CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-522/S-013

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION

NDA #	19-676, SE2-016	APR 6 2000
Drug Name	Nutropin (somatropin (rDNA origin) for injection)	
Sponsor	Genentech, Inc.	
Indication	Treatment for growth hormone deficiency (GHD)	
Review Documents	Vol. S34.1-S34.8, dated June 11, 1999 and S52.1-S52.2dated Nov. 19, 1999; SAS datasets dated Aug. 5, 1999 and February 18, 2000	
Medical Team (HFD-510)	Robert Perlstein M.D.; Saul Malozowski, M.D.	

The following review has been discussed with the medical review team.

HIGHLIGHTS OF THE EVALUATION

A significantly higher percent of subjects discontinuing the study early (65% vs. 37%), a smaller percent of subjects reaching near adult height (69% vs. 86%), and a higher percent of subject requiring bone age extrapolation (21% vs. 4%) were observed in the high dose 0.7 mg/kg/wk somatropin in comparison to the standard dose 0.3 mg/kg/wk. The sponsor reported a statistically significant higher increase in the last measured height after adjusting for protocol specified covariates of sex, previous growth rate, schedule for previous growth hormone therapy, baseline height, chronological age, bone age, and pubertal status in the high dose using the intent-to-treat subjects. Results of the analysis of covariance based on the pre-specified covariates indicated that improvement on the adjusted last measured height was primarily attributed to subjects completing the study.

Improvement in last standardized height relative to baseline standardized height was primarily observed in subjects whose baseline standardized heights were below the mean of normal subjects of same age and sex, constituting 90% of the study subjects, details can be found in pages 10-11.

1. BACKGROUND

Nutropin (generic name: somatropin (rDNA origin)) was approved for treatment of growth failure due to a lack of endogenous growth hormone (GH) on March 8, 1994. Genentech Inc. submitted this supplement on June 11, 1999 and November 19, 1999 in support of the addition of a higher pubertal dose for pubertal patients to the dosing section of the product insert. Genentech's rationale for two separate submissions was as follows. In the June, 1999 submission, the sponsor "elected to submit the data based on the fact that over 80% of subjects had discontinued treatment and 66% achieved near-adult height. Because bone age progressed equally in both groups and was similar at baseline, the last measured heights could be used to compare the two dose groups." The sponsor stated that it was an interim report with the cutoff date of June 2, 1998. In the November submission, the sponsor submitted more efficacy data at their scheduled four-month safety update report with the cutoff date of September 14, 1999.

This submission included one phase-III study, M0380g. This reviewer focuses on the efficacy evaluation regarding the objective of comparing somatropin growth hormone replacement dose of 0.7mg/kg/wk and standard dose of 0.3mg/kg/wk in improving linear growth and adult height in pubertal individuals with significant growth failure due to growth hormone deficiency (GHD).

The medical division (HFD-510) is interested in whether age interacts with somatropin received, and whether age is an important prognostic factor irrespective of which dose of somatropin being administered. The medical division is also interested in whether subjects who were shorter at baseline benefited more in the increase of height after somatropin treatment, please see "Effect of sex, baseline age and baseline height on height improvement" in page 8 under section 2.2.3.1 for details. This reviewer's efficacy evaluation can be found in Section 2. "Label" evaluations requested by the medical division can be found in Section 3.

Keywords: Clinical Study, NDA Review, dropouts, one study application.

2. EFFICACY OF SOMATROPIN (0.7 mg/kg/wk vs. 0.3 mg/kg/wk)

2.1 DESCRIPTION OF THE TRIAL

M0380g, a phase-III, randomized, multicenter (20 US centers), open-label study, was initiated on March 19, 1993 and was on-going at the time of the original NDA submission (June 1999), which included the interim report dated April 27, 1999. Eligible patients, including those who previously treated with growth hormone for at least 6 months, were randomized to receive either a standard dose (0.3 mg/kg/wk) or a high dose (0.7 mg/kg/wk) somatropin. Drug dose was adjusted every 6 months for weight changes. Follow-up visits were scheduled at 3-month intervals and up to 72 months according to study flow chart, as shown in Appendix I after the signature page (Sponsor Table 1 of p.25 of vol.52.1).

Original protocol plan was finalized on May 22, 1992. There were six amendments, of which five were made after trial initiation. According to the sponsor, the most important changes included (1) revising the study design to include dose modification every 6 months based on weight changes (January 4, 1993); (2) adding a secondary objective to comparing bone mineral density (BMD) between the treatment groups at the end of treatment (June 11, 1996); (3) allowing subjects who did not progress normally through puberty to receive sex-steroid replacement therapy while receiving somatropin and adding this covariate in the statistical analysis model of ANCOVA (March 5, 1997); and (4) revising the Informed Consent to include updated safety information (March 5, 1997).

The primary objective was to compare the safety and efficacy of Nutropin [somatropin (rDNA origin) for injection] administered daily at two dosage levels in improving linear growth and adult height. A secondary objective was to compare BMD at the end of treatment between the two treatment groups. Prospectively specified statistical analysis on the adult height was analysis of covariance with covariates of sex, previous growth rate, schedule for previous growth hormone therapy, baseline height, chronological age, bone age, and pubertal status. The sponsor amended the protocol four years after treatment initiation and added the covariate of "sex steroid replacement therapy." However, the sponsor decided not to include this covariate for the final ANCOVA model, stating that only 4 subjects received sex steroid replacement therapy. At least 60 patients per treatment arm was planned, which assumed a 2.0 cm difference in mean adult height between the two groups and a standard deviation also of 2.0 cm (after adjustment for covariates) with 95% power using a two-tailed test at the alpha=0.05 level.

The sponsor stated that treatment with somatropin would be discontinued when the bone age is > 16 years of age for boys and >14 years of age for girls and the growth rate is less than 2 cm/yr for one year. Follow-up visits for height measurement would be made every 6 months until adult height has been reached, in which "adult height" is defined as epiphyseal closure on hand-wrist bone age X-ray and no change (< 1cm) in height for 12 months. Treatment would continue until patients discontinue the study.

2.2 RESULTS

Eligible subjects (n=98) with growth hormone deficiency treated with standard-dose GH (approximately 0.3 mg/kg/wk) who had spontaneously entered puberty Tanner stage 2 or greater) were randomized to continue standard-dose GH (n=49) or to receive high-dose GH (0.7 mg/kg/wk) (n=48) as daily subcutaneous injections. One patient did not receive the study medication.

2.2.1 DEMOGRAPHIC AND BASELINE CHARACTERISTICS

There was a predominance of males (n=83, 86%). Subjects randomized to the two dose groups were comparable with regard to the following baseline characteristics: mean age at study entry (13.9 years, ranged from 10.6 years to 17.1 years), mean bone age (13.1 years, ranged from 9.6 years to 15.5 years), mean pretreatment growth rate, i.e., on standard GH therapy (8.5 cm/yr, ranged from 4.0 cm/yr to 15.0 cm/yr), and Tanner stage (3.0, ranged from 2 to 5).

REVIEWER'S EVALUATION AND COMMENTS

This reviewer confirmed the sponsor's report on the baseline characteristics. It is worthwhile to note that numerical imbalances were observed in baseline growth hormone related measurements. On average, subjects randomized to receive 0.7 mg/kg/wk somatropin appeared to have a higher duration of previous GH treatment [mean: 4.1 yr (range: 0.6 yr to 10.8 yr) vs. 3.5 yr (range: 0.5 yr to 9.7 yr)] and a higher previous pituitary GH treatment duration [mean: 1.60 yr (range: 0.25 yr to 4.69 yr)] compared to those randomized to 0.3 mg/kg/wk regimen [mean: 0.67 yr (range: 0.07 yr to 1.75 yr)]. In terms of previous growth rate, however, it was 8.5 cm/yr in both groups.

2.2.2 PATIENTS' ACCOUNTABILITY

Of the 97 patients receiving at least one dose of study medication, 48 completed the study as of November 19, 1999. From the sponsor's NDA report, subjects completed the study when the criteria for growth rate (<2.0 cm/yr) and bone age (≥14 years for females or ≥ 16 years for males) were met. Table 1 summarizes patients' accountability.

Table 1. Patients' accountability

	Somatropin 0.3 mg/kg/wk "Standard"-dose (n=49)	"Standard" As of June 2, 1998	somatropin 0.7 mg/kg/wk "High"-dose (n=48)	"High" as of June 2, 1998
# of subjects on-going	0	6	0	13
# of subjects completed study	31 (63%)	27	17 (35%)	14
# of subjects discontinued	18 (37%)	16 (33%)	31 (65%)	21 (44%)
Reason of early discontinuation				
Noncompliance	2 (4%)	2	4 (8%)	4
Lost to follow-up	0 (0%)	0	2 (4%)	2
Adverse event	2 (4%)	2	4 (8%)	3
Requested removal	12 (24%)	11	17 (36%)	11
Satisfied with height	6 (12%)	5	9 (19%)	9
Behavioral, personal, or unknown reasons	3 (6%)	3	6 (13%)	1
Tired of injections	1 (2%)	1	2 (4%)	1
Not specified	2 (4%)	2	0 (0%)	0
# of subjects with protocol violation	1 (2%)	1	1 (2%)	1
# of subjects discontinued at study termination	1 (2%)	0	3 (6%)	0

REVIEWER'S EVALUATION AND COMMENTS - Pattern of Distribution of Early Withdrawal

In the sponsor's original NDA submission dated June 11, 1999, which the sponsor termed as "an interim efficacy result", patients' accountability was summarized as of June 02, 1998 (see the 3rd and the 5th column of Table 1). It is noted that the trial was completed on April 12, 1999. The entire clinical trial database should have been available at the time of June submission. The sponsor's rationale of making two submissions is not clear. It is also not clear why the sponsor used September 14, 1999 instead of the actual trial completing date as the cutoff date for the November, 1999 submission. Differences in the distribution of "on-going patients", 6 patients in the standard dose group and 13 patients in the high dose group, were rather striking. In the standard dose group, 4 out of 6 patients completed the study and the remaining 2 discontinued [1 requested for removal due to "satisfied with height" and 1 discontinued at the time of study termination per investigator] the study earlier than expected. In contrast, only 3 out of 13 patients completed the study and the remaining 10 discontinued [1 AE, 6 requested for removal (5 were because of behavioral, personal, or unknown reasons and 1 tired of injections), and 3 discontinued at the time of study termination per investigators] early in the high dose group.

Overall, percentage of discontinuation was slightly higher in the high dose group (44% vs. 33% in the standard dose) as of June 12, 1998. The difference became drastic as of September 14, 1999 at the safety

update of November 19, 1999 (65% in the high dose group and 37% in the standard dose group, nominal p-value = 0.0083, Fisher's exact test). In sum, more patients in the high dose group were discontinued due to non-compliance (8% vs. 4%), lost to follow-up (4% vs. 0%), adverse event (8% vs. 4%), requested removal (36% vs. 24%), and discontinued at the time of study termination (6% vs. 2%) compared to the standard dose group. More details on the observed differential dropout rates can be found under "Impact of differential dropout on efficacy evaluation" in pages 6-7.

2.2.3 EFFICACY RESULTS

2.2.3.1 PRIMARY EFFICACY

Results of "near-adult height" and "last measured height" using the protocol specified analysis method of ANCOVA, in which the covariates were sex, previous growth rate, schedule for previous GH therapy, baseline height, chronological age, bone age, and pubertal status, excluding sex steroid replacement therapy (the sponsor stated that "only 4 patients received the therapy, an inadequate number for use as a covariate"), can be found in Table 4 of sponsor on "near-adult height" and in Table 5 of sponsor on "last measured height.", see Appendix II in pages 17-18.

- **LAST MEASURED HEIGHT (N=97) (intent-to-treat analysis)**

The sponsor stated that based on ANCOVA, subjects in the high-dose group were significantly taller at last measured height than subjects in the standard-dose group by an average of 2.8 cm (n=97, p=0.036, 95% CI 0.2-5.3 cm). The significant covariates were sex, baseline height, age, and bone age. It is noted that the difference was 2.6 cm (n=97, p=0.042, 95%CI 0.078-5.1 cm) in the June submission.

- **NEAR-ADULT HEIGHT (N=75) (evaluable analysis)**

Based on ANCOVA, subjects in the high-dose group were significantly taller at near-adult height than subjects in the standard-dose group by an average of 4.6 cm (n=75, p<0.001, 95% CI 2.6-6.5 cm). The significant covariates were sex, baseline height, and bone age. It is noted that the difference was 3.3 cm (n=64, p=0.0031, 95% CI 1.2-5.4 cm) and one more significant covariate was found, i.e., previous GH schedule in the June, 1999 submission. This analysis did not include all subjects receiving at least one dose of somatropin.

Summary of sponsor's results on the above efficacy outcomes after adjustment of protocol specified covariates excluding sex steroid replacement therapy, confirmed by this reviewer, can be found in Table 2 below.

Table 2. Adjusted# mean, adjusted mean difference, and its 95% CI of efficacy outcomes as of 09/14/1999.

Efficacy outcomes	Somatropin 0.3mg/kg/wk n adj.mean	Somatropin 0.7mg/kg/wk n adj.mean	Difference of (high – standard) adj.mean(95%CI)	P-Value ANCOVA
Last measured height (ITT, n=97)	49 164.6cm	48 167.4cm	2.8cm (0.2, 5.3)	0.036
Near-adult height (evaluable,n=75)	42 165.4cm	33 170.0cm	4.6cm (2.6, 6.5)	<0.001

adjusted for protocol prespecified covariates: sex, previous growth rate, schedule for previous GH therapy, baseline height, chronological age, bone age, and pubertal status, results were extracted from the sponsor report.

REVIEWER'S EVAULATION AND COMMENTS

- **MODIFICATION OF PRIMARY EFFICACY ENDPOINTS**

"Adult height" was defined as epiphyseal closure on hand-wrist bone age X-ray and no change (< 1 cm) in height for 12 months, whereas "near-adult height" was defined as the last measured height at bone age ≥ 16 years for boys or ≥ 14 years for girls. The sponsor stated that only 13 subjects had their growth rates of <1 cm/yr and a bone age at their last measured height [6 males and 2 females in the standard-dose group and 4

males and 1 female in the high-dose group]. Therefore, instead of the protocol specified primary efficacy endpoint "adult height", "near-adult height" was used as the primary efficacy variable.

BONE AGE EXTRAPOLATION

There were 75 subjects (42 in the 0.3 mg/kg/wk and 33 in the 0.7 mg/kg/wk) met the criterion for attaining near-adult height. From the NDA efficacy update, among these 75 subjects, 41 required bone age to be extrapolated to the date of their last measured height to meet the criterion. This reviewer requested the sponsor to submit indicators regarding bone age extrapolation. From the electronic datasets submitted on February 18, 2000, this reviewer found that 25 (51%) subjects in the standard dose group and 28 (58%) subjects in the high dose group had an extrapolated bone age. As shown in Table 3, there were 2 subjects (8% of those having extrapolated bone age or 4% of total subjects) in the standard dose group and 10 subjects (36% of those having extrapolated bone age or 21% of total subjects) in the high dose group not reaching their near-adult height, not having a bone age, and requiring bone age extrapolation. It appeared that percent of subjects requiring bone age extrapolation for determination of near-adult height was 5 times higher in the high dose somatropin treated subjects (21%) than those treated with standard dose somatropin (4%). This reviewer performed the protocol specified ANCOVA analysis on the last measured height excluding these 12 subjects whose bone ages were extrapolated. The result of this analysis was consistent with that of the analysis including these 12 subjects in terms of statistical significance.

Table 3. Distribution of patients' attaining relevant height measure during the trial period

	0.3 mg/kg/wk	0.7 mg/kg/wk	Total
Intent-to-treat patients	49	48	97
Attain near-adult height^	8 (16%)	5 (10%)	13
Attain near-adult height!	42 (86%)	33 (69%)	75
Subjects having extrapolated bone age–	25 (51%)	28 (58%)	53
Having bone age`	23	18	41
Requiring extrapolation for determination of near-adult height	2 (4%)	10 (21%)	12

^ growth rates of < 1cm/yr and a bone age X-ray at their last measured height,
! the last measured height at bone age ≥ 16 years for boys or ≥ 14 years for girls,
– the sponsor's electronic datasets submitted on February 18, 2000,
` the last height measurement and last bone age were not on the same date.

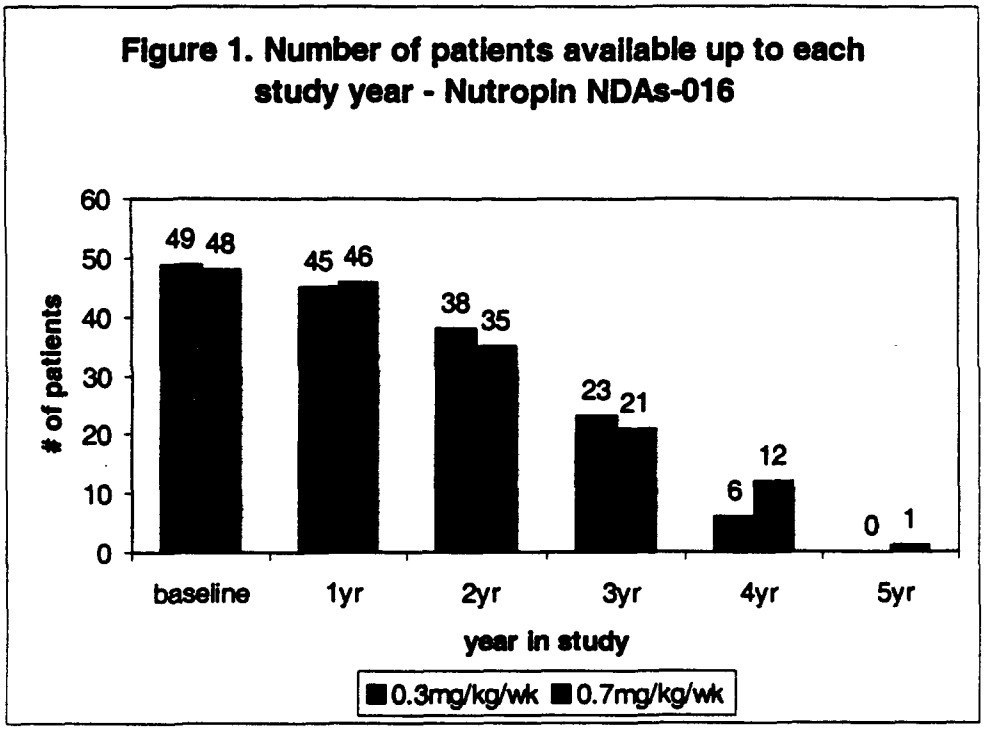
SUBJECTS MAY DISCONTINUE THE STUDY BEFORE OR AFTER TERMINATION OF GROWTH HORMONE SOMATROPIN TREATMENT

Traditionally, patients are treated with randomized treatment for the entire clinical trial period. Patients may or may not discontinue the study earlier than the trial period. Due to the nature of the growth hormone therapy, GH treatment was to be terminated when the bone age is > 16 years of age for boys and >14 years of age for girls and the growth rate is less than 2 cm/yr for one year. And, follow-up visits for height measurement was to be made every 6 months until adult height had been reached. Therefore, in this trial, patients may discontinue the study earlier either before or after GH treatment was terminated, see Table 4.

Table 4. Subject's completion status by study duration in years between 0.3mg and 0.7mg somatropin^

Treatment	Status	Study duration						
		0-<1yr	1-<2yr	2-<3yr	3-<4yr	4-<5yr	5-<6yr	Total
0.3mg/kg/wk (n=49)	Incomplete	4	4	5	3	2	0	18 (37%)
	Complete	0	3	10	14	4	0	31
	Sub-total	4	7	15	17	6	0	49
0.7mg/kg/wk (n=48)	Incomplete	2	9	7	5	7	1	31 (65%)
	Complete	0	2	7	4	4	0	17
	Sub-total	2	11	14	9	11	1	48

^ from the electronic database



Further exploration, as depicted in Table 4 and Figure 1 above, showed that although there were more dropouts in the high dose group (65% vs. 37%), number of subjects who were still available up to each study year between the high dose and the standard dose groups were not too different except those subjects who had stayed on study 4 years or more but less than 5 years.

IMPACT OF DIFFERENTIAL DROPOUT ON EFFICACY EVALUATION

From Table 1 in page 3, significantly more dropouts seen in the high dose group along with higher percentages with reasons of non-compliance, lost to follow-up, adverse events, and requested removal appeared to be a major discrepancy in the evaluation of primary efficacy on height related outcomes. Except for the number of subjects with protocol violation, there were greater percentages in all other reasons of discontinuation in the high dose group, only "requested removal-satisfied with height" was a positive reason relating to treatment efficacy. In addition, 42 (86%) subjects in the 0.3 mg/kg/wk somatropin and 33 (69%) subjects in the 0.7 mg/kg/wk somatropin reached near adult height. It is important to explore what the statistical significance observed on the last measured height using the intent-to-treat patients and on the near-adult height using the evaluable patients meant. To minimize potential bias induced by open-label design for height measurement and bias introduced by selected evaluable patients, analyses based on the intent-to-treat patients, the completers, and the incompleters may give more insights into somatropin effect with high dose. This reviewer performed the ANCOVA analyses on these efficacy outcomes and used the protocol pre-specified covariates excluding sex-steroid replacement therapy, which was consistent with the sponsor's model submitted in their NDA reports.

EFFICACY RESULTS SEPARATED BY COMPLETERS VS. INCOMPLETERS

Thirty-one subjects in the standard-dose and 17 subjects in the high dose completed the study. A completer analysis would include only 48 subjects, not 75 subjects who reached their near-adult height. Results of this reviewer's analyses are depicted in Table 5. This reviewer's analyses show that the positive results on adjusted last measured height and adjusted near-adult height appeared to be primarily driven by subjects who completed the study. In completers, mean difference in height improvement between the high dose and the standard dose was 3.7 cm with 95% CI of 1.1 cm to 6.4 cm based on the last measured height and was 4.3 cm with 95% CI of 1.6 cm to 7.1 cm based on near-adult height. In incompleters, the confidence

interval of the difference included zero, indicating that no significant height difference between the two dose groups. On average, height improvement was numerically higher in incompleters receiving the high dose relative to the standard dose.

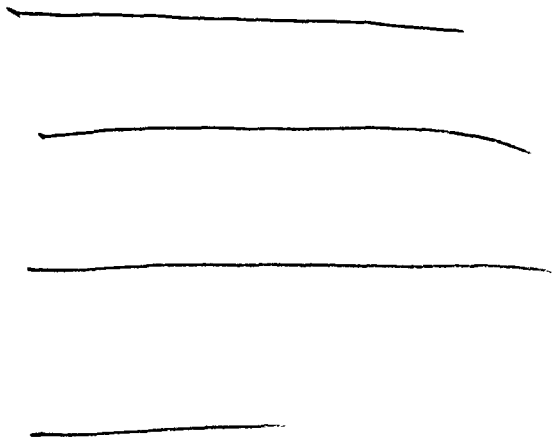
Table 5. Efficacy results separated by completers and incompleters

	Completers^			Incompleters~		
	Standard dose 0.3mg/kg/wk n adj. mean	High dose 0.7mg/kg/wk n adj. mean	Difference of 0.7mg-0.3mg (95% CI)	Standard dose 0.3mg/kg/wk n adj. mean	High dose 0.7mg/kg/wk n adj. mean	Difference of 0.7mg-0.3mg (95% CI)
Last measured height (cm)	31 163.9	16* 167.6	3.7cm (1.1, 6.4)	16* 161.7	30* 166.1	4.4cm (-1.9, 10.7)
Near-adult height (cm)	31 163.4	14* 167.8	4.3cm (1.6, 7.1)	9* 164.8	18* 167.8	3.0cm (-2.2, 8.2)

^ subjects whose reason of withdrawal was completion
~ subjects who didn't complete the study
* sample size represented # of subjects who had all measurements of covariates included in the ANCOVA analysis

This reviewer plotted the subject's baseline height versus their last measured height in each dosage group. Figure 2 provides visual comparisons between completers (solid triangle) and incompleters (open-circle) within a somatropin dose group (TXT=0 represents the standard dose 0.3 mg/kg/wk and TXT=1 represents the high dose 0.7 mg/kg/wk) and between dose groups. The graph depicts a more definite relationship of increasing baseline height vs. increasing last measured height in the completers in both dose groups and show that improvement in height was higher with the high dose GH treatment than with the standard dose GH treatment. However, a much weaker relationship was observed with the incompleters. For instance, incompleters with baseline height between 140 cm and 150 cm, improvement on last measured height varied greatly in the range of below 150 cm to 180+ cm.

Figure 2. Last Measured Height vs. Baseline Height by treatments (TXT=0, 0.3mg/kg/wk; TXT=1, 0.7mg/kg/wk) and by subject's status of completing the trial (incompleter: open-circle, completer:solid triangle) Nutropin NDA s-016



Furthermore, among completers, 100% of subjects (31/31) in the 0.3 mg/kg/wk somatropin and 88% (15/17) in the 0.7 mg/kg/wk somatropin reached near adult height. Two subjects in the high dose group completed the trial but had not reached their near-adult height. It is worthwhile to note that among subjects who discontinued from the trial early, 61% (11/18) in the 0.3 mg/kg/wk somatropin and 58% (18/31) in the 0.7 mg/kg/wk somatropin reached near-adult height.

EFFECT OF SEX, BASELINE AGE AND BASELINE HEIGHT ON LAST MEASURED HEIGHT

The medical division is interested in whether age interacted with somatropin received, and whether age is an important prognostic factor irrespective of which dose of somatropin being administered. This reviewer performed a few analyses to test if interaction between treatment and baseline age exists. Results of these analyses showed a p-value more than 0.20, indicating that there is no sufficient statistical evidence for interaction. The data also showed that sex, baseline bone age, and baseline height together are important prognostic factors for subject's last measured height and near-adult height irrespective of the standard dose or the high dose of somatropin.

The medical division is also interested in whether subjects who were shorter at baseline had a greater increase of height after somatropin treatment. Figure 2 gave a visual comparison between subject's baseline height and last measured height. If a subject has no further growth, a 45 degree line under the same scale on baseline height and last measured height would indicate no improvement in height. Thus, Figure 2 appeared to show that subjects who were shorter at baseline might or might not have height improvement with somatropin treatment. It seemed to depend upon subject's sex, age at baseline, and their status of completing the trial, etc.

This reviewer explored the relationship between last measured height and baseline height separately by male and female and separately by age at study entry. The cutoff of age at study entry was chosen to be the median for each gender, viz., ≤14.1 yr vs. >14.1 yr for males and ≤12.7 yr vs. >12.7 yr for females.

From Table 6 below, 95%CI of the last measured height overlapped between the standard dose and the high dose somatropin within each of these four subgroups. Numbers of subjects were too small in the female/age subgroup. For males, in general, high dose showed a numerically higher last measured height after adjusting for subject's baseline height. This pattern was observed in the younger age group and the older age group. Summary of further classifying subject based on their trial completion status was not presented due to small number of subjects.

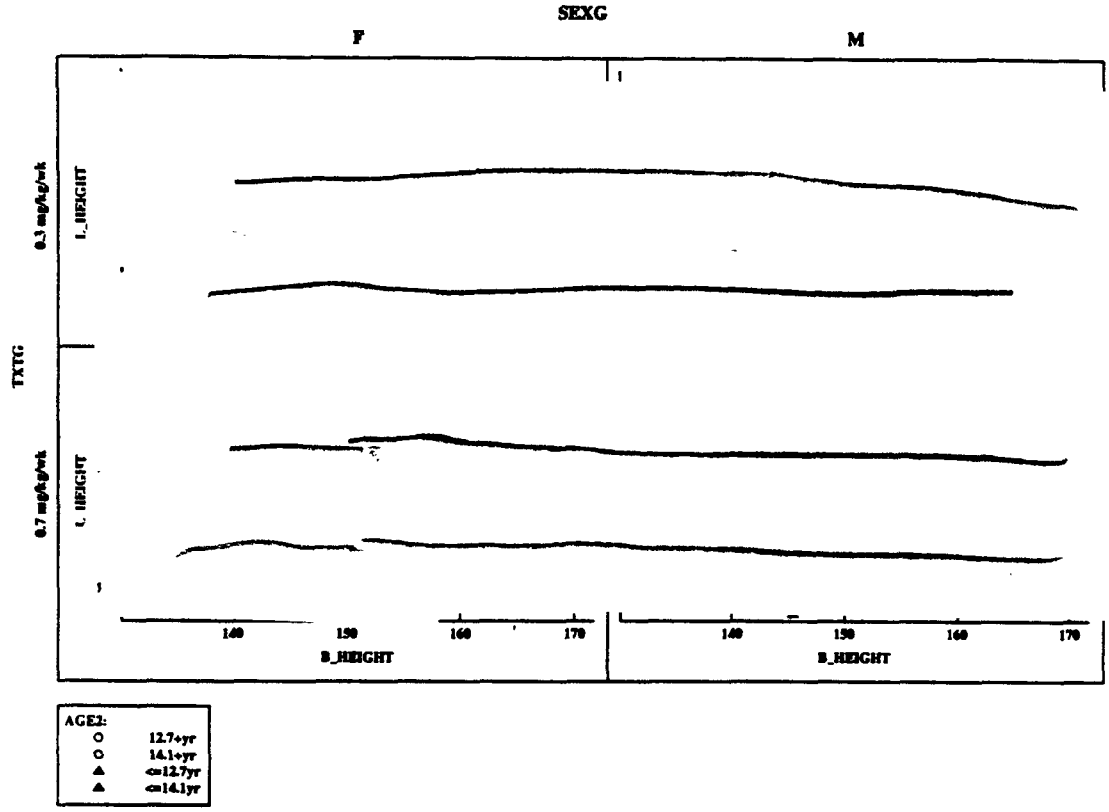
Table 6. Summary of last measured height by gender and age at baseline between two doses of somatropin

		Younger^ at study entry Adjusted mean~ (95%CI), n	Older^ at study entry Adjusted mean~ (95% CI), n
Male	0.3mg/kg/wk	170.1 (166.1, 174.1), 20	171.5 (168.5, 174.6), 22
	0.7mg/kg/wk	174.7 (170.6, 178.8), 19	174.4 (171.4, 177.4), 22
Female	0.3mg/kg/wk	154.8 (141.5, 168.2), 2	155.0 (148.8, 161.1), 5
	0.7mg/kg/wk	159.8 (151.4, 168.2), 5	151.2 (141.3, 161.1), 2

^ for males, younger means <= 14.1 years; for females, younger means <= 12.7 years at study entry,
~ adjusted for baseline height.

Graphical presentation of height improvement by sex and by age at study entry is depicted in Figure 3. Since numbers of female subjects were small, it is difficult to provide a summary for females. For males, in general, younger subjects (solid triangle) tended to have a greater height improvement relative to older subjects (open circle), especially in the high dose group.

Figure 3. Height Improvement by subgroup of male:female and younger:older Nutropin NDA S-016



- **PROTOCOL SPECIFIED PRIMARY OBJECTIVE & PRIMARY EFFICACY ENDPOINTS**

As stated in the protocol, the primary objective of this study was to compare the two dosages of somatropin in improving linear growth and adult height. In the statistical analysis section, the primary efficacy measure was adult height. There were no secondary efficacy measures mentioned. This reviewer summarized results of linear growth reported by the sponsor. In addition, summary of near-adult height of 13 subjects used by the sponsor to indicate that no subject reached adult height was also presented below.

LINEAR GROWTH

The mean duration of therapy was 2.7 ± 1.2 years (range of 0 to 5.4 years). Instead of reporting linear growth over time, the sponsor reported growth rate at year-1, at year-2, and at year-3 in subjects who were available at the time of evaluation. They were as follows: a higher mean rate with high-dose somatropin compared to the standard-dose treatment at year-1 [1.6 cm/yr higher in 87 subjects (43 in the standard dose and 44 in the high dose) completing one-year treatment], at year-2 [1.3 cm/yr higher in 69 subjects (36 in the standard dose and 33 in the high dose) completing 2-year treatment], and at year-3 [1.7 cm/yr higher in 41 subjects (20 in the standard dose and 21 in the high dose) completing 3-year treatment]. It appeared that 41 subjects completing 3-year of treatment were younger in chronological age (mean age: 13.2 vs. 14.5 years), bone age (mean: 12.5 vs. 13.7 years), and at a lower Tanner stage (mean: 2.6 vs.3.3) at baseline when compared to those 46 subjects completing 1-year of treatment only.

REVIEWER'S EVALUTAION AND COMMENTS

Of those subjects completing 3-year treatment, growth rate (cm/yr) appeared to decrease with each additional year of treatment: 9.1±2.0 in the standard dose and 10.2±1.8 in the high dose somatropin at year-1, 7.7±2.5 in the standard dose and 8.9 ±2.0 in the high dose somatropin between year-1 and year-2, 4.4±2.6 in the standard dose and.6.1±2.4 in the high dose somatropin between year-2 and year-3 as were depicted in Figure 3 of sponsor (see Appendix III in page 19).

SUBGROUP OF 13 SUBJECTS AND THEIR NEAR-ADULT HEIGHT

Although 13 subjects had growth rates of < 1 cm/yr and a bone age X-ray at their last measured height, these subjects did not meet the definition of adult height, which is epiphyseal closure on hand-wrist bone age X-ray and no change (<1 cm) in height for 12 months. The table below summarizes baseline height and last measured height between the standard dose (n=8) and the high dose (n=5) in this subgroup.

Height measurement	0.3 mg/kg/wk			0.7 mg/kg/wk		
	n	mean	sd	n	mean	sd
Baseline height (cm)	8	147.6	8.2	5	153.0	8.5
Last measured height (cm)	8	166.1	8.0	5	170.0	7.3

2.2.3.2 OTHER SUPPORTIVE EFFICACY RESULTS (reported by the sponsor)

- **CHANGE IN HEIGHT BY DURATION OF TREATMENT**

The sponsor performed an ANOVA, using sex and baseline bone age as covariates, on change in height by duration of treatment. Sponsor's results of effect on change in height are shown below.

Efficacy outcomes	Effect on change in height (cm) (high dose – standard dose) with 95% CI	High dose N	Standard dose N
Change in height by			
1-year	1.6 (0.8, 2.4)	45 (94%)	45 (92%)
2-year	2.4 (1.0, 3.8)	34 (71%)	38 (78%)
3-year	4.3 (2.5, 6.1)	22 (46%)	23 (47%)
4-year	5.7 (1.2, 10.1)	13 (27%)	7 (14%)

Of those subjects receiving 4 years of therapy (27% in the high dose group and 14% in the standard dose group), subjects were taller in the high-dose group than in the standard-dose group by an average of 5.7 cm, 95% CI, 1.2 – 10.1 cm.

- **STANDARDIZED HEIGHT**

Standardized height[1] computed using height standard deviation score (height SDS) was also reported. Mean height SDS was >1 SD below the mean in both treatment groups at baseline (-1.3 ±1.1SD in standard-dose and –1.2 ± 1.2SD in high dose). The sponsor reported that for subjects completing 3 years of treatment, the mean change from baseline was 1.4 ± 0.8SD in the high-dose group (n=22) compared with 0.9 ± 0.7SD in the standard dose group (n=22, nominal p=0.023).

---

[1]Standardized height is computed as follows:

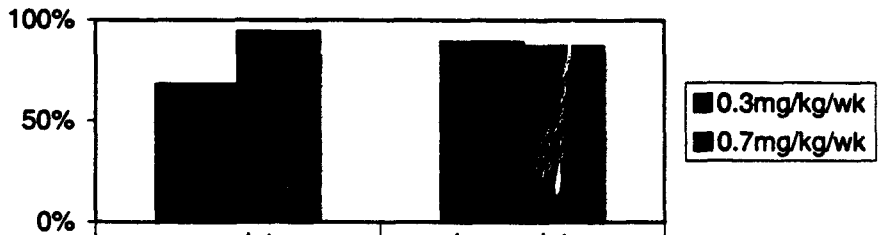
$$\frac{\text{Actual height} - \text{mean height of normal subjects of same age and sex*}}{\text{Height SD of normal subjects of same age and sex}}$$

*Where mean height of normal subjects of same age and sex is taken as the 50th percentile from the national center for health statistics (Am. J. of Clin. Nut. 32: pp.607-629).

REVIEWER'S EVALUATION AND COMMENTS

It is noted that when standardized height was used, 10% of subjects (4 in standard-dose and 6 in high dose) were higher than the mean height of normal subjects of same age and sex, as reported in the national center for health statistics (Am. J. of Clin. Nut. 32: pp. 607-629) at baseline. From the sponsor's table, subjects completing 1-year treatment and those completing 2-year treatment improvement in height (cm) was observed in both doses, but mean height by year-1 or by year-2 were still below the mean height of normal subjects of same age and sex* (0.6SD±1.0 below in the standard-dose and 0.3SD±1.1 below in the high dose group). Improvement in last standardized height relative to baseline standardized height was primarily observed in subjects whose baseline standardized heights were below the mean of normal subjects of same age and sex, constituting 90% of the study subjects.

Figure 4. Distribution of improvement on standardized height by subject's completion status Nutropin NDAs-016



	completer	incompleter
0.3mg/kg/wk	68%	89%
0.7mg/kg/wk	94%	87%

If the standardized height could be considered as a reasonable height measure after adjustment of subject's sex and age, then if a subject improved his/her standardized height after somatropin treatment, this subject might be considered to have improved his/her height. This reviewer explored improvement of last measured height standardized by their sex and age relative to their baseline standardized height, as shown in Figure 4. Improvement on the standardized height, defined as last standardized height greater than baseline standardized height, was similar in subjects not completing the study (89% in the standard dose and 87% in the high dose), whereas more subjects in the high dose group improved on the standardized height relative to their baseline standardized height (94%) compared to the standard dose group (68%) among completers. The result is consistent with the analysis of last measured height separated by completers and incompleters, see Table 5 in page 7.

- **PREDICTED ADULT HEIGHT**

The sponsor performed height prediction using standardized Bayley-Pinneau (B-P) method, which was based on height and bone age measurement.

REVIEWER'S COMMENTS

As sponsor pointed out, Bayley-Pinneau method has not been scientifically validated for any non-normal children. It is never a measure of efficacy. Such information should not be put in the label.

- **BONE AGE AND TANNER PUBERTAL STAGE**

The sponsor considered that change in bone age during each year of therapy is a measure of the rate of skeletal maturation and is related to the tempo of pubertal progression. The sponsor stated that cumulative change in bone age and rate of advancement in puberty assessed by Tanner pubertal stage for genitalia (males) or breasts (females) were similar in the two dose groups.

- **IGF – I**

IGF-I was measured by [redacted]. The sponsor reported that the differences between groups for the change from baseline, using log values or standardized scores, were not statistically significant at years 1, 2, or 3. The medical division requested the sponsor to (1) show the distribution of IGF-I levels across the two dose groups, (2) compare the baseline characteristics, IGF-I levels and near adult height for the 5 subjects with the following adverse events: change in nasal bridge, large shoe size, large hands and feet and jaw pain, with the rest of the patient population, (3) compare the subjects with supranormal IGF-I levels at baseline with the rest of the patient population. For a detailed discussion, please see medical review and evaluation.

2.2.4 SAFETY

According to the medical reviewer, primary safety concern related to an observed higher percent of subjects with their IGF-1 SDS greater than 2 (normal range is –2 to + 2) in the high dose group during the treatment period. Details of safety review can be found in the medical review and evaluation.

3. EVALUATION OF LABEL UNDER EFFICACY STUDIES AND DOSAGE

The medical review team requested review of efficacy label, specifically under "efficacy studies" and "dosage." Evaluation of Label is based on the sponsor's efficacy update submitted on January 09, 2000. The following are this reviewer's comments and suggestions.

3.1 NEAR-ADULT HEIGHT VS. LAST MEASURED HEIGHT

Label of ' [redacted]

REVIEWER'S EVALUATION AND COMMENTS

Instead of stating last measured height in the label, the sponsor reported the summary statistics of ' [redacted] ' height in subjects reaching near-adult height and called it last measured height. Not only does this not reflect differential dropout seen in the clinical trial, it consisted of only subjects evaluable for the near-adult height. This review and evaluation showed that improvement of either last measured height or near-adult height in the high dose somatropin over the standard dose somatropin were not equally observed between the completers and incompleters. In practice, when somatropin is to be applied to perbertal subjects with growth hormone deficiency, there will likely be a mixture of completers and incompleters. Therefore, the label needs be revised, "overstrike" indicated for deletion and "bold" indicated for addition.

[redacted]

3.2 EFFICACY OF HEIGHT - SUBJECTS COMPLETING 4.0 YEARS OF STUDY

The sponsor included "

REVIEWER'S EVALUTAION AND COMMENTS

The above estimated difference of — applies to only subjects completing 4.0 years of study, which is based on outcome criteria not baseline criteria. Given that significant differential dropout rates were observed between the two doses, and subjects may complete the study and benefit from treatment in less than 4 years, e.g., 2 years, it is suggested that the above label be removed.

3.3 STANDARDIZED HEIGHT - SUBJECTS COMPLETING 3.0 YEARS OF STUDY

REVIEWER'S EVALUTAION AND COMMENTS

The above label applies to only subjects completing 3 years of somatropin treatment. In addition, the last sentence of ' is only suggestive not conclusive. Again, this reviewer suggests that the above label be removed.

3.4 PROPER SUBGROUP REPORTING IN THE LABELLING

Alternatively, this reviewer suggests reporting subgroup results based on baseline characteristics. The majority of subjects are males (86%). According to the medical team leader, males are more prone to have growth hormone deficiency than females, trials of this nature generally have much less female than male. In this study there were only 7 females in each treatment group, the trial may not have reasonable amount of data on the last measured height and other efficacy outcomes for female subjects on each category of the prognostic factors pre-specified in the protocol, e.g., height by sex and age. However, presenting the last measured height adjusting for baseline height by sex would at least help reflect the corresponding height improvement for males and females, respectively. Example of a table summary can be found below.

Table -

* Adjusting for baseline height.
† 95% confidence interval

3.5 DOSAGE - PEDIATRIC GROWTH HORMONE DEFICIENCY

As written, "In pubertal patients, a weekly dosage of up to 0.7 mg/kg divided daily may be used.

REVIEWER'S EVALUATION AND COMMENTS

It is noted that somatropin dosage was adjusted in the clinical trial every 6 months according to weight change. Somatropin administration in the original clinical trial was either a weekly dosage of up to 0.3

mg/kg or up to 0.7 mg/kg of body weight divided into daily subcutaneous injection. IGF-I concentration was not monitored to aid dose adjustments or to optimize therapy, the last sentence needs be deleted. This reviewer suggests the label be written as
"In pubertal patients, a weekly dosage of up to 0.7 mg/kg divided daily may be used. ‡

4. SUMMARY

A multi-center, open-label, phase III study was conducted to compare the standard dose (0.3 mg/kg/wk) and the high dose (0.7 mg/kg/wk) somatropin in improving linear growth and adult height in pubertal subjects currently treated with standard dose of somatropin and with significant growth hormone deficiency. A total of 97 subjects with comparable age at entry (mean: 13.1 yr, range: 10.6 yr to 17.1 yr), pre-treatment growth rate (mean 8.5 cm/yr, range 4.0 to 15.0 cm/yr), and Tanner stage of at least 2 received study medication (49 subjects in the standard dose and 48 subjects in the high dose). Numerical imbalances in previous GH treatment duration and previous pituitary GH treatment duration were seen. Details can be found in section 2.2.1 in pages 2-3 of this review.

Differential dropout rates were observed between the standard dose 0.3mg/kg/wk somatropin (37%) and high dose 0.7mg/kg/wk somatropin (65%). In addition, 42 (86%) subjects in the 0.3mg/kg/wk somatropin and 33 (69%) subjects in the 0.7mg/kg/wk somatropin reached near adult height. This reviewer found that the numbers of subjects who were still available up to each study year between the high dose and the standard dose groups were not too different except those subjects who had stayed on study 4 years or more but less than 5 years.

Using the protocol specified analysis method of ANCOVA, which adjusted for seven prognostic factors of sex, previous growth rate, schedule for previous growth hormone therapy, baseline height, chronological age, bone age, and pubertal status, this reviewer's analysis shows that the positive results on adjusted last measured height and adjusted near-adult height in favor of the 0.7 mg/kg/wk dose appeared to be primarily driven by subjects who completed the study (Table 5 in page 7). Furthermore, among completers, 100% of subjects (31/31) in the 0.3mg/kg/wk somatropin and 88% (15/17) in the 0.7mg/kg/wk somatropin reached near adult height. Two subjects in the high dose group completed the trial and had not reached their near-adult height. It is worthwhile to note that among subjects discontinued from the trial early, 61% (11/18) in the 0.3mg/kg/wk somatropin and 58% (18/31) in the 0.7mg/kg/wk somatropin reached near-adult height.

There were 10 (10%) subjects (4 in the standardized dose and 6 in the high dose group) whose baseline standardized heights were above mean of normal subjects of same age and sex. Improvement in last standardized height relative to baseline standardized height was primarily observed in subjects whose baseline standardized heights were below the mean of normal subjects of same age and sex, constituting 90% of the study subjects, details can be found in pages 10-11.

5. CONCLUSION

According to the sponsor, no subjects in this trial reached their adult height, the protocol specified primary efficacy endpoint. Near-adult height and the last measured height at the end of the trial were evaluated as the primary efficacy outcomes. From this reviewer's evaluation, this multicenter, phase-III, randomized, open-label trial appeared to have demonstrated that subjects in the high-dose group were significantly taller at last measured height than subjects in the standard-dose group after adjustment of protocol pre-specified prognostic covariates. The height improvements measured by last measured height in the high dose 0.7 mg/kg/wk somatropin were primarily observed in subjects who completed the study. Such improvement of height was not shown significantly different between the standard dose and the high dose in subjects who prematurely discontinued the study.

/s/

Sue-Jane Wang, Ph.D.
Senior Mathematical Statistician

/s/

Concur: S. Edward Nevius, Ph.D. /s/ 10/00
Division Director, HFD-715

Todd Sahlroot, Ph.D.
Team Leader for HFD-510

cc:
Archival NDA 19-676 SE2-016
HFD-510/Div. File
HFD-510/SMalozowski, RPerlstein
HFD-510/CKing, CSO
HFD-715/Chron, ENevius, TSahlroot, SWang

SWANG/03-20-2000/nutropin_nda_s16
This review consists of 19 pages, including 6 reviewer tables, 4 reviewer figures, and 3 appendices.
Appendix I: Study flow chart (Table 1 of sponsor)
Appendix II: Table 4 and Table 5 of the sponsor
Appendix III: Figure 3 of the sponsor

Appendix I.

Table 1

Study Flowchart

Evaluations	Baseline [a]	Outpatient Visits [b]					
		3 Months	6, 18 Months	9, 15, 21 Months	12, 24, 36, 48, 60, 72 Months	27, 33, 39, 45, 51, 57, 63, 69 Months	30, 42, 54, 66 Months
Medical history	x						
Interval medical history		x	x	x	x	x	x
Physical examination	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
Bone age X-ray	x		x		x		x
CBC with differential and platelet count	x	x	x	x	x		
Routine urinalysis	x	x	x	x	x		
Serum chemistry panel	x	x	x	x	x		
T_4	x				x		
2-hr GTT, glucose level	x	x			x		
2-hr GTT, insulin level	x	x			x		
2-hr GTT, C-peptide level	x	x			x		
Hemoglobin A_{1c}	x	x	x	x	x		x
Plasma IGF-I	x	x	x	x	x		x
Anti-GH antibody	x	x	x	x	x		x
Testosterone (males)	x		x		x		x
Estradiol (females)	x		x		x		x

CBC=complete blood count; GTT=glucose tolerance test.

[a] Baseline assessments were obtained prior to study entry.

[b] Outpatient visits occurred at 3-month intervals.

Determinations of anti-GH antibody and IGF-I levels were made by Genentech (South San Francisco, CA). Bone age determinations were performed by the [redacted]. Complete blood count (CBC), differential, platelet count, serum chemistry panel, thyroid

Appendix II. Table 4 and Table 5 of sponsor

Table 4

Analysis of Covariance for Near-Adult Height:
Bone Age ≥16 Years for Males and ≥14 Years for Females at Last Measured Height (N=75)

R^2 = 0.82	Effect on Near-Adult Height (cm)	p-value
Intercept	84.1	<0.001
GH dose (high vs. standard) (95% Confidence interval)	+4.6 vs. 0 (2.6, 6.5)	<0.001
Sex (male vs. female)	+14.8 vs. 0	<0.001
Baseline bone age (per yr)	−3.9	<0.001
Baseline height (per cm)	+0.37	<0.001
Previous GH schedule (TIW vs. daily)	+3.5 vs. 0	0.058
Baseline chronological age (per yr)	−0.79	0.056
Baseline Tanner stage*		0.173
2 vs. (4 and 5)	+3.7 vs. 0	
3 vs. (4 and 5)	+2.4 vs. 0	
Previous growth rate (per cm/yr)	−0.01	0.959

Note: The covariates were specified in the protocol. However, only 2 subjects received sex steroid therapy during the study; therefore, this variable was not used as a covariate. Three missing previous growth rates were replaced with the sample mean. There were no significant dose by covariate interactions, p>0.20.

* Tanner stages: 2 = early, 3 = mid, 4 and 5 pooled = late puberty.

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(ar,jb,pw) Genentech, Inc.
Report File: /Endocrine/nutropin/m0380g/final/report/glm_nah.lis

Table 5

Analysis of Covariance for Last Measured Height: Intent-to-Treat (N=97)

$R^2 = 0.65$	Effect on Last Measured Height (cm)	p-value
Intercept	88.3	<0.001
GH dose (high vs. standard) (95% Confidence interval)	+2.8 vs. 0 (0.2, 5.3)	0.036
Sex (male vs. female)	+14.5 vs. 0	<0.001
Baseline bone age (per yr)	–4.3	<0.001
Baseline height (per cm)	+0.95	<0.001
Baseline chronological age (per yr)	–1.3	0.015
Previous GH schedule (TIW vs. daily)	+2.6 vs. 0	0.249
Previous growth rate (per cm/yr)	–0.28	0.453
BaselineTanner stage*		0.785
2 vs. (4 and 5)	+0.87 vs. 0	
3 vs. (4 and 5)	+1.3 vs. 0	

Note: The covariates were specified in the protocol. However, only 2 subjects received sex steroid therapy during the study; therefore, this variable was not used as a covariate. Three missing previous growth rates were replaced with the sample mean. One missing baseline bone age was replaced with a bone age calculated from the sample mean bone age delay (age minus bone age). There were no significant dose by covariate interactions, p>0.06.

* Tanner stages: 2 = early, 3 = mid, 4 and 5 pooled = late puberty.

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Appendix III.

Figure 3

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