CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020280/S008

MEDICAL REVIEW(S)

Group Leader's Note

Genotropin (Somatropin)
for GH deficiency in adults

NDA 20-280
Pharmacia UpJohn

October 27, 1997

This is the second NDA for the indication of growth hormone deficient adults. The major issues involved in the review of this indication are addressed by the following questions:

1. Is there plausibility for treating GH adult deficient subjects?

Abundant evidence supports that adults who had GH deficiency as children have subnormal muscular strength, exercise tolerance, and psychosocial adjustment. Less evidence is available for adults who acquired GHD in adulthood because of organic hypothalamic- pituitary disease. Only two of the pivotal studies in this NDA were designed to demonstrate functional, i.e., treadmill performance, benefit, and no effect was found in either study. Early trial -020 did show an effect with a larger dose, but the safety profile was judged unacceptable. We can presume that actual patient benefits beyond body composition effects probably occur with GH therapy, but this has not been shown demonstrated in this NDA.

2. Has the appropriate population of subject been identified?

The sponsor took a practical, but less defined approach in identifying GHD with one of several standard GH stimulation tests. This approach should not be a problem for congenital GHD, but some tests such as GHRH and arginine stimulation have a fairly high false positive rate in the general adult population. In some cases, adults with a history of hypothalamic-pituitary disease may nonetheless have intact GH secretion despite an abnormal stimulation test. Consistent use of the insulin tolerance test (ITT) would have reduced the number of false positive diagnoses, but it is a hazardous and somewhat impractical procedure for routine use. From the standpoint of overestimating efficacy in the controlled studies, the high false positive rate for some of these tests is not a problem because their effect would be to reduce efficacy.

As in the previous NDA, the sponsor appropriately avoided subjects with GH hyposecretion unassociated with organic hypothalamic-pituitary disease. It has been established that GH secretion progressively declines with age. By the seventh decade

most normal adults will fail to respond to an ITT. An even greater number will fail to respond to other tests. IGF-1 levels also decline, but the correlation with ITT response is only partial. The clinical significance of this much more widespread condition is very controversial, and there are no data to justify treating such persons with GH. It is hoped that physicians will not be confused by this indication into treating them until data are provided that would support such treatment.

3. *Is the dose regimen appropriate*?

The sponsor arrived at the single dosage used in these studies by considering the results of smaller studies. In particular, the study mentioned above clearly resulted in unacceptable adverse connective tissue reactions. Though formal long term dose response studies were not performed by the sponsor, the recommended dose appears to be about right in terms of IGF-1 responses. The recommendation for dose adjustment is somewhat imprecise but as good as available data allow.

4. *Is there a means of identifying responders and non-responders prospectively and/or during treatment?*

Any category of adult patients may require dosage reductions due to edema or connected tissue symptoms though it appears that downward adjustments are more likely for the obese and the older patients and upward adjustments in the weight normalized dosage may be more likely for women. Physicians might logically assume that they can rely on IGF-1 levels particularly to adjust dosage downward but symptoms and signs should also be taken into account as is reflected in the labeling.

5. *Is the proposed labeling as revised adequate?*

Yes, except for the lack of specification of the period of time over which the dose should be titrated upward. Since the approach that was taken in the trials was to adjust at four weeks this should be added but to be conservative a band should be given, i.e., 4-8

Conclusions and Recommendations:

The sponsor had adequately demonstrated an acceptable benefit/risk relationship for GH treatment of adults with both the adult acquired and childhood forms of GH deficiency. The final drug product labeling contains the important information necessary for

physicians to identify appropriate subjects and treat them safely and effectively, within the limits of the therapy's efficacy.

I recommend that the NDA be approved.

/S/ 10/30/97

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Alexander Fleming, M.D.

10/30/97

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Index

Section One

Introduction

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1.0 INTRODUCTION

Pharmacia & Upjohn AB (Pharmacia) is submitting this supplement to NDA 20-280 for the use of recombinant human growth hormone (rhGH) as replacement therapy in adult growth hormone deficiency (AGHD). The information provided is to support the following initiation and dosing regimen:

> ***Genotropin is indicated for long-term replacement therapy in adults with GHD of either childhood- or adult-onset etiology. GHD should be confirmed by an appropriate growth hormone stimulation test.***

> ***The dosage of Genotropin must be adjusted for the individual patient. The recommended dosage at the start of therapy is not more than 0.04 mg/kg/week. The dose may be increased according to individual patient requirements to a maximum of 0.08 mg/kg/week, depending upon patient tolerance of treatment. It may be necessary to decrease the dose for patients who are older or obese.***

Most of the information presented in this review was taken directly from the sponsor submission. The outcomes, the analysis of the data and the interpretation of these results are not. Like other hormone deficiency states, growth hormone (GH) deficiency in adulthood is now recognized as a clinical entity. Hypopituitary patients who receive conventional triple-hormone replacement therapy with corticosteroids, thyroxine and sex hormones, and who are severely deficient in GH, have several characteristic features, such as increased abdominal fat mass, decreased lean body mass and dehydration. Similar patients, who also receive replacement therapy with GH, benefit from decrease in fat mass, increase in lean body mass, increase in total body water. These changes, which are the most apparent ones occurring early during treatment, reflect the lipolytic, anabolic and antinatriuretic actions of GH. Emerging information in the medical literature suggests that by continuing GH treatment the overall effect of body composition is maintained. Improvements in cardiac function and bone mass have also been reported comparing baseline values to GH exposure after 12 months, but these studies were not properly controlled.

To date, data are available from 51 clinical trials which have been conducted by Pharmacia in 1145 patients diagnosed with AGHD. In Pharmacia trials, 573 patients were randomized to receive Genotropin, and 572 were randomized to receive placebo. The Phase III trials were designed with an initial double-blind, placebo-controlled treatment period followed by an open-label extension treatment period in which all patients received Genotropin. The planned duration of study drug treatment ranged up to 18 months.

Based on the sponsor's evaluation of all the clinical trials sponsored by Pharmacia including a GCP inspection and identification of endpoints of special interest to FDA, six trials have been designated as primary placebo-controlled clinical trials. The sponsor considers all six trials to be scientifically sound and demonstrate the efficacy of Genotropin treatment in patients with AGHD.

Although some of these trials include endpoints which evaluate functional improvement, it is important to note that, **aside from body composition, none of the functional endpoints is statistically significant at the end of 6-month, double-blind treatment**. An early trial performed by Sönksen (TRN 87-077/89-020) at a higher dose (the dose usually selected for treatment of pediatric growth hormone deficiency) demonstrated an improvement in body composition along with improvement in functional measures at the end of 6-month, double-blind treatment. The results of this trial were first published in the New England Journal of Medicine in 1989. A statistically significant and clinically important improvement was observed for the Genotropin-treated patients compared to the placebo patients for many parameters including the following:

- lean body mass
- fat mass
- total body water
- maximal exercise performance
- muscle strength
- stroke volume
- left ventricular end diastolic dimension

Laboratory changes included

- total cholesterol
- LDL-cholesterol
- LDL:HDL-cholesterol ratio

Although efficacy was demonstrated in this trial, **the side effect profile suggested that future trials be conducted at a lower dosage regimen**. This information was used to select the dosage regimen for the Pharmacia Phase III trials, however, the results of this study are not part of the six pivotal studies.

The cutoff date for completed trials and trials for clinical trial efficacy data is June 30, 1995 and the cutoff date for the literature is August 31, 1995.

The data provided in this submission demonstrate the benefits of GH replacement therapy in adults with GH deficiency. This concept is consistent with the success of hormone replacement therapy in patients with other hormone deficiencies, such as thyroid hormone.

2.0 CLINICAL PROGRAM OVERVIEW

The extent of the clinical trial program necessitated grouping the studies into different categories:

- Completed Primary Trials,
- Other Completed Trials,
- Trials with Final Data File, and
- Ongoing Trials with 12-Month Data.

The above groups of trials include data from 1145 patients. Moreover, an additional 1886 patients are participating in other ongoing trials. This total of 3031 patients does not include the patient exposure from ongoing investigator-sponsored trials and the compassionate use program.

A completed trial is defined as a trial for which there is a Pharmacia-approved trial report. Ongoing trials include studies which meet the following criteria: the data file is final (clean file), the efficacy data have not been analyzed by Pharmacia and the efficacy data are not reported in the literature.

2.1 Prototype Clinical Trial Design

Most of the trials had the same study design. Patients were randomized to receive either Genotropin or placebo during a 6-month, double-blind study period. This period was followed by an open-label period of varying length in which all the patients received Genotropin. Trials were prospectively designed to have the study medication code broken after all patients had completed the 12-month core protocol. However, in some trials, the code was broken after all the patients had completed the 6-month, double-blind period. In several studies the patients continued their treatment in open-label extension after this period. Figure 1 depicts the design of these studies.

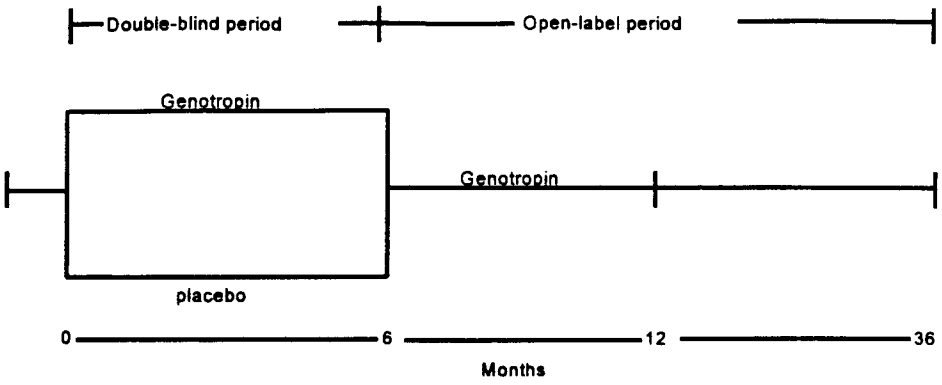

Figure 1. Prototype trial design with a 12-month core protocol.

In most of the trials, a starting dose of 0.0375 mg/kg/week for four weeks was used, after which the dose was increased to 0.75 mg/kg/week. This dose regimen was repeated for all patients after the double-blind placebo-controlled study period. The Genotropin dose administered could be individualized due to side effects. In addition, studies were performed to document pharmacological effects, pharmacokinetics and bioavailability of Genotropin in GH-deficient adult patients, and also to document the relationship between different doses and circulating levels of insulin-like growth factor I (IGF-I) and one of its binding proteins, IGF-BP3.

Each primary trial consisted of a parallel, randomized, 6-month, double-blind placebo-controlled treatment period followed by a 6-month, open-label Genotropin treatment period. Trials TRN 91-001/CTN 92-8124-016, TRN 91-081-01/CTN 92-8124-015, and TRN 91-081-02/CTN 93-8124-019 also included an additional open-label Genotropin treatment period of 12 months for the growth hormone treatment group and 18 months for the former placebo treatment group, to provide a total of 24 months of Genotropin treatment for each group. The efficacy review will be centered on the double blind section and the safety review will include all data available.

2.2 Phase III Protocol Admission Criteria

The protocol admission criteria for the phase III trials were as follows:

Inclusion Criteria

- GH deficiency (isolated or as part of hypopituitarism) likely to have existed for at least 24 months prior to inclusion.
- Stimulated maximum peak GH response less than 5 µg/L. Acceptable stimulation tests were arginine, glucagon, clonidine and insulin-induced hypoglycemia. Tests performed within five years prior to inclusion and after 20 years of age were accepted.
- Age
- Patients with multiple pituitary hormone deficiency on stable replacement therapy for at least 6 months.
- Informed consent obtained.

Exclusion Criteria

- Treatment with growth hormone during the last 12 months.
- Acute severe illness during the last 6 months.
- Pregnancy (to be excluded with test).
- Chronic severe liver disease (gamma-GT and/or ASAT (SGOT) and/or ALAT (SGPT) twice the upper limit of the normal range laboratory value.
- Chronic severe renal disease (S-creatinine higher than 120 micromoles/L or repeated positive test for hematuria or proteinuria).
- Supine blood pressure higher than 160 mm Hg systolic or higher than 100 mm Hg diastolic.
- Diabetes mellitus (Type I or II).
- History of malignancy (patients treated for cranial tumors or leukemia causing GH deficiency were accepted).

- Chronic medication, except pituitary replacement therapy, bromocriptine, contraceptives, and treatment of mild hypertension and mild asthma.

- Suspected non-cooperativeness.

- Known/suspected hypersensitivity to m-cresol.

2.3 Completed and Ongoing Trial Classification

In this summary, the efficacy results from growth hormone-deficient hypopituitary patients treated with Genotropin were derived from the clinical investigations listed in Table 1 and the literature.

Table 1. Trial classification

	Total		Studies with reports		Studies reported with ongoing extensions		Ongoing studies	
Type of trials	Number of Trials	Centers	Number of Trials	Centers	Number of Trials	Centers	Number of Trials	Centers
Multicenter	9	55	7	43	0	0	2	12
Multiple Independent	14	125	12	118	8	12	10	19
Single Center	28	28	14	14	0	0	14	14
Total	51	208	33	175	8	12	26	45

The six completed primary trials are listed in Table 2.

Table 2. Completed primary trials

Protocol/Report	Principal investigator/ Country	Number of patients enrolled	Double-blind (N)		All Genotropin (N)
			Genotropin	Placebo	
TRN 91-081-01/ CTN 92-8124-015 95 10 756	Rosen Sweden	25	12	13	25
TRN 91-081-02/ CTN 93-8124-019 95 10 679	Bramnert Sweden	23	12	11	23
TRN 91-001/ CTN 92-8124-016 95 10 410	Thoren Sweden	20	10	10	20
TRN 91-131-04 93 96 415	Monson/ Shalet UK	32	14	18	30
TRN 91-131-08 95 10 680	Monson/ Besser/Ross UK	52	27	25	52
CTN 92-8124-011 93 96 416	Holdaway New Zealand	20	10	10	19

3.0 TABLE OF ALL STUDIES AND DESIGN OF STUDIES

The abbreviations for the Table of All Studies are listed in Table 3.

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Table 3. Table of all studies: Abbreviations

Section	Abbreviation
General	NA = Not available NAP= Not applicable
Type of Study and Control(s)	PD = Pharmacodynamic PC = Placebo Control
Study Design	DB = Double blind OL = Open label OE = Open-label extension R = Randomized PG = Parallel Group CO = Crossover NV = Normal volunteer control group
Duration of Dosing	W = Week(s) M = Month(s)

4.0 POPULATION DESCRIPTION

4.1 Demographic Characteristics

Demographic characteristics at baseline for the primary trials and all trials are presented in Table 4.

Table 4. Demographic characteristics for the primary trials and all trials

	Primary trials				All trials			
	Genotropin N=85		Placebo N=87		Genotropin N=573		Placebo N=572	
Characteristic	n	%	n	%	n	%	n	%
Sex								
Male	44	51.8	57	65.5	321	56.0	310	54.2
Female	41	48.2	30	34.5	252	44.0	262	45.8
Age (years)								
Mean±SD	42.4±10.6		41.4±10.9		40.5±11.9		39.7±12.4	
Range								
Weight (kg)								
Mean±SD	79.8±19.2		77.8±16.8		78.0±20.0		76.4±18.1	
Range								
Height (cm)								
Mean±SD	168±11		169±9		167±11		167±11	
Range								
Body Mass Index (BMI)								
Mean±SD	28.2±6.2		27.2±4.6		27.8±5.8		27.4±5.3	
Range								

Table 4. Demographic characteristics for the primary trials and all trials

Characteristic	Primary trials				All trials			
	Genotropin N=85		Placebo N=87		Genotropin N=573		Placebo N=572	
	n	%	n	%	n	%	n	%
Ethnic origin								
Caucasian	83	97.6	85	97.7	514	89.7	512	89.5
Black	0	0.0	0	0.0	3	0.5	2	0.3
Oriental	0	0.0	0	0.0	4	0.7	3	0.5
Other	2	2.4	2	2.3	3	0.5	4	0.7
Not asked for/not available	0	0.0	0	0.0	49	8.6	51	8.9

a) Includes primary trials.

The demographic characteristics at randomization for patients receiving Genotropin or placebo were similar for the primary trials and all trials. Patients were on the average approximately 40 years of age and the overwhelming majority were Caucasian. There were slightly more males than females in the trials.

The etiology of growth hormone deficiency for patients in the primary trials and all trials is presented in Table 5.

Table 5. Etiology of growth hormone deficiency for patients in the primary trials and all trials

	Primary trials				All trials[a]			
	Genotropin N=85		Placebo N=87		Genotropin N=573		Placebo N=572	
Etiology	n	%	n	%	n	%	n	%
Pituitary tumor	54	63.5	51	58.6	299	52.2	277	48.4
Craniopharyngiomas	12	14.1	15	17.2	69	12.0	84	14.7
Idiopathic causes	4	4.7	9	10.3	66	11.5	77	13.5
Trauma	2	2.4	1	1.1	11	1.9	11	1.9
Other causes	13	15.3	11	12.6	108	18.8	104	18.1
Information not available	0	0.0	0	0.0	20	3.5	19	3.3

a) Includes primary trials.

In both the primary trials and all trials, the etiology of the patients' growth hormone deficiency was most often pituitary tumor followed by craniopharyngioma.

4.2 Diagnostic Criteria - International Consensus Conference October 1994

Previously, the diagnosis of AGHD had been readily established based upon peak growth hormone response to provocative stimuli. Diagnosis of this condition was based upon demonstration of an abnormally low plasma level of growth hormone in the presence of associated clinical signs and symptoms.

AGHD was defined has having:

- Known hypothalamic-pituitary disease
- ITT peak GH response < 3 µg/L

In both the primary trials and all trials, the most frequently used stimulation test was the insulin tolerance test.

The stimulation test results are displayed in Table 6.

Table 6. Stimulation test results

	Primary trials				All trials[a]			
	Genotropin N=85		Placebo N=87		Genotropin N=573		Placebo N=572	
Stimulation test result	n	%	n	%	n	%	n	%
GH peak <3 μg/L	74	87.1	82	94.3	525	91.6	526	92.0
GH peak ≥3, <5 μg/L	11	12.9	5	5.7	42	7.3	37	6.5
GH peak ≥5, <8 μg/L	0	0.0	0	0.0	2	0.3	6	1.0
GH peak ≥8 μg/L	0	0.0	0	0.0	1	0.2	2	0.3
Results not available	0	0.0	0	0.0	3	0.5	1	0.2

a) Includes primary trials.

Ninety-two percent of 1145 patients in all trials and 91% of 172 patients in the primary trials had a maximum growth hormone concentration less than 3 μg/L. Thus, a vast majority who participated in the trials fulfilled the diagnostic criteria of profound growth hormone deficiency.

Adult onset is defined as onset of growth hormone deficiency in patients who were greater than 17 years of age.

Baseline characteristics of growth hormone deficiency for the primary trials and all trials are presented in Table 7.

Table 7. Baseline characteristics of growth hormone deficiency for primary trials and all trials

Characteristic	Primary trials				All trials[a]			
	Genotropin N=85		Placebo N=87		Genotropin N=573		Placebo N=572	
	n	%	n	%	n	%	n	%
Isolated GH deficiency/ Multiple hormone deficiency								
Isolated GH deficiency	13	15.3	14	16.1	74	12.9	77	13.5
Multiple pituitary hormone deficiency	72	84.7	73	83.9	493	86.0	486	85.0
Information not available	0	0.0	0	0.0	6	1.0	9	1.6
Adult/Childhood onset of GH deficiency								
Adult onset (>17 years of age)	73	85.9	73	83.9	447	78.0	429	75.0
Childhood onset (≤17 years of age)	12	14.1	14	16.1	102	17.8	119	20.2
Information not available	0	0.0	0	0.0	24	4.2	24	4.2

a) Includes primary trials.

A majority of the patients had multiple pituitary hormone deficiency, and a majority had acquired their deficiency during adult life.

The etiology by onset of growth hormone deficiency for the primary trials is provided in Table 8.

Table 8. Etiology by onset of growth hormone deficiency for the primary trials

	Isolated GH deficiency				Multiple pituitary hormone deficiency			
	Adult onset N=21		Childhood onset N=6		Adult onset N=125		Childhood onset N=20	
Etiology	n	%	n	%	n	%	n	%
Pituitary Tumor	14	66.7	0	0.0	90	72.0	1	5.0
Craniopharyngioma	1	4.8	0	0.0	16	12.8	10	50.0
Idiopathic causes	0	0.0	4	66.7	3	2.4	6	30.0
Trauma	0	0.0	0	0.0	2	1.6	1	5.0
Other causes	6	28.6	2	33.3	14	11.2	2	10.0
Not available	0	0.0	0	0.0	0	0.0	0	0.0

As displayed in Table 8, the most common etiology of both multiple pituitary hormone deficiency and isolated growth hormone deficiency for adult onset patients in the primary trials was pituitary tumor.

As in the primary trials, most patients in all trials had multiple pituitary hormone deficiency, usually of adult onset. The most common etiology of both multiple pituitary hormone deficiency and isolated growth hormone deficiency for adult onset patients in all trials was pituitary tumor.

A majority of the patients had a deficiency of pituitary hormones in addition to growth hormone as displayed in Table 9.

Table 9. Deficiency of other pituitary hormones in addition to growth hormone for primary trials and all trials

	Primary trials				All trials[a]			
	Genotropin N=85		Placebo N=87		Genotropin N=573		Placebo N=572	
Deficiency	n	%	n	%	n	%	n	%
TSH	62	72.9	57	65.5	399	69.6	395	69.1
ACTH	59	69.4	59	67.8	394	68.8	376	65.7
Gonadotropin	68	80.0	68	78.2	437	76.3	437	76.4
ADH	17	20.0	17	19.5	125	21.8	133	23.3

a) Includes primary trials.

In both the primary trials and all trials, gonadotropin deficiency was the most common pituitary deficiency other than growth hormone. However, TSH and ACTH deficiency also occurred frequently.

4.3 Patient Disposition

The patient disposition in the primary trials and all trials for 0-6 months is presented in Table 10.

Table 10. Patient disposition in the primary trials and all trials

Trial Classification	Enrolled	Double-blind		Complete		Withdrawn	
		Genotropin	Placebo	Genotropin	Placebo	Genotropin	Placebo
Primary trials	172	85	87	78	84	7	3
All trials[a]	1145	573	572	516	537	57	35

a) Includes primary trials.

Of the 172 patients enrolled in the primary trials, 78 patients have completed the double-blind Genotropin treatment study period, 84 patients have completed the double-blind placebo treatment study period, and 10 patients were prematurely

terminated. Of the 1145 patients enrolled in all of the trials, 516 patients have completed the double-blind Genotropin treatment study period and 537 patients have completed the double-blind placebo treatment study period. Of the 1145 patients enrolled in all of the trials, 952 patients have completed the 6-12 month study period, 106 patients have completed the 12-18 month study period, and 192 patients have completed the 12- to 24-month study period.

5.0 METHODS

The data from all of the clinical trials and the literature were reviewed and evaluated. This section summarizes the evaluation of the methods used to measure the efficacy endpoints, a description of the databases which identify the location of information on specific topics and the actual results. Studies were performed at baseline and at fixed intervals. These intervals are described in detail in each study.

5.1 Endpoints

The endpoints evaluated in the clinical trials include both the signs and symptoms of AGHD.

The trials were designed to evaluate the signs of AGHD which include the following:

- Abnormal body composition
  - Increased fat mass,
  - Decreased lean body mass, and
  - Decreased total body water;
- Reduced muscle strength;
- Reduced exercise capacity;
- Decreased bone mass (osteopenia); and
- Increased cardiovascular risk factors (lipid metabolism).

The clinical program was not designed to collect the data to identify whether or not there was a clinically important functional improvement along with normalization of body composition and improvement in symptoms.

The parameters of interest and the endpoint variables for the completed trials that have been abstracted are listed in Table 11.

Table 11. Summary of endpoints abstracted

Parameter	Endpoint
Body composition	Fat mass Lean body mass Total lean body mass Trunk lean mass Trunk fat Lean/fat ratio Total body water
Functional measurements/Muscle strength	Muscle Strength: Quadriceps Isometric Muscle Force: Hip flexion Isometric Muscle Force: Hip extension Muscle function: Leg (quadriceps) Isometric muscle strength: Quadriceps Muscle strength: Hip abduction
Exercise capacity	Exercise performance Exercise performance, maximal Exercise performance, submaximal Work capacity Exercise capacity Exercise tolerance Maximum work load Heart rate
Pulmonary function	Ventilation volume Oxygen consumption Maximum oxygen uptake
Cardiovascular function	Left ventricular wall thickness Left ventricular wall mass Left ventricular mass (LVM) Left ventricular myocardial mass Ventricular mass Posterior wall thickness (PWTs) Stroke volume Cardiac output

5.2 Clinical Measurement

The methods used clinically to measure body composition, muscle function, exercise capacity, and cardiovascular function are summarized and described in the text and tables.

5.3 Data Organization

The study design and dosing information was collected for each trial.

A list of parameters generated from review of the reports and the publications was divided into primary and secondary parameters. All of the reports and publications were coded for information on the primary and secondary parameters. For the primary parameters, all the data for each time point were abstracted for presentation in this summary. The data for the secondary parameters were reviewed. The sponsor defined the clinically beneficial direction of change associated with each parameter.

For each parameter, in addition to the units and the method of measurement, the summary statistics (number of patients, mean, median, standard error, standard deviation, minimum and maximum) were collected for the baseline and each time point (duration of growth hormone treatment) and change from baseline for each treatment group. The results of the statistical analyses were abstracted for between and within treatment group comparisons. This included the statistical test used to evaluate treatment differences, the p-value, the direction of change from baseline, and the group favored for the between treatment analysis. Clinical improvement, as assessed by the investigator, also was abstracted.

6.0 BODY COMPOSITION

6.1 Measurements of Body Composition

Many procedures have been developed over the years for the determination of body composition (BC). Most of these have involved the determination of a known relatively constant parameter of a body compartment. The remaining parameters are then extrapolated from assumed relationships where objective measurement is not possible. Thus, these methods have a high degree of subjectivity. The procedures used in the six primary clinical trials evaluating the effects of growth hormone (GH) are shown in Table 12.

Table 12. Body composition: Methods of measurement

Methods	Study
Dual x-ray absorptiometry (DEXA)	TRN 91-001/CTN 92-8124-016, TRN 91-081-02/CTN 93-8124-019, TRN 91-131-04, TRN 91-131-08, CTN 92-8124-011
Two-compartment model with bioelectrical impedance analysis (BIA)	TRN 91-001/CTN 92-8124-016, TRN 91-081-01/CTN 92-8124-015, TRN 91-081-02/CTN 93-8124-019
Four-compartment model	TRN 91-081-01/CTN 92-8124-015, TRN 91-081-02/CTN 93-8124-019
Two-compartment potassium	TRN 91-081-02/CTN 93-8124-019

These techniques are compared in outline form in Table 13.

Table 13. Body composition: Comparison of methods of measurement

Methods	Validity
DEXA	Proven procedure for bone density.
CT	Well accepted and recognized method.
Two-compartment (BIA) and four-compartment models	Generally recognized and accepted. Objective measure of one component (in two-compartment model) and two components (in four-compartment model). Well accepted extrapolations.

6.1.1 DEXA

Transmission of energy through body tissues varies with the composition and density of each component. In this method, the energy is x-radiation produced by two monoenergic sources. The difference in transmission of energy then is used to calculate the composition. The original use of this technique was for the measurement of bone density of both peripheral and spinal locations. This is then adapted for either whole body, trunk, and/or peripheral limb measurement of other body components.

6.1.2 BIA

The Bioelectrical Impedance Analysis (BIA) method relies on the difference in electrical conductivity of fat-free mass in lean body mass and fat mass. In general, body fluids are responsible for electrical conduction and the cell membranes determine capacitance. The impedance can be divided into its geometrical components: resistance and reactance. In BIA, the resistance and reactance are measured by tetrapolar devices, which are now portable. BIA is used to calculate lean body mass and, thus, body fat and total body water in the two-compartment model on the basis of regression equations using anthropometric and BIA variables.

6.1.3 Computerized Tomography (CT)

Transmission of energy from x-radiation delineates specific body components in this technique. It is generally used in the thigh where areas of specific components can be delineated and compared to the total area surveyed.

6.1.4 Two-Compartment Model

In this technique the body fat (BF) and lean body mass (LBM) are calculated from the determination of the total body water (TBW) or the total body potassium (TBK). This assumes that the composition of the LBM remains constant and if potassium (K) is used for the calculation it assumes that intracellular K also remains constant. Total body water (TBW) is measured by bioelectric impedance (BIA) where a small electric current is passed through the body and a difference in transmission of current is seen between BF and LBM. TBW can also be determined from the measurement of K by whole body counting of the gamma radiation of naturally present K-40.

6.1.5 Four-Compartment Model

This technique involves the simultaneous measurement of TBW, TBK, and body weight (BW); from these the fat free extracellular solids (FFECS), the body cell mass (BCM), extracellular water (ECW), and BF are calculated as follows:

- BCM (kg) = $8.33 \times 10^{-3} \times$ TBK(mmol)
- Intracellular water (ICW)(kg) = 0.75 x BCM(kg)
- ECW (kg) = TBW(kg) - ICW(kg)
- FFECS (kg) = 0.12 BW_{norm}
- BF (kg) = BW - (BCM + ECW + FFECS)

Fat-free mass (or lean body mass) is the sum of BCM, ECW and FFECS.

BCM is calculated from K assuming constant intracellular K, a K to total body nitrogen (TBN) ratio of 3 mmol/g, and a protein content of 25%. TBW is calculated by the tritiated water method. TBN is determined from whole body counting of the gamma radiation produced by the decay of N^{14} to N^{15}.

6.1.6 Other Methods of Measurement

A number of additional techniques were also used. These techniques include skinfold thickness measurement, echography, microfat biopsies of the abdominal wall, dual-photon absorptiometry (DPA), infrared interactance, body fat computer, and underwater weighing. These techniques can be briefly summarized as follows:

• Skinfold Thickness	Pinched skinfolds measured with calipers and converted to percent body fat from body weight and height measurement. Means can be calculated from multiple sites.
• Echography	Measurement based on reflected energy from an x-ray source varying in intensity through differing tissues.
• Microfat Biopsies of Abdominal Wall	The number and morphology of fat cells evaluated with biopsies of abdominal wall and mid-thigh fat layers.
• Dual-Photon Absorptiometry (DPA)	Similar to DEXA but with a radioactive isotope energy source, usually gadolinium.
• Infrared Interactance	Spectrometric analysis of reflected waves obtained by infrared emission of 700-1100 nm wave length. Analyzed with a body fat computer.
• Underwater Weighing	Calculation of estimation of percent body fat based upon water displacement by submerging whole body in a tank.

7.0 MUSCLE STRENGTH

7.1 Measurements of Muscle Strength

The methods used in the six primary clinical trials to evaluate the effects of GH on skeletal muscle strength are shown in Table 14.

Table 14. Muscle strength: Methods of measurement

Methods	Study
Leg dynamometer (Quadriceps muscle strength)	TRN 91-131-08
Concentric extension/flexion (30 °/s, 60 °/s, 120 °/s, 180 °/s; right/left leg) Eccentric extension/flexion (30 °/s; right/left leg)	TRN 91-001/CTN 92-8124-016
Hand dynamometer	CTN 92-8124-011
Pulmonary function test Maximum expiratory pressure Maximum inspiratory pressure	TRN 91-081-01/CTN 92-8124-015

Electrodynamometers were also used in trials to measure peak voluntary isometric muscle force during neck flexion, elbow extension, hip flexion, hip extension, and elbow flexion. Maximum voluntary isometric strength of the quadriceps muscle also was measured using a strength testing chair with an additional percutaneous twitch superimposition technique used to test for maximal activation. Quadriceps muscle strength is considered to be the most reliable measurement.

8.0 EXERCISE CAPACITY

8.1 Measurements of Exercise Capacity

The methods used in the two of the six primary clinical trials to evaluate the effects of GH on exercise capacity are shown in Table 15.

Table 15. Exercise capacity: Methods of measurement

Methods	Study
Bicycle test Maximum work load Systolic blood pressure Maximum heart rate Oxygen consumption	TRN 91-001/CTN 92-8124-016
Treadmill test/Respiratory measurements Time on treadmill Maximum heart rate Maximum oxygen uptake Expiratory volume	TRN 91-131-08

9.0 CARDIOVASCULAR FUNCTION

9.1 Measurements of Cardiovascular Function

The methods used in the one of the six primary clinical trials to evaluate the effects of GH on cardiovascular function are shown in Table 16.

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Table 16. Cardiovascular function: Methods of measurement

Methods	Study
Echocardiography (left ventricular) End-systolic diameter End-diastolic diameter Posterior wall thickness Wall stress Stroke volume Cardiac output Left ventricular mass	TRN 91-081-02/CTN 93-8124-019
Sphygmomanometer Systolic blood pressure Diastolic blood pressure Systemic resistance	TRN 91-081-02/CTN 93-8124-019
Diamove Dynamic properties of aorta/carotid artery Maximum diameter Minimum diameter Mean diameter Strain Pressure - strain elastic modulus Stiffness	TRN 91-081-02/CTN 93-8124-019

Ventricular output and other aspects of cardiac function can be evaluated by echocardiography, a noninvasive technique that does not involve injections or insertion of a catheter. In echocardiography, pulses of ultrasonic waves, commonly at a frequency of 2.25 MHz, are emitted from a transducer that also functions as a receiver to detect waves reflected back from various parts of the heart. Reflections occur wherever acoustic impedance changes, and a recording of the echoes displayed against time on an oscilloscope provides a record of the movements of the ventricular wall, septum, and valves during the cardiac cycle. Vascular function, as assessed by blood pressure and arterial parameter measurements, provides additional ancillary information.

10.0 IGF-I

Serum IGF-I levels have been shown to be low in patients with hypopituitarism and a rapid increase in circulating IGF-I levels after treatment with GH has been observed in patients with GH deficiency. Also, in acromegaly, which is accompanied by elevated IGF-I levels, IGF-I levels fall with successful treatment of the GH hypersecretion.

Serum levels of IGF-I reflect spontaneous GH secretion in normal healthy individuals, and growth hormone deficiency, correspondingly, would generally be accompanied by low IGF-I levels. For adult hypopituitary patients with growth hormone deficiency, IGF-I levels are found to be low or subnormal but with a considerable overlap between levels in those with and without growth hormone deficiency. Among the 997 patients with available data on IGF-I, 568 patients (57%) had IGF-I levels lower than -2.0 standard deviation scores (SDS). The data are consistent with those reported in the literature, although different studies have obtained different percentages of low IGF-I levels.

10.1 Methods

Since IGF-I levels are age-dependent, a SDS has been calculated according to the formula IGF-I SDS = (elog Y_{obs} - elog Y_{pred})/SE, where Y_{obs} is the observed value, Y_{pred} = 5.95 - 0.0197 x age, and SE = 0.282. The normal limits for IGF-I SDS are defined as being between -2.0 and 2.0. Due to the fact that serum IGF-I was analyzed locally at the Karolinska Hospital using the hospital's own standards, IGF-I SDS calculations for Trial TRN 91-001 have been performed according to the formula IGF-I SDS = ^{10}log Y_{obs} - 2.555 + 0.00625*age)/0.104. For each defined study interval, SDS values were calculated for the mean±SD, the median, the 25th and 75th percentile levels, and the maximum and minimum values.

11.0 Subpopulation: Body Composition By Sex

The data were evaluated for body composition by sex in trial CTN 92-8124-007.

There were statistically significant differences between genders at baseline for most body composition variables, as expected, with females having higher fat mass, lower waist/hip ratio, and lower fat-free mass than males. The gender difference was generally maintained following Genotropin treatment. Females treated with Genotropin had a statistically significant (p=0.03) lower mean fat-free mass (determined by BIA) than males treated with Genotropin at 6 months, whereas mean fat-free mass of placebo-treated patients did not differ significantly between genders. This trend was maintained at 12 months (p=0.08). In addition, there was a statistically significant treatment x gender effect (p=0.024) on total body water (determined by deuterium oxide dilution), with males having a greater response to Genotropin treatment than females at 6 months, but not at 12 months. These effects of Genotropin treatment were not attributable to differences in baseline. However, for most variables males and females responded similarly to treatment (i.e. no statistically significant treatment x gender effect).

12.0 RATIONALE FOR DOSE SELECTION

The initial dose-finding trial in profound AGHD was conducted with the usual dosage regimen prescribed for pediatric patients with GH deficiency. Although within 6 months of treatment compared to placebo there was a statistically significant and clinically important improvement in body composition, exercise capacity, muscle strength, and cardiovascular function, the side effect profile necessitated decreasing the dose for the adult population. The side effects were the result of an adaptation from dehydration to normality. As noted in subsequent trials at lower doses, most of the side effects occur early during treatment. Thus, it is advisable to allow ample time for this adaptation to occur, and the dose must be titrated depending upon the patient's response.

Replacement therapy with GH aims to normalize circulating levels of growth hormone and its mediator, IGF-I. In patients with subnormal IGF-I levels before GH replacement therapy, IGF-I levels adjusted for sex and age may be used to guide dosing as well as to monitor treatment and side effects. In patients with IGF-I levels within the normal range before treatment starts, monitoring of IGF-I levels is useful to avoid super physiological levels of IGF-I.

Therefore, dose selection must be individualized for each patient based on signs, symptoms and maintenance of serum IGF levels within the normal range for age and sex.

Section Two

Study 91-081-01

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STUDY 91-081-01

The present review covers the data on the 6-month double-blind placebo-controlled study (TRN: 91-081-01) followed by 6 months of open somatotropin treatment. This study continued long-term (CTN 92-8124-015) where the patients receiving somatotropin for 12 months in the initial study were to receive somatotropin for an additional 24 months. The results presented, however, will center on the placebo-controlled study only (first six months).

1. OBJECTIVES

The primary objective of the initial study was:

To determine the effect of somatotropin replacement therapy on body composition in GH-deficient adults, as compared to a placebo-treated control group.

The secondary objectives of the initial study were:

To determine whether somatotropin treatment therapy improves Quality of Life (this will not be reviewed because the sponsor has withdrawn this claim) and to determine the safety of somatotropin replacement therapy, as compared to a placebo-treated control group.

To evaluate the effect of somatotropin replacement therapy on bone mineral density, respiratory muscle strength, serum lipids, and serum IGF-I, as compared to a placebo-treated control group.

2. PATIENTS, MATERIALS AND METHODS

2.1 Study design

The first six months of the initial study used a randomized, double-blind design with somatotropin treatment versus placebo. During the following six months both groups received somatotropin treatment.

2.2 Efficacy assessments

The primary efficacy variable was the changes in lean body mass, based on both the BIA and DEXA methods, after six months of treatment. The following assessments were made:

- total body water based on the BIA and DEXA methods;

- trunk lean mass based on the DEXA method;
- body fat based on both the BIA and DEXA methods;
- the lean/fat ratio based on both the BIA and DEXA methods;

2.3 Safety assessments

2.3.1 CLINICAL SAFETY ASSESSMENTS

Clinical safety examination consisted of physical examinations.

Complete physical examination

Height (standing)
Weight (with clothes but without shoes)
Supine blood pressure (after five minutes rest)
Supine pulse rate (after five minutes rest)
Head, ears, nose and throat
Eyes
Lymph glands
Thyroid gland
Heart
Lungs
Abdomen
Neurological
Muscles
Bones

Limited physical examination

Height (standing)
Weight (with clothes but without shoes)
Supine blood pressure (after five minutes rest)
Supine pulse rate (after five minutes rest)

2.3.4. LABORATORY SAFETY ASSESSMENTS

The following laboratory measurements were performed to document safety:
B-Hemoglobin, g/L
B-Leukocytes, $x10^9$/L
B-Thrombocytes, $x10^9$/L (except 15, 21 months visits)

B-Glucose (fasting), mmol/L
B-Insulin (fasting), mIU/L (except 15, 21 months visits)

B-HbA1c, %
S-Creatinine, µmol/L

S-Sodium, mmol/L
S-ALAT, µkat/L (except 15, 21 months visit)
S-Free T4, pmol/L
S-Testosterone, nmol/L (except 15, 21 months visits)

S-SHBG, nmol/L (not in continuation study)
S-Estradiol, nmol/L (except 15, 21 months visits)
U-Erythrocytes (test-strip)
U-Protein (test-strip)
U-Glucose (test-strip)

3. RESULTS

3.1 Protocol deviations

The study code was broken when all patient data from the first 6-month double-blind period were entered into the data base and not after 12 months, as stated in the protocol.

3.2 Study population

3.2.1. NUMBER OF PATIENTS

In order to have 20 assessable patients, a total of 25 patients with growth hormone deficiency were included. Twelve patients were randomly assigned to the somatotropin group and 13 patients assigned to the placebo group. All included patients completed the initial study and continued in the long-term study for 24 months receiving GH. No withdrawals occurred.

3.2.2 PATIENT CHARACTERISTICS

Patient characteristics at baseline are shown in Table 1 below. There were differences between the treatment groups in height (somatotropin group; 167 cm, and placebo group; 175 cm) and sex distribution (somatotropin group; 5 males and 7 females and placebo group; 11 males and 2 females).

In all patients the GH-deficiency was acquired in adulthood. Pituitary tumor was the most common cause for the GH-deficiency (10 of 12 patients in the somatotropin group and 9 of 13 patients in the placebo group). All patients also suffered from other hormone deficiencies in addition to GH-deficiency.

Table 1. Patient characteristics at baseline (Mean, SD, range and frequencies).

Group	Sex M/F	Age (years)	Height (cm)	Body weight (kg)	GH peak in provocation test	Years since diagnosis of GHD	Age at diagnosis	Earlier treatment with hGH,	Etiology	Other hormone deficiencies
Somatotropin n=12	5 M 7 F	50.0 7.5	167 10	81 18	29.3 6.8	0.1 0.1	4 6	45 10	12 No	10 pituitary tumor 2 craniopharyngioma	4 TSH, ACTH, LH/FSH, ADH 8 TSH, ACTH, LH/FSH
Placebo n=13	11 M 2 F	47.7 10.8	175 7	81 14	26.8 4.7	0.7 1.2	6 6	42 12	12 No 1 Yes	9 pituitary tumor 1 craniopharyngioma 1 cholesteatoma 1 empty sella 1 trauma	6 TSH, ACTH, LH/FSH 4 TSH,ACTH, LH/FSH, ADH 2 LH/FSH 1 ACTH, LH/FSH
Total study population n= 25	16 M 9 F	48.8 9.2	171 10	81 15	28.0 5.8	0.4 0.9	5 6	44 11	24 No 1 Yes	19 pituitary tumor 3 craniopharyngioma 1 cholesteatoma 1 empty sella 1 trauma	14 TSH, ACTH, LH/FSH 8 TSH, ACTH, LH/FSH, ADH 2 LH/FSH 1 ACTH LH/FSH

* BMI = Body Mass Index

The following patients in the somatotropin group were suffering from chronic illnesses or major sequelae from previous illness:

Patient no. 5; back pain
Patient no.10; dorsal insufficiency
Patient no.23; right eye cataract
Patient no.24; benign vertigo and difficulties in walking since childhood due to bilateral congenital hip joint luxation

The following patients in the placebo group were suffering from chronic illnesses or major sequelae from previous illness:

Patient no. 2; benign hypertonia
Patient no. 3: suspected sarcoidosis and partial blindness in the right eye following pituitary operation
Patient no. 9; weakness of the right knee after motorcycle accident

4.0 STUDY DRUGS

The dosage for each patient in the somatotropin group is shown in Table 2 below.

During the double-blind treatment period, all patients, except one in the somatotropin group, were within of the intended dosages: 0.375 mg/kg body weight/week (mean dosage 0.36) for the first month, and 0.75 mg/kg/week (mean dosage 0.72) for months 2 through 6. Patient no. 4 received 0.27 and 0.57 mg/kg/week for months 1, and months 2 through 6, respectively, during the double-blind period.

The mean dosage was decreased to 0.36 mg/kg/week after 12 months of treatment. It was decreased further to 0.51 mg/kg/week after 18 months. The mean dosage during the 19 to 24 months period was 0.48 mg/kg/week.

Two patients kept the same dosage throughout the study period (patients nos. 10 and 23). Two of 12 patients (nos. 8 and 24) had a dosage decrease before the 12th month's visit. All patients, except nos. 10 and 23, had dosage decreases between 12 and 19 months. Patients nos. 1, 4, 13 and 16 also had dosage decreases during the 19 to 24 months period. Patient no. 24 had a dosage increase during this period.

Patient no. 16 stopped treatment for 98 days in connection with medical evaluations after a serious adverse event .

Towards the end of the study, five patients received similar dosage as at entry to the study (patients nos. 4, 8, 13, 19 and 24).

Table 2. Dosage of test drug. mg/kg body weight and week. Somatotropin group.

Patient no.	Double blind somatotropin		Open somatotropin treatment		
	month 1	month 2 - 6	month 7 - 12*	month 13 - 18	month 19 - 24
1	0.36	0.69	0.57 after 12.0 months	0.57	0.48 after 22.7 months
4	0.27	0.57	0.42 after 12.0 months	0.42	0.27 after 19.2 months
5	0.30	0.60	0.60	0.45 after 18.9 months	0.45
8	0.33	0.66	0.45 for 6 days after 8.8 months 0.33 thereafter	0.21 after 18.8 months	0.21
10	0.42	0.84	0.84	0.84	0.84
11	0.36	0.72	0.72	0.63 after 16.0 months	0.63
13	0.33	0.66	0.66 after 11.8 months	0.45 after 17.5 months	0.36 after 22.5 months
16	0.13	0.27	0.27	0.00 after 13.8 months (98 days) 0.22 after 17.0 months	0.18 after 21.9 months
17	0.36	0.72	0.72	0.51 after 17.0 months	0.51
19	0.36	0.72	0.72	0.33 after 17.0 months	0.33
23	0.39	0.78	0.78	0.78	0.78
24	0.39	0.71	0.57 after 6.6 months 0.42 after 12.0 months	0.27 after 16.8 months	0.42 after 21.2 months

*During the 7th month the dose was decreased to the same level as for month 1.

5 Efficacy

5.1 CLINICAL EFFICACY VARIABLES

The LBM difference between placebo and GH, as estimated by BIA and four compartment procedures. No statistical significance differences were observed with either method between treatments groups in the primary efficacy variable (BIA:p=.11, four compoartment:p=.18) The median percent LBM increase was 1.4% for the GH group and a decrease of 1.3% in the placebo group. This did not reach statistical difference (p=.11)

No significant changes between groups were observed in all secondary endpoints. Therefore, the results of this study cannot support the claim of the sponsor.

5.2 LABORATORY EFFICACY VARIABLES

Markers of bone metabolism during the double-blind period

There was a statistically significant increase in osteocalcin ($p< 0.001$) and a statistically significant decrease in intact PTH ($p< 0.001$) for the somatotropin group at the end of the 6-month double-blind period. No statistically significant changes were observed in the placebo group. The differences between the treatment groups in osteocalcin and intact PTH were statistically significant ($p< 0.001$).

No statistically significant changes were observed within the somatotropin or the placebo group in 1,25-OH_2 vitamin D during the double-blind period. Nor was there a statistically significant difference between the groups at the end of the double-blind period.

In 25-OH vitamin D there was a statistically significant increase in both the somatotropin ($p=0.001$) and the placebo groups ($p< 0.001$) during the 6-month double-blind period. No statistically significant difference was present between the groups at the end of the double-blind period.

There was a statistically significant increase in procollagen III-propeptide within the somatotropin group ($p=0.001$), and a statistically significant decrease within the placebo group ($p<0.001$), resulting in a statistically significant difference between the groups ($p<0.001$).

5.2.1 Lipid metabolism during the double-blind period

A statistically significant decrease in cholesterol was found for the placebo group ($p=0.026$) at the end of the double-blind period, while the somatotropin group showed only a tendency ($p=0.064$). There was no significant difference between the groups (Table 3).

At the end of the double-blind period, no statistically significant changes in triglyceride levels were observed either within or between study groups (Table 3).

There was a tendency towards an increase in cholesterol HDL in the somatotropin group (p=0.082), and a tendency towards a decrease in the placebo group (p=0.078), giving a statistically significant difference between the groups (p=0.020) (Table 3).

The calculated LDL as well as the LDL/HDL ratio decreased significantly in the somatotropin group (p=0.024). There was also a statistically significant difference in ratio between the treatment groups at the end of the double-blind period (p=0.043) (Table 3).

Table 3. Lipid metabolism during the 6-month double-blind period. Absolute change from baseline over time by treatment group.

	Somatotropin group					Placebo group					
	Baseline		Change 0-6 months			Baseline		Change 0-6 months			
Variable	mean	SD	mean	SD	p-value within	mean	SD	mean	SD	p-value within	p-value between
Cholesterol	5.6 n=11	0.7	-0.4	0.7	0.064	6.1 n=13	0.8	-0.4	0.5	**0.026**	n.s.
Triglycerides	1.6 n=11	1.2	0.0	0.8	n.s.	1.5 n=13	0.6	-0.1	0.5	n.s.	n.s.
Cholesterol HDL	1.6 n=11	0.2	0.1	0.2	0.082	1.2 n=13	0.3	-0.1	0.2	0.078	**0.020**
LDL (calculated)	3.7 n=11	0.5	-0.5	0.6	**0.024**	4.2 n=13	0.7	-0.2	0.4	n.s.	n.s.
LDL/HDL ratio	3.3 n=11	1.0	-0.7	0.7	**0.024**	3.7 n=13	1.4	0.0	0.6	n.s.	**0.043**

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5.2.2 Serum IGF-I during the double-blind period

There was a statistically significant increase within the somatotropin group in both IGF-I and IGF-I SDS at the end of the double-blind period ($p<0.001$). The difference between the somatotropin and the placebo group was also statistically significant ($p<0.001$) (Table 4).

Table 4. **Effects of treatment on IGF-I during the 0 to 6 months double blind period. Absolute change from baseline over time by treatment group**

	Somatotropin group					Placebo group					
	Baseline		Change 0-6 months			Baseline		Change 0-6 months			
Variable	mean	SD	mean	SD	p-value within	mean	SD	mean	SD	p-value within	p-value between
IGF-I, g/L	67 n=12	44	156	64	**<0.001**	67 n=13	23	-3	22	n.s.	**<0.001**
IGF-I SDS	-3.33 n=12	2.13	4.80	2.01	**<0.001**	-3.16 n=13	1.50	-0.12	1.36	n.s.	**<0.001**

Nine of the 12 patients in the somatotropin group, and 11 of the 13 patients in the placebo group had IGF-I levels below 2 SDS the age-matched reference limits at baseline. After 6 months' double-blind somatotropin treatment, 10 of 12 patients were within normal aged-matched reference levels, while 2 of 12 patients exceeded these levels (>+2 SDS). In the placebo group, 10 of 13 patients were below normal aged-matched reference levels after 6 months treatment (<-2 SDS) and 3 of 13 were within normal range (2 SDS).

5.2.4 EFFICACY SUMMARY

The six-month randomized double-blind phase of the study was designed to document the effects of growth hormone treatment on body composition.

There were not statistically significant differences between the treatment groups in LBM.

No statistically significant difference between treatment groups was observed in respiratory muscle strength, or in bone mineral density.

A statistically significant increase in circulating levels of IGF-I was seen after 6 months. At baseline 9 of 12 patients in the somatotropin group and 11 of 13 patients in the placebo group had IGF-I levels below the age-matched reference

limits (<-2 SDS). After 6 months' double-blind somatotropin treatment, 10 of 12 patients had normal levels (within 2 SDS), while 2 of 12 had levels exceeding 2 SDS. In the placebo group, 3 of 13 were within and 10 of 13 below normal range after 6 months of double-blind treatment.

For lipids, HDL-cholesterol increased during somatotropin treatment in comparison to placebo, and the LDL/HDL ratio decreased statistically significantly.

6.0 Safety

6.1 CLINICAL SAFETY VARIABLES

6.1.1 Height and body weight

There was a statistically significant increase in height in the somatotropin and placebo groups at the end of the double-blind period ($p=0.001$ and $p<0.001$, respectively). No statistically significant difference between the groups was observed.

A statistically significant decrease in body weight was present in the somatotropin group ($p=0.009$) at the end of the double-blind period, giving a statistically significant difference between the somatotropin and the placebo group ($p=0.005$).

The statistically significant increase in height observed in both the somatotropin and the placebo group was maintained during the period when all patients were treated with somatotropin ($p=<0.001$).

The changes in body weight compared to baseline were inconsistent during somatotropin treatment. When all patients were pooled (combined group) a statistically significant decrease was present after 6 months of somatotropin treatment ($p=0.001$). However, this decrease was not present after 12 and 24 months of treatment.

6.1.2 Blood pressure and pulse rate

There were no statistically significant changes in diastolic blood pressure between groups. No statistically significant change or difference in pulse rate was observed during the double blind period.

6.2 LABORATORY SAFETY VARIABLES

All judgments of the clinical significance of a deviation in laboratory safety variables, whether a deviation was serious or non-serious, and its relationship to study medication, referred to in the present report, were made by the investigator.

Hemoglobin

There was a statistically significant increase within normal range in hemoglobin values between the somatotropin and the placebo groups (p=0.036).

Leukocytes

No statistically significant changes within groups, or difference between somatotropin and placebo treatment, was observed during the double-blind period.

Thrombocytes

There was a statistically significant increase within normal range in thrombocytes for the somatotropin group after 6 months' double-blind treatment (p=0.009), giving a statistically significant difference between the treatment groups (p=0.046).

Glucose

No statistically significant changes in fasting glucose between the groups, were observed at the end of the 6-month double-blind period.

Insulin

There was a statistically significant increase within normal range for the somatotropin group at the end of the double-blind period ($p<0.001$), giving a statistically significant difference between the treatment groups ($p=0.021$).

HbA1c

No statistically significant changes in HbA1c between the treatment groups.

Creatinine

Creatinine was statistically significantly decreased within normal range in both the somatotropin group ($p<0.001$) and the placebo group ($p=0.009$) at the end of the double-blind period.

The creatinine levels were statistically significantly decreased within normal range after 6 months ($p<0.001$) and 12 months ($p<0.001$), but not after 24 months of somatotropin continuation treatment.

Two patients had high creatinine levels; one at entry to the study (patient no. 7) and one during somatotropin treatment (patient no. 9). None of the deviations were judged to be of clinical significance.

Sodium

There was no statistically significant difference in sodium between the treatment groups.

When all patients were pooled (combined group), there were statistically significant increases within normal range after 6 months ($p<0.027$) and 12 months ($p=0.014$) of somatotropin continuation treatment.

Three patients with initially normal sodium levels, had below-normal values during somatotropin treatment (patients nos. 4, 9, and 25). Six patients had values below normal range at entry to the study and/or during placebo treatment (patients nos. 5, 8, 11, 12, 16, 18 and 22). In one of these patients (no. 22), the sodium level at 15 months was judged to be significantly below normal clinical range. The deviation was judged to be non-serious and not likely related to the study drug. No action was taken.

Potassium

There was no statistically significant difference between the treatment groups in potassium level at the end of the 6-month double-blind period.

A statistically significant increase (p=0.003) within normal range was observed for the total study population (combined group) after 12 months of somatotropin treatment, but not after 6 and 24 months of treatment.

Three patients with initially normal potassium levels had values below normal range at some visit during somatotropin treatment (patients nos. 13, 23 and 24). Patients nos. 1 and 2 had below-normal values at entry to the study and at several visits during the study period. The low level at 15 months in patient no. 1, and at 15 and 18 months in patient no. 2, were judged to be clinically significant. These deviations were judged to be non-serious and a relationship to the study drug was deemed unlikely. No action was taken.

ASAT

No statistically significant changes in ASAT within the treatment groups or difference between the groups were observed at the end of the 6-month double-blind period.

A statistically significant decrease within normal range was observed in ASAT after 24 months of somatotropin treatment for the total study population (p=0.010).

One patient with initially normal ASAT level had values above normal range after 6 months of somatotropin treatment (patient no. 11). This increase was judged to be clinically significant. The patient was within normal range at all other visits. Patient no. 7 had high ASAT levels at baseline and at 30 months and both were judged to be clinically significant. Two patients with initially high levels normalized during the study period (patients nos. 12 and 21). None of the clinically significant high levels were judged to be serious or related to the study drug. No action was taken.

ALAT

No statistically significant changes in ALAT within the treatment groups, or difference between the groups, were observed at the end of the 6-month double-blind period.

A statistically significant decrease within normal range was observed in ALAT after 12 months (p=0.010), but not after 6 and 24 months of somatotropin treatment for the total study population.

Three patients with initially normal ALAT levels had values above normal range at some visit during somatotropin treatment (patients nos. 3, 19 and 20). The elevations were judged to be clinically significant. Two patients with high levels at baseline and after 6 months on placebo, normalized during the study period (patients nos. 12 and 21). The elevated level after placebo in patient no. 21 was judged to be clinically significant. In patients nos. 7 and 11, with elevated values present at baseline, further elevations were also present at some visit during treatment. None of the clinically significant elevations were judged to be serious or related to the study drug. No action was taken.

Free T4

No statistically significant changes in free T4 within the treatment groups, or difference between the groups, were observed at the end of the 6-month double-blind period.

A statistically significant decrease within normal range was observed in free T4 after 6 and 12 months, but not after 24 months of somatotropin treatment for the total study population (p=0.026 and p=0.011, respectively).

One patient had values above normal free T4 range at entry to the study and during placebo treatment (patient no. 7). Six patients had above-normal values during somatotropin treatment (patients nos. 6, 10, 11, 15, 21 and 23). In patients nos. 6, 10 and 23, the deviations at 30, 6 and 6 months, respectively, were judged to be clinically significant. None of the elevated values was judged to be serious and no action was taken with the study drug. However, patient no. 10 had her thyroxin dosage reduced to 0.15 mg daily. For patients nos. 10 and 23, a relationship to the study drug was judged as possible. For patient no. 7 a normal level was deemed to be a clinically significant deviation.

Three patients had below-normal free T4 levels during somatotropin treatment (patients nos. 9, 18, and 20). The deviations in all patients were judged to be clinically significant. For patients nos. 9 and 20, a relationship to the study drug was judged to be probable and for patient no. 18, possible. These deviations were judged to be non-serious and no action was taken with the study drug. However, patient No. 18 had his thyroxin dosage increased to 0.15 mg daily (from 12 month visit).

In patients nos. 3 and 22, free T4 levels within normal range were judged to be clinically significant deviations.

Triiodothyronine

Triiodothyronine was measured during the long-term continuation study only. However, one deviation from normal range was observed at an extra determination at 12 months in patient no. 7. This high level (9.5 pmol/L; ref. 4.3-7.6) was judged to be of clinical significance but non-serious and no action was taken with the test drug.

Testosterone

No statistically significant changes in testosterone within the treatment groups, or difference between the groups, were observed at the end of the 6-month double-blind period.

There was a statistically significant decrease in testosterone level for the total study population (combined group) after 12 months of somatotropin treatment ($p=0.035$), but not after 6 and 24 months.

Six patient had values below normal range at entry to the study or during placebo treatment (patients nos. 2, 7, 15, 21, 22 and 23). Seven patients with normal testosterone levels at entry to the study or during placebo treatment had below-normal values at some visit during somatotropin treatment (patients nos. 3, 9, 11, 12, 14, 16 and 18). None of the deviations were judged to be clinically significant.

Sex hormone binding globulin (SHBG)

SHBG was measured during the initial study only. No statistically significant changes within the treatment groups, or difference between the groups, were observed after 6 months of treatment.

SHBG levels both below and above normal range were observed during baseline and during somatotropin treatment. The deviations judged as clinically significant are shown below. None of the deviations was judged as serious, any relationship to study medication was deemed unlikely and no action was taken.

Estradiol

No statistically significant changes in estradiol within the treatment groups, or difference between the groups, were observed at the end of the 6-month double-blind period.

There was a statistically significant decrease (within normal range) in estradiol for the total study population (combined group) after 12 months of somatotropin treatment.

Five patients had below-normal oestradiol levels at entry to the study (patients nos. 4, 10, 13, 19 and 24). Four of these remained low during somatotropin treatment (patients nos. 4, 10, 13, and 24). Two patients had above-normal values at entry to the study (patients nos. 3 and 7). The elevation in patient no. 3 was judged to be clinically significant, but not serious and not likely related to the study drug. No action was taken. Three patients with normal levels at entry to the study had values below normal range during somatotropin treatment (patients nos. 5, 6 and 17), and three initially normal patients, had values above normal range during somatotropin treatment (patients nos. 1, 11 and 23).

Bilirubin

Bilirubin was measured during the continuation study only. Four patients had values exceeding the normal range during somatotropin treatment (patients nos. 14, 15, 19 and 23). For two of the patients (nos. 14 and 19) the elevated values were judged to be clinically significant, not serious and a relationship to treatment was deemed unlikely. No action was taken.

Urinary-Erythrocytes

One patient had a positive hematuric test at baseline only (patient no. 13). Two patients (nos. 14 and 17) had positive tests both at baseline and during somatotropin treatment. Six patients had positive tests during somatotropin treatment (patients nos. 4, 10, 14, 17, 22 and 25). Several of these were clinically significant according to the investigator . The clinically significant elevations were judged as non-serious, except in patient no. 14 where the elevation at 30 months was serious according to the investigator. In patient no. 17, an X-ray of the kidneys and a gynecological investigation was carried out. No abnormalities were found and the positive u-erythrocyte findings were diagnosed as benign microscopic hematuria. However, a relationship to the study medication was deemed unlikely in all clinically significant positive u-erythrocyte tests. No changes were made in study medication.

Proteinuria

One patient (no. 13) had a positive urinary protein test at entry to the study (clinically significant) and five patients had positive tests during treatment (patients nos. 9, 12, 15, 20 and 24). In three of these (patients nos. 12, 17 and 24) the elevations were judged as clinically significant. The observed positive test in patient no. 17 was only observed at 9 months visit when an extra test was performed due to an extra control of hematuria. According to the investigator they were not serious, not likely to be related to study medication, and no action was taken.

Glucosuria

Glucose in urine was measured during the continuation study only. One patient (no. 25) had an elevated urinary glucose level after 24 months of treatment. The elevation was judged as clinically significant. It was not serious, a relationship to study medication was deemed unlikely, and no action was taken.

6.3 ADVERSE EVENTS

Twenty-one adverse events were reported by 9 patients during the double-blind placebo period and 33 events were reported by 11 patients during the double-blind somatotropin period. During the open somatotropin treatment 175 events were reported by 24 patients.

Upper respiratory tract infection was the most frequently reported individual adverse event during the double-blind period; 3 events were reported by 3 patients (nos. 14, 15 and 18) during the placebo period and 6 events were reported by 6 patients (5, 11, 13, 16, 19 and 24) during the somatotropin period.

Peripheral swelling was reported once by 6 patients (nos. 4, 8, 10, 13, 19 and 24) during the six months double-blind somatotropin period and once during the double-blind placebo period.

Hypesthesia was reported once by 4 patients (nos. 8, 13, 19 and 24), paraesthesia once by 3 patients (nos. 10, 16 and 24) and stiffness of extremities once by 3 patients (nos. 4, 8 and 24) during the six months double-blind somatotropin period. None of these symptoms were reported during the double-blind placebo period.

Migraine was the most frequently reported adverse event during the six months double-blind placebo period (4 reports in patient no. 25).

During the total somatotropin treatment (both double-blind and open period) the following adverse events were most frequently reported:
peripheral swelling - 25 events in 16 patients
upper respiratory tract infection - 23 events in 12 patients
arthralgia - 14 events in 10 patients
paraesthesia - 14 events in 9 patients
stiffness of extremities - 11 events in 9 patients
gastroenteritis - 11 events in 8 patients
hypesthesia - 7 events in 5 patients
back pain - 7 events in 4 patients
fatigue - 6 events in 6 patients
migraine - 4 events in 2 patients
pain in extremities - 4 events in 3 patients

6.3.1 SERIOUS ADVERSE EVENTS

There were 14 serious adverse events reported for 6 patients during somatotropin treatment.

Patient no. 2 was hospitalized for 5 days after 150 days on somatotropin treatment due to respiration insufficiency during aspiration when intubated in connection with a dental operation. He recovered completely after removal of gastric content from the airways followed by respirator therapy and antibiotic treatment. The event was judged as severe and not likely related to study medication. The medication continued unchanged. The patient was hospitalized again after 200 days for three days for gastroenteritis with diarrhoea and vomiting. The patient recovered completely. The event was judged as severe. A causal relationship to somatotropin was judged unlikely and study medication was continued. The patient has a 15 to 20 year history of gastroenteritis episodes requiring hospitalization and treatment with cortisone and saline infusion. Sixteen days later the patient was hospitalized for one day for local chest pain under the left pectoralis muscle, and nausea. The symptoms disappeared after single doses of paracetamol, codeine and prochlorperazine. The muscle pain was believed to be associated with previous heavy lifting. The event was judged to be moderately severe and a causal relationship to somatotropin was judged unlikely. Treatment with somatotropin remained unchanged. Later during the study (518 days on somatotropin therapy), the patient was hospitalized for one day for nausea, vertigo and hypertension. The symptoms disappeared when dosage of existing antihypertensive treatment was increased. The event was judged to be mild and a causal relation to somatotropin was judged unlikely. Treatment with somatotropin remained unchanged. At the end of the study (685 days on somatotropin therapy), the

patient was hospitalized for upper airway infection with coughing and fever. He recovered completely after antibiotic treatment. The event was judged to be severe and a causal relation to somatotropin was judged unlikely. Treatment with somatotropin remained unchanged.

Patient no. 3 was admitted to hospital after a grand mal seizure with unconsciousness and tiredness after 422 days on somatotropin therapy. The patient has epilepsy but took no anti-epileptic medication at the time. He recovered completely after treatment with diazepam and carbamazepin. According to the Adverse Event Report the event was judged to be severe, and according to the CRF it was judged as moderate. A causal relation to somatotropin was judged unlikely. Treatment with somatotropin was stopped for one day. Later (458 days on somatotropin), the patient was hospitalized for 10 days for high fever and chills. He recovered completely after switching anti-epileptic treatment and after treatment with prednisolone. The fever was believed to be either secondary to the anti-epileptic treatment or secondary to a progression of an existing sarcoidosis. The event was judged to be severe and a causal relationship to somatotropin was judged unlikely. Treatment with somatotropin remained unchanged.

Patient no. 5 was admitted to hospital for an upper airway infection followed by headache, nausea and vomiting after 213 days somatotropin treatment. The patient stayed in the hospital for 2 days. She was treated with glucose 5% and hydrocortisone. The patient was fully recovered after 14 days. The event was judged as moderate, a relationship to study medication was thought unlikely and dosage remained unchanged. After 616 days on somatotropin therapy the patient was hospitalized two days for migraine. The patient recovered completely after fasting, saline infusion and intravenous plus oral hydrocortisone. The event was judged as severe, a relation to study medication was judged unlikely and dosage remained unchanged.

Patient no. 16 was admitted to hospital for 1 day due to an anaphylactic shock after eating crab-fish. The patient was treated with adrenalin, betamethasone and glucose infusion. He recovered completely after 1 day. The event was judged as severe, a relation to study medication was deemed unlikely and dosage remained unchanged. Later the patient had two episodes of tachycardia during the open somatotropin treatment (after 409 and 420 days on somatotropin therapy). He had a history of supraventricular tachycardia. The patient recovered completely after i.v. treatment with verapamil and sotalol (first episode) and i.v. metoprolol plus cardioversion (second episode). The events were judged to be moderate and a causal relation to somatotropin was judged unlikely. Treatment with somatotropin was interrupted for 98 days while the tachycardia was further evaluated.

Patient no. 21 was admitted to hospital for pain in the left groin, fever and diarrhoea (diverticulitis) after 654 days on somatotropin therapy. The patient recovered completely after fasting, fluid substitution, antibiotic infusion and hydrocortisone injections. The event was judged to be severe and a causal relation to somatotropin was judged unlikely. Treatment with somatotropin remained unchanged.

Patient no. 24 was hospitalized for 2 days due to gastroenteritis after 253 days on somatotropin therapy. The patient recovered completely within 3 days after fasting and treatment with hydrocortisone. The event was judged as severe, a relation to study medication was deemed unlikely and dosage remained unchanged

6.4 SAFETY SUMMARY

Statistically significant increases were observed in height in both treatment groups at the end of the 6 months double-blind period. There was no statistically significant difference between the placebo and the somatotropin group. A statistically significant decrease in body weight was recorded in the somatotropin group after 6 months double-blind treatment, resulting in a statistically significant difference between the treatment groups. However, the changes during the open somatotropin treatment were inconsistent.

During somatotropin replacement, significant changes compared to baseline were seen in clinical chemistry and hematology tests. For the total study population there were increases within normal ranges in fasting blood glucose, fasting insulin as well as glycated hemoglobin levels at 6, 12 and 24 months. Clinically significant increases in fasting insulin levels were noted for 4 patients and in HbA1c levels for 2 patients. Hemoglobin and thrombocytes increased within normal limits during the double-blind period, but there were no difference at 12 or 24 months compared to study start. Leukocytes were increased after 24 months, but within reference limits. However, no change were seen during the double-blind period. For creatinine, sodium, potassium no consistent changes were noted, nor in ASAT or ALAT values. This was also true for bilirubin, free thyroxine levels as well as for SHBG, testosterone and oestradiol levels. However, individual patients showed occasional clinically significant deviant values.

Adverse event were reported by 9 patients (21 adverse events) during the double-blind placebo treatment and by 11 patients (33 events) during the double-blind somatotropin treatment. During the total somatotropin treatment period, adverse events were reported by 24 patients. The most frequently reported events were: peripheral swelling (26 events in 16 patients), upper respiratory

tract infection (23/12), arthralgia (14/10), paraesthesia (14/9), stiffness of extremities (11/9), gastroenteritis (11/8), hypesthesia (7/5) back pain (7/4), fatigue (6/6), pain in extremities (4/3) and migraine (5/2).

Serious adverse events were reported in six patients during somatotropin treatment, in none of the events was a causal relationship to treatment judged likely by the investigator.

7. DISCUSSION

All 25 patients had severe growth hormone deficiency as demonstrated by very low GH-peaks after an appropriate stimulation test. In eleven patients, the GH-deficiency was diagnosed within two years of study start, but the investigator judged it likely to have existed for a period exceeding two years. The patients were also regarded as being on stable replacement therapy with other pituitary hormones since more than two years. All patients had acquired their hypopituitarism during adulthood, and no patient had isolated GH-deficiency. Hence, the patients are representative for adults with pronounced growth hormone deficiency.

Their replacement therapy with cortisone, thyroxine and sex hormones was unchanged during the study for the majority of the patients. Dose adjustments were made in 11 patients.

Compliance to treatment was good both during the double-blind period and during the open somatotropin treatment. There was no withdrawal from treatment during the entire 24-month study period.

During the 6-month placebo-controlled treatment period the changes in LBM as assessed by BIA and the four compartment model did not differ between groups. There was no change in bone mineral density. A beneficial effect on lipids was documented, with an increase in HDL-cholesterol and a decrease in LDL/HDL ratio. No significant changes were observed in any of the secondary endpoints.

Serum IGF-I levels rose during treatment with a normalization in the majority of the patients. The doses used appear to be correct for normalizing IGF-I levels as group averages, but the need for individualizing dosing in order to avoid super physiological levels that were observed in two subjects is strongly suggested.

Adverse events considered to be related to somatotropin treatment such as fluid retention with symptoms like peripheral swelling, arthralgia, stiffness of extremities, hypothesia or paraesthesia were reported 72 times in 18 patients.

The dose was reduced in 15 of these patients. In 11 patients, these adverse symptoms had disappeared completely after 24 months somatotropin treatment. Untoward effects like these were expected and patients were specifically asked about them.

With regard to laboratory values, fasting blood glucose and insulin levels as well as amount of glycated hemoglobin rose during treatment, but remained within normal ranges.

8. CONCLUSION

The results of this study do not support the sponsor claim of benefit for the use of GH in adult GH deficient subjects.

Section Three

Study 91-001

APPEARS THIS WAY
ON ORIGINAL

STUDY 91-001

1.0 OBJECTIVES

The primary objective of the initial study (TRN 91-001) was to determine the effect of somatropin replacement therapy on body composition in GH-deficient adults compared to a placebo-treated control group.

Secondary objectives of the initial study were to determine whether somatropin replacement therapy improves quality of life, to determine the safety of somatropin replacement therapy compared to a placebo-treated control group, and to evaluate the effect of somatropin replacement therapy on bone mineral density, muscle strength, exercise capacity, serum IGF-I and plasma lipids as compared to a placebo-treated control group.

The primary objective of the continuation study (CTN 92-8124-016) was to determine long-term changes in body composition by somatropin replacement. Because this part of the studies were not properly controlled they will not be reviewed. The results of this extension study, however, indicate that the GH effects shown during the first six month are maintained.

2.0 PATIENTS, MATERIALS AND METHODS

2.1 Study design

The first 6 months of the initial study (TRN 91-001) used a randomized, double-blind design with somatropin treatment versus placebo.

2.1.1 Study population

Twenty patients (male and female) with GH-deficiency acquired in childhood or adulthood were included in the initial study, ten in each treatment group.

All patients wishing to continue somatropin treatment were included in the long-term continuation study.

Inclusion criteria in the initial study

- GH-deficiency (isolated or as part of hypopituitarism). Likely to have existed for at least 24 months.
- Stimulated maximum peak growth hormone response less than 5 µg/l. Acceptable stimulation tests were GHRH, arginine, glucagon, clonidine and insulin induced hypoglycemia. A test performed within 5 years prior to inclusion and after 20 years of age would be accepted only if it could be verified from source data. Otherwise, a new test was required.
- IGF-I level in serum below the normal range (normal range = 100 to 280 ng/ml).
- Age
- Patients with multiple pituitary hormone deficiency on stable replacement therapy for at least 6 months.
- Informed consent obtained.

Exclusion criteria in the initial study

- Treatment with growth hormone during the last 12 months.
- Acute severe illness during the last 6 months.
- Pregnancy (to be excluded with test).
- Chronic severe liver disease (gamma-GT and/or ASAT and/or ALAT twice the upper limit of the normal range of laboratory values).
- Chronic severe renal disease (S-creatinine > 120 µmol/l or repeated positive test for hematuria or proteinuria).
- Supine blood pressure > 160 mm Hg systolic or > 100 mm Hg diastolic.
- Diabetes mellitus (type I and II).
- History of malignancy (although patients treated for cranial tumors or leukemia, both causing GH-deficiency, were acceptable).
- Chronic medication, except pituitary replacement therapy, bromocriptine, contraceptives, treatment for mild hypertension and mild asthma.
- Suspected non-cooperativeness.
- Known or suspected hypersensitivity to m-cresol.

2.1.2. RANDOMIZATION PROCEDURE

The randomization of consecutive numbers to either of the two groups (somatropin/ placebo) in the double-blind phase and the preparation of the randomization list and emergency envelopes were performed at the Department of Biostatistics and Data Management, Peptide Hormones, Pharmacia, Stockholm, Sweden. A computerized randomization procedure was used.

Allocation of patient numbers in the double-blind phase was made by the investigator at the baseline visit. The patient was given the lowest available patient number in the series. The drugs (somatropin or placebo) for the 0 to 6-month double-blind period were pre-packed in numbered boxes according to the randomization list.

The study code was kept in sealed envelopes at the investigator site. The envelopes were not to be opened except in an emergency requiring knowledge of actual treatment. The code envelopes were to be returned to Pharmacia after completion of the study. The code was to be broken at the 12th month's visit.

2.1.3. BLINDING PROCEDURE

The initial study was double-blind and placebo-controlled during the first 6 months. The placebo was supplied in cartridges identical to the active somatropin cartridges.

2.2 Therapy

2.2.1 TREATMENT SCHEDULE

During the first 4 weeks of the first two 6-month periods in the initial study, the patients injected a volume corresponding to 0.375 mg/kg body weight/week and thereafter 0.75 mg/kg body weight/week for 5 months. The dosage of 0.75 mg/kg body weight/week was to be maintained during the continuation study. The weekly dose was divided into 7 daily, s.c. injections. Irrespective of body weight the maximum dose per day was not to exceed 12 mg.

The patients were instructed by a nurse how to inject themselves.

2.2.2 CONCOMITANT THERAPY

No other chronic medication was allowed when entering the initial study with the exception of pituitary replacement therapy, bromocriptine, contraceptives, treatment for mild hypertension and mild asthma. Adjustments on clinical grounds were allowed but were documented in the Case Report Forms. The patients were allowed to take any drug considered necessary for the treatment of any intercurrent disease of a less severe nature. During the long-term continuation study, all therapy necessary for the patient's welfare was allowed at the discretion of the investigator.

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.

All therapies were recorded in the Case Report Forms.

2.3. Patient characteristics

In order to ensure that the inclusion criteria were fulfilled and to enable verification of patient identity and status relative to source data, the patient's birth date, sex, ethnic origin, concomitant medication and laboratory values were recorded. A stimulation test was documented and IGF-I levels were checked. Year of diagnosis of GHD and other hormone deficiencies such as TSH deficiency, ACTH deficiency, LH/FSH deficiency, ADH deficiency and others were recorded. Earlier treatment with growth hormone, chronic diseases, medical history and physical examination were also recorded.

2.4 Efficacy assessments

2.4.1 CLINICAL EFFICACY ASSESSMENTS

Body composition was determined using Bioelectrical Impedance Analysis (BIA) and DEXA analysis.

Bone mineral density

Bone mineral density of the forearm (distal and proximal) was measured with single-photon absorptiometry (SPA). In this study bone mineral density of the total body, spine and the lumbar vertebral bodies L2 through L4 (dorsal position) and the lumbar vertebral bodies L2 and L3 (lateral position) were measured using DEXA.

2.4.2. LABORATORY EFFICACY ASSESSMENTS

The following laboratory measurements were performed in order to document efficacy of the drug.

Lipid analysis

Serum lipids were measured at baseline, 6 and 12 months (placebo group also at 18 months).

Effect on blood lipids was investigated with preparative ultracentrifugation and determination of VLDL-, LDL- and HDL-fractions of triglycerides and cholesterol. Subclassification of HDL with gradient gel electrophoresis was to be measured: HDL 2B, 2A, 3A, 3B, and 3C. S-cholesterol and S-triglycerides were also to be measured.

Lab measurements	Normal range
S-Osteocalcin, µg/l	<9 female <14 post menopausal <11 male
S-Procollagen I propeptide (S-PICP), IU/l	50-170, female 38-202, male
S-Procollagen III propeptide, IU/l	
S-Ca^{2+} (ionization) mmol/l	
S-Phosphate, mmol/l	
S-Alkaline phosphatase (ALP), µkat/l	<4.6
U-Hydroxyproline, mmol/24h	(only TRN 91-001)
(S-ICTP), µg/l	(only CTN 92-8124-016)
(U-PYD & U-DPYD), nmol/l	female (only CTN 92-8124-016) male (only CTN 92-8124-016)

Lab measurements	Changes in normal range during study
S-Ca (total calcium), mmol/l	(from CTN 92-8124-016)

IGF-I
Insulin-like growth factor I (IGF-I) is essential for growth and is supposed to mediate the growth-promoting effects of growth hormone postnatally.

IGF-I was to be measured at every visit.

2.4.3. CLINICAL SAFETY ASSESSMENTS

The clinical safety examination was similar to the previous study.

3. RESULTS

3.1 Study population

3.1.1. NUMBER OF PATIENTS

Twenty patients with growth hormone deficiency were included in the initial study from November 18, 1991 to March 27, 1992. Ten patients were randomized to the somatropin group and ten patients to the placebo group. All patients completed the 0 to 6-month double-blind period and the 6 to 12-month open period according to the protocol.

Nineteen patients continued into the continuation study. Patient no. 7 wished not to continue in the continuation study.

3.1.2. TREATMENT WITHDRAWALS

Initial study

There were no withdrawals during the 0 to 6-month double-blind period or during the 6 to 12-month open period in the initial study.

Continuation study

No patients withdrew during the 12-month long open period in the continuation study (months 12 to 24 for the somatropin group and months 18 to 30 for the pl/somatropin group).

3.2 PATIENT CHARACTERISTICS

Five females and five males, (mean age 41 years), were included in the somatropin group, and four females and six males, (mean age 40 years), were included in the placebo group. The distribution in age among the somatropin group was: one patient in the interval below 30 years (22 years), five patients 31 to 40 years, three patients 41 to 50 years and one patient above 50 years (57 years). The distribution in age among the placebo group was: seven patients 31 to 40 years, and three patients 41 to 50 years.

Peak GH response after the provocation test was 0.2 ng/ml in nine patients and 0.9 ng/ml in one patient in the somatropin group. In the placebo group, the peak GH response after provocation test was 0.2 ng/ml in nine patients and 2.0 ng/ml in one patient.

The mean years of GH-deficiency at the start of the study was 10.8 years in the somatropin group compared to 13.2 years in the placebo group. Six patients (nos. 1, 3, 6, 7, 14 and 20) were diagnosed as GH-deficient for less than two years prior to the study start but all these patients had other hormone deficiences. With regard to etiology and other pituitary hormone deficiencies, there were no important differences between the groups.

Patient no 2 had hyperuricemia diagnosed 1981, patient no 8 had psoriasis diagnosed 1989 and patient no 10 had had attacks of dizziness since 1987.

4.0 CONCOMITANT THERAPY

Patients with pituitary hormone deficiencies other than GH continued their routine replacement therapy when entering the trial. Changes in concomitant medication during the trial were recorded in seven patients in the somatropin group and in seven patients in the placebo group.

The changes in concomitant therapy in the somatropin group consisted of: temporary dose adjustments in cortisone acetate in three patients; no. 7, due to joint pain, no. 2, treated with hydrocortisone due to abdominal pain and no. 8, due to acute tonsillitis (this patient was at the same time also treated with erythromycin). Dose adjustments in cortisone acetate and thyroxine in patient (no. 19) were permanent. One patient (no. 1) stopped one treatment of pituitary insufficiency (nandrolone) and one patient (no. 12) stopped LH/FSH (estradiol) treatment. One patient (no. 13) was treated for tension headache.

In the pl/somatropin group, changes in concomitant therapy consisted of adjustments in cortisone acetate in two patients (nos. 5 and 20) due to gastroenteritis (patient no. 20) and adrenal insufficiency (patient no. 5). One patient (no. 3) had lumbago, another (no. 14) developed a cough and one patient (no. 16) was diagnosed with Herpes Zoster. Two patients (nos. 17 and 18) developed infections: bronchitis (no. 17) and pharyngitis (no. 18). Both were treated with penicillin.

4.1 Study medication

4.2 STUDY PRODUCT

During the first four weeks of the study, the dose target dose: 0.375 mg/kg/week). During the following five months, the (target dose: 0.75 mg/kg/week) in all patients except for patients nos. 7, 8 and 13 (all on somatropin). In patient no. 7 the dose was reduced from 0.78 to 0.63 mg/kg/week from the second month. Patient no. 8 had a dose reduction from 0.69 to 0.48 mg/kg/week between the third and the fourth month and an increase of the dose to 0.66 mg/kg/week from 4 months. In patient no. 13 the dose was reduced from 0.72 to 0.54 mg/kg/week from the second month.

At the end of the 6 to 12-month open period, 18 of 20 patients received a dosage which was within the range of of the intended dosage of 0.75 mg/kg/week.

4.3 COMPLIANCE

The number of missed injections was asked for at each visit. The number of patients who missed injections during the 0 to 6-month double-blind phase are shown in Table 1 below.

Table 1 Number of patients with missed injections during the double-blind 0-6 month phase.

	Somatropin n=10	Placebo n=10
No. of patients with missed injections	3	6
<5% missed injections	3	6
≥5% missed injections	0	0
Withdrawn patients during the period	0	0

In the pl/somatropin group patient no. 11 missed more than 10% of the injections corresponding to 77 injections (42.3%) and patient no. 14 missed more than 5% of the injections corresponding to 10 injections (5.5%) during the period 18 to 24 months with somatropin treatment. In the pl/somatropin group patient no. 18 missed more than 10% of the injections corresponding to 34 injections (15.2%) during the period 0 to 6 months with somatropin treatment.

Patient no. 15 in the somatropin group missed more than 5% of the injections during the 12 to 18-month open period corresponding to 17 injections (8.7%).

5.0 Efficacy

5.1 CLINICAL EFFICACY VARIABLES

5.1.1. Clinical efficacy variables, double-blind period

Body composition
Lean body mass

BIA method: The mean value of lean body mass at baseline was 51.8 kg for the somatropin group and 53.5 kg for the placebo group. After 6 months of treatment there was an increase of 2.8 kg in the somatropin group (p=0.002). The difference between the groups was statistically significant (p=0.028).

DEXA method: The mean value of lean tissue at baseline was 45.5 kg for the somatropin group and 49.0 kg for the placebo group. For the somatropin group there was an increase of 2.7 kg (p=0.004) at 6 months. There was a statistically significant difference between the groups (p=0.009).

Table 2 **Effects of treatment on body composition by bioelectrical impedance analysis (BIA) and DEXA during the 0 to 6-month double-blind period. Absolute change from baseline over time by treatment group.**

	Somatropin group			Placebo group			
	Baseline n=10	Change 0-6 months n=10		Baseline n=10	Change 0-6 months n=10		
Variable	**mean±SD**	**mean±SD**	**p***	**mean±SD**	**mean±SD**	**p***	**p****
Lean body mass (kg) BIA	51.8±12.6	2.8±1.3	**0.002**	53.5±10.1	0.5±3.3	n.s.	**0.028**
Lean body mass (kg) DEXA	45.5±10.6	2.7±1.4	**0.004**	49.0±10.5	0.4±1.6	n.s.	**0.009**

p* = p-value within group
p** = p-value between groups

Circumferences

The effects on circumferences are shown in Table 3 below.

The mean value of waist circumferences at baseline was 93.1 cm for the somatropin group and 92.6 cm for the placebo group. After 6 months of treatment there was a decreasing trend of 2.4 cm for the somatropin group (p=0.068). The difference between the treatment groups was statistically significant (p=0.045).

Table 3 **Effects of treatment on body circumferences during the 0 to 6-month double-blind period. Absolute change from baseline over time by treatment group.**

	Somatropin group					Placebo group					
	Baseline n=10		Change 0-6 months n=10			Baseline n=10		Change 0-6 months n=10			
Variable	**mean**	**SD**	**mean**	**SD**	**p***	**mean**	**SD**	**mean**	**SD**	**p***	**p****
Waist (cm)	93.1	22.5	-2.4	3.4	0.068	92.6	12.8	1.2	4.4	n.s.	**0.045**
Hip (cm)	102.5	14.5	-1.8	2.6	0.070	100.8	9.0	0.2	3.0	n.s.	0.074
Waist/Hip ratio	0.9	0.1	0.0	0.0	n.s.	0.9	0.1	0.0	0.0	n.s.	n.s.

p* = p-value within group
p** = p-value between groups

Bone mineral density

Femur neck: For the somatropin group there was a decrease of 3.21% from the mean baseline value of 0.91 g/cm^2 (p=0.027). No change was noted for the placebo group. There was a statistically significant difference between the groups (p=0.006).

There were no significant changes in any of the other bone mineral density assessments within or between the two groups.

Physical exercise capacity

There were no statistically significant changes or differences in physical exercise capacity during the double-blind period.

Muscle Strength

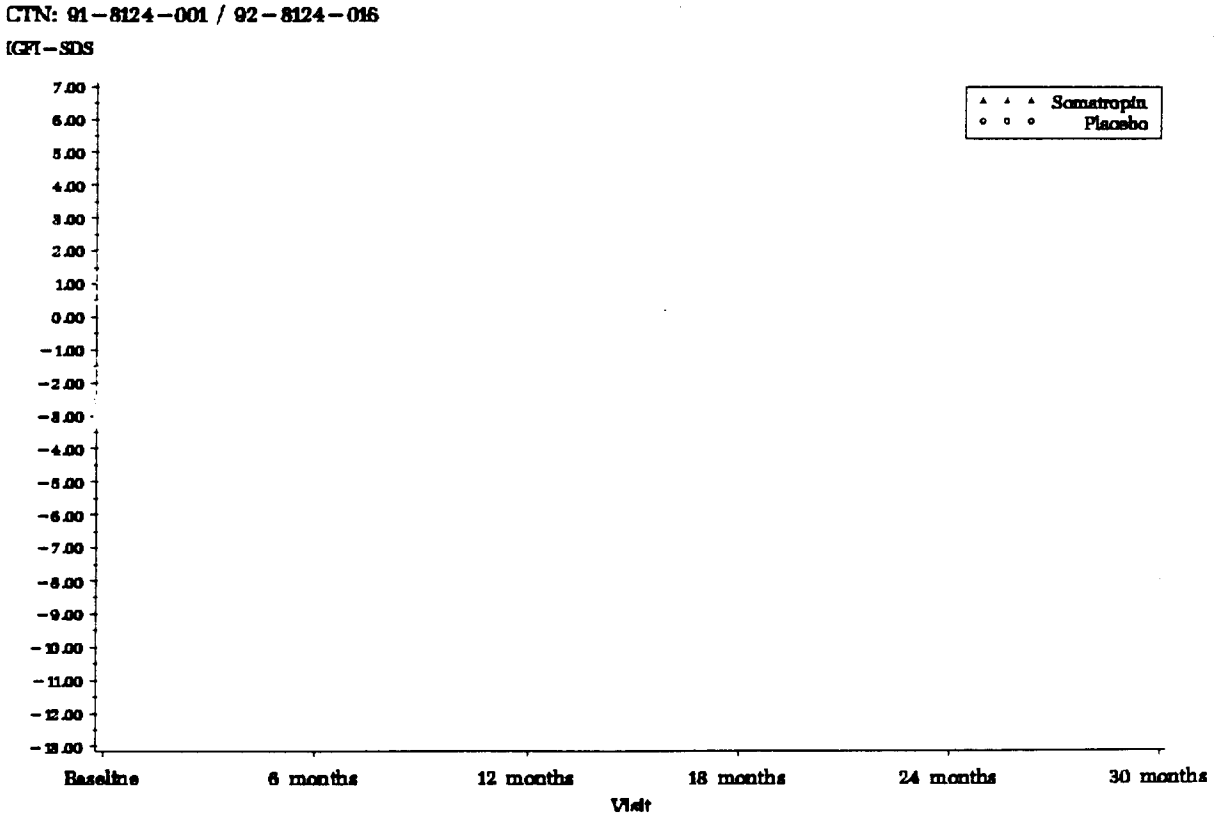
Left leg: There were no statistically significant differences between the somatropin group and the placebo group.

Right leg: There were no statistically significant differences between the somatropin group and the placebo group.

IGF-I

As shown in the following diagram IGF-I increased significantly in subjects receiving GH. Most of the subjects normalized IGF-I levels and two individuals had super physiological levels of IGF-I. This latter trend was seen also in the extension studies suggesting that GH dose may be excesive high.

Figure 1 Individual IGF-I SDS



LIPIDS

No significant changes between groups were seen in all lipid profiles..

5.2 EFFICACY SUMMARY

At the end of the **double-blind study phase** those patients who received somatropin showed a statistically significant increase in total body water and muscle mass (lean body mass) and a statistically significant decrease in fat mass (body fat) resulting in an improved lean/fat ratio compared to the placebo treated patients. The bone mineral density in the femoral neck, decreased statistically significantly. The IGF-I levels as well as the IGF-SDS showed a statistically significant increase for the somatropin group as compared to the placebo group.

6.0 Safety

6.1 CLINICAL SAFETY VARIABLES

Physical examination

Double-blind period

There were no statistically significant differences in changes in height, weight, systolic blood pressure, diastolic blood pressure and pulse rate between the groups during the double-blind 6-month period.

6.2 LABORATORY SAFETY VARIABLES

Double-blind period

The fasting blood glucose at baseline was 4.5 mmol/l and 4.2 mmol/l for the somatropin group and placebo group, respectively. There was an increase of 0.6 mmol/l (p=0.010) in blood glucose for the somatropin group during the first 6 months.

The fasting insulin increased by 8.8 mU/l (p=0.006) for the somatropin group during the double-blind period. The mean baseline insulin was 12.2 mU/l and 17.9 mU/l for the somatropin group and placebo group, respectively.

The blood HbA1c at baseline was 5.3% for the somatropin group and 4.7% for the placebo group.

The mean baseline serum ALAT value was 0.62 IU/l and 0.52 IU/l for the somatropin group and placebo group, respectively. There was a decrease of 0.25 IU/l (p=0.004) for the somatropin group. There was a statistically significant difference (p=0.017) between the groups during the double-blind period. All changes in laboratory safety are given in Table 4.

Table 4 **Effects of treatment on laboratory safety variables during the 0 to 6-month double-blind period. Absolute change from baseline over time by treatment group.**

	Somatropin group					Placebo group					
	Baseline n=10		Change 0-6 months n=10			Baseline n=10		Change 0-6 months n=10			
Variable	mean	SD	mean	SD	p*	mean	SD	mean	SD	p*	p**
B-hemoglobin (g/100 ml)	137	13	2	5	n.s.	140	16	3	6	n.s.	n.s.
B-leukocytes (x 10 ^{9} /l)	6.1	1.3	0.1	1.0	n.s.	7.4	1.0	-0.1	0.9	n.s.	n.s.
B-thrombocytes (x 10 ^{9}/l)	210	51	17	43	n.s.	287	43	9	40	n.s.	n.s.
B-glucose, fasting (mmol/l)	4.5	0.9	0.6	0.6	**0.010**	4.2	0.3	0.2	0.3	0.098	0.069
f-Insulin (mU/l)	12.2	3.0	8.8	12.4	**0.006**	17.9	13.5	-0.6	11.4	n.s.	0.095
B-HbA1c (%)	5.3	2.0	-1.1	0.9	**0.006**	4.7	1.4	-0.7	0.8	**0.010**	n.s.
Creatinine (µmol/l)	74	14	2	7	n.s.	75	20	6	9	0.098	n.s.
S-Na (mmol/l)	141	3	2	2	0.063	140	1	2	2	**0.027**	n.s.
S-K (mmol/l)	4.0	0.3	0.0	0.3	n.s.	4.2	0.1	-0.1	0.2	n.s.	n.s.
S-ASAT (IU/l)	0.53	0.15	0.03	0.12	n.s.	0.41	0.11	0.10	0.20	n.s.	n.s.
S-ALAT (IU/l)	0.62	0.28	-0.25	0.26	**0.004**	0.52	0.19	0.08	0.30	n.s.	**0.017**
S-urea (mmol/l)	5.2	1.3	-0.4	1.0	n.s.	4.7	1.2	-0.3	1.6	n.s.	n.s.

p* = p-value within group
p** = p-value between groups

6.3 ADVERSE EVENTS

Adverse events were actively asked for in both studies. Adverse events related to fluid retention were specifically asked for. Codes for body system and preferred terms, according to WHO recommendations, have been used.

Double-blind period

A total of 22 adverse events were reported during the 0 to 6-month double-blind period; 8 patients in the somatropin group and 1 patient in the placebo group. The most frequently reported adverse events were arthralgia (8 events), stiffness of extremities (4 events), edema peripheral (2 events) and pain in extremities (2 events). All other events were single reports.

Table 5 Frequency of adverse events

Body system	Preferred term (no. of patients)	Number of events	Relation (by event)		Treatment groups (by event)		
			Unlikely	Poss/ Prob.	Placebo double-blind (0-6 m)	somatropin double-blind (0-6 m)	somatropin open (6-24/30 m)
Skin & Appendages disorders	Eczema (1)	1	-	-	-	-	1
	Psoriasis (1)	1	-	-	-	-	1
	Total	**2**	**0**	**0**	**0**	**0**	**2**
Musculo-Skeletal system disorders	Arthralgia (12)	14	4	10	-	8	6
	Back pain (3)	4	2	-	-	-	4
	Fracture (1)	1	1	-	-	-	1
	Myalgia (3)	4	-	3	-	1	3
	Stiffness of extremities (7)	8	-	8	-	4	4
	Tendinitis (1)	2	2	-	-	-	2
	Total	**33**	**9**	**21**	**0**	**13**	**20**
CNS & PNS disorders	Dizziness (1)	1	1	-	-	-	1
	Headache (1)	1	1	-	-	-	1
	Migraine (1)	1		-	-	-	1
	Total	**3**	**2**	**0**	**0**	**0**	**3**
Vision	Visual field defect (1)	1	-	-	-	-	1
	Total	**1**	**0**	**0**	**0**	**0**	**1**
Psychiatric	Depression (2)	2	1	-	-	-	2
	Total	**2**	**1**	**0**	**0**	**0**	**2**
Gastro-Intestinal disorders	Abdominal pain (1)	1	1	-	-	-	1
	Diarrhoea (1)	1	1	-	-	-	1
	Gastritis (1)	1	-	-	-	-	1
	Gastroenteritis (1)	1	1	-	-	-	1
	Hemorrhage rectum (1)	1	1	-	-	-	1
	Vomiting (1)	1	1	-	-	-	1
	Total	**6**	**5**	**0**	**0**	**0**	**6**
Metabolic & Nutritional disorders	Thirst (1)	1	-	1	-	-	1
	Total	**1**	**0**	**1**	**0**	**0**	**1**
Endocrine disorders	Adrenal insuff (4)	5	5	-	-	1	4
	Total	**5**	**5**	**0**	**0**	**1**	**4**
Cardio-vascular	Heart disorder (1)	1	1	-	-	-	1
	Hypertension (1)	1	1	-	-	-	1
	Total	**2**	**2**	**0**	**0**	**0**	**2**
Respiratory systems disorder	Bronchitis (2)	2	2	-	-	-	2
	Epistaxis (1)	1	1	-	-	1	-
	Pharyngitis (2)	2	2	-	-	1	1
	Upper resp tract infect. (9)	11	9	-	1	-	10
	Total	**16**	**14**	**0**	**1**	**2**	**13**
General disorders	Edema (1)	1	-	1	-	1	-
	Edema peripheral (7)	7	1	6	-	2	5
	Pain, extremities (3)	4	-	4	-	2	2
	Swelling, peripheral (1)	1	-	1	-	-	1
	Total	**13**	**1**	**12**	**0**	**5**	**8**
Resistance mechan. disorders	Herpes Zoster (1)	1	1	-	-	-	1
	Total	**1**	**1**	**0**	**0**	**0**	**1**
TOTAL		**85**	**40**	**34**	**1**	**21**	**63**

6.4 SERIOUS ADVERSE EVENTS

The listing of serious adverse events is shown in Table 6.

Serious adverse events were reported in 5 patients; four patients in the somatropin group and one patient in the placebo group. In two patients, no 8 (somatropin group) and patient no 20 (placebo group) serious adverse events occured during the double-blind period. In three patients (nos. 2, 8 and 20) serious adverse events were reported twice. A total of 8 serious adverse events were reported during 0 to 24/30 months study period.

Patient no. 2 was a 36-year old male ( ) who had abdominal pain partly due to cortisol deficiency. This was described as two separate events in the CRFs. The patient was completely recovered after 3 days in hospital with cortisone infusion.

Patient no. 8 was a 39-year old (,) female who had acute tonsillitis with high temperature requiring 24 hours in hospital for treatment with cortisol and antibiotics. This was described as two separate events in the CRFs. The patient recovered completely after 3 days.

Patient no. 10 was a 45-year old ( ) male who was observed in hospital for 8 days due to increasingly frequent attacks of dizziness following start of GH treatment. These attacks have occurred since 1987. No clinically significant findings were reported for this observation.

Patient no. 19 was a 57-year old male ( ) who had rectal bleeding. X-ray of colon showed diverticulosis which was the most likely reason for the bleeding. The patient recovered completely.

Patient no. 20 was a 47-year old female (. The patient had gastroenteritis leading to cortisol deficiency that required hospitalization. The patient improved rapidly after cortisol infusion and recovered completely.

Table 6 Listing of Serious Adverse Events

Pat no/ therapy group	Age	Sex	Serious Adverse Event	Pref term WHO	No. of days on Rx* at onset	Severity	Relation with study drug	Action taken with study drug	Outcome
2 somatropin	36	male	Abdominal pain	Abdominal pain	421	Severe	Unlikely	None	Recovered - no residual effects
2 somatropin	36	male	Cortisol deficiency	Adrenal insufficiency	421	Moderate	Unlikely	None	Recovered - no residual effects
8 somatropin	39	female	Acute tonsillitis	Pharyngitis	175	Severe	Unlikely	None	Recovered no residual effects
8 somatropin	39	female	second cortisol deficiency	Adrenal insufficiency	175	Severe	Unlikely	None	Recovered - no residual effects
10 somatropin	45	male	Attacks of dizziness	Dizziness	337	Mild	Unlikely	None	Recovered - no residual effects
19 somatropin	57	male	Rectal bleeding	Haemorrhage rectum	628	Severe	Unlikely	None	Recovered - no residual effects
20 pl/soma	47	female	Gastroenteritis	Gastroenteritis	64	Severe	Unlikely	None	Recovered - no residual effects
20 pl/soma	47	female	Cortisol deficiency	Adrenal insufficiency	526	Severe	Unlikely	None	Recovered - no residual effects

*Rx - somatropin treatment

6.5 SAFETY SUMMARY

Mean weight was increased by 3.3 kg and mean height by 1.3 cm after 24 months with somatropin therapy. No difference compared to placebo was seen during the double-blind phase.

Mean systolic and diastolic blood pressure did not change statistically significantly during the study.

Fasting levels of blood glucose, insulin, and glycated hemoglobin increased during somatropin treatment.

During the placebo-controlled study period trends towards statistically significant differences between the treatment groups were observed for blood glucose and insulin levels. Two patients, nos. 10 and 11, were regarded by the investigator as having clinically significant hyperglycemia at 21 and 18 months, respectively, into the study. It is noteworthy that these patients had elevated HbA1c values at baseline. No patient developed clinical signs of diabetes or withdrew from treatment.

During somatropin replacement, only one additional change of statistical significance was seen in clinical chemistry compared to baseline; a decrease in serum levels of alanine aminotransferase activity (ALAT). However, this change was not apparent during continued treatment.

Adverse events were reported in all 20 patients during somatropin therapy, of which 9 patients reported adverse events already during the double-blind phase (8 patients during somatropin treatment and 1 patient during placebo treatment). The most commonly reported symptoms during the study period were arthralgia (14 events/12 patients), upper respiratory tract infection (11 events/9 patients), stiffness of extremities (8 events/7 patients), edema peripheral (7 events/7 patients), adrenal insufficiency (5 events/4 patients), back pain (4 events/3 patients), myalgia (4 events/3 patients) and pain in extremities (4 events/3 patients). All other events were reported in one or two patients.

Serious adverse events were reported in 5 patients during somatropin replacement, including one who also experienced a serious adverse event during the initial placebo period. A total of 8 serious adverse events occurred: cortisol deficiencies in three patients, which in one (patient no. 8) occurred in relation to an infection, a tonsillitis, and in the other two in conjunction with abdominal pain and gastroenteritis, respectively; one patient had attacks of dizziness and another suffered from rectal bleeding from colon diverticulosis. No event was regarded as causally related to somatropin treatment.

7. DISCUSSION

All 20 patients had severe growth hormone deficiency as demonstrated by very low GH peaks after an appropriate stimulation test. Six of the patients, however, had not been GH-deficient for two years prior to the study start by the date of the diagnosis of their GH deficiency, but were deemed likely to have been growth hormone deficient for two years as they had other pituitary hormone deficiencies and were on stable hormone replacement therapy. No patient had isolated GH-deficiency.

The replacement therapy with thyroxine and sex hormones was unchanged during the study for the majority of the patients. Dose adjustments were made in cortisone medication during the study, but this was not regarded to influence the result of the study.

Compliance to treatment was generally good in most of the patients. However, two patients missed more than 10% of the intended number of injections. There was one withdrawal from treatment during the entire 24-month study period.

Adherence to the study protocol was generally good and without any deviation that might have affected the study results. Hence, the study can be regarded as adequate and well-controlled with respect to the patients studied, compliance to treatment and adherence to study protocol.

During the 6-month placebo-controlled study period, several changes in body composition occurred which are in line with literature data. Total body water, lean body mass, and lean body mass/fat mass ratios increased and the amounts of fat mass decreased with little variability between the results obtained by the different methodologies used: BIA and DEXA. In addition, waist circumference decreased.

The changes in body composition noted during the early phase of the study were essentially maintained during continued treatment; particularly, increases in lean body mass, total body water, and lean tissue of the trunk..

Serum IGF-I levels rose during treatment with a normalization in the majority of the patients. Sensitivity to treatment appears to be individual, as different circulating levels are achieved despite the fact that those with low, normal or high IGF-I levels received virtually identical somatropin dosages. As a group, the used dosages appears correct in order to normalize IGF-I levels, but for the individual patient there is an apparent need to individualize dosing in order to avoid super physiological IGF-I levels.

Treatment was generally well tolerated. One patient did not wish to continue into the long-term continuation study.

Adverse events related to fluid retention with symptoms of, primarily, fullness and sense of tightness of extremities and reported as edema, arthralgia, stiffness and myalgia, were frequent during somatropin treatment, particularly during the first months. Their frequency, intensity and duration are similar to those reported in the literature. Also, carbohydrate metabolism appeared to be affected during treatment with increased levels of fasting blood glucose and fasting insulin.

8. CONCLUSION

The results of this study indicate that GH treatment of GHD adults resulted in significant improvement in body composition particularly increments in lean body mass, decrements in fat and waist circumference. The bone mineral density in the femoral neck, however, decreased statistically significantly. The IGF-I levels as well as the IGF-SDS showed a statistically significant increase for the GH group as compared to the placebo group. GH doses should be individualized for each patinet in order no to induce super physiological levels of IGF-I.