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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 Child[1*], Charmian A Quigley[2], Alan G Zimmermann[3], Cheri Deal[4], Judith L Ross[5], Eckhard Schönau[6], Werner F Blum[7]

[1]Lilly Research Laboratories, Eli Lilly and Company, Windlesham, UK; [2]Sydney Children's Hospital, Randwick, Australia; [3]Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, USA; [4]University of Montreal and CHU Ste-Justine, Montreal, Canada; [5]Department of Pediatrics, Thomas Jefferson University, Philadelphia, USA; [6]Children's Hospital, University of Cologne, Cologne, Germany; [7]University 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 SAGhE cohort demonstrated increased mortality and stroke risk in adulthood in patients born SGA, those with idiopathic short stature (ISS), and those with isolated idiopathic growth hormone deficiency (IsIGHD) treated with GH during childhood (1, 2).

Aims

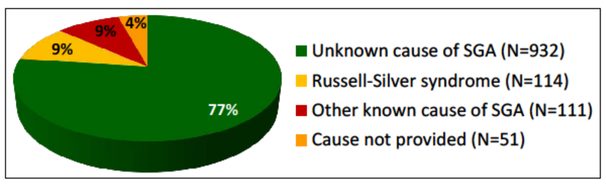
- To examine final height (FH) and safety outcomes in patients born SGA and treated with GH during routine clinical practice.
  - Using data collected in the prospective, multinational Genetics and Neuroendocrinology of Short Stature International Study (GeNeSIS) observational research programme.
  - 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=62)
  - FH population 3: as FH Population 2 and initial GH dose ≥0.2 and <0.3 mg/kg/wk (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 ≤-2.6 for all analysis populations (Table 1).

Table 1: Selected demographics and baseline characteristics by analysis population

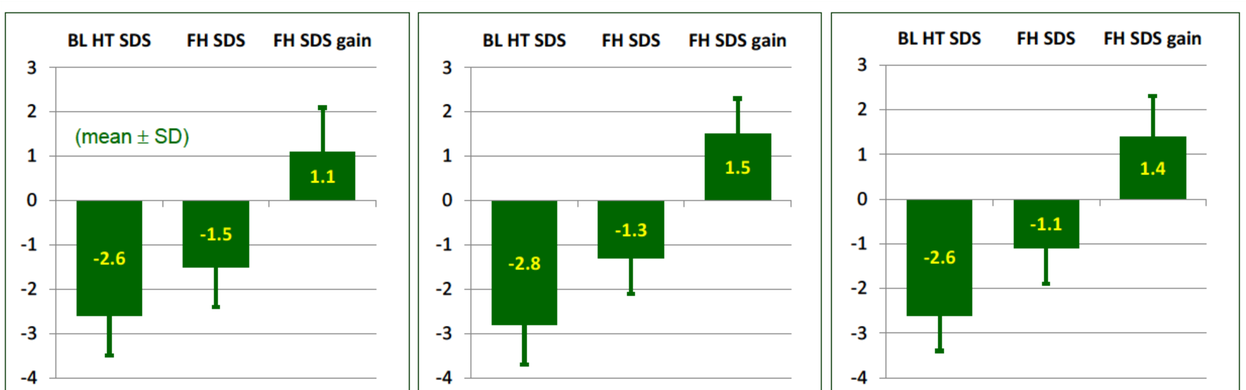
Variable (mean ± SD, unless stated)	All Patients	FH Population 1	FH Population 2	FH Population 3
Maximum N (lower for certain variables)	1144	203	62	26
Gender (%)	45 F / 55 M	57 F / 43 M	55 F / 45 M	58 F / 42 M
Chronological age (years)	8.2 ± 3.6	10.9 ± 3.1	8.3 ± 1.7	8.9 ± 1.9
BMI SDS	-1.4 ± 1.9	-0.9 ± 1.6	-1.3 ± 1.8	-1.5 ± 1.8
Height SDS	-2.7 ± 0.9	-2.6 ± 0.9	-2.8 ±0.9	-2.6 ± 0.8
IGF-I SDS	-1.5 ± 1.6	-1.5 ± 1.3	-2.1 ± 1.6	-2.1 ± 1.8
Initial GH dose (mg/kg/wk)	0.28 ± 0.10	0.28 ± 0.09	0.29 ± 0.08	0.25 ± 0.02

Abbreviations: F = female; FH = final height; M = male; N = number; SDS = standard deviation score; wk = week.

Patient outcomes and treatment characteristics at final height (Figure 2)

- Mean chronological age at final height was 16 years.
- Mean GH therapy duration was 5.0 years for FH population 1 and ~7 years for populations 2 and 3.
- GH dose (mg/kg/wk) varied little from initial to last reported dose.
- Mean FH SDS gain ranged from 1.1 to 1.5. depending on population analysed.

Figure 2: Final height gain and patient characteristics at final height by analysis population



FH Population 1 (N=203)

- Age: 16.1 ± 1.5 years
- BMI SDS: -0.3 ± 1.5
- Last GH dose: 0.30 ± 0.10 mg/kg/wk
- GH therapy duration: 5.0 ± 2.9 years

FH Population 2 (N=62)

- Age: 16.0 ± 1.2 years
- BMI SDS: -0.4 ± 1.6
- Last GH dose: 0.30 ± 0.10 mg/kg/wk
- GH therapy duration: 7.5 ± 1.8 years

FH Population 3 (N=26)

- Age: 16.0 ± 1.2 years
- BMI SDS: -0.8 ± 1.9
- Last GH dose: 0.28 ± 0.10 mg/kg/wk
- GH therapy duration: 6.8 ± 1.5 years

Abbreviations: BL = baseline; FH = final height; HT = height; N = number; SDS = standard deviation score; wk = week.

4) RESULTS: Safety Outcomes

Adverse events during GeNeSIS participation

- 1111 patients born SGA were eligible for assessment of treatment-emergent adverse events (TEAEs); mean duration of follow-up 3.2 ± 2.2 years.
- To place the rate of TEAEs in patients born SGA in context, data are provided also for all diagnoses in GeNeSIS, patients with ISS, and patients with IsIGHD.
- ≥1 TEAE was reported for 25% of patients born SGA, 23% for ISS, 16% for IsIGHD and 28% for all diagnoses; the most commonly reported TEAEs were similar across the different diagnoses (Table 2).

Table 2: TEAE rates in GH-treated patients born SGA and other diagnoses (specific events at rates ≥1.0%)

	SGA [N (%)][a]	ISS [N (%)]	IsIGHD [N (%)]	All Diagnoses [N (%)]
N	1111	2593	8897	20060
Patients with no TEAE	828 (75)	1994 (77)	7481 (84)	14508 (72)
Patients with ≥1 TEAE	283 (25)	599 (23)	1416 (16)	5552 (28)
Precocious puberty[b]	32 (2.9)	26 (1.0)	63 (0.7)	211 (1.1)
Headache[b]	27 (2.4)	69 (2.7)	138 (1.6)	529 (2.6)
Hypothyroidism[b]	22 (2.0)	31 (1.2)	40 (0.4)	577 (2.9)
Arthralgia[b]	19 (1.7)	47 (1.8)	104 (1.2)	321 (1.6)
ADHD[b]	18 (1.6)	64 (2.5)	110 (1.2)	323 (1.6)
Scoliosis[b]	13 (1.2)	40 (1.5)	96 (1.1)	358 (1.8)

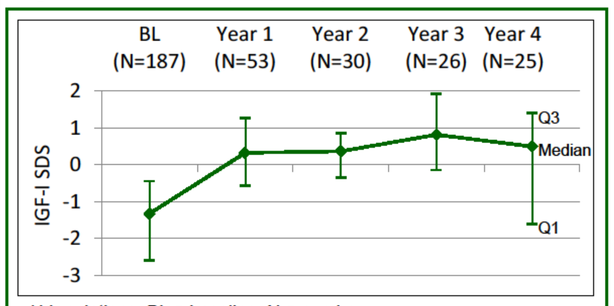
Abbreviations: ADHD = attention deficit hyperactivity disorder; N = number; TEAE = treatment-emergent adverse event.
[a] Additional TEAEs in SGA patients reported at ≥1.0%: asthma and acne (both 1.1%); presented by order of decreasing prevalence in the SGA group.
[b] Total cases of individual TEAE in study population, not by patient.

Specific safety outcomes and events

- The following key outcomes/events 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)
  - 4 cases of diabetes (2 type 2 [5], 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



Abbreviations: BL = baseline; N = number; Q = quartile; SDS = standard deviation score

- Mean IGF-I SDS was -1.5 ± 1.6 at baseline and was 0.8 ± 1.8 at 3 years of follow-up.
- 60 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 GeNeSIS 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, IsIGHD, 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.**

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GH and IGF Treatment
Christopher Child
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