A Four-Year, Open-Label, Multi-Center, Randomized, Two-Arm Study of Genotropin[®] in Patients with Idiopathic Short Stature: Comparison of an Individualized, Target-Driven Treatment Regimen to Standard Dosing of Genotropin[®] – Analysis of Two-Year Data

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Key Words

Short stature · Growth hormone · Individualized · Formula-based dose · Idiopathic short stature

Abstract

Background: Several models have been developed to predict growth response to growth hormone (GH) based on auxological and biochemical parameters for children with non-GH-deficient, idiopathic short stature (ISS). **Objective:** To demonstrate if an individualized, formula-based, target-driven GH regimen for children with ISS would lead to a height (Ht) gain to –1.3 SDS during the first 24 months of treatment of this 4-year study, with less variability than with standard weight-based dosing. **Methods:** A 4-year, open-label, multi-center, randomized, two-arm study comparing formula-based dosing of Genotropin[®] GH from 0.18 to 0.7 mg/kg/week versus standard FDA-approved ISS dosing of Genotropin[®] (0.37 mg/kg/week). Subjects (n = 316, 89 females) were prepubertal, 3–14 years of age, bone age 3–10

years (m) and 3–9 years (f), naive to GH treatment, Ht SDS –3 to –2.25, Ht velocity <25th percentile for bone age, and peak GH >10 ng/ml. **Results:** The majority (83%) of subjects had Ht SDS within the normal range by 2 years. All subjects displayed catch-up growth consistent with other studies of GH treatment of ISS. **Conclusion:** The formula-based therapy did not meet the primary endpoint achieving targeted gain with lower variability. No new safety concerns were found.

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Introduction

Non-growth hormone (GH)-deficient idiopathic short stature (ISS) is a potentially treatable cause of childhood growth failure amenable to GH therapy. This indication has been more controversial than others approved by the Food and Drug Administration (FDA), due to a lack of universal definition of the condition [1, 2], the apparent diversity of potential etiologies in individual cases [3], the

inclusion of children with constitutional short stature and/or familial short stature in research studies [4], the potentially high incidence in the population [5], the cost of long-term therapy [6, 7], and the uncertainty of adult height (Ht) outcome [8–10] and/or psychological benefits [9, 11, 12]. Mutations in several genes have been identified in children initially diagnosed with ISS, including those encoding the GH receptor [13], the insulin-like growth factor-I (IGF-I) receptor (also known as the type 1 IGF receptor) [14], and signal transducer and activator of transcription (STAT) 5b [15], demonstrating that some children with this condition have a definable basis for their growth failure. For the majority, however, no distinct etiology is found, although there is often a blurred line between ISS and familial and/or constitutional short stature [1].

Prior and limited studies of relatively low-dose GH treatment of children with ISS have shown significant variability in the improvements in final adult Ht [16, 17]. Newer data, derived from mathematical modeling, indicate that short-term improvements in Ht velocity in this population can be optimized by utilizing treatment regimens predicated on, among other factors, younger age of treatment initiation and earlier use of higher doses of GH, an approach that does not appear to evoke any unusual safety signals [18, 19]. Recently, a randomized trial of GH treatment in Swedish children with ISS showed that individualized, formula-based GH dosing according to multivariate non-linear prediction models diminished the variability of the observed Ht response [20]. This clinical study described by Kristrom et al. [20] is quite similar in its basic structure to our study. Both studies utilized a formula (derived from the work of Albertsson-Wikland et al. [24]) to predict the dose needed for catch-up growth within 2 years. However, there are also several differences between the studies. These differences include the patient base; Kristrom et al. studied 153 children, 110 with GH deficiency and only 43 with ISS, while we studied 316 children, all with ISS; children born small for gestational age (SGA) were included in the study described by Kristrom et al., while SGA was an exclusion criteria in our study. Additionally, the formulas used were of similar origin, but our formula was significantly modified from the original formula. The primary objective of the Kristrom study was to decrease the variability in the response to rhGH, while our study aimed to validate our 'modified formula', and secondarily to decrease the variability of the response to rhGH. Another significant difference is that our study was a 4-year study. After the initial 2 years, the children in the experimental arm had their doses lowered

to either 0.18 or 0.24 mg/kg/week, with the hypothesis that the growth rate established in the first 2 years of treatment would not decrease.

The usual treatment paradigm for children with ISS is to prescribe a uniform weight-based dose of GH as directed by the FDA-approved labeling, such as is typically employed with other FDA-approved indications. This approach may be flawed because all children are treated identically, a practice that ignores the inherent individual differences in sensitivity to GH. This practice results in an inefficient use of GH as more drug is used toward the end of treatment, when children are larger/heavier and may be less sensitive to exogenous treatment, and it increases the theoretical risks of increased serum IGF-I levels over a prolonged period [21, 22]. Thus, the current study was undertaken to explore the use of a mathematical formula to calculate individualized doses of GH to achieve targeted growth responses over a 2-year period compared to standard dosing and to develop an improved treatment regimen that achieves better short-term Ht outcomes. The formula determines the individualized dose by taking into account the general dose-response relationship between GH and the growth response in children with ISS, as well as several individualized, non-invasive parameters, including targeted Ht gain, mid-parental Ht (MPH), and various pretreatment auxological characteristics. Herein we report the planned, mid-point results of our study after 2 years of GH treatment (fig. 1).

Subjects and Methods

Patients and Study Design

This is a 4-year, open-label, multi-center randomized two-arm study of recombinant human GH (Genotropin®; Pfizer, Inc., New York, N.Y., USA) in subjects with ISS comparing a formula-based dose aimed at achieving a targeted Ht goal within 24 months, followed by a decrease to near-physiological dosing [23] for the remaining 2 years, versus standard weight-based dosing for 4 years. General inclusion criteria for entry into this study included that the subjects be prepubertal, previously untreated with GH, and have a bone age of 3–10 years for males and 3–9 years for females. Inclusion criteria used for the diagnosis of ISS were that subjects' Hts had to be between 2.25 and 3.0 SDS below the mean for age and gender (Ht SDS), their Ht velocity below the 25th percentile (–0.67 SD) for age, with peak GH >10 ng/ml after pharmacological stimulation (using local testing protocols) and normal karyotype (females). The entry criteria for the trial attempted to restrict subject enrollment to those individuals with ISS who would most likely attain a targeted Ht gain (i.e. not be so short that they would have insufficient time to catch up), as well as to those in whom non-GHD short stature was indeed the diagnosis (confirmed by normal GH stimulation test results). Lack of bone age delay was not required. Exclusion criteria included having been born SGA, al-

Fig. 1. Timeline and randomization scheme of standard and formula-based treatment arms for 4-year study. Blue box denotes current analysis of 2-year data. Color refers to online version only.

though if the alternative criteria of the consensus statement of the International Societies of Pediatric Endocrinology and the Growth Hormone Research Society were employed (Clayton, 2007, #477), some subjects would have been classified as SGA, and therefore excluded. Additional exclusion criteria included evidence of GH resistance/primary IGF-I deficiency, skeletal dysplasia, chronic diseases, excessive corticosteroid use, and presumed inability to comply with the protocol. Randomization to formula-based or standard dose, in a 2:1 ratio, was stratified by age (≤ 7 and > 7 years) and gender, but not by MPH. The prescribed dose was either one calculated at baseline (ranging between 0.18 and 0.7 mg/kg/week) using the individualized formula or a standard (FDA-approved) dose (for ISS) of 0.37 mg/kg/week. Written informed consent was obtained from all subjects and/or a legally acceptable representative before initiation of any protocol-specified procedures.

The formula employed in this trial to calculate formula-based dosing was developed by Pfizer specifically for use in this trial and remains proprietary. The formula builds upon previous work by Albertsson-Wikland et al. [24] and determines the individualized dose by modifying the general dose-response relationship between GH and the growth response in children with ISS with several individualized, non-invasive parameters such as the targeted Ht gain, MPH (reported or measured), and various auxological points (including data from birth, the first 2 years of life, and from the 2 years before GH treatment was initiated). The 5th percentile of the relevant distribution was used when replacing the missing values. Biochemical markers of GH production or responsiveness were not used in dose calculation in the formula-driven arm of the trial.

Endpoints/Statistical Methods

The study is 4 years in duration, but is divided into two phases. Phase 1 includes the screening and randomization plus the first 2 years of GH therapy, data from which will be presented and analyzed herein. In phase 2, encompassing the final 2 years of the trial, those initially receiving formula-based dosing are re-randomized to either of two maintenance doses, 0.24 or 0.18 mg/kg/week, and those on standard dosing continue at their same dose of GH (adjusted for weight) (fig. 1).

The primary efficacy endpoint is the *absolute on-target difference* (AOTD) that is a derived measure of the accuracy of the dose-predicting formula. The AOTD is defined as the difference be-

tween the expected and actual Ht SDS. In order to identify both over- and underestimations, the absolute value of the AOTD was reported. Ht SDS was calculated using National Center for Health Statistics pediatric growth charts [25], and target Ht SDS was pre-set at -1.3 (i.e. 10th percentile). The secondary endpoints are the variability of the 24-month Ht SDS, the time to reach -2.0 SDS (the normal Ht threshold), and the 2-year safety data. The planned sample size ($n = 312$) was based on the assumption that the month 24 Ht SDS is distributed with a mean of -1.3 SDS and standard deviation (SD) of 0.525 in the formula arm and -1.5 (0.7) in the standard treatment arm.

As per the analysis plan, a one-sided, 2.5% level superiority test was performed to evaluate the primary hypothesis that the formula-based dose arm is superior to the standard dose with respect to AOTD at 24 months, using an ANCOVA model with a square root of AOTD as a response variable and treatment, age stratum, gender, and baseline Ht SDS as model terms. The secondary efficacy endpoints were evaluated using Levene's test from one-way ANOVA (Ht SDS variability at 24 months), or using a Cox proportional hazards model, with terms for age, gender, treatment arm, and baseline Ht SDS. Secondary analyses were performed without an adjustment for multiplicity at a two-sided, 5% level. The last post-baseline observation carried forward rule (LOCF) was applied to replace missing data on Ht SDS for the efficacy endpoint analyses (except for the 'time cost' analysis). Efficacy analyses were performed on randomized subjects who received at least one dose of treatment and who had at least one post-baseline Ht SDS value available, according to the subject's treatment arm at randomization ('as-randomized'). The safety summaries were performed on subjects with at least one dose of study drug, evaluated according to the treatment that they actually received ('as-treated').

Study Assessments

Subject visits occurred every 4 months for a total of seven visits over the first 2 years. Stadiometer Ht in triplicate and physical examination, including assessments of Tanner stage (male external genitalia, female breasts, and pubic hair in both sexes), were performed at screening and at every visit through month 24. Blood samples were collected at screening and at month 12 and 24 visits for evaluation of IGF-I, IGFBP-3, complete blood count, free thyroxine, TSH, morning cortisol, and hemoglobin A_{1c} (laboratory

Table 1. Baseline characteristics (values are mean $\pm$ SD and range)

	Formula-based dose (n = 202)		Standard dose (n = 114)	
	boys (n = 144)	girls (n = 58)	boys (n = 83)	girls (n = 31)
Age, n (%)				
≤ 7 years	51 $\pm$ 35.4	19 $\pm$ 32.8	29 $\pm$ 34.9	8 $\pm$ 25.8
> 7 years	93 $\pm$ 64.6	39 $\pm$ 67.2	54 $\pm$ 65.1	23 $\pm$ 74.2
Ht, SDS	-2.54 $\pm$ 0.36 -4.6 to -1.6	-2.63 $\pm$ 0.34 -3.9 to -2.2	-2.47 $\pm$ 0.27 -3.2 to -2.0	-2.62 $\pm$ 0.39 -4.1 to -2.1
Gestational age, weeks	(n = 137) 38.4 $\pm$ 2.8 24 to 42	(n = 56) 38.5 $\pm$ 2.5 28 to 42	(n = 81) 38.6 $\pm$ 2.5 28 to 42	(n = 29) 37.8 $\pm$ 2.5 24 to 42
Birth weight, kg	(n = 136) 3.0 $\pm$ 0.65 0.7 to 4.3	(n = 57) 3.0 $\pm$ 0.55 0.8 to 3.9	(n = 82) 2.9 $\pm$ 0.53 1.4 to 4.2	(n = 28) 2.8 $\pm$ 0.76 1.0 to 4.1
Mother's Ht, SDS	(n = 135) -0.88 $\pm$ 1.05 -4.8 to 1.4	(n = 57) -0.94 $\pm$ 0.96 -3.3 to 1.8	(n = 81) -0.91 $\pm$ 0.93 -3.2 to 1.5	(n = 26) -0.98 $\pm$ 0.83 -2.1 to 1.2
Father's Ht, SDS	(n = 134) -0.64 $\pm$ 0.95 -3.7 to 1.6	(n = 56) -0.90 $\pm$ 1.05 -3.7 to 1.2	(n = 80) -0.72 $\pm$ 0.93 -2.7 to 1.3	(n = 25) -0.6 $\pm$ 0.99 -2.2 to 1.6
MPH, cm	(n = 134) 171.4 $\pm$ 5.28 155.1 to 183.2	(n = 56) 157.3 $\pm$ 5.53 146.0 to 170.0	(n = 80) 170.9 $\pm$ 4.64 160.2 to 181.8	(n = 25) 158.3 $\pm$ 4.64 150.0 to 167.5
Bone age, years	(n = 143) 7.1 $\pm$ 2.07 2.5 to 10.5	(n = 58) 6.9 $\pm$ 1.76 3.0 to 10.5	(n = 83) 7.0 $\pm$ 2.11 3.0 to 10.4	(n = 31) 6.9 $\pm$ 1.5 3.6 to 8.8

assessments were performed by Clearstone Laboratories, East Mississauga, Ont., Canada). In addition, a 2-hour oral glucose tolerance test was performed at months 12 and 24. Bone age radiography was performed at screening and at month 12 and 24 visits, and evaluated centrally by a single radiologist. Adverse events (AEs) were coded using MedDRA version 13.1 (Medical Dictionary for Regulatory Activities is used to report adverse event data from clinical trials).

Results

316 subjects (of 340 screened) were randomized (2:1 ratio): 202 into the formula-based and 114 into the standard dose group, with 198 and 118, respectively, treated in the two groups (4 subjects randomized to the formula-based arm but received the standard dose due to the dose being calculated to 0). The study was conducted at 40 study sites in the USA. Baseline characteristics are presented in table 1. No statistically significant baseline differences were observed between the two study groups.

Efficacy

There was no difference between the two treatment arms with respect to the AOTD endpoint (left, one-sided, standard and formula-based, 97.5% CI limit -0.071, $p = 0.576$). The proportion of subjects who reached a Ht of -2 SDS or taller at some point during the 24 months was similar between the two groups (83%), while 70 (34.7%) subjects in the individualized dose group and 43 (37.7%) in the standard dose group had reached Ht SDS of -1.3 or taller by month 24. Of these, all but 2 (1%) subjects in the formula-based arm and 1 (0.9%) in the standard arm remained at -2 SDS or taller at month 24. Among subjects with Ht SDS measurements at 24 months, 162 (88%) in the formula-based and 91 (90%) in the standard dose arm had a Ht SDS of -2 or taller. No difference was observed between the two treatment groups in median time to reaching a Ht of -2 SDS or taller (median 12 months in both arms, $p = 0.802$) and there was no difference with respect to the SD of the Ht SDS at month 24 ($p = 0.627$). The average formula-based GH dose was 0.063 mg/kg/day (equiva-

Fig. 2. Change from baseline Ht SDS at 12 and 24 months by gender and treatment arm (no significant differences between the two arms at either 12 or 24 months).

lent to 0.44 mg/kg/week) at baseline, 0.061 mg/kg/day (equivalent to 0.43 mg/kg/week) at month 12, and 0.060 mg/kg/day (equivalent to 0.42 mg/kg/week) at month 24.

Mean (SD) Ht SDS at baseline, month 12, and month 24 was -2.56 (0.36), -1.80 (0.38), and -1.42 (0.50), respectively, in the formula-based dose group and -2.51 (0.31), -1.80 (0.43), and -1.37 (0.48), respectively, in the standard dose group (no statistically significant difference between groups was observed at any time point). The change from baseline in Ht SDS at month 24 LOCF was 1.04 (0.54) and 1.03 (0.47), respectively, in the two groups. Figure 2 shows Ht SDS change from baseline by gender and dose group. In a multivariate model that included Ht SDS at baseline as a covariate in addition to dose group, neither age stratum nor gender was significantly related to change in Ht SDS at month 24.

Additional exploratory, post hoc analyses were performed by fitting a multivariate model with Ht SDS change from baseline at month 24 as a response variable and model terms for baseline Ht SDS, age stratum, gender, dose group, and IGF-I SDS change at month 24. An increase from baseline in IGF-I SDS was associated with greater change in Ht SDS ($p < 0.0001$). While the association between these two variables was similar across gen-

ders and treatment groups, a stronger association was observed in the younger compared to the older age stratum ($p = 0.0003$; fig. 3).

At baseline, mean (SD) bone age was 7.07 (1.95) years in the formula dose group compared with 6.85 (2.00) years in the standard dose group. Mean (SD) increase in bone age over baseline was 1.41 (1.01) and 1.38 (0.86) years at month 12, and 2.75 (1.16) and 2.76 (1.06) years at month 24, in the formula and standard dose groups, respectively (no statistically significant difference was observed at any time point). Change in bone age at either month 12 or 24 was not significantly correlated with Ht SDS change at 24 months in either group. Difference between bone age and chronological age was significantly related to chronological age at month 24 (fig. 4) and this relationship was similar across treatment groups. Finally, table 2 shows a summary of the difference between Ht SDS and MPH SDS by treatment group and gender, at baseline, month 12, and month 24. There were no statistically significant differences found between treatment or gender groups. There was no statistically significant difference in the results when the subjects who were outside of protocol Ht entrance criteria were included or excluded from the analysis.

Fig. 3. Change in Ht SDS versus change in IGF-I SDS, stratified by age. Pearson correlation coefficient: 0.746 in children age <7 years and 0.376 for ≥7 years.

Fig. 4. Difference of bone age and chronological age compared to chronological age at baseline and month 24.

Changes in Ht age (which is defined as the CDC reference table age group if the observed Ht were at 50%) at month 24 were significantly correlated with changes in bone age in the formula-based dose group (Pearson correlation coefficient 0.35, $p < 0.0001$) but not in the standard dose group (0.08, $p > 0.05$) (fig. 5).

The significant positive correlation was also present in the combined dataset (all subjects, regardless of dose), where the correlation coefficient was 0.26 with $p < 0.0001$.

At baseline, the majority of male and female subjects in both treatment groups were at Tanner stage 1 [195

Table 2. Summary of Ht SDS – MPH SDS by visit

	Formula-based dose (n = 202)			Standard dose (n = 114)		
	male	female	total	male	female	total
<i>Baseline</i>						
Number	134	56	190	80	25	105
Mean $\pm$ SD	-1.78 $\pm$ 0.69	-1.7 $\pm$ 0.81	-1.76 $\pm$ 0.73	-1.65 $\pm$ 0.68	1.82 $\pm$ 0.69	-1.69 $\pm$ 0.69
Median (min, max)	-1.7 (-3.4, 0.2)	-1.7 (-3.9, -0.2)	-1.7 (-2.9, 1.5)	-1.6 (-3.6, -0.3)	-1.87 (-3.2, -0.8)	-1.6 (-3.3, -0.3)
<i>Month 12</i>						
Number	128	51	179	79	23	102
Mean $\pm$ SD	-1.07 $\pm$ 0.73	-0.92 $\pm$ 0.89	-1.03 $\pm$ 0.77	-0.99 $\pm$ 0.79	-1.06 $\pm$ 0.77	-1 $\pm$ 0.78
Median (min, max)	-1.1 (-3, 1)	-0.7 (-2.9, 0.6)	-1 (-3, 1)	-0.8 (-2.9, 0.6)	-0.9 (-2.9, -0.1)	-0.9 (-3, 0.6)
<i>Month 24</i>						
Number	124	49	173	72	22	94
Mean $\pm$ SD	-0.72 $\pm$ 0.81	-0.53 $\pm$ 0.98	-0.66 $\pm$ 0.86	-0.53 $\pm$ 0.77	-0.62 $\pm$ 0.84	-0.55 $\pm$ 0.78
Median (min, max)	-0.7 (-2.7, 1.5)	-0.36 (-2.9, 1.1)	-0.6 (-2.9, 1.5)	-0.4 (-2.8, 1)	-0.6 (-2.3, 0.6)	-0.5 (-2.8, 1)

Fig. 5. Ht age change versus bone age change at month 24. Pearson correlation coefficient: combined arms, 0.26; formula-based dose, 0.35; standard dose, 0.08.

(98.48%) in the formula-based and 115 (97.46%) subjects in the standard dose group]. At month 24, 111 (56.06%) and 66 (55.93%) subjects were at stage 1, 40 (20.20%) and 28 (23.73%) at stage 2, 24 (12.12%) and 9 (7.63) at stage 3, and 5 (2.53%) and 1 (0.85%) subjects at stage 4 in the two groups respectively. No subjects in the formula-based group and 1 in the standard dose group progressed to stage 5.

Safety

Overall, the number of AEs, as well as laboratory test, vital sign, and physical examination abnormalities, was similar between the two groups and was consistent with the frequencies found in pediatric subjects with ISS receiving commercial treatment with Genotropin®. There was a similar proportion of subjects with all-causality AEs in both treatment groups (76.3% in formula-based vs. 78% in standard dose), but a higher proportion of subjects with treatment-related AEs in the formula-based dose group (30.3%) compared with the standard dose group (23.7%). There were no deaths in this study. There was a higher proportion of subjects with serious adverse events (SAEs) in the standard dose group compared with the formula-based dose group (5.1 vs. 1.5%); however, none were found to be treatment-related. A similar proportion of subjects in both treatment groups discontinued study treatment due to all-causality and treatment-related AEs. Of the 3 (1.5%) subjects in the formula-based group, 1 (0.5%) discontinued due to treatment-related peripheral edema, and 2 due to skeletal dysplasia, related to 'other-genetic'. One (0.8%) subject in the standard dose group discontinued due to treatment-related impaired glucose tolerance. A similar proportion of subjects in both treatment groups had their dose reduced or temporarily discontinued due to all-causality AEs [19 (9.6%) subjects in the formula-based dose group and 10 (8.5%) subjects in the standard dose group], but a higher proportion of subjects in the formula-based dose group [8 (4.0%)] had their dose reduced or temporarily discontinued due to treatment-related AEs (included headache,

dizziness, hallucinations, disorientation, bronchitis, carpal tunnel, diplopia, and peripheral edema) compared with none in the standard dose group. The median (min, max) hemoglobin A_{1c} changed from baseline [5.0 (4.0–5.8) and 5.1 (4.3–6.0) to 5.3 (4.3, 6.1) and 5.4 (4.3, 6.1)] in the formula-based versus standard dose groups, respectively, at 24 months. Serum IGF-I concentrations >1.1 times the upper limit of normal for age and sex were noted in 18.8 and 14.7% at 24 months in the formula-based versus standard dose groups, respectively. In all safety evaluations, the observed numerical differences were not evaluated for statistical significance.

Discussion

In the present study, individualized formula-based GH dosing was compared to standard weight-based dosing to allow children with ISS to be treated using a method that was designed to allow them to reach a predetermined Ht SDS. The results of the trial show that using a formula-derived dose that targeted Ht to –1.3 SDS (10th percentile) did not lead to a more consistent rapid attainment of that goal when compared to weight-based dosing. However, while neither group met the outcome goal of –1.3 SDS, both groups reached a mean Ht SDS of –1.4 after the first 24 months of the trial. The similar Ht gain in both groups suggests that the current FDA-approved dose may be sufficient to allow for catch-up growth to population norms in patients with ISS. Importantly, the mean Ht gain for both groups was similar, +1.04 SDS in the formula-based arm and +1.03 SDS in the standard treatment arm, with 83% of subjects reaching the normal range (defined as >–2 SDS) within the first 24 months of the study. The subjects in both groups also gained Ht SDS in comparison to their MPH SDS by 24 months.

Interestingly, changes in serum concentrations of change in IGF-I SDS between both baseline and 12- or 24-month assessments also correlated with change in Ht SDS at 24 months. This observation, noted in both standard and formula-based groups, was statistically significant in the formula group, for both boys and girls. The lack of correlation in the subgroup of girls >7 years of age in the weight-based dose arm suggests that sex hormone augmentation of growth in puberty may need to be considered in further development of formula-based dosing. The correlation with both serum IGF-I and younger age reaffirms the importance of these two variables in assessing which patients may be the most appropriate candidates for GH therapy.

That both groups attained similar catch-up growth in the initial 2 years of this 4-year study may not be unexpected when viewed in light of the IGF-I response achieved. If biochemical markers were utilized in the formula arm and dose-adjusted based upon these results throughout the trial, it is possible that the GH dosing would have been more similar between the two groups. Previous models in both GH-sufficient and GH-deficient patient populations point to targeted IGF-I dosing as a potential method to improve responsiveness [20–22].

Ultimately, the evaluation of the 4-year data may provide further insight into the comparative effectiveness of higher dosing in the initial treatment phase of treatment, followed by lower dosing in the maintenance of growth phase; this paradigm has been demonstrated in the group of children born SGA without catch-up growth. Hence, while not a parallel patient population, this finding has been displayed in this subgroup of children treated who have some degree of GH resistance [26].

The lack of attainment of the projected Ht gain in the formula arm in the prescribed time may be due to several factors. First, it is possible that the chosen target Ht was low for family Ht genetics, that is, if, for example, the MPH were 0 SDS (instead of –1.3 SDS), targeting towards the higher Ht may have allowed for greater catch-up growth. Second, it may be that the integration of a physiologically relevant biochemical marker, such as IGF-I or overnight GH concentrations, into the formula arm would have allowed for more precise fine-tuning of the GH dosing. As noted above, the auxological criteria used in the formula may reflect endogenous GH production, incorporating basal or titrated IGF-I levels, with targeted SDSs, may be a mechanism that would promote better Ht gains [21, 22]. However, the work of Albertsson-Wikland et al. [24] suggests that this may not add to the precision of some prediction models.

It is possible that the entry criteria for the trial contributed to a Ht gain in both treatment groups that was slightly less than targeted. In patients with familial short stature, subtle bone anomalies, as well as yet to be defined abnormalities in the GH-IGF-I signaling cascade, could further account for both short stature and a restricted response to GH. Finally, while all study subjects appeared to meet the prespecified entry criteria to the study, as noted in the Results section, at data analysis, 18 subjects were found to be outside of the entry Ht criterion of –3.0 to –2.25 SDS. Analyses done without those subjects were consistent with the inclusive analysis.

An important outcome of the study is a reaffirmation, at least on a short-term basis, of the efficacy of GH treat-

ment in children with ISS. While not a placebo-controlled trial, as was the pivotal NIH trial [5], the current study employed GH doses in both the weight- and formula-based groups that demonstrated, in a large cohort, that significant short-term Ht gains can be achieved in children with non-GHD short stature. As the current group of subjects is well defined and is being prospectively evaluated, the results of the subsequent 2 years of the trial, as well as any adult Ht data that is reliably obtained from those subjects who can be tracked through adolescence, may further support the use of GH in this patient population. The relatively low drop-out and discontinuation rates also suggest that GH treatment, as used in this trial, was perceived by the subjects as beneficial and was well tolerated. No new safety signals were seen over the 24-month period of study using a dosing range similar to that employed in clinical practice in the United States [27]. The results of this study are encouraging from this perspective. In evaluating the growth response of subjects in the formula-driven arm, in light of the recent data suggesting possible long-term risks of higher doses of GH, it is reassuring that the doses dictated by the formula promoted growth similar to that seen with the FDA-approved dose for ISS with a good safety profile [28–31].

Ultimately, this trial attempted to use auxological data to provide a model to determine GH responsivity and statural Ht gain. Attempting to use a patient population representative of an ISS cohort seen by most practitioners may have eliminated those patients who could have provided greater responsivity to a purely auxological dosing regimen. In addition, while the target Ht goal of -1.3 SD for a general population seems a reasonable one, if an MPH-adjusted target Ht goal were chosen, it could provide a more realistic expectation of growth response in a specific population. Finally, at least over the initial years of treatment, inclusion of biochemical responsiveness, as noted by IGF-I changes, could improve the formula-derived dosing regimen used in this study.

In summary, interim analysis of the initial 2 years of data from this 4-year study demonstrates that GH is effective in improving Ht velocity of children with ISS. While an auxologically-based, formula-driven dose of GH administered for 2 years, compared to standard weight-based dosing over a similar time period, did not appear to be more efficacious in improving the Ht velocity of children with ISS in this study, final analysis of the 4-year data may yield information that would allow adjustments in the current GH-dosing paradigm. Additional analysis points to the importance of initiation of GH at a younger age as a way to maximize growth response. The

second phase of the study employs two ‘physiological doses’ of GH (0.18 and 0.24 mg/kg/week), in addition to the standard dose (0.37 mg/kg/week) [30]. Since all dose groups are starting at a similar Ht SDS, the second phase of the study will allow for the direct comparison of the three doses and the assessment of the lowest dose necessary to maintain their previously gained Ht. We are, therefore, hopeful that the second phase of this study may result in an improved treatment paradigm for children with ISS to allow rapid catch-up growth, while using less GH over the entire treatment period.

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