Safety and Efficacy of Long Acting GH Formulations

By Paul Saenger, New York
Growth Hormone Secretory Patterns

• The use of currently available somatropin (rhGH) products relies on the assumption that the beneficial action of GH is largely preserved, even when administered in a non-physiologic fashion.

• The truth regarding this assumption has been confirmed in numerous clinical studies, in both children and adults, over the last 5 decades.

Jostel A. Shalet S Treat Endocrinol 2006 5: 139-45
Concerns re long acting GH

- Is long acting GH physiologic?

- GH is secreted throughout the day in 6 to 8 discrete peaks

- Concerns about long acting GH:

- Does it lead to unphysiologically high GH and/or IGF-1 levels. Does it affect bone maturation, carbohydrate tolerance, antibody formation?

- Is the growth velocity as good as with daily GH
Is Daily rhGH “Natural”? Current Replacement Therapy in Pediatric GHD

Slide courtesy of Dr. Paul Fielder
Compliance and Persistence

- A major cause of failure of growth hormone (GH) therapy can be patient noncompliance and non-persistence with the prescribed regimen.

- Steady decline in persistence rates within first 11 months of GH treatment, to 67% in pediatric patients and 54% in adults. (unpublished data Caremark, Inc. Birmingham, Al, January to December 2005)

- Only 44% of pediatric patients, initiated in 1997, remained on therapy after 4 years
  - Declining to 20% for 4-year persistence rate for those that began GH therapy at the same age in 2001
    (unpublished data, NCGS, Genentech, Inc., South San Francisco, CA, Jan 1, 2006)

Rosenfeld R., Bakker B.; Compliance and persistence in pediatric and adult patients receiving growth hormone therapy; Endocrine Practice Vol 14 No 2 March 2008.
Adherence to Medication

Lars Osterberg, M.D., and Terrence Blaschke, M.D.

Drugs don’t work in patients who don’t take them.

— C. Everett Koop, M.D.

Adherence to (or compliance with) a medication regimen is generally defined as the extent to which patients take medications as prescribed by their health care providers. The word “adherence” is preferred by many health care providers, because “compliance” suggests that the patient is passively following the doctor’s orders and that the treatment plan is not based on a therapeutic alliance or contract established between the patient and the physician. Both terms are imperfect and uninformative descriptions of medication-taking behavior. Unfortunately, applying these terms to patients who do not consume every pill at the desired time can stigmatize these patients in their future relationships with health care providers. The language used to describe how patients take their medications needs to be reassessed, but these terms are still commonly used. Regardless of which word is preferred, it is clear that the full benefit of the many effective medications that are avail-
Adherence to Medication

Table 3. Strategies for Improving Adherence to a Medication Regimen.

- Identify poor adherence
  - Look for markers of nonadherence: missed appointments (“no-shows”), lack of response to medication, missed refills
  - Ask about barriers to adherence without being confrontational
- Emphasize the value of the regimen and the effect of adherence
- Elicit patient’s feelings about his or her ability to follow the regimen, and if necessary, design supports to promote adherence
- Provide simple, clear instructions and simplify the regimen as much as possible
- Encourage the use of a medication-taking system
- Listen to the patient, and customize the regimen in accordance with the patient’s wishes
- Obtain the help from family members, friends, and community services when needed
- Reinforce desirable behavior and results when appropriate
- Consider more “forgiving” medications when adherence appears unlikely:
  - Medications with long half-lives
  - Depot (extended-release) medications
  - Transdermal medications

• Development rationale for a sustained release product:
  - Better patient compliance through less frequent dosing
  - Comparable efficacy and safety profile to daily hGH products

• Ideal target:
  - Once-a-week subcutaneous injection

• Historic Case
  - Nutropin Depot (Genentech), discontinued

• Current Developments
  - PEG-GH (Pfizer abandoned and Novo Nordisk, abandoned as well in 2010)
  - Targeted pegylation (Merck-Serono/Ambrx), abandoned by Merck-Serono
  - Inhaled GH (Lilly – abandoned)
  - Crystalline GH (Altus) abandoned
  - GH contained in Na-hyaluronate matrix (Biopartners/LG Life Sciences)
  - Ligand-receptor fusion of GH with extracellular domain receptor. (300 times reduced clearance of fusion protein). Richard Ross, UK, Ipsen
1. Long acting GHRH (Theragen EMD Serono) for AIDS wasting, visceral obesity

2. GHRH MK preparation for metabolic disease M. Thorner USA
New Developments: Prolor, Israel weekly or by weekly

Versartis, monthly hopes to be best in class
Pharmacokinetics of Nutropin Depot™ in Pediatric GHD

Slide kindly provided by Dr. Paul Fielder

- **Tmax ~ 0.5-0.6 days**
- **Cmin ~ ? days**

Graph showing:
- Mean ± SD
- 0.75 mg/kg subcutaneous injection (n=12)
- 1.5 mg/kg subcutaneous injection (n=8)

Legend:
- Initial Release Phase (Days 0-2)
- Sustained Release Phase

Time (days):
0 5 10 15 20 25 30

Concentration (ng/mL):
0.1 1 10 100 1000

Slide dimensions: 720x540
1.5 mg/kg once monthly (n=36)
0.75 mg/kg twice monthly (n=38)

n=69 (93%) completed 6 months
n=61 elected to continue
n=56 completed 12 months

<table>
<thead>
<tr>
<th>Pretreatment growth rate (n=69)</th>
<th>4.5+/-2.3 cm/yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 months annualized growth rate (n=69)</td>
<td>8.4+/-2.1 cm/yr</td>
</tr>
<tr>
<td>12 months growth rate (n=56)</td>
<td>7.8 cm/yr</td>
</tr>
</tbody>
</table>
Analysis on safety and efficacy of a novel sustained release rhGH (LB03002), given once-a-week for 24 months to pre-pubertal children with Growth Hormone Deficiency (GHD)

Authors: Peter F¹, Savoy C²; Kim J³, Ji HJ ³, Juhasz M⁴, Saenger P⁵ and the BioPartners/LG Life Sciences Study Group

Presenter: Saenger P⁵

¹ BUDA Hospital, Budapest; ² BioPartners, Baar; ³ LG Life Sciences, Seoul; ⁴ Accelsiors, Budapest; ⁵ Albert Einstein College of Medicine, New York
LB03002: Product

- Composition
  - Solid microparticles: hGH, sodium hyaluronate and lecithin
  - Injection vehicle: medium-chain triglycerides (MCT)
Study Design

- **Main Objectives**
  - Safety and efficacy of LB03002 doses, comparative PK/PD of LB03002 vs. daily hGH

- **Subjects**
  - GH-naïve children with insufficiency of endogenous GH secretion
  - N = 51 (12 or 13 per dose arm)

- **Design**
  - Assessor-blinded, active-controlled phase II/IIIa study

- **Dose**
  - LB03002 (0.2, 0.5 & 0.7 mg/kg/week)
  - Daily hGH (0.03 mg/kg/day = 0.21mg/kg/week)

---

**Dose-finding period**

<table>
<thead>
<tr>
<th>Daily hGH</th>
<th>1 wk</th>
<th>3 weeks</th>
<th>12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>LB03002</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PK/PD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.7</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Continuation period**

- Optimal dose (0.5)
Major Inclusion Criteria

• Confirmed diagnosis of GHD determined by 2 independent GH provocation tests (all plasma GH levels centrally measured):
  - GHD defined as a peak plasma GH level of < 7 ng/mL and
  - the absence of any spontaneous GH peak > 7 ng/mL, monitored 3 hours before at least one stimulation test

• Pre-pubertal children, GH-naïve (Boys aged 4-10 years; girls aged 4-9 years) with primary and secondary insufficiency of GH secretion

• HT SDS ≤ -2.0 below the mean height for CA and sex according to Prader et al

• HV SDS ≤ -1.0 below the mean HV for CA and sex according to Prader et al

• Baseline IGF-1 level standardized for age and sex < -1.0 SDS

• BA ≤ 9 years for boys; ≤ 8 years for girls (centrally read)
Major Exclusion Criteria

• Any clinically significant abnormality likely to affect growth or the ability to evaluate growth such as, but not limited to:
  - chronic diseases like renal insufficiency
  - diabetes mellitus
  - malnutrition (body mass index [BMI] above -2SD and below +2SD of mean BMI for the chronological age and sex)
  - albumin below lower limit of normal (LLN) of the central laboratory for a patient to be included

• Closed epiphyses

• Poorly controlled pituitary insufficiencies of other axes
Height Velocity

![Graph showing height velocity over different periods (BL, 0-12 Months, 12-24 Months, 0-24 Months). The graph includes bars for each period with values for HV (cm/year) at 0.2, 0.5, 0.7, and GE (growth velocity). The bars are color-coded: red, blue, green, and yellow. The graph illustrates the height velocity trends across the specified periods.](image-url)
Change in Height Velocity SDS

0-12 Months
12-24 Months
0-24 Months

Δ HV SDS

0.2 0.5 0.7 GE

0.2 0.5 0.7 GE

0.2 0.5 0.7 GE
Bone Maturation

- Summary of bone maturation (Greulich-Pyle)
- Ratio of bone age (BA) / chronological age (CA)
Pharmacokinetics (hGH)

Geometric mean hGH (after first dose)
- 0.2mg/kg/week (N = 10)
- 0.5mg/kg/week (N = 10)
- 0.7mg/kg/week (N = 8)
Pharmacokinetics (hGH)

- No accumulation of hGH with LB03002 given once-a-week over the dose range studied
- Dose proportionality across the three LB03002 doses (AUC)
Pharmacodynamics (IGF-I)

Geometric mean IGF-I (after first dose)
- 0.2mg/kg/week (N = 10)
- 0.5mg/kg/week (N = 10)
- 0.7mg/kg/week (N = 8)
Pharmacodynamics (IGF-I SDS and IGFBP-3 SDS)

**IGF-I SDS**

- Pre
- V 1
- V 3

**IGFBP-3 SDS**

- Pre
- V 1
- V 3

0.2 mg/week
0.5 mg/week
0.7 mg/week
Genotropin
IGF-1 Sampling
Conclusions PK/PD (hGH, IGF-I, IGFBP-3)

- Sustained, dose-related release of rhGH from the formulation
- No accumulation of hGH and IGF-I
- Prolongued elevation of IGF-I over the dosing interval returning to pre-dosing levels before next dosing
- Significant increase of IGF-I and IGFBP-3 into the normal range within 3 months of treatment initiation
Twelve months safety and efficacy of LB03002, a new sustained release formulation of rhGH, as compared to daily rhGH therapy in treatment-naïve children with growth failure due to insufficient secretion of endogenous growth hormone (GHD): a phase III, multi-center, randomized, parallel group trial

Paul Saenger
Introduction

- LB03002 is a s.c. injectable sustained release formulation of rhGH which is formulated as sterile microparticular powder for reconstitution to a suspension in medium chain triglycerides (MCT) prior to injection.

- Nine studies have been conducted worldwide in healthy adults as well as in children with insufficient secretion of GH across all phases as part of the LB03002 clinical development program.

- The annualised height velocities (HV) observed in children with GHD treated with LB03002 (0.5 mg/kg/week) were comparable to those seen with daily rhGH products in two dose-finding studies conducted in Europe (BPLG-003) and Korea (SHCL002). Based on the results of these studies, the dose chosen for the pivotal BPLG-004 Phase III study reported here was selected as 0.5 mg/kg/week.
Study Design

Patient population:
• pre-pubertal, treatment-naïve children with
• idiopathic or organic GH insufficiency (isolated or multiple) defined as
• peak plasma GH level of \( \leq 7.0 \text{ ng/mL} \) in two independent provocation tests

Design:
• open label, active-controlled, parallel-group phase III study

Objectives:
• to demonstrate the clinical comparability (non-inferiority) of LB03002 and Genotropin®
• to demonstrate efficacy and safety
Eligibility Criteria

- Pre-pubertal children with isolated or multiple GH insufficiency
- Boys aged 3-12 years; girls aged 2-11 years
- Peak serum GH level of \( \leq 7.0 \) ng/mL in two different provocation tests (centrally assessed)
- GH-treatment naïve
- HT SDS \( \leq -2.0 \)
- HV SDS \( \leq -1.0 \)
- IGF-I SDS \( \leq -0.5 \) (centrally assessed)
- No evidence of tumour growth or malignant disease
# Diagnosis and Demographics

<table>
<thead>
<tr>
<th></th>
<th>LB03002 N=91</th>
<th>Genotropin® N=87</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idiopathic GHD</td>
<td>83 (91%)</td>
<td>77 (89%)</td>
</tr>
<tr>
<td>Organic GHD</td>
<td>8 (9%)</td>
<td>10 (12%)</td>
</tr>
<tr>
<td>Isolated GH Deficiency</td>
<td>41 (45%)</td>
<td>39 (45%)</td>
</tr>
<tr>
<td>Multiple Hormone Deficiencies</td>
<td>50 (55%)</td>
<td>48 (55%)</td>
</tr>
<tr>
<td>Chronological age Bone age (GP)</td>
<td>Years Mean (SD)</td>
<td>7.8 (2.5) 4.4 (2.2)</td>
</tr>
<tr>
<td>Gender</td>
<td>Male (%)</td>
<td>56 (62%)</td>
</tr>
</tbody>
</table>
Efficacy Results

• Primary efficacy parameter (HV after 12 months treatment)
  - Non-inferiority of LB03002 to Genotropin® was demonstrated (lower bound of 95% CI for the difference of LB03002 - Genotropin® was -1.22cm)

• Secondary efficacy parameter (HVSDS (M12), IGF-I and IGFBP-3 (M1, 3, 6, 9, 12))
  - Results were comparable between LB03002 and Genotropin®
Discontinued Patients

• 1 patient in LB03002 arm withdrew consent after month 3 (reason not disclosed)

• 1 patient in LB03002 arm was discontinued because of an “unlikely related“ SAE (neoplasm progression*)

• All but 9 out of 87 patients chose to roll-over into the extension phase (2nd treatment year)

* Follow up cytology results found no malignant cells
Data Set Analysed

• 178 patients received at least one dose of study medication (= full analysis set = ITT = safety set)

• 9 protocol violators

• 169 patients in per protocol set:
  - LB03002: N=86
  - Genotropin: N=83
Height Velocity

Per Protocol Set

![Graph showing Height Velocity (HV) comparison between LB03002 and Genotropin at Baseline and 12 Months.](image_url)
Height Velocity SDS

Per Protocol Set

Baseline

12 months

LB03002
Genotropin

HV SDS
Height SDS

Per Protocol Set

Baseline

12 months

LB03002
Genotropin
Primary Efficacy Analysis

- The study was designed to demonstrate non-inferiority of LB03002 to Genotropin® in terms of HV after 12 months treatment
  
  - The non-inferiority margin (difference in mean HV between treatment groups after 12 months treatment) was set to -1.8 cm/year
  
  - Non-inferiority was achieved if the lower bound of the two-sided 95% CI for the treatment difference was above -1.8 cm/year

- If non-inferiority was concluded from the primary analysis it was to be investigated next if the lower bound of the 95% CI for the treatment difference was above -1.5 cm/year
### Main Growth Parameters

**Full analysis set**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>LB03002 (N=91)</th>
<th>Genotropin® (N=87)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HV (cm/year)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>2.69</td>
<td>2.93</td>
</tr>
<tr>
<td>12 Months</td>
<td>11.63</td>
<td>11.97</td>
</tr>
<tr>
<td>Increase in HV Δ</td>
<td>8.94</td>
<td>9.04</td>
</tr>
<tr>
<td>HV SDS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>-3.16</td>
<td>-3.05</td>
</tr>
<tr>
<td>12 Months</td>
<td>5.68</td>
<td>6.13</td>
</tr>
<tr>
<td>Increase in HV SDS Δ</td>
<td>8.84</td>
<td>9.18</td>
</tr>
<tr>
<td>HT SDS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>-4.34</td>
<td>-4.36</td>
</tr>
<tr>
<td>12 Months</td>
<td>-3.06</td>
<td>-3.03</td>
</tr>
<tr>
<td>Gain in HT SDS Δ</td>
<td>1.31</td>
<td>1.33</td>
</tr>
</tbody>
</table>
Mean IGF-1 and IGFBP-3 SDS

Full analysis set

IGF-1

IGFBP-3
IGF-1 SDS

Safety Set
Bone Maturation

Per Protocol Set
Comparison to KIGS Data *(Ranke et al., 2007)*

<table>
<thead>
<tr>
<th>Parameter</th>
<th>0.5 mg/kg LB03002</th>
<th>KIGS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>7.82 ± 2.5</td>
<td>7.10 ± 3.3</td>
</tr>
<tr>
<td><strong>Bone age (years)</strong></td>
<td>4.35 ± 2.2</td>
<td>5.1 ± 3.0</td>
</tr>
<tr>
<td><strong>Height velocity (cm/year)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>2.69 ± 1.1</td>
<td>4.9 ± 2.0</td>
</tr>
<tr>
<td>Month 12</td>
<td>11.72 ± 2.6</td>
<td>9.1 ± 2.7</td>
</tr>
<tr>
<td><strong>Height SDS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>- 4.34 ± 1.8</td>
<td>-3.5 ± 1.1</td>
</tr>
<tr>
<td>Month 12</td>
<td>- 3.06 ± 1.5</td>
<td>-2.6 ± 1.1</td>
</tr>
</tbody>
</table>

Local Tolerability

• Overall local tolerability as assessed by investigator and by parents/patients was considered good to very good

• The incidence of injection site reactions (pain, tenderness, erythema, warmth, swelling) was higher in patients treated with LB03002

• The most frequently reported injection site reaction in the LB03002 group was injection site swelling

• Injection site reactions were transient and mostly mild in intensity
Safety Results: Anti-hGH Antibody

- 30 patients (33%) in the LB03002 group tested positive for potentially biologically relevant anti-hGH antibodies vs. 3 (3.4%) in the Genotropin group.

- The presence of antibodies had no detectable effect on growth (e.g. gain in height velocity below) and IGF-I levels and was not associated with a higher incidence of injection site reactions.

\[
\text{p}=0.344
\]
IGF-I Exposure (Baseline-Adjusted AUC Per Year) in Anti-hGH Positive and Negative Patients

p=0.226
# Hb A1c and Glucose

<table>
<thead>
<tr>
<th>Parameter</th>
<th>LB03002 (N=91)</th>
<th>Genotropin® (N=87)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hb A1c (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal range 3.9 – 6.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>n=91 5.10 ± 0.34</td>
<td>n=87 5.11 ± 0.29</td>
</tr>
<tr>
<td>Month 12</td>
<td>n=82 5.14 ± 0.28</td>
<td>n=79 5.14 ± 0.34</td>
</tr>
<tr>
<td><strong>Glucose (mmol/l)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal range 3.08 – 6.44</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>n=91 4.23 ± 0.80</td>
<td>n=87 4.11 ± 0.80</td>
</tr>
<tr>
<td>Month 12</td>
<td>n=84 4.45 ± 0.67</td>
<td>n=80 4.67 ± 0.55</td>
</tr>
</tbody>
</table>
## Diabetes mellitus and impaired glucose tolerance

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LB03002 (N=91)</td>
</tr>
<tr>
<td></td>
<td>n (%)</td>
</tr>
<tr>
<td></td>
<td>Genotropin® (N=87)</td>
</tr>
<tr>
<td></td>
<td>n (%)</td>
</tr>
<tr>
<td><strong>Incidence of diabetes mellitus</strong> *</td>
<td>no</td>
</tr>
<tr>
<td></td>
<td>91 (100)</td>
</tr>
<tr>
<td></td>
<td>yes</td>
</tr>
<tr>
<td></td>
<td>-</td>
</tr>
<tr>
<td><strong>Incidence of impaired glucose</strong></td>
<td>no</td>
</tr>
<tr>
<td>tolerance **</td>
<td>90 (98.9)</td>
</tr>
<tr>
<td></td>
<td>yes</td>
</tr>
<tr>
<td></td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>* defined as a fasting glucose level of &gt;126 mg/dL [&gt;7.0 mmol/L] at two or more consecutive visits</td>
<td></td>
</tr>
<tr>
<td>** defined as a fasting glucose level of &gt; 100 mg/dL [&gt;5.6 mmol/L] at two or more consecutive visits</td>
<td></td>
</tr>
</tbody>
</table>
At screening, at initiation, after 1 month and further on in 3-monthly intervals up to 24 months, all patients were assessed for fasting glucose, insulin and Hb A1C.

HOMA index was calculated for each visit (Allard P et al, Clinical Chemistry (2003) 49: 644-649).

Fasting glucose, insulin and Hb A1C data were analyzed by two-way analysis of variance, using Holm-Sediak method (SAS statistics)*

* Performed by Dr Zvi Zadik
Glucose Metabolism: Results of Two-way Analysis of Variance

- HOMA index:
  - No significant difference in changes of HOMA index level, across all 4 treatment arms, over the 24 months treatment (p=0.624)

- Insulin:
  - No significant difference in changes of insulin levels across all 4 treatment arms, over the 24 months treatment (p=0.810)

- Hb A1C:
  - No significant difference in changes of HbA1C levels, across all 4 treatment arms, over the 24 months treatment (p=0.650)
Glucose Metabolism: Results of Multiple Linear Regression Analysis

• A multiple linear regression analysis was performed with:
  - dependent variable = insulin
  - independent variables = glucose levels, visit and treatment (i.e. 0.2, 0.5, 0.7mg/kg/week and Genotropin)

• Outcome of Analysis:
  - The variables that have a statistically significant effect on insulin levels, were glucose concentration and duration of treatment (visit)
  - None of the 3 doses of LB03002, nor Genotropin, showed a clinically relevant effect on insulin levels
Serious Adverse Events

• 4 patients (2 LB, 2 Genotropin) experienced 5 SAEs:
  - Dengue fever
  - Neoplasm progression*
  - Tonsillitis (2)
  - Upper respiratory tract infection

• All “unrelated“ or “unlikely related“ to study medication and resolved

• Only one SAE led to study discontinuation

* Follow up cytology results found no malignant cells
## Safety Results: Treatment-Emergent AE

### TEAEs Occurring in > 5% of Patients in Either Treatment Group

<table>
<thead>
<tr>
<th>Condition</th>
<th>LB03002 (n=91)</th>
<th>Genotropin® (n=87)</th>
</tr>
</thead>
<tbody>
<tr>
<td>General disorders and Administration site conditions</td>
<td>43 (47.3)</td>
<td>19 (21.8)</td>
</tr>
<tr>
<td>Endocrine disorders</td>
<td>28 (30.8)</td>
<td>23 (26.4)</td>
</tr>
<tr>
<td>Infections and Infestations</td>
<td>21 (23.1)</td>
<td>31 (35.6)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>15 (16.5)</td>
<td>15 (17.2)</td>
</tr>
<tr>
<td>Investigations</td>
<td>15 (16.5)</td>
<td>17 (19.5)</td>
</tr>
<tr>
<td>Respiratory disorders</td>
<td>14 (15.4)</td>
<td>14 (16.1)</td>
</tr>
<tr>
<td>Blood and lymphatic disorders</td>
<td>11 (12.1)</td>
<td>19 (21.8)</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>11 (12.1)</td>
<td>13 (14.9)</td>
</tr>
</tbody>
</table>

### Severity of TEAEs

<table>
<thead>
<tr>
<th>Severity</th>
<th>LB03002 (n=91)</th>
<th>Genotropin® (n=87)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>64 (70.3)</td>
<td>55 (63.2)</td>
</tr>
<tr>
<td>Moderate</td>
<td>36 (39.6)</td>
<td>27 (31.0)</td>
</tr>
<tr>
<td>Severe</td>
<td>7 (7.7)</td>
<td>6 (6.9)</td>
</tr>
</tbody>
</table>

### Serious Adverse Events

<table>
<thead>
<tr>
<th>Condition</th>
<th>LB03002 (n=91)</th>
<th>Genotropin® (n=87)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tonsilitis</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Dengue Fever</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Upper Resp. tract infection</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Neoplasm progression†</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

* All SAEs are unlikely related or unrelated, and resolved.
† Patient with a SAE of neoplasm progression discontinued treatment; follow up cytology showed no malignant cells.
Local Tolerability Assessments by the Patient/Parent: Safety Set

<table>
<thead>
<tr>
<th>Parameter</th>
<th>LB03002 (N=91)</th>
<th>Genotropin® (N=87)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pain</strong></td>
<td>none</td>
<td>≥40.7%</td>
</tr>
<tr>
<td></td>
<td>severe</td>
<td>2 (2.2%), 2 visit</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 (1.1%), 3 visit</td>
</tr>
<tr>
<td><strong>Tenderness</strong></td>
<td>none</td>
<td>≥68.1%*</td>
</tr>
<tr>
<td><strong>Erythema</strong></td>
<td>none</td>
<td>≥73.6%*</td>
</tr>
<tr>
<td><strong>Warmth</strong></td>
<td>none</td>
<td>≥93.4%*</td>
</tr>
<tr>
<td><strong>Injection Site Swelling</strong></td>
<td>none</td>
<td>≥64.8%*</td>
</tr>
</tbody>
</table>

* all other mild
** all other mild to moderate
Conclusions Safety

• No clinically relevant adverse events, related to treatment with LB03002 in all dose groups

• Injection site reactions were mostly mild, transient and resolved within 2 to 3 days post-dose, without intervention

• All laboratory parameters relevant for safety assessment, including fasting glucose, HOMA index, insulin and Hb A1c, did not show any clinically relevant changes from baseline

• LB03002 was safe and well tolerated in all dose groups
# 1\textsuperscript{st} and 2\textsuperscript{nd} year growth

<table>
<thead>
<tr>
<th>First year/second year treatment</th>
<th>Time of assessment</th>
<th>LB03002/LB03002 (N=87)</th>
<th>Genotropin /LB03002 (N=80)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HV (cm/year)</td>
<td>Baseline</td>
<td>2.64 ± 1.11</td>
<td>2.87 ± 1.04</td>
</tr>
<tr>
<td></td>
<td>End of 1\textsuperscript{st} year</td>
<td>11.72 ± 2.58</td>
<td>12.16 ± 3.09</td>
</tr>
<tr>
<td></td>
<td>End of 2\textsuperscript{nd} year</td>
<td>8.33 ± 1.92</td>
<td>7.28 ± 2.34</td>
</tr>
</tbody>
</table>
Safety Summary

• No statistically significant difference in incidence of TEAEs between treatment groups

• Majority of TEAEs were mild or moderate

• All laboratory parameters relevant for safety assessment, including fasting glucose, and Hb A1c, did not show any clinically relevant changes from baseline

• Antibodies to hGH were more frequent in the LB03002 group but were not clinically relevant

• Patients in the LB03002 group experienced more injection site reactions
Overall Conclusions

• LB03002, a sustained-release human recombinant growth hormone formulation for weekly s.c. injection showed comparable efficacy and safety to daily formulation

• Non-inferiority of LB03002 was demonstrated for the primary efficacy parameter (HV)

• There was no difference in the observed growth patterns and secondary efficacy parameters showed similar improvements in both treatment groups

• Treatment with LB03002 resulted in more patients developing antibodies to hGH which did not affect growth

• Treatment with LB03002 lead to more injection site reactions, which were classified mainly as mild or moderate

• LB03002 was safe and well tolerated with a low incidence of SAEs and AEs leading to discontinuation of medication
Overall Conclusions

- For the dose range (0.5 and 0.7mg/kg/week) of LB03002 investigated, comparable height velocity to daily rhGH was shown.

- Overall, LB03002 was safe and well tolerated in all dose groups.
We would like to thank all of the participating patients and their families, as well as the global network of principal investigators, research nurses, study coordinators and operations staff.

Bashnina Borisovna Elena
Bettendorf, Markus
Bolshova-Zubkovskaya, Elena
Calland Ricarte Bezerra, Izabel
Calliari, Luis Eduardo
Cernich, Joseph
Cicognani, Alessandro
Daaboul, Jorge
Desai, Meena
Dharmalingam, Mala
El Kholi, Mohamed
Geffner, Mitchell E.
Ghizzoni, Lucia
Grimberg, Adda

Hoineff, Claudio
Khadgawat, Rajesh
Khadilkar, Vaman
Kocova, Mirjana
Larin, Oleksander
Mahadevan, Sriram
Mericq, Veronica
Moutinho de Souza, Flávio
Muzsnai, Agota
Paskova, Magdalena
Peterkova, Valentina
Popa, Mircea
Radiuk, Klavdia
Spinola e Castro, Angela
Maria Starzyk, Jerzy

In collaboration with Biopartners and LG Life Sciences
VRS-317: Construct

Designed to improve PK, reduce clearance
110 hr half-life in monkeys

hGH = 22 kDa
VRS-317 = 119 kDa
Improved In Vivo Potency

Juvenile Cynomolgus monkeys (n=4/group)

Expected total dose/month is lower than daily hGH (potential to dose 1/10 daily hGH dose)
**Human Dosing Projections**

*Expected total dose/month is lower than daily hGH*

- Maintain VRS-317 plasma level at or above 1 nM
- Same volume of distribution as monkeys
- 3.1 fold lower elimination rate than monkeys
- 161 Fold Safety Factor at Starting Dose

> 0.2 mg/kg VRS-317/month (0.04 mg/kg hGH) sustains level above 1 nM
Concerns about long acting GH

- Study data in children and adults are limited
- Consequences of different signaling patterns via JAK/STAT vs MAP-kinase pathways remain to be investigated further
- Consequences for intermediary metabolism unknown
- Present data suggest similar effect on glucose metabolism
- Some of the pleiotropic GH effects other than “cm” and body fat mass may differ between daily s.c. versus sustained release GH formulations
Differential sensitivity of hepatic responses to continuous GH

from Wells et al, Endocrinology 1994: 134, 2135-214

Slide courtesy of Prof. ICAF Robinson
Differences Between Single Dose and Continuous GH

• Both increase body weight and bone growth.
• Continuous GH results in differential organ growth in rodents.
• Continuous GH results in higher IGF-I and IGFBP-3 levels in rats and monkeys.
• Continuous GH results in higher GHBP levels in rats.
• Continuous GH appears more lipolytic in rodents.
• Continuous GH results in slightly higher IGF-I and IGFBP-3 levels in humans.

Slide kindly provided by Dr. Paul Fielder
Glucose Levels
Adherence to Medication

Lars Osterberg, M.D., and Terrence Blaschke, M.D.

Drugs don’t work in patients who don’t take them.

— C. Everett Koop, M.D.

Adherence to (or compliance with) a medication regimen is generally defined as the extent to which patients take medications as prescribed by their health care providers. The word “adherence” is preferred by many health care providers, because “compliance” suggests that the patient is passively following the doctor’s orders and that the treatment plan is not based on a therapeutic alliance or contract established between the patient and the physician. Both terms are imperfect and uninformative descriptions of medication-taking behavior. Unfortunately, applying these terms to patients who do not consume every pill at the desired time can stigmatize these patients in their future relationships with health care providers. The language used to describe how patients take their medications needs to be reassessed, but these terms are still commonly used. Regardless of which word is preferred, it is clear that the full benefit of the many effective medications that are avail-
Adherence to Medication

Table 3. Strategies for Improving Adherence to a Medication Regimen.

<table>
<thead>
<tr>
<th>Identify poor adherence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Look for markers of nonadherence: missed appointments (“no-shows”), lack of response to medication, missed refills</td>
</tr>
<tr>
<td>Ask about barriers to adherence without being confrontational</td>
</tr>
<tr>
<td>Emphasize the value of the regimen and the effect of adherence</td>
</tr>
<tr>
<td>Elicit patient’s feelings about his or her ability to follow the regimen, and if necessary, design supports to promote adherence</td>
</tr>
<tr>
<td>Provide simple, clear instructions and simplify the regimen as much as possible</td>
</tr>
<tr>
<td>Encourage the use of a medication-taking system</td>
</tr>
<tr>
<td>Listen to the patient, and customize the regimen in accordance with the patient’s wishes</td>
</tr>
<tr>
<td>Obtain the help from family members, friends, and community services when needed</td>
</tr>
<tr>
<td>Reinforce desirable behavior and results when appropriate</td>
</tr>
<tr>
<td>Consider more “forgiving” medications when adherence appears unlikely†</td>
</tr>
<tr>
<td>Medications with long half-lives</td>
</tr>
<tr>
<td>Depot (extended-release) medications</td>
</tr>
<tr>
<td>Transdermal medications</td>
</tr>
</tbody>
</table>

- Development rationale for a sustained release product:
  - Better patient compliance through less frequent dosing
  - Comparable efficacy and safety profile to daily hGH products

- Ideal target:
  - Once-a-week subcutaneous injection
Long Acting Formulations - Background

• At least 5 companies are pursuing the development of long acting formulations of growth Hormone. They range from various pegylated versions to crystalline growth hormone.

• Several companies presented their data at ENDO 2010 in San Diego and will also be presenting their data at ESPE 2010 in Prague.

• We will present today data on the comparative phase of the BPLG-004 study which was completed in June 2009.
Eligibility Criteria cont‘d

• Chromosomal and congenital abnormalities (“syndromes”)

• Clinically significant abnormalities likely to affect growth such as, but not limited to:
  
  ➢ chronic diseases like renal insufficiency
  
  ➢ diabetes mellitus
  
  ➢ malnutrition (body mass index [BMI] above -2SD and below +2SD of mean BMI for the chronological age and sex)
  
  ➢ albumin below lower limit of normal of the central laboratory

• Closed epiphyses

• Poorly controlled pituitary insufficiencies of other axes
Non-Inferiority Margin

Non-inferiority Margins and 95% Confidence Intervals

-1.8 cm/year

$\Delta HV^*$

-2  -1  0  1  2

-1.222  0.334

95% CI per protocol set

95% CI full analysis set

*LB03002-Genotropin® (cm/year)
CI = confidence interval
$HV = height velocity$
BPLG003 – Pharmacodynamics week 13

IGF-1

Semilogarithmic view

Mean IGF-1 serum concentration (ng/mL)

0 12 24 36 48 72 120 168

0 1 10 100

time (h)

Visit 3 LB03002 0.2 mg/kg/week
Visit 3 LB03002 0.5 mg/kg/week
Visit 3 LB03002 0.7 mg/kg/week

IGFBP-3

Semilogarithmic view

Mean IGFBP-3 serum concentration (ng/mL)

0 12 24 36 48 72 120 168

500 1000 1500 2000 2500 3000 3500 4000

time (h)

Visit 3 LB03002 0.2 mg/kg/week
Visit 3 LB03002 0.5 mg/kg/week
Visit 3 LB03002 0.7 mg/kg/week
# Bone Maturation

## Full analysis set

<table>
<thead>
<tr>
<th>Parameter</th>
<th>LB03002 (N=91)</th>
<th>Genotropin® (N=87)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronological age</td>
<td>7.82</td>
<td>7.78</td>
</tr>
<tr>
<td>Bone age</td>
<td>4.35</td>
<td>4.42</td>
</tr>
<tr>
<td>Bone maturation</td>
<td>0.542</td>
<td>0.549</td>
</tr>
<tr>
<td><strong>Month 12</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone age</td>
<td>6.62</td>
<td>6.35</td>
</tr>
<tr>
<td>Bone maturation</td>
<td>0.692</td>
<td>0.681</td>
</tr>
<tr>
<td><strong>Change from baseline</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone age</td>
<td>2.03</td>
<td>1.79</td>
</tr>
<tr>
<td>Bone maturation</td>
<td>0.158</td>
<td>0.124</td>
</tr>
</tbody>
</table>
Efficacy Summary

• Non-inferiority of LB03002 to Genotropin® in terms of annualized HV after 12 months treatment was demonstrated at the 95% and 99% confidence level

• LB03002 and Genotropin® showed similar improvements for other efficacy parameters

• IGF-1 and IGFBP-3 levels increased equally in both treatment groups, moving towards the normal range within 1 month

• Results were similar for both the full analysis and per protocol sets.
## Non-Inferiority Margin

12 months HV in children with GHD with other somatropin products

<table>
<thead>
<tr>
<th>Study</th>
<th>Product</th>
<th>Height Velocity (cm/year)</th>
<th>Mean change (cm/year)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Pre-treatment</td>
<td>After 12 months treatment</td>
</tr>
<tr>
<td>Martha et al. 1992</td>
<td>Humatrope®</td>
<td>3.8±0.2</td>
<td>8.8±0.3</td>
</tr>
<tr>
<td>BP-EU-003</td>
<td>Humatrope®</td>
<td>3.4 ± 1.1</td>
<td>10.5 ± 2.8</td>
</tr>
<tr>
<td>Mortensen et al. 1991</td>
<td>Norditropin®</td>
<td>4.6±0.31</td>
<td>8.3±1.4</td>
</tr>
<tr>
<td>Rasmussen et al. 1988</td>
<td>Norditropin®</td>
<td>4.1±2.4</td>
<td>8.3±2.5</td>
</tr>
<tr>
<td>Bierich, 1987</td>
<td>Genotropin®</td>
<td>3.7±1.7</td>
<td>12.0±4.2</td>
</tr>
<tr>
<td>Job et al. 1988</td>
<td>Genotropin®</td>
<td>3.2±1.3</td>
<td>8.1±1.5</td>
</tr>
<tr>
<td>Vicens-Calvet et al. 1988</td>
<td>Genotropin®</td>
<td>3.3±0.6</td>
<td>9.8±2.4</td>
</tr>
<tr>
<td>Wilton &amp; Gunnarsson, 1988</td>
<td>Genotropin®</td>
<td>3.6±1.3</td>
<td>9.3±2.6</td>
</tr>
<tr>
<td>Pavia et al. 1992</td>
<td>Saizen®</td>
<td>4.0±1.5</td>
<td>10.1±2.4</td>
</tr>
<tr>
<td>MacGillivray et al. 1996</td>
<td>Somatropin</td>
<td>4.1±1.6</td>
<td>11.4±2.5</td>
</tr>
</tbody>
</table>
Treatment-Emergent Adverse Events (TEAEs)

- The incidence of TEAEs was similar in both treatment groups (difference not statistically significant)
- Majority of TEAEs were mild or moderate
- Most common TEAEs in the LB03002 group were general and administration site conditions
- Most common TEAEs in the Genotropin group were infections (mainly URTIs)
- Majority of TEAEs other than injection site reactions were unrelated or unlikely related to study medication
Glucose and Fat Metabolism

• HbA1c within normal range in all patients at all visits

• Fasting glucose and insulin showed no significant difference in changes between treatment groups

• Total cholesterol and triglycerides showed no significant difference in changes between treatment groups
Back-Up
# Demographics and Diagnosis

<table>
<thead>
<tr>
<th></th>
<th>LB03002 (n=91)</th>
<th>Genotropin® (n=87)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years), Mean (SD)</strong></td>
<td>7.8 (2.5)</td>
<td>7.8 (2.5)</td>
</tr>
<tr>
<td><strong>Gender, n</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>56</td>
<td>55</td>
</tr>
<tr>
<td>Female</td>
<td>35</td>
<td>32</td>
</tr>
<tr>
<td><strong>Height (cm), Mean (SD)</strong></td>
<td>102.15 (14.92)</td>
<td>101.75 (15.05)</td>
</tr>
<tr>
<td><strong>Weight (kg), Mean (SD)</strong></td>
<td>17.02 (6.14)</td>
<td>17.15 (6.05)</td>
</tr>
<tr>
<td><strong>Bone Age GP (years)</strong></td>
<td>4.4 (2.2)</td>
<td>4.4 (2.3)</td>
</tr>
<tr>
<td><strong>Ethnic Origin, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>57 (62.6%)</td>
<td>56 (64.4%)</td>
</tr>
<tr>
<td>Afro-Carribean</td>
<td>1 (1.1%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Asian</td>
<td>31 (34.1%)</td>
<td>29 (33.3%)</td>
</tr>
<tr>
<td>Other</td>
<td>2 (2.2%)</td>
<td>2 (2.3%)</td>
</tr>
<tr>
<td><strong>Primary GHD : Secondary GHD</strong></td>
<td>83 : 8</td>
<td>77 : 10</td>
</tr>
<tr>
<td><strong>Isolated GH deficiency</strong></td>
<td>41 (45%)</td>
<td>39 (45%)</td>
</tr>
<tr>
<td><strong>Multiple GH deficiency</strong></td>
<td>50 (55%)</td>
<td>48 (55%)</td>
</tr>
</tbody>
</table>
Non-Inferiority Margin

-1.8 cm/year

*LB03002-Genotropin® (cm/year)
CI= confidence interval
HV = height velocity
Local Tolerance

Events Indicative of Administration Site Conditions

<table>
<thead>
<tr>
<th>System Organ Class Preferred Term</th>
<th>LB03002 (N=91)</th>
<th>Genotropin® (N=87)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients n (%)</td>
<td>Events E</td>
</tr>
<tr>
<td>Any injection site reaction</td>
<td>35 (38.5)</td>
<td>86</td>
</tr>
<tr>
<td>Injection site swelling</td>
<td>26 (28.6)</td>
<td>40</td>
</tr>
<tr>
<td>Injection site pain</td>
<td>9 (9.9)</td>
<td>15</td>
</tr>
<tr>
<td>Injection site erythema</td>
<td>8 (8.8)</td>
<td>9</td>
</tr>
<tr>
<td>Injection site discolouration</td>
<td>7 (7.7)</td>
<td>11</td>
</tr>
<tr>
<td>Injection site nodule</td>
<td>4 (4.4)</td>
<td>9</td>
</tr>
<tr>
<td>Injection site reaction</td>
<td>1 (1.1)</td>
<td>1</td>
</tr>
<tr>
<td>Injection site warmth</td>
<td>1 (1.1)</td>
<td>1</td>
</tr>
<tr>
<td>Injection site bruising</td>
<td>0 (0.0)</td>
<td>0</td>
</tr>
<tr>
<td>Injection site haemorrhage</td>
<td>0 (0.0)</td>
<td>0</td>
</tr>
</tbody>
</table>

Source: Table 5.2.6.1, Section 14.1

E = number of events; N = number of patients in group; n = number of patients with data.
Human Dosing Projections

**Expected total dose/month is lower than daily hGH**

- Maintain VRS-317 plasma level at or above 1 nM
- Same volume of distribution as monkeys
- 3.1 fold lower elimination rate than monkeys

161 Fold Safety Factor at Starting Dose

- >0.2 mg/kg VRS-317/month (0.04 mg/kg hGH) sustains level above 1 nM
Improved In Vivo Potency

Juvenile Cynomolgus monkeys (n=4/group)

Expected total dose/month is lower than daily hGH (potential to dose 1/10 daily hGH dose)
VRS-317: Construct

Designed to improve PK, reduce clearance
110 hr half-life in monkeys

hGH = 22 kDa
VRS-317 = 119 kDa
Twelve months safety and efficacy of LB03002, a new prolonged release formulation of rhGH, as compared to daily rhGH therapy in treatment-naïve children with growth failure due to insufficient secretion of endogenous growth hormone (GHD)*: a phase III, multi-center, randomized, parallel group trial

* In cooperation with Biopartners’ and LG Life Sciences’ GH Study Group; In memoriam of late Prof Mircea Popa, Bucharest, Romania, who significantly contributed to this trial.
DISCLOSURE STATEMENT
Study Design (1/2)

Objectives:
To demonstrate the clinical comparability (non-inferiority) in terms of safety and efficacy of LB03002 and Genotropin®

Design:
Open label, active-controlled, parallel-group phase III study

Primary Efficacy Endpoint:
Height velocity (HV) after 12 months treatment

(according to annex to CHMP guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance (EMEA/CPMP/42832/05/): GUIDANCE ON SIMILAR MEDICINAL PRODUCTS CONTAINING SOMATROPIN)
Study Design (2/2)

- Daily Genotropin
- Screening
- Weekly LB03002

1st treatment year: Comparative period
- Randomization
- V 1
  - Day 1
  - 12 Months
- V 6

2nd treatment year: Extension period
- Switch-over of Genotropin patients
- V 10
  - 24 Months

3rd and 4th treatment year: Follow-up period
- Weekly LB03002
- V 14
  - 36 Months
- V 18
  - 48 Months

Cut-off point for primary analysis (non-inferiority test)
Height Velocity

![Bar Chart]

- **Baseline**
- **12 Months**

**LB03002**

per protocol set
Height Velocity SDS

per protocol set
Height SDS

Baseline

12 Months

per protocol set
Gain in Height SDS

Δ HT SDS

12 Months

per protocol set
Non-inferiority Test

\[ \Delta \text{HV}^* \]

-2 \hspace{2cm} -1 \hspace{2cm} 0 \hspace{2cm} 1 \hspace{2cm} 2

- Inferiority
- Non-inferiority
- Superiority

95% CI per protocol set
99% CI per protocol set
95% CI full analysis set
99% CI full analysis set

*LB03002-Genotropin® (cm/year)
Pharmacodynamics

IGF-I SDS

IGFBP-3 SDS

LB03002
Genotropin

safety set
Efficacy Summary

- Non-inferiority of LB03002 to Genotropin® in terms of annualized HV after 12 months treatment could be shown at the 95% and 99% confidence level for a non-inferiority margin of 1.8 as well as 1.5 cm/year.

- LB03002 and Genotropin® showed similar improvements for other efficacy parameters (including increase in HT-SDS and bone maturation).

- IGF-I and IGFBP-3 levels increased equally in both treatment groups, moving towards the normal range within 3 months.

- Results were similar for both the full analysis (ITT) and per protocol (PP) sets.
## Treatment-emergent Adverse Events

| Patient with at least one: | LB03002  
N=91 | Genotropin®  
N=87 |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>n (%)</td>
<td></td>
</tr>
<tr>
<td>TEAE</td>
<td>75* (82%)</td>
<td>63* (72%)</td>
</tr>
<tr>
<td>Serious TEAE</td>
<td>2 (2%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Severe TEAE</td>
<td>5 (6%)</td>
<td>6 (7%)</td>
</tr>
<tr>
<td>TEAE leading to permanent discontinuation</td>
<td>1 (1%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

* difference not statistically significant
Serious Adverse Events

- 4 patients (2 LB, 2 Genotropin) experienced 5 SAEs:
  - Recurrence of astrocytoma
  - Dengue fever
  - Tonsillitis (2)
  - Upper respiratory tract infection
- All “unrelated” or “unlikely related” to study medication
30 patients (33%) in the LB03002 group tested positive for anti-hGH antibodies at two or more consecutive visits vs. 3 (3.4%) in the Genotropin group

The presence of antibodies had no detectable effect on growth and IGF-I levels and was not associated with a higher incidence of injection site reactions

Most antibody-positive patients had low to moderate antibody titres
Injection Site Reactions

- “Global tolerability“ as assessed by investigator and by parents/patients was considered good to very good in most cases

- Injection site reactions (pain, tenderness, erythema, warmth, swelling) were transient and mostly mild in intensity

- The incidence of “injection site swelling“ and „injection site erythema“ was statistically significantly higher in LB03002 patients
Safety Summary

- No statistically significant difference in incidence of TEAEs between treatment groups
- Majority of TEAEs were mild or moderate
- Mean changes in laboratory parameters were small and unremarkable with no difference between treatment groups
- Antibodies to hGH were more frequent in the LB03002 group but were not clinically relevant
- Despite a higher frequency of injection site reactions (mostly “swelling“) in the LB03002 group, tolerability was considered by patients and investigators as good to very good in most cases
Overall Conclusions

- LB03002 was safe and well tolerated with a low incidence of SAEs and AEs leading to discontinuation of medication.
- Non-inferiority of LB03002 could be shown for the primary efficacy parameter (HV).
- There was no difference in the observed growth patterns and secondary efficacy parameters showed similar improvements in both treatment groups.
- Treatment with LB03002 resulted in more patients developing antibodies to hGH, which did not affect growth.
- Treatment with LB03002 lead to more injection site reactions, which were classified mainly as mild or moderate.
Back up slides
Study Design

Subjects:
Pre-pubertal, treatment-naive children with primary or secondary GH insufficiency (isolated or multiple)

Treatment:
- Once weekly LB03002: 0.5 mg/kg/week
- Daily Genotropin®: 0.03 mg/kg/day (= 0.21 mg/kg/week)
<table>
<thead>
<tr>
<th>Characteristics at Baseline</th>
<th>LB03002 N=91</th>
<th>Genotropin N=87</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>7.8 (2.5)</td>
<td>7.8 (2.5)</td>
</tr>
<tr>
<td>Gender (n)</td>
<td>Male (62%)</td>
<td>55 (63%)</td>
</tr>
<tr>
<td>Bone Age GP(months)</td>
<td>52.2 (26.3)</td>
<td>53 (28)</td>
</tr>
<tr>
<td>HT SDS</td>
<td>- 4.34</td>
<td>- 4.36</td>
</tr>
<tr>
<td>HV SDS</td>
<td>- 3.16</td>
<td>- 3.05</td>
</tr>
<tr>
<td>IGF-I SDS</td>
<td>- 4.34</td>
<td>- 4.39</td>
</tr>
</tbody>
</table>
## Diagnosis

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>LB03002 (N=91)</th>
<th>Genotropin (N=87)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary GHD</td>
<td>83 (91%)</td>
<td>77 (89%)</td>
</tr>
<tr>
<td>Secondary GHD</td>
<td>8 (9%)</td>
<td>10 (12%)</td>
</tr>
<tr>
<td>Isolated GH Deficiency</td>
<td>42 (46%)</td>
<td>39 (45%)</td>
</tr>
<tr>
<td>Multiple Hormone Def.</td>
<td>49 (54%)</td>
<td>48 (55%)</td>
</tr>
</tbody>
</table>
Gain in Height Velocity SDS

12 Months

ΔHV SDS

per protocol set
IGF-I SDS

Baseline 12 Months

LB03002

safety set
Bone Maturation

![Bar chart showing bone maturation ratio BA/CA at baseline and 12 months. The chart indicates a comparison between baseline and 12 months for the per protocol set with data point LB03002.]

per protocol set
Primary Efficacy Analysis

- The study was designed to demonstrate non-inferiority of LB03002 to Genotropin® in terms of HV after 12 months treatment.

- The non-inferiority margin (difference in mean HV between treatment groups after 12 months treatment) was set to 1.8 cm/year.

- Non-inferiority was achieved if the lower bound of the two-sided 95% (99%*) CI for the treatment difference was above -1.8 cm/year (-1.5 cm/year*).

- Methodology applied: analysis of covariance (ANCOVA).

*tested in a step-down procedure.
Treatment-emergent Adverse Events

- Majority of TEAEs were mild or moderate
- Most common TEAEs in the LB03002 group were general and administration site conditions*
- Most common TEAEs in the Genotropin group were infections (mainly URTIs)
- Majority of TEAEs other than injection site reactions were unrelated or unlikely related to study medication

* difference statistically significant (p=0.0005)
Discontinued Patients

- 1 patient in LB03002 arm withdrew consent after month 3 (reason not disclosed)
- 1 patient in LB03002 arm was discontinued because of an “unlikely related” SAE (recurrence of astrocytoma)
- All but 9 patients chose to roll-over into the extension phase (2nd treatment year)
Anti-hGH Antibodies

Figure 1.19
Height, IGF-1, anti-hGH titre and local tolerability for patient 69-4 (LB03002)
(baseline HTSDS=-6.32, change from baseline at month 12 for height=11.2 and for HVSDS=3.64)
## Events Indicative of Administration Site Conditions

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>LB03002 (N=91)</th>
<th>Genotropin® (N=87)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Preferred Term</td>
<td>Patients n (%)</td>
<td>Events E</td>
<td>Patients n (%)</td>
</tr>
<tr>
<td>General and administration site conditions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injection site swelling</td>
<td>17 (18.7)</td>
<td>26</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Injection site erythema</td>
<td>6 (6.6)</td>
<td>6</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Injection site discolouration</td>
<td>5 (5.5)</td>
<td>9</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Injection site nodule</td>
<td>2 (2.2)</td>
<td>3</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Injection site mass</td>
<td>1 (1.1)</td>
<td>1</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Injection site reaction</td>
<td>1 (1.1)</td>
<td>1</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Injection site warmth</td>
<td>1 (1.1)</td>
<td>1</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Injection site bruising</td>
<td>0 (0.0)</td>
<td>0</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>Injection site haemorrhage</td>
<td>0 (0.0)</td>
<td>0</td>
<td>2 (2.3)</td>
</tr>
</tbody>
</table>

*Source: Table 5.2.2.1, Section 14.1*

E = number of events; N = number of patients in group; n = number of patients with data.
Glucose and Fat Metabolism

- HbA1c within normal range in all patients at all visits
- Fasting glucose and insulin showed no significant difference in changes between treatment groups
- Total cholesterol and triglycerides showed no significant difference in changes between treatment groups
Patient Distribution

- **Europe** (n=88)
- **USA** (n=8)
- **Latin America** (n=12)
- **India** (n=60)
- **Egypt** (n=12)

**randomized patients (n=180)**
# Main Growth Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>LB03002 (91)</th>
<th>Daily rhGH (N=87)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HV (cm/year)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>2.69</td>
<td>2.93</td>
</tr>
<tr>
<td>12 Months</td>
<td>11.63*</td>
<td>11.97*</td>
</tr>
<tr>
<td>HV SDS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>-3.16</td>
<td>-3.05</td>
</tr>
<tr>
<td>12 Months</td>
<td>5.68</td>
<td>6.13</td>
</tr>
<tr>
<td>HT SDS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>-4.34</td>
<td>-4.36</td>
</tr>
<tr>
<td>12 Months</td>
<td>-3.06</td>
<td>-3.03</td>
</tr>
<tr>
<td>Gain in HT SDS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 12 Months</td>
<td>1.31</td>
<td>1.33</td>
</tr>
</tbody>
</table>

* Lower limit of 99% CI (ANCOVA) above pre-defined 1.5 cm non-inferiority margin.