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Original Article

The long-term safety and effectiveness of growth hormone treatment in Japanese children with short stature born small for gestational age

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Abstract. This study aimed to characterize the safety and effectiveness of GH treatments, in usual clinical practice, in children with short stature born small for gestational age (SGA). This was a multicenter, open-label, non-interventional study (NCT01110928) conducted at 150 sites in Japan (2009–2018). The primary objective was to assess the type and frequency of serious adverse drug reactions (SADRs) associated with long-term GH use. Overall, 452 naïve and 46 non-naïve (previously treated) children were enrolled. GH treatment was well-tolerated, with SADRs occurring in 1.3% (6/452) and 0% (0/46) of naïve and non-naïve children, respectively. No new safety concerns or notable changes in glucose metabolism were identified during long-term treatment. Altogether, 57 children (32 naïve and 25 non-naïve) reached near adult height (NAH). In naïve and non-naïve children, mean ± standard deviation (SD) height standard deviation score (SDS) at NAH were –2.03 ± 0.77 and –1.53 ± 0.81, respectively, representing a change of +0.85 ± 0.72 and +1.24 ± 0.66 from baseline height SDS, respectively. Mean treatment duration to NAH was 4.29 (naïve) and 7.26 (non-naïve) yr. Thus, long-term GH treatment for short stature in children born SGA was confirmed to have a good safety profile and was effective for improving adult height.

Key words: GH, Norditropin®, small for gestational age, Japan, observational study

Introduction

Small for gestational age (SGA) is commonly characterized by a birth weight and/or birth length that is at least two standard deviations below the mean for the gestational age in the reference population (1). SGA has many etiologies, such as genetic causes, maternal health and obstetric factors, including placental insufficiency and fetal epigenetics (2). Thus, children born SGA comprise a heterogeneous group (2).

Overall, approximately 90% of children born SGA catch up to their genetic height potential by approximately 2 yr of age (3, 4). Children who do not catch up in growth remain short in stature for the rest of their life (5). Therefore, children who remain short may be eligible GH treatment to support the achievement of a final adult height within their genetically predicted range (6, 7).

Children born SGA who are not treated with GH are at a higher risk for cardiovascular disease, insulin resistance, type 2 diabetes, and dyslipidemias compared with those born with a normal weight (8, 9). In children with short stature born SGA, GH treatment has been shown to raise postprandial insulin levels but not affect glycosylated hemoglobin (HbA1c), fasting glucose, or glucose tolerance (10, 11). The discontinuation of GH treatment leads to a return to pre-treatment mean insulin levels (12).

Although there are robust data regarding the long-term efficacy and safety of GH treatment in a mainly Caucasian population, few data are available in Japanese children born SGA (13, 14). The estimated prevalence of SGA in Japan is 3.5% (15) and 0.06% of Japanese children with short stature born SGA meet the criteria for GH treatment at 3 yr of age (15). These criteria are birth weight and birth length below the tenth percentile for the gestational age, birth weight or birth length at least −2.0 standard deviation score (SDS) for

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the gestational age, and 2.5 SDS below the mean height for the age (15).

This post-marketing surveillance study was carried out based on the requirements of the Japanese pharmaceutical affairs law and as a post-approval commitment to the Pharmaceuticals and Medical Devices Agency (PMDA) for the marketing authorization of Norditropin® (recombinant human GH, somatropin, Novo Nordisk A/S, Denmark) for children born SGA in Japan. The aim of this study was to characterize the safety and effectiveness of GH in usual clinical practice in children with short stature born SGA. This report assessed the type and frequency of serious adverse drug reactions (SADRs) associated with the long-term use of GH. Data on growth, as assessed by height, and quality of life (QoL) were also evaluated.

Patients and Methods

Ethics

The study was conducted in accordance with the Declaration of Helsinki and the Guidelines for Good Pharmacoepidemiology Practice (Revision 2, April 2007). Prior to study initiation, the study protocol and other relevant documentation were reviewed and approved by an independent ethics committee (IEC)/institutional review board (IRB). Written informed consent was obtained from the children's parents/legal guardians and, when possible, the children themselves provided assent.

Patients

Children with short stature born SGA who did not have epiphyseal closure were eligible for enrollment in the study. Children could be either naïve to treatment ("naïve") or could have previously received GH treatment in a multicenter, randomized, controlled, double-blind, parallel-group trial (NCT00184717; (16)) and then completed the post-marketing clinical trial ("non-naïve"). For non-naïve children enrolled in the study, GH treatment was continued uninterrupted. Children diagnosed with diabetes or malignancy were excluded.

Study design

This was a multicenter, open-label, observational, non-interventional study (NCT01110928) conducted at 150 sites in Japan. The study was initiated in November 2009 and children were recruited between December 2009 and November 2013. Based on the agreement with the PMDA, the study was to be conducted until final height was achieved. Data were collected until the 13th of December, 2018.

GH (Norditropin NordiFlex® or Norditropin® FlexPro®, Novo Nordisk A/S) was prescribed and titrated by the physician in accordance with the approved dose guidelines in Japan (17, 18), namely 0.23 mg/kg/wk (0.033 mg/kg/d). The dose could be increased to 0.47 mg/kg/wk (0.067 mg/kg/d) in case of poor growth response. As a result of the observational nature of the study, there were no interventions in standard care or any procedure carried out by the investigator during the study. Data for each child were collected by the investigator using an individual paper case report form (CRF; 1 CRF per child per year). Children were not called in for premature discontinuation or for a missed visit. If a child was prematurely withdrawn from the study, the investigator was to ensure that the procedures for the last visit (treatment compliance, GH dose, growth data, laboratory tests, adverse events, QoL questionnaire) were undertaken, if possible. The primary reason for discontinuation (adverse drug reaction [ADR], non-compliance with protocol, or other) was recorded in the CRF.

The primary objective of the study was to observe the type and frequency of SADRs during long-term use of GH in usual clinical practice. The secondary safety objective was to determine the frequency of abnormal glucose metabolism during long-term GH use. The secondary effectiveness objective was to evaluate the frequency with which near adult height (NAH) was achieved. The psychological effects of long-term GH treatment were evaluated using a QoL questionnaire.

The safety of the treatment was continuously assessed by recording adverse events, specifically SADRs, as well as puberty, bone age, and IGF I levels. A SADR was defined as a serious adverse event for which a causal relationship between the product and the occurrence was suspected, i.e. judged possible or probable by the reporting or reviewing healthcare professional. Puberty was defined by Tanner staging (male: testicular volume (left/right) ≥ 4 mL or pubic hair ≥ Tanner stage 2; female: breast or pubic hair ≥ Tanner stage 2 or onset of menarche). Bone age was determined locally via assessment by the investigator, using the Tanner–Whitehouse second edition method standardized for Japanese children (19, 20) or the Greulich and Pyle method (21). Serum IGF I levels were assessed in the course of routine clinical practice according to the usual laboratory procedure at each site. The IGF I SDS were calculated using Japanese reference values of serum IGF I concentrations in children by gender and age (22).

Effectiveness of the treatment was assessed by evaluating growth, including height velocity. Height SDS were calculated based on Japanese data regarding standard height by gender and age (23). The achievement of NAH was defined as signs of puberty and a height velocity of < 2 cm/yr, or males having a bone age of ≥ 17 yr and females having a bone age of ≥ 15 yr. In the absence of bone age, chronological age (≥ 17 yr for males and ≥ 15 yr for females) or a Tanner pubertal stage of 4 or 5 (according to the genitalia for boys and breasts for girls) at the time of their last height measurement could be used.

The QoL questionnaire (24) that was completed at baseline and yearly thereafter was completed by the child

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or their legally authorized representative and compared with their age-matched peers. The questionnaire survey (25) was developed based on the TNO-AZL Children's Quality of Life survey (26) and was evaluated by a contract research organization (CMIC Co., Ltd., Tokyo, Japan). The choice of answer to each question was quantified from 3 (favorable) to 1 (not favorable). The answer "not known" was not included in the analysis. The questionnaire survey consisted of six subsections: physical discomfort (5 questions), physical health (7 questions), contact with other children (6 questions), reactions from adults (5 questions), physical appearance (6 questions), and behavior (14 questions).

Statistics

The completed CRFs were collected by the sponsor yearly and upon study completion. The data were then analyzed by the sponsor using SAS® Version 9 or higher (SAS Institute, Cary, NC, USA). The full analysis set (FAS) consisted of all children who received at least one dose of GH and was used to assess all safety endpoints. The effectiveness analysis set (EAS) was defined as all children included in the FAS with baseline data and at least one measurement of height at 1-yr post-baseline. The safety analyses were carried out for both naïve and non-naïve children. In this report, puberty and NAH are reported for both naïve and non-naïve children, while other endpoints, including the effectiveness endpoints, are reported for naïve children only.

Continuous variables were represented as mean ± SD or median [interquartile range (IQR)] where appropriate. Categorical data were represented as the number and proportion of children in each category, whereby percentages did not include missing data. The frequency of SADRs was represented both annually and by the total study period. Moreover, the change from baseline in each effectiveness endpoint was tabulated by treatment duration (year).

Statistical tests and comparison of values before and after GH treatment were performed using paired *t*-tests for continuous variables, such as height. All tests were performed using a two-sided $\alpha = 0.05$ and a 95% confidence interval (CI). Results are reported as mean ± SD unless otherwise stated.

Results

Patient disposition

In total, 486 naïve and 46 non-naïve children born SGA were enrolled in the study (**Fig. 1**). Notably, 4 children from one center were excluded from the analyses because the center did not agree to publish their data.

In total, completed and signed CRFs were available for 456 of the 486 naïve children, and were included in the FAS. The non-naïve children included 43 of the 62 children who had participated in a previous phase 3 clinical trial (NCT00184717 (16)) as well as 3 children who had been withdrawn from that study. All 46 non-naïve children were included in the FAS. The EAS comprised 433 naïve children; 19 children in the FAS were excluded from the EAS as a result of missing effectiveness data (**Fig. 1**).

During the study, 171 naïve and 25 non-naïve children discontinued treatment (**Fig. 1**). The most frequent reasons for discontinuation were deviations from the criteria to continue treatment (naïve n = 43; non-naïve n = 13), child's request (naïve n = 41; non-naïve n = 4), parent's decision (naïve n = 25; non-naïve n = 8), and termination of financial support of medical costs (naïve n = 19; non-naïve n = 1).

Baseline characteristics

At baseline, the mean age of the naïve children included in the EAS was 5.50 ± 3.07 yr, with 47.8% of the children were female (**Table 1**). The mean height SDS at baseline were below the normal population range (–2.98 ± 0.63) and the mean height velocity SDS were below 0 (–1.79 ± 2.05). The mean IGF I SDS were also below 0 (–1.07 ± 1.74).

GH dose

The mean dose of GH in naïve children included in the FAS (n = 452) was 0.248 ± 0.068 mg/kg/wk at the start of the treatment (Supplementary Fig. 1). After 1 yr of treatment, there was a significant increase in the mean GH dose from baseline (0.061 ± 0.071 mg/kg/wk; n = 400; $P < 0.001$). The mean GH dose remained significantly higher than baseline from yr 1 to yr 7 ($P < 0.001$) and the mean GH dose at yr 7 was 0.332 ± 0.085 mg/kg/wk (n = 62). After 8 yr of follow-up, there were only six children with data on GH dose. The mean GH dose remained within the range approved in Japan for the treatment of children with short stature born SGA (0.23–0.47 mg/kg/wk) throughout the study (18). During the analysis, an outlier (2.70 mg/kg/wk) was excluded from the yr 6 data (confirmed by the Smirnov–Grubbs' outlier test).

Safety

SADRs

During the study, seven SADRs were reported in 6 of the 452 naïve children (1.3%) and no SADRs were reported in the non-naïve children. Of the SADRs reported, adenoidal hypertrophy (two events in two [0.4%] children) and epilepsy (two events in two [0.4%] children) were the most common. Neither of the two children who reported epilepsy as an SADR during the study had a history of epilepsy. One event each of otitis media, thyroiditis, and tonsillar hypertrophy were reported in three individual children. Except for one case of epilepsy, which was reported not recovered, all the SADRs were reported as recovered (n = 5) or recovering (n = 1) at the end of the study period.

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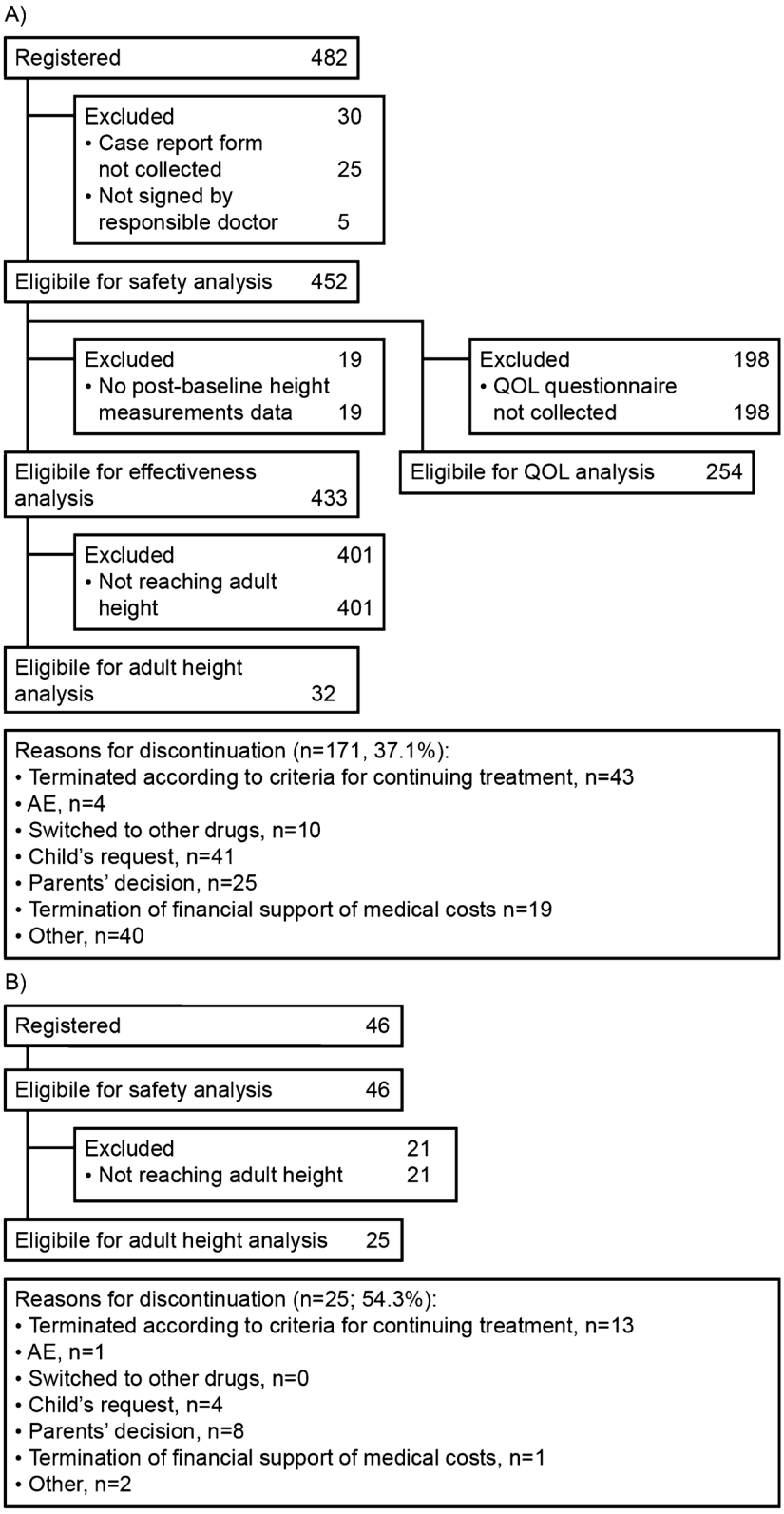

Fig. 1. Disposition of children A) naïve to treatment and B) non-naïve to treatment. More than one reason for discontinuation could have been provided for each child. AE, adverse event; QoL, quality of life.

Adverse events that led to treatment discontinuation

Discontinuation of GH treatment due to adverse events was reported for five children (naïve, n = 4; non-naïve, n = 1). One naïve child discontinued GH treatment as a result of pneumonia and thyroiditis. Other reasons for discontinuation were proteinuria (n = 1), ovarian germ cell teratoma (n = 1), hepatoblastoma (n = 1), and injection site rash (n = 1).

The case of ovarian germ cell teratoma was reported as a serious adverse event in a girl aged 12

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Table 1. Baseline characteristics for naïve children in the effectiveness analysis set (EAS)

Characteristic	n	All (n = 433)	n	Male (n = 226)	n	Female (n = 207)
Number of children		433 (100%)		226 (52.2%)		207 (47.8%)
Age [yr]	433	5.50 (3.07)	226	5.72 (3.22)	207	5.27 (2.88)
Height [cm]	433	97.98 (16.79)	226	99.62 (17.26)	207	96.19 (16.11)
Height SDS	433	–2.98 (0.63)	226	–2.89 (0.58)	207	–3.08 (0.67)
Weight [kg]	432	14.61 (6.34)	225	15.30 (6.69)	207	13.85 (5.86)
Weight SDS	432	–2.01 (0.64)	225	–1.96 (0.55)	207	–2.07 (0.72)
Height velocity [cm/yr]	327	5.53 (1.62)	169	5.59 (1.77)	158	5.47 (1.46)
Height velocity SDS	327	–1.79 (2.05)	169	–1.63 (2.25)	158	–1.97 (1.79)
IGF I [ng/mL]	421	113.51 (69.31)	219	108.27 (69.47)	202	119.18 (68.86)
IGF I SDS	400	–1.07 (1.74)	207	–0.93 (1.89)	193	–1.23 (1.57)
Gestational age [wk]	428	35.4 (4.6)	222	35.0 (4.7)	206	35.9 (4.5)
Height at birth [cm]	396	40.65 (5.62)	208	40.40 (5.95)	188	40.93 (5.22)
Height SDS at birth	390	–2.49 (0.89)	204	–2.34 (0.94)	186	–2.65 (0.81)
Weight at birth [g]	429	1717.2 (692.1)	223	1686.9 (700.3)	206	1750.0 (683.4)
Weight SDS at birth	420	–2.07 (0.69)	218	–2.09 (0.74)	202	–2.06 (0.63)

Data are mean (SD) unless otherwise stated. SDS, standard deviation score.

yr 5 mo who had been receiving GH for approximately 5 yr (non-naïve). No concomitant disease or relevant medical history were reported. The tumor was removed by surgery and the child made a full recovery. The event was considered unlikely to be related to the treatment. GH treatment was stopped at the time of diagnosis.

The hepatoblastoma was diagnosed in a boy aged 3 yr 11 mo in the naïve group at approximately 6 mo after starting GH treatment. The child had been born prematurely (27 wk and 5 d) with an extremely low birth weight (553 g) and had previously had surgery at 5 mo for an inguinal hernia and at 2 yr and 4 mo for an umbilical hernia. The child was reported as recovering following treatment. The hepatoblastoma was reported as a serious adverse event (severe severity) and was considered unlikely to be related to the GH treatment.

Glucose metabolism

HbA1c levels in naïve children in the FAS were within the normal range (4.6–6.2%) at baseline (mean 5.28% ± 0.26, n = 234) and during the follow-up period (**Fig. 2**). A significant increase from baseline was seen after 1 yr of treatment (mean 5.32% ± 0.25; n = 246; P < 0.001), with levels remaining significantly elevated from baseline to yr 7 of treatment (mean 5.48% ± 0.25; n = 57; P < 0.001).

Hyperglycemia (one event in one child), impaired glucose tolerance (one event in one child), and glucose present in urine (one event in one child) were reported as adverse events after the start of GH treatment. All three events were considered mild in severity and non-serious and were reported as recovered at the end of the follow-up period. Two events, namely glucose present in urine and impaired glucose tolerance, were considered to be possibly related to the treatment by the sponsor.

Bone age

No concerns in regards to excessive bone maturation were raised during the study. At baseline, the ratio

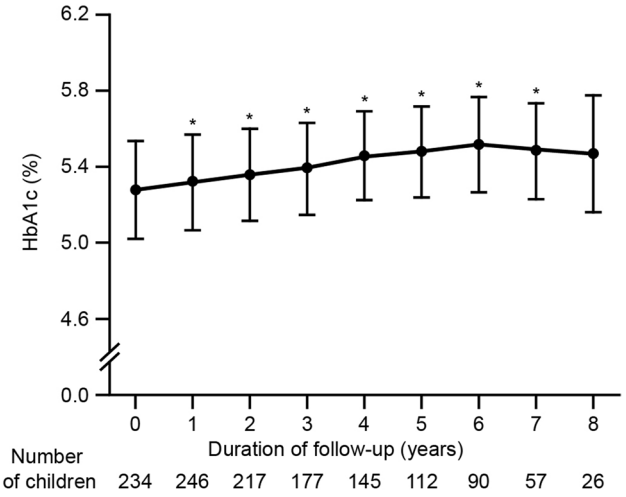

Fig. 2. Glycosylated hemoglobin (HbA1c) levels (National Glycohemoglobin Standardization Program: NGSP) by the duration of follow-up for naïve children in the full analysis set (FAS). Values are represented as mean ± standard deviation (SD). * P < 0.001 compared with the baseline.

between mean bone age and chronological age was 0.78 ± 0.19 (Supplementary Fig. 2), indicating that the mean bone age at baseline (4.17 ± 2.24 yr) was slightly retarded relative to the mean chronological age (5.50 ± 3.07 yr). The ratio between the mean bone age and chronological age increased during the study and after 6 yr of GH treatment, the mean bone age was similar to the chronological age as shown by the ratio between bone age and chronological age, which was close to 1 (1.01 ± 0.09). In naïve children, the mean Δbone age/Δchronological age was above 1 throughout the study period (1.08 ± 0.70 from baseline to yr 1 and 1.24 ± 0.56 from yr 5 to yr 6).

In non-naïve children, the ratio between mean bone age and chronological age at baseline was 0.85 ± 0.18. This ratio increased during the study and after 4 yr of

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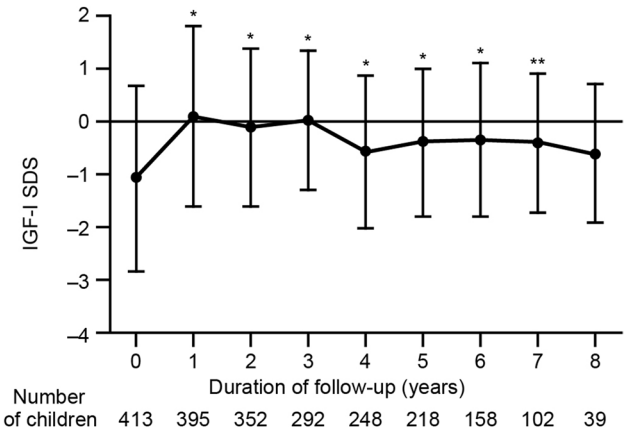

Fig. 3. IGF I standard deviation score (SDS) by the duration of follow-up for naïve children in the full analysis set (FAS). Values are represented as mean ± standard deviation (SD). * P < 0.001 compared with the baseline; ** P < 0.005 compared with the baseline.

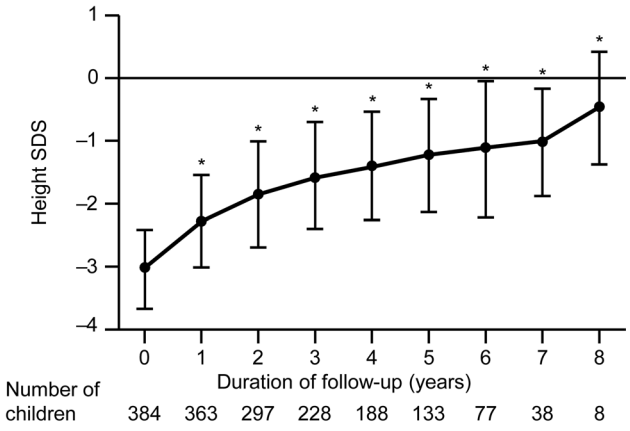

Fig. 4. Height standard deviation score (SDS) by the duration of follow-up for naïve children in the effectiveness analysis set (EAS). Values are represented as mean ± standard deviation (SD). * P < 0.001 compared with the baseline.

treatment, mean bone age was similar to chronological age, as shown by the bone age/chronological age ratio, which was close to 1 (1.03 ± 0.13). In non-naïve children, the mean Δbone age/Δchronological age was 0.94 ± 0.84 during the first yr and increased to 1.52 ± 0.76 from yr 3 to yr 4. As a result of the small number of children in this group, trends in these data could not be identified after yr 6 (n = 3).

IGF I

Mean IGF I SDS increased after the start of GH treatment (**Fig. 3**). After 1 yr, there was a significant increase in mean IGF I SDS from below 0 (–1.08 ± 1.74; n = 413) to close to 0 (0.10 ± 1.68; n = 395; P < 0.001). After the first year, there was a decrease in the mean IGF I SDS. However, mean values remained significantly higher than the baseline after 7 yr (–0.41 ± 1.29; n = 102; P < 0.05) but still within the normal range (–2.00 to +2.00).

Effectiveness

An increase in height SDS from baseline was observed after the start of GH treatment (**Fig. 4**). Mean height SDS in naïve children increased from –3.02 ± 0.65 (n = 384) at baseline to –1.23 ± 0.91 (n = 133; P < 0.001) after 5 yr of GH treatment, which represents a mean increase in height SDS of 1.80 ± 0.72. Height SDS remained above baseline during yr 7 and 8. However, the small number of children for whom data was available at yr 7 and 8 have made interpretation of data trends less reliable. The greatest mean change in height SDS from baseline was observed after the first year of GH treatment (0.76 ± 0.37). After 2 yr of GH treatment, the mean height SDS were within the normal population range (between –2 and +2 SDS; –1.85 ± 0.85).

Height velocity (cm/yr) and height velocity SDS

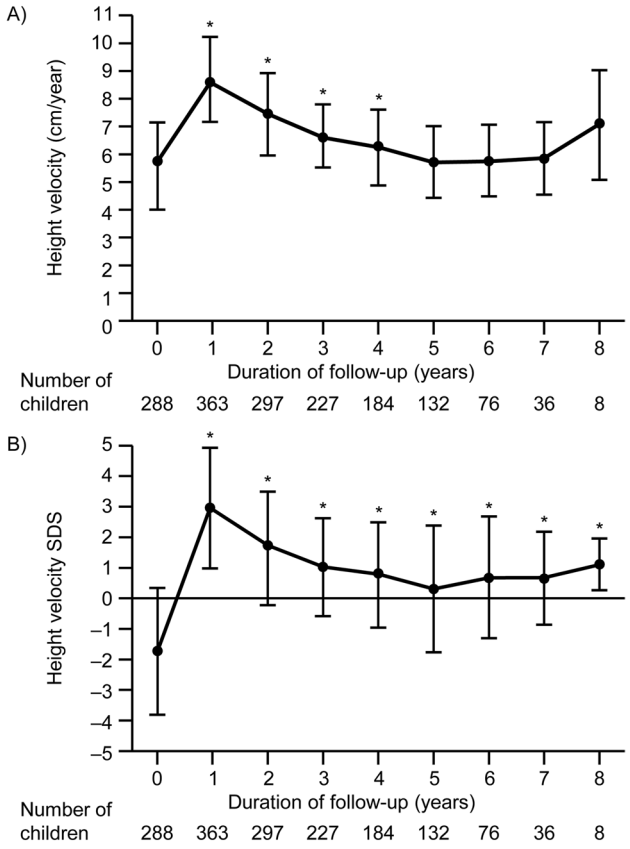

Fig. 5. A) Height velocity (cm/yr) and B) height velocity standard deviation score (SDS) by the duration of follow-up for naïve children in the effectiveness analysis set (EAS). Values are represented as mean ± standard deviation (SD). * P < 0.001 compared with the baseline.

data by the duration of follow-up for naïve children in the EAS are shown in **Fig. 5**. A significant increase in height velocity was observed after 1 yr of GH treatment. Mean height velocity increased from 5.63 ± 1.63 (n =

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288) at the start of GH treatment to 8.69 ± 1.54 (n = 363) after 1 yr, which represents a mean increase of 3.09 ± 2.21 (P < 0.001). Height velocity remained significantly higher than baseline until yr 4 (6.24 ± 1.37; n = 184; P < 0.001 compared with baseline), after which it returned to values close to the baseline. The mean height velocity SDS increased from the low values (–1.76 ± 2.09; n = 288) at the start of the treatment to values above 0 (2.98 ± 1.98; n = 363; P < 0.001) after 1 yr of GH treatment. The mean height velocity SDS remained significantly elevated (P < 0.001) compared with the baseline during the remainder of the follow-up period.

A summary of the demographic characteristics of the 57 (naïve, n = 32; non-naïve, n = 25) children who achieved NAH during the study is shown in **Table 2**. Among the naïve children who reached NAH (7 males and 25 females), the mean NAH was 160.3 ± 4.2 cm (mean NAH SDS, –1.77 ± 0.75) in males and 146.6 ± 6.4 cm (mean NAH SDS, –1.55 ± 0.85) in females. The changes in the height SDS to NAH were 0.85 ± 0.53 in males and 0.85 ± 0.77 in females. The mean pubertal height gain (from the onset of puberty to NAH) was 22.4 ± 6.7 cm in males and 17.5 ± 8.5 cm in females. The mean age at which NAH was achieved was 17.7 ± 0.9 yr in males and 15.0 ± 1.2 yr in females. The mean duration of treatment to NAH was 4.29 ± 1.64 yr. The growth patterns for all naïve children, including those who reached NAH, classified by gender, are shown in Supplementary Fig. 3.

Among the non-naïve children (9 males and 16 females) who achieved NAH, the mean height was 159.7 ± 5.8 cm (mean height SDS, –1.48 ± 0.77) for males and 146.6 ± 6.4 cm (mean height SDS, –1.55 ± 0.85) for females at NAH, an increase of 1.15 ± 0.55 for males and 1.29 ± 0.72 for females from the start of the study. The mean duration of treatment to NAH for non-naïve children was 7.26 ± 2.07 yr. No relationship between baseline age and NAH was observed (r = –0.232).

Out of the 57 children who achieved NAH, 33 (57.9%) had discontinued GH treatment prior to reaching NAH. Data for these 33 children were included in the NAH analyses.

Puberty

As shown in **Fig. 6**, 54.9% of male naïve children had onset of puberty by 11.5 yr of age compared with 56.5% of male non-naïve children. For females, 68.4% of non-naïve and 64.2% of naïve children had pubertal onset by 10.5 yr of age. Precocious puberty was reported as an ADR in three children (0.7%; 1 male and 2 females).

QoL score

QoL was analyzed in 254 naïve children in the FAS who completed the QoL questionnaire. A significant increase in the mean total QoL score from baseline was reported after 1 yr (baseline: 2.30 ± 0.31, n = 192; yr 1: 2.37 ± 0.31, n = 190); a change from baseline of 0.06 ± 0.23 (P < 0.005; **Fig. 7**). The mean values for the total QoL score remained higher than baseline during the remainder of the study. After 8 yr, the mean total QoL score was 2.55 ± 0.26 (P = 0.080 compared with the baseline). Significant increases in the QoL scores for the domains 'physical discomfort of your child' and 'reactions from adults towards your child' compared with the baseline were reported during the study.

Discussion

In this study, we evaluated the long-term safety and effectiveness of GH treatment for up to 9 yr in 452 children who were naïve to GH treatment and up to 11 yr in 46 children who had been previously exposed to GH. Our study also included 57 children (naïve, n = 32; non-naïve, n = 25) who achieved NAH.

Table 2. Characteristics of the children (n = 57) who achieved near adult height

Characteristic	Naïve			Non-naïve			Total		
	Total (n = 32)	Male (n = 7)	Female (n = 25)	Total (n = 25)	Male (n = 9)	Female (n = 16)	Total (n = 57)	Male (n = 16)	Female (n = 41)
Baseline									
Age (yr)	10.8 ± 2.1	12.7 ± 1.4	10.3 ± 1.9	5.4 ± 1.1	5.4 ± 1.2	5.4 ± 1.1	8.4 ± 3.2	8.6 ± 4.0	8.4 ± 2.9
Height SDS	–2.85 ± 0.41	–2.63 ± 0.55	–2.92 ± 0.35	–2.76 ± 0.45	–2.63 ± 0.51	–2.84 ± 0.40	–2.81 ± 0.42	–2.63 ± 0.51	–2.89 ± 0.37
Pubertal onset									
Age (yr)	11.8 ± 1.6	13.2 ± 0.7	11.4 ± 1.6	11.0 ± 1.3	11.7 ± 1.0	10.6 ± 1.3	11.4 ± 1.5	12.4 ± 1.1	11.1 ± 1.5
Height (cm)	–	137.9 ± 6.1	128.7 ± 8.3	–	139.4 ± 9.5	133.9 ± 8.5	–	138.7 ± 8.0	130.7 ± 8.7
Height SDS	–2.56 ± 0.56	–2.57 ± 0.66	–2.56 ± 0.54	–1.08 ± 0.74	–1.10 ± 0.65	–1.06 ± 0.80	–1.91 ± 0.98	–1.75 ± 0.98	–1.98 ± 0.98
NAH									
Age (yr)	15.6 ± 1.6	17.7 ± 0.9	15.0 ± 1.2	14.8 ± 1.6	16.0 ± 1.2	14.1 ± 1.3	15.2 ± 1.6	16.7 ± 1.4	14.6 ± 1.3
Height (cm)	–	160.3 ± 4.2	145.5 ± 4.9	–	159.7 ± 5.8	146.6 ± 6.4	–	159.9 ± 5.0	145.9 ± 5.5
Height SDS	–2.03 ± 0.77	–1.77 ± 0.75	–2.10 ± 0.78	–1.53 ± 0.81	–1.48 ± 0.77	–1.55 ± 0.85	–1.81 ± 0.82	–1.61 ± 0.75	–1.89 ± 0.84
Other									
Δ Height SDS	0.85 ± 0.72*	0.85 ± 0.53	0.85 ± 0.77†	1.24 ± 0.66	1.15 ± 0.55	1.29 ± 0.72	1.02 ± 0.71‡	1.02 ± 0.54	1.02 ± 0.77§
Δ Height after pubertal onset (cm)	–	22.4 ± 6.7	17.5 ± 8.5†	–	20.2 ± 9.6	12.7 ± 4.5	–	21.2 ± 8.3	15.6 ± 7.5§
Treatment duration (yr)	4.29 ± 1.64	4.13 ± 1.21	4.34 ± 1.76	7.26 ± 2.07	8.73 ± 2.08	6.44 ± 1.59	5.60 ± 2.35	6.72 ± 2.91	5.16 ± 1.97

Data are represented as mean ± SD. * n = 31; † n = 24; ‡ n = 56; § n = 40. EAS, effectiveness analysis set; NAH, near adult height; Δ Height after pubertal onset, change in height after onset of puberty; SDS, standard deviation score.

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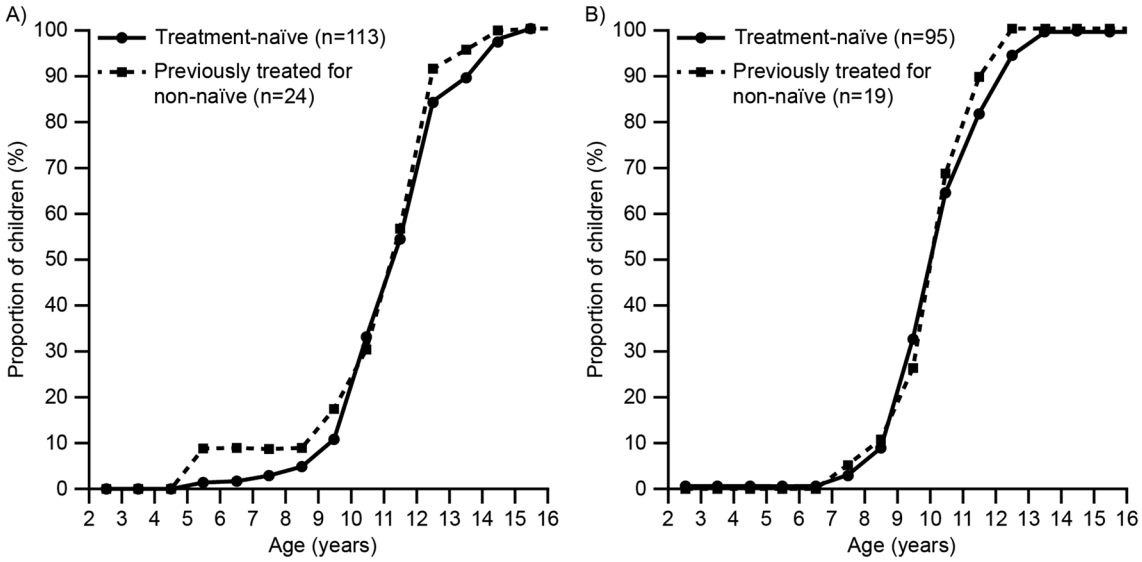

Fig. 6. Frequency curves of pubertal onset by the age at pubertal onset for A) male and B) female children in the full analysis set (FAS). Onset of puberty was defined as: One of Tanner parameters stage II; testicular volume ≥ 4 mL (boys) or presence of menses (girls).

The frequency of SADRs, the primary endpoint of the study, was low, at 1.3% (6/452 naïve children) and 0.0% (0/46 non-naïve children). The SADRs were mostly conditions frequently reported in childhood and no safety concerns were raised based on the cases reported during this study. The safety profile, as assessed by the SADRs observed in this study, was similar to that reported in previous studies involving GH-treated Japanese children born SGA (27, 28).

An increase in fasting insulin levels and glucose-stimulated insulin levels during GH treatment has been previously reported in children with short stature born SGA who received long-term GH treatment (11), suggesting that relative insulin resistance may develop during long-term GH treatment (11, 29). Furthermore, insulin resistance has also been described in non-GH treated children born SGA as young as 1 yr (30), as well as in prepubertal children born SGA (31, 32). In the present study, a small increase in HbA1c was observed during 8 yr of GH treatment but mean values remained below the upper limit of the normal range (4.6–6.2%). None of the children enrolled in the study developed diabetes and no concerns regarding the measured glucose metabolism parameters were raised in participants who received GH treatment for up to 9 yr. Among the 88 prepubertal Japanese children born SGA treated with GH at a dose of 0.23 or 0.47 mg/kg/wk for 3 yr, Yokoya and colleagues reported a statistically significant increase in HbA1c, fasting blood glucose, and fasting and sigma immunoreactive insulin in the oral glucose tolerance test during GH treatment when compared with baseline values (27). However, all mean values in the study remained within the normal range. In another study involving 61 children with short stature born SGA, HbA1c levels remained within the normal range for up to 15 yr of GH treatment (0.47 mg/kg/wk) (13). Previous studies have suggested that there is a decrease in insulin sensitivity which occurs during puberty that compensates for the increase in insulin secretion (29). Therefore, at least part of the changes in insulin resistance observed during long-term GH treatment may be accounted for by natural changes in insulin metabolism in children transitioning into puberty. Overall, our study raised no concerns regarding the effect of long-term GH treatment on glucose metabolism in Japanese children with short stature born SGA.

In our study, we observed that the IGF I SDS increased shortly after starting GH treatment and remaining constantly close to 0 SDS thereafter. These data are reassuring and do not suggest an inappropriate increase in IGF I SDS. An increase in IGF I SDS to approximately +2 after the start of GH treatment was reported by Tanaka *et al.* (13). The lower mean IGF I SDS following initiation of GH treatment reported in our study when compared with those reported by Tanaka *et al.* (13) may reflect the under-dosing of GH and it is possible that higher doses of GH could have produced more pronounced improvements in height outcomes. There may also be differences in the IGF I response associated with GH treatment in children born SGA depending on the etiology of their condition and whether or not they are GH deficient (33).

The mean height SDS of naïve children enrolled in our study increased from below the normal population reference range (–3.02 ± 0.65) to within the normal population range (between –2 and +2 SD; –1.85 ± 0.85) after 2 yr of GH treatment. After 8 yr of GH treatment, the mean height SDS was approximately –0.5 (–0.48 ± 0.90), a mean increase in SDS of 2.73 ± 1.12 from the start of the treatment. Thus, the mean height SDS were normalized (between –2 and +2 SD) in the naïve children following the initiation of GH treatment. The greatest

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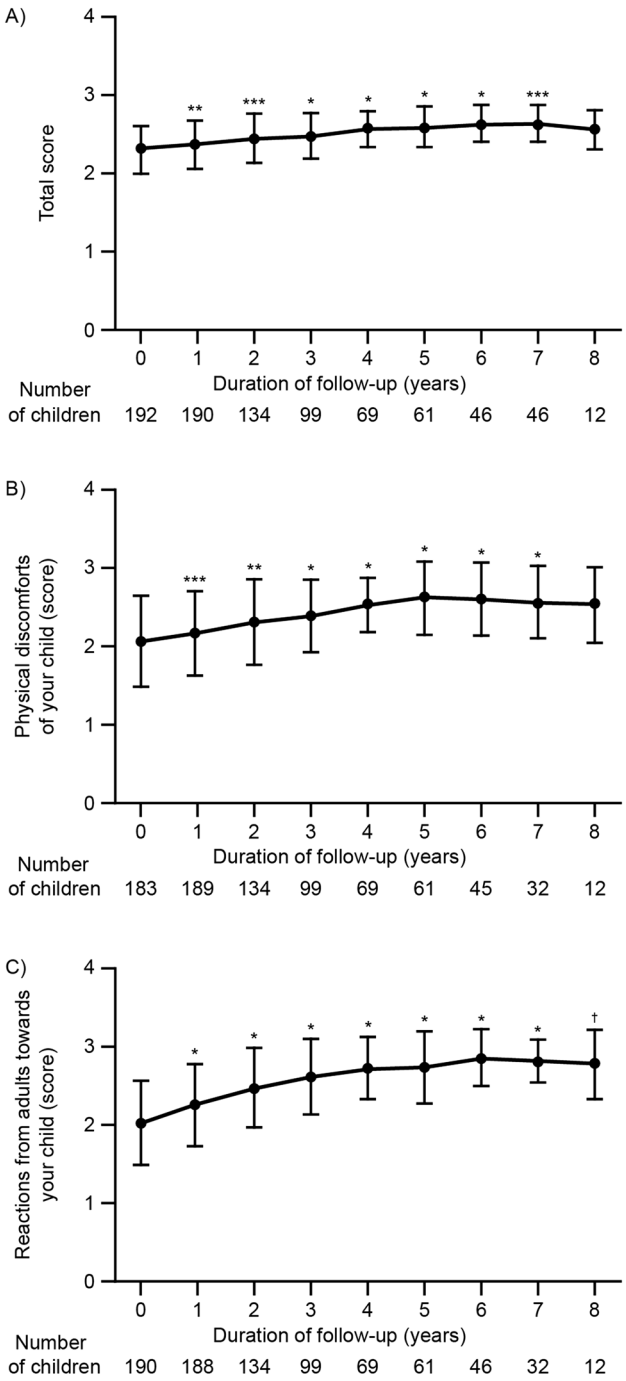

Fig. 7. Quality of life (QoL) A) total score, B) domain: physical discomfort and C) domain: reactions from adults towards your child for naïve children included in the QoL analysis set by duration of follow-up. Values are represented as mean ± standard deviation (SD). * $P < 0.001$ compared with the baseline; ** $P < 0.005$ compared to the baseline; *** $P < 0.01$ compared with the baseline; † $P < 0.05$ compared with the baseline.

annual change in mean height SDS from baseline in naïve children (0.76 ± 0.37) was observed during the first year of treatment. This was reflected by a significant increase from baseline in height velocity (cm/yr) and height SDS after 1 yr. It is worth mentioning that since the mean height SDS for chronological age at enrollment in our study for naïve children was below −3.0 SD and the mean growth velocity SDS for chronological age before starting GH treatment was below −1.5 SD that the degree of short stature would have almost certainly worsened without treatment in many of these children. An increase in height SDS during the first 7 yr of GH treatment in Japanese children with short stature born SGA has been previously reported (14, 16, 27). Tanaka *et al.* (16) reported a mean increase in height SDS from baseline of 1.22 ± 0.51 and 2.01 ± 0.64 in children receiving a GH dose of 0.033 ± 0.231 and 0.067 ± 0.462 mg/kg/d, respectively, for 5 yr. In another study, Yokoya and colleagues reported that administering a higher dose of GH (0.47 mg/kg/wk) in children who had a poor growth response during or after the second year of treatment, in accordance with the Japanese guideline-based second year treatment schedule (18), improved the growth response (27). These data suggest that although some children respond well to a low GH dose of 0.23 mg/kg/wk, those with a poor initial response may subsequently show an improvement in growth following an increase in the dose of GH administered. Therefore, it has been suggested that after commencing treatment with a low dose of GH, there should be a periodical review of the dose administered in the initial years and that the GH dose may be increased if the observed growth response is considered insufficient (27). In our study, the increase in the mean GH dose from 0.248 ± 0.068 mg/kg/wk at enrollment to 0.346 ± 0.078 mg/kg/wk during the course of the study (at yr 4) shows that there was a titration of the GH dose administered in normal clinical practice. The GH doses reported in this study are within the range recommended (0.23–0.47 mg/kg/wk) for treating children with short stature born SGA in Japan (18).

Almost all children in our study started puberty within the normal range for healthy Japanese children (34, 35), as has previously been reported in GH-treated children with short stature born SGA (14, 36). Precocious puberty was reported in three children. Together, these data suggest that, in general, there was no inappropriate acceleration of puberty due to GH treatment that may have limited the potential for growth.

No inappropriate advancement of bone age relative to chronological age was observed during our study. Nevertheless, it is possible that height SDS for bone age remained below-average in children who exhibited a below average gain in height during GH treatment. Previous studies have found conflicting results in regards to the progression of bone age during GH treatment in children with short stature born SGA, with some reporting no excessive progression of bone age relative to chronological age during GH treatment (16, 27) and others describing that bone age exceeded chronological age in some children following GH treatment (14). In children with GH deficiency (GHD), bone age was retarded relative to chronological age when they entered puberty (37). A more rapid advancement in bone age in children born SGA than in children with GHD may result

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in an elevated bone age relative to chronological age at puberty and consequently a lower pubertal height gain in some GH-treated children born SGA when compared with children with GHD (38).

In the present study, mean height SDS at NAH were –2.03 in naïve children and –1.53 in non-naïve children. In a previous controlled trial, van Pareren *et al.* reported mean adult height SDS of –1.1 ± 0.7 and –0.9 ± 0.8 after treatment with a GH dose of 3 IU/m^2/d (approximately 0.033 mg/kg/d) and 6 IU/m^2/d (approximately 0.067 mg/kg/d), respectively, for 7.5 to 7.9 yr (39). However, in a similar trial Carel *et al.* reported mean adult height SDS of –2.1 ± 1.1 after 2.7 yr of GH treatment at a daily dose of 0.2 IU/kg/d (0.067 mg/kg/d) (40). Other studies have reported mean NAH SDS of –1.2 ± 0.7 (7) and –1.4 to –1.9 (41), while a meta-analysis of randomized controlled studies conducted up to the attainment of adult height involving 391 GH-treated children born SGA reported that the mean height gained to adult height was 1.5 SD in treated children when compared with 0.25 SD in untreated children (42). In Japanese children, Tanaka *et al.* (13) reported a mean NAH SDS of –1.6, representing a mean change in height SDS from baseline to NAH of +1.9 in boys and +1.8 in girls. Our results are therefore comparable to previous reports. However, it is important that care is taken in extrapolating NAH SDS values to adult height SDS. Our data on NAH SDS were calculated based on reference values of the standard height at the age when each child fulfilled the criteria for NAH and may, therefore, represent an overestimation of adult height. In contrast, if adult height SDS are estimated from the observed NAH based on the standard height at the age of 17.5 yr for Japanese boys and girls (43) and assuming the observed NAH equals adult height, the mean adult height SDS for boys and girls, respectively, in our study would be –1.80 ± 0.72 and –2.41 ± 0.93 in naïve children and –1.91 ± 1.00 and –2.19 ± 1.21 in non-naïve children.

Our study has several limitations relating to the evaluation of the NAH SDS in naïve children as a result of the restrictions imposed by the study duration. Mean age at the start of GH treatment for the naïve children who achieved NAH was 10.8 yr and the mean duration of GH treatment was 4.29 yr. As the median (range) age at the start of treatment for the whole population of naïve children was 4.0 (3.0–14.0), only those children in the naïve group who were at the upper end of the age range (10 yr or older) at the start of treatment achieved NAH. Therefore, the results of the NAH SDS for naïve children obtained in our study may not be applicable in clinical practice as most children born SGA start GH treatment at a young age (13). Furthermore, in the naïve children who achieved NAH, the mean age of pubertal onset was 13.2 yr for boys and 11.4 yr for girls. This was later than in the overall population of naïve children included in this study and also later than reported in a previous study on GH-treated children with short stature born SGA (boys 11.7 yr, girls 9.6 yr) (13). Therefore, our data suggest that it is likely that the children in the naïve group who achieved NAH had delayed puberty. Finally, children in the naïve group who reached NAH exhibited a limited gain in height from the start of the treatment. This may be attributed to the short duration of the pre-pubertal GH treatment, which was approximately 0.5 yr in males and 1.1 yr in females. Evidence suggests that a longer duration of GH treatment before puberty onset is associated with improved clinical outcomes in regards to adult height in children with short stature born SGA (41). In a randomized controlled trial, children who received GH treatment for more than 2 yr before puberty gained 1.7 SD in height (almost 12 cm in increased adult height), while those treated for less than 2 yr before puberty gained 0.9 SD in height (9 cm in increased adult height) (7). Indeed, the gain in height after the onset of puberty in our naïve children who reached NAH was 22.4 cm in males and 17.5 cm in females, as a result of the late onset of puberty in these patients. In contrast, the gain in height reported after the onset of puberty in untreated children with short stature was 25.8 cm in males and 18.9 cm in females (44).

Overall, 25 (54.3%) of the 46 non-naïve children enrolled in our study achieved NAH. The mean NAH SDS for these children was –1.53, with 76.0% of children achieving a NAH SDS of > –2. These data are similar to those reported in a cohort of Japanese children with short stature born SGA who were mostly treated with a daily GH dose of 0.067 mg/kg/d (13).

The comparison of the baseline demographics of the children enrolled in this trial with the previous phase 3 trial and the characteristics of the overall children population in that phase 3 trial (16) showed that the two populations had very similar clinical characteristics. The baseline age and mean gain in height SDS during the phase 3 trial for the non-naïve children who participated in the present study were similar to those of the children from the phase 3 trial who did not continue into the present study (4.58 ± 1.20 yr and 1.72 ± 0.74, n = 31, compared to 4.89 ± 1.29 yr and 1.61 ± 0.72, n = 19). These data suggest that there was no selection bias related to age or growth achieved while receiving GH treatments before this study. Among the non-naïve children in our study, the mean change in height after the onset of puberty was 20.2 cm in males and 12.7 cm in females, which was lower than previously reported in untreated children with short stature (44). In children with idiopathic short stature, GH treatment (3.0 IU/m^2/d) was associated with an acceleration in bone age (45). Therefore, the lower than expected gain in height following puberty observed in the present study may also be due, at least in part, to an inappropriate acceleration of bone age, thereby reducing the potential for growth after puberty.

In the present study, the mean height SDS at NAH were higher in non-naïve children than in the children who were treatment naïve. This is likely because the non-naïve children started GH treatment at a younger age and therefore had a longer total GH treatment duration overall and, notably, a longer duration of GH

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treatment before puberty. However, we did not find a correlation between NAH SDS and baseline age (r = –0.233, P = 0.0815, n = 57) in the combined NAH SDS data from naïve and non-naïve children. Nevertheless, GH dose and duration of treatment may be an important determinant of height gain in short children born SGA (46). Thus, children who start treatment earlier have enough time to catch up to the normal height range even when receiving a lower GH dose, whereas those who start treatment later may also catch up, although they may require an increase in the dose of GH.

After the start of the GH treatment, we observed a significant improvement in the total QoL score from baseline, as well as in the domains that were related to height, including physical discomfort and the perception of the child by adults from outside the family. Statistically significant improvements in these scores were observed after only 1 yr of GH treatment. Bannink and colleagues reported that adolescents born SGA who experienced an increase in height following GH treatment had an improved QoL compared with untreated adolescents born SGA (26). Moreover, an improvement in QoL items related to stature has previously been reported in children with short stature born SGA after 2 yr of GH treatment (27, 47) and in physical, social, and emotional QoL items after just 1 yr of GH treatment.

A limitation of our study, in common with other real-world evidence data was that treatment regimens and assessments may not have been consistent between study centers, thereby reflecting regional differences in treatment protocols. Accordingly, centers may have differed in the manner in which the GH dose was adjusted throughout the study and in assessments of bone age and pubertal staging. Nevertheless, our data provide an accurate reflection of the treatment of children with short stature born SGA currently used clinical practice in Japan. As mentioned previously, it is also possible that our data on NAH are not applicable to all Japanese children with short stature born SGA treated with GH owing to the limited duration of the study which meant that only children who were older at study enrollment were able to achieve NAH within the study follow-up period.

Conclusion

The results of this non-interventional study evaluating the long-term safety and efficacy of GH in Japanese children with short stature born SGA who did not exhibit closure of epiphyseal discs demonstrated that long-term GH treatment in clinical practice posed no new safety concerns and demonstrated the long-term effectiveness of the treatment, particularly in regards to height and QoL.

Conflict of Interests: HN and YN are employees of Novo Nordisk Pharma Ltd. RH, TT, and SY have received honoraria from Novo Nordisk Pharma Ltd. RH and TT have received research funding from Novo Nordisk Pharma Ltd.

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