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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

19-676/S-016

Medical Review(s)

Medical Officer's Review of NDA 19-676,
Supplement #16 for Nutropin

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DMEDP/ODE II/ORM/CDER HFD-510

Letter Date: 11 June 1999

Stamp Date/Date Received, CDER:: 14 June 1999

Date Received, Medical Officer: 30 June 1999

Date Review Completed: 17 March 2000

Drug Name: Nutropin

Generic Name: Somatropin (rDNA origin) for
Injection

Trade Name: Nutropin

Sponsor: Genentech, Inc.

1 DNA Way

South San Francisco, CA 94080-4990

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1.1 Pharmacological Category: Recombinant human growth hormone (rhGH).

Related Drugs: All of the rhGH products - all presently formulated for daily injection.

1.2 Modification of Indication: Treatment of patients with growth failure due to lack of endogenous GH secretion with larger amounts of rhGH during puberty results in an improved near adult height (NAH).

1.3 Dosage Form, Dosage Recommended and Route of Administration: Reconstituted injectable suspension. The proposed dosage is 0.7 mg/kg/week administered subcutaneously (SC) as a daily injection.

1.4 On-Site Inspections by CDER: It was decided by this medical reviewer and his team leader that on-site inspections could be waived for this submission because of the small numbers of patients treated at any give site.

1.5 Review of Financial Disclosure: A review of financial disclosure was not necessary because the sponsor certified that the clinical investigators had no financial arrangements with the sponsor of the covered studies.

1.6 Correspondence with Sponsor/Genentech:

11/19/99 Safety and Efficacy Updates arrive as planned.

12/13/99 Telcon involving myself and Ms. Fiona Cameron (Senior Manager, Regulatory Affairs). Question posed by me regarding location of _____ November 1999 submission.

1/10/00 Telcon involving myself and Ms. Cameron. _____ located in November 1999 submission.

1/28/00 Telcon involving myself and Dr. Ken Attie (Senior Research Physician). Request made by me for additional statistical analyses regarding subset of patients with acromegaloid complaints.

2/10/00 Additional statistical analyses arrive as planned.

2/25/00 Telcon involving myself, Dr. Attie and Ms. Cameron.

Request made by me for additional statistical analyses regarding IGF-1 responses in the 2 dose groups and possible predictors of optimal response.

3/3/00 Additional statistical analyses arrive as planned.

3/3/00 Telcon involving myself and Ms. Cameron. Two additional questions posed by me regarding protocol design.

3/6/00 Telcon involving myself and Ms. Cameron. Request made by me for specific figures and tables in a more accessible format.

3/7/00 Answers to questions posed by me on 3/3/00 received by secure email from Ms. Cameron.

3/9/00 Revised figures and tables arrive as planned.

3/13/00 Telcon involving myself and Ms. Cameron. Request made for 1 specific figure in more accessible format.

3/14/00 Requested figure arrives as planned.

2.1 Materials Reviewed:

All clinical data in the original 8 volume submission received on 6/14/99. The data were primarily reviewed electronically after the NDA submission was placed on a secure website by CDER personnel.

Safety (and Efficacy) Update received on 11/19/99 - also reviewed electronically.

Supplemental statistical analyses received in 2/00 and 3/00.

2.2 Relevant INDs and NDAs:

Nutropin	NDAs 19-676 and 20-168, and IND	—
Nutropin AQ	NDA 20-522 and IND	—
Protropin	NDA 19-107 and IND	—

3 Chemistry/Manufacturing Controls

See Chemistry Review in the original Nutropin NDA (19-676).

4. Preclinical Pharmacology/Toxicology

See Pharmacology/Toxicology Review. In view of the well known properties of rhGH, a standard battery of toxicology studies was not required.

5. Related Clinically Oriented Reviews

5.1 Statistical Review

See Statistical Review. The medical reviewer collaborated with the statistical reviewers.

5.2 Biopharmaceutics Review and Human Pharmacology, Pharmacokinetics (PK) and Pharmacodynamics (PD)

See Biopharmaceutics Review in the original Nutropin NDA (19-676): A formal review was not accomplished for this supplemental NDA because PK studies were not submitted and the PK characteristics of rhGH are well established.

6 Clinical Background

6.1 Post-Marketing Experience

Nutropin (and other recombinant human growth hormone [rhGH] products) has been used to successfully treat growth hormone deficiency (GHD) in thousands of patients during the last decade. The observed safety profile has been good. The currently recommended regimen is 0.3 mg/kg/wk administered as daily or 6 times per week injections. The serious adverse effects associated with rhGH therapy are rare.

6.2 Foreign Experience None.

6.3 Relevant Literature

Literature regarding the use of rhGH in the treatment of children with GHD, in particular during the pubertal years, was reviewed for the last 15 years. Appropriate references are cited in the text of this review.

6.4 Relevant Background Information/Rationale for all Clinical Studies

At the present time, children with GHD are treated with a constant dosage of rhGH per kilogram of body weight (0.3 mg/kg/week divided into daily doses) throughout childhood and adolescence (puberty). However, the final adult height (FAH) achieved in these children is often more than 2 standard deviations (SD) below that predicted by their parental heights (1). Although this treatment regimen typically results in significant gains in predicted adult height (PAH) before puberty, such gains are generally not seen during puberty. This may be due to inadequate dosing of rhGH during adolescence, resulting in a subnormal pubertal growth spurt. Genentech Study M0380g investigated the utility of a higher dose of rhGH during puberty for increasing adult height (AH).

The normal pubertal growth spurt is thought to be a consequence of the direct and/or indirect actions of sex steroids on cartilage and bone, associated with increased circulating and/or local concentrations of GH and insulin-like growth factor I (IGF-I). Sex steroids, primarily estrogen, eventually result in epiphyseal fusion and the cessation of growth.

During normal puberty, the blood levels of GH and IGF-I increase dramatically and are much greater than those observed in childhood or adulthood (2-9). Rose et al (2) demonstrated an approximate doubling of the mean 24 hour GH concentration in boys and girls from ages 8 to 14 years. It is generally agreed that the increased concentration of

GH (and IGF-I) during puberty contributes at least in part to the pubertal growth spurt.

The height gained during the pubertal growth spurt is one of the main determinants of FAH accounting for approximately 17% of adult male height and 12% of adult female height (10). It is these differences that are largely responsible for differences in final height of adult men and women (11).

The pubertal development of children with GHD has been reported to be impaired (delayed and shorter duration) compared with normal adolescents (12-14). Attempts to maximize growth during puberty have included experimental treatment with gonadotropin-releasing hormone (GnRH) analogs to inhibit puberty and thus delay sex steroid-induced epiphyseal closure. In 1 study, early pubertal GHD children treated with rhGH and GnRH analog for 3 years achieved greater PAH than GHD children treated with rhGH plus placebo (15). Although delaying the progression of puberty resulted in a decreased growth rate, bone age (BA) advancement was significantly retarded.

Several investigators have evaluated the efficacy of larger replacement doses of rhGH during puberty (to mimic the normal physiologic increase) to enhance the pubertal growth spurt of GHD children. In the most recently published study, treatment of pubertal GHD subjects with 35 ug/kg/day Q12H resulted in greater pubertal height gain than that observed in pubertal GHD patients treated with 70 or 30 ug/kg/day - although mean FAH, when corrected for parental height, was between 0 and 1 standard deviation score (SDS) in all 3 treatment groups (16). Of note, the mean levels of IGF-I were similar in all 3 treatment groups and the individual levels of IGF-I remained within the upper normal range. In another study, 4 year results showed that GHD boys randomized to "high dose" rhGH (~0.4 mg/kg/week) at the onset of puberty achieved higher mean growth rates than GHD boys treated with "standard doses" of rhGH (~0.2 mg/kg/week) - although this trend did not reach statistical significance (17-18). Although the rate of BA maturation was similar in the 2 dose groups, pubertal maturation appeared to be accelerated in the boys receiving the "high dose" of rhGH - which led the authors to speculate that the "high dose" of rhGH may result in a lower height outcome.

Study M0380g was designed by the sponsor to compare the efficacy, safety and tolerability of 0.7 mg/kg/week and 0.3 mg/kg/week of rhGH (Nutropin, Genentech) in the treatment of early pubertal GHD subjects. The sponsor hypothesized that the larger dose would result in greater increases in growth rate (without undue advancement of BA), and therefore a greater AH.

7 Description of Clinical Data Sources

7.1 Study Design for Clinical Trial M0380g

Table 1. M0380g - Brief Summary of Clinical Trial

Study Number	# of Sites	Design	Treatment Arms	Duration of Treatment	Patient Type
M0380g	20	Open Label, Randomized, Phase III	0.3 mg/kg/wk (n=49) 0.7 mg/kg/wk (n=48)	Attainment of near-adult height	Previously Treated patients

7.2 Patient Disposition See Table 3 (M0380g).

7.3 Patient Demographics See Table 4 (M0380g).

7.4 Extent of Exposure See Section 8.1.4.9.1 (M0380g).

8 Reviewer's Critical Analysis of Individual Studies

8.1 M0380g

8.1.1 Objectives

The primary objective of this study was to compare the safety and efficacy of Nutropin (somatropin [rDNA origin] for injection) administered daily at 2 dosage levels in improving linear growth and AH in pubertal individuals with significant growth failure due to GHD.

A secondary objective was to compare bone mineral density (BMD) at the end of treatment between the 2 treatment groups.

8.1.2 Study Design

8.1.2.1 Description of the Study

M0380g was a Phase III, multicenter (20 medical centers), open label study of Nutropin in pubertal children with GHD initiated on 19 March 1993 and completed on 12 April 1999. Subjects were enrolled and randomized to either a standard dose (0.3 mg/kg/wk, n=49) or a high dose (0.7 mg/kg/wk, n=48) of rhGH administered as a daily injection. During randomization, an effort was made to maintain balance between the 2 dose groups with respect to sex, schedule of previous rhGH therapy (three times weekly or daily), BA, chronological age (CA),

pubertal status (Tanner stage), previous 1 year growth rate, height SDS for age and sex, and study center. The protocol-defined primary outcome measure was AH (e.g., defined as epiphyseal closure on hand-wrist BA X-ray and no change [<1 cm] in height for 1 year), but because many subjects had not achieved AH after several years of treatment, the primary outcome measure was changed to near-adult height (NAH) (e.g., defined as BA ≥ 16 years for males and ≥ 14 years for females, and growth rate <2 cm/yr for 1 year). Additional measures of growth assessed included change from baseline to last measured height (LMH), change in height SDS, change in BA, and change in Bayley-Pinneau PAH (B-P PAH). Patients were monitored carefully for any and all adverse effects, in particular those known to be associated with rhGH therapy. Follow-up visits were projected and accomplished at 3 month intervals and included updated histories (including reports of any intercurrent illnesses, use of concomitant medications, and occurrence of adverse events) and physical examinations (including precise height measurements). Laboratory profiles (including blood sugars, glycosylated hemoglobin and IGF-I levels) were obtained every 3 months for 2 years and then annually. BA assessments were performed every 6 months.

Treatment with Nutropin was discontinued when NAH was achieved. Follow-up visits for height measurements continued every 6 months until AH was reached. Dual energy X-ray absorptiometry (DEXA) scans (whole body and anteroposterior [AP] spine) were performed at or within 1 month of treatment discontinuation.

8.1.2.2 Protocol Amendments

The protocol was amended 6 times. The following are the most significant changes made: 1) The first amendment, dated 4 January 1993 (Serial No. 108 to IND [redacted]) revised the study design to include dose modification based on weight changes; 2) The second amendment, dated 25 August 1993 (Serial No. 129 to IND [redacted]) updated the Informed Consent to include the risk of intracranial hypertension; 3) The third amendment dated 3 December 1993 (Serial No. 132 to IND [redacted]) changed the inclusion criteria regarding previous treatment with rhGH to "previous treatment with rhGH for at least 6 months" from "previous treatment with rhGH for at least 1 year at 0.25 to 0.35 mg/kg/week"; 4) The fifth amendment, dated 11 June 1996 (Serial No. 183 to IND [redacted]), added a secondary outcome measure - a comparison of BMD determined by DEXA scan in the 2 treatment groups at the time of treatment discontinuation; 5) The sixth amendment, dated 5 March 1997 (Serial No. 191 to IND [redacted]), allowed subjects who did not progress normally through puberty to receive sex steroid replacement therapy while receiving Nutropin treatment. In addition, the Risks and Discomforts section of the Informed Consent was updated to include possible joint pain and the possible effect of Nutropin on the concentration of steroids, anticonvulsants, and cyclosporin.

8.1.3 Materials and Methods

8.1.3.1 Subjects

8.1.3.1.1 Subject Selection

The protocol called for the enrollment of at least 60 pubertal children with GHD previously treated with rhGH. In fact, 97 pubertal children with GHD were enrolled in the study and randomized to receive 1 of 2 dose regimens of Nutropin:

Standard dose group: 0.3 mg/kg/week (49 subjects)

High dose group: 0.7 mg/kg/week (48 subjects)

8.1.3.1.2 Inclusion Criteria

Subjects had to fulfill the following criteria to be eligible for entry into the study:

- Documented GHD by two standard stimulation tests with peak GH levels of <10 ng/mL prior to original rhGH treatment
- Previous treatment with rhGH for at least 6 months
- Males with CA 10-18 years, testes ≥ 4 mL, and BA ≤ 14 years
- Females with CA 8-16 years, breasts Tanner stage ≥ 2 , and bone age ≤ 12 years
- Thyroxine (T4) level within normal limits
- Signed Informed Consent by parent or legal guardian and subject as appropriate

Reviewer Comment:

Although not explicitly stated in the protocol, height data needed to be available for at least 6 months prior to study enrollment (see screening visit Case Report Form).

8.1.3.1.3 Exclusion Criteria

Subjects who met any of the following criteria were excluded from study entry:

- thyroid stimulating hormone (TSH), adrenocorticotrophic hormone (ACTH), or gonadotropin deficiency (excepting TSH deficient subjects with normal T4)
- Prior or current treatment with estrogens or androgens
- Spinal irradiation
- Growth failure due to other reasons including: disorders of genitourinary, cardiopulmonary, gastrointestinal, or nervous systems; nutritional or vitamin deficiencies; osteochondrodystrophies or any

dysmorphic syndrome or chromosomal abnormality, including Turner's syndrome

--Intrauterine growth retardation

--History of malignancy diagnosed and/or treated within the past year

--Current enrollment in another Genentech clinical trial utilizing Nutropin

Reviewer Comment:

Although not explicitly stated in the protocol, potential subjects with the following diagnoses/disorders were excluded from the study as well:

-- Clinical suspicion and/or laboratory confirmation of previously unknown and untreated endocrine disease including hypo- or hyperthyroidism, hypoadrenalism and Cushing's syndrome, and treatment with supraphysiologic amount of glucocorticoid compound

--Diabetes mellitus

--Hypothalamic/pituitary tumors diagnosed or treated in the past year

--Allergy or sensitivity to any components of Nutropin formulation

--Known bleeding disorders

8.1.3.1.4 Subject Discontinuation

Subjects were discontinued for the following reasons:

---Medical conditions that required study discontinuation

---Intercurrent illness that could have, in the judgment of the investigator, tended to affect assessments of clinical and mental status to a significant degree

---Noncompliance with the protocol (e.g., more than 2 weeks of treatment missed in any 3 month period or evidence of consistent noncompliance)

---Subject, parent, or guardian desire to discontinue participation

8.1.3.1.5 Subject Replacement

No comment in the submission.

8.1.3.2 Study Treatment

8.1.3.2.1 Method of Treatment Assignment

Subjects were randomized to either the standard dose or the high dose arm in such a way as to maintain a balance with respect to sex, schedule of previous rhGH therapy (three times weekly or daily), BA, CA, pubertal status (Tanner stage), previous 1 year growth rate, height SDS, and study center.

8.1.3.2.2 Formulation

Nutropin was supplied as a sterile, lyophilized powder in 10 mL vials. Each vial contained 10 mg of somatropin, 90 mg of mannitol, 3.4 mg of glycine, USP, for isotonicity, and 3.4 mg of sodium phosphates (0.8 mg of sodium phosphate monobasic and 2.6 mg of sodium phosphate dibasic) for pH balance.

The vial contents were reconstituted with 1-5 mL of Bacteriostatic Water for Injection, USP (benzyl alcohol-preserved) provided by Genentech, Inc.

8.1.3.2.3 Dosage and Administration

See Section 8.1.3.1.1.

8.1.3.2.4 Dosage Modification

The Nutropin dose was adjusted every 6 months for weight changes in all study patients.

8.1.3.2.5 Concomitant Therapy

Other medications which were considered necessary for the subject's welfare and would not interfere with the study medication or affect growth were given at the discretion of the investigator.

Subjects who did not progress normally through puberty were considered for sex steroid replacement therapy. The dosing and management of such subjects were discussed with the Medical Monitor on an individual basis.

8.1.3.3 Study Assessments

8.1.3.3.1 Screening and Pre-treatment Assessments

To confirm subject eligibility and to establish baseline measurements, the following assessments were accomplished:

- Verification that all admission criteria were met, including documentation of GHD based on at least two GH stimulation tests
- Medical history, including prior height data
- Complete physical examination, including height (average of 3 heights), weight, and Tanner stage
- BA X-ray
- Complete blood count (CBC) with differential and platelet count
- Complete urinalysis (UA) with microscopic examination

---Serum chemistry panel, including total protein, albumin, globulin, A/G ratio, total bilirubin, ALT (SGPT), AST (SGOT), alkaline phosphatase, GGT, LDH, BUN, creatinine, uric acid, calcium, inorganic phosphorous, cholesterol, sodium, potassium, chloride, CO2

---T4

---Hemoglobin A_{1c}

---2 hour glucose tolerance test (GTT) (fasting and 2 hour glucose, insulin and c-peptide levels)

---Anti-GH antibodies

---IGF-I

---Testosterone (males)

---Estradiol (females)

8.1.3.3.2 Assessments during Treatment

8.1.3.3.2.1 Efficacy Parameters

8.1.3.3.2.1.1 Primary Efficacy Parameter**

The protocol-defined primary outcome measure was AH (e.g., defined as epiphyseal closure on hand-wrist BA X-ray and no change [<1 cm] in height for 1 year), but because many subjects had not achieved AH after several years of treatment, the primary outcome measure was changed to NAH (e.g., defined as BA ≥ 16 years for males and ≥ 14 years for females, and growth rate <2 cm/yr for 1 year). At these BA, -98% of AH has been reached (24). Note: If BA was missing at the LMH, it was extrapolated from the previous BA using the change in CA. Extrapolation of BA was used for the sole purpose of determining eligibility of the subject for this analysis; it was not used in any other analyses.

8.1.3.3.2.1.2 Supportive Efficacy Parameters**

Additional measures of growth assessed included change from baseline to LMH, growth rate, change in height SDS, change in BA, and change in B-P PAH.

Change in IGF-I levels and the titer of anti-GH antibodies were determined as well.

Standardized Height/Height SDS was computed as follows:

Actual Height - Mean Height of Normal Subjects of Same Age and Sex / Height SD of Normal Subjects of Same Age and Sex. Height standardized for age and sex permits comparisons of subjects' heights with normal children of the same CA and sex. BA determinations using the method were performed at the

by a reviewer masked to information relative to subject and dose. IGF-I and anti-GH antibody titer determinations were performed by Genentech, Inc. (South San Francisco, CA).

**During the study, height and Tanner stage were determined every 3 months, BA was assessed every 6 months, and IGF-I and anti-GH antibody measurements were performed every 3 months for 2 years and then every 6 months until study completion. See Table 2.

Reviewer- Comment:

Although not explicitly stated in the protocol, the prestudy growth rate was determined as follows: For all subjects, height measurements at least 6 months prior to the start of the study were collected. The height used for the prestudy growth rate had to be at least 6 months prior to study enrollment (see screening visit Case Report Form). Any prestudy growth rates based on heights less than 6 months prior to study enrollment were considered unreliable (2 in the standard dose group and 1 in the high dose group), and were not used when analyzing baseline characteristics.

8.1.3.3.2.1.3 Secondary Efficacy Parameter

BMD assessment was performed at study discontinuation only. To correct the spine BMD determined by DEXA for bone size, bone mineral apparent density (BMAD) was calculated for the lumbar spine using the spine BMAD = bone mineral content (BMC) + area^{3/2} equation. Total body BMC was partially corrected for body size, calculated as BMC + height.

8.1.3.3.2.2 Safety Parameters

Safety assessments were made based on adverse event reports, histories and physical examinations every 3 months, and laboratory studies at appropriate intervals. See Table 2.

CBC, differential, platelet count, serum chemistry panel, thyroid function tests, insulin and C-peptide levels, hemoglobin A_{1c} measurements, and urinalyses were determined for all subjects by

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Table 2. M0380g - Flowchart of Baseline and On-Study Efficacy and Safety Parameters*

Evaluations	Baseline	3*	6,18*	9,15,21*	12,24, 36,48, 60,72*	27,33, 39,45, 51,57, 63,69*	30,42, 54,66*
Medical history	X						
Interval medical history		X	X	X	X	X	X
Physical exam	X	X	X	X	X	X	X
Height and weight	X	X	X	X	X	X	X
Blood pressure and temperature	X	X	X	X	X	X	X
Tanner stage	X	X	X	X	X	X	X
Testosterone (males)	X		X		X		X
Estradiol (females)	X		X		X		X
Bone age	X		X		X		X
Anti-GH antibodies	X	X	X	X	X		X
CBC, diff, platelets	X	X	X	X	X		
Complete UA	X	X	X	X	X		
Chemistry panel	X	X	X	X	X		
T4	X				X		
Hemoglobin A _{1c}	X	X	X	X	X		X
2 hour GTT with glucose, insulin & C-peptide levels	X	X			X		
IGF-I	X	X	X	X	X		

*Table derived from submission. *Months

8.1.3.4 Statistical Analysis

8.1.3.4.1 General Comments

Fisher's exact test for proportions, the two-sample t-test for between-group comparisons, and the paired t-test for within-group changes were used for assessments of safety and efficacy. The significance level for all comparisons was 0.05; no adjustments were made for multiple testing. Log values were used when necessary because of skewed data. Simple linear regression lines were included in some graphs for visual reference only. Statistical analyses were performed using SAS and S-Plus.

8.1.3.4.2 Sample Size Calculation

The original primary outcome measure was AH. Assuming a 2.0 cm difference in mean AH between the 2 dose groups, a SD of 2.0 cm (after adjustment for covariates), and 30 subjects in each dose group, there was ~95% power using a two-tailed test at the $\alpha=0.05$ level.

8.1.3.4.3 Efficacy Analysis

8.1.3.4.3.1 Primary Efficacy Analysis

NAH were compared in the standard dose and high dose groups using analysis of covariance (ANCOVA). The protocol-defined covariates were sex, previous growth rate, schedule for previous rhGH therapy (three times weekly or daily), baseline height, CA, BA, sex steroid replacement therapy, and pubertal status (Tanner stage).

8.1.3.4.3.2 Intent to Treat (ITT)

An ITT analysis, including all enrolled subjects, was performed to support the primary analysis. In this analysis, the LMH obtained (during treatment or at a posttreatment visit) was used for all subjects, including those in whom NAH was not achieved. As with the analysis of NAH, the LMH were compared in the standard dose and high dose groups using ANCOVA and the same protocol-specified covariates.

8.1.3.4.3.3 Supportive Efficacy Analyses

The change in height observed in the 2 dose groups after 1, 2, 3, and 4 years of therapy were compared using ANCOVA. Growth rate, standardized height, B-P PAH, BA, and IGF-I levels were compared in the 2 dose groups after 1, 2, and 3 years of therapy using t-tests.

8.1.3.4.3.4 Secondary Efficacy Analysis

BMD data were limited and were therefore summarized with simple descriptive statistics.

8.1.3.4.4 Safety Analysis

Adverse events, including intercurrent illnesses, were both tabulated and summarized by treatment group and body system using COSTART preferred terms. Laboratory values outside the reference ranges were flagged. Laboratory and other safety values (including vital signs) were summarized with simple descriptive statistics by dose group.

8.1.3.4.5 Data Quality Assurance

The sponsor states that accurate, consistent, and reliable data were ensured through the use of standard practices and procedures. Given the paucity of patients at each testing site, it was not felt that on-site inspections by the Agency were necessary.

8.1.4 Results

8.1.4.1 Subject Eligibility and Treatment Assignment

Ninety seven pubertal subjects with GHD at 20 medical centers in the United States were enrolled and treated with at least 1 dose of either 0.3 mg/kg/wk Nutropin (49 subjects, standard dose group) or 0.7 mg/kg/wk Nutropin (48 subjects, high dose group). All 97 subjects were included in evaluations of drug safety and an ITT analysis of LMH, and 75 subjects achieved NAH, the primary efficacy measure.

8.1.4.2 Protocol Violations and Deviations

Prior to the sixth protocol amendment allowing sex steroid replacement therapy during the study, 2 subjects were discontinued when they started sex steroid replacement treatment.

8.1.4.3 Patient Disposition

Of the 97 subjects enrolled/treated in this trial, 48 completed the study (by meeting the criteria for NAH described earlier), and 49 patients discontinued prematurely from the study. More patients in the high dose group discontinued (31) compared with the standard dose group (18). The most common reason for discontinuation was satisfaction with attained height (9 in the high dose group and 6 in the standard dose group). Six patients were discontinued because of noncompliance (4 in the high dose group and 2 in the standard dose group), and 6 patients were discontinued because of adverse events. Of note, 2 of the 4 patients in the high dose group who discontinued because of adverse events had developed "acromegaloid" features (e.g., broadening of the nasal ridge and increased shoe size), and 1 of the 9 patients in the high dose group who discontinued because of satisfaction with attained height also commented on a remarkable increase in hand and feet size (see Section 8.1.4.9.4 ahead). See Table 3.

Table 3. M0380 - Patient Disposition*

	Nutropin 0.3 mg/kg/wk	Nutropin 0.7 mg/kg/wk	Total
Number of subjects enrolled and treated	49	48	97
Number of subjects who completed study	31	17	48
Number of subjects who discontinued	18	31	49
Patient requested removal	12	17	29
Satisfied with attained height	6	9	15
Behaviorial, personal or unknown reasons	5	6	11
Tired of inj	1	2	3
Adverse event	2	4	6
Noncompliance	2	4	6
Lost to follow-up	0	2	2
Protocol violation	1	1	2
Discontinued at time Of study termination	1	3	4

*Table derived from submission

8.1.4.4 Patient Demographics and Baseline Characteristics

As depicted in Table 4, subjects randomized to the 2 treatment arms were very well matched with respect to demographics and baseline characteristics. Most of the patients were Caucasian males with a diagnosis of idiopathic GHD. Mean CA was -14, BA was -13, Tanner stage was -3 and previous year growth rate was -8.5 cm/yr in the 2 dose groups. Mean height SDS and BP PAH SDS were -1.4 and -1.1 in the standard dose group, and -1.2 and -0.9 in the high dose group.

Table 4. M0380g - Demographics and Patient Characteristics*

	Nutropin 0.3 mg/kg/wk (n=49)	Nutropin 0.7 mg/kg/wk (n=48)
Sex, n		
Male	42	41
Female	7	7
Etiology of GHD, n		
Idiopathic	47	45
Organic	2	3
Race, n		
Caucasian	45	45
Black	2	0
Hispanic	2	3
Asian	0	0
Mean±SD (Range)		
Age (yr)	14.0±1.6 (10.7 to 17.1)	13.7±1.6 (10.6 to 16.3)
Bone age (yr)	13.1±1.3 (10.0 to 15.5)	13.1±1.3 (n=47) (9.6 to 15.2)
Tanner stage	3.0±1.0	2.9±0.8
Previous growth rate (cm/yr)	8.5±1.8 (n=47)	8.5±2.2 (n=47)
Duration of previous GH treatment (yr)	3.5±2.6 (0.5 to 9.7)	4.1±2.9 (0.6 to 10.8)
Height (cm)	151.9±9.3 (134.8 to 170.7)	151.7±9.4 (131.2 to 168.2)
Height SDS	-1.4±1.1 (-3.4 to 1.7)	-1.2±1.1 (-4.5 to 1.3)
Maximum stimulated GH (ng/ml)	5.7±2.6	5.3±2.7
Bayley-Pinneau predicted adult height SDS	-1.1±1.1	-0.9±1.2 (n=47)
Mid-parental target height SDS	-0.4±0.8 (n=48)	-0.3±0.7 (n=46)

*Table derived from submission

8.1.4.5 Compliance

As noted in Section 8.1.4.3, 6 patients were discontinued because of significant noncompliance (4 in the high dose group and 2 in the standard dose group). Seventeen other patients had isolated episodes of noncompliance (e.g., missing 2 weeks of injections in a 3 month period), and either completed the study or requested premature discontinuation.

8.1.4.6 Concomitant Therapy

The use of concomitant medications by subjects during the study was reviewed by the Medical Monitor. Only 4 patients were treated concomitantly with sex steroid replacement therapy during the study (after the sixth protocol amendment was effected). Eleven subjects were receiving appropriate amounts of L-thyroxine replacement therapy for hypothyroidism at study initiation; 3 additional patients were begun on L-thyroxine therapy during the study. Other medications used by subjects were generally those prescribed to treat preexisting conditions or routine childhood ailments.

8.1.4.7 Efficacy Results

8.1.4.7.1 Primary Efficacy Results

a. NAH

Seventy five subjects met the criteria for attaining NAH (42 in the standard dose group and 33 in the high dose group). Twenty two subjects discontinued early without achieving NAH (7 in the standard dose group and 15 in the high dose group). More patients in the high dose group discontinued early without attaining NAH because of non-compliance, protocol exclusion and failure to followup (see Table 3).

Forty six of the 75 subjects achieving NAH completed the study (31 in the standard dose group and 15 in the high dose group), while 29 subjects discontinued early (mostly because they were satisfied with the height achieved - see Table 3) but still met the criteria for NAH (11 in the standard dose group and 18 in the high dose group). Of note, 41 of the 75 subjects attaining NAH required BA to be extrapolated to the date of their LMH to meet the criterion.

LMH for subjects attaining NAH (adjusted for baseline height and the other 6 covariates noted in Section 8.1.3.4.3.1) in the standard and high dose groups were compared using ANCOVA. Although sex steroid replacement therapy was a protocol-specified covariate, it was not used in the analysis because only 4 subjects received sex steroid therapy during the study.

The ANCOVA demonstrated that subjects in the high dose group were significantly taller at NAH than subjects in the standard dose group by an average of 4.6 cm ($n=75$; $p<0.001$; 95% confidence intervals [CI] of 2.6-6.5 cm). The significant covariates were sex, baseline height, and BA.

There were no differences between the dose groups at NAH in CA (17.2 ± 1.3 years), BA (16.9 ± 0.9), or duration of rhGH therapy (3.0 ± 1.0). However, for subjects attaining NAH, the height SDS at LMH was significantly greater in the high dose group (0.0 ± 1.2) compared with the standard dose group (-0.7 ± 0.9) ($p=0.002$). The change in

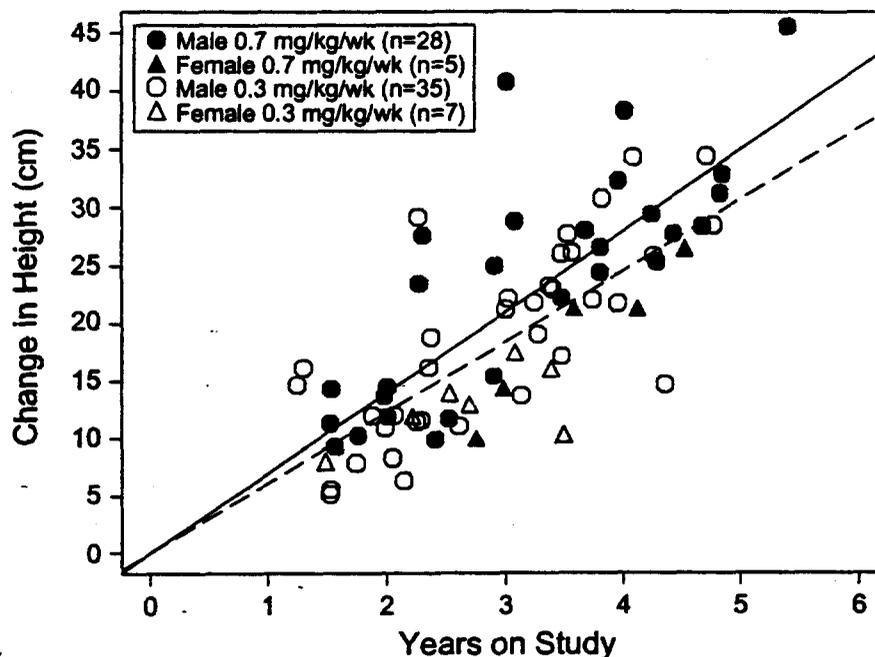
height SDS for subjects achieving NAH was also significantly greater in the high dose group (1.1 ± 1.0 versus 0.6 ± 0.8 , $p=0.012$).

Note: As per the Agency's statistical reviewer, when the 48 subjects (data available for 47) who completed the study are analyzed separately by ANCOVA, the patients in the high dose group were still significantly taller (3.7 cm) than the subjects in the standard dose group. However, when the 49 subjects (data available for 46) who did not complete the study for any reason are analyzed separately by ANCOVA, the difference between the 2 groups was not significantly different. On the other hand, the Agency's statistical reviewer found that amongst subjects who attained NAH and did ($n=41$) or did not ($n=34$) require final BA to be extrapolated, the patients in the high dose group achieved a significantly greater LMH.

The change in height from baseline to LMH for subjects attaining NAH ($n=75$) is plotted by treatment duration in Figure 1. The divergence of the simple linear regression lines indicates that the difference between the groups for change in height increased with years of treatment. Therefore, the positive effect of the higher dose (compared with the standard dose) on change in height increased with the duration of therapy.

Figure 1

Change from Baseline to Last Measured Height (cm) by Dose Group for Subjects Attaining Near-Adult Height

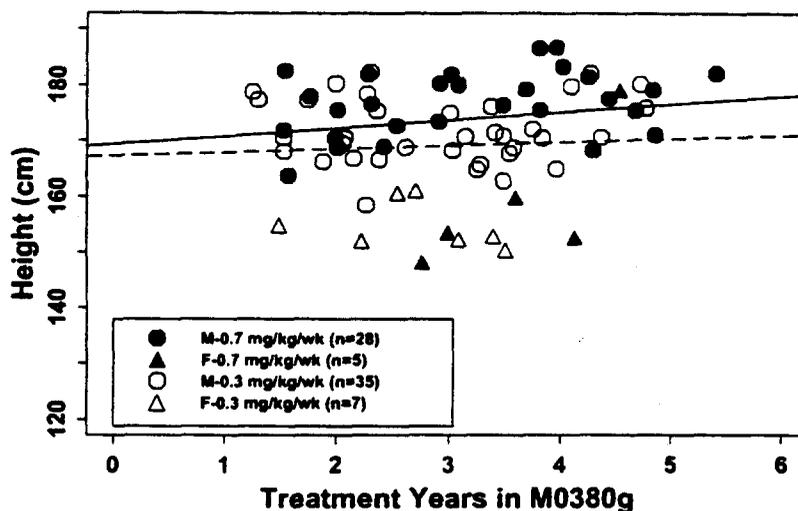


The solid line represents linear regression for the 0.7 mg/kg/wk group; the dashed line represents linear regression for the 0.3 mg/kg/wk group.

LMH for subjects attaining NAH (n=75) is plotted by duration of treatment in Figure 2. It demonstrates that taller heights were observed across the high dose group at multiple time points (e.g., the greater mean value for LMH for subjects achieving NAH in the high dose group was not the result of only a few subjects, and NAH was not attained after only 1 year of therapy).

Figure 2

Last Height by Duration of Treatment
for Subjects Attaining Near Adult Height



b. LMH - ITT Analysis

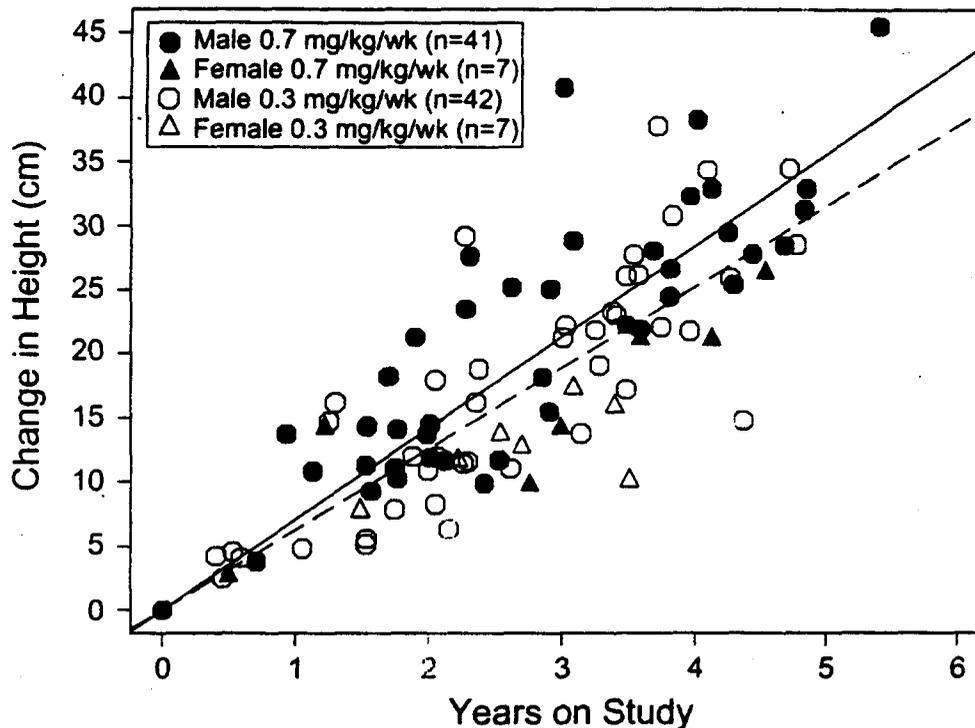
LMH was used for all subjects, regardless of whether or not NAH was achieved, in the ITT analysis. Once again, ANCOVA was used to compare LMH (adjusted for baseline height and the other 6 covariates noted in Section 8.1.3.4.3.1) in the 2 dose groups. Subjects in the high dose group were significantly taller at LMH than subjects in the standard dose group by an average of 2.8 cm (n=97; p=0.036; 95% CI of 0.2-5.3 cm). The significant covariates were sex, baseline height, CA, and BA. There were no differences between the dose groups at LMH in CA (17.0±1.5 years), BA (16.4±1.3), or duration of rGH therapy (2.7±1.2).

The change in height from baseline to LMH is plotted by treatment duration for all enrolled subjects (n=97) in Figure 3. As was the case in the analysis of NAH, the difference between groups for change in height increased with years of treatment (once again) suggesting an increasing positive effect of the higher dose over time. The minimum values for CA, BA, and duration of treatment were notably less at LMH in the ITT analysis than those seen at NAH (e.g., some of the patients were younger and treated for a shorter duration). Taken together,

this may explain in part why the difference between the dose groups was greater at NAH (4.6 cm) than at LMH in the ITT analysis (2.8 cm)

Figure 3

Change from Baseline to Last Measured Height (cm) by
Duration of Treatment for All Enrolled Subjects



The solid line represents linear regression for the 0.7 mg/kg/wk group;
the dashed line represents linear regression for the 0.3 mg/kg/wk group.

8.1.4.7.2 Supportive Efficacy Results

a. Change in Height by Duration of Treatment

The change in height by duration of treatment (e.g., after 1, 2, 3 and 4 years of on-study therapy) was compared in the 2 dose groups using ANCOVA (the covariates were sex and BA). After 1 year of therapy, subjects in the high dose group were taller than the subjects in the standard dose group by an average of 1.6 cm (n=90; $p < 0.0001$; 95% CI of 0.8-2.4 cm). After each subsequent year of treatment, the difference between the 2 groups increased. After 4 years of therapy, subjects in the high dose group were taller than the subjects in the standard dose group by an average of 5.7 cm (n=20; $p = 0.024$; 95% CI of 1.2-10.1 cm). Just as in the primary analyses described above, the difference

between the groups for change in height increased with years of treatment. See Table 5.

Table 5. M0380g - Analysis of Covariance for Change in Height (cm) by Years Treated*

	Effect on Change in Height (cm)	p-value
1 Year (standard dose, n=45; high dose, n=45), R ² =0.35		
GH dose (if high dose)	+1.6	<0.001
95% CI	0.8, 2.4	
Sex (if male)**	+2.3	<0.001
Baseline bone age (per year)	-0.83	<0.001
2 Years (standard dose, n=38; high dose, n=34), R ² =0.54		
GH dose (if high dose)	+2.4	0.002
95% CI	1.0, 3.8	
Sex (if male)**	+6.4	<0.001
Baseline bone age (per year)	-2.2	<0.001
3 Years (standard dose, n=23; high dose, n=22), R ² =0.70		
GH Dose (if high dose)	+4.3	<0.001
95% CI	2.5, 6.1	
Sex (if male)**	+10.0	<0.001
Baseline bone age (per year)	-2.5	<0.001
4 Years ^a (standard dose, n=7; high dose, n=13), R ² =0.52		
GH dose (if high dose)	+5.7	0.024
95% CI	1.2, 10.1	
Sex (if male)**	+10.6	0.004
Baseline bone age (per year)	-2.7	0.014

^a The equation from the ANCOVA was as follows: Change in height (cm) = 54.0 (if high dose) + 48.4 (if standard dose) + 10.6 (if male) - 2.7 x baseline bone age (yr)

*Table derived from submission

b. Growth Rate

The mean prestudy growth rate was 8.5 cm/yr in both treatment groups for subjects completing Month 12 (and for all enrolled subjects as well). The mean Month 0-12 growth rate (9.8 cm/yr) in the high dose group (n=44) was significantly greater than the mean Month 0-12 growth rate (8.2 cm/yr) in the standard dose group (n=43) (delta=1.6 cm; p=0.001 between groups). Thirty four subjects in the high dose group as opposed to 23 subjects in the standard dose group had a growth rate ≥8 cm/yr, while 22 subjects in the standard dose group as opposed to 6 subjects in the high dose group had a growth rate ≤8 cm/yr. For subjects completing 24 months of therapy, the difference between the 2 dose groups did not attain statistical significance (n=69; p=0.063 between groups). Nonetheless, nineteen subjects in the high dose group as opposed to 13 subjects in the standard dose group had a growth rate ≥8 cm/yr, while 25 subjects in the standard dose group as opposed to 12 subjects in the high dose group had a growth rate ≤8 cm/yr. The difference in growth rate between the 2 treatment groups

was more pronounced at Month 36, and did reach statistical significance despite the reduced number of subjects ($n=41$; $\Delta=1.7$ cm/yr; $p=0.038$ between groups). Ten subjects in the high dose group as opposed to 7 subjects in the standard dose group had a growth rate ≥ 6 cm/yr, while 15 subjects in the standard dose group as opposed to 10 subjects in the high dose group had a growth rate ≤ 6 cm/yr. Of note, the cohort treated for 36 months were younger in CA and BA, and at an earlier Tanner stage of puberty, than the cohort treated for 12 months.

Mean growth rates for each dose group for subjects completing 3 years of treatment ($n=41$) are shown in Figure 4. After each year of treatment, the mean growth rate in the high dose group exceeded the mean growth rate in the standard dose group by a similar increment. The lines in the graph parallel each other because the data is additive (rather than cumulative) at each time point. Figure 5 shows box plots of the growth data for each dose group for each of the first 4 treatment years and also reflects the greater growth rates observed in the high dose group after each year of therapy. Furthermore, the distribution of growth rates was clearly shifted to the right for the high dose group compared with the standard dose group at each time point. These data indicate that the differences in growth rates were not caused by a few patients but the groups as a whole.

Figure 4

Growth Rates for Subjects Completing 3 Years in Study
(Mean \pm SD)

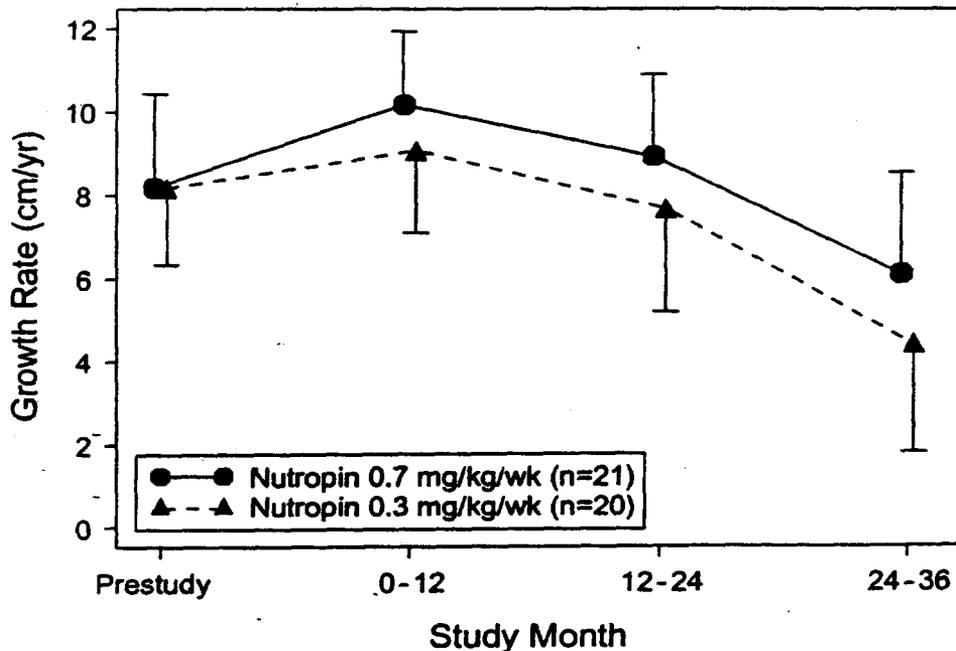
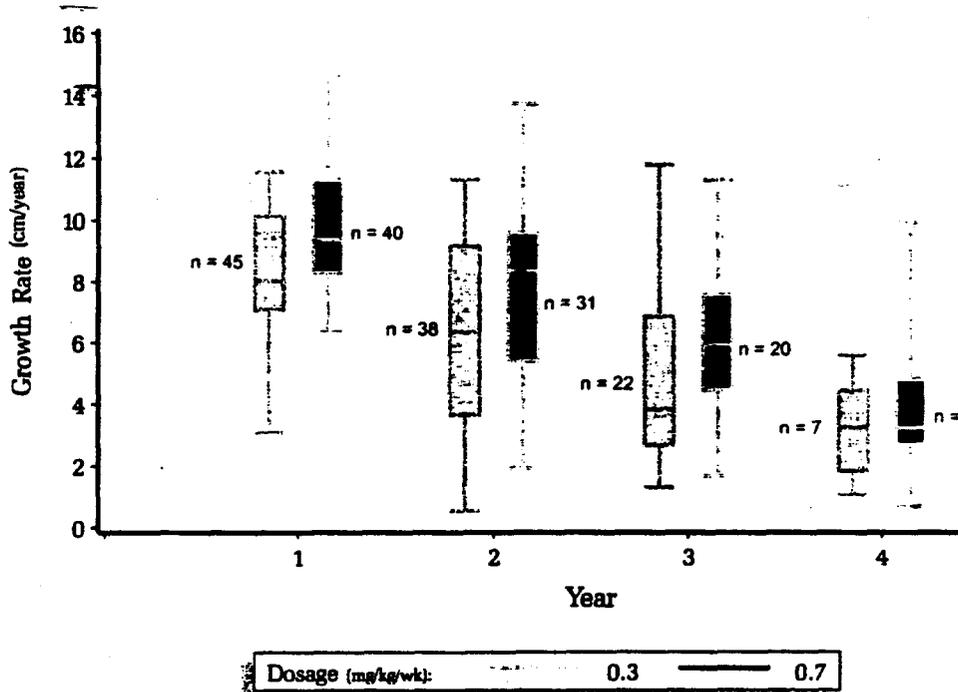


FIGURE 5

Growth Rate Distributions



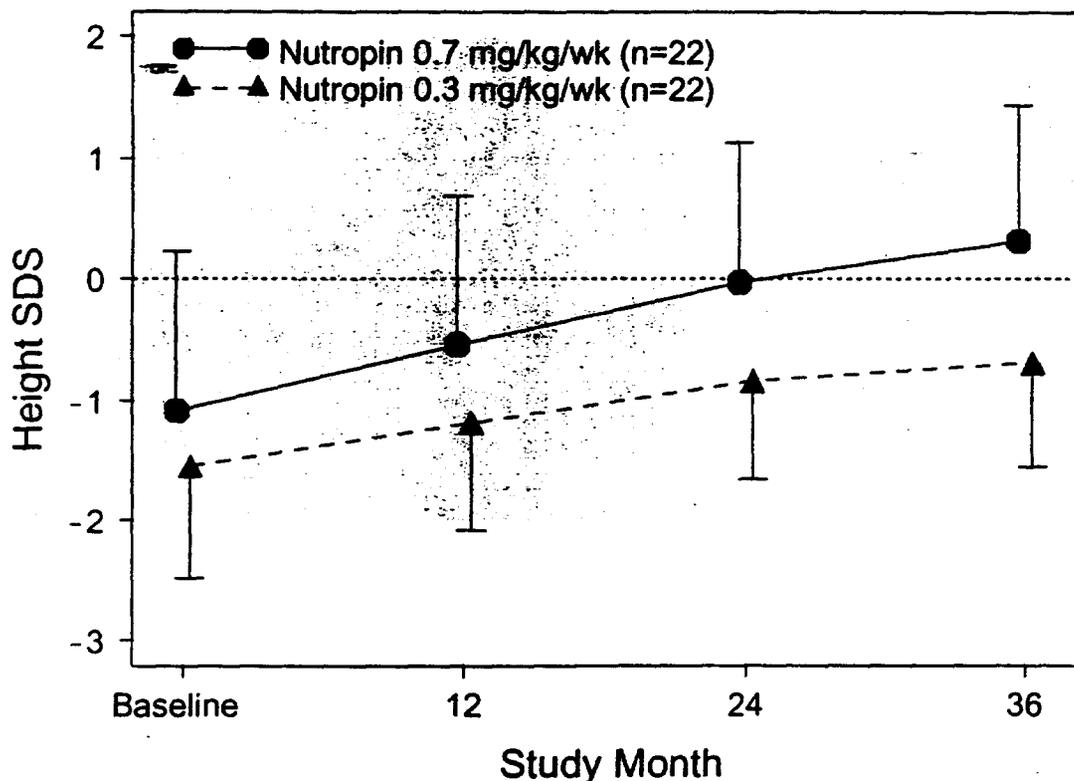
Note: Line within box is the median, box limits are the 25/75th pctls., line limits are min/max values.

c. Standardized Height

Mean height SDS was >1 SD below the mean in both treatment groups at baseline (see Table 4). After 1 year of treatment, the mean change in height SDS was significantly greater in the high dose group (0.6 ± 0.3) compared with the standard dose group (0.4 ± 0.4) ($n=45$ in each group; $\Delta=0.2$; $p=0.024$ between groups). The difference between the 2 dose groups for the mean change in height SDS from baseline increased with continued therapy. After 3 years of treatment, the mean change in height SDS from baseline was 1.4 ± 0.8 in the high dose group compared with 0.9 ± 0.7 in the standard dose group ($n=22$ in each group; $\Delta=0.5$; $p=0.023$ between groups). Mean height SDS by duration of treatment for subjects completing 3 years of therapy are shown in Figure 6.

Figure 6

Height SDS for Subjects Completing 3 Years in Study
(Mean \pm SD)

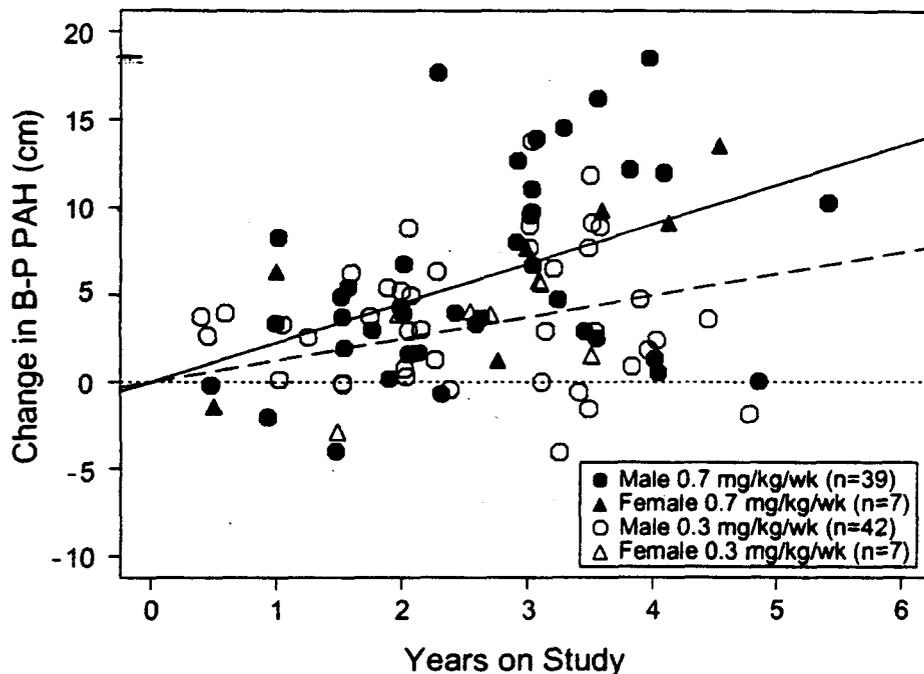


d. B-P PAH

The standardized B-P PAH was similar in the 2 treatment groups at baseline (~ 1 SD below the mean; see Table 4). After 3 years of treatment, the change in standardized B-P PAH from baseline was 1.3 SD (8.4 cm) in the high dose group compared with 0.8 (4.8 cm) in the standard dose group ($n=20$ in each group; $\Delta=0.5$ SD or 3.6 cm; $p<0.032$ between groups). The change from baseline to last B-P PAH (cm) by duration of therapy for each dose group is shown in Figure 7. The divergence of the simple linear regression lines indicates that the difference between the 2 dose groups for change from baseline to last B-P PAH increased with years of treatment suggesting an increasing positive effect of the higher dose over time. Figure 8 is a plot of LMH in subjects attaining NAH minus baseline B-P PAH (cm) by duration of therapy. LMH minus baseline B-P PAH was greater in the high dose group at all time points. As in the case of the change from baseline to last B-P PAH, the difference between the 2 dose groups for LMH minus baseline B-P PAH increased over time.

Figure 7

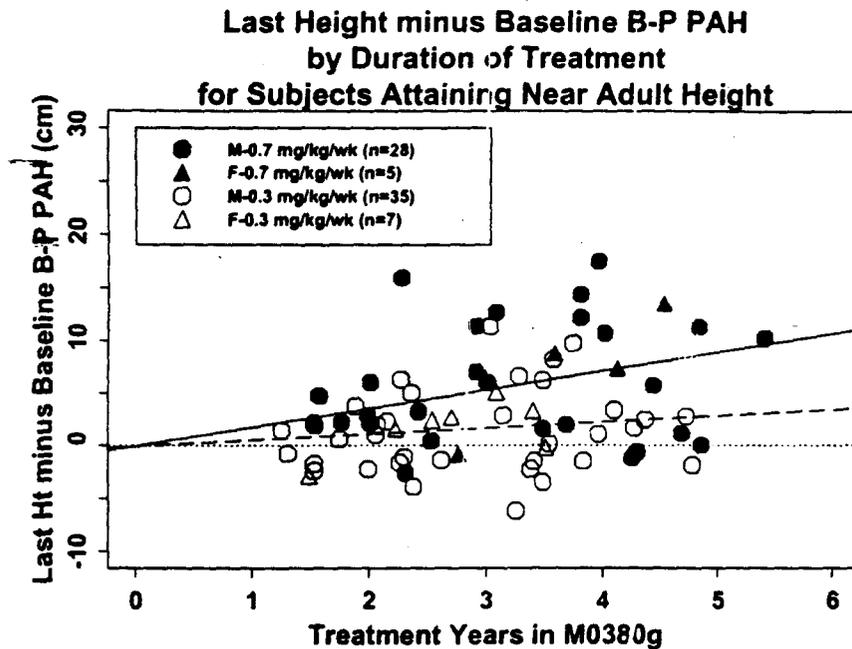
Change from Baseline to Last Bayley-Pinneau Predicted Adult Height (cm) by Treatment Year



The solid line represents linear regression for subjects treated with 0.7 mg/kg/wk; the dashed line represents linear regression for subjects treated with 0.3 mg/kg/wk. The dotted, horizontal line at 0 indicates no change from baseline and is provided as a visual reference.

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Figure 8



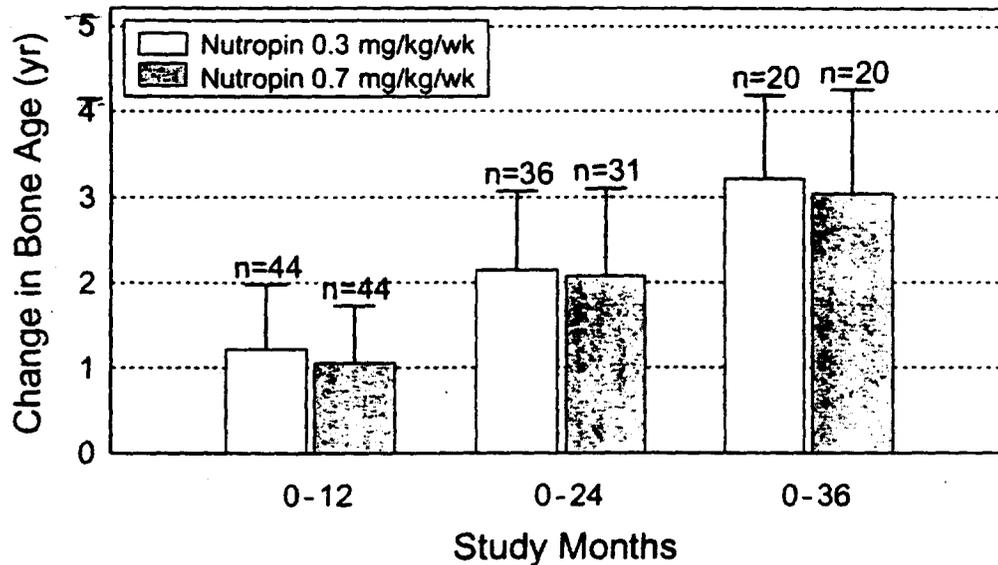
Note: The simple linear regression lines are included for visual reference only. The dotted line indicates zero on the vertical axis (no difference between last height and baseline PAH).

e. BA and Tanner Pubertal Stage

The mean change in BA was -1 year per year of treatment in both dose groups (see Figure 9 - a plot of cumulative change in BA for subjects completing 1, 2 and 3 years of therapy). In addition, the rate of advancement of Tanner pubertal stage was similar in the 2 dose groups (data not shown), and there were no statistically significant differences between dose groups in mean change from baseline for testosterone levels in males. These data suggest that the greater increases in absolute height, height SDS and growth rate in the high dose group compared with the standard dose group were achieved without an acceleration of the rate of skeletal maturation or pubertal progression, leading to improved NAH.

Figure 9

Cumulative Change in Bone Age (yr) for Subjects
Completing 1, 2, and 3 Years in Study (Mean \pm SD)



f. IGF-I (implications for efficacy and safety)

IGF-I was measured by radioimmunoassay (RIA) following acid-ethanol extraction. In both dose groups, review of the IGF-I responses revealed a large amount of interindividual and intraindividual variability (e.g., many subjects who had IGF-I values above the upper limit of the normal range [$>+2$ SDS] at 1 or more time points also had values within the normal range [between -2 and $+2$ SDS] at other times).

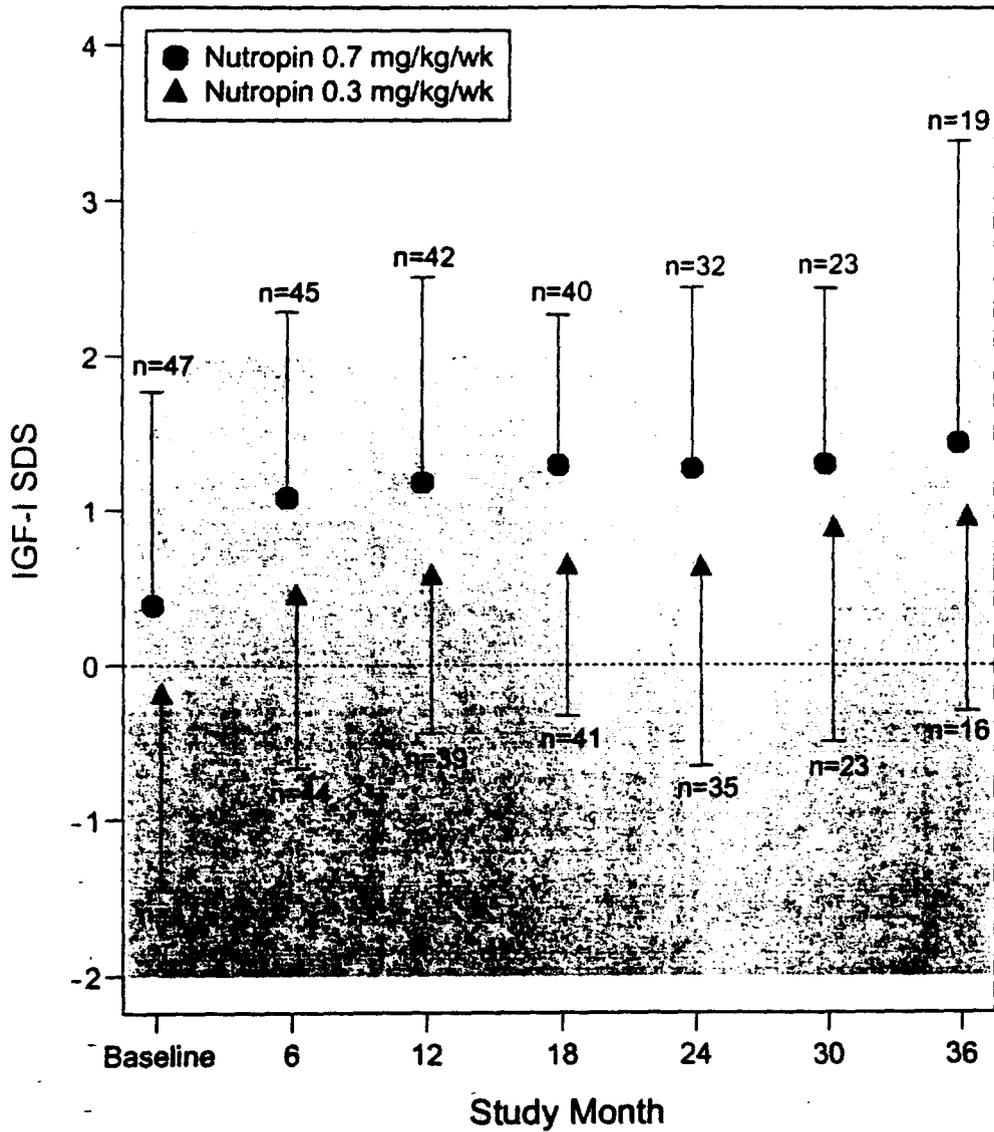
The changes from baseline, using IGF-I SDS or log values, were not significantly different in the 2 treatment groups after 1, 2, or 3 years of treatment. Moreover, mean IGF-I SDS values were within the high normal range (between 0 and $+2$ SDS), and not significantly different, in the 2 dose groups at all time points during the study (see Figure 10). Clearly, the greater growth observed in the high dose group cannot be correlated with a definitively greater IGF-I response. The lack of correlation between growth parameters and IGF-I response in GHD children treated for many years with conventional amounts of rhGH is well established in the literature (19).

Furthermore, the administration of the larger dose of rhGH to subjects with an elevated baseline IGF-I level (n=7) did not necessarily result in a further increase in IGF-I (see Figure 11); in $\sim 50\%$ of these patients, sustained elevation of IGF-I was observed during the study, while in the remaining $\sim 50\%$, IGF-I levels were mostly within normal limits. In

fact, the mean IGF-I level decreased in these patients. This data suggests that the IGF-I response was not consistently proportional to the dosage of rhGH administered.

Figure 10

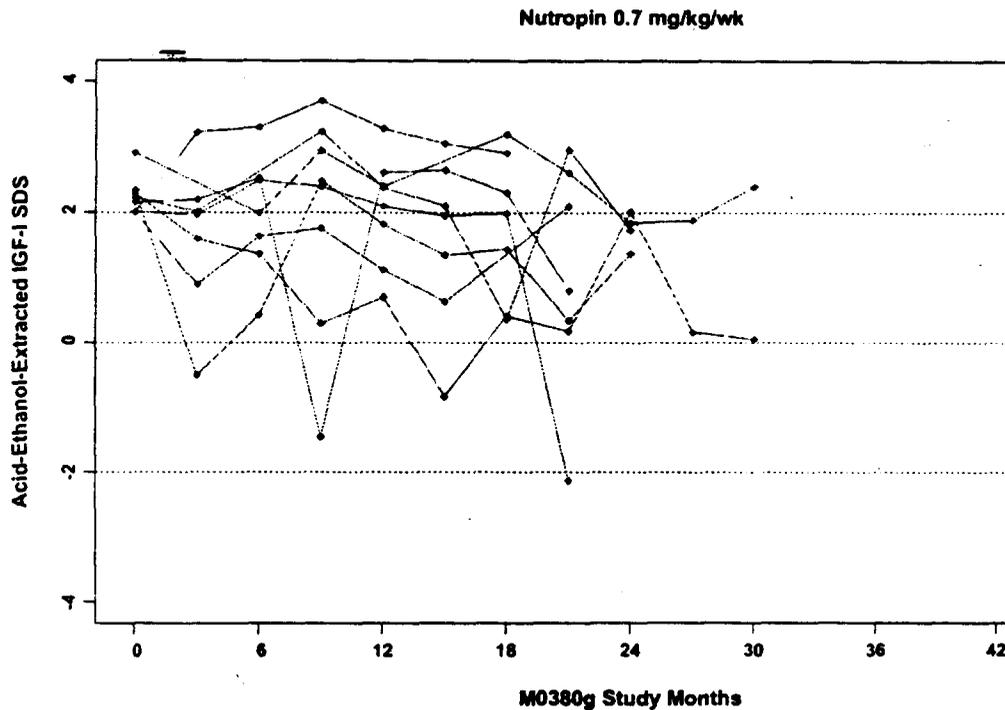
Acid-Ethanol-Extracted IGF-I SDS by Dose Group
(Mean \pm SD)



Shaded area represents normal range.

Figure 11

Acid-Ethanol-Extracted IGF-I SDS

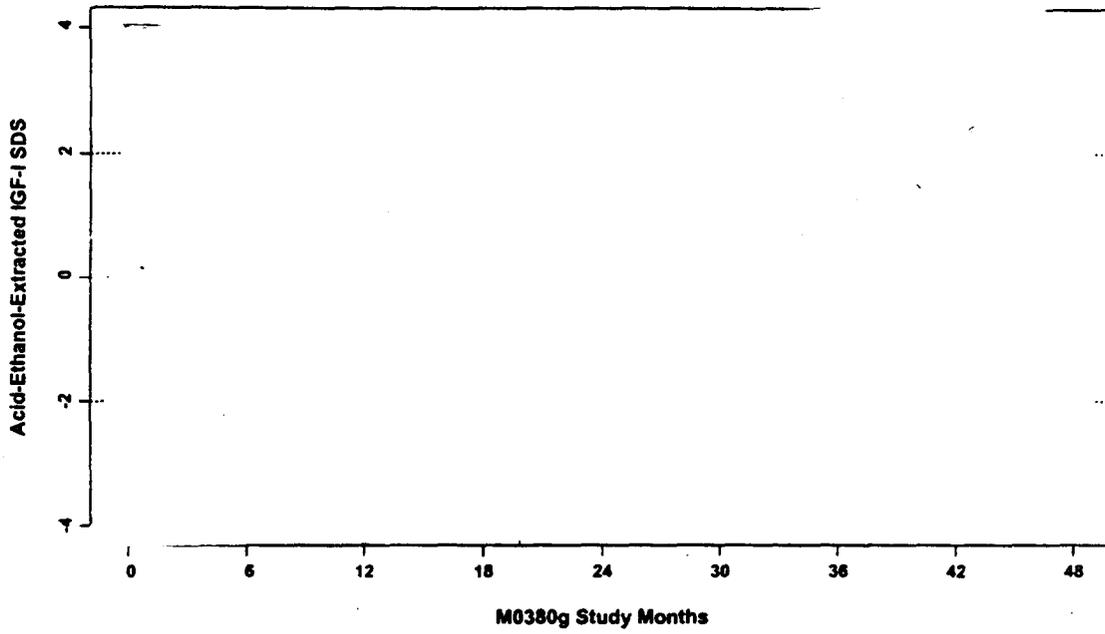


Nonetheless, mean and median values for IGF-I and IGF-I SDS increased to a greater extent in the high dose group compared with the standard dose group. Median values rose from 508 to 681 mg/L in the high dose group after 1 year of therapy compared with a change from 427 to 589 mg/L in the standard dose group. In addition, the incidence of IGF-I levels above the normal range during therapy was greater in the high dose group. Twenty of the 49 subjects (41%) in the standard dose group had at least 1 value above the normal range during the study compared with 30 of the 47 subjects (64%) in the high dose group ($p=0.027$ between groups). In addition, 5 of the 49 subjects (10%) in the standard dose group had ≥ 3 IGF-I values above the normal range during the study compared with 19 of the 47 subjects (40%) in the high dose group.

Eight subjects (7 in the high dose group and 1 in the standard dose group) had IGF-I levels above the normal range at baseline, and all 8 of these subjects had at least 1 high value during therapy. If these subjects are excluded, and only patients with normal baseline values of IGF-I are analyzed, 19 of the 48 subjects (40%) in the standard dose group compared with 23 of the 40 subjects (58%) in the high dose group had at least 1 IGF-I value above the normal range during therapy

Figure 12
Acid-Ethanol-Extracted IGF-I SDS

Nutropin 0.7 mg/kg/wk



(a difference which is no longer significant; $p=0.133$ between groups). However, further analysis of the 7 patients in the high dose group with baseline IGF-I levels above the normal range reveals that only 4 of the 7 subjects had reasonably sustained elevations of IGF-I levels during the study; in the 3 remaining subjects, IGF-I values decreased into the normal range for the most part after initiation of therapy (Figure 11). As a result, if these subjects are excluded, and only patients with normal baseline values of IGF-I are analyzed, 4 of the 48 subjects (8%) in the standard dose group compared with 14 of the 40 subjects (35%) in the high dose group had ≥ 3 IGF-I values above the normal range during the study (e.g., a significant difference between the 2 dose groups persists!). Note: Although most of the subjects with IGF-I SDS above the mean at baseline had IGF-I SDS $< +2$ during the study, most subjects who developed IGF-I SDS $> +2$ during the trial had baseline IGF-I values above the mean in both dose groups. Even amongst subjects with normal baseline IGF-I values, a greater number in the high dose group (~55%) compared with the standard dose group (~41%) had baseline IGF-I values above the mean (between 0 and +2 SDS). This may explain in part why more subjects in the high dose group had single and multiple IGF-I SDS above the normal range during the study.

The greater number of patients in the high dose group with single and multiple IGF-I SDS above the normal range during the study (even after the exclusion of subjects with elevated baseline IGF-I values) is demonstrated graphically in Figure 12 (individual line plots for each patient in the high dose group) versus Figure 13 (individual line plots for each patient in the standard dose group), Figures 14 and 15 ("equal n" and "unequal n" stacked bar graphs showing the percentage of patients with IGF-I SDS $> +2$ SD in the 2 dose groups after 1, 2 and 3 years of therapy), and Table 6 (percentage of patients with IGF-I SDS $> +2$ SDS in the 2 dose groups at 3 month intervals - ~25% in the high dose group and ~10% in the standard dose group).

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Figure 13

Acid-Ethanol-Extracted IGF-I SDS

Nutropin 0.3 mg/kg/wk

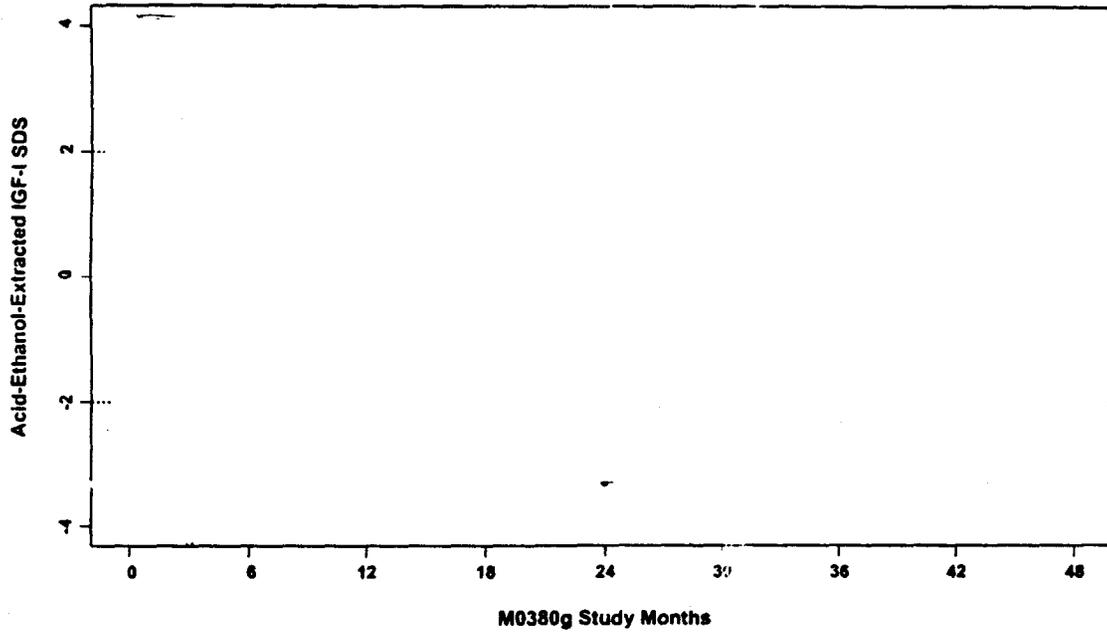


FIGURE 14
Genentech Study M0380g
IGF-I SDS by Dose Group (# of Patients)
Excluding Subjects with Baseline IGF-I >2.0
Subjects with Baseline, M12, M24, and M36 Values

Baseline			Month 12			Month 24			Month 36		
	0.3	0.7		0.3	0.7		0.3	0.7		0.3	0.7
<-2	1	1	<-2	0	0	<-2	1	0	<-2	1	0
-2 to 0	6	8	-2 to 0	8	1	-2 to 0	1	2	-2 to 0	0	3
0 to 2	6	9	0 to 2	6	14	0 to 2	10	10	0 to 2	10	8
>2	0	0	>2	1	3	>2	1	6	>2	2	7
TOTAL	13	18									

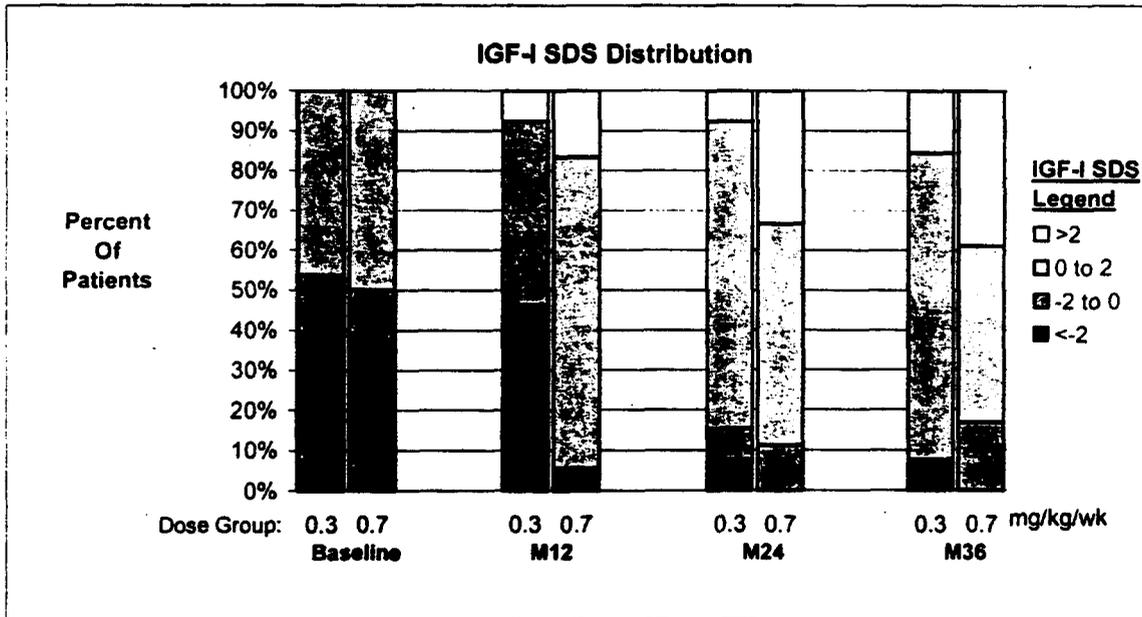


Figure 15
Genentech Study M0380g
IGF-I SDS by Dose Group (# of Patients)
Excluding Subjects with Baseline IGF-I SDS >2.0

Baseline			Month 12			Month 24			Month 36		
	0.3	0.7		0.3	0.7		0.3	0.7		0.3	0.7
<-2	2	2	<-2	0	1	<-2	2	1	<-2	1	1
-2 to 0	25	16	-2 to 0	13	3	-2 to 0	6	3	-2 to 0	0	3
0 to 2	19	22	0 to 2	20	24	0 to 2	24	15	0 to 2	13	8
>2	0	0	>2	5	7	>2	2	9	>2	2	7
TOTAL	46	40	TOTAL	38	35	TOTAL	34	28	TOTAL	16	19

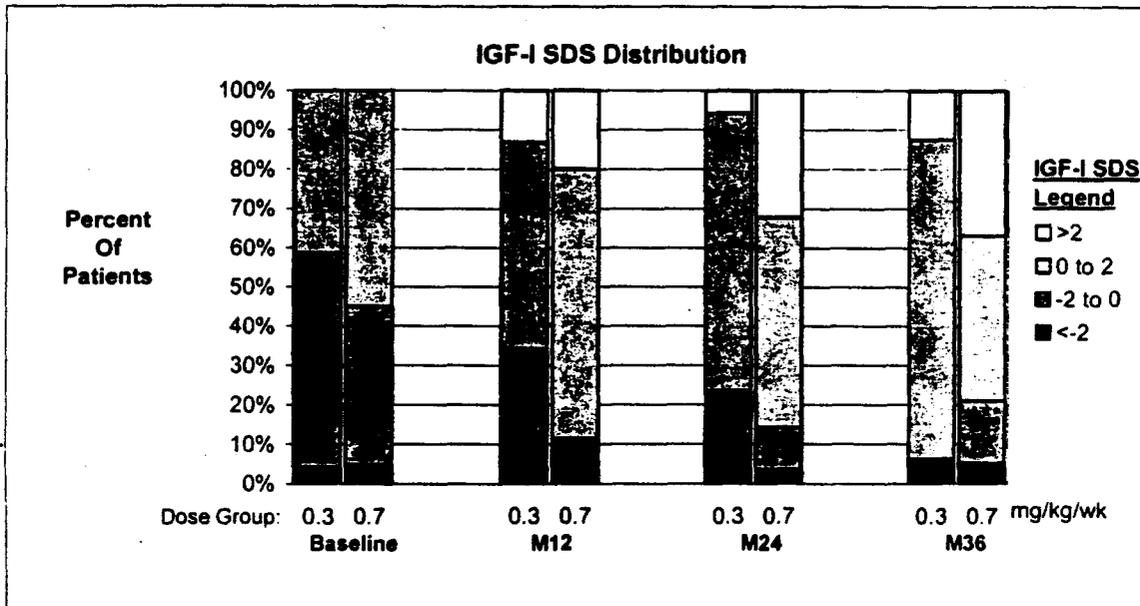


Table 6. M0380g - IGF-I SDS Distribution by Dose Group
(Subjects with Baseline IGF-I SDS >+2 Omitted)

0.3 mg/kg/wk

Frequency Col Pct	BASE	M3	M6	M9	M12	M15	M18	M21	M24	M27	M30	M33	M36
> 2 to 4 SD	0 0.00	0 0.00	3 6.98	2 4.76	5 13.16	3 7.50	1 2.50	4 11.76	2 5.88	3 20.00	5 22.73	3 37.50	2 12.50
0 to 2 SD	19 41.30	25 58.14	25 58.14	33 78.57	20 52.63	23 57.50	30 75.00	23 67.65	24 70.59	9 60.00	13 59.09	5 62.50	13 81.25
< 0 to -2 SD	25 54.35	15 34.88	15 34.88	7 16.67	13 34.21	14 35.00	9 22.50	5 14.71	6 17.65	3 20.00	3 13.64	0 0.00	0 0.00
< -2 SD	2 4.35	3 6.98	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	2 5.88	2 5.88	0 0.00	1 4.55	0 0.00	1 6.25
Total	46	43	43	42	38	40	40	34	34	15	22	8	16

0.7 mg/kg/wk

Frequency ColPct	BASE	M3	M6	M9	M12	M15	M18	M21	M24	M27	M30	M33	M36
> 2 to 4 SD	0 0.00	6 17.14	8 20.51	6 15.79	7 20.00	7 20.00	8 23.53	8 24.24	9 32.14	5 45.45	6 28.57	3 30.00	7 36.84
0 to 2 SD	22 55.00	22 62.86	24 61.54	27 71.05	24 68.57	23 65.71	23 67.65	20 60.61	15 53.57	5 45.45	12 57.14	5 50.00	8 42.11
< 0 to -2 SD	16 40.00	6 17.14	6 15.38	4 10.53	3 8.57	4 11.43	3 8.82	3 9.09	3 10.71	1 9.09	3 14.29	2 20.00	3 15.79
< -2 SD	2 5.00	1 2.86	1 2.56	1 2.63	1 2.86	1 2.86	0 0.00	2 6.06	1 3.57	0 0.00	0 0.00	0 0.00	1 5.26
Total	40	35	39	38	35	35	34	33	28	11	21	10	19

See ahead for further comments regarding comparative IGF-I responses in the 2 dose groups in various subgroups (efficacy), and in the cohort of 5 patients with "acromegaloid" features compared with the rest of the subjects in the high dose group and the subjects in the standard dose group (safety).

g. Subgroup analyses

g.1 Preface

Although not contained in the original submission, I felt it was important to define what baseline characteristics, if any, impacted the response to therapy in the high and standard dose groups. Toward that end, the sponsor (at my request) selected several relevant baseline characteristics (baseline CA, duration of prior therapy with rhGH, height SDS at baseline, baseline IGF-I level and sex), divided each of these characteristics into subcategories with sufficient numbers of patients to allow comparisons within and between groups, and then compared several outcome variables (growth rate, height SDS, B-P PAH, IGF-I SDS, and last height SDS for subjects attaining NAH) in these subcategories in both dose groups.

g.2 Baseline CA Subcategories = >15,13-15,<13 yrs

As expected, in both dose groups, younger subjects grew better than older subjects, and growth rate waned more quickly in the older subjects. The higher dose resulted in **greater growth rates** after 1, 2 and 3 years of therapy in younger and older patients as well. Gains in height SDS were greater in the older subjects in both dose groups. After 2 years of therapy, the change in height SDS was greater in younger patients receiving the larger dose; the change in height SDS in older patients was the same in both dose groups. After 2 years of therapy the change in B-P PAH SDS was **greater in younger and older patients as well**. After 2 years of therapy, the change in IGF-I was greater in older patients receiving the larger dose; the change in IGF-I in younger patients was the same in both dose groups. Height SDS at NAH was significantly greater in younger and older patients as well in the high dose group (see Table 7). The data presented suggest that older patients (as well as younger patients) benefit from larger doses of rhGH during puberty.

Table 7. M0380g

Pubertal Growth Hormone Deficiency
 Patients at Near Adult Height - Last Height SDS by Baseline Age Category

Treatment Dose=0.3 mg/kg/wk

BLAGECAT	N Obs	N	Mean	Std Dev	Minimum	Maximum
> 15	9	9	-0.9	0.7		—
13-15	18	18	-0.9	0.9		—
< 13	15	15	-0.3	0.9		—

Treatment Dose=0.7 mg/kg/wk

BLAGECAT	N Obs	N	Mean	Std Dev	Minimum	Maximum
> 15	8	8	-0.2	1.2		—
13-15	9	9	-0.5	0.9		—
< 13	16	16	0.5	1.2		—

g.3 Duration of Prior rhGH Therapy
 Subcategories = >5, 2-5, <2 yrs

The higher dose resulted in **greater growth rates** after 1, 2 and 3 years of therapy in shorter prior duration, and **even more so in longer prior duration patients as well**. The higher dose also resulted in **greater height SDS and B-P PAH SDS** after 1, 2 and 3 years of therapy in shorter prior duration and longer prior duration patients as well. Minimal effects on IGF-I responses were observed. Subjects with longer prior duration of rhGH therapy tended to have greater/more normal height SDS at baseline and therefore greater height SDS at NAH in both dose groups. Height SDS at NAH was significantly greater in shorter prior duration and longer prior duration patients as well in the high dose group (see Table 8). The data presented suggest that longer prior duration subjects (as well as shorter prior duration patients) benefit from larger doses of rhGH during puberty.

Table 8. M0380g

Pubertal Growth Hormone Deficiency
 Patients at Near Adult Height - Last Height SDS by Prev GH TX Duration Category

Treatment Dose=0.3 mg/kg/wk

PGHCAT	N Obs	N	Mean	Std Dev	Minimum	Maximum
> 5	14	14	-0.5	1.0		—
2-5	14	14	-0.7	0.8		—
< 2	14	14	-0.9	0.9		—

Treatment Dose=0.7 mg/kg/wk

PGHCAT	N Obs	N	Mean	Std Dev	Minimum	Maximum
> 5	12	12	0.5	1.2		—
2-5	11	11	-0.4	0.8		—
< 2	10	10	-0.1	1.3		—

g.4 Height SDS at Baseline

Subcategories = >-1(taller), -1 to -2, <-2(shorter)

The higher dose resulted in **minimally greater growth rates, height SDS and B-P PAH SDS** after 1, 2 and 3 years of therapy in subjects who were shorter at baseline and **taller at baseline as well**. There was a slight tendency for the subjects who were taller at baseline (>-1 SDS) to have higher baseline IGF-I levels*. Height SDS at NAH was significantly greater in subjects who were shorter at baseline **and taller at baseline as well** in the high dose group. However, it is important to note that subjects who were taller at baseline achieved satisfactory NAH with BOTH the standard dose (-0.1 height SDS) and high dose (+0.6 height SDS) of rhGH (see Table 9). **The data presented suggest that patients who are taller at baseline may NOT benefit from larger doses of rhGH during puberty.**

Note: This conclusion is further supported by an independent analysis performed by the Agency's statistical reviewer. She observed that subjects who entered the study with height SDS larger than the mean (10%) were able to attain a satisfactory LMH after treatment with the standard dose of rhGH.

Table 9. M0380g

Pubertal growth Hormone Deficiency
 Patients at Near Adult Height - Last Height SDS by Baseline HTSDS Category

Treatment Dose=0.3 mg/kg/wk

HTSDCAT	N Obs	N	Mean	Std Dev	Minimum	Maximum
> -1	15	15	-0.1	0.8		—
-2 to -1	18	18	-0.9	0.8		—
< -2	9	9	-1.4	0.6		—

Treatment Dose=0.7 mg/kg/wk

HTSDCAT	N Obs	N	Mean	Std Dev	Minimum	Maximum
> -1	17	17	0.6	0.9		—
-2 to -1	10	10	-0.6	1.0		—
< -2	6	6	-0.6	1.5		—

g.5 Baseline IGF-I Level

Subcategories = IGF-I SDS >+2 and Normal IGF-I in High Dose Group, and Normal IGF-I in Standard Dose Group

The baseline characteristics of the 7 subjects with elevated baseline IGF-I levels were compared with the other subjects in the high dose group and the subjects in the standard dose group. The subjects with elevated baseline IGF-I levels were slightly taller with height SDS (~-0.9) and B-P PAH SDS (~-0.7) closer to normal, had received rhGH therapy for a longer duration prior to study enrollment (~4.7 yrs), and were further along in puberty (~Tanner 3.4). The mean growth rates (and height SDS) of these 7 patients during the study were similar to those seen in the other subjects in the high dose group (and greater than those observed in the patients in the standard dose group).

The IGF-1 responses of this special cohort have previously been discussed in Section 8.1.4.7.2.e and the individual line plots are reflected in Figure 11. The IGF-1 response was unpredictable; both sustained elevation (~50%) and normalization (~50%) of IGF-I were observed during the study. Fasting and 2 hour postprandial glucose levels, and hemoglobin A_{1c}, were no different in this group of patients compared with the other subjects in the high dose group and all of the subjects in the standard dose group. The data presented suggest that patients with elevated baseline IGF-I levels may still benefit from larger doses of rhGH during puberty.

g.6 Sex

Female subjects in the high dose group had substantial improvement in growth rates, height SDS and B-P PAH SDS compared with female subjects in the standard dose group. Height SDS at NAH was comparable in females (height SDS -0.6) and males (height SDS +0.2). See Table 10. Figure 8 earlier in this review demonstrates that in females (as well as males) LMH at NAH minus baseline B-P PAH was greater in the high dose group at all time points and the difference between the 2 dose groups for LMH minus baseline B-P PAH increased over time.

Table 10. M0380g

Pubertal Growth Hormone Deficiency
Patients at Near Adult Height - Last Height SDS by Sex

Treatment Dose=0.3 mg/kg/wk

SEX	N Obs	N	Mean	Std Dev	Minimum	Maximum
Male	35	35	-0.6	0.9	---	---
Female	7	7	-1.1	0.7	---	---

Treatment Dose=0.7 mg/kg/wk

SEX	N Obs	N	Mean	Std Dev	Minimum	Maximum
Male	28	28	0.2	1.0	---	---
Female	5	5	-0.6	1.9	---	---

g.7 Summary Comments

Older age, longer duration of prior rhGH therapy, sex and elevated baseline IGF-I SDS did not preclude a benefit from high dose rhGH. Subjects with elevated baseline IGF-I values who are treated with a larger dose of rhGH during puberty require monitoring of the IGF-I response and adjustments as necessary. On the other hand, subjects whose height after entering puberty is close to or above the normal mean (height SDS >-1) probably do not require a higher dose of rhGH during puberty to reach a desirable AH.

8.1.4.7.3 Secondary Efficacy Parameters

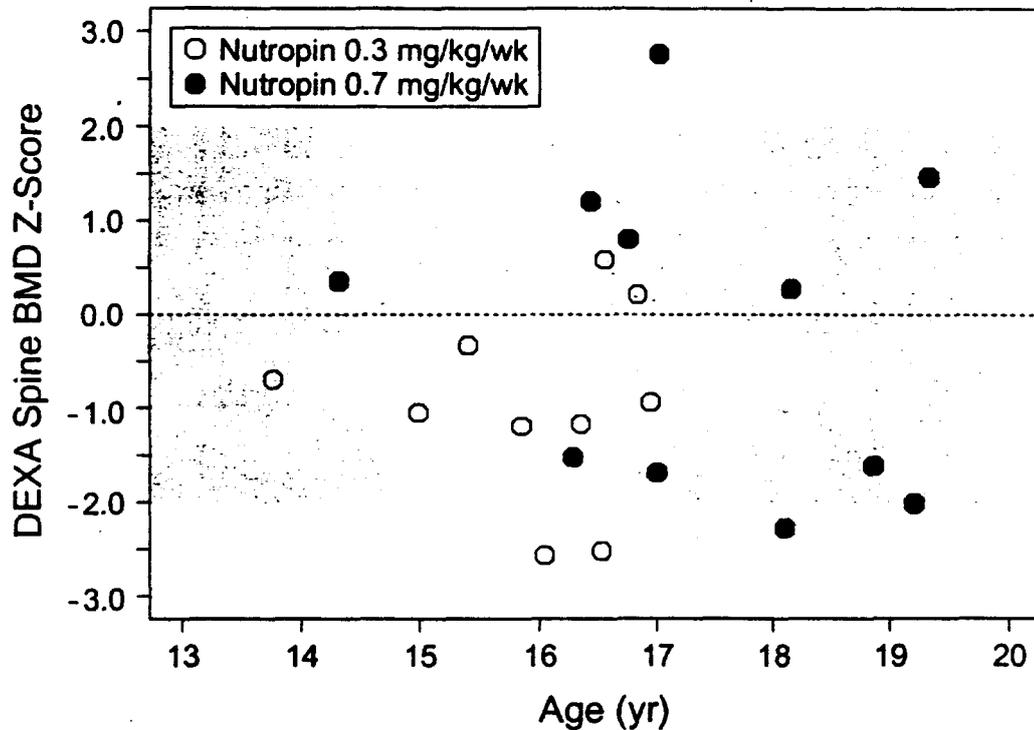
a. BMD

Only 31 subjects had BMD DEXA scans at study conclusion. The 2 dose groups did not differ in mean total body or spine BMD (expressed as gm/cm² or z-scores/SDS), spine BMAD or total body corrected BMC. None of the measures of BMD showed a

relationship to treatment duration or CA. However, the average spine and total body z-scores for both the standard and high dose groups were lower than those of the general population. The distribution of spine BMD z-scores is shown in Figure 16 by age for each dose group.

Figure 16

DEXA Spine Bone Mineral Density



Shaded area is the normal range.

b. Anti-GH Antibodies

Serum samples were assayed for antibodies to GH by RIA every 3 months. At baseline, 17 subjects (37%) in the high dose group and 8 subjects (17%) in the standard dose group were antibody positive (e.g., titer >1.0); the prevalence of subjects who were antibody positive declined steadily in both groups during the study. Mean antibody titer levels were slightly higher in the standard dose group at baseline and throughout the study, and decreased in both groups during the study. Antibody binding capacities were determined in all subjects in the high dose group with a positive titer at their first visit after baseline. No subject had a binding capacity value >2.0 mg/L.

8.1.4.8 Pharmacokinetic Analysis

No data submitted or necessary.

8.1.4.9 Safety Results

8.1.4.9.1 Extent of Exposure

The 49 subjects in the standard dose group were exposed to Nutropin for 131 subject-years (average=32.0 months/subject); the 48 subjects in the high dose group were exposed to Nutropin for 137 subject-years, (average=34.2 months/subject).

8.1.4.9.2 Deaths

There were no deaths during the study.

8.1.4.9.3 Serious Adverse Events

Four serious adverse events occurred during the study in the standard dose group. Three of these 4 events were the result of accidental injuries and not felt to be related to the study drug; Nutropin was continued in all of these subjects. A fourth subject developed progressively worsening scoliosis during the trial and required surgical intervention; Nutropin was discontinued at the time of surgery (see Sections 8.1.4.9.5.1.f and 8.1.4.9.4).

Six serious adverse events occurred in 5 subjects during the study in the high dose group. Four of these events were not felt to be related to study drug (e.g., traumatic fracture of the right epicondyle requiring pinning, hospitalization for depression, osteomyelitis/abscess of the tibia requiring surgical drainage, and subsequently, a tibial repair); Nutropin was continued in all of these subjects. A fifth subject developed progressively worsening scoliosis during the trial and required spinal fusion after 2.6 years on-study (see Section 8.1.4.9.5.1.f). A sixth subject developed right hip pain which responded to bedrest and discontinuation of study drug (see Section 8.1.4.9.4).

8.1.4.9.4 Adverse Events Leading to Withdrawal

Two patients in the standard dose group discontinued because of scoliosis requiring surgery (see Sections 8.1.4.9.3 and 8.1.4.9.5.1.f), and thigh pain.

In the high dose group, subjects 6-221 (coarsening facial features and broadening of the nasal bridge) and 1516-225 (large shoe size) discontinued because of "acromegaloid" adverse events (see Section

8.1.4.9.5.2). Subject 685-222 discontinued because of painful swelling of his left ankle requiring casting, and an "elevated" IGF-I level performed outside of study; he had attained a satisfactory height (177.3 cm) at the time of study discontinuation. Subject 50-222 discontinued because of right hip pain (see Section 8.1.4.9.3).

8.1.4.9.5 Adverse Events Potentially Associated with rhGH therapy

8.1.4.9.5.1 Adverse Events Previously Associated with rhGH Therapy

a. None of the more severe but unusual adverse events associated with rhGH therapy (i.e. intracranial hypertension, proliferative retinopathy, slipped capital femoral epiphysis, hypercalcemia, or pancreatitis) occurred during this trial. In addition, no cases of leukemia were reported.

b. Hypothyroidism - Eleven subjects were receiving appropriate amounts of L-thyroxine replacement therapy for hypothyroidism at study initiation (8 in the standard dose group and 3 in the high dose group). Hypothyroidism occurring (3) or worsening (2) during the trial was reported in 5 subjects (3 in the high dose group and 2 in the standard dose group).

c. Gynecomastia - Four subjects in the high dose group and 2 subjects in the standard dose group reported gynecomastia during the trial. It is also possible that the gynecomastia observed in these subjects was a consequence of puberty per se.

d. Allergy - There were no reports of allergic reactions attributable to Nutropin in either dose group.

e. Arthralgia or myalgia was reported by 9 subjects in the standard dose group and 8 subjects in the high dose group (none of the patients in the high dose group complained of myalgia). One subject in each group had complaints consistent with carpal tunnel syndrome.

f. Scoliosis was reported in 3 subjects in the high dose group and 2 subjects in the standard dose group. One subject in each group required surgical intervention.

g. Edema - Two patients in the standard dose group experienced mild peripheral edema, while no cases of edema were reported in the high dose group.

h. Skin - Skin tags were noted in 1 subject in the high dose group. During the study, 1 subject in the standard dose group had a benign irregular nevus removed, and 1 subject in the high dose group had a benign mole removed.

i. Hyperglycemia

Patients with known diabetes mellitus were not enrolled in this study. Glucose metabolism was monitored by measurement of fasting and postprandial glucose, insulin and C-peptide levels, as well as hemoglobin A_{1c}.

Mean fasting and postprandial glucose values did not change significantly during the study in either dose group, and there were no significant differences between the groups at any time point. There was a slightly greater increase in fasting insulin and fasting C-peptide levels in the high dose group compared with the standard dose group after 2 years, but not after 3 years, of therapy. The change in median postprandial insulin values was greater in the high dose group compared with the standard dose group after 1 and 2 years, but not after 3 years, of treatment. Mean hemoglobin A_{1c} increased very slightly in both dose groups after 1 and 2 years of therapy, but, by Month 36, the means had returned to baseline; again, there were no differences between the 2 treatment groups at any time point.

No subject developed diabetes mellitus during the study. De novo, sporadic elevations of glucose were observed only in the standard dose group. Subject 144-223 in the standard dose group developed decreased glucose tolerance, and Subject 166-224, also in the standard dose group, had elevated postprandial glucose levels only at Months 3 to 12. No cases of hyperglycemia were reported in the high dose group.

As noted in Section 8.1.4.7.2.g.5, fasting and 2 hour postprandial glucose levels, and hemoglobin A_{1c}, were no different in the 7 patients in the high dose group with elevated baseline IGF-I levels compared with the other subjects in the high dose group and all of the subjects in the standard dose group. In addition, there was no evidence of glucose intolerance in the 5 patients with "acromegaloid" adverse events (see Section 8.1.4.9.5.2).

Two subjects in the high dose group reported hypoglycemia (in 1 subject during an oral GTT [glucose 43 mg%], and spontaneously [glucose 46 mg%] in another subject).

8.1.4.9.5.2 Unusual "Acromegaloid" Adverse Events Exclusively Reported in the High Dose Group

Five subjects were singled out by the sponsor and this reviewer for having unusual "acromegaloid" adverse events. Two of these subjects discontinued prematurely from the study because of these adverse events. Subject 6-221 (see Section 8.1.4.9.4) was noted to have coarsening of his facial features and broadening of the nasal ridge at Months 24 to 33. This patient had borderline high IGF-I values at Month 18 (930 ng/ml) and Month 21 (844 ng/ml). He discontinued from the study at Month 33. His peak on-study growth rate was 8.6 cm/yr

(baseline growth rate 9.0 cm/yr), and his LMH was at the lower end of his mid-parental target height, indicating that he did not grow excessively. Subject 1516-225 (see Section 8.1.4.9.4) was discontinued from the study at Month 21 because his feet and shoe size had substantially increased. His baseline IGF-I was slightly elevated (843 ng/ml) and, for most of the study, remained close to that level (peak value 1015 ng/ml at Month 6). Both of his parents were tall; therefore, his LMH was at his mid-parental target height, indicating that he did not grow excessively.

Subject 159-223 chose to discontinue from the study at Month 36 because of "quite a substantial height". At that time, he noted that his hands and feet had grown "quite a bit". He frequently missed injections and his IGF-I levels were normal to low throughout the study. His NAH was within the normal range and at the upper end of his mid-parental target height. Of note, this subject received testosterone because of pubertal arrest and lack of bone age progression; this may help to explain his relatively tall stature at NAH. Subject 2-016 complained of jaw pain between Months 9 and 18. However, he was noted to have "nodular growth of the jaw" at baseline. His baseline IGF-I level was normal (675 ng/ml), but between Months 9 and 18, his IGF-I values were high normal to high (range, 806 ng/ml to 1076 ng/ml), and between Months 21 and 36 rose even higher (range, 972 ng/ml to 1802 ng/ml). This subject had a tall father; therefore, his NAH was within the mid-parental target height range, indicating that he did not grow excessively. Subject 19-607 complained of temporomandibular joint pain at Month 3. However, he reported the same pain at baseline. His IGF-I values were normal during the study. His LMH (at Month 21) was within the normal range, and close to his mid-parental target height, indicating that he did not grow excessively.

The lack of excessive growth in 4 of these subjects and the presence of similar complaints prior to study initiation in 2 of these patients argue to some extent against the presence of a truly "acromegaloid" subset in the high dose group. Nonetheless, the symptoms described are certainly suggestive of GH excess and the elevated IGF-I values in 3 of these patients are somewhat disturbing.

Therefore, at the request of this reviewer, the sponsor compared this cohort with the other subjects in the high dose group and all of the subjects in the standard dose group. At baseline, the "acromegaloid" subset were older (mean CA 14.7 yrs versus 13.6 yrs in the remaining subjects in the high dose group), had longer prior rhGH treatment (mean duration 7.2 yrs versus 3.7 yrs in the remaining subjects in the high dose group), and were taller (mean height SDS -0.8 versus -1.2 in the remaining subjects in the high dose group). Analysis of the growth response in these 3 groups revealed comparable gains in height SDS in the "acromegaloid" subset and the remaining subjects in the high dose group which were greater than those seen in the standard dose group; however, the growth rates in the "acromegaloid" subset tended to be less than those observed in the remaining patients in the

high dose group (by ~1 cm/yr) after 1, 2 and 3 years of therapy, and only marginally greater than the growth rates observed in the standard dose group. The mean increase in IGF-I observed in the "acromegaloid" subset (52 ng/ml) was actually less than that seen in the other 2 groups. As noted in Section 8.1.4.9.5.1.i, there was no evidence of glucose intolerance in the 5 patients with "acromegaloid" adverse events.

It is not unreasonable to postulate that a subset of patients in the high dose group who were older, taller and previously treated longer at baseline would 1) grow somewhat less well (at least as assessed by growth rate), and 2) be more prone to develop "acromegaloid" side effects, than the remaining subjects in the high dose group (e.g., near optimal results were already present ["the container was almost full"] before the dose of rhGH was increased). However, it should be noted that the subset analyses described in Section 8.1.4.7.2.g only partially support this hypothesis. Although subjects with baseline height SDS >-1 did not require the higher dose of rhGH to achieve a desirable, near-normal AH, older age and longer duration of prior rhGH therapy (as well as sex and elevated baseline IGF-I SDS) did not preclude a growth benefit from high dose rhGH.

8.1.4.9.5.3 Distribution of Last Height SDS and Last Height Minus Mid-Parental Target Height - Absence of Gigantism in High Dose Group

At the request of this reviewer, the sponsor analyzed the distribution of the last height SDS for each dose group for all subjects (Table 11; n=97) and for subjects attaining NAH (Table 12; n=75). Both tables show a normal proportion of subjects above the mean in the high dose group (52% in Table 11 and 57.6% in Table 12), and a subnormal proportion of subjects above the mean in the standard dose group (~24% in Tables 11 and 12). In Tables 11 and 12, only 1 subject had a height SDS >+2 - an expected result. Table 12 also shows that 40.5% of subjects in the standard dose group had a height SDS <-1 (<16th percentile), compared with only 21.2% of subjects in the high dose group.

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Table 11. M0380g

Pubertal Growth Hormone Deficiency - Last Height SDS by Treatment Group

TABLE OF LTHTSD BY TXDOS

LTHTSD(Last HT SDS) TXDOS(Treatment Dose)

Frequency	0.1 mg/k 1g/wk	0.3 mg/k 1g/wk	Total
> 2 SD	1 2.08	0 0.00	1
1 to 2 SD	8 16.67	1 2.04	9
0 to 1 SD	16 33.33	11 22.45	27
-1 to 0 SD	11 22.92	16 32.65	27
-2 to -1 SD	10 20.83	17 34.69	27
< -2 SD	2 4.17	4 8.16	6
Total	48	49	97

*Note: +1 SD is equivalent to 84%; +2 SD is equivalent to 97.7%

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Table 12. M0380g

Pubertal Growth Hormone Deficiency - Last Height SDS by Treatment Group for Subjects at Near Adult Height

TABLE OF LHTSD BY TXDOS

LHTSD (Last HT SDS) TXDOS (Treatment Dose)

Frequency	TXDOS		Total
Col Pct	0.7 mg/k lg/wk	0.3 mg/k lg/wk	
> 2 SD	1	0	1
	3.03	0.00	
1 to 2 SD	5	0	5
	15.15	0.00	
0 to 1 SD	13	10	23
	39.39	23.81	
-1 to 0 SD	7	15	22
	21.21	35.71	
-2 to -1 SD	6	14	20
	18.18	33.33	
< -2 SD	1	3	4
	3.03	7.14	
Total	33	42	75

*Note: +1 SD is equivalent to 84%; +2 SD is equivalent to 97.7%

In addition, the sponsor analyzed the distribution of last height minus mid-parental target height for each dose group for subjects attaining NAH. Table 13 shows the proportion of subjects within 5 and 10 cm of target height (e.g., target height range defined at mid-parental target height +/- 10 cm [20]), and those outside of that range. Only 4 subjects in the high dose group had NAH >10 cm above mid-parental target height (including the 1 subject in Tables 11 and 12 with last height SDS >+2). Table 13 also shows that 22% of subjects in the standard dose group had NAH >5 cm below Tanner target height, compared with only 12.9% of subjects in the high dose group.

Table 13. M0380g

Pubertal Growth Hormone Deficiency

Difference (cm) = Last Height minus Mid-Parental Target Height by Treatment Group for Subjects at Near Adult Height

TABLE OF TARGDIFF BY TXDOS

Frequency Col Pct	TARGDIFF (Last \overline{HE} - Midparent Target)		Total
	0.7 mg/k lg/wk	0.3 mg/k lg/wk	
> 10 cm	4	0	4
	12.90	0.00	
5 to 10 cm	5	4	9
	16.13	9.76	
0 to 5 cm	12	8	20
	38.71	19.51	
-5 to 0 cm	6	20	26
	19.35	48.78	
-10 to -5 cm	3	6	9
	9.68	14.63	
< -10 cm	1	3	4
	3.23	7.32	
Total	31	41	72

Frequency Missing = 3

*Note: +1 SD is equivalent to 84%; +2 SD is equivalent to 97.7%

Three of 4 subjects with NAH >10 cm above mid-parental target height were <11.3 cm above target height, and had last height SDS within the normal range, indicating that they had short parents. The last height of the fourth subject was 2.9 cm above her target height range even though she had a very tall father; her last height SDS was 2.6. Two of these 4 subjects (including the female patient just described) began the study at -50th percentile (height SDS -0). Three of these 4 subjects had elevated baseline IGF-I levels (including 1 of the patients who began the study with height SDS at -50th percentile). None of these 4 subjects reported "acromegaloid" side effects (e.g, change in face, hands, feet, etc). These observations further support the view that GHD patients entering puberty on conventional amounts of rhGH with -normal height SDS +/- elevated IGF-I levels (and perhaps elevated IGF-I levels +/- -normal height SDS) do not require an increase in rhGH dosage to achieve a normal, desirable AH (see Sections 8.1.4.7.2.g.4 and 8.1.4.7.2.g.7).

It can reasonably be concluded then that the heights achieved with the high dose of rhGH spanned the normal range and were not indicative of

gigantism due to GH excess. Furthermore, it should be noted that the subset analyses described in Section 8.1.4.7.2.g **did not reveal any evidence of excessive growth** (as assessed by last height SDS) **in any of the defined subgroups** (e.g. older or younger at baseline, longer or shorter duration of prior rhGH therapy, height SDS closer to or further from the mean at baseline, male or female, baseline IGF-I elevated or within the normal range).

8.1.4.9.6 IGF-I Responses

Please refer to detailed comparison of IGF-I responses in the 2 treatment groups in Section 8.1.4.7.2.f. As demonstrated in several figures and tables, although the mean IGF-I SDS were in the high normal range and not significantly different in the 2 dose groups, many more patients in the high dose group had IGF-I SDS above the normal range (>+2) at multiple time points during the study.

8.1.4.9.7 Physical examination and Vital Signs

No consequential changes occurred during the study in either dose group other than those already described in Sections 8.1.4.9.3, 8.1.4.9.4 and 8.1.4.9.5.

8.1.4.9.8 Miscellaneous Laboratory Parameters

During the course of this study no consequential, clinically significant or consistent changes were observed in renal function, urinalyses, hematologic parameters, electrolytes, calcium, phosphate, alkaline phosphatase, lipids or liver function in either dose group.

8.1.5 Discussion/Summary

8.1.5.1 Preface

Although pituitary GH secretion approximately doubles during normal puberty, the current dosing recommendation is to maintain the dose of rhGH used in childhood/prepubescence (0.3 mg/kg/week) during adolescence. Study M0380g was designed to compare the efficacy (NAH, growth rate, height SDS and other growth parameters) and safety of a standard dose and high dose of Nutropin in pubertal GHD subjects.

Otherwise healthy male and female GHD subjects previously treated with standard dose rhGH therapy (-0.3 mg/kg/wk) who had spontaneously entered puberty (Tanner stage ≥ 2) were recruited and enrolled in the study. Subjects were randomized to continue standard dose rhGH therapy or switch to high dose rhGH (0.7 mg/kg/wk) administered as daily SC injections. Treatment was projected to be continued until

NAH was attained (e.g., growth rate <2 cm during last year of treatment, and BA was ≥ 14 years for females or ≥ 16 years for males).

There was a preponderance of males in the study (83 of 97 subjects). The 2 dose groups were well matched for an assortment of relevant baseline characteristics. The mean CA was ~ 14 years, mean BA was ~ 13 years, mean pretreatment growth rate was 8.5 cm/yr, and mean height SDS was ~ -1.3 .

Of the 97 subjects enrolled, 45 were treated for 3 or more years. Forty eight subjects completed the study, and 49 discontinued (more in the high dose group). Twenty nine of the 49 patients who discontinued requested early removal from the study; the majority stated that they were satisfied with the height achieved as the reason for discontinuation (especially in the high dose group).

8.1.5.2 Discussion of Efficacy Results

8.1.5.2.1 Primary Efficacy Results

The primary efficacy endpoint was NAH. Seventy five subjects attained NAH (46 completers and 29 patients who discontinued early mostly because of satisfaction with height achieved). Forty one of the seventy five patients attaining NAH required BA to be extrapolated to the date of their LMH to meet the criterion. LMH for subjects attaining NAH (adjusted for baseline height and the other 6 covariates noted in Section 8.1.3.4.3.1) in the standard and high dose groups were compared using ANCOVA. The ANCOVA demonstrated that subjects in the high dose group were significantly taller at NAH than subjects in the standard dose group by an average of 4.6 cm ($n=75$; $p<0.001$; 95% CI of 2.6-6.5 cm). Subjects in the high dose group were also significantly taller by ANCOVA when only 1) study completers (46 of 48 achieved NAH), and 2) subjects who attained NAH and did ($n=41$) or did not ($n=34$) require final BA at LMH to be extrapolated were separately analyzed; subjects who did not complete the study for any reason were also taller after treatment with the larger dose of rhGH, but the result did not reach statistical significance.

Taller heights were observed across the high dose group at multiple time points indicating that the greater mean value for LMH for subjects attaining NAH in the high dose group was not the result of only a few subjects, and that NAH was not attained after only 1 year of therapy. The mean height SDS at NAH was greater in the high dose group (0.0 ± 1.2) than the standard dose group (-0.7 ± 0.9 ; similar to results observed in previous Genentech studies with standard doses of rhGH [1]).

Similar results were observed when all subjects were included (ITT analysis), using the LMH regardless of whether or not NAH was attained. ANCOVA demonstrated that subjects in the high dose group

were significantly taller at LMH than subjects in the standard dose group by an average of 2.8 cm (n=97; p=0.036; 95% CI of 0.2-5.3 cm).

In both the primary efficacy analysis of NAH and the ITT analysis of LMH per se, the difference between the groups for change in height increased with duration of therapy suggesting an increasing positive effect of the higher dose over time. More than likely, the difference between the dose groups at NAH (4.6 cm) was greater than the difference at LMH in the ITT analysis (2.8 cm) because the mean duration of on-study rhGH treatment was greater in the subjects attaining NAH (3.0 years as opposed to 2.7 years).

Clearly, subjects in the high dose group grew more substantially than patients in the standard dose group, and the difference between the 2 dose groups increased with duration of therapy. A variety of supportive efficacy analyses confirmed these findings and are briefly summarized in the succeeding paragraphs.

8.1.5.2.2 Supportive Efficacy Results

The change in height by duration of treatment (e.g., after 1, 2, 3 and 4 years of on-study therapy) was also compared in the 2 dose groups using ANCOVA. Just as in the primary analyses described above, the difference between the 2 groups for change in height increased after each year of treatment. After 4 years of therapy, subjects in the high dose group were taller than the subjects in the standard dose group by an average of 5.7 cm (n=20; p=0.024; 95% CI, of 1.2-10.1 cm). A difference of approximately 5 cm (2 inches) is generally considered to be a clinically significant outcome.

After each year of treatment, the mean growth rate in the high dose group exceeded the mean growth rate in the standard dose group by a similar increment. The mean Month 0-12 growth rate was 1.6 cm greater in the high dose group compared with the standard dose group (p=0.001), and the Month 24-36 growth rate was 1.7 cm greater in the high dose group (p=0.038). The distribution of growth rates was clearly shifted to the right for the high dose group compared with the standard dose group at each time point indicating that the differences in growth rates were not caused by a few patients, but the groups as a whole.

After 3 years of therapy, the cumulative mean change in height SDS was greater in the high dose group (1.4) compared with the standard dose group (0.9) (p=0.023). In addition, the change in standardized B-P PAH from baseline, and LMH minus baseline B-P PAH, were greater in the high dose group at all time points, and the difference between the 2 dose groups for both of these growth outcome parameters increased with years of treatment once again suggesting an increasing positive effect of the higher dose over time.

Although it is well established that treatment of GHD children with conventional doses of rhGH is associated with a normal rate of BA advancement, the effect of higher doses of rhGH was not known. In this study, the mean change in BA was -1 year per year of treatment in

both dose groups. In addition, the rate of advancement of Tanner pubertal stage was similar in the 2 dose groups, and there were no statistically significant differences between dose groups in mean change from baseline for testosterone levels in males. **These data suggest that the greater increases in absolute height, height SDS and growth rate in the high dose group compared with the standard dose group were achieved without an acceleration of the rate of skeletal maturation or pubertal progression, resulting in improved B-P PAH and LMH.**

IGF-I levels were also frequently determined in all subjects in each dose group during this study. Although elevated IGF-I levels were observed more frequently in subjects in the high dose group (see ahead to Discussion of Safety Results), the large interindividual and intraindividual variability in IGF-I values in both groups resulted in differences between groups for the change from baseline (using IGF-I SDS or log values) that were not statistically significant after 1, 2, or 3 years of treatment. Moreover, mean IGF-I SDS values were within the high normal range (between 0 and +2 SDS), and not significantly different, in the 2 dose groups at all time points during the study. **Clearly, the greater growth observed in the high dose group cannot be correlated with a definitively greater IGF-I response.** The lack of correlation between growth parameters and IGF-I response in GHD children treated for many years with standard amounts of rhGH is well established in the literature (19).

8.1.5.2.3 Subgroup Analyses

At the request of this reviewer, **subgroup analyses** were performed to define what baseline characteristics, if any, impacted the response to therapy in the high and standard dose groups. Relevant baseline characteristics (baseline CA, duration of prior therapy with rhGH, height SDS at baseline, baseline IGF-I level and sex) were divided into subcategories which were then compared with regard to several outcome variables (growth rate, height SDS, B-P PAH, IGF-I SDS, and last height SDS for subjects attaining NAH) in both dose groups.

The higher dose (compared with the standard dose) resulted in greater growth rates after 1, 2 and 3 years of therapy and a greater height SDS at NAH in younger (<13 yrs) and older patients (>15 yrs) (and also in patients with shorter [<2 yrs] and longer [>5 yrs] duration of prior rhGH therapy) - **suggesting that GHD patients of all ages and any duration of prior rhGH therapy benefit from larger doses of rhGH after the onset of puberty.** Furthermore, female subjects in the high dose group (n=7) had substantial improvement in growth rates, height SDS and B-P PAH SDS compared with female subjects in the standard dose group (n=7), and height SDS at NAH was comparable in females (height SDS -0.6) and males (height SDS +0.2) - **suggesting that female gender does not preclude a benefit from larger doses of rhGH**

Height SDS at NAH was significantly greater in subjects who were shorter at baseline (height SDS <-2) and taller at baseline as well

(height SDS >-1) in the high dose group. However, it is important to note that subjects who were taller at baseline achieved a satisfactory NAH with BOTH the standard dose (-0.1 height SDS) and high dose (+0.6 height SDS) of rhGH. In addition, 2 of 4 subjects in the high dose group with NAH >10 cm above mid-parental target height (who by inference may well have achieved a satisfactory AH with standard dose therapy) began the study at ~50th percentile (height SDS ~0) (see Sections 8.1.4.9.5.3 and 8.1.5.3). Furthermore, subjects who entered the study with height SDS larger than the mean (10%) were able to attain a satisfactory LMH after treatment with the standard dose of rhGH. **This data suggests that GHD patients whose standardized heights are closer to normal after a course of treatment with conventional amounts of rhGH during prepubescence/childhood do not require larger doses of rhGH during puberty to attain a desirable AH.**

Seven subjects in the high dose group had elevated baseline IGF-I values (see ahead to Discussion of Safety Results). The mean growth rates (and height SDS) of these 7 patients during the study were similar to those seen in the other subjects in the high dose group (and greater than those observed in the patients in the standard dose group). **This data suggests that subjects with relatively high IGF-I levels at baseline may still benefit from a larger dose of rhGH during puberty.** On the other hand, the subjects (discussed in the preceding paragraph) with baseline standardized heights closer to normal (height SDS >-1) (who attained a desirable AH with standard doses of rhGH) tended to have higher baseline IGF-I levels. In addition, 3 of 4 subjects in the high dose group with NAH >10 cm above mid-parental target height (who by inference may well have achieved a very satisfactory AH with standard dose therapy) had elevated baseline IGF-I values (see Sections 8.1.4.9.5.3 and 8.1.5.3). **This data suggests that subjects with relatively high baseline IGF-I levels do NOT require a larger dose of rhGH during puberty to attain a desirable AH. In summary, the evidence is inconclusive, and it remains unclear at this time whether patients with elevated baseline IGF-I levels achieve a more satisfactory AH after treatment with larger doses of rhGH during puberty.**

8.1.5.2.4 Secondary Efficacy Results

It has recently been reported that, despite treatment with conventional amounts of rhGH during childhood and adolescence, young adults with childhood-onset GHD have significant decreases in BMD. Therefore, a secondary objective of this study (fifth protocol amendment submitted in June 1996) was to assess the effect of the 2 dose regimens on total body and spine BMD at the end of therapy. Mean total body BMD/BMC, spine BMD/BMD z-score/BMAD were the same in each treatment group. However, the average total body and spine BMD z-scores in both groups were lower than those of the general population. These results are consistent with the hypothesis that young patients with GHD are at risk for reduced bone mass.

The results of anti-GH antibody determinations were not significant. The prevalence of subjects who were antibody positive (as well as mean

antibody titer levels) declined during the study. All antibody binding capacity measurements were <2 mg/L in the high dose group.

8.1.5.3 Discussion of Safety Results

8.1.5.3.1 General Comments

No deaths were reported during the study. Two of 10 serious adverse events (1 case of aggravated scoliosis requiring surgery in each dose group) were probably related in part to study drug (e.g., rapid growth induced by rhGH aggravated preexisting scoliosis). One of 2 patients in the standard dose group who discontinued because of an adverse event required surgery for scoliosis (see previous sentence); 2 of 4 subjects in the high dose group who discontinued because of an adverse event had "acromegaloid" complaints (see Sections 8.1.5.3.3 and 8.1.4.9.5.2).

Regarding events previously associated with rhGH therapy:

None of the more severe but unusual adverse events associated with rhGH therapy (e.g., intracranial hypertension [incidence of headache, blurred vision, nausea or vomiting was similar in the 2 groups and not felt to be related to rhGH therapy], proliferative retinopathy, slipped capital femoral epiphysis, hypercalcemia, or pancreatitis) occurred during this trial. In addition, no cases of leukemia were reported.

The incidence of new onset or aggravated hypothyroidism, gynecomastia, arthralgia, carpal-tunnel complaints, scoliosis, and nevi was similar in both groups. Peripheral edema and myalgia were only reported by subjects in the standard dose group.

Patients with known diabetes mellitus were not enrolled in the study. Mean fasting/postprandial glucose and hemoglobin A_{1c} levels did not change significantly during the study in either dose group. There was a slightly greater increase in median fasting and postprandial insulin levels in the high dose group compared with the standard dose group after 2 years, but not after 3 years, of therapy. No subject developed diabetes mellitus during the study. Sporadic elevations of glucose were observed ONLY in the standard dose group! In addition, there was no evidence of glucose intolerance in the 7 patients with elevated baseline IGF-I levels, and the 5 patients with "acromegaloid" adverse events. **Although a theoretical significant concern of the sponsor and the Agency before the trial was initiated, treatment with the larger dose did not appear to result in glucose intolerance - a very important negative finding!**

8.1.5.3.2 IGF-I Responses

Although the changes from baseline for IGF-I SDS were not significantly different in the 2 treatment groups after 1, 2, or 3 years of treatment (and mean IGF-I SDS values were within the high

normal range [between 0 and +2 SDS], and not significantly different, in the 2 dose groups at all time points during the study), mean and median values for IGF-I and IGF-I SDS increased to a greater extent in the high dose group compared with the standard dose group. In addition, the incidence of IGF-I levels above the normal range during therapy was greater in the high dose group. Five of the 49 subjects (10%) in the standard dose group had ≥ 3 IGF-I values above the normal range during the study compared with 19 of the 47 subjects (40%) in the high dose group. Even if the 7 patients in the high dose group with elevated baseline IGF-I levels (all of whom had at least 1 on-study high value) are excluded from this analysis, a significant difference between the 2 dose groups persists (e.g., 35% of the subjects in the high dose group compared with 8% of the subjects in the standard dose group had ≥ 3 IGF-I values above the normal range during the study).

On the other hand, most subjects who developed IGF-I SDS $>+2$ during the trial had baseline IGF-I values above the mean in both dose groups, and amongst subjects with normal baseline IGF-I values, a greater number in the high dose group (~55%) compared with the standard dose group (~41%) had baseline IGF-I values above the mean (between 0 and +2 SDS). The sponsor proposes that this may partially explain why more subjects in the high dose group had single and multiple IGF-I SDS above the normal range during the study. The sponsor also provides a recent reference which concludes that, in addition to the well known dramatic increase in IGF-I during adolescence with increasing age or pubertal stage, there is a significant variation in serum IGF-I levels with age within a given Tanner stage (21) (information which was not incorporated into the reference ranges used in this study). However, the rate of pubertal progression and the change from baseline for testosterone (in males) was similar in the 2 dose groups; it is therefore difficult to conclude that the use of the standard reference range resulted in more IGF-I SDS values above the normal range in the high dose group compared to standard dose group.

Therefore, it is reasonable to conclude that a very significant percentage of pubertal GHD subjects treated with the higher dose of rhGH can be expected to manifest multiple abnormal IGF-I values over time. It has recently been reported in adults that elevated levels of IGF-I may be associated with carcinoma of the breast (22) and prostate (23). Moreover, it is well known that acromegalic patients (with very high levels of IGF-I) are at risk for neoplasia, in particular colon cancer. **Therefore, prudence dictates that adolescents switched to the high dose of rhGH require careful monitoring of IGF-I levels and appropriate dosage decrements when elevated IGF-I values are observed.**

The administration of the larger dose of rhGH to the 7 subjects with an elevated baseline IGF-I level **did not necessarily** result in a further increase in IGF-I (e.g., in ~50% of these patients, sustained or further elevation of IGF-I levels was observed during the study, while in the remaining ~50%, IGF-I levels essentially normalized). This

data suggests that the IGF-I response was not consistently proportional to the dosage of rhGH administered and that, given the unpredictability of the IGF-I response in subjects with elevated baseline IGF-I values, these patients, if switched to high dose therapy, require even more intensive monitoring of IGF-I levels.

8.1.5.3.3 Unusual "Acromegaloid" Adverse Events Exclusively Reported in the High Dose Group

Five patients in the high dose group were singled out by the sponsor and this reviewer for having unusual "acromegaloid" side effects. These adverse events (reported exclusively by subjects in the high dose group) included 2 cases of temporomandibular joint discomfort, 1 case of broadening of the nasal bridge and coarsening of facial features, 1 case of increased size of the hands and feet, and 1 case of "large shoe size." Each of these adverse events has already been discussed at length in Section 8.1.4.9.5.2. The lack of excessive growth in 4 of these subjects and the presence of similar complaints prior to study initiation in 2 of these patients argue to some extent against the presence of a truly "acromegaloid" subset in the high dose group. Nonetheless, the symptoms described are certainly suggestive of GH excess and the elevated IGF-I values in 3 of these patients are somewhat disturbing.

When compared with the other subjects in the high dose group and all of the subjects in the standard dose group, the "acromegaloid" subset were older and taller (mean height SDS closer to normal) at baseline, and had longer prior rhGH treatment. In addition, as assessed by growth rates, these patients did not grow as well as the other subjects in the high dose group. The mean increase in IGF-I observed in the "acromegaloid" subset was actually less than that seen in the other 2 groups, and there was no evidence of glucose intolerance in these patients.

It is not unreasonable to postulate that a subset of patients in the high dose group who were older, taller and previously treated longer at baseline would 1) grow somewhat less well and 2) be more prone to develop "acromegaloid" side effects, than the remaining subjects in the high dose group (e.g., near optimal results were already present before the dose of rhGH was increased). However, as stated earlier, only patients with baseline height SDS closer to normal seem not to require the higher dose of rhGH to achieve a desirable AH.

8.5.3.3.4 Distribution of Last Height SDS and Last Height Minus Mid-Parental Target Height - Absence of Gigantism in High Dose Group

Analysis of the distribution of the last height SDS for all subjects in each dose group and for subjects attaining NAH demonstrates a normal proportion of subjects above the mean in the high dose group

(~50%) and a subnormal proportion of subjects above the mean in the standard dose group (~25%). Analysis of the distribution of last height minus mid-parental target height for subjects attaining NAH demonstrates only 4 subjects in the high dose group with NAH >10 cm above mid-parental target height. Three of these 4 subjects were <11.3 cm above target height, and had last height SDS within the normal range, indicating that they had short parents. None of these 4 subjects reported "acromegaloid" side effects.

Furthermore, it should be noted that the subset analyses described in Section 8.1.4.7.2.g did not reveal any evidence of excessive growth (as assessed by last height SDS) in any of the defined subgroups (e.g., older or younger at baseline, longer or shorter duration of prior rhGH therapy, height SDS closer to or further from the mean at baseline, male or female).

It therefore can reasonably be concluded then that the heights achieved with the high dose of rhGH spanned the normal range and were not indicative of gigantism due to GH excess.

8.1.6 Labeling

8.1.6.1 Changes in Label Proposed by Sponsor

Efficacy Studies

Growth Hormone Deficiency (GHD) In Pubertal Patients

Draft

dose group, 3.2 yr in the standard-dose group). Thus, the relative gains in height were achieved without undue advancement of bone age.

Dosage

Pediatric Growth Hormone Deficiency (GHD)

A weekly dosage of up to 0.30 mg/kg of body weight divided into daily subcutaneous injection is recommended. In pubertal patients, a weekly dosage of up to 0.70 mg/kg divided daily may be used. [

]

8.1.6.2 Labeling Proposed by Medical Reviewer

Efficacy Studies

Growth Hormone Deficiency (GHD) In Pubertal Patients

[

Draft

]

Dosage

Pediatric Growth Hormone Deficiency (GHD)

pin

8.1.7 Conclusions

8.1.7.1 Efficacy

a. The treatment of pubertal GHD subjects with 0.7 mg/kg/week of Nutropin resulted in statistically significant, clinically important improvements in AH compared with the standard dose of 0.3 mg/kg/wk. Subjects in the high dose group were significantly taller at NAH than subjects in the standard dose group by an average of 4.6 cm . Similar results were observed when LMH was analyzed in all subjects (ITT). After 4 years of therapy, subjects in the high dose group were taller than the subjects in the standard dose group by an average of 5.7 cm . In both the primary efficacy analysis of NAH and the ITT analysis of LMH per se, the difference between the groups for change in height increased with duration of therapy suggesting an increasing positive effect of the higher dose over time.

b. Supportive efficacy analyses demonstrated statistically significant improvements in growth rate, height SDS and B-P PAH in subjects in the high dose group compared with the standard dose group.

c. The greater increases in absolute height, height SDS and growth rate in the high dose group compared with the standard dose group were achieved without an acceleration of the rate of skeletal maturation or pubertal progression, resulting in improved B-P PAH and LMH.

d. The greater growth observed in the high dose group could not be correlated with a definitively greater IGF-I response

e. Older age, longer duration of prior rhGH therapy, and female sex did not preclude a benefit from high dose rhGH. On the other hand, subjects whose height after entering puberty is close to or above the normal mean (height SDS >-1) probably do not require a higher dose of rhGH during puberty to reach a desirable AH.

f. It remains unclear at this time whether patients with elevated baseline IGF-I levels achieve a more satisfactory AH after treatment with larger doses of rhGH during puberty. The data are conflicting and inconclusive.

g. Mean total body BMD/BMC, spine BMD/BMD z-score/BMAD were the same in each treatment group. However, the average total body and spine BMD z-scores in both groups were lower than those of the general population. These results are consistent with the hypothesis that young patients with GHD are at risk for reduced bone mass.

8.1.7.2 Safety

a. The incidence of adverse events known to be associated with Nutropin was not increased in the high-dose group. In addition, the severe but unusual rhGH-related adverse effects did not occur at all. This lends credence to the notion that adolescence is a period of greatest tolerance to elevated circulating levels of GH and IGF-I.

b. There was no evidence of glucose intolerance in the subjects in the high dose group.

c. Five patients in the high dose group appeared to develop "acromegaloid" side effects (e.g., coarsening of facial features, enlargement of hands and feet, jaw pain). The lack of excessive growth in 4 of these subjects and the presence of similar complaints prior to study initiation in 2 of these patients argue to some extent against the presence of a truly "acromegaloid" subset in the high dose group. Nonetheless, the symptoms described are certainly suggestive of GH excess and the elevated IGF-I values in 3 of these patients are somewhat disturbing. These patients were older and taller at baseline, had longer duration of prior rhGH therapy, and did not appear to grow quite as well when compared to the other subjects in the high dose group.

d. The heights achieved with the high dose of rhGH spanned the normal range and were not indicative of gigantism due to GH excess.

The distribution of height SDS at final height were more normal in the high dose group than the standard dose group. Only 4 patients in the high dose group had NAH >10 cm above mid-parental target height. Three of these 4 subjects had last height SDS within the normal range, indicating that they had short parents. None of these 4 subjects reported "acromegaloid" side effects. Moreover, there was no evidence of excessive growth in any patient subset (e.g., older or younger at baseline, height SDS closer to or further from the mean at baseline, male or female, or longer or shorter duration of prior rhGH therapy).

e. Although the changes from baseline for IGF-I SDS were not significantly different in the 2 treatment groups after 1, 2, or 3 years of therapy, the incidence of IGF-I levels above the normal range during the study (>+2 IGF-I SDS) was greater in the high dose group. Even after excluding the 7 patients in the high dose group with elevated baseline IGF-I levels, a significant difference between the 2 dose groups was observed (e.g., 35% of the subjects in the high dose group compared with 8% of the subjects in the standard dose group had ≥ 3 IGF-I values above the normal range during the study). Therefore, it is reasonable to conclude that a very significant percentage of pubertal GHD subjects treated with the higher dose of rhGH can be expected to manifest multiple abnormal IGF-I values over time. The long term safety consequences of this finding, in particular with regard to tumorigenesis, are not known.

f. When the larger dose of rhGH is administered to patients with elevated baseline IGF-I levels, the IGF-I response is variable and unpredictable.

8.1.8 Recommendations

8.1.8.1 Efficacy

a. In view of the significant efficacy reported in the trial, serious consideration should be given to increasing the dose of rhGH in all GHD children at the onset of puberty.

b. Once initiated, therapy should be continued until at least NAH is attained, which may take several years in some patients.

c. Therapy should be individualized. Patients with height SDS >-1 probably should not be switched to high dose therapy. It is unclear if patients with elevated IGF-I should receive high dose therapy. Older age, female gender and longer duration of prior therapy with rhGH are NOT reasons to avoid high dose therapy.

8.1.8.2 Safety

a. Adolescents switched to the high dose of rhGH require careful monitoring of IGF-I levels, and appropriate dosage decrements when elevated IGF-I values are observed in order to maintain IGF-I levels within the normal age- and sex-adjusted reference range. This is especially true for patients with elevated baseline levels of IGF-I who are placed on high dose therapy.

b. All pubertal GHD patients placed on high dose therapy should be monitored carefully for the well known common and uncommon adverse effects of rhGH therapy. In addition, clinicians should be vigilant in detecting "acromegaloid" phenomena, such as acral changes of the face, hands and feet. Older subjects with a long prior duration of conventional rhGH therapy whose baseline height SDS is close to the mean may possibly be at greater risk for acral changes.

c. Patients placed on high dose therapy should also be monitored carefully for the development of neoplasia and recurrence of preexisting pituitary tumors.

d. Although the high dose of rhGH was well tolerated in this pivotal study, the number of patients exposed was too small to properly assess the incidence of adverse sequelae. Therefore, the sponsor should provide the Agency with a comprehensive plan for Phase IV post marketing surveillance as a condition for approval of this NDA.

ISI (M1) 3/24/2000

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CC: Original NDA 19-676; HFD-510 NDA 19-676
Original IND [redacted] HFD-510 IND [redacted]
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