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A 2-year multicentre, open-label, randomized, controlled study of growth hormone (Genotropin®) treatment in very young children born small for gestational age: Early Growth and Neurodevelopment (EGN) Study

Short Title: Growth hormone therapy in very young children

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Summary

Objective In Europe, growth hormone (GH) treatment for children born small for gestational age (SGA) can only be initiated after 4 years of age. However, younger age at treatment initiation is a predictor of favourable response. To assess the effect of GH treatment on early growth and cognitive functioning in very young (<30 months), short-stature children born SGA.

Design 2-year, randomized controlled, multicentre study (NCT00627523; EGN study), in which patients received either GH treatment or no treatment for 24 months.

Patients Children aged 19–29 months diagnosed as SGA at birth, and for whom sufficient early growth data were available, were eligible. Patients were randomized (1:1) to GH treatment (Genotropin®, Pfizer Inc.) at a dose of 0·035 mg/kg/day by subcutaneous injection, or no treatment.

Measurements The primary objective was change from baseline in height standard deviation score (SDS) after 24 months of GH treatment.

Results Change from baseline in height SDS was significantly greater in the GH treatment versus control group at both month 12 (1·03 *vs* 0·14) and month 24 (1·63 *vs* 0·43; both $P < 0·001$). Growth velocity SDS was significantly higher in the GH treatment versus control group at 12 months ($P <$ 0·001), but not at 24 months. There was no significant difference in mental or psychomotor development indices between the two groups.

Conclusions GH treatment for 24 months in very young short-stature children born SGA resulted in a significant increase in height SDS compared with no treatment.

Introduction

In Europe, growth hormone (GH) treatment is indicated for use in short-stature children born small for gestational age (SGA) who fail to demonstrate postnatal catch-up growth; however, treatment cannot be initiated before 4 years of age,[1] compared with 2 years in the United States. Data from patient registries both in the United States and Europe show that in clinical practice, the average age at the start of treatment is closer to 8 years. This is too late to facilitate height normalization and results in only a moderate height gain for most patients.[2-5] Younger age at treatment initiation as well as higher GH dose, are major predictors of favourable response.[2,6] Beside the risk of persistent short stature (which occurs in up to 10% of children[7]), being born SGA is also associated with subtle impairments in cognitive performance and educational achievement.[8,9] Studies on the effect of GH therapy on cognitive development in children born SGA have shown contradictory results;[10-13] however, the children in these studies were aged 3 years or older.

We conducted this two-arm study to assess the effect of 24 months of GH treatment on early growth and cognitive functioning in very young, short-stature children born SGA who started GH therapy before the age of 30 months. The aim was to document changes in height, growth velocity, head growth and mental and psychomotor development.

Subjects and methods

Study design

In this 2-year, randomized controlled, multicentre study (ClinicalTrials.gov NCT00627523; acronym: EGN study), very young children in whom SGA was diagnosed at birth, and for whom sufficient birth and early growth data were available, were allocated to either GH or no treatment (Fig. 1). The study was approved by the Ethics Committees of participating centres and conducted in accordance with the Declaration of Helsinki. After an initial screening visit (at least 1 but no more than 6 months before randomization), hospital visits were planned at randomization, and 3, 6, 12, 18 and 24 months. Informed consent was obtained from a parent/parents/legal guardian. The first patient was enrolled on 26 February, 2008 and the last patient completed the study on 30 December, 2013.

Inclusion/exclusion criteria

Inclusion criteria were: born SGA [birth length and/or weight below –2 standard deviations (SD) for gestational age using country-specific standards]; age between 19 and 29 months; standing height below –2·5 SD at screening visit; normal karyotype in girls (for exclusion of Turner syndrome); normal screening laboratory values. Patients presenting with any of the following were excluded: severe intra-uterine growth restriction (birth length below –4 SD for gestational age) if associated

with dysmorphic features; severe prematurity (gestational age <32 weeks); ongoing catch-up growth [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 (e.g., foetal alcohol syndrome); severe perinatal complications (e.g., asphyxia, sepsis, necrotising enterocolitis, respiratory distress syndrome if associated with long-term sequelae); other specific reason for short stature (e.g., osteochondrodysplasia); other hormone therapy or systemic glucocorticoid treatment in past 6 months (use of topical or inhaled corticosteroids was permitted).

Randomization and treatment

Eligible patients were randomized (using a computer-generated randomization schema) in a 1:1 ratio to GH treatment [Genotropin®, (somatropin), Pfizer, New York, NY, USA]; 0·035 mg/kg/day administered by parents as an evening subcutaneous injection using a 5·3-mg pen injection device, or no treatment. For ethical reasons, a daily injection of placebo was not administered. Individual doses of 0·035 mg/kg/day, based on actual body weight, were calculated at randomization and administered using the closest dosing step of the injection pen. The starting dose (weeks 1 and 2) was one-third of the weight-calculated dose. The dose was adapted to body weight after 4 weeks and at each visit. Parents were instructed to keep a daily record card and to return all used and unused vials at each visit. Compliance was monitored by counting all vials and by review of dose record cards at each visit.

Study objectives

The primary endpoint was change from baseline in height SDS after 24 months of GH treatment. Secondary objectives were comparison of mental and psychomotor development between the two groups using the Bayley Scale of Infant Development–Second edition (BSID-II); assessment of the effect of GH treatment on growth velocity, body weight, body mass index (BMI) and head growth. Bone age was an additional assessment. The safety of GH treatment was also monitored.

Assessments

Standing height, body weight, head circumference and blood pressure were measured at study entry and at 6, 12, 18 and 24 months. Measurements were made at each visit by the same investigator or trained nurse using a standard protocol. SDS values were calculated for height, weight and head circumference using the Prader reference.[14] Pubertal staging, by the Tanner scale,[15] and visual inspection of the injection site (GH group only) were also performed at each visit. BMI was calculated as weight (kg) divided by height (m)^2. Mental and psychomotor development was assessed at study entry and at 12 months by an appropriately qualified clinical psychologist, using the BSID-II,[16] which includes two subscales: a mental scale, yielding a Mental Developmental Index (MDI), and a motor

scale, yielding a Psychomotor Developmental Index (PDI). Each index has a mean score of 100 and SD of 15. The validity of this instrument is well established.[17] An X-ray of the non-dominant hand using the Greulich and Pyle method was performed in both groups at randomization, and at 12 and 24 months to determine bone age.[18]

All observed or volunteered adverse events (AEs; from informed consent through and including 28 calendar days after the last treatment) regardless of treatment group or suspected causal relationship, were recorded at each visit. Fasting blood samples were collected from patients in the GH group at each visit and at study start and end in the control group for assessment of standard safety clinical chemistry, including glucose, glycated haemoglobin (HbA1c), insulin-like growth factor-I (IGF-I), insulin-like growth factor binding protein-3 (IGFBP-3) levels, and standard haematology parameters. Total IGF-1 (after acid-ethanol extraction) and IGFBP-3 levels were assessed by radioimmunoassay. Free thyroxin (fT4) and thyroid stimulating hormone (TSH) concentrations were measured at study start and 24 months in all patients, and additionally, at 12 months in the GH group.

Sample size determination and statistical analysis

The sample size estimation was based on pairwise comparison of change in height SDS at 24 months. A total of 34 patients, 17 per group, was deemed sufficient to detect a statistically significant difference in height SDS of 0·7 with at least 85% power using a 2-sided test at a 5% significance level and a common SD of 0·65. Assuming an attrition rate of 18%, recruitment of 42 patients was planned. The last observation carried forward (LOCF) method was used to impute missing efficacy data. Change in height SDS at 12 and 24 months was analyzed using LOCF data in an analysis of covariance (ANCOVA) with baseline height SDS and treatment as covariates. To support the primary analysis, an identical analysis was conducted using per protocol analysis set (PPAS), for which patients with major protocol deviations were excluded, and missing values were not imputed. Change in growth velocity SDS at 12 and 24 months was analyzed using LOCF data in an ANCOVA, with baseline growth velocity SDS and treatment as covariates. Measures for MDI and PDI of the BSID-II score were taken at baseline and at 12 months, and changes from baseline (for patients with both measurements) were analyzed at 12 months using observed data in the full analysis set (FAS) and an ANCOVA, with baseline score, age, gender and treatment as covariates. A two-sided α level of 5% was considered for all statistical analyses.

Results

Baseline characteristics

In total, 52 patients from 16 centres in eight European countries were screened for the study. Nine patients were considered screen failures; 43 were randomized. Twenty-one patients were treated in the GH group and 22 patients received no treatment in the control group. Nineteen patients in the GH

group and 20 in the control group completed the study. Two patients from the GH group withdrew, one due to insufficient clinical response and one for non-specified reasons. Two patients from the control group withdrew because of unwillingness to participate further. Twenty-one (95·5%) and 14 (63·6%) patients in the GH group and 21 (100·0%) and 15 (71·4%) were included in the FAS and PPAS, respectively. Clinical and auxological characteristics of the patients at baseline (FAS except where indicated) are presented in Table 1. There was no significant difference between the GH and control groups in any baseline characteristic (Table 1). Body weight, BMI and head circumference measurements were slightly larger in males versus females in both groups (data not shown).

Height SDS

Results from ANCOVA showed that the change from baseline in height SDS was significantly greater in the GH versus control group, at both month 12 [adjusted mean (standard error, SE): 1·03 (0·12) *vs* 0·14 (0·12); $P < 0·001$] and month 24 [primary endpoint; adjusted mean (SE): 1·63 (0·13) *vs* 0·43 (0·13); $P < 0·001$; Fig. 2**; Table 2**]. Results using the PPAS were consistent with those using the FAS [adjusted mean (SE) at 24 months: 1·79 (0·14) *vs* 0·41 [0·14]; $P < 0·001$). The mean (SD) change from baseline in height in the GH versus control groups was 11·13 (1·89) cm versus 7·62 (1·33) cm at 12 months and 19·92 (2·48) cm versus 14·34 (1·37) cm at 24 months. After 24 months, 10 GH-treated patients had a height SDS above the lower limit of normal, while only one patient in the untreated group attained a height SDS above –2 SD. At 24 months, the mean (SD) height SDS was –2·09 (0·70) in the GH group and –3·18 (0·72) in the control group. The mean (SD) change from baseline to month 24 in height SDS was greater in males than in females in both groups: 2·54 (0·62) versus 1·36 (0·70) in the GH group and 0·55 (0·44) versus 0·20 (0·26) in the control group.

Growth velocity SDS, head circumference SDS and BMI

Results from ANCOVA of change from baseline in growth velocity SDS are shown in Fig. 3. While growth velocity SDS was significantly higher in the GH versus control group at 12 months ($P < 0·001$), this difference was no longer statistically significant at 24 months **(Table 2)**. Twenty patients in the GH group were assessed for growth velocity SDS at 12 months; of these, 19 had a growth velocity SDS greater than –2 SD. Changes from baseline in **height,** head circumference SDS and BMI **were assessed by descriptive statistics and** are detailed in Table 2. Change from baseline in mean (SD) head circumference SDS was greater in the GH versus control group at both 12 [0·26 (0·52) *vs* 0·02 (0·59)] and 24 months [0·39 (0·64) *vs* 0·08 (0·60)].

Mental and psychomotor development indexes

Change from baseline in MDI and PDI are shown in Table 2. Both baseline and follow-up MDI and PDI values were similar in the GH and control group. Although no formal analysis was conducted, it

is noteworthy that while the change in MDI score was greater in males (10·3) than females (9·1), in the GH group, the change in PDI was lower in males (0·8) versus females (11·8).

Bone age

Mean change (SD) from baseline to 24 months in bone age was greater in the GH versus control group (21·20 [7·28] and 18·78 [8·18] months, respectively), and was more pronounced in males versus females [23·13 (9·08) *vs* 19·92 (5·89) in the GH group and 21·6 (6·06) *vs* 16·0 (9·38) in the control group].

Adverse events

A greater number of all-causality, treatment-emergent adverse events (TEAEs) were reported in the GH group [119 events in 21 (100%) patients] versus the control group [52 events in 19 (86·4%) patients]. Similarly, the incidence of all-causality serious AEs was higher in the GH versus control group [6 (28·6%) *vs* 2 (9·1%), respectively], as were severe AEs [3 (14·3%) *vs* 0, respectively]. One serious AE (4·8%) and one severe AE (4·8%) in the GH group were considered treatment-related. Adverse events (system organ classification) occurring in ≥3 patients in either arm are listed in Table 3. The most commonly reported AE was infection and infestation, occurring in 20 (95·2%) and 15 (68·2%) patients in the GH and control groups, respectively. The most common treatment-related TEAE was adenoidal hypertrophy, reported in two patients (9·5%) in the GH group. Three patients in the GH group had a dose reduction or temporary discontinuation due to AEs, but none was treatment-related.

Other measurements

No notable median change from baseline to last observation was recorded for laboratory safety parameters, with the exception of platelet count (–5500/mm³ and 41,000/mm³ in the GH and control groups, respectively), alkaline phosphatase (6 U/L and –23 U/L, respectively) and IGF-1 (56 ng/mL and 9·5 ng/mL, respectively). Free thyroxin, IGFPB-3 and IGF-1 levels were inside normal limits in all patients. Thyroid-stimulating hormone was >1·2 times the upper limit of normal (ULN) in 1 (4·5%) patient in the control group. Decreases from baseline in both systolic and diastolic blood pressure were numerically greater in the GH versus control group. Respective mean (SD) measurements at 24 months were: systolic, –9·0 (18·56) and –2·4 (13·85) mmHg; diastolic, –5·1 (17·26) and –0·1 (8·98) mmHg.

Discussion

In this study in short-stature children born SGA with failure to show catch-up growth by 2 years, who received GH treatment (or no treatment) at a very young age (<30 months) for 24 months, GH therapy was associated with a statistically significant increase from baseline in height SDS at 24 months, meeting the primary endpoint of the study. This improvement in stature after 2 years (i.e., a mean increase of 1·2 SD above the control group) is clinically relevant in early childhood;[19,20] however, no change in mental or psychomotor development was observed in the GH versus control group, but the study was not powered on this endpoint. There was no excessive increase in serum IGF-I in patients who received GH treatment (all study measurements were below the ULN). The increase in height SDS observed in our study is the highest reported to date in short-stature pre-pubertal children born SGA. Indeed, half of the children who received GH treatment achieved a height SDS above –2 SD. However, comparison of these results with those of previous studies in older children is hampered by onset of puberty in a variable percentage of patients, and lack of a randomized, parallel control groups.[21,22] There are relatively few studies of GH treatment in very young (<30 months) short-stature SGA children. In the only study that enrolled children below the age of 36 months, a height increase after 2 years of 1·6 SD was observed.[23] This is comparable with the results reported here despite the use of an almost 50% lower GH dose in the current study (0·035 *vs* 0·067 mg/kg/day). While a greater growth response was observed with 0·067 mg/kg/day versus 0·035 mg/kg/day,[24] the lower dose was chosen for the present study because serum IGF-I levels above reference ranges and excessive growth of the lower face bones (indicative of hypersomatotropism) have been reported with higher doses,[25,26] as has more rapid bone maturation.[6,21,22] We observed a positive effect of GH therapy on head growth, which agrees with studies in children born SGA aged between 3 and 8 years at onset of treatment.[27,28] We hypothesized that earlier initiation of GH therapy (before 30 months of age) might not only result in a more rapid increase in head growth but also improve neurodevelopment, since head growth and neurodevelopment benefits are linked in this population.[27,29] Despite observing rapid head growth in the GH group, there was no significant difference in mental or motor development between the two groups after 1 year. It is not clear from the current literature[30] how much head circumference increase during GH treatment is related to GH and/or IGF-I-induced brain growth and how much is to cranial bone development. Similar to the results of our study, van der Reijden-Lakeman and colleagues[10] and Puga and colleagues[11] did not report any effect of GH therapy on neurocognitive development. However, these studies did not include a randomized untreated group and enrolled much older children. Similarly, in a smaller, but 1:1 randomized trial of 34 Belgian pre-pubertal (3–8 years of age) short-stature children born SGA, no beneficial effect of 2 years of GH therapy was reported on intellectual ability, as assessed by the Wechsler Preschool and Primary Scale of Intelligence Revised, and the Wechsler Intelligence Scale for Children.[13] In contrast, van Pareren and colleagues[12] reported an improvement in IQ after 2 years of GH therapy in their study of 74 short-stature children born SGA (mean age 7·3 years). However, no control group was included, and only an abbreviated

approach to measure intelligence (two of 12 subtests of the Wechsler Intelligence Scale for Children Revised) was used.

Although GH treatment is deemed appropriate for use in short children born SGA, experience in very young children is limited. Furthermore, as concerns have been raised that GH treatment may increase pre-existing risk for cardiovascular disease and Type 2 diabetes in this population, we made every effort to document changes in glucose metabolism and blood pressure. Consistent with other studies, we found no change in plasma glucose or HbA1c concentrations in GH-treated patients. Due to the lack of assay sensitivity, insulin resistance could not be evaluated. In accordance with other studies,[31-33] a decrease in blood pressure was observed in GH-treated patients over the course of our study. It is known that this effect is independent of GH dose or history of prematurity.[31,32] The exact mechanism remains unclear, but GH-induced lowering of circulating metalloproteinase-9 has been proposed.[33] In contrast to the findings of Ibanez and colleagues,[34] but in accordance with most other studies, we did not observe a significant change in neutrophil levels.

In the current study, more than twice as many AEs were recorded in the GH versus control group. We cannot exclude the possibility that parents of patients in the control group may have been less likely to report AEs as they knew that their children were not receiving study treatment. Nonetheless, the AEs observed during the study were consistent with the safety profile of biosynthetic GH and reflected the background occurrence of common childhood infections in this young age group. In previous studies in young children born SGA, infections of the upper respiratory tract were recorded in up to 67% of GH-treated children.[23,25]

The strengths of this study are its randomized design, the specific age group studied, and the analysis of data for domains other than growth, e.g., neurodevelopment. The importance of the control group in evaluating growth response in very young SGA children is demonstrated by the finding of a spontaneous, although limited, catch-up growth in untreated children despite having a growth velocity SDS below 0 at inclusion. It is known that premature infants may show catch-up growth up to 60 months after birth;[35] however, in our study, only SGA children born at gestational age >32 weeks without serious neonatal complications were included. This study does have some shortcomings; only a limited number of children were studied (although sufficient to show a significant increase above spontaneous growth in the control group), and the lack of follow-up in the GH group after the age of 30 months does not permit conclusion that early treatment improves final height. Our results on cognitive and motor functioning should be interpreted with caution as only one assessment (at 12 months) was made and the study was not powered to assess these effects. We cannot exclude that the seriousness and/or type of any developmental delay might have influenced our cognitive and motor functioning results; despite being an exclusion criteria, eight of the randomized children had a MDI or PDI score greater or less than 3 SD (range 55–145), but they were included by investigators as only raw data were available at randomization.

In conclusion, GH therapy **given for 24 months in a cohort of 21** very young (aged 24–30 months **at randomization**) short-stature children born SGA who failed to show early catch-up growth was well tolerated and promoted a rapid growth recovery. **The limited number of patients, the short duration of treatment and inclusion of SGA patients with severely delayed neurodevelopment may have obscured a** beneficial effect on neurodevelopment, despite a significant effect on accelerated head growth.

References

1 National Institute of Clinical Excellence (2010) NICE technology appraisals [TA188].

2 Ranke, M.B. & Lindberg, A. (2010) Height at start, first-year growth response and cause of shortness at birth are major determinants of adult height outcomes of short children born small for gestational age and Silver-Russell syndrome treated with growth hormone: analysis of data from KIGS. *Hormone Research in Paediatrics*, **74,** 259-266.

3 Chernausek, S.D., Breen, T.J. & Frank, G.R. (1996) Linear growth in response to growth hormone treatment in children with short stature associated with intrauterine growth retardation: the National Cooperative Growth Study experience. *Journal of Pediatrics*, **128,** S22-27.

4 Savendahl, L., Blankenstein, O., Oliver, I. *et al.* (2012) Gender influences short-term growth hormone treatment response in children. *Hormone Research in Paediatrics*, **77,** 188-194.

5 Ross, J., Lee, P.A., Gut, R. *et al.* (2010) Factors influencing the one- and two-year growth response in children treated with growth hormone: analysis from an observational study. *International Journal of Pediatric Endocrinology*, **2010,** 494656.

6 Boguszewski, M., Albertsson-Wikland, K., Aronsson, S. *et al.* (1998) Growth hormone treatment of short children born small-for-gestational-age: the Nordic Multicentre Trial. *Acta Paediatrica*, **87,** 257-263.

7 Karlberg, J. & Albertsson-Wikland, K. (1995) Growth in full-term small-for-gestational-age infants: from birth to final height. *Pediatric Research*, **38,** 733-739.

8 Lundgren, E.M., Cnattingius, S., Jonsson, B. *et al.* (2001) Intellectual and psychological performance in males born small for gestational age with and without catch-up growth. *Pediatric Research*, **50,** 91-96.

9 Larroque, B., Bertrais, S., Czernichow, P. *et al.* (2001) School difficulties in 20-year-olds who were born small for gestational age at term in a regional cohort study. *Pediatrics*, **108,** 111-115.

10 van der Reijden-Lakeman, I., Slijper, F.M., van Dongen-Melman, J.E. *et al.* (1996) Self-concept before and after two years of growth hormone treatment in intrauterine growth-retarded children. *Hormone Research*, **46,** 88-94.

11 Puga, B., Gil, P., de Arriba, A. *et al.* (2012) Neurocognitive development of children born small for gestational age (SGA). An update. *Pediatric Endocrinology Reviews*, **9,** 716-726.

12 van Pareren, Y.K., Duivenvoorden, H.J., Slijper, F.S. *et al.* (2004) Intelligence and psychosocial functioning during long-term growth hormone therapy in children born small for gestational age. *Journal of Clinical Endocrinology and Metabolism*, **89,** 5295-5302.

13 Lagrou, K., Vanderfaeillie, J., Froidecoeur, C. *et al.* (2007) Effect of 2 years of high-dose growth hormone therapy on cognitive and psychosocial development in short children born small for gestational age. *European Journal of Endocrinology / European Federation of Endocrine Societies*, **156,** 195-201.

14 Prader, A., Largo, R.H., Molinari, L. *et al.* (1989) Physical growth of Swiss children from birth to 20 years of age. First Zurich longitudinal study of growth and development. *Helvetica Paediatrica Acta. Supplementum*, **52,** 1-125.

15 Tanner, J.M. (1986) Normal growth and techniques of growth assessment. *Clinics in Endocrinology and Metabolism*, **15,** 411-451.

16 Bayley, N. (1993) *Bayley scales of infant development–Second edition*. Harcourt Brace, San Antonio, TX.

17 Provost, B., Crowe, T.K. & McClain, C. (2000) Concurrent validity of the Bayley Scales of Infant Development II Motor Scale and the Peabody Developmental Motor Scales in two-year-old children. *Physical & Occupational Therapy in Pediatrics*, **20,** 5-18.

18 Greulich, W. & Pyle, S. (1959) *Radiographic atlas of skeletal development of the hand and wrist*. Stanford University Press, Stanford, CA.

19 Hermanussen, M., Lange, S. & Grasedyck, L. (2001) Growth tracks in early childhood. *Acta Paediatrica*, **90,** 381-386.

20 Johnston, L.B. & Savage, M.O. (2004) Should recombinant human growth hormone therapy be used in short small for gestational age children? *Archives of Disease in Childhood*, **89,** 740-744.

21 Chatelain, P., Job, J.C., Blanchard, J. *et al.* (1994) Dose-dependent catch-up growth after 2 years of growth hormone treatment in intrauterine growth-retarded children. Belgian and French Pediatric Clinics and Sanofi-Choay (France). *Journal of Clinical Endocrinology and Metabolism*, **78,** 1454-1460.

22 Fjellestad-Paulsen, A., Czernichow, P., Brauner, R. *et al.* (1998) Three-year data from a comparative study with recombinant human growth hormone in the treatment of short stature in young children with intrauterine growth retardation. *Acta Paediatrica*, **87,** 511-517.

23 Argente, J., Gracia, R., Ibáñez, L. *et al.* (2007) Improvement in growth after two years of growth hormone therapy in very young children born small for gestational age and without spontaneous catch-up growth: results of a multicenter, controlled, randomized, open clinical trial. *Journal of Clinical Endocrinology and Metabolism*, **92,** 3095-3101.

24 de Zegher, F. & Hokken-Koelega, A. (2005) Growth hormone therapy for children born small for gestational age: height gain is less dose dependent over the long term than over the short term. *Pediatrics*, **115,** e458-462.

25 Tanaka, T., Fujieda, K., Yokoya, S. *et al.* (2008) Efficacy and safety of growth hormone treatment in children born small for gestational age in Japan. *Journal of Pediatric Endocrinology and Metabolism*, **21,** 423-431.

26 van Erum, R., Carels, C., Verbeke, G. *et al.* (1997) Craniofacial growth in short children born small for gestational age: two years follow-up after high-dose growth hormone treatment. *Journal of Craniofacial Genetics and Developmental Biology*, **17,** 184-189.

27 Arends, N.J., Boonstra, V.H. & Hokken-Koelega, A.C. (2004) Head circumference and body proportions before and during growth hormone treatment in short children who were born small for gestational age. *Pediatrics*, **114,** 683-690.

28 Hokken-Koelega, A., van Pareren, Y. & Arends, N. (2005) Effects of growth hormone treatment on cognitive function and head circumference in children born small for gestational age. *Hormone Research*, **64 Suppl 3,** 95-99.

29 Darendeliler, F., Baş, F., Gökçe, M. *et al.* (2008) The effect of growth hormone treatment on head circumference in growth hormone-deficient children. *Turkish Journal of Pediatrics*, **50,** 331-335.

30 Segal, D.G., Pescovitz, O.H., Schaefer, G.B. *et al.* (2004) Craniofacial and acral growth responses in growth hormone-deficient children treated with growth hormone. *Journal of Pediatrics*, **144,** 437-443.

31 Sas, T., Mulder, P. & Hokken-Koelega, A. (2000) Body composition, blood pressure, and lipid metabolism before and during long-term growth hormone (GH) treatment in children with short stature born small for gestational age either with or without GH deficiency. *Journal of Clinical Endocrinology and Metabolism*, **85,** 3786-3792.

32 de Kort, S.W., Willemsen, R.H., van der Kaay, D.C. *et al.* (2009) The effect of growth hormone treatment on metabolic and cardiovascular risk factors is similar in preterm and term short, small for gestational age children. *Clinical Endocrinology*, **71,** 65-73.

33 Willemsen, R.H., van Dijk, M., de Kort, S.W. *et al.* (2008) Plasma matrix metalloproteinase-9 levels and blood pressure in short children born small for gestational age and effects of growth hormone treatment. *Clinical Endocrinology*, **69,** 264-268.

34 Ibanez, L., Fucci, A., Valls, C. *et al.* (2005) Neutrophil count in small-for-gestational age children: contrasting effects of metformin and growth hormone therapy. *Journal of Clinical Endocrinology and Metabolism*, **90,** 3435-3439.

35 Brandt, I., Sticker, E.J., Gausche, R. *et al.* (2005) Catch-up growth of supine length/height of very low birth weight, small for gestational age preterm infants to adulthood. *Journal of Pediatrics*, **147,** 662-668.

[[Figure legends]]

Fig. 1 Study design.
GH, growth hormone.

Fig. 2 Change from baseline in height SDS at 12 and 24 months.
GH, growth hormone; LS, least squares; SDS, standard deviation score; SE, standard error.

Fig. 3 Change from baseline in growth velocity SDS at 12 and 24 months.
GH, growth hormone; LS, least squares; SDS, standard deviation score; SE, standard error.

Table 1 Patient demographics at baseline (FAS, unless otherwise stated)

Demographic, Mean (SD)	**GH (*N* = 21)**	**Control (*N* = 21)**	**Mean Difference (SE)**	***P* Value**
Age*, *n*	21	22	0·48 (1·00)	0·637
Months	24·9 (3·26)	24·4 (3·32)		
Gender*, *n* (total)	21	22	–	0·432
Male, *n*	8	11		
Female, *n*	13	11		
Height				
cm	78·4 (3·19)	79·7 (3·66)	–1·35 (1·06)	0·211
SDS	–3·87 (0·97)	–3·48 (0·74)	–0·39 (0·27)	0·150
Growth velocity				

cm/year	9·3 (5·54)	10·9 (7·15)	–1·60 (1·97)	0·423
SDS	–0·004 (4·911)	–0·887 (6·394)	–0·891(1·76)	0·616
Weight, kg	9·30 (1·24)	9·49 (1·44)	–0·198 (0·42)	0·636
BSID-II scores[†], *n*	16	21		
MDI	86·6 (18·01)	84·6 (18·94)	1·99 (6·15)	0·748
PDI	80·4 (19·34)	85·8 (17·00)	–5·39 (5·99)	0·374
Head circumference, *n*				
cm	47·6 (1·90)	47·0 (1·93)	0·58 (0·59)	0·336
SDS	–1·19 (1·30)	–1·72 (1·28)	0·531(0·40)	0·190
BMI, kg/m^2	15·1 (1·79)	14·9 (1·47)	0·25 (0·50)	0·621
Bone age, *n*	21	20		
Months	18·81 (5·65)	19·10 (4·97)	–0·291 (1·66)	0·862

BSID-II, Bayley Scales of Infant Development–Second edition; BMI, body mass index; FAS, full analysis set; GH, growth hormone; MDI, Mental Development Index; PDI, Psychomotor Development Index; SD, standard deviation; SDS, standard deviation score; SE, standard error.

N numbers are per overall *N*, except where indicated.

*Safety Analysis Set. One subject was randomized to the GH group, but did not receive any treatment. This subject was excluded from the FAS, but was included in the control group for the safety analysis.

[†]Five patients in the GH group had a baseline test conducted post-dosing. These patients were excluded from the analysis. Nine subjects (eight at baseline, one at 12 months) had MDI or PDI scores

that were less or greater than 3 SD (range 55–145), but remained in the study due to Investigator decision and were included in the FAS.

Table 2 Change from baseline in **height, height SDS, growth velocity SDS,** head circumference SDS, and BMI, MDI and PDI scores (FAS)

Change From Baseline	**GH (*N* = 21)**	**Control (*N* = 21)**	**LS Mean Difference**	***P* Value**
Assessed by Descriptive Statistics				
Height, cm				
At 12 months, *n*	**20**	**19**		
Mean (SD)	**11.13 (1.89)**	**7.62 (1.33)**	**–**	**–**
At 24 months, *n*	**20**	**20**		
Mean (SD)	**19.92 (2.48)**	**14.34 (1.37)**	**–**	**–**
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/m^2)				
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)	–	–
Assessed by ANCOVA Model				
Height SDS				
At 12 months, *n*	**21**	**21**		
Mean (SD)	**1·03 (0·12)**	**0·14 (0·12)**	**0·89 (0·17)**	**<0·001**
At 24 months, *n*	**21**	**21**		
Mean (SD)	**1·63 (0·13)**	**0·43 (0·13)**	**1·20 (0·19)**	**<0·001**
Growth velocity SDS				
At 12 months, *n*	**21**	**21**		
Mean (SD)	**1·65 (0·56) 21**	**–1·59 (0·56)**	**3·24 (0·80)**	**<0·001**
At 24 months, *n*	**21**	**21**		
Mean (SD)	**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

ANCOVA, analysis of covariance; BMI, body mass index; BSID-II, Bayley Scale of Infant Development–Second edition; FAS, full analysis set; LS, least squares; MDI, Mental Development Index; PDI, Psychomotor Development Index; SD, standard deviation; SDS, standard deviation score; SE, standard error.

*Five patients in the GH group had a baseline test conducted post-dosing. These patients were excluded from the analysis, as were patients who did not complete the BSID-II assessment at 12 months.

Table 3 Treatment-emergent adverse events reported in ≥3 patients in either arm (safety analysis set*)

	GH Group (*N* = 21)		**Control Group (*N* = 22)**	
	All-causality *n* (%)	Treatment-related *n* (%)	All-causality *n* (%)	Treatment-related *n* (%)
Pyrexia	9 (42·9)	0	4 (18·2)	0
Nasopharyngitis	8 (38·1)	0	6 (27·3)	0
Upper respiratory tract infection	8 (38·1)	0	1 (4·5)	0
Bronchitis	6 (28·6)	0	6 (27·3)	0
Vomiting	4 (19·0)	0	4 (18·2)	0
Varicella	4 (19·0)	0	1 (4·5)	0
Diarrhoea	4 (19·0)	0	0	0

Laryngitis	4 (19·0)	0	0	0
Gastroenteritis	3 (14·3)	0	3 (13·6)	0
Adenoidal hypertrophy	3 (14·3)	2 (9·5)	0	0
Conjunctivitis	3 (14·3)	0	2 (9·1)	0
Ear infection	3 (14·3)	0	1 (4·5)	0
Cough	3 (14·3)	0	1 (4·5)	0
Otitis media	3 (14·3)	0	1 (4·5)	0
Viral infection	3 (14·3)	0	0	0

*One subject was randomized to the GH group, but did not receive any treatment. This subject was excluded from the FAS, but was included in the control group for the safety analysis.

FAS, full analysis set; GH, growth hormone.