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A two-year multi-centre, open-label, randomized, two-arm study of Genotropin® treatment in very young children born small for gestational age: early growth and neurodevelopment (EGN) study

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Background

- In Europe, growth hormone (GH) therapy is indicated for use in children born small for gestational age (SGA) who fail to demonstrate catch-up; however, treatment should be initiated no earlier than 4 years of age, as opposed to 2 years of age in the United States.[1]
- Initiation of therapy at younger age and use of higher doses are predictors of successful early growth in short-stature children born SGA who are treated with GH therapy.[2,3]
- Being born SGA is associated with subtle impairments in cognitive performance and educational achievement.[4] Studies conducted to investigate the potential beneficial effect of GH therapy on cognitive development in short-stature children aged >3 years who were born SGA have yielded inconsistent results.[5,6]
- Only few studies have been conducted to assess the efficacy and safety of GH treatment in very young (aged <30 months) short-stature children born SGA.[7]

Objective

- This study was conducted to assess the effects of 24 months of Genotropin treatment on growth (height gain, body weight, body mass index [BMI], and head growth), psychomotor development, and bone maturation in short-stature children born SGA, starting at the age of 24 to 30 months.

Methods

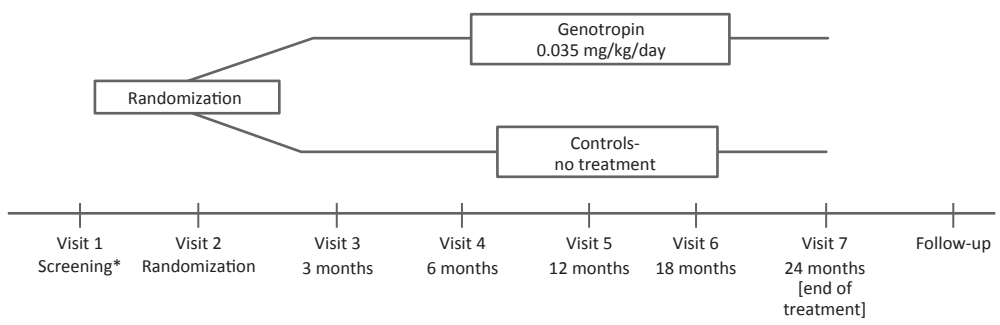
Key eligibility criteria

- Aged between 19 and 29 months and height below –2.5 standard deviation (SD) at screening
- Born SGA (birth length and/or weight below –2 SD for gestational age, using country-specific standards)
- ≥1 measurement of length between 12 and 18 months of age
- Normal karyotype (females) for exclusion of Turner syndrome
- Subjects presenting with any of the following were excluded:
  - Severe intrauterine growth retardation (birth length below –4 SD for gestational age) if associated with dysmorphic features
  - Severe prematurity (gestational age <32 weeks)
  - Ongoing catch-up growth (defined as growth velocity standard deviation score [SDS] at inclusion >0 based on at least 4 months' measurement interval)
  - Severe familial short stature (father's height <155 cm or mother's height <145 cm)
  - Defined neurological defects and/or severe neurodevelopmental delay
  - Defined syndromes (eg, foetal alcohol syndrome)
  - Severe perinatal complications (eg, asphyxia, sepsis, necrotising enterocolitis, respiratory distress syndrome if associated with long-term sequelae)
  - Other specific reason for short stature (eg, osteochondrodysplasia)
  - Receiving other hormone therapy or systemic glucocorticoids (current or within 6 months; use of topical or inhaled corticosteroids was permitted)

Study design and treatment

- This open-label, randomized, controlled, multi-centre phase 3b study was initiated in 2008.
- Eligible subjects were randomized in a 1:1 ratio to receive either Genotropin at a dose of 0.035 mg/kg/day or no treatment (**Figure 1**). Genotropin dose adjustment was performed at each visit.
- The primary endpoint was change from baseline in height SDS after 24 months of treatment with Genotropin.

Figure 1. **Study design**



*Performed at least 4 weeks but >6 months before randomization.

Assessments

- Standing height, body weight, BMI, head circumference, and pubertal status were assessed at study entry and at 6, 12, 18, and 24 months. SDS values were calculated for height and weight using the Prader reference[8] and for BMI using the Cole reference.[9]
- Assessment of psychomotor development using the Bayley Scales of Infant Development, 2nd edition ([BSID-II®)[10] was performed at study entry and at 12 months.
- An x-ray of the left hand and wrist was performed at study entry and at 12 and 24 months to permit assessment of bone age using the method of Greulich and Pyle.[11]
- All observed or volunteered adverse events (AEs) were reported.
- Blood samples were taken for monitoring of fasting blood glucose, insulin-like growth factor-1 (IGF-1), insulin-like growth factor binding protein-3 (IGFPB-3), thyroxine (FT4), thyroid stimulating hormone (TSH), alkaline phosphatase, platelets, leucocytes, haematocrit, alanine aminotransferase, albumin, sodium, potassium, calcium, urea, and creatinine.

Statistical analysis

- Change in height SDS at 12 and 24 months was analysed using LOCF data in an ANCOVA with baseline height SDS and treatment as covariates.
- Change in growth velocity SDS at 12 and 24 months was analysed using LOCF data in an ANCOVA, with baseline growth velocity SDS and treatment as covariates.
- Change in MDI and PDI of the BSID-II scale was analysed at 12 months using observed data in an ANCOVA, with baseline value, age, gender, and treatment as covariates.

Results

- In total, 52 subjects from 16 centres from 8 European countries were screened for the study.
- 43 children (21 in Genotropin arm [13 male, 8 female]; 22 in control arm [11 male, 11 female]), aged 19–29 months, and presenting a height below –2.5 SD at screening received treatment (**Table 1**).
- 19 subjects in the Genotropin arm and 20 in the control arm completed the study.

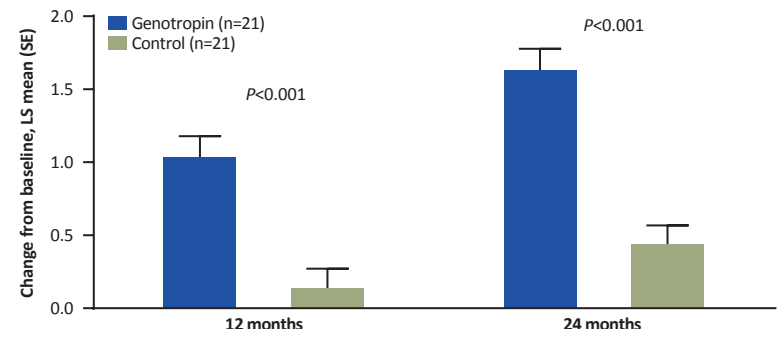
Table 1. **Subject demographics at baseline (FAS)**

Demographic, mean (SD)	Genotropin (N=21)	Control (N=21)
Age*, n	21	22
Months	24.9 (3.26)	24.4 (3.32)
Height		
cm	78.4 (3.19)	79.7 (3.66)
SDS	–3.87 (0.968)	–3.48 (0.737)
Growth velocity		
cm/year	9.33 (5.54)	10.92 (7.15)
SDS	–0.004 (4.911)	0.887 (6.394)
Weight, kg	9.30 (1.24)	9.49 (1.44)
BSID-II scores, n	16	21
MDI	86.6 (18.01)	84.6 (18.94)
PDI	80.4 (19.34)	85.8 (17.00)
Head circumference, n		
cm	47.6 (1.90)	47.0 (1.93)
SDS	–1.19 (1.30)	–1.72 (1.28)
BMI, kg/m²	15.1 (1.79)	14.9 (1.47)
Bone age, n	21	20
Months	18.81 (5.65)	19.10 (4.97)

n numbers are per overall N, except where indicated.
*Data on age were collected at screening only. BSID-II, Bayley Scales of Infant Development, 2nd edition; BMI, body mass index; FAS, full analysis set; MDI, Mental Development Index; PDI, Psychomotor Development Index; SD, standard deviation; SDS, standard deviation score.

- Genotropin treatment significantly increased height SDS compared with untreated controls at both month 12 and month 24 (primary endpoint) (**Figure 2**).
- The Δheight in the Genotropin versus control arm was 11.13 cm versus 7.62 cm at 12 months and 19.92 versus 14.34 cm at 24 months.
- Outcomes for other study endpoint measures are listed in **Table 2**.
- Mean change in bone age is shown in **Figure 3**.

Figure 2. **Change from baseline in height SDS at 12 and 24 months**



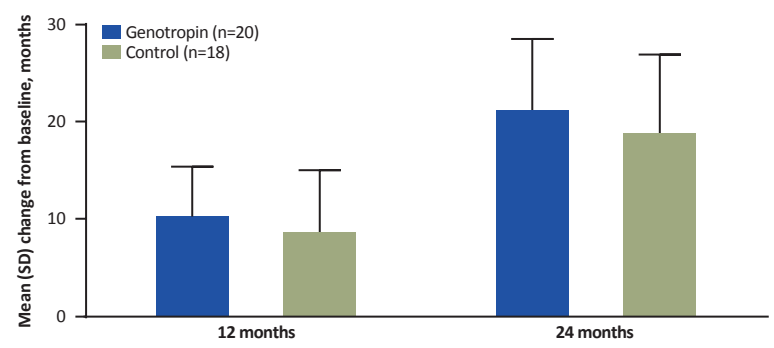
LS, least squares; SE, standard error.

Table 2. **Summary of other endpoint measures**

Change from Baseline	Genotropin (N=21)	Control (N=22)	LS Mean Difference	*P* value
Growth velocity SDS, LOCF				
At 12 months, n	21	21		
LS mean (SE)	1.65 (0.56)	–1.59 (0.56)	3.24 (0.80)	<0.001
At 24 months, n	21	21		
LS mean (SE)	0.74 (0.57)	–0.03 (0.57)	0.77 (0.81)	0.348
MDI score at 12 months, n	15	19		
LS mean (SE)	10.97 (5.34)	8.55 (4.74)	2.43 (7.19)	0.738
PDI score at 12 months, n	15	17		
LS mean (SE)	4.04 (3.04)	8.55 (2.84)	–4.51 (4.27)	0.301
Head circumference SDS				
At 12 months, n	20	18		
Mean (SD)	0.26 (0.52)	0.02 (0.59)	–	–
At 24 months, n	20	20		
Mean (SD)	0.39 (0.64)	0.08 (0.60)	–	–
BMI (kg/m²)				
At 12 months, n	20	19		
Mean (SD)	–0.62 (0.65)	–0.29 (0.68)	–	–
At 24 months, n	20	20		
Mean (SD)	–0.58 (0.82)	–0.55 (0.78)	–	–

BMI, body mass index; LOCF, last observation carried forward; LS, least squares; MDI, Mental Development Index; PDI, Psychomotor Development Index; SD, standard deviation; SDS, standard deviation score; SE, standard error.

Figure 3. **Mean change in bone age at 12 and 24 months**



SD, standard deviation.

Safety

- Treatment-emergent AEs (TEAEs) are listed in **Table 3**. A greater number of all-causality AEs was reported in the Genotropin arm versus the control arm.
- The most commonly reported TEAE in both arms was infection and infestation.
- Treatment-related serious AEs (adenoidal and tonsillar hypertrophy) were reported in 1 subject (4.8%) in the Genotropin arm.
- No notable median change from baseline to last observation in any of the laboratory safety parameters was observed, with the exception of platelet count and alkaline phosphatase (data not shown).
- FT4, IGFPB-3, and IGF-1 levels were inside normal limits in all subjects in the study. TSH was found to be >1.2 times the upper limit of normal in 1 (4.5%) patient in the control arm.

Table 3. **Treatment-emergent adverse events**

	Genotropin (N=21)		Control (N=22)	
	All Causality	Treatment-Related	All Causality	Treatment-Related
Subjects evaluable for AEs, n	21	21	22	22
Total AEs, n	119	8	52	0
Subjects with AEs, n (%)	21 (100.0)	5 (23.8)	19 (86.4)	0
Subjects with serious AEs, n (%)	6 (28.6)	1 (4.8)	2 (9.1)	0
Subjects with severe AEs, n (%)	3 (14.3)	1 (4.8)	0	0
Subjects with infections and infestations, n (%)	20 (95.2)	–	15 (68.2)	–
Subjects with adenoidal hypertrophy	3 (14.3)	2 (9.5)	0	0

AE, adverse event.

Conclusions

- In very young, short-stature (height SDS below –2.5) children who were born SGA and who failed to show early catch-up growth at approximately 2 years of age, administration of Genotropin therapy at a dose of 0.035 mg/kg/day for 24 months resulted in significant growth recovery as measured by change from baseline in height SDS.
- While a significant increase in head growth occurred during Genotropin treatment, no significant change in psychomotor and mental development was observed, although the study was not powered on this endpoint.
- Genotropin therapy was well tolerated in very young children born SGA. The AEs observed in this study were consistent with the safety profile of GH therapy and the background occurrence of common childhood infections in this age group.

Acknowledgments

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