Final Height and Safety Outcomes in Growth Hormone (GH)-Treated Children
Born Small for Gestational Age (SGA): Experience from a Large, Multinational, Prospective Observational Study

Christopher J Child1, Charmian A Quigley2, Alan G Zimmermann1, Cheri Deal4, Judith L Ross3, Eckhard Schönau6, Werner F Blum7
1Lilly Research Laboratories, Eli Lilly and Company, Windermere, UK; 2Sydney Children's Hospital, Randwick, Australia; 3Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, IN; 4University of Montreal and CHU Ste-Justine, Montreal, Canada; 5Department of Pediatrics, Thomas Jefferson University, Philadelphia, USA; 6Children's Hospital, University of Cologne, Cologne, Germany; 7University Children's Hospital, University of Giessen, Giessen, Germany  *Presenting Author: Employed by and stockholder of Eli Lilly and Company

1) BACKGROUND AND AIMS

Background
• GH treatment in short children born small for gestational age (SGA) has a growth-promoting effect in both the short- and long-term.
• Previous disclosure from the French SACHGE cohort demonstrated increased mortality and stroke risk in adulthood in patients born SGA, those with idiopathic short stature (ISS), and those with isolated growth hormone deficiency (IGHD) treated with GH during childhood (1, 2).

Aims
• To examine final height (FH) and safety outcomes in patients born SGA and treated with GH during routine clinical practice.
• To use data collected in the prospective, multinational Genetics and Neuroendocrinology of Short Status (GenesNBS) observational research programme.
• Final height was defined by at least 1 of the following: closed epiphyses, height velocity <2 cm/year, or last bone age >14 years (girls) or >16 years (boys).

2) PATIENTS AND METHODS

Patients
• 1208 GH-treated patients with SGA diagnosis were included in safety analyses (Figure 1).

Figure 1: Summary of SGA diagnoses

- Four populations were defined for height analyses:
  - All patients: baseline height available (N=1144)
  - FH Population 1: baseline and final height available (N=203)
  - FH Population 2: as FH Population 1 and baseline age ≥4 and <11 y; ≥5 y GH treatment (N=462)
  - FH Population 3: as FH Population 2 and initial GH dose ≥2.0 and <0.3 mg/kg/week (N=26).

Statistics
• Standard deviation scores (SDS) for height and BMI were calculated using age- and gender-matched data from the US National Center for Health Statistics.

3) RESULTS: Demographics and Final Height (FH) Outcomes

Patient demographics and baseline characteristics.
• Mean chronological age ranged from 8.3 to 10.9 years for the different FH populations; mean height SDS was ±2.0 for all analysis populations (Table 1).

Table 1: Selected demographics and baseline characteristics by analysis population

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean ± SD</th>
<th>All Patients</th>
<th>FH Population 1</th>
<th>FH Population 2</th>
<th>FH Population 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>11.1 ± 2.1</td>
<td>11.3 ± 2.1</td>
<td>11.2 ± 2.0</td>
<td>11.2 ± 2.0</td>
<td>11.1 ± 2.1</td>
</tr>
<tr>
<td>Sex (% MALE</td>
<td>49.4</td>
<td>49.6</td>
<td>49.4</td>
<td>49.6</td>
<td>49.4</td>
</tr>
<tr>
<td>BMI SDS</td>
<td>-1.2 ± 1.6</td>
<td>-0.6 ± 1.1</td>
<td>-1.1 ± 1.3</td>
<td>-1.2 ± 1.5</td>
<td>-1.5 ± 1.6</td>
</tr>
<tr>
<td>Height SDS</td>
<td>0.29 ± 0.9</td>
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<tr>
<td>Age (y)</td>
<td>12.0 ± 2.1</td>
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<td>12.0 ± 2.0</td>
<td>12.0 ± 2.0</td>
</tr>
<tr>
<td>Sex (% MALE</td>
<td>50.6</td>
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<td>50.6</td>
<td>50.6</td>
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<td>-1.5 ± 1.3</td>
<td>-1.5 ± 1.6</td>
<td>-1.8 ± 1.6</td>
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</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>12.6 ± 2.1</td>
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<td>12.6 ± 2.0</td>
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<tr>
<td>Sex (% MALE</td>
<td>50.9</td>
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Please refer to the table for detailed demographics and baseline characteristics by analysis population.

4) RESULTS: Safety Outcomes

Adverse events during GenesNBS participation
• 1111 patients born SGA were enrolled for assessment of treatment-emergent adverse events (TEAEs); mean duration of follow-up was 3.2 ± 2 years.
• To place the ratio of TEAEs in patients born SGA in context, data are also provided for all patients in GenesNBS, patients with ISS, and patients with IGHD.

Table 2: TEAE rates in GH-treated patients born SGA and other diagnoses (specific events at rates ≥1%)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Rate (%)</th>
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<tr>
<td>N</td>
<td></td>
</tr>
<tr>
<td>1111</td>
<td>2593</td>
</tr>
<tr>
<td>Patients with no TEAE</td>
<td>828 (75)</td>
</tr>
<tr>
<td>Patients with ≥1 TEAE</td>
<td>235 (21)</td>
</tr>
</tbody>
</table>

Precocious puberty |
• 32 (3) | 20 (2) | 82 (4) | 190 (9) |

Headache |
• 27 (2) | 18 (2) | 47 (2) | 132 (6) |

Hyperthyroidism |
• 22 (2) | 31 (2) | 40 (2) | 57 (2) |

Arthralgia |
• 19 (2) | 14 (1) | 104 (4) | 321 (16) |

ADHD |
• 18 (2) | 16 (2) | 64 (2) | 321 (16) |

Scoliosis |
• 12 (1) | 25 (1) | 40 (2) | 321 (16) |

Specific safety outcomes and events
• The following key outcomes were reported:
  - 2 deaths (1 case associated with displaced ventriculoperitoneal shunt and VACTERL association [3], 1 case of stroke associated with MELAS syndrome [4])
  - 1 malignancy (B-cell lymphoma)
  - 1 case of diabetes (2 type 2, 1 type 1, and 1 case in the patient with MELAS syndrome)
  - No cases of stroke except the fatal case in the patient with MELAS syndrome.

Insulin-like growth factor I (IGF-I) at baseline and during follow-up

Figure 3: Median (Q1, Q3) serum IGF-I SDS in GH-treated patients during 4 years of follow-up

- Mean IGF-I SDS was -1.5 ± 1.6 and was 0 ± 1.8 at 3 years of follow-up.
- 90% of 280 patients (21%) with ≥1 postbaseline IGF-I measurement had ≥1 IGF-I SDS value >2.
- 24 of 177 patients (14%) with ≥2 postbaseline IGF-I measurements had ≥1 IGF-I SDS value >2.

5) DISCUSSION

• FH SDS gain ranged from 1.1 to 1.5 SDS for the different FH populations; those who started youngest and were treated for longest (FH population 2) had the greatest height gain.
• The height gains observed during GenesNBS participation for patients born SGA were similar to those in previous studies that used GH doses similar to the approved dose in Europe (6, 7).
• Rates of TEAEs in patients born SGA were similar to those observed for ISS, IGHD, and all diagnoses combined.

6) CONCLUSIONS

• Data from a cohort of patients born SGA treated with GH in routine clinical practice demonstrated:
  - Substantial height SDS gain from baseline to final height
  - Serum IGF-I concentrations during GH treatment generally within the upper normal range
  - No additional safety concerns specific to GH treatment of patients born SGA relative to other short stature diagnoses.

7) REFERENCES