

**Public Assessment Report
for paediatric studies submitted in accordance
with Article 46 of Regulation (EC) No1901/2006, as
amended**

**Genotropin / Genotropin MiniQuick
(somatropin)**

DK/W/0008/pdWS/005

Marketing Authorisation Holder: Pfizer

Rapporteur:	DK
Finalisation procedure (day 90):	09-08-2016

ADMINISTRATIVE INFORMATION

Invented name of the medicinal product:	Genotropin Genotropin MiniQuick
INN (or common name) of the active substance(s):	Somatropin
MAH:	Pfizer
Currently approved Indication(s)	<p><u>Children</u></p> <p>Growth disturbance due to insufficient secretion of growth hormone (growth hormone deficiency, GHD) and growth disturbance associated with Turner syndrome or chronic renal insufficiency.</p> <p>Growth disturbance [current height standard deviation score (SDS) < - 2.5 and parental adjusted height SDS < - 1] in short children born small for gestational age (SGA), with a birth weight and/or length below - 2 SD, who failed to show catch-up growth [height velocity (HV) SDS < 0 during the last year] by 4 years of age or later.</p> <p>Prader-Willi syndrome (PWS), for improvement of growth and body composition. The diagnosis of PWS should be confirmed by appropriate genetic testing.</p> <p><u>Adults</u></p> <p>Replacement therapy in adults with pronounced growth hormone deficiency.</p> <p>Adult Onset: Patients who have severe growth hormone deficiency associated with multiple hormone deficiencies as a result of known hypothalamic or pituitary pathology, and who have at least one known deficiency of a pituitary hormone not being prolactin. These patients should undergo an appropriate dynamic test in order to diagnose or exclude a growth hormone deficiency.</p> <p>Childhood Onset: Patients who were growth hormone deficient during childhood as a result of congenital, genetic, acquired, or idiopathic causes. Patients with childhood onset GHD should be reevaluated for growth hormone secretory capacity after completion of longitudinal growth. In patients with a high likelihood for persistent GHD, i.e. a congenital cause or GHD secondary to a pituitary/hypothalamic disease or insult, an insulin-like growth factor-I (IGF-I) SDS < - 2 off growth hormone treatment for at least 4 weeks should be</p>

	considered sufficient evidence of profound GHD. All other patients will require IGF-I assay and one growth hormone stimulation test.
Pharmaco-therapeutic group (ATC Code):	H01AC01
Pharmaceutical form(s) and strength(s):	Powder and solvent for solution for injection 1.3 mg, 5 mg, 5.3 mg, 12 mg 0.2 mg, 0.4 mg, 0.6 mg, 0.8 mg, 1 mg, 1.2 mg, 1.4 mg, 1.6 mg, 1.8 mg, 2 mg

I. EXECUTIVE SUMMARY

No SmPC and PL changes are proposed.

II. RECOMMENDATION

No further action required.

III. INTRODUCTION

On 10 October 2014, the MAH submitted a completed paediatric study for Genotropin, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended, on medicinal products for paediatric use.

A short critical expert overview has also been provided.

The MAH stated that the submitted paediatric study does not influence the benefit risk for Genotropin and that there is no consequential regulatory action.

IV. SCIENTIFIC DISCUSSION

IV.1 Information on the pharmaceutical formulation used in the study(ies)

Somatropin (Genotropin®) has received worldwide approval for the treatment of GH deficiency in children and adults since 1987. Genotropin® treatment in short children born small for gestational age (SGA) has been approved by European Medicines Agency (EMA) in 2003, starting not earlier than at an age of 4 years. In practice average age at start is around 8 years, allowing only a moderate height gain and too late to normalize final height.

Evidence indicates that a more efficient response to GH treatment in short children born SGA is achieved in early childhood as general responsiveness to GH is higher and body weight is lower. The vast majority (approximately 90%) of children born SGA demonstrate catch-up growth towards a normal size after a few months to one year of life with complete normalization at an age of 2 years. Consequently, it can not be recommended to initiate therapy before the age of 2 years.

The rest (approximately 10%) fail to attain length and weight within 2 standard deviations (SD) of normal range (<-2 standard deviation score [SDS]) and grow at a velocity below the mean for age. In these children, both intrauterine and extrauterine growth is strongly restricted. These short SGA children will remain short during infancy and childhood and will face difficulties related to their reduced size. As spontaneous catch-up growth is improbable after the age of 2 years most short children born SGA remain short in final height representing more than 20% of total short adults.

In a large survey, KIGS (Pfizer International Growth Database) including 613 children born SGA, GH dose and age at start of treatment were the best predictors of growth response in the first year of GH therapy. During the second year of therapy, first year response and age at start of treatment were the most important predictors. Furthermore, data from the Pivotal European Trials on SGA (Pharmacia SGA: Pivotal European Trials at 7 months) suggest that after 72 months of treatment, those children who were 3 years of age at the onset of treatment achieved an additional average 0.5 SD in height compared to children who were 6 years of age at onset of

treatment and treated with a comparable dose of GH. In general, the younger the child is the better the responsiveness to GH treatment, with a continuous decrease in responsiveness seen towards puberty.

In conclusion, it is well argued to test if treatment initiation at the age of 2 years would improve the outcome of somatropin therapy in SGA.

IV.2 Clinical aspects

1. Introduction

The MAH submitted a final report for:

A Two-Year Multi-Centre, Randomized Two Arm Study of Genotropin Treatment In Very Young Children Born Small For Gestational Age: Early Growth And Neurodevelopment (EGN)
Study/Protocol No.: A6281287

2. Clinical study(ies)

➤ Description

➤ Methods

Primary Objectives•

To assess the effect of 24 months of treatment with GH therapy at a dose of 0.035 mg/kg/d on height in short SGA children starting treatment at 24-30 months of age, compared to untreated controls, in randomized subjects.

Secondary Objectives•

To compare overall psychomotor development between the two groups using the Bayley Scale of Infant Development, 2nd edition (BSID-II).

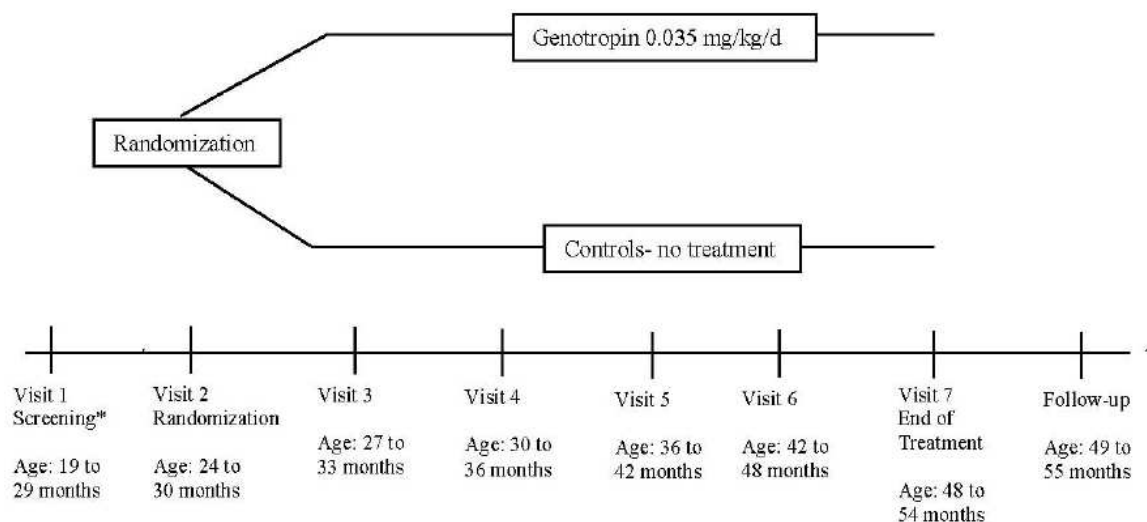
To determine the effect of GH treatment on body weight, body mass index (BMI) and head growth.

To demonstrate safety of GH treatment in young SGA children.

Study design

Eligible subjects were randomized in a 1:1 ratio to either Genotropin® at a dose of 0.035 mg/kg/d for 24 months or no Genotropin® treatment (Figure 1). Subjects who satisfied the inclusion and exclusion criteria were randomly assigned to treatments based on an algorithm designed to minimize treatment imbalance. The subject randomization was performed using a computer generated randomization scheme. The subjects were treated for 24 months up to the age of between 48-54 months. Controls remained untreated up to this age. Due to ethical reasons, the control group of small children was not administered daily placebo but remained untreated until the age of 48-54 months (when Genotropin® had been completed in the Genotropin® group).

Figure 1: Study Design and Plan



Assessor's comment: The study design is acceptable and for ethical reason it can be accepted to have an untreated control group (assuming that the patients are offered active therapy after the completion of the study).

Study population /Sample size

Subjects were required to meet all of the following inclusion criteria to be eligible for enrollment into the study:

1. Caucasian male or female subjects aged between 19-29 months at screening Visit 1. Evidence of a personally signed and dated informed consent document indicating that the subject (or a legal representative) had been informed of all pertinent aspects of the study.
2. Born SGA (birth length and/or weight <-2 SD for gestational age, using country-specific standards).
3. Height below -2.5 SD at screening (19-29 months of age).
4. At least one measurement of length between 12 and 18 months of age.
5. Normal karyotype in girls to exclude Turner syndrome.
6. Screening laboratory values within normal limits, or abnormalities clinically insignificant in the judgment of the investigator.

Subjects presenting with any of the following were to be excluded from the study:

1. Severe Intra-Uterine Growth Retardation (IUGR) (birth length below -4 SD for gestational age), if associated with dysmorphic features.
2. Severe prematurity (Gestational Age [GA] <32 weeks of gestation).
3. Ongoing catch-up growth (defined as growth velocity SDS at inclusion >0 based on at least 4 months measurement interval).
4. Severe familial short stature defined as: Father's height below 155 cm or mother's height below 145 cm.
5. Defined neurological defects and/or severe neurodevelopmental delay.
6. Defined syndromes such as fetal alcohol syndrome.

7. Severe perinatal complications like asphyxia, sepsis, Necrotizing Enterocolitis (NEC), respiratory distress syndrome, if associated with long-term sequelae (like short bowel syndrome, Broncho Pulmonary Dysplasia [BPD], cerebral palsy etc).
8. Other specific reason for short stature (eg, osteochondrodysplasia).
9. Any severe, acute or chronic illness (neurological, respiratory, gastrointestinal [eg, Coeliac disease etc] which in the opinion of the investigator may interfere with the interpretation of safety or efficacy evaluations).
10. Were unlikely to comply with the protocol eg, inability to return for follow-up visits, or is unlikely to complete the study.
11. Was participating in any other studies involving investigational or marketed products.
12. Was currently treated with systemic glucocorticoids or had been treated with glucocorticoids for a period of one week or longer in the past 6 months. Topical or inhaled corticosteroids were permitted.
13. Subjects receiving other hormone treatment were not eligible for this study (except stable thyroid hormone replacement).
14. Any subject who met any contraindication specified in the Genotropin® Core Data Sheet, such as hypersensitivity to the active substance or to any of the excipients or any evidence of tumor activity.

<i>Assessor's comment: The inclusion and exclusion criteria are acceptable.</i>

Treatments

The treatment administered was: Genotropin® at a dose of 0.035 mg/kg/d for 24 months.

The starting dose for the first 2 weeks was 1/3 of the calculated dose (eg, 0.2 mg if the calculated dose was 0.6 mg). After 2 weeks the dose was increased to 2/3 of the calculated dose. After 4 weeks the daily dose was the dose calculated on body weight at randomization. The dose adaptation according to increased body weight between visits was performed at each clinical visit. If due to the dosing steps of the injection device the calculated dose could not be applied, rounding may have been necessary. Due to rounding the highest dose of 0.035 mg/kg/d was not exceeded.

Outcomes/endpoints

Primary Endpoint

Change from baseline in height SDS, after 24 months of treatment.

Secondary Endpoints

Change from baseline in height velocity SDS after 24 months of treatment.

Change from baseline in height SDS and height velocity SDS, after 12 months of treatment.

Change from baseline in mental and psychomotor development using the MDI and PDI (normalized for all subjects using US ranges) of the Bayley Scale after 12 months of treatment.

Head circumference (SDS) (cm) at all time points of the study.

Change from baseline in body weight and BMI.

Assessor's comment: The change in height SDS as primary endpoint is well established as the preferred efficacy result in therapy with somatropin during childhood.

Safety Endpoints

Clinical laboratory tests, AEs, vital signs, and AEs were also evaluated.

X-ray of the subject's non-dominant hand and wrist was performed once a year during the study period at the local radiology department. The bone ages were estimated by the same assessor with the method of Greulich/Pyle. The bone age determination was performed as a routine assessment for growth retarded children.

Pubertal staging was assessed for signs of pathological puberty using the Tanner scale. This included assessment of pubic hair growth, testis volume in boys and breast development in girls. Pubertal staging was performed as a routine assessment for growth retarded children.

Statistical Methods

The sample size estimation was based on a pairwise comparison of Genotropin® versus untreated controls for the primary endpoint, change in height SDS at 24 months. A sample size of 34 subjects, 17 per treatment group, was sufficient to detect a statistically significant difference in height SDS with at least 85% power if the true underlying difference was 0.7.

This calculation was based on a 2-sided test at a significance level of 5% and a common SD of 0.65 (based on historical data from a Pfizer SGA database of similarly aged children [less than 4 years old at the beginning of treatment]). Assuming an attrition rate of 18%, a total of 42 subjects were to be recruited into the study. The actual number of subjects recruited was 43 subjects.

Summary statistics, including n, mean, SD, median, minimum and maximum values were presented for all continuous variables. Summaries by visit were based on observed data only; a further summary to last time point was also conducted.

Descriptive summary statistics for the absolute values of height SDS, as well as the change from baseline value to each post-baseline visit (Visit 5 and Visit 7), were presented by gender and overall for each treatment group. Similar summary statistics were presented for height. Furthermore, all observed and derived data were listed by treatment group.

The analysis of covariance (ANCOVA) model as described in the SAP was used to fit the appropriate baseline value as covariate. Missing values were imputed using the last observation carried forward (LOCF) method. The mean (SD) score for height SDS was plotted by visit and treatment group.

To support the interpretation of the primary analysis, an identical analysis as described above, based on the per protocol (PP) population was conducted. Missing values were not imputed for the PP analysis.

➤ Results

Recruitment/ Number analysed

In total, 52 subjects were screened for the study, of these, 9 subjects were considered screen failures (Table 3). The remaining 43 subjects were randomized to receive either study drug (Genotropin®) or were not treated (Control group). Twenty-one (21) subjects were treated in the Genotropin® group and 22 subjects received no treatment in the Control group. At the end of

Month 24, a total of 39 subjects, 19 (90.5%) subjects in the Genotropin® group and 20 (90.9%) subjects in the Control group, had completed the study.

Table 3: Subject Evaluation and Subject Disposition

	N	Genotropin® (N=21)	Control (N=22)
Screened	52		
Screen failures	9		
Assigned to study treatment	43	22	21
Treated		21*	22
Completed (n [%])		19 (90.5)	20 (90.9)
Discontinued (n [%])		2 (9.5)	2 (9.1)
Relationship to study drug not defined		2 (9.5)	2 (9.1)
Insufficient clinical response		1 (4.8)	0
No longer willing to participate in study		0	2 (9.1)
Other		1 (4.8)	0

A total of 43 subjects were randomized to a treatment group (Table 5). With the exception of one subject, all subjects randomized to the Genotropin® group were included in the full analysis set (FAS). Subject 10081001 did not receive any study drug and was therefore counted in the Control group for the safety analysis set (SAF). The subject was randomized on the 21 August 2008 and then withdrew on 28 August 2008, leaving no post-baseline efficacy or safety data. Therefore, as per the definition of the populations in the SAP, this subject was excluded from both the FAS and per protocol (PP) populations. All 43 subjects were included in the analysis of AEs and summary of laboratory data. The PP set included 29 subjects (14 subjects [Genotropin® group]; 15 subjects [Control group]).

Table 5: Subject Evaluation Groups

Number (%) Subjects	Genotropin® (N=21)	Control (N=22)
Assigned to study treatment	22	21
Treated	21*	22
Analyzed for Efficacy		
Full Analysis Set*	21 (95.5)	21 (100.0)
Per Protocol Analysis Set	14 (63.6)	15 (71.4)
Analyzed for Safety		
Safety Analysis Set	21 (100.0)	22 (100.0)
AE	21 (100.0)	22 (100.0)
Laboratory data	21 (100.0)	22 (100.0)

Efficacy results

The mean (SD) change from baseline in height SDS for observed data showed a steady increase during the study with a greater change in the Genotropin® group compared to the Control group. In the Genotropin® group, mean (SD) change from baseline was 1.153 (0.6356) at Month 12 and in the Control group was 0.119 (0.4696).

Using LOCF data at Month 12, the same trend of a greater mean (SD) change from baseline in the Genotropin® group: 1.088 (0.6857) compared to the Control group: 0.079 (0.4769) was observed.

Table 17: Analysis of Change from Baseline in Growth Velocity SDS at Month 12 using LOCF, Full Analysis Set

	Outcome	Genotropin® (N=21)	Control (N=21)
Visit 5 / Month 12	LS Mean (SE) ^a	1.65 (0.56)	-1.59 (0.56)
	95% CI for LS Mean	(0.52, 2.79)	(-2.72, -0.45)
	<u>Genotropin® vs Control</u>		
	LS Mean Difference (SE)		3.24 (0.80)
	95% CI for LS Mean Difference		(1.63, 4.85)
	p-value ^b		<0.001

Table 14: Analysis of Change from Baseline in Height SDS at Month 12 using LOCF, Full Analysis Set

	Outcome	Genotropin® (N=21)	Control (N=21)
Visit 5 / Month 12	LS Mean (SE) ^a	1.03 (0.12)	0.14 (0.12)
	95% CI for LS Mean	(0.79, 1.27)	(-0.10, 0.38)
	<u>Genotropin® vs Control</u>		
	LS Mean Difference (SE)		0.89 (0.17)
	95% CI for LS Mean Difference		(0.55, 1.23)
	p-value ^b		<0.001

Mean (SD) height SDS at baseline was -3.874 (0.9678) in the Genotropin® group and -3.484 (0.7374) in the Control group (Table 9). At Month 24, the mean (SD) change from baseline in height SDS was 1.738 (0.9637) in the Genotropin® group 0.326 (0.4462) in the control group. At Month 24, the least squares mean (LS Mean) standard error (SE) difference between the Genotropin® group and Control group was 1.20 (0.19), suggesting that subjects in the Genotropin® treatment group had a statistically significantly greater change from baseline in height SDS compared to subjects receiving no treatment (p<0.001). When the per protocol analysis set was analyzed using observed cases, the same significant difference at Month 24 was observed.

Table 9: Summary of Height SDS at Month 24 using LOCF, Full Analysis Set

	Genotropin® (N=21)		Control (N=21)	
	Observed	Change from baseline	Observed	Change from baseline
Baseline				
n	21		21	
Mean (SD)	-3.874 (0.9678)		-3.484 (0.7374)	
Median	-3.661		-3.350	
Min, Max	-5.64, -2.49		-5.07, -2.09	
Visit 7 / Month 24				
n	21	21	21	21
Mean (SD)	-2.136 (0.7168)	1.738 (0.9637)	-3.158 (0.7081)	0.326 (0.4462)
Median	-2.178	1.849	-3.005	0.279
Min, Max	-3.15, -0.67	-0.19, 3.25	-5.17, -1.81	-0.66, 1.48

Table 10: Analysis of Change from Baseline in Height SDS at Month 24 using LOCF, Full Analysis Set

	Outcome	Genotropin® (N=21)	Control (N=21)
Visit 7 / Month 24	LS Mean (SE) ^a	1.63 (0.13)	0.43 (0.13)
	95% CI for LS Mean	(1.37, 1.90)	(0.16, 0.70)
	<u>Genotropin® vs Control</u>		
	LS Mean Difference (SE)		1.20 (0.19)
	95% CI for LS Mean Difference		(0.82, 1.59)
	p-value ^b		<0.001

Table 12: Analysis of Change from Baseline in Growth Velocity SDS at Month 24 using LOCF, Full Analysis Set

	Outcome	Genotropin® (N=21)	Control (N=21)
Visit 7 / Month 24	LS Mean (SE) ^a	0.74 (0.57)	-0.03 (0.57)
	95% CI for LS Mean	(-0.42, 1.90)	(-1.19, 1.13)
	<u>Genotropin® vs Control</u>		
	LS Mean Difference (SE)		0.77 (0.81)
	95% CI for LS Mean Difference		(-0.87, 2.42)
	p-value ^b		0.348

Assessor's comment: Efficacy of Genotropin for growth improvement was clearly demonstrated in comparison to a control group not treated. This confirms previous documentation of somatotropin in children with GHD.

Safety results

There were no deaths on the study

A total of 43 subjects were included in the analysis of AEs for the 24 month study period. A greater number of all causality treatment-emergent adverse events (TEAEs) were reported in the Genotropin® group compared to the Control group: 119 events in 21 (100%) subjects (Genotropin® group) and 52 events in 19 (86.4%) subjects (Control Group).

A greater number of subjects in the Genotropin® group reported all causality SAEs and severe AEs compared to the Control group. All causalities SAEs were reported by 6 (28.6%) subjects and 2 (9.1%) subjects in the Genotropin® group and Control group, respectively, and all causalities severe AEs were reported in 3 (14.3%) subjects in the Genotropin® group and no subjects in the Control group. However, due to small sample size the study has no power to statistically analyze a clear difference in frequency for the individual AEs. No subjects in either group permanently discontinued the study due to AEs. Three (14.3%) subjects temporarily discontinued/dose reduced study drug due to all causalities TEAEs in the Genotropin® group. Five (23.8%) subjects in the Genotropin® group reported treatment-related TEAEs.

Treatment-related SAEs and treatment-related severe AEs were reported in 1 (4.8%) subject each (Table 18). There were no dose reductions or temporary discontinuations due to treatment-related TEAEs.

Table 18: Treatment-Emergent Adverse Events (All Causalities and Treatment-Related), Safety Analysis Set

Number of Subjects	Genotropin® (N=21) n (%)		Control (N=22) n (%)	
	All Causalities	Treatment related	All Causalities	Treatment related
Subjects evaluable for AEs	21	21	22	22
Number of AEs	119	8	52	0
Subjects with AEs	21 (100.0)	5 (23.8)	19 (86.4)	0
Subjects with serious AEs	6 (28.6)	1 (4.8)	2 (9.1)	0
Subjects with severe AEs	3 (14.3)	1 (4.8)	0	0
Subjects discontinued due to AEs	0	0	0	0
Subjects with dose reduced or temporary discontinuation due to AEs	3 (14.3)	0	0	0

Table 19: Treatment-Emergent Adverse Events Reported in ≥2 Subjects by System Organ Class and Preferred Term (All Causalities and Treatment-Related), Safety Analysis Set

System Organ Class Preferred Term	Genotropin® (N=21) n (%)		Control (N=22) n (%)	
	All Causalities	Treatment related	All Causalities	Treatment related
Ear and Labyrinth Disorders	2 (9.5)	--	0	--
Conductive deafness	2 (9.5)	--	0	--
Eye Disorders	3 (14.3)	--	2 (9.1)	--
Conjunctivitis	3 (14.3)	--	2 (9.1)	--
Gastrointestinal Disorders	7 (33.3)	--	7 (31.8)	--
Abdominal pain	2 (9.5)	--	0	--
Diarrhoea	4 (19.0)	--	0	--
Vomiting	4 (19.0)	--	4 (18.2)	--
General Disorders and Administration Site Conditions	10 (47.6)	--	4 (18.2)	--
Pyrexia	9 (42.9)	--	4 (18.2)	--
Infections and Infestations	20 (95.2)	--	15 (68.2)	--
Bronchitis	6 (28.6)	--	6 (27.3)	--
Ear infection	3 (14.3)	--	1 (4.5)	--
Exanthema subitum	2 (9.5)	--	0	--
Gastroenteritis	3 (14.3)	--	3 (13.6)	--
Gastroenteritis viral	2 (9.5)	--	0	--
Hordeolum	2 (9.5)	--	0	--
Laryngitis	4 (19.0)	--	0	--
Nasopharyngitis	8 (38.1)	--	6 (27.3)	--

System Organ Class Preferred Term	Genotropin® (N=21) n (%)		Control (N=22) n (%)	
	All Causalities	Treatment related	All Causalities	Treatment related
Otitis media	3 (14.3)	--	1 (4.5)	--
Pharyngitis	2 (9.5)	--	1 (4.5)	--
Rhinitis	2 (9.5)	--	2 (9.1)	--
Tonsillitis	2 (9.5)	--	1 (4.5)	--
Upper respiratory tract infection	8 (38.1)	--	1 (4.5)	--
Varicella	4 (19.0)	--	1 (4.5)	--
Viral infection	3 (14.3)	--	0	--
Musculoskeletal and Connective Tissue Disorders	2 (9.5)	--	0	--
Psychiatric Disorders	2 (9.5)	--	0	--
Insomnia	2 (9.5)	--	0	--
Respiratory, Thoracic and Mediastinal Disorders	7 (33.3)	2 (9.5)	2 (9.1)	0
Adenoidal hypertrophy	3 (14.3)	2 (9.5)	0	0
Cough	3 (14.3)	--	1 (4.5)	--
Rhinorrhoea	2 (9.5)	--	0	--
Skin and Subcutaneous Tissue Disorders	4 (19.0)	--	2 (9.1)	--
Eczema	2 (9.5)	--	1 (4.5)	--
Vascular Disorders	2 (9.5)	--	0	--
Haematoma	2 (9.5)	--	0	--

Assessor's comment: It is to be expected that patients on active treatment will report more AEs than patient untreated. This correlates with high adherence to the treatment. Side effects to Genotropin are well known in clinical practice and are described in the SmPC. However, no

patients discontinued the study due to AEs. Overall, the AEs observed were consistent with the well-established safety profile of Genotropin® and reflected the background occurrence of common childhood infections in this age group.

Bone age

The assessment of bone age is of special interest in trials of somatropin in children, since accelerated bone maturation relative to chronologic age may influence final height.

Mean (SD) bone age at baseline was 18.81 (5.645) months in the Genotropin® group and 19.10 (4.973) months in the Control group. Overall, mean (SD) change from baseline in bone age showed a steady increase during the study with a greater change in the Genotropin® group compared to the Control group. At Month 12, the mean (SD) change from baseline in bone age was greater than 8 months in both groups; 10.25 (5.210) months in the Genotropin® group and 8.67 (6.408) months in the Control group. At Month 24, the mean (SD) change from baseline in bone age was greater than 18 months in both groups; 21.20 (7.281) months in the Genotropin® group and 18.78 (8.179) months in the Control group.

Visit		Genotropin (N=21)		Control (N=21)	
		Observed	Change from Baseline	Observed	Change from Baseline
Baseline	N	21		20	
	Mean (SD)	18.81 (5.645)		19.10 (4.973)	
	Median	18.00		19.50	
	Min, Max	9.0, 30.0		9.0, 24.0	
Visit 5/ Month 12	N	20	20	19	18
	Mean (SD)	29.10 (6.086)	10.25 (5.210)	27.37 (5.927)	8.67 (6.408)
	Median	30.00	9.50	30.00	8.50
	Min, Max	21.0, 42.0	0.0, 18.0	18.0, 36.0	-6.0, 22.0
Visit 7/ Month 24	N	20	20	19	18
	Mean (SD)	40.05 (8.016)	21.20 (7.281)	36.84 (7.559)	18.78 (8.179)
	Median	39.50	21.00	36.00	20.00
	Min, Max	27.0, 54.0	8.0, 36.0	28.0, 53.0	6.0, 35.0

Assessor's comment: The change in bone age (median) after 24 months was 21 months in Genotropin group and 20 months in control group, which is not significantly different.

Pubertal (Tanner) Stage

The assessment of pubertal stage is of special interest in trials of somatropin.

At baseline, all subjects in the FAS were at pubic hair Stage 1, all male subjects were at genitalia Stage 1, and all female subjects were at breast Stage 1. The subjects remained at Stage 1 throughout the study (at Month 24, only 2 subjects had missing data).

Assessor's comment: All children remained in pubertal stage 1.

V. MEMBER STATES OVERALL CONCLUSION AND RECOMMENDATION

➤ Overall conclusion

This study (A6281287) was a Phase 3b study to assess the effect of 24 months of Genotropin® treatment on height in short SGA children who failed to show catch-up growth by 2 years of age starting treatment at 24-30 months of age, compared to untreated controls.

A total of 43 subjects were included in the study and evaluated for efficacy and safety. Genotropin® treatment statistically significantly increased height SDS compared to untreated controls at both Month 12 and Month 24.

Genotropin® was well-tolerated raising no safety concerns. Observed AEs were consistent with the well-established safety profile of Genotropin® and reflected the background occurrence of common childhood infections in this age group. Of specific interest, no unexpected safety signal was observed concerning bone age or pubertal stage.

➤ Recommendation

No further action required.