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Final Height (FH) SDS Gain of Growth Hormone (GH) Treated Children with SHOX Deficiency: Describing Observational and Clinical Trial Data

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INTRODUCTION

- Patients with mutations or deletions within the coding or enhancer regions of the short stature homeobox-containing (SHOX) gene have a broad spectrum of phenotypic characteristics including variable degrees of impaired growth. Children with SHOX deficiency may also present with skeletal anomalies consistent with mesomelic skeletal dysplasia, including dysmorphic signs, short forearms and lower legs, and bowing of the forearm and tibia.
- GH treatment has been shown to increase growth of patients with SHOX deficiency, and in a multinational clinical trial, GH was shown to increase growth rate and FH.[1]
- This analysis describes patients with SHOX deficiency who have been treated with GH up to FH in both an observational setting (Genetics and Neuroendocrinology of Short Stature International Study; GeNeSIS) and in GDFN, a randomised clinical trial (study B9R-MC-GDFN). The regulated clinical trial setting aimed to show results in a controlled manner likely to represent optimal dosing practice, whereas the observational setting may be more representative of routine clinical practice.

OBJECTIVE

- The aim of the present analysis was to describe the FH outcome after GH treatment of SHOX-deficient patients in an observational study and a regulated clinical trial.

PATIENTS AND METHODS

- GeNeSIS is a prospective, multinational, observational program designed to examine the long-term safety and efficacy of GH treatment and includes GH-treated children with SHOX deficiency.
- GDFN was a randomized clinical trial in which patients with SHOX deficiency and short stature were GH-treated or untreated for the first 2 years after trial entry and then all received GH thereafter.
- GDFN enrolled patients who were prepubertal at the start of GH treatment, whereas GeNeSIS could enrol patients at any stage of pubertal development.
- Both studies included patients who were followed until they achieved FH.
- Height was evaluated from standard deviation score (SDS) calculated using data from a central European reference population.[2] Body mass index (BMI) SDS was determined from European reference charts.[3] FH is expressed in height SDS for age at the time of the measure.
- Study populations analysed met all of the following criteria:
  - Patients diagnosed with SHOX deficiency
  - Short stature treated with GH during study
  - Reached FH during study follow-up
- Last observed height was considered FH if any of the following criteria applied:
  - Closed epiphyses
  - Height velocity <2 cm/year
  - Last bone age >14 years in girls / >16 years in boys
- Number of SHOX-deficient patients who achieved FH and included in this analysis:
  - 85 in GeNeSIS
  - 28 in GDFN

STATISTICS

Descriptive statistics are shown, with mean ± standard deviation (SD), and 95% confidence intervals (CI).

RESULTS

- Patients in the clinical trial, GDFN, had a lower mean age at the start of GH therapy than patients in the observational study, GeNeSIS (Table 1).
- Mean bone age delay (bone age – chronological age) at start of GH therapy was similar for the two studies.
- Mean age at FH and dose of GH were similar for the two studies.
- Mean duration of GH treatment was greater for patients in the clinical trial than for patients in the observational study.

Table 1. Patient characteristics and GH treatment

Variable	GeNeSIS (N=85)	GDFN (N=28)
Gender, Female (%)	61 (71.8)	15 (53.6)
Age at GH start (years)	11.1 ± 2.3 (10.6 – 11.6)	9.2 ± 2.4 (8.3 – 10.2)
Age at FH (years)	15.5 ± 1.5 (15.2 – 15.9)	15.5 ± 1.3 (15.0 – 16.0)
Bone age delay at GH start (years)	-0.7 ± 1.5 (-1.1 – -0.3)	-0.9 ± 0.7 (-1.2 – -0.6)
GH dose at start (mg/kg/week)	0.32 ± 0.11 (0.30 – 0.35)	0.36 ± 0.02 (0.35 – 0.37)
GH dose last reported (mg/kg/week)	0.33 ± 0.10 (0.30 – 0.35)	0.38 ± 0.02 (0.37 – 0.38)
GH treatment duration (years)	4.18 ± 2.27 (3.68 – 4.68)	6.02 ± 2.01 (5.24 – 6.79)
Time in study (years)	4.43 ± 2.33 (3.93 – 4.94)	7.10 ± 1.58 (6.49 – 7.71)

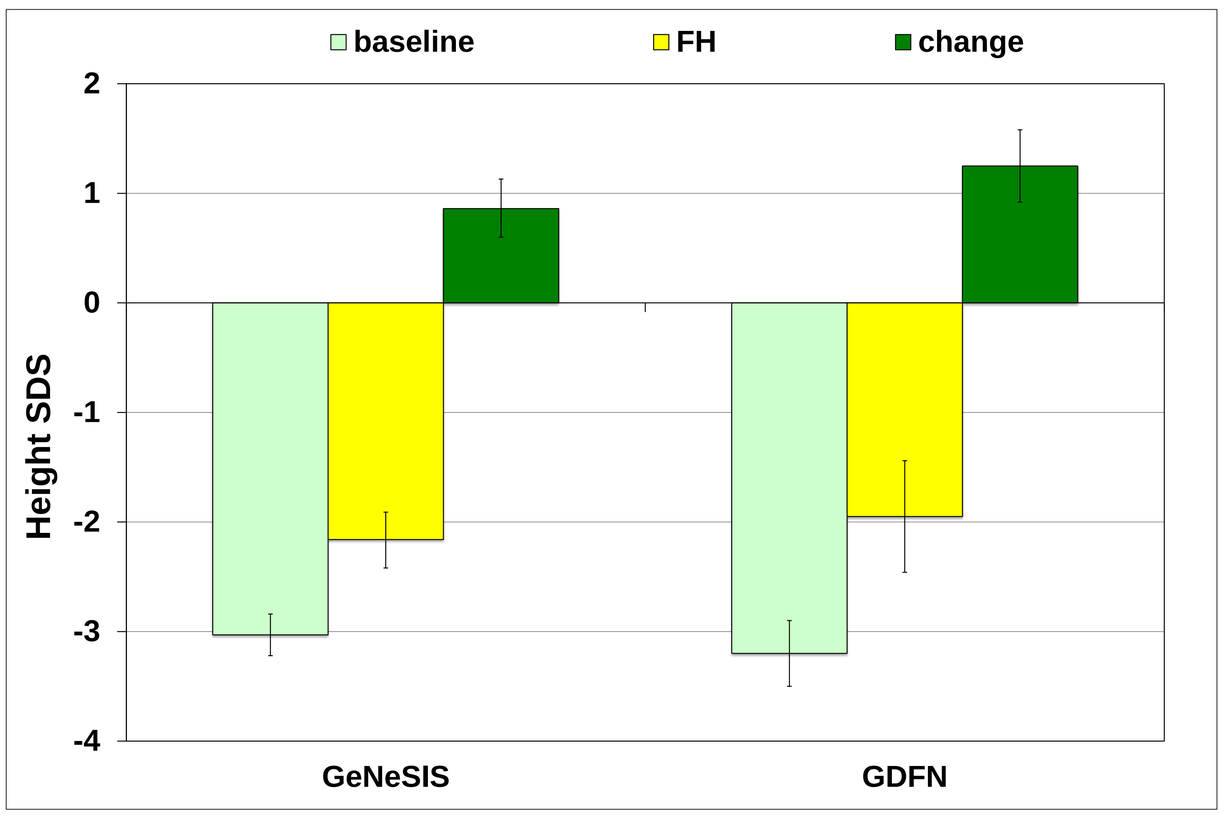
Values are mean ± SD (95% CI)

CONCLUSIONS

- **GH treatment was associated with a gain in height SDS at FH, both in a clinical trial and in a real-life observational setting.**
- **In the observational setting, GH treatment was started at a higher mean age and was administered for a shorter duration.**

- Height SDS was increased from baseline at the FH measurement to a similar extent in both the GeNeSIS observational study and the GDFN clinical trial (Figure 1).
- In the GeNeSIS observational study, a FH within the normal range (greater than -2 SDS) was achieved by 49% of patients.
- In the GDFN clinical trial, 57% of patients had FH within the normal range.

Figure 1. Height SDS at baseline, FH SDS and change from baseline to FH in each study



- Patients in GDFN had a similar BMI SDS to patients in GeNeSIS, at both the start of GH therapy and at FH, and the gain at FH was very similar in both studies (Table 2).

Table 2. Body mass index standard deviation score (BMI SDS) at GH therapy start and at FH

Variable	GeNeSIS (N=85)	GDFN (N=28)
BMI SDS at GH start	-0.13 ± 1.88 (-0.54 – 0.28)	0.53 ± 1.06 (0.12 – 0.95)
BMI SDS at FH	0.62 ± 1.52 (0.28 – 0.96)	1.24 ± 1.37 (0.71 – 1.77)
Change in BMI SDS at FH	0.77 ± 1.37 (0.46 – 1.07)	0.71 ± 0.78 (0.41 – 1.01)

Values are mean ± SD (95% CI)

SUMMARY

- 28 children in a clinical trial and 85 children in an observational study, who presented with a diagnosis of SHOX deficiency, were treated with GH for short stature and were followed up to FH.
- Patients in the clinical trial started GH treatment at a younger mean age and were treated for a longer mean duration than patients in the observational study.
- Mean gain in height SDS from GH start to FH for patients in the observational study (0.86; 95% CI 0.60 – 1.13) was similar to that for patients in the clinical trial (1.25; 95% CI 0.92 – 1.58).

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