

## CLINICAL STUDY

# Pharmacokinetic and pharmacodynamic profile of a new sustained-release GH formulation, LB03002, in children with GH deficiency

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## Abstract

**Objective:** LB03002 is a novel, sustained-release recombinant human GH, developed for once-a-week s.c. injection. To evaluate the suitability for long-term GH replacement therapy in children with GH deficiency (GHD), the present study assessed the pharmacokinetic (PK) and pharmacodynamic (PD) profiles of LB03002 at three doses.

**Study design and patients:** The randomised, comparator-controlled, assessor-blinded, phase II study assessed 37 (24 boys, 13 girls) pre-pubertal, GH-naïve children with GHD, in 11 European centres, for PK and PD analyses. GH, IGF1 and IGFBP3 concentrations were measured following the last daily GH dose and the first and 13th once-a-week administration of LB03002 at doses of 0.2, 0.5 or 0.7 mg/kg.

**Results:** GH  $C_{max}$  values after the three doses of LB03002 were increased up to fourfold, with a clear dose proportionality. For each LB03002 dose, GH area under the concentration versus time curve did not increase from the first to 13th (month 3) administration, indicating no accumulation of circulating GH. IGF1  $C_{max}$  showed a progressive increase during LB03002 administration. Conversely, IGFBP3 showed a rapid increase in  $C_{max}$ . IGF1 SDS were fully normalised after 3 months of treatment, whereas IGFBP3 SDS were already in the normal range for all the three LB03002 dosages after 1 week.

**Conclusions:** At the doses used, LB03002 has a suitable profile for long-term treatment to promote growth in children with GHD. The quantitative changes in IGF1 and IGFBP3 indicate adequate stimulation of the IGF system by LB03002 and the pattern of increase is comparable with that seen in GHD children in a standard IGF1 generation test using daily GH.

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## Introduction

Recombinant human GH (rhGH) is primarily used to replace GH action in hypopituitary patients with GH deficiency (GHD), in children to promote GH-dependent growth and in adults to correct GHD-induced metabolic abnormalities. To exert these effects over the long term, rhGH has to be administered by daily s.c. injections, and treatment modalities and algorithms in growing children are now well established (1). However, daily injections represent a real burden to patients and to overcome this limitation, long-acting preparations of GH (2–5) or, more recently, also of GHRH (6, 7) have been developed and tested in both children (2, 3) and adults (8) with GHD. At present, none of these products is commercially available.

LB03002 is a new subcutaneously administered sustained-release GH suspension of microparticles, consisting of GH incorporated into a matrix of sodium

hyaluronidate and lecithin, which are dispersed in an oil base of medium-chain triglycerides (MCTs) before injection. LB03002 and rhGH used in the formulation originate from LG Life Sciences (Seoul, South Korea). rhGH is manufactured utilising the yeast *Saccharomyces cerevisiae* as the expression system. The resulting rhGH molecule has a primary structure that is identical to that of endogenous 22 kD pituitary GH and showed comparable pharmacological profile and biological actions with other marketed rhGH brands (9). In an earlier study (10), we analysed the pharmacokinetic (PK) and pharmacodynamic (PD) properties of the sustained-release GH formulation, LB03002, in GH-deficient adults and showed a profile suitable for clinical use. We now report the PK and PD profiles of the same preparation in GH-naïve children with GHD, which were evaluated during the initial 3 months of a study assessing the 1- and 2-year efficacy and safety of LB03002.

## Patients and methods

### Patients and study design

This was an assessor-blinded, randomised, comparator-controlled, multicentre phase II study in pre-pubertal GH-naïve children with GHD. The study protocol had two main objectives: define the PK/PD profile of the new sustained-release GH formulation (LB03002) in this population, and, based on the results obtained, establish the optimal dose to stimulate adequate long-term longitudinal growth. In the present report, we describe the results of the initial 3-month PK/PD study phase. Overall, 52 patients with established GHD (height  $\leq -2$  s.d., height velocity  $\leq -1$  s.d. and a GH peak  $< 7.0$   $\mu\text{g/l}$  in two different GH stimulation tests) from 11 centres in different European countries were enrolled into the study, and 37 patients with an age of  $6.5 \pm 2.1$  years participated in the PK/PD study. Demographic parameters of the patients are summarised in Table 1.

All patients initially received a commercially available rhGH preparation (Genotropin) at a daily replacement dose of 0.03 mg/kg for 7 days. After a 3-week washout period, the patients were randomised to one of the three different doses of LB03002 once a week (group 1: 0.2 mg/kg, group 2: 0.5 mg/kg, group 3: 0.7 mg/kg) for a period of 3 months. The PK/PD profile of daily-injected GH was assessed on day 7 of Genotropin treatment, and that of the sustained-release formulation during the first and last weekly injection of LB03002 (13th dose at month 3). Safety assessments included recording of adverse events, regular monitoring of vital signs, clinical chemistry and assessment of injection site observations. Informed consent and assent respectively were obtained from all participants and/or their guardians; the protocol was approved by the local ethical committee and the study was conducted according to the declaration of Helsinki.

LB03002 was provided as dry powder in vials containing the equivalent of 12 mg of rhGH and prior

to injection was reconstituted with 0.6 ml of MCT, producing a stable, homogeneous suspension of rhGH at a concentration of 20 mg/ml. The comparator product genotropin was given by once-daily s.c. injection using the Genotropin Pen delivery device, containing 5.3 mg rhGH in 0.3% *m*-cresol, mannitol and water for injection.

### PK/PD assessments

For the PK/PD profile of daily GH, blood samples were taken for GH measurement at 0.5, 0, 1, 2, 3, 4, 6, 8, 10, 12, 16, 20 and 24 h after dosing and for IGF1 and IGFBP3 measurement at 0.5, 6, 12, 16, 24, 48, 96 and 168 h. For the PK and PD profile of LB03002, samples were taken at 0, 6, 12, 16, 24, 36, 48, 72, 120 and 168 h after injection. PK parameters for GH included the observed maximum serum concentration ( $C_{\text{max}}$ ), the sample time at which  $C_{\text{max}}$  was observed ( $T_{\text{max}}$ ), the half-life ( $T_{1/2}$ ) and the area under the concentration versus time curve (AUC). AUC was calculated using the trapezoidal rule until the value was below the limit of quantification (LOQ) and was assessed as the actual value and AUC normalised by dose (AUC/dose).

For PD parameters, IGF1 and IGFBP3, the variables  $C_{\text{max}}$ ,  $T_{\text{max}}$ , AUC and dose-normalised AUC were evaluated, similar to GH assessments. Mean daily exposure was calculated by dividing the AUC by 7 days. IGF1 and IGFBP3 concentrations were also converted to SDS by reference to the respective method-specific normative data from a normal healthy population (11, 12).

All assays for PK and PD assessments were performed at a central laboratory (Endocrine Research Laboratories, Ludwig-Maximilians University, Munich, Germany). Serum concentrations of GH and IGF1 were both measured using an automated chemiluminescent assay system (Nichols Advantage, Nichols Institute Diagnostics, Bad Nauheim, Germany). For GH measurement, within-assay coefficient of variation (CV)

**Table 1** Baseline demographics and clinical data.

	LB03002			Daily GH
	0.2 mg/kg per week (n=13)	0.5 mg/kg per week (n=13)	0.7 mg/kg per week (n=13)	0.03 mg/kg per day (n=12)
Age (years), mean $\pm$ s.d.	7.04 $\pm$ 2.05	7.08 $\pm$ 2.06	7.77 $\pm$ 2.08	7.33 $\pm$ 2.26
Gender, male/female (%)	54/46	62/38	62/38	58/42
Type of deficiency (n)				
Isolated GHD	10	8	6	6
Multiple pituitary deficiency	3	5	6	5
Not known	0	0	1	1
Height SDS, mean $\pm$ s.d.	-5.00 $\pm$ 1.61	-3.94 $\pm$ 0.81	-4.64 $\pm$ 1.32	-4.52 $\pm$ 1.39
HV (cm/year), mean $\pm$ s.d.	3.54 $\pm$ 1.45	3.98 $\pm$ 1.59	3.16 $\pm$ 1.37	3.81 $\pm$ 1.49
HV SDS, mean $\pm$ s.d.	-3.26 $\pm$ 1.34	-2.56 $\pm$ 1.78	-3.42 $\pm$ 1.68	-2.65 $\pm$ 2.06
Peak GH <sup>a</sup> ( $\mu\text{g/l}$ ), mean $\pm$ s.d.	1.80 $\pm$ 1.65	2.03 $\pm$ 1.71	1.29 $\pm$ 0.91	1.65 $\pm$ 1.57
IGF1 SDS, mean $\pm$ s.d.	-6.93 $\pm$ 2.77	-5.53 $\pm$ 2.33	-7.41 $\pm$ 3.06	-5.80 $\pm$ 2.97
IGFBP3 SDS, mean $\pm$ s.d.	-2.38 $\pm$ 2.88	-3.45 $\pm$ 1.73	-4.02 $\pm$ 1.38	-3.14 $\pm$ 2.25

<sup>a</sup>Mean from two stimulation tests.

was 3.5, 2.2 and 2.9% at concentrations of 1.4, 10.5 and 28.0 µg/l respectively. Between-assay variation at the same concentrations was 7.9, 2.7 and 5.9% respectively. The LOQ was 0.2 µg/l and the linear working range 0.2–50 µg/l. For the IGF1 measurement, the intra-assay CV was 11.5, 5.1 and 3.5% at concentrations of 42, 262 and 522 µg/l respectively. At the same concentrations, between-assay CV was 10.6, 10.6 and 10.2%; the LOQ was 1 µg/l and the linear range 10–1000 µg/l.

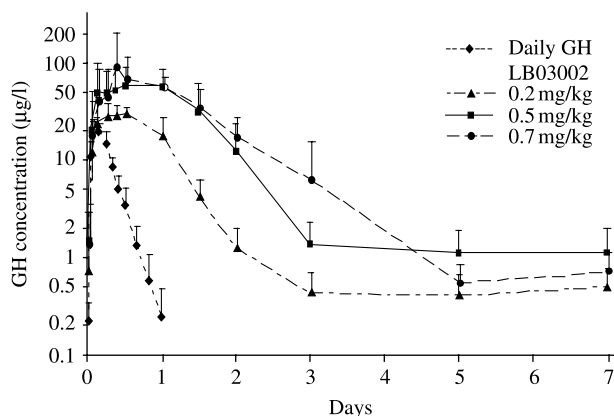
Serum concentrations of IGFBP3 were determined using the automated Immulite 2000 chemiluminescence assay system (DPC Biermann, Bad Nauheim, Germany). At concentrations of 1750, 4400 and 5500 µg/l, the intra-assay CV was 2.8, 2.4 and 1.8% respectively, and between-assay CV was 2.9, 5.9 and 3.3% respectively. The LOQ was 500 µg/l and the linear range 500–10 000 µg/l. Age- and sex-adjusted reference ranges for this method have been published (12).

For all PK and PD parameters, mean values, s.d. and 95% confidence intervals (CI) were estimated. All values are presented as means with s.d., and those in tables are presented as means with 95% CI.

## Results

### PK profile of GH

The PK profiles of GH in the three groups dosed with LB03002 are shown for the 13th dose in Fig. 1. Baseline GH levels were below 1 µg/l in all patients, rose rapidly after the administration of the daily GH formulation at 0.03 mg/kg and returned to pre-dose levels within 24 h. After the administration of LB03002, serum GH concentrations showed a delayed and variably extended peak at 12–24 h after the dosing. Concentrations remained elevated through 24 h and then gradually



**Figure 1** Serum GH levels after the administration of daily GH and after the last weekly administration of LB03002 at doses of 0.2, 0.5 and 0.7 mg/kg; GH levels are plotted on a logarithmic scale as group arithmetic mean + s.d.

declined; levels were not back to pre-dose levels until 72 h for the 0.2 and 0.5 doses, and until 120 h for the 0.7 mg/kg dose.

The PK parameters for daily GH and LB03002 are summarised in Table 2. At the end of study period 1, PK values for daily GH were comparable in all the three groups, although patients in group 2 showed a greater  $C_{max}$  and AUC than the patients in the other two groups. With the LB03002 dosing of the three groups in period 2, after the first and 13th LB03002 administration, an extended peak was seen with an average  $T_{max}$  ranging between 10- and 20-h post-dose, which was the longest after the first 0.7 mg/kg dose.  $C_{max}$  increased in a dose-proportional way, although for the 0.7 mg/kg dose it was slightly lower after the first administration. AUC increased proportionally in the dose range investigated, and mean AUC values after the first and 13th dose (i.e. within 3 months of treatment initiation) did not differ, indicating that no accumulation of GH released from once-weekly LB03002 occurred over the dose range studied. For all the three LB03002 dose groups, dose-normalised AUC (AUC/dose) was comparable, but somewhat lower than the AUC following the injection of daily GH. Mean  $T_{1/2}$  calculated for LB03002 was in the range of 9.3–12.0 h and shown to be consistent for the three different dose groups and across the PK profiles taken after the first and 13th dose.

### PD changes

IGF1-related parameters are summarised in Table 3. In the three treatment groups, baseline IGF1 values ranged from  $14.8 \pm 14.1$  to  $20.2 \pm 20.1$  µg/l. Median  $T_{max}$  values for IGF1 after daily GH were 12–16 h and ranged from 36 to 72 h after LB03002 administration, consistent with the prolonged release of GH from the sustained-release formulation. This resulted in an IGF1 profile with an extended peak after ~48 h and a gradual return to pre-dosing levels by the end of the dosing interval. After the first administration of LB03002, the dose dependency of the IGF1 response was not very pronounced, with the 0.5 mg/kg LB03002 group having the lowest  $C_{max}$  and AUC values. However, with continued administration of LB03002, the effect on IGF1 induction became dose dependent across all the three dose groups. After 3 months, median IGF1 AUC values were increased over baseline by 52, 258 and 352%, and  $C_{max}$  by 93, 250 and 277%, for the three dose groups respectively (Fig. 2). These relative increases were dose related, but not directly dose proportional.

IGFBP3 levels for the three dose groups are shown in Fig. 3. The profile of IGFBP3 was somewhat different because the increase in  $C_{max}$  values after LB03002 administration was more rapid and less progressive than that for IGF1. To examine this difference, baseline IGF1 and IGFBP3 values as well as their mean peak concentration values after the first and last

**Table 2** Serum GH pharmacokinetic parameters of daily GH (day 7 of treatment) and of LB03002 (first and last once-weekly administration) at doses of 0.2, 0.5 and 0.7 mg/kg; values are mean (approximate 95% CI).

	Group 1 0.2 mg/kg dose (n=10)	Group 2 0.5 mg/kg dose (n=10)	Group 3 0.7 mg/kg dose (n=8)
Pre-treatment GH ( $\mu\text{g/l}$ )	0.35 (0.1: 0.6)	0.54 (0.2: 0.9)	0.75 (-2.0: 3.5)
Daily rhGH, 0.03 mg/kg			
$T_{\text{max}}$ (h)	3.40 (2.2: 4.6)	2.90 (2.1: 3.7)	3.88 (-12.2: 19.9)
$C_{\text{max}}$ ( $\mu\text{g/l}$ )	23.8 (16.7: 30.9)	28.2 (21.2: 35.2)	22.7 (-1.3: 46.7)
AUC ( $\mu\text{g/l h}$ )	147 (117.2: 176.8)	172 (139.1: 204.9)	147 (123.0: 171.0)
$T_{1/2}$ (h)	2.47 (2.0: 3.0)	2.81 (2.2: 3.4)	2.63 (2.1: 3.2)
LB03002, first dose			
$T_{\text{max}}$ (h)	13.2 (6.1: 20.3)	12.9 (7.7: 18.1)	21.0 (12.4: 29.6)
$C_{\text{max}}$ ( $\mu\text{g/l}$ )	32.8 (19.5: 46.1)	81.9 (55.5: 108.3)	87.4 (50.7: 124.1)
AUC/dose	111 (-45.2: 267.2)	123 (90.7: 155.3)	114 (93.8: 134.2)
$T_{1/2}$ (h)	12.0 (-11.5: 35.5)	9.29 (6.9: 11.6)	11.0 (9.1: 12.9)
LB03002, last dose			
$T_{\text{max}}$ (h)	10.5 (6.7: 14.3)	14.4 (6.1: 22.7)	17.6 (11.2: 24.0)
$C_{\text{max}}$ ( $\mu\text{g/l}$ )	37.2 (29.2: 45.2)	74.7 (54.5: 94.9)	108.6 (35.7: 181.5)
AUC/dose	118 (46.5: 189.5)	136 (91.2: 180.8)	114 (94.3: 133.7)
$T_{1/2}$ (h)	11.6 (8.5: 14.7)	10.2 (7.7: 12.7)	11.5 (9.0: 14.0)

administrations of LB03002 were transformed into SDS. As shown in Fig. 4, mean peak IGF1 SDS values increased in the normal range by the last LB03002 administration at month 3, while IGFBP3 SDS values were already in the normal range for all the three LB03002 dose groups following the first administration, i.e. within 1 week.

Prolonged LB03002 administration did not result in overstimulation of the IGF1 system; at month 3, i.e. after the 13th dose of the sustained-release formulation, only three patients, one in each dose group, had a  $C_{\text{max}}$  IGF1 value >2.0 SDS (0.2 mg/kg group: 2.41 SDS, 0.5 mg/kg group: 3.37 SDS, 0.7 mg/kg group: 2.93 SDS). In the same patients at the same time points, IGFBP3 SDS values were in the upper normal range (1.43, 2.16 and 0.83 SDS respectively).

## Safety

Ten patients reported 17 adverse events during the study; all were mild to moderate and resolved without

specific intervention. Two events of injection site erythema and one event of hyperthermia were considered possibly related to the study drug. Other reported events were hypothyroidism, headache, pain in extremity and abnormal liver function test. No significant changes were observed in the measures of glucose metabolism and in the clinical chemistry panel. One serious adverse event was reported, which was a case of Quincke's oedema in a patient treated with Genotropin; subsequent testing established that the patient was allergic to certain food components and the allergy test on Genotropin was negative. The event was judged as unrelated to the study drug by the investigator and the patient continued Genotropin treatment.

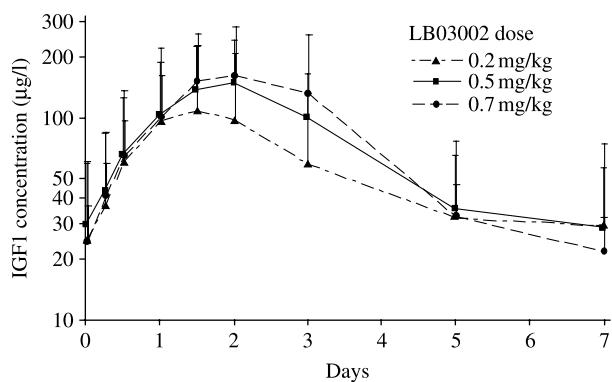
## Discussion

LB03002 is a novel sustained-release rhGH preparation that has previously been shown to produce elevated GH levels in adult patients with GHD for an extended

**Table 3** Serum IGF1 parameters after daily GH administration (day 7 of treatment) and after LB03002 (first and last once-weekly administration) at doses of 0.2, 0.5 and 0.7 mg/kg; values are mean (approximate 95% CI).

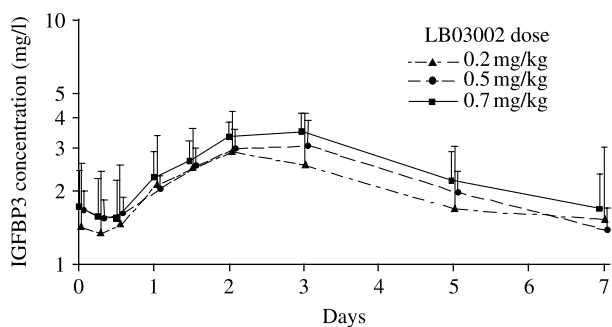
	Group 1 0.2 mg/kg dose (n=10)	Group 2 0.5 mg/kg dose (n=10)	Group 3 0.7 mg/kg dose (n=8)
Pre-treatment ( $\mu\text{g/l}$ )	16.3 (2.4: 30.2)	20.2 (7.5: 32.9)	14.8 (4.8: 24.8)
Daily rhGH, 0.03 mg/kg			
$T_{\text{max}}$ (h)	11.0 (5.1: 16.9)	15.0 (10.9: 20.9)	10.8 (4.9: 16.7)
$C_{\text{max}}$ ( $\mu\text{g/l}$ )	50.2 (12.6: 87.8)	43.9 (20.2: 67.6)	54.9 (26.8: 83.0)
AUC/day ( $\mu\text{g/l h d}$ )	651 (107.7: 1194.3)	491 (276.6: 705.4)	583 (256.3: 909.7)
LB03002, first dose			
$T_{\text{max}}$ (h)	50.4 (24.2: 76.6)	43.2 (40.0: 47.8)	63.0 (54.2: 71.8)
$C_{\text{max}}$ ( $\mu\text{g/l}$ )	81.0 (14.0: 148.0)	67.9 (39.9: 95.9)	117.0 (69.1: 164.9)
AUC/day ( $\mu\text{g/l h d}$ )	876 (31.7: 1720.3)	791 (386.2: 1195.8)	1409 (867.8: 1950.2)
LB03002, last dose			
$T_{\text{max}}$ (h)	36.0 (29.8: 42.2)	42.0 (38.0: 46.0)	43.5 (39.1: 47.9)
$C_{\text{max}}$ ( $\mu\text{g/l}$ )	113 (30.8: 195.2)	152 (93.5: 210.5)	164 (80.6: 247.4)
AUC/day ( $\mu\text{g/l h d}$ )	1340 (276.8: 2403.2)	1777 (990.2: 2564.8)	1945 (764.0: 3126.0)



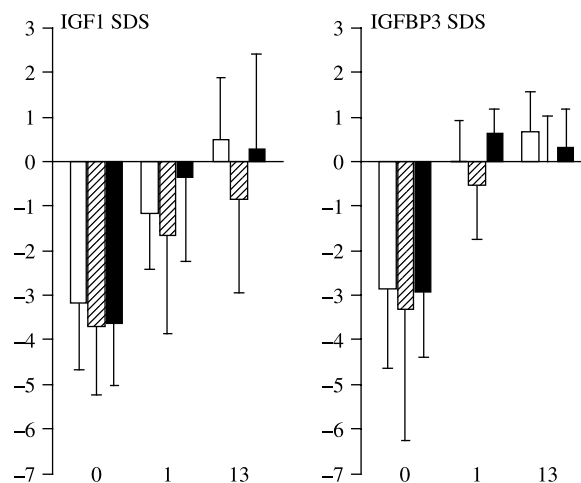


**Figure 2** Serum IGF1 levels after weekly administration of LB03002 at doses of 0.2, 0.5 and 0.7 mg/kg for 3 months; IGF1 levels are plotted on a logarithmic scale as group arithmetic mean + s.d.

period after dosing, with concomitant increases in serum IGF1 and IGFBP3 concentrations (10). The present phase II study in GH-deficient children of prepubertal age shows that LB03002 displays a profile that is comparable with that seen in adults (10); after single LB03002 doses in the range of 0.2–0.7 mg/kg, elevated GH concentrations, with no burst release, are obtained over an extended period ranging from 72 to 120 h, resulting in an AUC that was proportional to the LB03002 dose administered. In addition, mean AUC values after the first and last LB03002 administration did not differ, indicating no accumulation of GH released from the injected preparation over at least a 3-month dosing period. The GH concentration curves indicate that the largest amount of GH released from the injection site appeared in the bloodstream in the first 48 h after injection; on the other hand, comparison of the dose-normalised AUCs after LB03002 with AUCs after daily rhGH indicate that GH exposure after LB03002 is ~75–80% of that after daily rhGH.



**Figure 3** Serum IGFBP3 levels after weekly administration of LB03002 at doses of 0.2, 0.5 and 0.7 mg/kg for 3 months; IGFBP3 levels are plotted on a logarithmic scale as group arithmetic mean + s.d.



**Figure 4** Mean peak IGF1 and IGFBP3 SDS values at baseline and after the first and last (at 3 months) once-weekly administration of LB03002, at doses of 0.2 (open bars), 0.5 (hatched bars) and 0.7 mg/kg (closed bars). 0, 1 and 13 indicate the study week.

However, this ‘estimated relative bioavailability’ is higher than the 50% previously reported for another slow-release formulation, Nutropin Depot (3).

Baseline IGF1 and IGFBP3 concentrations as well as SDS values were low, indicating that the study population consisted of children with severe GHD. The PD assessment from IGF1 and IGFBP3 measurements revealed a profile consistent with the prolonged GH-levels and the doses of LB03002 administered. However, the pattern of response of the two parameters to injected LB03002 was different. While IGFBP3 was already normalised after the first dosing (within 1 week), IGF1 showed a slower and more progressive increase and was normalised at the end of the 3 months of continuous LB03002 regimen.

Although based on a limited number of patients, this difference in response of IGF1 and IGFBP3 seems to support observations reported in GH-deficient and SGA children during the IGF1 generation test (13–18). For GH-deficient and SGA children, it was shown that IGF1 levels do not plateau after 1 week of GH treatment and that close to normal IGF1 levels are reached after 3 months of GH administration, while IGFBP3 increased into the normal range much earlier (17, 18); a comparable pattern for IGF1 and IGFBP3 is seen in the present study with LB03002. Therefore, we believe that the difference in response time for IGF1 and IGFBP3 reflects a specific initial response to GH in children with GHD, rather than a specific PD effect related to the sustained-release formulation. With ongoing administration of LB03002, IGF1 levels normalise, indicating that the doses chosen adequately stimulate the IGF system. After 3 months, mean IGF1 and IGFBP3 SDS values were both in the

normal range, indicating that no overstimulation occurred. Of note, the most pronounced increase in IGF1 level was observed in the same three patients who had the most pronounced increase in IGFBP3. It has been suggested that such a parallelism of response might be considered safe, because a concurrent IGFBP3 rise might prevent an unphysiological high elevation of free IGF1 (19).

In conclusion, we have presented PK and PD data of a new sustained-release rhGH formulation after single and continuous weekly dosing over 3 months in pre-pubertal GH-naïve children with GHD. The results indicate that, at once-a-week doses of 0.2, 0.5 and 0.7 mg/kg, LB03002 was shown to be safe and well tolerated. Based on the PK and PD profiles obtained, LB03002 is a suitable candidate for investigating long-term treatment to promote growth in GH-deficient, GH treatment-naïve, pre-pubertal children, and such studies utilising a dose of 0.5 mg/kg are presently ongoing.

### Declaration of interest

Financial support for this study was provided by BioPartners GmbH, Switzerland, and LG Life Sciences Ltd, South Korea. CS is employed by BioPartners GmbH and H-JJ is employed by LG Life Sciences. FP, MJ, MB and PS have each received consultancy fees from BioPartners GmbH.

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