Three-Year Efficacy and Safety of LB03002, a Once-Weekly Sustained-Release Growth Hormone (GH) Preparation, in Prepubertal Children with GH Deficiency (GHD)

Ferenc Péter, Martin Bidlingmaier, Conrad Savoy, Hyi-Jeong Ji, and Paul H. Saenger

Buda Children's Hospital (F.P.), 1023 Budapest, Hungary; Medizinische Klinik Campus Innenstadt (M.B.), 80336 Munich, Germany; Biopartners GmbH (C.S.), 6340 Baar, Switzerland; LG Life Sciences Ltd. (H.-J.J.), Seoul 110-062, South Korea; and Albert Einstein College of Medicine (P.H.S.), Bronx, New York 10467

Background: GH treatment currently requires daily sc injections, resulting in suboptimal compliance. A GH regimen with fewer injections may offer patients and caregivers a less arduous option. LB03002 is a novel sustained-release GH formulation for once-weekly dosing.

Patients and Methods: GH-deficient, GH-naive prepubertal children were randomized to four groups who received 0.2 mg/kg/wk LB03002 for 12 months, followed by 0.5 mg/kg/wk for another 24 months (n=13); 0.5 mg/kg/wk LB03002 for 36 months (n=13); 0.7 mg/kg/wk LB03002 for 12 months, followed by 0.5 mg/kg/wk for another 24 months (n=13); or daily GH 0.03 mg/kg/d for 24 months, switched to 0.5 mg/kg/wk LB03002 for 12 months (n = 12).

Results: Height velocity increased in all groups; the increase was less for the 0.2 mg/kg/wk LB03002 group at 12 ($P = 0.008$) and 24 months ($P = 0.030$), with no statistically significant differences at any time for the 0.5 mg/kg/wk and 0.7 mg/kg/wk LB03002 groups, *vs.* daily GH. Height SD score gain at 12 months was significantly ($P = 0.023$) less for the 0.2 mg/kg/wk group (1.05 $\pm$ 0.38) than daily GH (1.47 $\pm$ 0.29), but with no statistically significant difference for the 0.5 mg/kg/wk (1.37 $\pm$ 0.39) and 0.7 mg/kg/wk (1.50 $\pm$ 0.44) LB03002 groups *vs.* daily GH. There were no significant differences in height SD score gain between any groups at 24 and 36 months. Bone maturation did not differ for any LB03002 dose compared with daily GH. Serum IGF-I concentrations increased as expected, with no long-term differences between groups. Mean fasting glucose and glycosylated hemoglobin concentrations did not exceed normal ranges for any treatment group at any time.

Conclusion: LB03002 at doses of 0.5 mg/kg/wk and 0.7 mg/kg/wk was shown to be effective and safe with once-weekly dosing in GH-deficient children, and 0.5 mg/kg/wk LB03002 was chosen as the optimal dose for long-term assessment. **(*J Clin Endocrinol Metab* 97: 400–407, 2012)**

The currently available GH replacement therapy regimens require daily injections, which may cause considerable compliance issues in children and adults who need GH treatment due to GH deficiency (GHD) (1). A sustained-release formulation requiring fewer injections may provide a considerable improvement in adherence and during recent years, several different GH formulations with extended half-lives have been developed (2). The pharmacodynamic (PD) and pharmacokinetic (PK) properties of these compounds result in an extended GH action and prolonged increase of IGF-I concentrations, suitable for a GH therapy regimen avoiding the burden of daily injections.

Although the PK and PD properties of different formulations have been published (3–8), clinical data on their use is still very limited and available only from relatively short-term studies performed either in children (9) or adults (10) with

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Abbreviations: BA, Bone age; CA, chronological age; GHD, GH deficiency; HbA1c, glycosylated hemoglobin; HSDS, height SDS; HV, height velocity; PD, pharmacodynamic; PK, pharmacokinetic; rhGH, recombinant human GH; SDS, SD score.

TABLE 1. Demographic and baseline clinical data of the patients, by randomized treatment group

	LB03002			
	0.2 mg/kg/wk	0.5 mg/kg/wk	0.7 mg/kg/wk	Daily GH, 0.03 mg/kg/d
N	13	13	13	12
Chronological age (yr)	7.0 ± 2.0	7.1 ± 2.1	7.8 ± 2.1	7.3 ± 2.3
BA/CA	0.46 ± 0.17	0.48 ± 0.13	0.44 ± 0.17	0.43 ± 0.14
Male/female (n/n)	7/6	8/5	8/5	7/5
Pituitary deficiency[a]				
Isolated GHD (n)	10	8	6	6
Multiple deficiencies (n)	3	5	6	5
Peak GH (μg/liter)	1.80 ± 1.65	2.03 ± 1.71	1.29 ± 0.91	1.65 ± 1.57
Height (cm)	98.9 ± 11.1	104.7 ± 10.5	102.9 ± 9.1	103.0 ± 12.9
Weight (kg)	15.7 ± 4.5	17.2 ± 3.8	16.8 ± 2.7	18.1 ± 5.9
HSDS	−5.02 ± 1.56	−3.92 ± 0.81	−4.53 ± 1.27	−4.53 ± 1.38
HVSDS	−3.54 ± 1.32	−2.80 ± 1.71	−3.38 ± 1.81	−2.82 ± 1.94
IGF-I SDS	−6.93 ± 2.77	−5.53 ± 2.33	−7.41 ± 3.06	−5.80 ± 2.97

[a] Deficiency status was not specified for one patient in the 0.7 mg/kg/wk group and one patient in the daily GH group.

GHD. In children, only one study has evaluated the efficacy and safety of a depot GH preparation over the period of 1 yr (9). In that study, Nutropin Depot given to GH-deficient, GH-naive children once or twice per month over 12 months produced clinically relevant catch-up growth, with a growth rate that was, however, somewhat reduced compared with that usually seen during the initial phase of treatment with daily GH injections.

LB03002 is a novel once-weekly sustained-release formulation of recombinant human GH (rhGH) contained in sodium hyaluronate microparticles, which are suspended in medium-chain triglycerides before injection. The rhGH substance in LB03002 is manufactured using the yeast *Saccharomyces cerevisiae* as the expression system; this molecule has a primary structure identical with that of endogenous 22-kDa pituitary GH and has an identical pharmacological profile and biological actions as other marketed daily GH formulations (11).

In adults with GHD, it was shown that LB03002 maintained elevated serum GH and IGF-I concentrations for a period up to 7 d (7). The PK/PD profile of weekly injections of LB03002 in children with GHD was found to be comparable to that seen in adults, with elevated serum GH concentrations lasting up to 120 h and normalized IGF-I concentration after sc injections (8). The present report details the growth response to LB03002 administered once per week over a period of 3 yr, compared with daily GH injection, in a group of 51 prepubertal GH-naive children with a diagnosis of GHD.

Patients and Methods

Patients and study design

This was a randomized, controlled, multicenter phase II/IIIa study in 11 centers in European countries (Hungary, Poland, Romania, Russia, Serbia, and Ukraine). Informed consent was obtained from all study participants and/or their guardians; the protocol was approved by the appropriate local ethical committees, and the study was conducted according to Good Clinical Practice Guidelines and the Declaration of Helsinki. The clinical study was monitored by an Independent Drug Safety and Efficacy Monitoring Board, comprising two experts in pediatric endocrinology, one in adult endocrinology, and one biostatistician.

The primary objectives were to explore the optimal LB03002 dose to stimulate adequate long-term longitudinal growth and to establish the long-term safety profile of the compound. Prepubertal children were enrolled with a diagnosis of GHD determined by height less than or equal to −2 SD score (SDS), height velocity (HV) less than or equal to −1 SDS, and GH peak below 7.0 mg/liter in two different GH stimulation tests, which were assessed centrally. Patients were excluded if they had congenital or chromosomal abnormalities or evidence of tumor growth; computed tomography/magnetic resonance imaging was performed locally at the discretion of the investigators. GHD was isolated for 30 (59%) patients, and 19 (37%) had additional TSH deficiency, with status unspecified for two patients (4%) (Table 1).

Patients were randomized to daily injections of GH (Genotropin, 0.03 mg/kg/d, n = 12) or to the following doses of LB03002 once per week: 0.2 mg/kg (n = 13), 0.5 mg/kg (n = 13), and 0.7 mg/kg (n = 13). Treatments with the described doses of daily GH and LB03002 were maintained until the end of the first study year. On the basis of a blinded analysis of safety and efficacy data conducted after 6 months, the Independent Drug Safety and Efficacy Monitoring Board and the Coordinating Investigator recommended that for all patients receiving LB03002 the dose level of 0.5 mg/kg/wk should be used in the 12- to 24-month treatment period. An unblinded analysis comparing the three LB03002 doses with daily GH for efficacy and safety after 12 months confirmed the dose selection. During the second year, patients who had been on the 0.2 and 0.7 mg/kg/wk LB03002 doses were shifted to 0.5 mg/kg/wk; during the third year, all patients, including those who were previously on daily GH, received LB03002 at the dose 0.5 mg/kg/wk.

LB03002 was provided as a dry powder containing 0.2 mg rhGH in 1 mg LB03002 and reconstituted with medium-chain triglycerides, ready for sc injection; all doses reported for LB03002 refer to the amount of GH administered. The reference

product, Genotropin daily GH, was given once daily by sc injection using the Genotropin pen 5.3 delivery device. The injections were administered, either by the patient or by a parent or guardian, into the upper arm, buttocks, thighs, or abdomen. The site was changed at each injection, and the injection site was recorded. The dose was adjusted to body weight at scheduled visits from the 3-month visit onward.

Study assessments

Height measurements were taken at baseline and after 6, 12, 24, and 36 months, and height was calculated as height SDS (HSDS). Change in height from baseline was determined at each time point and divided by time for the period of measurement to determine annualized HV, which was either expressed in centimeters per year (HV) or as SDS (HVSDS). Both HSDS and HVSDS were calculated using the Swiss Growth Reference Standard (12). Bone age (BA) was determined centrally by the Greulich and Pyle method (13) and expressed in relation to chronological age (CA).

Serum IGF-I concentrations were measured at a central laboratory (Ludwig-Maximilians University, Munich, Germany) at 3-monthly intervals in the LB03002-treated groups on d 4 ± 1 after the last injection. This time point was chosen to represent an approximate median IGF-I level between the peak (t_{max}: 1.5–2.5 d after injection) and trough (d 7) established for LB03002 (in-house data). From baseline to the end of the second study year, serum IGF-I was measured by a chemiluminescent two-site immunoassay (Nichols Advantage; Nichols Institute Diagnostics, Bad Nauheim, Germany), whereas samples during the third treatment year were measured with the DPC (Diagnostic Products Corp., Los Angeles, CA) Immulite 2000 IGF-I assay (14); a systematic comparison at the central laboratory indicated acceptable correlation. Serum concentrations were transformed into SDS values by reference to specific normative data from a normal healthy population (14, 15).

Safety was evaluated at each study visit by treatment-emergent adverse event reporting, monitoring of vital signs (pulse rate and blood pressure), routine hematology and blood chemistry, fasting glucose and glycosylated hemoglobin (HbA1c) concentrations measured at a central laboratory, screening for antibodies against GH, and determination of antibodies against *S. cerevisiae* protein. Adverse events were coded using MedDRA version 8.0 (Medical Dictionary for Regulatory Activities: www.meddramsso.com). The methodologies for the assessment of antibodies against GH and *S. cerevisiae* have been previously reported (11).

Statistical analysis

Continuous variables are reported as mean ± SD unless otherwise stated. ANOVA was used to examine baseline differences among the treatment groups. The primary efficacy analysis used an analysis of covariance for the difference in HV and HSDS between LB03002 treatment groups and the daily GH group, with adjustments for gender, baseline age and HV, and study center. Secondary efficacy analyses consisted of ANOVA for treatment groups followed by pairwise comparisons between the unadjusted means for each dose level of LB03002 and daily GH at each visit after baseline. For both the primary and secondary analyses, Dunnett's method for comparisons of several treatments with a control was used to adjust for multiplicity of pairwise comparisons.

Results

Efficacy

The baseline demographic characteristics of the patients randomized to each treatment group are presented in Table 1. Patients were well matched between groups for CA, gender distribution, and degree of GHD as indicated by IGF-I SDS. All patients were prepubertal before starting GH treatment, and the degree of delay in bone development was comparable between groups.

The growth data for the four treatment groups are presented in Table 2. During the first 12 months of treatment, HV catch-up compared with the normal population occurred in all four groups, with a dose-dependent pattern of response in the three LB03002 groups. The mean growth rate during the first year was lower in the 0.2 mg/kg/wk LB03002 dose group compared with the other groups, whereas the highest mean HV was observed in the 0.7 mg/kg/wk LB03002 dose group. However, the growth responses for the 0.5 and 0.7 mg/kg/wk LB03002 groups were comparable to the daily GH group during the first year. After the shift in dose of the 0.2 mg/kg/wk group to the higher 0.5 mg/kg/wk dose, further catch-up growth was observed during the second year. In the third year, after the change in the daily GH group to 0.5 mg/kg/wk LB03002 treatment, HV did not differ between any of the four treatment groups. The least square mean differences (with 95% confidence limits) in HV (centimeters per year) between the LB03002 dose groups as randomized and the daily GH group are presented in Fig. 1. The difference was significant ($P = 0.008$) for the 0.2 mg/kg/wk LB03002 group during the first year and remained significant ($P = 0.030$) after the second year, despite the catch-up due to the LB03002 dose increase during the second year. Differences between the other LB03002 dose groups and the daily GH group (switched to LB03002, 0.5 mg/kg/wk in the third year) were not statistically significant at any yearly time point.

All four treatment groups had statistically significant gains from baseline in HSDS at yr 1, which were sustained over the 36-month study period (Table 2). When the daily GH group was shifted to weekly LB03002 injection after 24 months, HSDS gain was maintained to the 36-month end of study; HSDS gain was similar for all four groups at the 36-month endpoint, when all groups had been shifted to the 0.5 mg/kg/wk LB03002 dose. Least square mean differences in HSDS gain between each LB03002 treatment group and the daily GH treatment group (Fig. 2) showed a similar pattern of change to that seen for HV. The difference in HSDS gain during the first 12 months of treatment between the 0.2 mg/kg/wk LB03002 group and the daily GH group was statistically significant ($P =$

TABLE 2. Height growth and bone maturation during treatment with once-weekly LB03002 or daily GH in prepubertal children with GH deficiency

	LB03002			Daily rhGH, 0.03 mg/kg/d, and then LB03002, 0.5 mg/kg/wk
	0.2 and then 0.5 mg/kg/wk	0.5 mg/kg/wk	0.7 and then 0.5 mg/kg/wk	
N	13	13	13	12
HV (cm/yr)[a]				
Baseline	3.31 ± 1.45	3.77 ± 1.51	3.18 ± 1.48	3.66 ± 1.34
12 months	9.67 ± 1.51	11.75 ± 1.88	12.44 ± 2.34	12.17 ± 1.34
24 months	9.05 ± 0.97	9.89 ± 1.45	10.28 ± 1.61	10.44 ± 0.86
36 months	8.54 ± 0.97	9.01 ± 1.33	9.30 ± 1.22	9.18 ± 0.76
HSDS				
Baseline	−5.02 ± 1.56	−3.92 ± 0.81	−4.53 ± 1.27	−4.53 ± 1.38
12 months	−3.97 ± 1.28	−2.55 ± 0.61	−3.03 ± 1.11	−3.06 ± 1.27
Gain from baseline	1.05 ± 0.38	1.37 ± 0.39	1.50 ± 0.44	1.47 ± 0.29
24 months	−3.10 ± 1.24	−1.87 ± 0.59	−2.22 ± 1.13	−2.17 ± 1.08
Gain from baseline	1.91 ± 0.53	2.05 ± 0.63	2.30 ± 0.65	2.36 ± 0.49
36 months	−2.56 ± 1.26	−1.49 ± 0.75	−1.86 ± 1.26	−1.89 ± 1.05
Gain from baseline	2.50 ± 0.74	2.43 ± 0.78	2.67 ± 0.66	2.64 ± 0.68
BA/CA				
Baseline	0.46 ± 0.17	0.48 ± 0.13	0.44 ± 0.17	0.43 ± 0.14
12 months	0.56 ± 0.18	0.61 ± 0.16	0.57 ± 0.19	0.53 ± 0.18
24 months	0.70 ± 0.17	0.70 ± 0.15	0.64 ± 0.19	0.69 ± 0.18
36 months	0.79 ± 0.18	0.78 ± 0.14	0.72 ± 0.16	0.75 ± 0.17

Values are mean ± SD.

[a] HV was calculated as change in height from baseline to each time point/time.

0.023), but the progressive increase in HV with the increase in dose to 0.5 mg/kg/wk LB03002 resulted in cumulative 24- and 36-month HSDS gains not statistically different for the group randomized to 0.2 mg/kg/wk LB03002 compared with that of other groups. HSDS gains in the groups randomized to 0.5 and 0.7 mg/kg/wk LB03002 doses were not significantly different from that of the daily GH group at any time.

Onset of puberty, from stage 1 to stage 2, was recorded in two boys (one each in the 0.2 and 0.5 mg/kg/wk LB03002 groups, aged 13.1 and 12.9 yr, respectively) and in three girls (one aged 9.9 yr in the 0.2 mg/kg/wk LB03002 and two in the daily GH group, aged 11.5 and 13.1 yr). However, these changes did not appear to affect the overall growth responses because the progress in BA maturation was comparable among all four groups, as shown in Table 2 by the BA/CA values. A comparison of BA progression between the four treatment groups did not show any statistical significance (data not shown).

Mean baseline IGF-I SDS in the four treatment groups ranged from −7.41 ± 3.06 to −5.53 ± 2.33 (Table 1), and

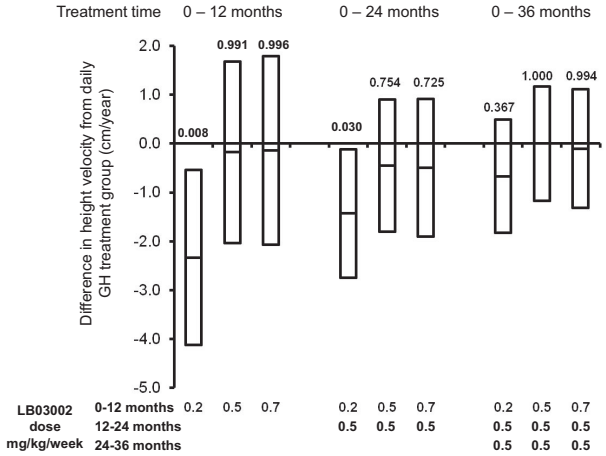

FIG. 1. Difference in height velocity (centimeters per year) between each LB03002 treatment group and the daily GH treatment group by time of treatment and LB03002 dose. *Bars* show adjusted means with 95% confidence intervals; *numbers above each box* show *P* value for difference between LB03002 treatment and daily GH.

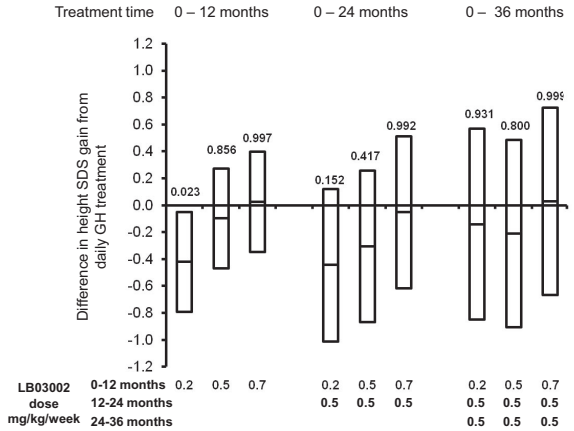

FIG. 2. Difference in height SDS gain between each LB03002 treatment group and the daily GH treatment group by time of treatment and LB03002 dose. *Bars* show adjusted means with 95% confidence intervals; *numbers above each box* show *P* value for difference between LB03002 treatment and daily GH.

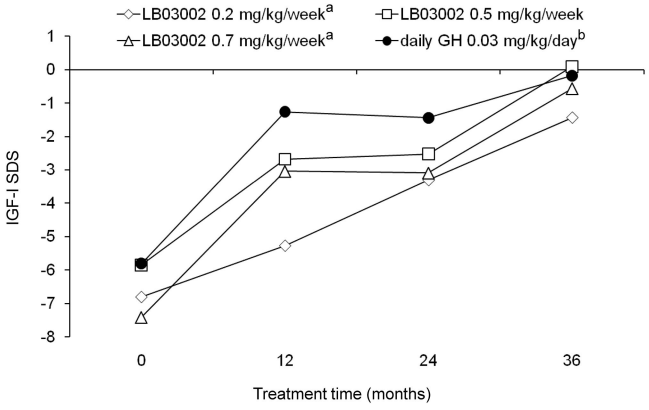

FIG. 3. Mean IGF-I SDS by time of treatment and treatment group. [a] dose changed to 0.5 mg/kg/wk from 12 months onward; [b] daily GH switched to LB03002 0.5 mg/kg/wk from 24 months onward; all samples during LB03002 treatment were drawn at 4 d after dose.

the changes during treatment are presented in Fig. 3. There was a significant increase from baseline to 36 months in all groups, but the increase with 0.2 mg/kg/wk LB03002 was delayed compared with the other groups. A further increase was seen in this group after 12 months treatment, when their LB03002 dose was increased to 0.5 mg/kg/wk.

Safety

Over the 36 months of study, 42 of the 51 patients (82.4%) reported a total of 319 adverse events. There were 53 events reported by 12 patients in the 0.2 mg/kg/wk group, 117 events reported by 12 patients in the 0.5 mg/kg/wk LB03002 group, 98 events reported by nine patients in the 0.7 mg/kg/wk LB03002 group, and 51 events reported by nine patients in the daily GH treatment group. Most events were considered mild in severity (257 of 319, 80.6%), with 51 (16.0%) moderate, and seven (2.2%) severe (one, three, one, and two patients for the 0.2, 0.5, and 0.7 mg/kg/wk LB03002 groups and the daily GH group, respectively), which were all considered unrelated to treatment. Injection site reactions, which were considered to be related to treatment, were reported by three patients, one from each of the LB03002 dose groups. The most common event considered by investigators as possibly related to study treatment was pain in extremity (reported by five patients); also considered possibly related to study treatment were pyrexia in three patients, abnormal liver function tests in two patients, and hypothyroidism in two patients. Only one patient stopped treatment temporarily due to an event of pyrexia. Hypocortisolism was experienced by three patients, one from each of the 0.2 mg/kg/wk LB03002, 0.5 mg/kg/wk LB03002, and daily GH groups. There were 14 patients who developed laboratory values indicative of hypothyroidism and started T_4 replacement while on study, including two who started T_4 between screening and inclusion.

Serum IGF-I SDS increased rapidly in all treatment groups, with no evidence of a difference in response between treatment groups over the 36 months; specifically, there was no change in IGF-I SDS for the daily GH group when switched to 0.5 mg/kg/wk LB03002 from 24–36 months. Mean fasting glucose concentration increased from 4.05 ± 0.67 mmol/liter at baseline to 4.91 ± 0.48 mmol/liter at 12 months in the 0.7 mg/kg/wk group but decreased to 4.68 ± 0.49 mmol/liter at 24 months; there were no other notable changes from baseline in fasting glucose (data not shown) in any treatment group. There were no statistically significant between-group differences at any time point, and mean concentration did not exceed the normal range at any time point for any group. There was an increase from baseline in mean HbA1c concentration that was statistically significant in the 0.5 mg/kg/wk LB03002 group (Table 3). However, mean values remained within the normal range (<6%) at all times for each group, and there were no significant differences between groups at any time point. No patients discontinued due to abnormal glycemia, and no individuals were considered to have impaired glucose control.

TABLE 3. HbA1c concentration during treatment with once-weekly LB03002 or daily GH in prepubertal children with GHD

	LB03002				
	0.2 mg/kg/wk	**0.5 mg/kg/wk**	**0.7 mg/kg/wk**	**Daily GH**	***P* value[a]**
HbA1c (%)					
Baseline	5.3 ± 0.7	5.3 ± 0.6	5.2 ± 0.6	5.1 ± 0.3	0.423
12 months	5.3 ± 0.3	5.4 ± 0.3	5.3 ± 0.3	5.5 ± 0.5	0.795
24 months	5.2 ± 0.2[c]	5.2 ± 0.2	5.2 ± 0.4[c]	5.1 ± 0.2	0.581
36 months	5.4 ± 0.3[c]	5.5 ± 0.3	5.3 ± 0.3[c]	5.3 ± 0.2[c]	0.372
P value[b]	0.353	0.034	0.254	0.340	

[a] *P* value between groups at each time by ANOVA.

[b] *P* value over time by ANOVA.

[c] Groups switched to treatment with 0.5 mg/kg/wk LB03002; upper limit of normal was 6.6%.

Over the 36-month period, four blood samples from three patients on LB03002 treatment demonstrated positive anti-yeast antibody activity, and only one patient, from the 0.5 mg/kg/wk LB03002 group, had two consecutive positive samples. A positive test for serum anti-hGH antibodies was seen on two or more consecutive visits for eight patients on LB03002: six in the 0.5 mg/kg/wk group and one each in the 0.2 and 0.7 mg/kg/wk groups. However, the safety profile and growth response did not appear to be different in these patients from that of the overall cohort of patients. No patient on daily GH had positive sera for anti-hGH.

Discussion

The current report presents the 3-yr growth data in GH-deficient, GH-treatment-naive children treated with LB03002, a new sustained-release GH formulation administered once a week. The same GH formulation has recently been shown to be effective in control of body composition for at least 6 months in GH-deficient adults (16). The present study was initially designed as a dose-finding study, and thus, the number of treated children was limited. However, this is the first report documenting the longer-term efficacy of treatment with a sustained-release GH in pediatric patients with GHD. A previous study with a different GH formulation, Nutropin Depot, provided efficacy and safety data in children with GHD for a period of up to 24 months (9, 17), whereas the current data covered a full 36-month period. In addition, the randomization in the present study allowed direct comparison of the sustained-release formulation *vs.* daily GH injections for 2 yr. The study was carried out in prepubertal children with GHD, in whom the growth response was not affected by timing and progress of pubertal development. The results clearly demonstrated that the growth response with the LB03002 formulation was quantitatively and qualitatively comparable with that seen with daily GH for 2 yr.

The first-year growth velocity was approximately 12 cm/yr for the 0.5 and 0.7 mg/kg/wk LB03002 doses and 9.7 cm/yr for the 0.2 mg/kg/wk LB03002 dose, compared with approximately 12 cm/yr for 0.03 mg/kg/d daily GH, which was higher than that previously reported for the study with Nutropin Depot where first-year growth velocity was 7.9 cm/yr for the highest dose examined and no daily GH comparator included (9). Only with the lower dose of LB03002 (0.2 mg/kg/wk) was HV and height gain statistically significantly different from that seen with daily GH. For the second and third treatment years, the LB03002 dose of 0.5 mg/kg/wk was chosen, which maintained an adequate growth rate during the following 24 months. This dose of LB03002 was also able to maintain growth rate in the group of patients who were shifted from daily GH to the sustained-release formulation for the third study year. In addition, no undue acceleration of BA was seen with the 0.5 mg/kg/wk LB03002 dose, confirming that the growth-promoting action delivered with this weekly regimen was physiological.

The adverse event profile of weekly LB03002 did not differ from that of daily GH, with the exception of injection site reactions, although these occurred in only three patients and with no dose relationship. There were no reports of injection site lipoatrophy in the present study, which was a reported event in several adult patients given multiple weekly injections of a pegylated formulation of GH (18). However, that mainly occurred when the injection site was not rotated (18), indicating the importance of changing site at each injection. Hypothyroidism and hypocortisolism developed in 27 and 6% of patients, respectively; these are known side effects of GH treatment, particularly in cases of organic GHD, and the incidences were consistent with other studies using daily GH (19–21).

No significant differences in glucose homeostasis were seen for the LB03002 groups compared with the daily GH at any time, and no individual patients were classified as having impaired glucose control. A transient increase from baseline in mean fasting glucose was noted with the 0.7 mg/kg/wk dose of LB03002 and in mean HbA1c with the 0.5 mg/kg/wk dose although not with the higher dose of 0.7 mg/kg/wk. Although there have been concerns of a potential effect of GH administration on glucose homeostasis (22), there is little evidence for a negative effect in GH-treated children unless other risk factors are present (23, 24). The current study did not indicate an increased risk of impaired glucose metabolism with LB03002 administration over 36 months. Serum IGF-I SDS increased rapidly, with an initial dose relationship for the LB03002-treated groups (8); there were no differences at any time for LB03002 groups compared with the daily GH group, and there was no change in mean IGF-I SDS when the daily GH group was switched to LB03002 from 24 months onward. Formation of anti-yeast and somatropin antibodies was detected in some patients but was not considered to be of clinical relevance and was in line with previous reports on treatment with daily GH preparation of the same origin as the GH used for the LB03002 sustained-release formulation (11).

In summary, treatment of prepubertal children with GHD for up to 3 yr with the sustained-release GH formulation LB03002 given once weekly resulted in an efficacy and safety profile that did not differ from that of conventional GH replacement with daily injection. Al-

though promising, the data presented were obtained in a phase II/IIIa study in a limited number of GH-deficient children. Confirmation of effectiveness will be required from additional adequately controlled phase III studies, which are presently ongoing (25).

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Address all correspondence and requests for reprints to: Dr. Paul Saenger, Department of Pediatrics, Albert Einstein College of Medicine, Bronx, New York 10467. E-mail: PHSaenger@aol.com.

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