Section Six

Study 91-131-08

APPEARS THIS WAY
ON ORIGINAL

STUDY: 91-131-08

1. OBJECTIVES

The primary objective of the study was to evaluate effects of Genotropin on body composition (changes in lean body mass versus fat).

Secondary objectives were: to compare GH replacement therapy in different patient groups; to evaluate the effect of GH on bone mineral density, muscle function and structure as well as cardiac and skeletal biochemistry.

2. PATIENTS, MATERIALS AND METHODS

2.1 Study design

The first six months of the study was randomized, double-blind with somatotropin treatment versus placebo. After the initial 6-month double-blind period, the study was continued as an open study for another 6 months during which all patients were treated with somatotropin.

2.1.1 Study population

Initially twenty patients were planned to be recruited and entered by this center. In the original protocol a total of two hundred GH deficient adults (males and females) were to be assessable for efficacy (change in body composition and quality of life) in this multiple independent trial. A randomization list for 300 patients was prepared to allow for withdrawals and patients showing poor compliance.

Inclusion criteria were:

- Growth hormone deficiency (isolated or as parts of hypopituitarism), likely to have existed for 24 months.

- Stimulated maximum peak growth hormone response less than 5 µg/L. Acceptable stimulation tests were arginine, glucagon, clonidine and insulin induced hypoglycemia. A test performed within 5 years prior to inclusion and after 20 years of age was accepted, if it could be verified from source data. Otherwise a new test was required.

- Age

- Patients with multiple pituitary deficiency should have been on stable replacement therapy (6 months).

- Informed consent obtained.

- Patient should have a normal resting ECG and no clinical evidence of ischemic heart disease.

Exclusion criteria were:

- Treatment with growth hormone during the last 12 months.

- Acute severe illness during the last 6 months.

- Pregnancy (should be excluded with test).

- Women of child-bearing age who were not using a reliable method of contraception.

- Chronic severe liver disease (gamma-GT and/or ASAT and/or ALAT twice upper limit of normal range laboratory values).

- Chronic severe renal disease (S-Creatinine>120 µml/L or repeated positive test for hematuria or proteinuria).

- Supine blood pressure >160 mmHg systolic or >100 mmHg diastolic.

- Diabetes mellitus (type I and II).

- A history of malignancy. (Patients who had received treatment for cranial tumors or leukemia, where the treatment caused the GHD, were accepted into the study).

- Chronic medication except pituitary replacement therapy, bromocriptine, contraceptives, treatment for mild hypertension and mild asthma. (Valid at study start). In a core protocol amendment the medication restriction was changed and "stable anticonvulsant therapy" was accepted. This restriction was further changed in a later amendment to "all concomitant medication is permitted but must be clearly documented. Where bone mineral density is being measured, any medication which may effect this, should be permitted".

- Suspected non-cooperativeness.

- Known/suspected hypersensitivity to m-cresol.

3. Therapy

3.1 TREATMENT SCHEDULE

The dose was 0.375 mg/kg/week during the first four weeks of each 6-month period and thereafter 0.75 mg/kg/week for five months. The weekly dose was divided into seven daily s.c. injections. Irrespective of body weight, maximum dose per day should not exceed 12 mg.

3.1.2 CONCOMITANT THERAPY

No other investigational drug could be used concomitantly with the test drug. The patients were not allowed to participate concurrently in any other clinical study.

The patients were allowed to take any drug judged necessary for treatment of any intercurrent disease of a less severe nature. Treatment for pituitary replacement therapy was allowed but was held as constant as possible. Adjustments on clinical grounds were allowed and had to be documented.

All chronic and temporary therapy was recorded in the Case Report Form.

3.2 Patient characteristics

The following general patient characteristics were reported at baseline: birth-date, sex and ethnic origin. Patient characteristic information at baseline regarding growth hormone deficiency were: year of diagnosis, date, GH peak and type of last stimulation test, and etiology. Other hormone deficiencies (TSH, ACTH, LH/FSH, ADH, other) were recorded. For patients with previous treatment with growth hormone the start and end date, dose and adverse events during the previous treatment period were recorded. Other chronic illnesses or sequela from previous diseases were also recorded.

3.3 Efficacy assessments

3.3.1 CLINICAL EFFICACY ASSESSMENTS

Body composition

The measurements of body composition were assessed by two methods:

1. Dual X-ray Absorptiometry (DEXA)

2. Deuterium labeled water

Bone mineral density

Assessments of bone mineral density were made of the hip, spine and forearm. As specified in center amendment, measurements of bone mineral density (DEXA), were performed. These additional tests were measurements of BMD (g/cm^2) of the lumbar spine L1-L4, femoral neck, femoral trochanter area, femoral intertrochanter, femoral Ward´s area, total hip area, 1/3 distal radius, and the whole body.

Muscle strength

Maximum voluntary contraction of the quadriceps was measured isometrically on the subject´s dominant leg. Each subject was seated in a specially adapted chair and asked to push each leg against a strap around the ankle, attached to a strain gauge and amplifier. This was repeated five times with a 30 seconds recovery between efforts. The highest two values were recorded (Newton).

3.4. Safety assessments

3.4.1 CLINICAL SAFETY ASSESSMENTS

Clinical safety examination consisted of physical examinations. A complete physical examination was performed at the screening visit, baseline, 6 and 12 months. A limited physical examination was performed at 3 and 9 months. Parameters monitored were similar to those assessed in the previous studies.

3.5 RESULTS

3.5.1 Protocol deviations

GH deficiency was diagnosed within less than two years before study start in two patients (nos. 78 and 99).

Five patients were not on stable hormonal replacement (nos. 86 and 95 estrogen; nos. 90 and 96 testosterone; no. 99 desmopressin).

Clinical chemistry and hematology tests outside reference limits at background were not repeated at baseline for 24 patients.

S-ALAT measurements were not made.

Total T3 and T4 were measured instead of free T3 and free T4, which were stated in the protocol.

Two patients in each group (somatotropin patients nos. 80 and 88, and placebo patients nos. 246 and 293) missed >10% of the injections during the first 6 months of the study. Two patients in the somatotropin group (nos. 80 and 132) and five patients in the pl/somatotropin group (nos. 81, 82, 241, 23 and 293) missed >10% of the injections during the last 6 months of the study.

Concomitant medication was not asked for at the first month's visit.

Two patients in the somatotropin group took osteoporosis medication concomitantly. Patient no. 99 took calciferol from baseline and throughout the entire study and patient no. 94 took etidronate sodium and calcium carbonate from the 6th study month.

Body composition was measured with deuterium labeled water. The tracer was incorrectly diluted and no useful information was obtained.

Quadriceps biopsies were taken, but the analysis has not yet been performed.

Magnetic resonance spectroscopy was planned for studying cardiac and muscle intracellular biochemistry. However, this had to be abandoned due to poor patient tolerability and cost.

3.6 Study population

3.6.1 NUMBER OF PATIENTS

Fifty-two patients with growth hormone deficiency were included in the study from April 15, 1992 to November 10, 1993. Twenty seven patients were randomized to the somatotropin group and 25 to the placebo group.

Four patients in the somatotropin group and two patients in the placebo group did not complete the study.

3.6.2 Treatment withdrawals

Six patients were withdrawn from the study.

Table 1 Patient withdrawals from the study

Pat. no.	Treatment group	Days in the study/on Rx drug	Reason(s) for withdrawal (Investigator's term)
74	Somatotropin	49/49	Adverse event: generalized aches and pains in muscle Consent withdrawn - interferes with work
95	Somatotropin	188/188	Consent withdrawn
244	Somatotropin	157/157	Non-compliance, too busy to come to hospital Consent withdrawn
247	Somatotropin	88/88	Adverse event: carpal tunnel syndrome
77	Pl/somatotropin	259/90	Adverse event: aches and pains in knees and ankles, swelling of hands and feet, stiffness after sitting and in the morning.
85	Pl/somatotropin	269/59	Adverse event: Swelling of hands and ankles pain in joints

3.6.3 PATIENT CHARACTERISTICS

Fifteen males and 12 females, (mean age 40 years), were included in the somatotropin group and 13 males and 12 female, (mean 39 years) were included in the placebo group. The mean number of years since GHD diagnosis was 10 years in the somatotropin group and 12 years in the placebo group. In two patients (nos. 99 and 78), less than two years had elapsed since diagnosis. This was, however, noted by the investigator to likely have existed for more than two years in one of the mentioned patients (no. 99). Peak GH response after provocation test are given in Table 2.

Table 2 Peak GH response

Peak GH response (mU/L)	**Somatotropin** n=27	**Placebo** n=25
≤ 3	20	19
>3 ≤6	2	3
>6 ≤9	5	2
>9 <10	0	1

The most common etiology in both groups were pituitary tumor (somatotropin: 18 of 27 vs. placebo: 13 of 25) whereas craniopharyngioma was more common in the placebo group (somatotropin: 2 of 27 vs. placebo: 7 of 25). The majority of the patients had multiple pituitary hormone deficiencies (somatotropin; 20 of 27 vs. placebo; 19 of 25).

Patient demographics are given in Table 3 below and individual data is given in Table 40 at the end of the report.

Table 3 Patient demographic data

	Somatotropin			Placebo		
	mean	SD	range	mean	SD	range
Sex (number of male/female)	15/12	-	-	13/12	-	-
Age (years)	40	11	21-60	39	11	22-60
Height (cm)	168	11	144-189	165	9	145-185
Weight (kg)	80	17	43-112	74	16	55-113
Body mass index	28	5	19-41	27	5	22-42
GH peak in provocation test (mU/L)	2.5	2.7	0.5-8.7	2.2	2.5	0.5-9.4
Years since diagnosis of GHD (years)	10	8	0-29	12	7	0-34
Age at diagnosis of GHD (years)	30	11	13-58	27	12	7-52
Earlier treatment with hGH (yes/no)	3/24	-	-	6/19	-	-
Etiology (number of patients):						
Pituitary tumor	18	-	-	13	-	-
Chraniopharyngioma	2	-	-	7	-	-
Trauma	2	-	-	0	-	-
Radiotherapy non-function tumor	1	-	-	0	-	-
Radiotherapy medulloblastoma	1	-	-	0	-	-
Radiotherapy post prolactinoma	1	-	-	1	-	-
Craniotomy for arachnoid cyst	1	-	-	0	-	-
Post-partum necrosis of pituitary	1	-	-	0	-	-
Radiotherapy for Cushing's disease	0	-	-	1	-	-
Idiopathic	0	-	-	3	-	-
Other hormone deficiencies (number of patients):						
ACTH deficiency yes/no	13/14	-	-	12/13	-	-
TSH deficiency yes/no	14/13	-	-	15/10	-	-
ADH deficiency yes/no	4/23	-	-	5/20	-	-
LH/FSH deficiency yes/no	18/9	-	-	15/10	-	-
Aldosterone deficiency yes/no	2/25	-	-	0/25	-	-
No other deficiency yes/no	6/21	-	-	5/20	-	-

3.7 CONCOMITANT MEDICATION

At study start, there was a restriction in the use of concomitant medication. Approved medications were pituitary replacement therapy, bromocriptine, contraceptives, treatment for mild hypertension and mild asthma. In core protocol amendment 3, dated April 13, 1993, the restriction was further changed to "all concomitant medication is permitted but must be clearly documented. Where bone mineral density is being measured, any medication which may effect this, should not be permitted".

3.7.1 Study medication

3.7.2 STUDY DRUGS

During the first four weeks of the study,
(target dose 0.375 mg/kg/week). During the following five months
(target dose 0.75 mg/kg/week) for all patients

except two in the somatotropin group. One of these patients (no. 102) had a dose reduction at 3 months to 0.36 mg/kg/week and one patient (no. 247) had a dose reduction before 3 months to 0.36 mg/kg/week. Three patients in the somatotropin group were withdrawn (nos. 74, 244, 247) during the first 6-month period and one patient (no. 95) was withdrawn at the 6th month's visit.

At the start of the 6-month open period the dosage was reduced for all patients to the dosage given at study start, the dose range being 0.36-0.39 mg/kg/week. The dose was increased back to 0.75 mg/kg/week after four weeks to reach full dosage for months 8 to 12 for all patients except in one in the somatotropin group (no. 103), who had a dose reduction at 9.5 months to 0.36 mg/kg/week and two patients in the placebo group. One of the placebo treated patients (no. 79) had the dose reduced to 0.36 mg/kg/week at 7 months and one patient (no. 131) never received the scheduled dose increase at 8 months. Two patients in the placebo group (nos. 77 and 85) were withdrawn during the 6 month open period.

3.7.3 COMPLIANCE

The number of missed injections was asked for at each visit.

4. Efficacy

The presentation of the efficacy results in the tables is divided into two parts. The first part covers the results from the initial 6-month placebo-controlled double-blind phase. The second part cover the results during somatotropin replacement therapy.

The absolute values presented in the text are mean values for each variable. Tables of all variables measured are presented. These tables include mean baseline values, mean changes during the study and statistical significance analysis. P-values ≤ 0.10 are given in the tables.

4.1 CLINICAL EFFICACY VARIABLES

Body composition

There was no statistically significant change in body weight during treatment, neither during the double-blind study period nor during the following treatment in any of the treatment groups.

Changes in body composition during the double-blind period are shown in Table 4. The variables measured were lean body mass, fat mass, lean/fat ratio.

In the somatotropin group there was an increase in lean body mass and a decrease in fat mass (both totally, and measured in the truncal area), and accordingly, there was an increase in the lean/fat ratio. No statistically significant changes were noted in the placebo group, and thus, taken together, the differences in these changes between the treatment groups were statistically significant.

Table 4 Effect of treatment on body composition (DEXA)

Variable	Somatotropin group					Placebo group					
	Baseline		Change 0-6 months			Baseline		Change 0-6 months			
	mean n=19	SD	mean n=17	SD	p-value within	mean n=16	SD	mean n=16	SD	p-value within	p-value between
Lean body mass (kg)	52.483	12.458	2.386	2.162	**0.001**	48.513	13.313	0.348	2.144	n.s.	**0.009**
Fat mass (kg)	23.370	10.330	-2.661	2.138	**<0.001**	22.159	8.408	0.472	2.158	n.s.	**<0.001**
Lean/Fat ratio	2.57	0.94	0.58	0.61	**<0.001**	2.38	0.89	-0.01	0.16	n.s.	**<0.001**
Fat mass in trunk area (kg)	11.106	5.349	-1.939	1.228	**<0.001**	9.914	3.357	0.433	1.735	n.s.	**<0.001**
Fat mass in trunk area (%)	27.51	9.47	-4.61	2.84	**<0.001**	27.35	5.65	0.37	2.68	n.s.	**<0.001**
Fat mass in whole body (%)	29.24	9.15	-3.20	2.60	**<0.001**	30.26	7.07	0.13	1.71	n.s.	**<0.001**
Lean body mass in trunk area (kg)	27.404	6.450	1.331	1.349	**0.001**	25.563	6.303	0.329	1.280	n.s.	**0.038**
Lean body mass in trunk area (%)	71.12	9.36	4.52	2.78	**<0.001**	71.14	5.64	-0.35	2.67	n.s.	**<0.001**
Lean body mass in whole body (%)	67.54	8.94	3.16	2.58	**<0.001**	66.37	7.01	-0.13	1.70	n.s.	**<0.001**

The changes in body composition in the somatotropin treatment group during the 6 month placebo-controlled period were maintained during continued open treatment (Table 5). In comparison to baseline values, the changes in all the measured variables were statistically significant.

Similar changes in body composition to those observed in the somatotropin treated group during the 6-month placebo-controlled period, were also seen in the formerly placebo treated patients (pl/somatotropin) once they received somatotropin (Table 5).

Table 5 **Effect of treatment on body composition (DEXA Scan) during the somatotropin period. Absolute change from baseline over time by treatment group. (For the original placebo group baseline = 6th-month's visit)**

		Baseline		Change 0-6 months			Change 0-12 months		
Variable	Group	mean	SD	mean	SD	p-value	mean	SD	p-value within
Lean body mass (kg)	somatotropin	52.483 n=19	12.458	2.386 n=17	2.162	**0.001**	2.573 n=16	2.573	**0.001**
	pl/ somatotropin	48.862 n=16	14.123	2.341 n=14	1.847	**0.001**	-	-	-
Fat mass (kg)	somatotropin	23.370 n=19	10.330	-2.661 n=17	2.138	**<0.001**	-1.561 n=16	2.823	**0.065**
	pl/ somatotropin	22.632 n=16	9.747	-1.500 n=14	1.671	**0.004**	-	-	
Elog lean body mass	somatotropin	3.932 n=19	0.249	0.044 n=17	0.042	**0.001**	0.047 n=16	0.045	**0.001**
	pl/ somatotropin	3.857 n=16	0.247	0.049 n=14	0.040	**0.001**	-	-	-
Lean/fat ratio	somatotropin	2.57 n=19	0.94	0.68 n=17	0.61	**<0.001**	0.52 n=16	0.65	**0.004**
	pl/ somatotropin	2.38 n=16	0.90	0.53 n=14	0.79	**<0.001**	-	-	-
Elog lean/fat ratio	somatotropin	0.869 n=19	0.430	0.180 n=17	0.152	**<0.001**	0.149 n=16	0.175	**0.006**
	pl/ somatotropin	0.802 n=16	0.365	0.151 n=14	0.163	**<0.001**	-	-	-
Fat mass in trunk area (kg)	somatotropin	11.106 n=19	5.349	-1.939 n=17	1.228	**<0.001**	-1.328 n=15	1.602	**0.015**
	pl/ somatotropin	10.346 n=16	4.483	-1.214 n=14	1.161	**<0.001**	-	-	-
Fat mass in trunk area (%)	somatotropin	27.51 n=19	9.47	-4.61 n=17	2.84	**<0.001**	-3.54 n=15	3.28	**0.001**
	pl/ somatotropin	27.73 n=16	6.51	-3.21 n=14	2.75	**<0.001**	-	-	-
Fat mass in whole body (%)	somatotropin	29.24 n=19	9.15	-3.20 n=17	2.60	**<0.001**	-2.69 n=15	3.01	**0.005**
	pl/ somatotropin	30.39 n=16	7.42	-2.67 n=14	2.40	**<0.001**	-	-	-
Lean body mass in trunk area (kg)	somatotropin	27.404 n=19	6.450	1.331 n=17	1.349	**0.001**	1.170 n=15	1.224	**0.005**
	pl/ somatotropin	25.892 n=16	6.944	0.821 n=14	8.555	**0.005**	-	-	-
Lean body mass in trunk area (%)	somatotropin	71.12 n=19	9.36	4.52 n=17	2.78	**<0.001**	3.42 n=15	3.23	**0.002**
	pl/ somatotropin	70.79 n=16	6.52	3.17 n=14	2.74	**<0.001**	-	-	-
Lean body mass in whole body (%)	somatotropin	67.54 n=19	8.94	3.16 n=17	2.58	**<0.001**	2.61 n=15	2.95	**0.005**
	pl/ somatotropin	66.24 n=16	7.34	2.57 n=14	2.42	**<0.001**	-	-	-

Waist and hip circumferences

There were no significant difference between the groups in waist, hip and waist/hip ratio.

Bone mineral density

Bone mineral density (BMD) was measured by DEXA in lumbar spine L1-L4, femoral neck, femoral trochanter, femoral intertrochanter, femoral Ward's area, total hip area, 1/3 distal radius as well as the whole body. Changes did not reach statistical significance, neither when compared to baseline values for each treatment group, nor when the changes in the two groups were compared.

Muscle strength and exercise tolerance

There were no statistically significant differences of change in quadriceps muscle strength between the groups.

Maximal heart rate decreased in the somatotropin group and increased in the placebo group. In the placebo group maximum oxygen uptake decreased during the placebo period ($p<0.02$). A similar but statistically insignificant decrease was also seen in the somatotropin group. However, during open somatotropin treatment the pl/somatotropin group had a significant increase of maximum oxygen uptake ($p<0.049$, VO_2 ml/kg/min. and $p<0.003$, VO_2 L/min.) whereas no significant improvement could be seen in the somatotropin group.

4.2 LABORATORY EFFICACY VARIABLES

Changes in IGF-I and IGF-I SDS are given in Tables 6 and 7. There was a significant difference between the groups in the change of IGF-I ($p<0.001$) and IGF-I SDS ($p<0.001$). IGF-I and IGF-I SDS increased significantly for the somatotropin group compared to baseline during the double-blind phase, as well as in the former placebo group during the 6-month open somatotropin treatment.

Table 6 Effect of treatment on IGF-I during the 0-6 months double-blind period. Absolute change from baseline over time by treatment group

Variable	Somatotropin group					Placebo group					p-value between
	Baseline		Change 0-6 months			Baseline		Change 0-6 months			
	mean	SD	mean	SD	p-value within	mean	SD	mean	SD	p-value within	
IGF-I	109 n=27	56	210 n=24	148	<0.001	84 n=25	48	-3 n=23	26	n.s.	<0.001
IGF-I SDS	-2 n=27	2	4 n=24	2	<0.001	-3 n=25	2	0 n=25	1	n.s.	<0.001

Table 7 **Effect of treatment on IGF-I during the somatotropin period. Absolute change from baseline over time by treatment group. (For the original placebo group baseline = 6th month's visit)**

		Baseline		Change 0-6 months			Change 0-12 months		
Variable	Group	mean	SD	mean	SD	p-value	mean	SD	p-value within
IGF-I	somatotropin	109 n=27	56	210 n=24	148	<0.001	184 n=21	133	<0.001
	pl/ somatotropin	81 n=25	43	137 n=23	117	<0.001			
IGF-I SDS	somatotropin	-2 n=27	2	4 n=24	2	<0.001	4 n=21	2	<0.001
	pl/ somatotropin	-3 n=25	2	3 n=22	2	<0.001			

Number of patients within, above and below the age matched reference limits are given in Table 8. The months in the table refer to the visit months i.e., the original baseline is used for the pl/somatotropin group.

Table 8 **Number of patients with IGF-I values above/below/between age-matched reference limits at each visit**

	Somatotropin			Pl/somatotropin		
Visits	Below ref. limit	Within ref. limit	Above ref. limit	Below ref. Limit	Within ref. limit	Above ref. limit
Baseline	12	15	0	16	9	0
6 months*	1	11	12	18	7	0
12 months	1	10	10	6	10	6

* 6th month's visit= redefined "baseline" for the pl/somatotropin group

4.3 EFFICACY SUMMARY

Measurement of body composition with DEXA showed statistically significant differences between the groups in all variables measured. Lean body mass increased, fat mass decreased and lean/fat ratio increased in the somatotropin group. These changes were maintained during continued treatment.

There was no difference between the groups in waist, hip and waist/hip ratio during the double-blind phase, nor during continued treatment.

In BMD there was a significant difference between the groups in the measurements of the whole body. There was a decrease in the somatotropin group and an increase in the placebo group.

There were no statistically difference of change in quadriceps muscle strength between the groups during the double-blind period, though a significant increase was observed in both groups. No significant change was observed in the exercise tolerance test.

IGF-I and IGF-I SDS values showed statistically significant differences in changes between the groups. IGF-I and IGF-I SDS increased in the somatotropin group. The increase in IGF-I and IGF-I SDS values were maintained throughout the study.

5. Safety

5.1 CLINICAL SAFETY VARIABLES

The systolic blood pressure in the somatotropin group decreased by 6 mmHg after 6 months compared to baseline (p=0.046), which remained unchanged after 12 months (p=0.009). There were no significant changes in diastolic blood pressure or pulse.

Weight was unchanged in both groups, both during the double-blind period and during the open period.

Height increased compared to baseline in the somatotropin group with 0.6 cm (p=0.001).

5.2 Laboratory safety variables

A significant difference between the treatment groups was observed in HbA1c at 6 months (p= 0.011). The mean value increased significantly compared to baseline in the somatotropin group(p=0.021), while there was a small decrease in the placebo group.).

Serum glucose levels and thrombocytes increased during the open phase (6-12 months) in the former placebo group (p=0.001 and 0.001, respectively).

Serum potassium and ASAT in the GH group, decreased compared to baseline at 12 months (p=0.023 and 0.034, respectively).

Laboratory values outside reference limits

The values outside reference limits described per laboratory test variable and the values given in the tables were measured anytime during the trial i.e., from background/baseline to the last assessment. Number of patients with values outside reference limits before and during treatment, respectively, are given in Table 9 for the double-blind phase and Table 10 for the somatotropin phase. In these tables each patient with abnormal values is counted once per interval (before/during therapy). Therefore, minor discrepancies between the numbers given in these tables and the numbers given in the following text may be found.

Table 9 Patients with abnormal values in clinical chemistry and hematology tests, before and/or during therapy, respectively

	Somatotropin				Placebo			
	Before therapy		During therapy		Before therapy		During therapy	
	above	below	above	below	above	below	above	below
B-Hemoglobin	1	6	1	6	0	6	0	6
B-Leukocytes	3	0	2	2	0	0	0	0
B-Thrombocytes	0	2	0	1	0	1	0	2
B-Glucose (fasting)	0	12	0	8	0	8	0	7
HbA1c	0	1	0	0	0	0	0	0
S-Creatinine	6	0	2	0	6	0	8	0
S-Sodium	0	0	0	1	0	0	0	0
S-Potassium	0	2	0	4	0	1	0	1
S-ASAT	2	0	0	0	0	0	2	0
S-Total T4	1	1	2	4	1	0	1	0
S-Total T3	2	0	0	0	0	1	0	0

Table 10 Number of patients with values outside reference limits before and during therapy, respectively

	Somatotropin			
	Before therapy		During therapy	
	above	below	above	below
B-Hemoglobin	1	14	2	18
B-Leukocytes	4	0	2	2
B-Thrombocytes	0	4	0	2
B-Glucose (fasting)	0	22	3	17
HbA1c	0	1	0	2
S-Creatinine	14	0	8	0
S-Sodium	0	0	0	1
S-Potassium	0	4	0	8
S-ASAT	4	0	0	0
S-Total T4	3	1	2	6
S-Total T3	2	1	0	1

5.3. ADVERSE EVENTS

Adverse events were actively asked for and adverse events related to fluid retention were specifically sought. Events have been listed in chronological order.

A total of 125 adverse events were reported in the somatotropin group and 57 adverse events were reported in the placebo group during the 0-6 months double-blind period. The most frequently reported symptoms (>5 events in any of the groups) during the double-blind phase were peripheral swelling (somatotropin: 18, placebo: 4), pain in the extremities (somatotropin: 11, placebo: 1), headache (somatotropin: 8, placebo: 5) and fatigue (somatotropin 5, placebo: 0). Eleven events of peripheral swelling were reported during the double-blind phase in one patient and 4 events of pain in the extremities were reported in one patient, both in the somatotropin group.

During the 6-12 month period there were 153 adverse events reported in both groups. Adverse events were totally reported in 46 of the patients in the study.

The most frequently reported adverse events during the entire study (>10 events in any of the groups) were respiratory tract infections, peripheral swelling, pain/pain extremities, headache, stiffness generalized/stiffness extremities, fatigue, arthralgia and paraesthesia.

Forty-nine events of respiratory disorders were reported in 29 patients, whereof 7 events were reported during the double-blind period in the placebo group.

Peripheral swelling was reported as 38 events in 14 patients. Seventeen events of peripheral swelling were reported in a single patient. Six events were reported from among three patients in the placebo group during the double-blind phase.

Headache was reported in 19 events in 11 patients, whereof five events in three patients in the placebo group during the double-blind phase.

Stiffness generalized/stiffness extremities was reported in 15 events in 12 patients. None of the events was reported in the placebo group during the placebo phase.

Fatigue was reported in 14 events in 10 patients during the somatotropin phase.

Arthralgia was reported in 13 events in 10 patients during the somatotropin treatment.

Paraesthesia was reported in 12 events in six patients, while four events were reported in two patients during the double-blind phase.

5.4 SERIOUS ADVERSE EVENTS

Serious adverse events (SAEs) were reported in two patients (nos. 87 and 98) during the 0-6 month double-blind phase. Both were reported in the somatotropin group. A third patient (no. 88) had three SAEs during the second 6 months' period of the study. A causal relationship with study drug was deemed in two of the SAEs: carpal tunnel syndrome and headache (no. 88). Patients with SAE are given in Table 11.

Table 11 Patients with Serious Adverse Events during the trial

Patient no/ therapy group	Age	Sex	Serious Adverse Event	Treatment duration at onset	Severity	Relation with study drug	Action taken with study drug	Outcome
87/ Somatotropin	32	F	Meningitis	166 days	Severe	Unlikely	Interrupted	Complete recovery
88/ Somatotropin	39	F	Carpal tunnel syndrome	211 days	Moderate	Possible	Interrupted	Complete recovery
			Removal of polyp from right sinus	317 days	Moderate	Unlikely	None	Complete recovery
			Headache	332 days	Severe	Possible	None	Recovery with sequale
98/ Somatotropin	23	F	Intranasal antiostomy sinus.	22	Moderate	Unlikely	None	Complete recovery

Patient no. 87 was a 32-year-old female who had meningitis for 12 days. She was hospitalized and treated with benzylpenicillin and rifampicin. The SAE was deemed to be life threatening. The patient recovered completely.

Patient no. 88 was 39-year-old female who had three different serious adverse events.

- The first SAE was an operation for carpal tunnel syndrome and she was hospitalized for one day.
- The second SAE was a removal of a polyp from right sinus. She was hospitalized for five days.
- At the third SAE she was hospitalized for 14 days due to severe headache. No cause was found.

Patient no. 98 was a 23-year-old female who had an intranasal antrostomy and sinus wash-out for maxillary sinusitis.

Patients withdrawn due to adverse events are given in Table 12.

Table 12 Patients who were withdrawn due to adverse events from the study

Pat. no.	Treatment group	Days in the study/on Rx drug	Reason(s) for withdrawal
74	Somatotropin	49/49	Generalized aches and pains in muscle Consent withdrawn - interferes with work
247	Somatotropin	88/88	Carpal tunnel syndrome
77	Pl/somatotropin	259/90	Aches and pains in knees and ankles, swelling of hands and feet, stiffness after sitting and in the morning.
85	Pl/somatotropin	269/59	Swelling of hands and ankles, pain in joints

5.6 SAFETY SUMMARY

There were no statistical significant differences between the groups in blood pressure, heart rate, weight or height during the double-blind phase.

HbA1c increased during somatotropin treatment in both groups. These changes were generally within normal range limits.

Adverse events were reported in 46 patients. The most frequently reported adverse events were (events/patients) respiratory tract disorders (49/29), peripheral swelling (38/14), headache (19/11), stiffness generalized/stiffness extremities (15 /12), fatigue (14/10), arthralgia (13/10), and paraesthesia (12/6)

Four patient withdrew due to adverse events during somatotropin replacement (myalgia, carpal tunnel syndrome, arthralgia+peripheral swelling+stiffness and arthralgia+peripheral swelling, respectively).

Serious adverse events were reported in three patients during somatotropin replacement therapy. One patient had 3 serious adverse events. Two SAE were deemed to be possibly related to somatotropin replacement (carpal tunnel syndrome and headache). The other SAE were meningitis, removal of polyp from right sinus and intranasal antrostomy of sinus.

6. DISCUSSION

All patients had pronounced growth hormone deficiency as demonstrated by low serum GH peaks after an appropriate stimulation test. Two patients however, had not been diagnosed as growth hormone deficient for two years, although one was regarded as likely having been growth hormone deficient for two years. Most of the patients were on stable replacement therapy for other

pituitary hormone deficiencies. In five patients, however, some changes in estrogen, testosterone, and desmopressin therapies, were made. Two of the patients received concomitant medications possibly interfering with the results of the bone mineralization assessments. Compliance was generally good. The results can be regarded as a representative for GH replacement therapy for adult patients with GH deficiency.

During the 6-month placebo-controlled study period, several changes in body composition occurred. Thus, the amount of fat mass decreased and lean tissue increased, without affecting body weight. Theses changes were noted both for the truncal area as well as for the whole body, and resulted in an increase in the lean/fat ratio. These changes in body composition were maintained during continued treatment.

Serum levels of IGF-I rose during treatment from relatively low or normal values according to age and sex-matched control levels to normal, and for some patients to high levels. The sensitivity to growth hormone replacement seems to vary widely among individuals, and even if, according to group responses, the dosages used appear to be correct, dosing should be individualized for each patient to avoid super physiological levels of IGF-I. Treatment was generally well-tolerated. Six patients withdrew from the study, four of whom because of adverse events, all likely related to fluid retention induced by the treatment. In fact, the majority of reported adverse events that were regarded as possibly or probably related to the therapy by the investigator were those related to fluid retention: edema, arthralgia, stiffness, myalgia, paraesthesia, and myalgia. Their frequency, intensity and duration were similar to those reported in the literature.

7. CONCLUSSION

GH treatment in subjects with adult GH deficiency resulted in increments in lean body mass and decrements in fat tissue. These changes were maintained during the extension studies. Normalization of IGF-I was attained in the GH treated patients. GH dosing should, however, be individualized in order no to reach super physiological changes in this marker.

Section Seven

Study 92-8124-011

APPEARS THIS WAY
ON ORIGINAL

Study 92-8124-011

1. OBJECTIVES

Primary: To determine the effect of somatotropin replacement therapy on body composition in GH-deficient adults as compared to placebo treatment.

Secondary: To evaluate the effect of somatotropin replacement therapy on serum IGF-I, hand grip strength, bone mineral density and lipid metabolism as compared to placebo treatment.

To elucidate the safety of somatotropin replacement therapy.

2. PATIENTS, MATERIALS AND METHODS

2.1 Study design

The first 6 months of the study were randomized and double-blind with Genotropin treatment versus placebo.

After the initial 6-month double-blind phase, the study was continued as an open study for another 6 months, and all patients in both groups received Genotropin.

2.2 Study population

Twenty patients (males and females), 10 in each treatment group, assessable for efficacy with GH deficiency acquired in childhood or adulthood, were included in the trial. A randomization list for 30 patients was prepared to allow for drop-outs, withdrawal and patients showing bad compliance.

Inclusion and exclusion criteria were similar to the previous studies

2.3.1 STUDY PRODUCT

Genotropin 16 IU for

2.3.2. COMPLIANCE

The number of missed injections was asked for at each visit and documented in the Case Report Forms.

2.3.4. CONCOMITANT THERAPY

Pituitary replacement therapy, bromocriptine, contraceptives, therapy for mild hypertension and mild asthma were allowed; other chronic concomitant medication was not permitted. An attempt was made to hold treatment for pituitary replacement constant. Adjustments on clinical grounds were allowed but were documented in the CRFs.

No other investigational drugs were allowed to be used concomitantly with the test drug. The patients were not allowed to participate concurrently in any other clinical study. The patients were allowed to take any drug judged necessary for the treatment of any intercurrent disease.

2.3.5 Patient characteristics

Patients, males or females, between the [redacted] years who are growth hormone deficient, with a stimulated maximum peak GH response less than 5µg/L, were included.

2.4 Efficacy assessments

2.4.1 CLINICAL EFFICACY ASSESSMENTS

Body composition and bone mineral density

Dual-energy projection methods have been used over the past decade for the measurement of bone and soft-tissue composition *in vivo*. Dual-photon absorptiometry (DPA) using a radio-nuclide source has been performed for the measurements of bone mineral density (BMD) and bone mineral content (BMC), both locally in the spine and proximal femur, and also for the total body. Total body bone mineral content correlates highly with the actual skeletal mass and with total body calcium by neutron analysis *in vivo* because calcium is a constant fraction (about 37%) of the mineral component in bone. One by-product of such total DPA scans is a measure of the relative lean/fat composition in areas where no bone is present.

DEXA was also used to assess these parameters.

Additional investigation

Hand grip strength assessment using a hand dynamometer was performed on all patients.

2.4.2. LABORATORY EFFICACY ASSESSMENTS

The following laboratory assessments were performed:

- IGF-I
- total-cholesterol
- LDL-cholesterol
- HDL-cholesterol
- triglycerides

2.5 Safety assessments

Safety assessments were performed as in previous studies.

2.6 RESULTS

2.6.1 Protocol deviations

Several protocol deviations were recorded by the investigators. Most of them were the result of the need of medications due to either the underlying condition of intercurrent disorders. Other deviations included GH dosing changes and evaluations that did not specifically met the timing of the original protocol. None of these deviations appear to be relevant.

Diagnosis of GH deficiency

Diagnosis of GH deficiency less than 24 months prior to baseline for pats. nos. 2, 6, 8, 12, 13, 14, 16, 18 and 19. Comments were made by the investigator that all patients were likely to have had GH deficiency at least 24 months prior to study inclusion based on the diagnosis dates of other pituitary hormone deficiencies.

Deviations in assessments

TSH and urea determinations were included in the CRF, but the assessments were not noted in the protocol or in the protocol amendment.

Assessments of HDL-cholesterol, LDL-cholesterol, Apolipoprotein A and B, ALAT, spine bone mineral density and femoral neck bone mineral density were not performed.

2.7 Study population

NUMBER OF PATIENTS

A total of 20 (10 Genotropin and 10 placebo) patients with growth hormone deficiency were randomized and included in the study. Nineteen included patients (excluding patient no. 17) completed the 6-month double-blind study period (10 Genotropin and 9 placebo) and 17 patients (excluding patient nos. 11, 17 and 19) completed the following 6-month open-label study period (9 Genotropin and 8 former placebo).

TREATMENT WITHDRAWALS

There were three withdrawals from treatment, as follows:

Patient no. 11 (Genotropin group) withdrew after the 9th month's visit, 282 days after the baseline visit, due to worsening of carpal tunnel syndrome.

Patient no. 17 (placebo group) withdrew 21 days after the baseline visit due to personal reasons; the patient felt uncomfortable with daily injections.

Patient no. 19 (placebo group) withdrew after the 6th month's visit, 210 days after the baseline visit, due to a relapse of Cushing's Disease.

PATIENT CHARACTERISTICS

There were 4 females and 6 males in the Genotropin group, and 2 females and 8 males in the placebo group, with a group mean age of 46.8 ± 7.9 years and 39.6 ± 12.2 years, respectively. Group mean values for height and weight were similar for both groups; 167.0 ± 11.7 cm and 82.0 ± 16.1 kg; 168.0 ± 12.4 cm and 78.9 ± 26.6 kg, for the Genotropin and placebo groups, respectively.

The mean value for the GH peak at the latest stimulation test was similar for the two treatment groups, 0.6μg/L. The duration of the growth hormone deficiency was estimated to be at least 2 years for all patients when the onset of GHD was defined according to the first diagnosed pituitary deficiency. With regard to etiology and other pituitary hormone deficiencies, no differences between the study groups were noted. In 9 of 10 patients in both study groups, at least two other pituitary functions were affected.

2.8. CONCOMITANT THERAPY

Patients with hormonal deficiencies, other than GH, continued their replacement therapy as before entering the trial. Three patients with gonadal deficiencies were not replaced and one of them having a borderline thyroid disorder did not receive thyroid either.

2.8 Study medication

STUDY PRODUCTS

During the first four weeks of the study, the GH
(target dose 0.375 mg/kg/week). After the first four weeks,
(target dose 0.75 mg/kg/week). Prior to the 6th month's visit, the study dose was reduced and/or temporarily interrupted in seven

patients due to adverse events; pats. no. 4 (fluid retention), no. 11 (worsening of carpal tunnel syndrome), no. 12 (musculo-skeletal aches and pain and increased serum IGF-I above normal range), no. 13 (edema), no. 16 (injection site reaction), no. 18 (lethargy and aggression) and no. 19 (weight gain and fluid retention).

At six months the dose . (target dose 0.375 mg/kg/week). After six months and 4 weeks, the (target dose 0.75 mg/kg/week). Between the 6th and 12th month's visits, six patients had a reduction and/or temporary interruption in Genotropin treatment due to adverse events: pats. no. 6 (fluid retention), no. 9 (fluid retention), no. 12 (increased serum IGF-I above normal range), no. 13 (edema), no. 14 (IGF-I above normal range), and no. 18 (hyperactivity). One patient, no. 11 (worsening of carpal tunnel syndrome), was permanently withdrawn from treatment after the 9th month's visit.).

For patient no. 1, the actual dose was limited, according to the protocol, after the first 4 weeks of the each six-month period to 0.57 and 0.563 mg/kg/week, respectively, (target dose 0.750 mg/kg/week) due to excessive body weight.

2.9. COMPLIANCE

The number of missed injections was requested at each visit. No injections were missed by 3 of 10 Genotropin patients during the first 6-month study period, while the other seven patients missed from In the placebo group, no injections were missed for 4 of 9 patients, while the other five patients missed from

During the open study period (months 7 to 12), 4 of 9 Genotropin patients missed no injections whereas the other five Genotropin patients missed from 0.6 to 4.2%. For the 8 patients in the former placebo group, no injections were missed by 3 patients, 4 patients missed from 0.6 to 5.4% of the injections, and one patient missed 13.7% of the injections. Overall, during the entire 12-month study period, 2 of 9 Genotropin patients missed no injections, and the other seven missed from 0.6 to 4.9% of the injections.

The most frequent reason given by the patient regarding missed injections was forgetting to take the injections, while the second most common reason concerned adverse events.

3. EFFICACY

3.1. CLINICAL EFFICACY VARIABLES

Body composition and bone mineral density

Table 2 below shows for each variable mean ± SD values at baseline and the mean values for the respective changes (+ and - indicates an increase and decrease, respectively during the period shown).

Table 2. **Effects on body composition during treatment**

	Baseline		months 0 - 6 double-blind period			months 7 - 12 open period		months 7 - 12 open period(¤)		months 0 - 12 total period	
	Genotropin	placebo	Genotropin	placebo	p-value between	Genotropin	p-value within	former placebo	p-value within	Genotropin	p-value within
Lean Body Mass, kg											
2-comp. Model	47.3±12.2	48.3±15.6	+0.2	-0.0	ns	+0.6	0.098	+2.2	ns	+0.6	ns
Body Fat, kg											
2-comp. Model	31.0±9.6	26.0±9.4	-1.7	+1.2	**0.046**	-1.9	**0.027**	-1.3	ns	-3.1	**0.008**
Lean/Fat ratio											
2-comp. Model	1.61±0.47	1.94±0.55	+0.04	-0.02	ns	+0.14	**0.039**	+0.48	0.055	+0.19	**0.004**

(¤) during the 6-month-long open period, the former placebo group was receiving Genotropin therapy.

Lean body mass

No significant change in lean body mass was observed in Genotropin-treated patients compared to placebo-treated patients after 6 months of treatment (months 0 to 6). Lean body mass was not significantly changed for either of the treatment groups during either of the study periods.

Body fat mass

A significant change in body fat mass was achieved in the Genotropin group compared to the placebo group (p=0.046) after 6 months of treatment (months 0 to 6), whereas no significant change was noted within either group. During the following 6-month open period, a significant decrease in body fat mass was observed for the Genotropin group (p=0.027), but not for the former placebo group. Body fat mass was significantly decreased (p=0.008) for the Genotropin group during the total 12-month study period.

Lean/fat ratio

No significant change in the lean/fat ratio was seen for the Genotropin group compared to the placebo group after 6 months of treatment, nor was there any change within either group. However, during the following 6-month open period, there was a significant increase in the lean/fat ratio for the Genotropin group (p=0.039). In addition, a trend towards a significant increase (p=0.055) in the lean/fat ratio was observed for the former placebo group during the open period. During the total 12-month period, the lean/fat ratio was significantly increased within the Genotropin group (p=0.004).

Waist, Hip Circumferences and Waist/Hip Ratio

No significant changes in waist and hip circumferences, or the waist/hip ratio, were observed when comparing the Genotropin and placebo groups after 6 months of

treatment. There were no significant changes for the placebo group for any of these three variables after 6 months of treatment. A significant decrease in waist circumference was achieved within the Genotropin group (p=0.020) during the first 6-month period, which was also present after 12 months (p=0.020), but the values measuring change within the open study period (months 7-12) were not in themselves significant. A trend towards a significant decrease (p=0.055) in the waist/hip ratio was observed for the Genotropin group during the first 6-month period. No significant decrease in hip circumference was seen for the Genotropin group for any period.

Bone mineral density

No significant change in total body bone mineral density was observed when comparing Genotropin-treated patients to placebo-treated patients after 6 months of treatment. A significant decrease was observed within the Genotropin group during the 6-month double blind period (p=0.010) and the total 12-month study period (p=0.012). No significant change occurred in total body bone mineral density for either treatment group during the 6-month open period.

Additional investigations

Hand grip strength

A statistically significant reduction in hand grip strength (p=0.0495) was noted for placebo-treated patients compared to Genotropin-treated patients after 6 months of treatment. No significant change in hand grip strength was observed within either of the treatment groups during any of the study periods.

3.2. LABORATORY EFFICACY VARIABLES

Serum IGF-I

Central Analysis

At baseline, 5 of 10 patients in the Genotropin group and 6 of 10 patients in the placebo group had a IGF-I SDS value below the normal limit (- 2).

Serum IGF-I was assessed in 10 Genotropin-treated patients and 9 placebo-treated patients after 6 months and after 12 months in 9 and 8 patients in the Genotropin group and former placebo group, respectively. Missing values are due to patient withdrawals.

A significant increase in serum IGF-I was achieved in the Genotropin treated group compared to the placebo treated group (p=0.0007) during the 6-month double-blind study period. This rise in serum IGF-I was significant also within the Genotropin group (p=0.002) after 6 months of treatment. After 6 months of treatment, serum IGF-I was within or above the age-matched reference range for all patients in the Genotropin group. For the placebo group, the same six patients who had IGF-I SDS values below -

2 at baseline still had a value lower than - 2 after placebo treatment. A significant increase in S-IGF-I was achieved within the former placebo group (p=0.008) during the following 6-month open period.

During the entire 12-month study period, serum IGF-I was significantly improved within the Genotropin group (p= 0.004).

At 12 months all patients in the Genotropin group and all patients but one in the former placebo group (no. 8) had a IGF-I SDS value within or above normal range (± 2).

Lipid metabolism - cholesterol and triglycerides

After 6 months of treatment, no significant change in cholesterol was observed for the Genotropin group compared to the placebo group. A significant decrease in total cholesterol was achieved for Genotropin treated patients (p=0.027) during the total 12-month trial period, whereas no significant change was noted within any single six-month period for either group.

Above normal-range triglycerides values were seen in one patient in the Genotropin group and 3 patients in the placebo group before treatment start. No significant changes in triglycerides were observed in Genotropin-treated patients compared to placebo-treated patients after 6 months of treatment nor were any significant changes seen for either treatment group during any study period.

3.3 EFFICACY SUMMARY

During the 6-month double-blind treatment period, a significant decrease in body fat was achieved in Genotropin-treated patients compared to placebo treated patients, but no changes in lean body mass were observed. After 6 months of treatment, serum IGF-I was significantly higher in the Genotropin group compared to the placebo group. Hand grip strength was maintained in the Genotropin group, whereas a reduction in hand grip strength was observed for the placebo-treated group. A significant decrease in waist circumference and bone mineral density was observed within the Genotropin group after 6 months of treatment.

At the end of the subsequent 6-month open period (Open label), serum IGF-I levels were significantly increased within the former placebo group. In the original Genotropin group, body fat was significantly decreased and the lean/fat ratio was significantly increased during this 6-month open-treatment study period (months 7 to 12).

4. Safety

4.1 CLINICAL SAFETY VARIABLES

Physical examination

There was no change in body weight between the Genotropin group and the placebo-treated patients after the double-blind phase, nor within either treatment groups during the following 6-month open phase, or when measured over the entire 12-month study period.

Pulse, systolic and diastolic blood pressure at rest did not change for the Genotropin group when compared to placebo group during the double-blind phase, nor within either treatment group during the following 6-month open phase, or when measured over the entire 12-month study period.

4.1.1 LABORATORY SAFETY VARIABLES

Mean values for the respective changes in blood glucose, fructosamine, serum insulin and C-peptide during the period shown are presented in Table 3.

Table 3. Change in blood glucose, fructosamine, insulin and C-peptide during treatment

	Baseline		months 0-6 double-blind period			months 0-6 open period		months 6-12 open period(¤)		months 0-12 total period	
	Genotropin	placebo	Genotropin	placebo	p-value between	Genotropin	p-value within	former placebo	p-value within	Genotropin	p-value within
Blood glucose	4.9;0.4	4.9;0.7	+0.3	-0.2	**0.026**	+0.3	**0.008**	+0.2	ns	+0.1	ns
mmol/L											
Fructosamine	218.5;25.1	228.1;24.0	+16.2	+5.0	ns	+16.2	**0.027**	-6.8	ns	+12.1	0.098
µmol/L											
Insulin	11.7;6.5	17.0;16.2	+2.7	+9.8	ns	+2.7	ns	-0.43	ns	+1.0	ns
mU/L											
C-peptide	0.48;0.20	0.51;0.24	+0.19	0.16	ns	+0.19	**0.020**	+0.06	ns	+0.06	ns
nmol/L											

(¤) during the 6-month open period (months 7-12) the former placebo group was receiving Genotropin therapy.

Laboratory assessments with values reported as abnormal and comments upon the clinical significance are shown below.

Glucose

All values recorded were within normal range. A statistically significant increase in blood glucose was noted for the Genotropin group (p=0.008) during the 6-month double-blind period. This change was, however, no significant when examined over the total 12-month trial period. The change in blood glucose for the Genotropin group was also significantly different compared to the placebo group after 6 months of

treatment (p=0.026). However, no significant increase in blood glucose was seen for the former placebo group during the subsequent 6-month open Genotropin treatment period.

Fructosamine

No statistically significant change in fructosamine was observed for the Genotropin group compared to the placebo group after 6 months of treatment. However, a significant increase in fructosamine was noted for the Genotropin group (p=0.027) during the 6-month double blind period, whereas no significant change was seen for the Genotropin group when examined over the entire 12-month trial period. The individual deviations from normal range are shown below. The deviations were judged by the investigator to be of no clinical significance.

	Pat. no.	Group	Baseline	Month 6	Month 12	Normal Range
Fructosamine,	2	Genotropin	**181**	232	204	
µmol/L	10	Genotropin	**193**	220	220	
	13	Genotropin	**184**	225	219	
	14	placebo	**199**	250	221¤	
	19	placebo	201	**177**	-	

¤ indicates a patient who received placebo treatment during the first 6 months of the study and Genotropin treatment thereafter

Insulin

No significant change in serum insulin was observed for the Genotropin group compared to the placebo group after 6 months of treatment. No significant changes were seen for either treatment group during any of the study periods.

C-peptide

No significant change in C-peptide was observed for the Genotropin group compared to the placebo group after 6 months of treatment. A significant increase in C-peptide was noted for the Genotropin group (p=0.020) during the 6-month double-blind period. However, the increase was not statistically significant over the entire 12-month trial period.

Hemoglobin

The individual deviations from normal range are were judged by the investigator to be of no clinical significance.

Leukocytes

Deviations from normal values were observed in two subjects on GH and four on placebo. All are considered of no clinical significance.

Creatinine

The individual deviations from normal range are shown below. The 12th month's value (*) in patient no. 15 was deemed clinically significant by the investigator. The other deviations were judged by the investigator to be of no clinical significance.

	Pat. no.	Group	Baseline	Month 6	Month 12	Normal Range
Creatinine,	4	Genotropin	**0.13**	**0.13**	0.12	0.05-0.12
mmol/L	15	Genotropin	0.11	0.11	**0.13***	

ASAT

The individual deviations from normal range are shown below. The deviations were judged by the investigator to be of no clinical significance.

	Pat. no.	Group	Baseline	Month 6	Month 12	Normal Range
ASAT, U/L	1	placebo	**56**	31	**48**¤	<45
	2	Genotropin	25	22	**47**	

¤ indicates a patient who received placebo treatment during the first 6 months of the study and Genotropin treatment thereafter

GGT

The individual deviations from normal range are shown below. The deviations were judged by the investigator to be of no clinical significance.

	Pat no.	Group	Baseline	Month 6	Month 12	Normal Range
GGT, U/L	2	Genotropin	28	25	**73**	<50 females
	8	placebo	**54**	**63**	46¤	<60 males
	16	placebo	32	**66**	36¤	

¤ indicates a patient who received placebo treatment during the first 6 months of the study and Genotropin treatment thereafter

4.3. ADVERSE EVENTS

A summary of the clinical adverse events by body system and number of patients with adverse events is shown below in Table 4. Events with onset during the double-blind period are listed separately from events originating during the open Genotropin period of the study.

A total of 63 clinical adverse events were reported during Genotropin treatment and 32 adverse events during placebo treatment in 18 out of 20 patients.

During the 6-month double-blind period, 23 adverse event were reported in 9 out of 10 patients in the Genotropin group. A relationship to Genotropin treatment was considered by the investigator as possible or probable and unlikely for 6 and 13 events, respectively. No judgment was received for 4 of the events.

Most frequently reported adverse events were respiratory tract infections, gastrointestinal system disorders and events related to fluid retention e.g., arthralgia and edema. These events led to a temporary dose reduction due to fluid retention in three patients.

Among the 32 adverse events reported during the placebo period for in 9 out of 10 patients, 5 of these events were considered possibly or probably related to treatment whereas the remaining 27 events were considered unlikely to be related to treatment. Most frequently reported adverse events were gastrointestinal system disorders, headache and psychiatric disorders. The events led to a temporary dose reduction and/or interruption due to mood change in one patient, injection site reaction in another patient and weight gain in the third patient.

During the subsequent 6-month study period (months 7 to 12), 27 adverse event were reported in 9 patients in the Genotropin group. A relationship to Genotropin was considered by the investigator as probable or possible and unlikely for 9 and 13 events, respectively. No judgment was received for 5 of the events.

Most frequently reported adverse events were respiratory tract infections, gastrointestinal system disorders and events related to fluid retention e.g., arthralgia, pain in the extremities and edema. Two of the events, fluid retention in one patient and pain in extremities in another patient led to a temporary dose reduction.

In the former placebo group, 13 adverse events were reported during the 6-month open study period (month 7 to 12) for 7 patients. Six of these events were considered possibly or probably related to treatment and 6 events were considered unlikely to be related to treatment. No judgment was received for one event. Most frequently reported events were events related to fluid retention. The events led to a dose reduction due to mood change in one patient and fluid retention in another patient. Treatment was discontinued in pat no. 19 because of relapsed Cushings disease.

Table 4. Reported clinical adverse events during the 12-month study period

Body system Event description Disorder	No. of pats.	Freq. (% of pats.)	No. of events	Causal relation		Double-blind period 0-6 months		Open period 6-12 months	
				unlikely	possible/ probable	placebo	Genotropin	former placebo	Genotropin
Skin and appendages	3	15	3	3		2	1		
- Skin rash				1		1			
- Pruritus				1			1		
- Sunburn				1		1			
Musculo-skeletal system	8	40	8*	5	2	2	2	1	3
- Tendinitis				1					1
- Interphalangeal pain					1		1		
- Arthralgia				1	1		1		2
- Thumb pain				1		1			
- Fracture right fibula				1		1			
- Muscular pain				1				1	
Central & peripheral nervous system	8	40	15	11	4	7	1	5	2
- Tingling, hand, fingers				1	2		1		2
- Epilepsy				1		1			
- Headache				3		3		1	
- Headaches & dizziness, worse				1		1			
- Postural dizziness				1		1			
- Voice hoarseness				1				1	
- Vocal cord paresis				1				1	
- Hyperactivity					1			1	
- Dizziness				2		1		1	
- Cramps, legs					1	1			
Vision disorders	1	5	1	1					1
- Corneal ulcer				1					1
Special senses others, disorders	1	5	1	1			1		
- Altered taste				1			1		
Psychiatric disorders	4	20	5	5		4		1	
- Forgetfulness				1		1			
- Lethargy				1		1			
- Panic attack				1				1	
- Emotional lability				1		1			
- Aggression				1		1			
Gastro-Intestinal system	10	50	13	12	1	6	3	1	3
- Gastroenteritis				1		1			
- Diarrhea				1	1	1	1		
- Abdominal pain				3		2		1	
- Constipation				1		1			
- Gingivitis				1					1
- Dyspepsia				1					1
- Vomiting				2			1		1
- Nausea				2		1	1		
Endocrine disorders	6	30	7**	2	2	1	3		3
- ADH deficiency diagnosed				1		1			
- Gynecomastia					1		1		1
- Mastalgia				1	1		1		1
- Hypoadrenalism							1		
- Hypothyroidism									1
Cardiovascular disorders	1	5	1*					1	
- Hypertension								1	

* one event not judged by the investigator

** three events not judged by the investigator

continued on following page

Table 4. Continued

Body system Event description Disorder	No. of pats.	Freq. (% of pats.)	No. of events	Causal relation		Double-blind period 0-6 months		Open period 6-12 months	
				unlikely	possible/ probable	placebo	Genotropin	former placebo	Genotropin
Respiratory system	5	25	11***	9		1	4		6
- Upper resp. tract infection				4		1	3		
- Influenza				3					3
- Shortness of breath				1					1
- Scattered crackles, lung basis									1
- Scattered rhonchi									1
- Bronchitis				1			1		
Urinary system	1	5	1	1		1			
- Urinary hesitancy				1		1			
Reproductive, female	1	5	1	1		1			
- Vaginal bleeding				1		1			
Body as a whole - General	17	85	24***	7	15	4	7	4	9
- Edema					2	1	1		1
- Weight gain					2			1	
- Fatigue				1			1		
- Fluid retention					5		2	1	2
- Chest pain				3		2	1		
- Traumatic amputation distal phalanx				1				1	
- Worsening Carpal tunnel syndrome					1		1		
- Periorbital cellulitis									
- Pain in extremities				1					1
- Sore hands				1	4	1	1		4
- Relapse Cushing's disease									1
					1			1	
Application site	3	15	3	1	2	2	1		
- Superficial bruising at inj. site					2	1	1		
- Thigh hematoma				1		1			
Resistance mechanism	1	5	1	1		1			
- Ear infection				1		1			

*** two events not judged by the investigator

4.3.1 SERIOUS ADVERSE EVENTS

Four serious adverse events were reported during the study. Furthermore, two patients, nos. 11 and 19 were so labeled according to protocol because the patients were withdrawn from the trial by the investigator due to the adverse event.

Patient no. 5 had a worsening headache which resulted in hospitalization for 3 days between the 3rd and 6th month's visits. A causal relationship with Genotropin treatment was considered to be unlikely.

Patient no. 8 experienced vaginal bleeding between the 3rd and 6th month's visits requiring a dilatation and curettage (D/C). A causal relationship with Genotropin treatment was considered to be unlikely.

Patient no. 15 was hospitalized due to periorbital cellulitis after 10 months of treatment. A causal relationship with Genotropin treatment was considered to be unlikely.

Patient no. 16 experienced an infected thigh hematoma after 5 months of treatment which resulted in hospitalization. A causal relationship with Genotropin treatment was considered to be unlikely.

normal levels for all but one patient, pointing to the need for individualization of dose for optimal treatment with respect to normalization of serum IGF-I levels.

During treatment, beneficial effects were observed in body composition, namely, reduction in the amount of body fat. No favorable changes in either lean body mass or waist circunference were seen during the placebo controlled part of the study To elucidate a possible functional implication of these body composition changes, hand grip strength was measured in this study, and a difference could be noted between patients treated with Genotropin and those treated with placebo. Thus, the Genotropin treated patients maintained their strength, while a reduction was observed during placebo treatment.

Effects on bone mineralization were also determined. The primary effect of Genotropin treatment was a prompt decrease in bone density (within six months), and this decrease was still present after one year of treatment.

With the dosages used, (target dose 0.75 mg/kg/week), reported adverse events, particularly symptoms related to fluid retention, were common but decreased with time and/or dose reduction.

6.0 CONCLUSION

This 6-month study demonstrates that body fat is decreased in subjects with adult GHD treated with GH. No changes were observed either in lean body mass or in waist circumference between the GH treated and the placebo group. Decreases in bone mineral density were observed in the GH treated group while no effects on lipids were achieved. Circulating IGF-I levels increased in the GH treated group.

Treatment with Genotropin in patients suffering from pronounced growth hormone deficiency due to pituitary/peripituitary disorders, or their treatment, appears to be safe at the doses used and for up to 12 months; reported adverse events related to fluid retention were common but decreased with time and/or dose reduction.

Section Eight

Summary and Recommendations

Summary and recommendations

The data that compose this NDA are derived from six small similarly designed double blind studies. AGHD individuals were randomized and treated either with GH (n=85) or placebo (n=87) for six months.

Individuals with AGHD form a very heterogeneous group. Some with this disorder are young and were previously treated with GH during childhood and adolescence. Others are older and became GHD as a result of pituitary tumors and the sequelae of the surgical and/or radiation therapeutic approaches. Some having had Cushing's syndrome were overweight and others had weight excess due, in part, to hypothalamic disregulations. In contrast to GHD of childhood in which males are more common than females, AGHD tend to have an even sex distribution. In addition, when these studies were performed, tests such as clonidine were used for the diagnosis of AGHD. Now, there is clear consensus that the clonidine test is not adequate because it elicits less than maximal GH secretory responses in normal older adults. All these variables, in addition to the sample size, reduce the likelihood of consistent findings across these studies.

Despite all these variables, most of the studies have shown a statistically significant treatment effect of GH when given to GH deficient adults. Moreover, when the data of all studies are pooled, a clear statistical difference favoring GH is observed ($p<.00001$) with respect to increased LBM (see statistical review). Thus, the data support the sponsor's claim that GH is effective in inducing changes in body composition, particularly in decreasing fat mass and increasing LBM. This is accompanied, in most of the studies, of a statistically significant change in waist circumference. Because adult patients with GHD are prone to cardiovascular disease, these GH induced changes may be protective for these patients.

A statistical significant association between somatotropin treatment and elevations of IGF-I, arthralgia, stiffness and pain in extremities, edema, peripheral swelling and paresthesias was also found. All other adverse events did not differ between groups and are not believed to be the result of GH treatment.

It is worth noting that IGF-I levels at the dose recommended in the label seem to be elevated in excess of 2 SD above the mean in approximately 20% or more of the patients. This sensitivity to GH therapy appears to be affected by age (older patients more prone than younger), obesity (heavier patients more affected), and sex (females less susceptible than males). Recent recommendations of the
suggest that treatment with GH for AGHD should take into consideration these variables when adjusting GH doses. These recommendations will be included in the label, in order to avoid overdosing patients.

Additionally, in most of the studies bone density was negatively affected by GH treatment at the six month mark. This trend tend to reverse in the open label studies

(12-24 more months) and information in the literature suggests that initially GH has this negative effect on bone remodeling but with time bone accretion occurs. Thus, this finding should be listed in the label.

The number of AGHD is limited and we therefore expect that a small group of sub-specialists will be prescribing GH. Hence, as with currently happens with insulin therapy individualization will be needed. The current label addresses this issue properly and we will request the manufacturer to focus on this specific point in the promotional material.

Pharmacia Upjohn has gained insights and experience with subjects with AGHD in the last seven years, and at the present time they are following more than 1500 patients with this condition worldwide. Some of these patients have been followed for more than five years. Information provided to the Agency indicates that most of the listed adverse reactions occur early after starting GH therapy, they improve or disappear with time and/or with dose reductions, and that no untoward reactions have yet occurred that could be directly linked to GH.

Glucose intolerance and diabetes, conditions more commonly seen in middle age individuals, were reported in AGHD subjects treated with GH. It seems that these subjects were heavier than the norm and most of them had evidence of glucose intolerance or insulin resistance before GH was started. It is still unknown whether the benefit of treatment with GH on this sub-population outweighs the risks of glucose intolerance, diabetes, and the potential complication that may occur. This should has been properly addressed in the label.

The small sample size of the studies reviewed and their short exposure (more patients no more than one year) limit our ability to assess long term safety in a group of patients that will be treated for years. This is particularly relevant in most of AGHD patients that become GH deficient due to a pituitary tumor. Little is known of the natural history of these tumors and less on whether GH may have any growth promoting effects that will lead to further complications requiring surgery, radiation or additional medications. The close monitoring that these subjects receive, given their previous medical history, makes physicians more alert to the potential recurrence of primary tumors.

Moreover, the long term effects of GH on other tissues such a the breast and the prostate remain unknown. Whether normalization of GH in adults that tend to decrease endogenous GH secreation with age will pose an unexpected danger remains unknown.

The information presented in this document clearly indicates that GH has a positive effect on body composition and that it tends to normalize it. Adverse reactions tend to be dose related and decrease or disappear with time. The benefit risk ratio analysis suggest that the benefit of GH treatment of GHDA outweighs the currently known risks.

Based upon the information reviewed and the recommendations of all other reviewers, I recommend the approval of this NDA if all the pending labeling issues are satisfactorily resolved.

/S/

Saul Malozowski, M.D., Ph.D.

September 22, 1997

APPEARS THIS WAY
ON ORIGINAL