29)	12.55 ± 3.00	(32)
Weight SDS	-2.39 ± 0.81	(29)	-2.38 ± 0.75	(32)
BMI SDS	-1.53 ± 1.45	(29)	-1.67 ± 1.42	(32)
Serum IGF-I (ng/mL)	126.24 ± 55.41	(29)	114.47 ± 42.42	(30)
Serum IGF-I SDS	-0.02 ± 1.23	(29)	-0.25 ± 0.97	(30)

Mean ± SD (n).

with the Declaration of Helsinki, Good Clinical Practice and Good Post-marketing Study Practice issued by the Ministry of Health, Labour and Welfare. The study protocol was approved by the independent ethics committee or institutional review board for each study site.

All patients themselves or the patients' parents/legal guardians provided written informed consent before participation in the study.

Results

Subject characteristics and disposition

Of the 62 subjects, one subject did not receive GH during the study period, and the remaining 61 subjects were analyzed for effectiveness and safety. In this report, one subject who continuously received the Study 002 dose of 0.033 mg/kg/d throughout this study was included. The clinical characteristics of the 61 subjects (n = 29, 0.033/0.067 mg group; n = 32, 0.067/0.067 mg group) at birth and the start of GH treatment are shown in Table 1. Demographic characteristics

were similar between the two treatment groups.

Eleven subjects were still participating in this study at the cutoff date for this analysis. Twenty-two subjects completed the study because they met the treatment termination criteria: n = 10, "reaching a height SDS of 0 SD for chronological age"; n = 9, "reaching a bone age of 17 yr in boys or 15 yr in girls"; n = 2, "annual height velocity < 2 cm after achieving peak velocity at puberty"; n = 1, "height velocity for chronological age < 1.0 cm/yr". Two subjects completed the study on the date of marketing approval (i.e., they did not enter the post-marketing phase). The remaining 26 subjects exited the study early (early termination). The most common reason for early termination was withdrawal of consent (n = 19). Other reasons included adverse drug reaction (jaw malformation), personal reasons, protocol deviation and modification of the treatment strategy.

Effectiveness

Eleven subjects (6 boys and 5 girls) achieved near adult height (NAH), which was defined as

Table 2 Achievement of near adult height in subjects

No.	Treatment dose (mg group)	Initial		Onset of puberty		Completion/discontinuation				
		Age (yr)	Height SD score	Age (yr)	Height (cm) [SD score]	Age (yr)	Height (cm) [SD score]	Δ Height SD score after initial dose	Δ Height (cm) [SD score] after onset of puberty	
Boys (n=6)										
1	0.067/0.067	7.4	-2.8	11.1	136.1 [-0.9]	16.1	159.2 [-1.7]	1.1	23.1 [-0.8]	
2	0.033/0.067	7.8	-3.3	11.4	135.4 [-1.3]	15.9	162.7 [-1.0]	2.3	27.3 [0.3]	
3	0.033/0.067	7.5	-3.2	12.5	142.6 [-1.1]	16.8	164.9 [-0.8]	2.4	22.3 [0.3]	
4	0.067/0.067	5.4	-3.0	11.4	139.4 [-0.7]	14.8	158.4 [-1.1]	1.9	19.0 [-0.4]	
5	0.067/0.067	7.6	-5.3	12.3	121.4 [-3.7]	16.5	140.7 [-5.1]	0.2	19.3 [-1.4]	
6	0.067/0.067	7.5	-3.6	10.5	126.4 [-2.0]	15.8	158.4 [-1.7]	1.9	32.0 [0.3]	
Mean		7.2	-3.5	11.5	133.6 [-1.6]	16.0	157.4 [-1.9]	1.6	23.8 [-0.3]	
Girls (n=5)										
1	0.033/0.067	5.5	-3.4	11.0	134.9 [-1.2]	14.8	151.4 [-1.0]	2.4	16.5 [0.2]	
2	0.067/0.067	4.7	-3.3	10.4	129.4 [-1.5]	15.2	149.3 [-1.5]	1.8	19.9 [0.0]	
3	0.033/0.067	6.2	-4.0	9.5	121.5 [-2.0]	12.8	138.8 [-2.3]	1.7	17.3 [-0.3]	
4	0.067/0.067	5.3	-4.3	7.5	109.3 [-2.5]	13.7	139.3 [-3.0]	1.3	30.0 [-0.5]	
5	0.067/0.067	6.0	-2.4	8.7	123.7 [-0.9]	13.0	148.7 [-0.8]	1.6	25.0 [0.1]	
Mean		5.5	-3.5	9.4	123.8 [-1.6]	13.9	145.5 [-1.7]	1.8	21.7 [-0.1]	

For one girl (subject No. 5), the GH treatment dose was reduced to 0.033 mg/kg/day after 36 mo.

an “annual height velocity < 2 cm after achieving peak velocity at puberty” or “reaching a bone age of 17 yr in boys or 15 yr in girls.” Among the subjects, the mean NAH was 157.4 cm in boys and 145.5 cm in girls; the change in height SDS from the start of GH therapy was 1.6 in boys and 1.8 in girls. The mean pubertal height gain (from onset of puberty to NAH) was 23.8 cm in boys and 21.7 cm in girls (Table 2).

Changes in the height velocity (cm/yr) are shown in Fig. 1. In both groups, the mean height velocity increased remarkably 1 yr after the start of GH treatment: from 5.36 cm/yr (n = 29) to 8.09 cm/yr (n = 29) in the 0.033/0.067 mg group and from 5.45 cm/yr (n = 32) to 9.72 cm/yr (n = 32) in the 0.067/0.067 mg group. In both groups, a gradual decrease in the height velocity was observed after 2 yr of treatment.

Improvements in height SDS were observed throughout the 10-yr study period (Fig. 2). The mean height SDS in the 0.033/0.067 mg group improved from -3.14 (n = 29) at baseline to -1.76

(n = 5), and it improved from -3.09 (n = 32) at baseline to -1.25 (n = 6) in the 0.067/0.067 mg group. The mean change in height SDS (Δ height SDS) from baseline to 10 yr of treatment was 1.66 (n = 5) in the 0.033/0.067 mg group and 2.25 (n = 6) in the 0.067/0.067 mg group.

The changes in BMI-SDS over the 10-yr period are shown in Fig. 3. BMI-SDS in the 0.033/0.067 mg group changed from -1.53 (n = 29) at baseline to -0.91 (n = 5), and in the 0.067/0.067 mg group, it changed from -1.67 (n = 32) at baseline to -1.29 (n = 6). There was no difference in BMI-SDS between the 0.033/0.067 mg and 0.067/0.067 mg groups at baseline or in each treatment yr.

Onset of puberty

The percentage of subjects who entered puberty is shown in Fig. 4 (onset of puberty was defined as secondary sexual characteristics at Tanner Stage II). In addition, the plot charts of pubertal onset according to age and height in the

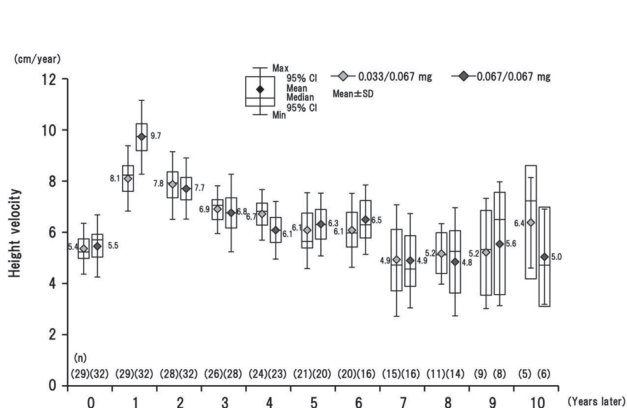


Fig. 1. Changes in height velocity.

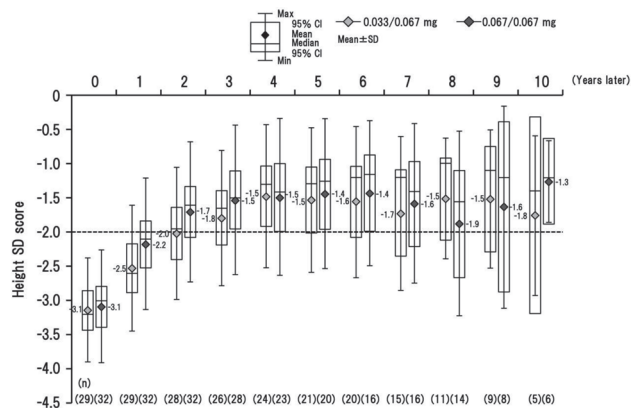


Fig. 2. Changes in height SDS.

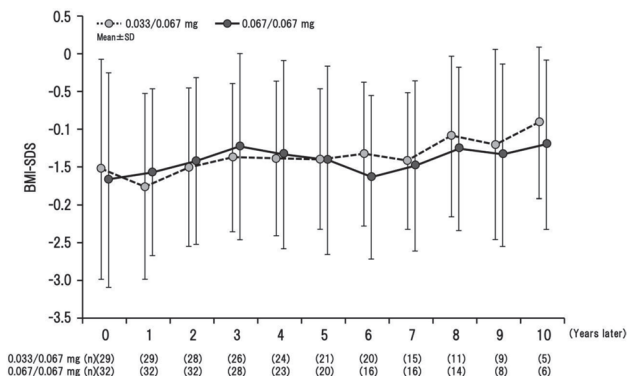


Fig. 3. Changes in BMI-SDS.

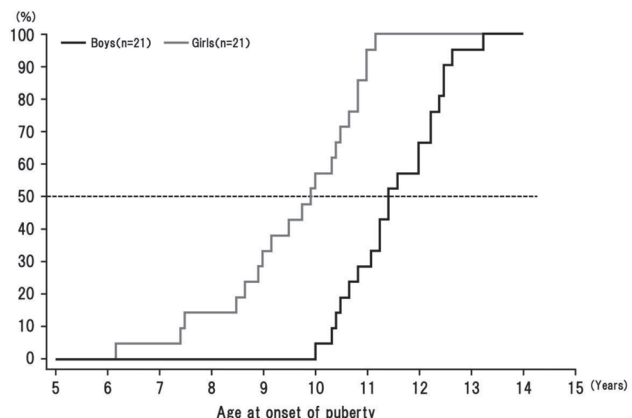


Fig. 4. Cumulative percentage of subjects who entered puberty.

boys and girls are shown in Fig. 5. During this study, pubertal onset was observed in 21 boys at a median age of 11.4 and in 21 girls at a median age of 9.9. All of the subjects developed puberty within the normal age range for Japanese children except for one girl who developed early puberty at the age of 6 yr 2 mo, which was diagnosed as precocious puberty in 36 mo after the initial dosage. The mean height at onset of puberty (mean \pm SD) was 137.0 \pm 7.2 cm in boys and 125.5 \pm 9.0 cm in girls.

Safety

The most common all-cause adverse events in both treatment groups were upper respiratory tract infection in 53 subjects (86.9%), influenza-like symptoms in 31 subjects (50.8%), otitis media

in 28 subjects (45.9%), gastroenteritis in 27 subjects (44.3%) and conjunctivitis in 20 subjects (32.8%). Treatment-related adverse events are listed in Table 3. Throughout the 10-yr treatment period, there were 50 treatment-related adverse events in 19 (31.1%) of the 61 subjects, with no obvious differences between the groups in the incidence and types of adverse events.

Serious adverse events regardless of causality were observed in 15 subjects, and no deaths were reported. Of these subjects, treatment-related serious adverse events were reported in two subjects (adenoidal hypertrophy) that were moderate in severity and reported to be resolving or to have resolved. Except for these events, a causal relationship with the

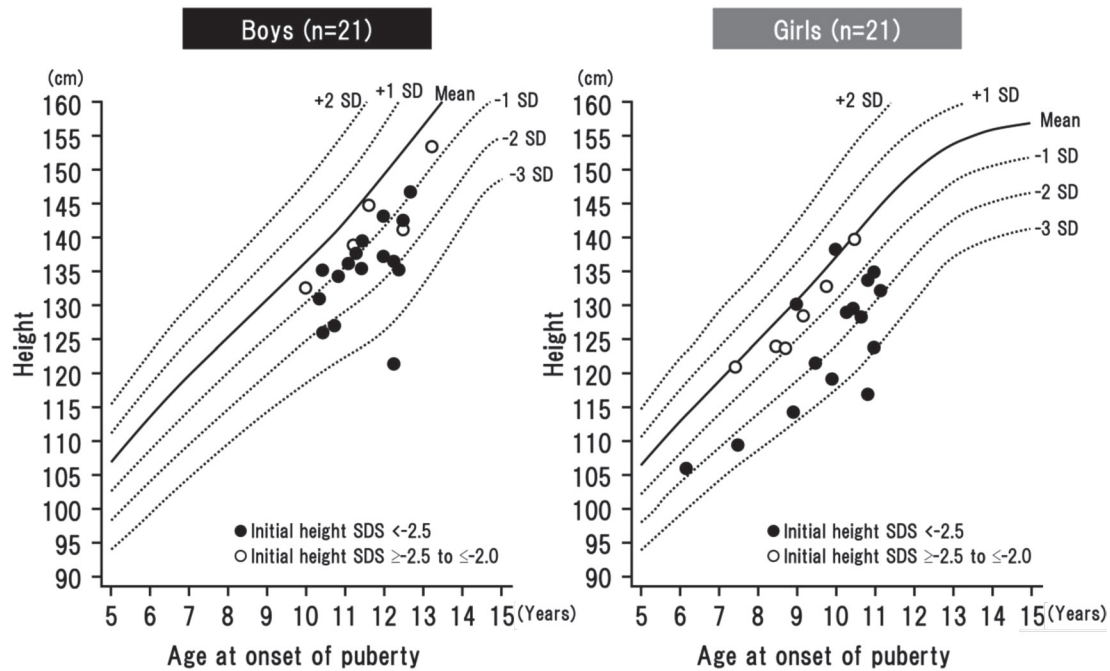


Fig. 5. Plot chart of pubertal onset age and height.

study drug was ruled out for all serious adverse events. Treatment-related adverse events leading to permanent discontinuation were reported in one girl in the 0.067/0.067 mg group (jaw malformation [verbatim term: mandibular protrusion]). However, this event was mild in severity, and her condition was stable, although the outcome was classified as not resolved.

Forty-four abnormal changes in laboratory test results were reported as adverse events in 22 subjects (36.1%). By the time of this analysis, most of these events had been resolved.

No notable changes in glycated hemoglobin (HbA1c) levels were observed in either group, and the levels remained generally within the reference range throughout the 10-yr period in all subjects. After 10 yr of GH treatment, the HbA1c (%; Japan Diabetes Society; mean \pm SD) levels gradually increased from 4.49 ± 0.37 ($n = 29$) at baseline to 5.10 ± 0.32 ($n = 5$) in the 0.033/0.067 mg group and from 4.56 ± 0.32 ($n = 31$) at baseline to 5.27 ± 0.18 ($n = 6$) in the 0.067/0.067 mg group. Based on an oral glucose tolerance test, one subject showed a diabetic

pattern at mo 36 but recovered to a normal pattern at mo 48. At mo 72, the results revealed borderline pattern diabetes.

No clinically significant changes were observed for bone age. The ratio of the mean bone age to chronological age was approximately 0.9 at baseline and remained at that level for the second yr of treatment, after which it increased gradually to approximately 1 and remained stable. No trends were observed that indicated excessive bone maturation (Fig. 6).

Discussion

In the present study, the mean height SDS improved from -3.14 SD at baseline to -1.48 SD at mo 48 in the 0.033/0.067 mg group and from -3.09 SD at baseline to -1.53 SD at mo 36 in the 0.067/0.067 mg group, but limited further improvement was observed in either group; these results are consistent with previous reports (4–6). Therefore, even with high-dose GH treatment for SGA short stature, the effective time for catch-up growth is only approximately 3–4 yr.

Table 3 Treatment-related adverse events

Frequency of adverse drug reactions in this long-term study (10 years)

	N (%)
Adverse drug reaction	
Total number of patients	61
The number of patients with adverse drug reaction (%)	19 (31.1)
WHO-ART system-organ classes, preferred terms	
Skin and appendages disorders:	3 (4.9)
Alopecia	1 (1.6)
Eczema	1 (1.6)
Verruca	1 (1.6)
Musculo-skeletal system disorders:	2 (3.3)
Arthralgia	2 (3.3)
Central & peripheral nervous system disorders:	2 (3.3)
Headache	2 (3.3)
Gastro-intestinal system disorders:	1 (1.6)
Abdominal pain	1 (1.6)
Mouth cyst	1 (1.6)
Liver and biliary system disorders:	1 (1.6)
SGOT Increased	1 (1.6)
SGPT Increased	1 (1.6)
Metabolic and nutritional disorders:	2 (3.3)
Glucose tolerance abnormal	1 (1.6)
Hyperglycemia	1 (1.6)
Endocrine disorders:	4 (6.6)
Puberty precocious	1 (1.6)
Endocrine disorder NOS	1 (1.6)
Thyroxine decreased	1 (1.6)
Adenoid hypertrophy	2 (3.3)
Respiratory system disorders:	1 (1.6)
Pharyngitis	1 (1.6)
White cell and RES disorders:	2 (3.3)
Eosinophilia	1 (1.6)
Leukocytosis	2 (3.3)
Lymphocytes atypical	1 (1.6)
Urinary system disorders:	2 (3.3)
Albuminuria	1 (1.6)
Haematuria	1 (1.6)
Foetal disorders:	1 (1.6)
Jaw malformation	1 (1.6)
Body as a whole-general disorders:	4 (6.6)
Chest pain	1 (1.6)
Fever	2 (3.3)
Pain	2 (3.3)
Application site disorders:	4 (6.6)
Injection site pain	1 (1.6)
Injection site reaction	1 (1.6)
Injection site bleeding	2 (3.3)
Resistance mechanism disorders:	1 (1.6)
Abscess	1 (1.6)
Secondary terms:	2 (3.3)
Molluscum contagiosum	1 (1.6)
Scoliosis	1 (1.6)

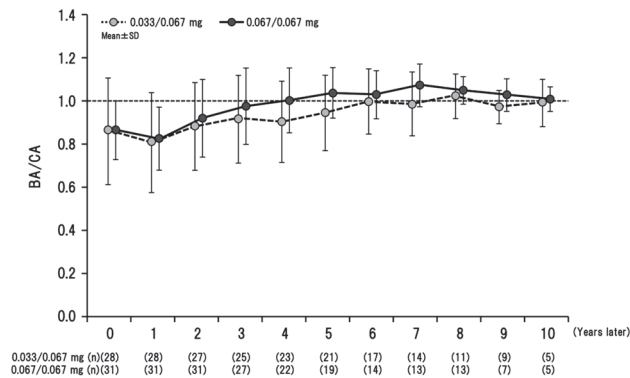


Fig. 6. Changes in bone age/chronological age.

It is known that the maximum catch-up period is 2–3 yr in patients with GH deficiency (GHD). This discrepancy may be largely attributable to the differences in approved therapeutic doses between indications.

In a previous report (5) where the therapeutic effect, as measured by the mean height SDS and Δ height SDS, was compared between subpopulations stratified by initial height SDS (< -2.5 vs. ≥ -2.5 to ≤ -2.0), the time course for the Δ height SDS was almost the same in both subpopulations. Between-group analysis (0.033/0.067 mg vs. 0.067/0.067 mg) of the subpopulations by initial height SDS also demonstrated no significant difference in Δ height SDS during the period of same-dose treatment (0.067/0.067 mg/kg/d) up to yr 6. Meanwhile, the 17 subjects with a higher initial height SDS (i.e., ≥ -2.5 to ≤ -2.0) reached a normal height (> -2.0 SD) at yr 1.

A stature > -2 SD is academically defined as normal, which results in a height of 159.2 cm in boys and 147.5 cm in girls as the adult height. Clinically, the minimum adult height that children of short stature and their parents desire is typically 160 cm for boys (-1.86 SD) and 150 cm for girls (-1.53 SD), which are higher than the minimum limits of the academically defined normal ranges, especially for girls.

Excellent effects on adult height were observed by van Pareren *et al.* (8), with as many as 85% of subjects achieving a normal adult height

(mean adult height SDS: -1.1 , 0.033 mg/kg/wk; -0.9 , 0.067 mg). In Japan, complete reports regarding adult height after GH treatment for SGA short stature are lacking. In our Study 007, 5 of 6 boys and 3 of 5 girls almost achieved normal stature. Although it is not conclusive because of the small numbers of subjects, it seems there is no difference in adult height between 0.033/0.067 mg and 0.067/0.067 mg groups. In the present analysis, the mean improvement in height SDS from the start of GH treatment to achievement of adult height was ≥ 1.5 SD for both boys and girls; however, the adult height may still be unsatisfactory for patients because the height SDS at the start of GH treatment was very low. Owing to the observed intersubject variability, further investigation is important.

While a consensus concerning evaluation of GH treatment during puberty has not been reached in discussions among expert groups, parameters to be considered were detected in this study: age at onset of puberty, height at onset of puberty and height gains during puberty.

The median age at the onset of puberty was 11.4 in boys and 9.9 in girls, both of which are similar to those of healthy children (9, 10) and consistent with the findings of Boonstra *et al.* (11). Meanwhile, it is known that short-statured children generally experienced delayed onset of puberty, subsequently resulting in a more apparent improvement in adult height SDS compared with the pre-puberty SD score (12). The age at the onset of puberty in untreated short-statured children born SGA is unknown. An improvement in height SDS of approximately $+0.5$ SD between 8 and 18 yr of age with SGA short stature, as that reported by Albertsson-Wickland *et al.* (2), suggests delayed puberty. Therefore, the similarities in age at the onset of puberty between the children with SGA short stature in our study and healthy children implies that the high-dose GH treatment may have slightly accelerated the onset of puberty. According to Kamp *et al.* (13), high-dose GH treatment for idiopathic short stature can accelerate the

onset of puberty. Moreover, precocious puberty is used as a diagnostic criterion for Russell-Silver syndrome. For these reasons, further investigations on the influence of GH on puberty, cases of precocious puberty and the age at the onset of puberty in untreated short children born SGA are needed.

Given the strong positive correlation between height at the onset of puberty and adult height, to achieve the desired adult height, children should have a sufficient height by the time of pubertal onset. The height at the onset of puberty in healthy children is approximately 145 cm in boys (9) and 135 cm in girls (10), whereas the height at the onset of puberty in children with SGA short stature is 5–10 cm shorter. Analysis in children with idiopathic short stature has demonstrated that boys and girls who are shorter than 135 and 132.5 cm, respectively, at the onset of puberty will have difficulty achieving adult heights of more than 160 and 150 cm, respectively, and represent a group with a high risk of short adult stature resulting from early puberty for height (14). Although the median age at the onset of puberty was comparable between children with SGA short stature in our study and healthy children, 6 of 21 boys and 16 of 21 girls were considered to have early puberty for height. As girls reach the age for puberty earlier than boys do clinically, they may enter puberty without sufficient catch-up growth and are more likely to have early puberty for height. To achieve a higher height at the onset of puberty, GH treatment should be initiated early. Because treatment for SGA short stature is approved for patients older than 3 yr, it is ideal to screen for the disease during the 3-yr check-up.

A mean pubertal height gain of 25.8 cm in boys and 18.9 cm in girls has been reported among children with short stature (14). When the pubertal height gain is plotted by age at onset of puberty in idiopathic short stature and GH treated SGA short children, the two patient groups are generally considered to be similar, indicating that even high-dose GH

treatment is not expected to yield a significantly greater pubertal growth than that in untreated short children. The extent of height gain is approximately 1.8 SD over an approximate 4-yr period; therefore, GH treatment may have limited efficacy with a very low height SDS at baseline. Thus, as we have discovered through our investigation of GH treatment for SGA short stature, it is important to increase the subject's height as much as possible before the onset of puberty to improve adult height. In SGA children who enter puberty with a short stature, it is necessary to increase pubertal growth for normalization of their adult height. Combination with gonadotropin-releasing hormone analogs has been shown to be effective for GHD and is also expected to be beneficial in cases of SGA short stature (15); however, most of these combinations are not covered by the National Health Insurance system in Japan.

The BMI-SD score, an indicator of body size, slowly increased throughout the GH treatment period, approaching a normal value. The observed change was consistent with the change in the obesity index, without a tendency toward obesity even after 10 yr of treatment.

Most of the adverse events occurred incidentally owing to infection. One subject discontinued the GH treatment permanently because of jaw malformation, which was likely attributable to the high-dose GH treatment. Regarding glucose tolerance, the HbA1c levels remained generally within the reference range; however, 1 subject showed elevated blood glucose levels, which then normalized, and this subject was not considered to have overt diabetes.

Acceleration of bone age relative to the chronological age was minimal during the first 1–2 yr of treatment. In contrast, a clinical study for GHD (16) showed that bone age progressed by approximately 1.3 yr after 1 yr of treatment. This discrepancy might be explained by the difference in age at the start of GH treatment, with the age being approximately 5 yr on average in our study, which was younger than the age (8–9 yr)

in the GHD study. Individuals with a younger chronological age at the start of GH treatment may have a different sensitivity to GH in terms of accelerated bone age. However, the ratio of bone age to chronological age in the present study approached 1, indicating that the bone age caught up to the chronological age before the average height was reached. In GH-treated GHD children, the bone age rarely catches up to the chronological age, even at the onset of puberty. Since it has been reported that high-dose GH accelerates bone age (13), the possibility that high-dose treatment induced the difference between GHD and SGA short stature cannot be ruled out.

Conclusions

The growth-promoting effects of GH in short children born SGA were confirmed in this interim analysis of a long-term clinical study, which evaluated data for up to 10 yr of GH treatment.

Since there is a positive correlation between the height at onset of puberty and adult height, our data suggested it is important to achieve a sufficient height before the onset of puberty in order to achieve the desired adult height.

The mean height SDS 10 yr after GH treatment improved to more than +1.5 SDS from the start of GH treatment; therefore, normalization of adult height can be expected in SGA short-statured children with a mild level at the start of GH treatment. Although the median age at onset of puberty in children with SGA short stature was approximately the same as that of healthy children, the height at the onset of puberty in GH-treated SGA short children was not normalized. Our data indicated earlier application of GH treatment provides a benefit, and attempts to increase pubertal growth in GH-treated SGA children who enter puberty with a short stature may be also necessary to normalize their adult height.

Further follow-up investigation is needed in order to evaluate the long-term effects of GH treatment, although no new safety concerns were

observed with high-dose GH treatment, such as adverse events and influence on glucose tolerance.

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Conflict of interest: TS, SH and NO are employed by Pfizer Japan. SH is a statistician and was in charge of statistical analysis. TT, SY, YS, HT and JM, who are advisors for this Pfizer-sponsored clinical study, reviewed the

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