

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

**Genotropin
(somatropin)**

DK/W/0008/pdWS/006

Marketing Authorisation Holder: Pfizer

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

ADMINISTRATIVE INFORMATION

Invented name of the medicinal product:	Genotropin
INN (or common name) of the active substance(s):	Somatropin
MAH:	Pfizer
Currently approved Indication(s)	<p><u>Children</u> 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> Replacement therapy in adults with pronounced growth hormone deficiency.</p> <p><u>Adult Onset:</u> 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><u>Childhood Onset:</u> 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 insulinlike growth factor-I (IGF-I) SDS < - 2 off growth hormone treatment for at least 4 weeks should be considered sufficient evidence of</p>

	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

I. EXECUTIVE SUMMARY

No SmPC and PL changes are proposed.

II. RECOMMENDATION

No further action required.

III. INTRODUCTION

On 31 July 2015, 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)

Genotropin is a recombinant human growth hormone (rhGH), somatropin, with activity in growth improvement during childhood prior to epiphyseal closure. Most clinical trials to document efficacy and safety have been performed in children. Genotropin is approved for the following pediatric indications:

- Growth retardation associated with GH deficiency,
- Growth retardation associated with Turner syndrome (TS),
- Growth retardation associated with Chronic renal failure,
- Prader Willi syndrome,
- Growth retardation (height < -2,5 SDS and adjusted parent height < -1 SDS) in children who were born small for gestational age and who did not catch up (growth velocity <0 SDS during the last year) at 4 years of age or more.

Chronic therapy with pharmacological doses of glucocorticoids is associated with a variety of side effects that negatively impact the prolonged use of these potent, anti-inflammatory agents. When administered to growing children, the side effects of glucocorticoid treatment are compounded further by a potent and significant suppression of linear growth. Glucocorticoids affect both the release and actions of GH. It has been observed that 40% of subjects with a history of systemic juvenile idiopathic arthritis (JIA) treated with glucocorticoids for at least 2 years during childhood had a final height standard deviation score (SDS) under -2 SDS and more than 80% had a final height below their target height. Furthermore, height loss seems to be correlated in JIA children with duration of prednisone therapy. Previous published investigations have reported that GH therapy can improve short-term linear growth in children chronically treated with glucocorticoids.

Assessor's comment:

Children with glucocorticoid therapy is not an approved indication for Genotropin.

IV.2 Clinical aspects

1. Introduction

The MAH submitted a final report for:

Evolution of Growth Rate in Children With Growth Retardation Related to Long-Term Glucocorticosteroid Therapy and Treated by Genotonorm (Protocol Number: A6281271)

2. Clinical study

➤ Description

The study was managed by Pfizer, Inc. (the sponsor) and conducted by investigators contracted by and under the direction of the sponsor. The investigators were responsible for adhering to the study procedures described in the protocol, for keeping records of study drug, and for accurately completing and signing the case report forms (CRFs)/data collection tools (DCTs) supplied by the sponsor.

Medical and clinical monitoring of this study was conducted by the sponsor or its designated representatives. Data management, data analysis, biostatistics, and medical writing were completed by a contract research organization (CRO), LINCOLN, Boulogne-Billancourt, France.

Quality assurance audits were performed at six centers (1001, 1003, 1004, 1009, 1011 and 1019) by the sponsor's own independent quality assurance group or by CRO and/or individual contract personnel under the group's direction. These audits were conducted according to the sponsor's procedures and GCP guidelines.

One site in this study, site 1001, was found to have GCP issues and was discontinued. The study staff supporting the conduct of this study at this site repeatedly demonstrated an insufficient understanding and execution of both the protocol and GCP requirements and guidelines. Consequently, study activities were not sufficiently conducted according to the protocol and source documentation were not always complete, attributable, and/or accurately reported to the sponsor. This significantly impacted the reliability and confidence of the data reported to the sponsor on the CRFs as confirmed through source data verification processes.

Assessor's comment:

The sponsor rightfully closed site 1001, which showed non-compliance with GCP. The sample size remaining after exclusion of site 1001 was sufficient to evaluate the goals of the study.

➤ Methods

- Objective(s)

Primary objective:

To show an increase in height after 3 years of GH treatment, however subjects were followed for up to 5 years of treatment (as per amendment 2). Height SDS for chronological age (CA) after 3 years was compared to height SDS for CA before inclusion in the trial.

Secondary objectives:

- To estimate the evolution of height and GR after 1, 2 and 3 years of GH treatment,
- To estimate the prognostic factors of total height increased (in SDS for CA) and GR (SDS for CA) after 3 years of GH treatment,
- To confirm the good clinical and biological safety of GH treatment in such children,

Assessor's comment:

The primary end-point Height-SDS is an accepted and appropriate efficacy end-point in children treated with somatropin.

- Study design

This was a prospective, longitudinal, open, non-randomised, uncontrolled study. Although subjects were followed up for 5 years (as per amendment 2), the main criterion of efficacy was the difference between height SDS for CA after 3 years and height SDS for CA at Visit 2 (Month 0 [M0]).

Assessor's comment:

The open, uncontrolled design limits the ability to conclude on the efficacy.

- Study population /Sample size

This trial was designed to show a 1 SDS increase in height (SDS for CA) after 3 years of GH treatment. From previous publications it was estimated that the standard deviation of the difference in height before and after 3 years of GH treatment was 1.6 SDS. With an alpha risk of 5%, a power of 90% and a two-sided paired t-test the sample size should be 29 children. Therefore, 30 children should be included in the present trial.

Assessor's comment:

Sample size calculation is difficult in this type of open-label, uncontrolled trials. Moreover, the heterogeneous background of the patients (the only common background was the need for glucocorticoids) limits the ability to conclude on specific diseases. Finally, the design of the study mostly resembles a compassionate-use program with heterogeneity of patients as it was at the discretion of the physician to recruit patients.

Inclusion Criteria

Eligible subjects were expected to meet the following and all other qualifying criteria:

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

- Evidence of a personally signed and dated informed consent document indicating that the subject (or a legal representative) has been informed of all pertinent aspects of the study,
- Subjects who were willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures,
- As per amendment 4, male and female subjects of childbearing potential had to agree to use a highly effective method of contraception throughout the study and for 28 days after the last dose of assigned treatment. A subject was considered of childbearing potential if, in the opinion of the investigator, he/she is biologically capable of having children and is sexually active.

Female subjects who were not of childbearing potential (i.e. meet at least one of the following criteria):

- o Have undergone hysterectomy or bilateral oophorectomy,
- o Have medically confirmed ovarian failure,
- o Subjects who are clinically pre-pubertal.

A request for GH treatment could be issued if all the following criteria were fulfilled:

1. Bone age <15 years for males and <13 years for females (as per amendment 1),
2. Naïve child: measured height < -2 SDS for CA,
Child currently treated by GH: annual GR \geq 0 SDS for CA,
3. Glucocorticoid treatment over the last 12 months at least,
4. Glucocorticoid treatment was anticipated to be sustained for one more year at least,
5. GH treatment request by a physician (working in a hospital paediatric department or in a hospital endocrinology and metabolic disease department and, who is a paediatrician and/or a paediatric endocrinologist) who can initiate Genotonorm treatment according to the French SmPC,
6. The child benefits of the French social security cover,
7. Evidence of a personally signed and dated informed consent document indicating that the subject's parents/guardians and from the subject himself/herself if he/she was able to receive and understand the information have been informed of all pertinent aspects of the trial.

Exclusion Criteria

Subjects were ineligible to participate in this study if any of the following criteria were met:

1. Glucose intolerance on an OGTT dated less than 3 months or diabetes mellitus,
2. Syndrome known to be associated with an increased risk of cancer e.g., family history of adenomatous polyposis,
3. Pathological condition or disease for which GH treatment was already approved in France,
4. Participation in any other studies involving investigational or marketed products, concomitantly or within 30 days prior to entry in the study,
5. Unable and/or unlikely to comprehend and/or follow GH treatment and/or the protocol,
6. A previous history of intolerance or hypersensitivity to the study drug, or to drugs with similar chemical structures,
7. Subjects who are known or are suspected allergic to the preservative metacresol,
8. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with trial participation or investigational product administration or may interfere with the interpretation of trial results and, in the judgment of the investigator, would make the subject inappropriate for entry into this trial. Somatropin was

not to be used when there was any evidence of activity of a tumor. Intracranial tumors had to be inactive and antitumor therapy had to be completed prior to starting growth hormone therapy. Treatment had to be discontinued if there was evidence of tumor growth.

- Treatments

Genotropin was administered subcutaneously at a weekly dose of 0.46 mg/kg divided in seven daily subcutaneous injections with the maximal daily dose not to exceed 50 µg/kg/day.

The investigator scheduled an additional clinic visit within 8 weeks to review the dose of growth hormone that the study subject was receiving and if appropriate, to provide the study subject/parent/caretaker with a reduced dose of GH that did not exceed 50 µg/kg/day. The dosage was flexible since the investigator reviewed the dosage of GH for each subject at an additional clinic appointment; thereafter Genotropin was to be administered with a maximum dosage not to exceed 50 µg/kg/day. If on two consecutive measurements serum IGF-1 was >2 SDS then the Genotropin dose had to be decreased by 20%.

The weekly dose was divided into seven daily subcutaneous injections.

Genotropin treatment could be administered during a 5-year period (as per amendment 2) following the SmPC, in particular with regard to Safety recommendations and Contraindications. At the end of each yearly visit, GH treatment could be continued only and only if:

1. Continuation of GH treatment was decided by the investigator,
2. Sustained glucocorticoid therapy or stopped <6 months,
3. Height \leq +1 SDS for CA,
4. BA <16 years for males and <14 years for females,
5. Evidence of a personally signed and dated informed consent documents (dated on 13/Nov/2008 and 06/Jan/2009) indicating that the subject's parents/guardians and from the subject himself/herself if he/she was able to receive and understand the information have been informed of all pertinent aspects of the trial.

- Outcomes/endpoints

The endpoint parameters were assessed after 3 years of therapy (which was later extended to 5 years by an amendment to the protocol):

- Height in cm at the following visits: 10-14 months previous screening, Visit 1 (screening), Visit 2 (M0), Visit 3 (M12), Visit 4 (M24), Visit 5 (M36), Visit 6 (M48) and Visit 7 (M60).
The height measurements were consistently performed at the same time of the day by using a wall-mounted device (e.g. Harpenden Stadiometer). The standing height of the subjects was measured at each visit. Each child was measured twice and the mean of these measurements recorded in the CRF as the present height.
- Height SDS for Chronological Age at the following visits: 10-14 months previous screening, Visit 1 (screening), Visit 2 (M0), Visit 3 (M12), Visit 4 (M24), Visit 5 (M36), Visit 6 (M48) and Visit 7 (M60).
- Height SDS for Bone Age at the following visits: Visit 1 (screening), Visit 3 (M12), Visit 4 (M24), Visit 5 (M36), Visit 6 (M48) and Visit 7 (M60).

Assessor's comment:

The endpoint Height-SDS for chronological age is well established as an appropriate efficacy measurement in children. Height-SDS for bone age is also a relevant variable, which gives information of predicted final height potential.

- **Statistical Methods**

Continuous variables were presented using summary statistics: number of observations, arithmetic mean, standard deviation (SD), median, minimum and maximum values and the 95% two-sided confidence interval (CI) for the mean. Categorical variables were presented as counts and percentages.

An analysis of covariance (ANCOVA) was used to look at the change from baseline in height SDS after 3 years (using the status of subjects (previously treated with GH / naïve to GH treatment) and baseline value as covariate). Assumptions of normality and heteroscedasticity were assessed. If the assumptions were not met, non-parametric equivalent analyses were used (e.g. Wilcoxon signed rank test instead of paired t-test and ANCOVA on ranks instead of ANCOVA).

The Full Analysis Set (FAS) was defined as all subjects who were not treated at site 1001, received at least one injection of GH and had at least one post-baseline measurement of height. Subjects were analysed according to the treatment received. This was labeled as the “FAS – excluding site 1001” for reporting purposes. Only data from children with informed consent (signed by the subject's parents/guardians or from the subject himself/herself if he/she was able to receive and understand the information) were included in the analysis set. If informed consent was withdrawn during the study only data up to the date of withdrawal were used.

The Per Protocol (PP) Analysis Set was defined as all subjects who were not treated at site 1001, received at least one dose of GH treatment, had at least one subsequent rating of height and with no major protocol violation until the first three years post initiation of treatment and with total GH treatment duration of 36 months or more.

A per protocol analysis was performed if less than 90% of the children included in the FAS were also included in the PP Analysis Set. Only primary efficacy analyses corresponding to the 3 years of treatment was run using the PP Analysis Set.

The Safety Analysis Set was defined as all subjects (including those from site 1001) who received at least one study dose of GH. Subjects were analysed according to the treatment actually received. For purposes of sensitivity, all efficacy analyses were repeated including data from all sites. For these analyses, the FAS included all subjects who received at least one injection of GH and had at least one post-baseline measurement of height. This was labeled as the “FAS – including site 1001” for reporting purposes.

For sensitivity analyses the PP analysis set was defined as all subjects who received at least one dose of GH treatment, had at least one subsequent rating of height and with no major protocol violation until the first three years post initiation of treatment and with total GH treatment duration of 36 months or more. This was labeled as the “PP analysis set – including site 1001” for reporting purposes. Prior to database freeze, subjects with major deviations were identified, listed and documented including details of the type of major protocol deviation.

All subjects who were not treated at site 1001, received at least one study dose of GH were included in the sensitivity analyses for Safety. This was labeled as the “Safety analysis set – excluding site 1001” analysis set for reporting purposes.

➤ **Results**

- **Recruitment/ Number analysed**

Given the issues with site 1001, the Sponsor determined that the data from this site would be excluded from all efficacy analyses. Sensitivity analyses were conducted by repeating the

analyses including the data from site 1001. For analysis of safety data, all sites were included and sensitivity analyses were conducted by repeating the analyses excluding the data from site 1001. On 31 August 2011 the IEC was informed that site 1001 was closed prematurely for GCP compliance issue. Of note, this site had recruited 41 subjects into the study and the total number of subjects from other sites and who received GH treatment was 59, which still exceeded the required sample size estimated for this study. The number of subjects available for the primary analysis of the change from baseline in height (SDS) for CA at month 36 for the FAS excluding site 1001 was 30 subjects which was equal to the required sample size estimated for this study.

- Baseline data

A total of 108 subjects participated in the study. Nine subjects were withdrawn during the screening phase: seven subjects because entrance criteria were not met, one subject because of consent withdrawal, one subject died before receiving study treatment. One subject was withdrawn during the open phase, before study treatment intake for protocol violation, namely participation in another clinical study (Table 16.2.1.2).

Ninety eight (98) subjects received at least one dose of study treatment. Due to GCP issues, subjects enrolled at site 1001 were not included in the main efficacy analysis. However, these subjects were included in the main safety analysis.

Table 3: Subject disposition – Safety analysis set – including and excluding site 1001

Number of Subjects	Including Site 1001	Excluding site 1001
Screened	108	67
Assigned to study treatment	98	59
Treated	98	59
Completed	35 (35.7%)	21 (35.6%)
Discontinued	63 (64.3%)	38 (64.4%)
Did not meet continuation criterion	16 (16.3%)	7 (11.9%)
No longer willing to participate in the study	11 (11.2%)	8 (13.6%)
Study terminated by Sponsor	11 (11.2%)	
Insufficient clinical response	7 (7.1%)	7 (11.9%)
Adverse events	6 (6.1%)	6 (10.2%)
Subject died	3 (3.1%)	3 (5.1%)
Protocol violation	2 (2.0%)	1 (1.7%)
Lost to follow-up	1 (1.0%)	1 (1.7%)
Other	6 (6.1%)	5 (8.5%)
Analyzed for safety (AEs)	98	59

Considering all sites, 73 out of 98 subjects (74.5%) were excluded from the PP analysis. In the sensitivity analysis without site 1001, 38/59 (64.4%) subjects were excluded from the PP analysis.

Table 4: Reasons of exclusion from PP analysis set – Safety analysis set – including and excluding site 1001

Description of exclusion reason	Including site 1001 (N=98)	Excluding site 1001 (N=59)
Total number of subjects excluded from PP analysis set	73	38
<u>Exclusion from FAS (No post-baseline measurement of height)</u>	1 (1.4%)	1 (2.6%)
<u>Protocol deviation: Inclusion/exclusion criteria</u>		
Glucocorticoid treatment not over the last 12 months at least	29 (39.7%)	7 (18.4%)
Child currently treated by GH, Annual GR not ≥ 0 SDS for CA	2 (2.7%)	1 (2.6%)
<u>Protocol deviation: Post-initiation of study treatment</u>		
Glucocorticoid treatment was not sustained for at least one more year	40 (54.8%)	13 (34.2%)
Not treated for at least 36 months	34 (46.6%)	23 (60.5%)
Not 75% compliant with dosing during first three years	3 (4.1%)	2 (5.3%)
<u>Protocol deviation: Criteria for continuation of GH treatment</u>		
Glucocorticoid treatment was not sustained (not stopped for more than 6 months) at visit 3	3 (4.1%)	1 (2.6%)
Glucocorticoid treatment was not sustained (not stopped for more than 6 months) at visit 4	3 (4.1%)	2 (5.3%)
BA was not < 16 years for males and not < 14 years for females at visit 4	2 (2.7%)	2 (5.3%)
Break of study treatment for ≥ 9 months	2 (2.7%)	1 (2.6%)
Continuation of GH treatment was not decided by the investigator at Visit 3	1 (1.4%)	
Measured Height not $\leq +1$ SDS for CA at Visit 4	1 (1.4%)	
BA was not < 16 years for males or not < 14 years for females at Visit 3	1 (1.4%)	1 (2.6%)

Assessor's comment:

In total, a high percentage of subjects did not complete the study and these patients were excluded in the PP data set. Most common reasons for excluding subjects from the PP analysis were glucocorticoid treatment not sustained for at least one more year (40/73; 54.8%), GH treatment for less than 36 months (34/73; 46.6%), and glucocorticoid therapy was not received for at least 12 months in the year preceding study inclusion (29/73; 39.7%).

Out of 98 subjects in the Safety analysis set, 74 subjects (75.5%) were male and 24 subjects (24.5%) were female. Age at screening ranged from 2 to 18 years, with an overall median age of 12.5 years. Male subjects were older at screening compared to their female counterpart (median age: 13 and 10 years for male and female subjects respectively). Demographic data for the safety population is shown in Table 8.

Table 8: Summary of Demographic and Baseline Characteristics – Safety analysis set – including site 1001

	Male (N=74)	Female (N=24)	Total (N=98)
Sex			
Male			74 (75.5%)
Female			24 (24.5%)
Age at screening (years)			
Mean (SD)	12.4 (3.0)	9.9 (3.3)	11.8 (3.2)
Median (range)	13.0 (4.0; 18.0)	10.0 (2.0; 14.0)	12.5 (2.0; 18.0)
Age category at screening n (%)			
< 4 years		1 (4.2%)	1 (1.0%)
≥ 4 and < 8 years	7 (9.5%)	4 (16.7%)	11 (11.2%)
≥ 8 and < 12 years	15 (20.3%)	10 (41.7%)	25 (25.5%)
≥ 12 years	52 (70.3%)	9 (37.5%)	61 (62.2%)
BA (years) at screening			
Mean (SD)	10.0 (2.8)	8.5 (2.9)	9.6 (2.9)
Median (range)	11.0 (3.0; 14.0)	9.0 (2.5; 12.8)	10.1 (2.5; 14.0)
Race n (%)			
White	53 (71.6%)	17 (70.8%)	70 (71.4%)
Black	8 (10.8%)	1 (4.2%)	9 (9.2%)
Asian	2 (2.7%)	1 (4.2%)	3 (3.1%)
Other	3 (4.1%)	3 (12.5%)	6 (6.1%)
Not done	8 (10.8%)	2 (8.3%)	10 (10.2%)
Height (cm) at M0			
Mean (SD)	135.2 (14.5)	125.7 (16.5)	132.9 (15.5)
Median (range)	135.6 (97.0; 159.7)	130.3 (88.4; 145.2)	134.6 (88.4; 159.7)
Weight (kg) at M0			
Mean (SD)	37.1 (11.7)	30.6 (9.5)	35.5 (11.5)
Median (range)	36.1 (14.9; 73.4)	33.9 (12.4; 42.0)	35.3 (12.4; 73.4)
BMI (kg/m ²) at M0			
Mean (SD)	19.9 (4.1)	18.7 (2.1)	19.6 (3.7)
Median (range)	18.8 (14.3; 33.4)	19.1 (14.3; 21.9)	18.9 (14.3; 33.4)

Source: Table 14.1.2.1

Note: If the value was missing at visit 2, the screening value was used as baseline (Month 0).

Assessor's comment:

Two thirds were males and only 25% were females. Median age was 13 years for males and 10 years for females, range was 4-18 years and 2-14 years for males and females respectively. Approximately 10% were ≤8 years. When combining this, it appears that more than 50% of the study population were males ≥12 years. This should be kept in mind when analysing study results, limiting a generalisation to e.g. females <4 years. Nevertheless, as previously discussed, due to the low number of included patients, the open-label design of the study and the heterogeneous study population (see below for indications for steroid use/primary diagnosis), firm conclusions cannot be made on basis of the present study.

The primary diagnosis of study participants was classified into autoimmune diseases, inflammatory diseases, renal and urinary disorders, transplantation, congenital disorders, blood disorders, genetic disorders, and others (Table 10). The most frequent category was renal and urinary disorders (39 subjects, 39.8%), followed by inflammatory disease (30 subjects, 30.6%), autoimmune disease (17 subjects, 17.3%), and transplantation (17 subjects, 17.3%).

The most common primary diagnoses were nephrotic syndrome in 30 subjects, transplantation in 17 subjects and juvenile arthritis (both chronic and idiopathic) in 15 subjects. It should be noted that subjects might fall into more than one classification since the primary diagnosis might consist of several conditions.

Table 10: Primary diagnosis – Safety analysis set – including site 1001

Category, primary diagnosis ^{a)}	Primary diagnosis n (%) (N=98)
Auto-immune disease	17 (17.3%)
Lupus	6
Crohn's disease	2
Enteropathy	2
Granulomatosis	2
Other (Evan's syndrome, sarcoidosis, acute immune deficiency, auto-immune hepatitis, auto-immune hemolytic anemia)	5
Inflammatory disease	30 (30.6%)
Juvenile arthritis (chronic and idiopathic)	15
Uveitis	7
Dermatomyositis	4
Still's disease	2
Other (Behcet disease, inflammatory syndrome, asthma, respiratory insufficiency/pulmonary fibrosis)	4
Renal and urinary disorders	39 (39.8%)
Nephrotic syndrome	30
Renal failure	5
Renal dysplasia	3
Mesangial sclerosis	1
Other (Uropathy, end stage renal failure of unknown etiology)	3
Transplantation	17 (17.3%)
Renal transplantation	12
Liver transplantation	6
Digestive transplantation	3
Stem cell transplantation	1
Congenital disorder	5 (5.1%)
Urethral valves	2
Other (Hirschsprung disease/cirrhosis, congenital ataxia, surrenal hypoplasia)	3
Blood disorder	2 (2.0%)
Anemia	2
Neutropenia	1
Genetic disorder	3 (3.1%)
Alagille syndrome	2
Biliary atresia	1
Other	1 (1.0%)

Assessor's comment:

Not surprisingly is the most common primary diagnosis within the group of renal and urinary system disorders, inflammatory diseases and autoimmune diseases. Though the only inclusion criteria related to the glucocorticoid treatment was (1) Glucocorticoid treatment over the last 12 months at least, and (2) Glucocorticoid treatment was anticipated to be sustained for one more year at least, it is, based on the primary diagnoses, anticipated that all patients were treated with systemic glucocorticoids. Commonly prescribed glucocorticoid treatments were prednisone, prednisolone, and methylprednisolone. Unfortunately, there is no information regarding mean (median and range) dose of glucocorticosteroids at baseline.

- Efficacy results

Table 6: Populations included in main analysis sets

	Previously treated with GH	Previously GH naïve	Overall
Overall	8	100	108
FAS – excluding site 1001	4 (50.0%)	54 (54.0%)	58 (53.7%)
PP analysis set – excluding site 1001		21 (21.0%)	21 (19.4%)
Safety analysis set – including site 1001	7 (87.5%)	91 (91.0%)	98 (90.7%)

At baseline, the mean height SDS for CA was -2.91 (± 1.19), ranging from -7.49 to -0.96 in the FAS. During the study, the mean height SDS for CA gradually increased: at M36, mean height SDS for CA was -2.12 (± 1.40) ranging from -5.58 to 0.42 and the mean change from baseline was +0.80 (± 1.03), which was statistically significant from zero ($p < 0.001$). Results were supported by analysis using the PP analysis set. Mean height SDS for CA was -2.86 (± 0.89) at baseline and it was -2.13 (± 1.28) at M36. The mean change from baseline in height SDS for CA was +0.81 (± 1.18) at M36, which was statistically significant from zero ($p = 0.008$).

Table 12: Height (SDS) for CA and change from baseline in height (SDS) for CA over 5 years – Full analysis set / PP analysis set – excluding site 1001

	Full analysis set		PP analysis set	
	Height (SDS) for CA	Change from baseline in height (SDS) for CA	Height (SDS) for CA	Change from baseline in height (SDS) for CA
Month 0 (baseline)				
n	58		21	
Mean (SD)	-2.91 (1.19)		-2.86 (0.89)	
Median (range)	-2.70 (-7.49; -0.96)		-2.50 (-4.75; -1.62)	
Month 12				
n	50	50	19	19
Mean (SD)	-2.49 (1.08)	0.28 (0.57)	-2.57 (0.95)	0.21 (0.41)
Median (range)	-2.44 (-5.58; -0.50)	0.23 (-0.95; 1.53)	-2.41 (-4.45; -1.09)	0.22 (-0.49; 1.15)
Month 24				
n	41	41	20	20
Mean (SD)	-2.43 (1.30)	0.57 (0.95)	-2.44 (1.12)	0.46 (0.94)
Median (range)	-2.23 (-6.17; -0.17)	0.64 (-1.46; 2.95)	-2.31 (-4.79; -0.17)	0.29 (-0.81; 2.67)
Month 36				
n	30	30	19	19
Mean (SD)	-2.12 (1.40)	0.80 (1.03)	-2.13 (1.28)	0.81 (1.18)
Median (range)	-1.99 (-5.58; 0.42)	0.68 (-1.60; 3.17)	-2.05 (-4.69; 0.42)	0.63 (-1.60; 3.17)
p-value		<0.001		0.008
(Student's paired t-test)				

An ANCOVA on the change from baseline in height SDS for CA after three years was performed using the status of subjects (previously treated with GH / naïve to GH treatment) and baseline value as covariates.

Table 14: ANCOVA: difference in height (SDS) for CA adjusted for GH treatment and baseline value in SDS for CA – Full analysis set / PP analysis set – excluding site 1001

	Full analysis set	PP analysis set
Number of subjects	30	19
Baseline mean (SD)	-2.92 (1.29)	-2.94 (0.91)
Adjusted* mean change from baseline (SE)	0.98 (0.40)	0.81 (0.27)
95% CI	[0.15; 1.80]	[0.25; 1.38]
p-value	0.022	0.008

Source: [Table 14.2.1.5](#) and [Table 14.2.1.6.1](#)

*adjustment on GH treatment at enrollment (previously treated with GH/previously naïve) and baseline value

Assessor's comment:

Efficacy, expressed as an increase in Height-SDS, was observed in both data sets, approximately 1 SDS. It should be noted, that the sample size for obtaining final end-point is limited.

- Safety results

In the Safety analysis set, 98 subjects were evaluable for treatment duration. The median treatment duration was 36.0 months, ranging from 2.1 months to 72.3 months.

Most common TEAEs regardless of causality populated the System Order Classes (SOC) Infections and infestations (46 subjects, 46.9%), Gastrointestinal disorders (35 subjects, 35.7%), and Musculoskeletal and connective tissue disorders (32 subjects, 32.7%).

Table 8: Summary of Demographic and Baseline Characteristics – Safety analysis set – including site 1001

	Male (N=74)	Female (N=24)	Total (N=98)
Sex			
Male			74 (75.5%)
Female			24 (24.5%)
Age at screening (years)			
Mean (SD)	12.4 (3.0)	9.9 (3.3)	11.8 (3.2)
Median (range)	13.0 (4.0; 18.0)	10.0 (2.0; 14.0)	12.5 (2.0; 18.0)
Age category at screening n (%)			
< 4 years		1 (4.2%)	1 (1.0%)
≥ 4 and < 8 years	7 (9.5%)	4 (16.7%)	11 (11.2%)
≥ 8 and < 12 years	15 (20.3%)	10 (41.7%)	25 (25.5%)
≥ 12 years	52 (70.3%)	9 (37.5%)	61 (62.2%)
BA (years) at screening			
Mean (SD)	10.0 (2.8)	8.5 (2.9)	9.6 (2.9)
Median (range)	11.0 (3.0; 14.0)	9.0 (2.5; 12.8)	10.1 (2.5; 14.0)

Considering only treatment related TEAEs: 38 subjects (38.8%) reported 57 TEAEs related to study treatment. Five subjects (5.1%) reported a serious TEAE related to study treatment, three subjects (3.1%) experienced at least one severe TEAE related to study treatment, and four subjects discontinued study treatment due to a TEAE related to study treatment. Twenty (20) subjects (20.4%) interrupted the study treatment temporarily or reduced the dose due to a TEAE related to study treatment.

Table 44: Summary of TEAEs – Safety analysis set – including site 1001

	Treatment-Emergent Adverse Events (All Causalities)	Treatment-Emergent Adverse Events (Treatment Related)
	n (%) with at least one TEAE	n (%) with at least one TEAE
n	98	98
TEAEs	84 (85.7%)	38 (38.8%)
Serious TEAEs	45 (45.9%)	5 (5.1%)
Severe TEAEs	38 (38.8%)	3 (3.1%)
Discontinuations due to TEAEs	9 (9.2%)	4 (4.1%)
Temporary discontinuations or dose reductions due to TEAEs	26 (26.5%)	20 (20.4%)

There were five deaths reported in this study:

- [Subject 10091008](#) experienced severe acute encephalopathy, which was considered as serious and leading to death before study treatment intake.

- Subject 10031001 experienced severe cardiopulmonary failure which was considered as serious, not related to study drug and leading to death during the open treatment period.
- Subject 10111002 had a road accident which was considered as serious, not related to study drug and leading to death during the open treatment period.
- Subject 10191003 experienced severe acute asthma which was considered as serious, not related to study drug and leading to death during the open treatment period.
- Subject 10241002 experienced severe thrombotic microangiopathy, which was considered as serious, not related to study drug and leading to permanent study drug and study discontinuation. This subject died after his premature withdrawal.

All deaths were considered as not treatment related.

Forty seven (47) subjects reported a total of 129 SAEs. Forty five (45) subjects (45.9%) reported a total of 116 serious TEAEs. However, most of these TEAEs were not considered treatment related by the investigator. Five subjects (5.1%) reported a serious TEAE considered treatment related:

- Subject 10011022 experienced moderate BIH. The study treatment was temporarily interrupted and this TEAE resolved within a month's time approximately.
- Subject 10011027 experienced severe headache. The study treatment was temporarily interrupted and this TEAE resolved within a week.
- Subject 10011028 experienced severe intracranial pressure increased. The study treatment was temporarily interrupted and this TEAE resolved within four months.
- Subject 10091006 had a moderate treatment compliance issue. No action with respect to the study treatment was taken and this TEAE resolved within three days.
- Subject 10151001 experienced mild hyperglycemia. The study treatment was temporarily interrupted and this TEAE resolved within a week.

Assessor's comment:

The five adverse events with relation to Genotropin are previously recognised as associated with growth hormone therapy in children, and they are included in the SmPC as potential adverse reactions.

Table 48: Other significant TEAEs – Safety analysis set – including site 1001

SOC/PT	Incidence of TEAE; n (%) all causality (N=98)	Incidence of TEAE; n (%) treatment-related (N=98)
General disorders and administration site condition		
Injection site pain	1 (1.0%)	1 (1.0%)
Metabolism and nutrition disorders		
Glucose tolerance impaired	8 (8.2%)	7 (7.1%)
Hyperglycaemia	2 (2.0%)	1 (1.0%)
Diabetes mellitus	1 (1.0%)	1 (1.0%)
Hypoglycaemia	1 (1.0%)	
Type II diabetes mellitus	1 (1.0%)	
Investigations		
Insulin-like growth factor increased	13 (13.3%)	13 (13.3%)

At screening, the mean height SDS for Bone Age was -0.29 (± 1.15). From screening to M12, the mean height SDS for BA decreased slightly (-0.36 ± 1.52), but increased thereafter up to year 3:

at M36, the mean height SDS for BA was 0.14 (± 1.48) and the resulting change from baseline was +0.31 (± 1.17). This increase was not statistically significant from zero ($p=0.244$). Mean change from baseline in height SDS for BA decreased again to - 0.08 (± 1.30) at M48 and +0.01 (± 1.33) at M60; however, it should be noted that few subjects were evaluable at these later time-points.

Table 19: Height (SDS) for BA and change from baseline in height (SDS) for BA over 5 years – Full analysis set – excluding site 1001

	Height (SDS) for BA	Change from baseline in height (SDS) for BA
Screening (baseline)		
n	51	
Mean (SD)	-0.29 (1.15)	
Median (range)	-0.30 (-3.00; 2.36)	
Month 12		
n	40	36
Mean (SD)	-0.36 (1.52)	-0.02 (0.99)
Median (range)	-0.42 (-4.94; 4.28)	0.07 (-2.15; 2.92)
Month 24		
n	29	26
Mean (SD)	0.11 (1.36)	0.28 (1.18)
Median (range)	-0.17 (-2.04; 3.34)	0.15 (-2.89; 2.62)
Month 36		
n	24	21
Mean (SD)	0.14 (1.48)	0.31 (1.17)
Median (range)	0.14 (-3.70; 4.27)	0.09 (-1.98; 2.91)
p-value (Student's paired t-test)		0.244
Month 48		
n	13	13
Mean (SD)	-0.26 (1.28)	-0.08 (1.30)
Median (range)	-0.35 (-3.37; 1.73)	0.33 (-2.28; 1.98)
Month 60		
n	7	7
Mean (SD)	-0.19 (1.15)	0.01 (1.33)
Median (range)	-0.38 (-1.46; 2.15)	0.16 (-2.29; 1.75)

Assessor's comment:

Long-term treatment with Genotropin in these children under glucocorticoid therapy did not change bone age relatively to chronologic age.

At screening, mean fasting glucose level was 4.5 (± 0.7) mmol/L and mean 2-hours post-load glucose level was 5.6 (± 1.2) mmol/L. Mean fasting plasma glucose remained relatively stable during the study: the mean fasting glucose level was 4.6 (± 0.5) mmol/L at M36 and 4.5 (± 0.6) mmol/L at M60, while the mean change from screening was 0.3 (± 0.6) mmol/L at M36 and 0.3 (± 0.4) mmol/L at M60, respectively.

Mean 2-hours post-load glucose levels increased to 6.1 (± 1.4) mmol/L at M12 with a mean change from baseline of 0.6 (± 1.5) mmol/L. The mean 2-hours post-load glucose levels remained relatively stable thereafter being 6.4 (± 1.6) mmol/L at M36 and 6.3 (± 1.5) mmol/L at M60, respectively. The mean change from screening in 2-hours post-load glucose levels was 0.7 (± 1.7) mmol/L at M36 and 1.2 (± 1.8) mmol/L at M60, respectively.

Table 50: Plasma glucose (mmol/L) at fasting and 120 min after glucose ingestion over 5 years – Safety Analysis Set – including site 1001

	Fasting glucose (mmol/L)		Glucose 120 min (mmol/L)	
	Value at time-point	Change from screening	Value at time-point	Change from screening
Screening				
n	91		94	
Mean (SD)	4.5 (0.7)		5.6 (1.2)	
Median (range)	4.6 (1.2; 5.8)		5.7 (2.7; 8.5)	
Month 12				
n	69	64	66	64
Mean (SD)	4.6 (0.7)	0.1 (0.6)	6.1 (1.4)	0.6 (1.5)
Median (range)	4.6 (2.9; 6.1)	0.1 (-1.6; 1.2)	6.1 (2.9; 10.4)	0.4 (-2.4; 5.9)
Month 24				
n	59	55	59	57
Mean (SD)	4.7 (0.6)	0.2 (0.4)	6.1 (1.4)	0.5 (1.3)
Median (range)	4.7 (3.1; 5.9)	0.2 (-0.8; 1.0)	6.2 (2.8; 8.5)	0.7 (-2.6; 5.0)
Month 36				
n	45	40	41	39
Mean (SD)	4.6 (0.5)	0.3 (0.6)	6.4 (1.6)	0.7 (1.7)
Median (range)	4.6 (3.5; 5.9)	0.4 (-1.1; 1.4)	6.0 (2.8; 12.4)	0.7 (-2.4; 6.5)
Month 48				
n	20	19	19	19
Mean (SD)	4.7 (0.4)	0.3 (0.4)	6.1 (1.1)	0.7 (1.3)
Median (range)	4.8 (3.9; 5.4)	0.3 (-0.2; 1.1)	6.2 (3.2; 8.0)	0.6 (-2.3; 2.2)
Month 60				
n	14	11	13	13
Mean (SD)	4.5 (0.6)	0.3 (0.4)	6.3 (1.5)	1.2 (1.8)
Median (range)	4.5 (3.2; 5.9)	0.3 (-0.6; 1.2)	5.8 (4.2; 9.9)	1.3 (-1.4; 5.3)

Assessor's comment:

No change in fasting blood glucose values was observed during the study period. A slight increase in 2-hours post-load glucose was introduced on initiation of therapy (at 12 months evaluation) and remained stable thereafter.

V. MEMBER STATES OVERALL CONCLUSION AND RECOMMENDATION

➤ Overall conclusion

Increase in Height-SDS was demonstrated in patients on glucocorticoid therapy during a 3 year (5 year) period of Genotropin treatment. However, the limited sample size, the heterogeneous patient group and the open, non-controlled design of the trial makes it insufficient to reach final conclusions on efficacy. Reports of adverse events in the trial did not identify new information on Genotropin, which was not previously included in the SmPC.

➤ Recommendation

No further action required.