Efficacy and safety of LB03002, a once-weekly sustained-release human GH for 12-month treatment in Korean children with GH deficiency

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Abstract

Purpose: The purpose of this study was to investigate the efficacy and safety of LB03002, a sustained-release human GH (SR-hGH), compared with that of daily rhGH for 12 months in children with GH deficiency (GHD).

Methods: A total of 73 children with GHD were screened and 63 eligible subjects were randomized in a 1:1 ratio of LB03002 (SR-hGH) to daily rhGH treatment group. LB03002 was administered once weekly at a dose of 0.5 mg/kg while daily rhGH was administered for 6 consecutive days with equally divided doses to make a total of 0.21 mg/kg per week. Treatments were given for 12 months by s.c. injections. Injection site reactions and adverse events were investigated throughout the study period.

Results: The mean (S.D.) height velocity (HV) showed a clinically significant increase after the 6-month treatment: 3.00 (1.15) cm/year at screening to 9.78 (1.98) cm/year at 6 months in the LB03002 group; 2.39 (1.63) cm/year at screening to 10.56 (2.65) cm/year at 6 months in the daily rhGH group. The increased HV at 12 months was still maintained in both the groups: 9.06 (1.63) cm/year at 12 months in the LB03002 group; 9.72 (2.32) cm/year at 12 months in the daily rhGH group. Most of the adverse drug reactions were mild and tolerable. No subjects were withdrawn due to adverse events.

Conclusion: Weekly injection of LB03002 at a dose of 0.5 mg/kg per week was confirmed to have comparable efficacy to daily injection of rhGH at a dose of 0.21 mg/kg per week. Both formulations were well tolerated.

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Introduction

At present, standard GH therapy is given by daily s.c. injection, which creates problems with compliance and adherence for patients, parents, and caregivers (1). Longer acting formulations of a variety of medicines have long been identified as a viable strategy for improving adherence to a medication regimen (2, 3, 4).

LB03002 is a once-weekly sustained-release formulation of recombinant human GH manufactured using genetically modified Saccharomyces cerevisiae and contained in sodium hyaluronate microparticles, which are suspended in medium-chain triglycerides before injection (5). The pharmacokinetic and pharmacodynamic profile of LB03002 has been established in both children and adults with GH deficiency (GHD) (6, 7). Preliminary efficacy and safety results from studies on GH-deficient children and adults have shown LB03002 to be a suitable candidate for long-term replacement therapy in patients with GHD (8, 9). In this study, the primary objective was to evaluate the long-term efficacy and safety of LB03002 compared with daily rhGH treatment for 12 months.
Subjects and methods

Subjects

This study was conducted in 14 centers in South Korea in accordance with the ethical principles of Declaration of Helsinki and good clinical practice, and the protocol was approved by each institutional review board. From May 2005 to February 2007, prepubertal children aged 3 years or older were screened for study participation if their parents or legal representatives provided written informed consents. Children were determined to have GHD if peak GH levels were <10 ng/ml in response to at least two GH stimulation tests (using clonidine, insulin, or levodopa). For those subjects who had been diagnosed with multiple pituitary hormone deficiencies or organic GHD, confirmatory GH stimulation test was exempted if they had records of previous GH stimulation test results indicating complete GHD (<5 ng/ml). The following inclusion criteria were also used to screen the children: i) open epiphyses; ii) height at or below the 3rd percentile for age and sex (not applicable if a child had organic GHD or GH treatment history); iii) height velocity (HV) at or below the 25th percentile for age and sex (reference to the chart of Tanner); iv) bone age (BA) of 10 years or below for girls and 12 years or below for boys; v) no previous GH treatment within 6 months before starting the study; vi) normal thyroid function or normal thyroid function maintained by hormonal therapy; and vii) height measurements at least 6 months apart before study initiation.

If children had any of the following conditions, they were excluded: i) causes of short stature other than GHD, such as chronic renal failure or Turner syndrome; ii) history of having resistance to GH; iii) concurrent chronic diseases such as diabetes; iv) possibility of allergic reaction or hypersensitivity to the ingredients of the study drugs; v) history of spinal irradiation; vi) active pituitary tumor or recurrence of pituitary tumor within 12 months before study initiation; vii) critically acute condition caused by complications from open heart surgery, abdominal operation, or multiple accidental injuries; viii) acute respiratory failure; or ix) treatment with other investigational drugs within 30 days before study initiation.

Of 73 screened children, 63 were randomized to receive one of the two study drugs. Fifty-eight subjects completed the 6-month treatment period and 53 subjects (84%) completed the 12-month treatment period (Fig. 1). Of ten early withdrawn subjects, three subjects randomized to daily rhGH group never received a study drug and were excluded from all analysis subsets. The reasons for early withdrawal of those remaining seven subjects who were excluded were as follows: consent withdrawal or lost to follow-up (three subjects in LB03002 and one subject in daily rhGH), GH level >10 ng/ml at screening (one subject in LB03002), abnormal thyroid function (one subject in LB03002), abnormal thyroid function (one subject in daily rhGH), and advanced Tanner stage during study period (one subject in daily rhGH). One subject in LB03002 who completed the 12-month treatment but experienced advancement in Tanner stage during the study period was also excluded.

Study drug

The eligible subjects were randomized in a ratio of 1:1 to receive one of the two study drugs for 6 months (26 weeks): LB03002, sustained-release human GH (SR-hGH, Eutropin Plus Inj.), dosed at 0.5 mg/kg per week or daily rhGH (Eutropin) dosed at 0.21 mg/kg per week. At the end of the 6-month treatment, subjects were rolled over to a 12-month (52 weeks) extension study to receive an additional 6-month treatment if their parents or legal representatives provided written consent. LB03002 was administered subcutaneously at a dose of 0.5 mg/kg per week once a week while a weekly dose of 0.21 mg/kg per week of daily rhGH was administered in six equally divided daily doses. The dose of LB03002 was chosen from the pharmacokinetic/pharmacodynamic Phase II/IIIa study of LB03002. The Medical Guideline of American Association of Clinical Endocrinologists (AACE) recommended 0.3 mg/kg per week, six times a week, s.c. administration for the treatment of childhood-onset GHD patients and the dose regimen of hGH was changing to six to seven times administration a week. In this study, therefore, the dose regimen of 0.21 mg/kg per week, six times a week administration was used with the purpose of obtaining approval for this dose regimen, which was a real regimen in clinics (0.17–0.21 mg/kg

Figure 1 Subject disposition.

in daily rhGH), and advanced Tanner stage during study period (one subject in daily rhGH). One subject in LB03002 who completed the 12-month treatment but experienced advancement in Tanner stage during the study period was also excluded.
Statistical analysis

The primary objective of this study was to demonstrate the efficacy of LB03002 compared with daily rhGH in terms of between-group difference in the HV after 1-year treatment. The minimum number needed to achieve 80% power at 5% level of significance (one-sided) was 26; thus, 32 subjects in each group were to be enrolled considering 20% drop-out rate. Efficacy evaluation was primarily based on the results of per-protocol set comprising subjects who completed the study without major protocol violations, and it was also carried out with full analysis set comprising all subjects who were dosed at least once and had posttreatment efficacy data. Safety analysis was performed with data from all subjects who were dosed at least once and had posttreatment safety data. For continuous variables, between-group difference was tested using t-test and difference within a group was tested using paired t-test; for categorical variables, between-group difference was tested using χ² test or Fisher’s exact test, and difference within a group was tested using McNemar test. All statistical analysis was performed using SAS version 9.1.3 (SAS Institute, Inc., Cary, NC, USA). All tests used α = 0.05 as the level of significance. The mean is presented with s.d. and median is presented with range (min, max).

Results

Characteristics of study subjects

Clinical characteristics of both groups are shown in Table 1. Distribution of age, sex, weight, and baseline auxological data was similar between the groups (Table 1). Thirty-six subjects had organic GHD; of these, 28 (78%) had been diagnosed with craniopharyngioma, two with empty sella syndrome, one with septo-optic dysplasia, and the remaining five with other pathological lesions. Thirteen subjects (43%) in each group had hGH treatment history with median (range) treatment duration as follows: 427 (35–1925) days in the LB03002 group and 488 (31–2067) days in the daily rhGH group. All subjects except one subject in the LB03002 group had <10 ng/ml of peak GH level to GH provocation tests. BA lagged chronological age (CA) by 2–3 years.

Annualized HV

Our analysis showed a clinically significant increase in mean HV in both the groups after 6-month treatment: 3.00 (1.15) cm/year at screening to 9.78 (1.98) cm/year at 6 months in the LB03002 group; 2.39 (1.63) cm/year at screening to 10.56 (2.65) cm/year at 6 months in the daily rhGH group. The increased HV at 12 months was still maintained in both the groups (Fig. 2): 9.06 (1.63) cm/year at 12 months in the LB03002 group; 9.72 (2.32) cm/year at 12 months in the daily rhGH group. There was no significant between-group (LB03002 – daily rhGH) difference in HV change (posttreatment–pretreatment).
Secondary efficacy results

The results for height SDS for CA and BA, bone maturation, IGF1, and IGFBP3 are presented in Table 2. Height SDS for both CA and BA significantly increased ($P < 0.0001$) at 12 months but without accelerating bone maturation, showing the bone maturation index in both groups $< 1$. Significant increases in the levels of posttreatment IGFI and IGFBP3 were observed in both the groups. There were no significant between-group differences in these secondary efficacy variables.

Safety

About 80% of subjects experienced at least one adverse event regardless of causality: 80% (24/30) in the LB03002 group and 83% (25/30) in the daily rhGH group. The most frequently reported adverse event was upper respiratory infection (URI): 15 subjects (50%) in the LB03002 group and 23 subjects (77%) in the daily rhGH group experienced URIs; all events were mild in intensity and not related to the study drug. Adverse drug reactions (ADRs) that were considered to be related to the study drugs were observed in 11 subjects (eight in LB03002 and three in daily rhGH). Those events were mostly mild in intensity except one case of moderate myalgia (LB03002) and resolved on its own except one case of mild weight increase (LB03002), which was later found to be temporary in nature. There were 12 serious adverse events (SAEs) reported in eight subjects: gastroenteritis, inguinal hernia repair, pyrexia (two events), pharyngotonsillitis, pneumonia, and calculus bladder were reported in five subjects in the LB03002 group; convulsion (two events), epilepsy, gastroenteritis rotavirus, and pneumonia were reported in three subjects in the daily rhGH group. All SAEs were evaluated as ‘not related to the study drug’ and resolved with appropriate treatment. No deaths or SAEs related to the study drug occurred during the 12-month treatment period. In case of injection site reactions based on the diary data, pain was repeatedly recorded in LB03002 0.5 mg/kg per week

![Figure 2](https://www.eje-online.org)
the diaries of subjects who received daily rhGH while it disappeared gradually in subjects who received LB03002. Other local reactions such as warmth, swelling, and redness were more frequently reported in the LB03002 group than in the daily rhGH group; however, these reactions were usually mild, resolved in 5 days, and occurred infrequently. The occurrence rate of these reactions was slightly higher with LB03002 on the first day of injection; however, those reactions disappeared by the time the next injection was given. There was a decreasing tendency in the frequency of injection site reactions with repeated administration in both the groups (Table 3).

There were no clinically relevant findings with glucose, HbA1c, thyroid function test, or lipid profile (total cholesterol, triglyceride, HDL-cholesterol), except significant increases in phosphate and alkaline phosphatase (ALP), and total cholesterol more than 200 mg/dl in 15 subjects (25%). There was no difference between treatment groups for the number of subjects with abnormal laboratory values in hematology, clinical chemistry, glucose homeostasis, and lipid profile.

One of 30 (3%) subjects in the LB03002 group was anti-hGH antibody positive during the 12-month treatment, while 13 of 30 (43%) subjects in the daily rhGH group were anti-hGH antibody positive. Seven of 13 antibody-positive subjects in the daily rhGH group had a history of hGH treatment, and three were already positive before treatment with the study drug. Although the number of antibody-positive patients was not large enough for the statistical analysis, the exploratory subgroup analysis performed on major efficacy variables such as HV, height SDS, bone maturation, and IGF1 by antibody formation indicated that growth seemed not to be attenuated by the presence of these antibodies (data not presented).

Table 3 Number of subjects experiencing each local reaction.

<table>
<thead>
<tr>
<th></th>
<th>LB03002 0.5 mg/kg per week</th>
<th>Daily rhGH 0.21 mg/kg per week</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Week 1</td>
<td>Week 26</td>
<td></td>
</tr>
<tr>
<td>Warmth</td>
<td>n=28</td>
<td>n=24</td>
<td>n=21</td>
</tr>
<tr>
<td>Mild</td>
<td>6</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Moderate</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Erythema</td>
<td>n=28</td>
<td>n=23</td>
<td>n=21</td>
</tr>
<tr>
<td>Mild</td>
<td>9</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Moderate</td>
<td>5</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Severe</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Swelling</td>
<td>n=28</td>
<td>n=23</td>
<td>n=21</td>
</tr>
<tr>
<td>Mild</td>
<td>8</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Moderate</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Severe</td>
<td>1</td>
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</table>

n, number of subjects whose diary was completed for each solicited local reaction during the first week of injection at every visit.
Discussion

This study investigated the efficacy and safety of weekly injection of 0.5 mg/kg per week LB03002 compared with daily injection of rhGH dosed at 0.21 mg/kg per week in 63 children with GHD in Korea. HV significantly increased with both treatments: 3.00 cm/year (1.15 cm/year) at screening to 9.78 cm/year (1.98 cm/year) at 6 months in the LB03002 group; 2.39 cm/year (1.63 cm/year) at screening to 10.56 cm/year (2.65 cm/year) at 6 months in the daily rhGH group, and increased HV at 12 months was still maintained in both the groups. The between-group difference in HV both at 6 and 12 months showed that there was no significant difference in the efficacy of both treatments in terms of accelerating growth rate.

HV result (9 cm/year after 12-month treatment) observed in this study was higher than that obtained in another study using Nutropin Depot, where HV observed in this study was higher than that obtained accelerating growth rate.

In conclusion, 6-month annualized HV data of this study demonstrated that weekly injection of LB03002 at a dose of 0.5 mg/kg per week was comparable to daily injection (for 6 days/week) of rhGH at a divided dose of 0.21 mg/kg per week in increasing growth rate of prepubertal GHD patients. The actual HV at 12 months was confirmed to be comparable between LB03002 and daily rhGH. The safety of LB03002 was also well tolerated.

Declaration of interest

None of the authors have any conflict of interest to disclose.

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References


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