CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER for: 019676, S013

MEDICAL/STATISTICAL REVIEW(S)

STATISTICAL and MEDICAL JOINT REVIEW

NDA #: 19-676 SE1-013

Drug: Nutropin (somatotropin)

Sponsor: Genentech Inc.

Indication: Replacement of endogenous GH in patients with adult GH deficiency

Date of Submission: 2/1/99

Statistical Reviewer: Joy Mele, M.S. (HFD-715)

Medical Reviewer: Saul Malozowski, M.D. (HFD-510)

Introduction

The sponsor has submitted the results of a single study (M0381g) in childhood-onset growth hormone deficient (CO-GHD) adults to support the following change to the *Clinical Pharmacology* section of the label for Nutropin:

[redacted]

On May 14th, 1999, the sponsor proposed and additional change in the *Clinical Pharmacology, Minearl Metabolism* section of the label for Nutropin:

[redacted]

Study M0381g was designed to assess the affect of GH administration on body composition; bone mineral density (BMD) was a secondary endpoint. An additional study conducted by the sponsor assessed BMD in adult-onset growth hormone deficient (AO-GHD) study M0431g but the results were not significant and are summarized only briefly at the end of this review. Therefore, this amendment focuses on the outcomes for CO-GHD adults in Study M0381g. Bone metabolic markers (alkaline phosphatase, calcium and inorganic phosphorus) were also assessed during the study.

Background

GH actions influence numerous tissues and organ systems. Among those the skeleton is one target known to be affected by GH.

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Many hormonal systems, among those GH, are known to modulate bone remodeling. GH is critical to induce longitudinal bone growth, in part, by stimulating the number of cartilage cells. This effect is due to direct GH action and it is also mediated by the local and systemic production of IGFs. Bone remodeling encompasses both bone accretion and loss. During childhood and adolescence bone formation increases. When growth ceases and final height is achieved bone accretion continues, particularly in the spine. Peak bone mass is reached late in the third decade of life. After this period, bone mass decreases.

Most studies in subjects with GH excess, as seen in patients with acromegaly, suggest that cortical bone is increased as a result of GH elevations. There are discrepancies in reports of the effects on trabecular bone using different methods such as CT, DEXA and histomorphometry. While some indicate similar trends to those observed in cortical bone due to GH action, others dispute these claims.

In GHD, bone mass seems to be reduced, particularly in CO-GHD. Several studies have reported osteopenia in this cohort. Using single and dual photon absorptiometry the lumbar spine of 30 CO-GHD adult males showed decrement between 9-19%, when compared with normal controls, in a cross sectional study (J Clin Edocrinol Metab, 74:118, 1992). Similar results in a study of analogous characteristics were reported in 70 subjects (J Bone Miner Res, 9:1319, 1994) where 33% of subjects had BMD 2 SD below normal. These findings applied to both isolated GHD and GHD associated with multiple hormonal deficiencies, suggesting the GH role on bone remodeling is significant. There is no evidence, however, that discontinuation of GH administration in young GHD adults results in bone loss. This strongly suggests that the lack of skeletal mass in this patient population is due, in great part, to insufficient acquisition of bone mass during childhood secondary to suboptimal GH therapy before cessation, and/or to inadequate pituitary hormonal replacement. Moreover, in the studies listed above it is unknown whether patients reached "final adult height" or whether their bone age was mature or still remained, to a certain extent, pubertal or prepubertal.

There is no solid data indicating that CO-GHD subjects are more prone to suffer fractures, although AO patients appear to have a higher fracture frequency when compared to normals ((Eur J Endocrinol, 137:240, 1997.) Additional hormonal deficiencies as well as age of onset of these deficiencies may confound these results. Younger patients with AO-GHD that have achieved final adult height may have failed to accrue peak bone mass due to early onset of the hormonal deficiency or due to inadequate replacement of associated pituitary hormonal deficiencies.

The literature regarding the effects of GH supplementation or replacement in CO GHD patients is still emerging. Most studies show effects on serum markers of bone formation that seem to remain elevated as long as GH is given. The results of GH effects

in short term studies, however, failed to show improvements in BMD in CO-GHD adults. Decrements in this parameter were seen consistently in 3-6 months studies both in CO and AO-GHD. This is currently reflected in all GH labels for adult GHD indications.

Findings of decreased BMD have been more contentious in AO-GHD. Positive findings seem to be more apparent in subjects most affected and improvements have been reported in those whose IGF-I levels were more elevated as a result of higher GH doses during treatment. Estrogen appears to play a positive role in this balance, and a gender effect, particularly in cycling women or in those appropriately replaced with estrogen and progesterone, remains to be clarified.

Study M0381g

Study M0381g is a double-blind randomized placebo-controlled multicenter study. Adults with childhood-onset documented GHD who had not received GH for at least one year were eligible for this study. Entry criteria included age of 35 years or less and bone age of 14 years or greater for females and 15 years or greater for males.

The primary endpoints in this study were percent lean body mass and physical performance (strength and endurance). BMD was measured as a secondary endpoint. Patients were followed for 2 years; BMD was measured by DEXA scan at baseline and Months 6, 12, 18 and 24. Spinal BMD at Month 24 is the primary focus of this supplemental NDA; results for other relevant endpoints are briefly summarized.

Medical Reviewer's Comments

Of notice in this study is entry criteria for age and bone age. Six patients (9%) younger than 18 years old participated in the study, probably because their growth rates were slowing down and they were considered good candidates to be treated as adults, although this could be considered inadequate because they were not indeed adults. Bone age data was not available for most of the patients and was not presented in the NDA.

Generally the bone age is expected to be similar to the chronological age. In subjects older than 18 years old, it is expected that the bone age will be mature. As stated in the introduction, patients younger than 30 years old will not have accrued "mature" BMD because this accretion process continues during the third decade of life. Therefore the six subjects under18 years old that the sponsor defines as adults were still in the process of accruing BMD and had more than a decade ahead to do so. Thus, any changes in BMD that we may observe as a result of an intervention, particularly in these young subjects, may be accelerated by the treatment, but would not necessarily fail to occur if more time were to elapse.

Analyses were performed with and without these young patients and the results did not differ. Due to the small number of patients enrolled in the study, the review includes all patients enrolled.

Patient Disposition

A total of 64 CO-GHD patients (21 to placebo, 20 to Nutropin 0.0125 mg/kg/day and 23 to Nutropin 0.025 mg/kg/day) were randomized to treatment at 18 US sites.

The number of patients with spinal BMD data after 1 year, 1½ years and 2 years on therapy are shown in Table 1. Only 52% of placebo patients, 70% of Nutropin 0.0125 patients and 57% of Nutropin 0.025 patients have complete data. Using all available data, FDA defined a last-observation-carried-forward (LOCF) dataset consisting of 62% of the placebo patients, 75% of the Nutropin 0.0125 patients and 70% of the Nutropin 0.025 patients. For the sponsor's LOCF dataset, only data from Month 18 was carried forward. The inclusion of four additional patients in the FDA LOCF analyses did not produce results notably different from the sponsor's results.

Table 1. Study M0381g Sample Sizes

	Placebo	Nutropin 0.0125 mg/kg/day	Nutropin 0.025 mg/kg/day
Randomized	21 (100%)	20 (100%)	23 (100%)
Baseline spinal BMD	16 (76%)	17 (85%)	20 (87%)
1 year spinal BMD	15 (71%)	17 (85%)	17 (74%)
1½ year spinal BMD	15 (71%)	17 (85%)	14 (61%)
2 year spinal BMD	14 (67%)	15 (75%)	14 (61%)
Baseline and 2 year spinal BMD	11 (52%)	14 (70%)	13 (57%)
Baseline and LOCF BMD	13 (62%)	15 (75%)	16 (70%)
Sponsor's LOCF	12 (57%)	14 (70%)	14 (61%)

The rate of discontinuation for any cause was approximately 33%, 20% and 32% for placebo and for each of the GH doses, respectively (Table 2). The rate of dropouts for non-compliance was three times higher in the GH arms compared to placebo. This trend is reversed when abandonment was as per patient request.

Table 2. Study M0381g Reasons for Discontinuation

	Placebo	Nutropin 0.0125 mg/kg/day	Nutropin 0.025 mg/kg/day
ADE	2 (9.5%)	0	1 (4%)
Lost-to-Follow-up	1 (5%)	0	1 (4%)
Non-Compliance	1 (5%)	3 (15%)	4 (17%)
Patient Request	3 (14%)	1(5%)	1 (4%)
Other	0	0	1 (4%)

Patient Demographics

Patient characteristics at baseline are summarized in Table 3 for all randomized patients (total n=64) and in Table 4 for patients with baseline and 2 year spinal BMD data (total n=38). Patients ranged in age from 15 to 34 years; the majority of the patients were Caucasian males. The treatment groups were comparable with regard to maximum stimulated growth hormone level, years of organic GHD and HRT use. Some treatment group imbalances were observed for gender and etiology. For the low dose of Nutropin the ratio of males to females was equal whereas for the placebo group and high dose, more males than females were entered. In the high dose group, a larger percentage of the

patients had GHD of organic origin while for the other 2 treatment groups the majority of the patients had idiopathic GHD.

Of all the patients entered with idiopathic GHD, 67% males were males and 89% were on HRT (primarily sex and thyroid HRT with 17% on glucocorticoids). For the patients with GHD due to organic causes, 45% were males; 100% were taking thyroid hormone; 75% were taking sex hormones; and 75% glucocorticoids.

Table 3. Study M0381g Characteristics of All Randomized Patients

	Placebo (n=21)	Nutropin 0.0125 mg/kg/day (n=20)	Nutropin 0.025 mg/kg/day (n=23)
Age (years) Range	24 (15-34)	24 (17-32)	23 (16-30)
Years of organic GHD	14 (n=9)	13 (n=9)	14 (n=13)
Max stim GH (ng/ml)	0.8	0.7	0.7
Gender			
Male	62%	50%	70%
Female	38%	50%	30%
% Caucasian	95%	75%	87%
Idiopathic	57%	55%	43%
Organic	43%	45%	57%
HRT			
Glucocorticoid	57%	50%	52%
Sex steroid	81%	75%	65%
Thyroid	86%	80%	87%

Table 4. Study M0381g Characteristics of Patients with Baseline and 2 year spinal BMD Data

	Placebo (n=11)	Nutropin 0.0125 mg/kg/day (n=14)	Nutropin 0.025 mg/kg/day (n=13)
Age (years) Range	24 (15-34)	25 (17-32)	23 (16-30)
Years of organic GHD	14 (n=5)	11 (n=6)	15 (n=9)
Max stim GH (ng/ml)	0.7	0.6	0.6
Gender			
Male	55%	50%	62%
Female	45%	50%	38%
% Caucasian	91%	79%	100%
Idiopathic	55%	57%	31%
Organic	45%	43%	69%
HRT			
Glucocorticoid	36%	57%	46%
Sex steroid	73%	79%	54%
Thyroid	91%	86%	85%

Medical Reviewer's Comments

Case series of pediatric patients with GHD state that 10 % of these subjects are GHD due to organic causes (tumors, malformations, etc.) Ninety percent are considered

to be idiopathic in origin. While organic etiologies usually lead to multiple hormonal deficiencies in addition to GH, idiopathic patients tend to have isolated GHD in most cases. Organic patients and those idiopathic with multiple hormonal deficiencies are more difficult to treat, because among other reasons they require more medications. Some of these medications or these deficiencies are known to affect bone accrual. Gonadal deficiencies can lead to deficits in BMD accrual or early loss of BMD. Similarly, over-replacement of thyroid and glucocorticoid hormones may lead also to loss of bone.

Literature generated by this sponsor, that has been the dominant leader in the field in the US since the introduction of rhGH and has been following thousands of children with this condition, reports that 67 % of idiopathic patients have isolated GHD, with a sex ratio of 4/1 males, and the remaining one third has multiple hormonal deficiencies. The sex distribution for the latter group is not provided but it can be estimated that organic causes are evenly distributed among sexes.

Given this published information regarding the demographics of GHD children and assuming that approximately ⅔ of idiopathic GHD children will be GHD as adults, it appears that the patient distributions for study M0381g for sex and etiology are plausible. One would expect about 68% males and 58% idiopathic based on the aforementioned assumptions. Nevertheless, these distributions are inconsistent with some published data of CO-GHD adults that report a large percentage of males and of idiopathic GHD patients.

When analyzing the replacement therapies in the idiopathic patients, it is unusual that 67% are receiving some kind of replacement therapy when the literature states that >50% of idiopathic patients have isolated GHD. It is not known how these patients were recruited and whether before randomization more classical patients were dropped and not enrolled. What is clear is that this patient population may not be representative of CO-GHD patients and that the results of this study may not be necessarily extrapolated to subjects with CO-GHD with less complex medical histories. However, in small studies such as this one, allocation of one or two subjects to any given arm may result in imbalances, therefore this unexpected discrepancy of the patient distribution. from what is reported in the literature, may be attributed to chance.

Statistical Methods

According to the protocol, all endpoint comparisons would be made at Months 12 and 24 using analysis of covariance (ANCOVA) with baseline as a covariate. In the NDA, the sponsor states that " the Jonckheere-Terpstra test for monotone trend in dose response was used to test between-group changes in BMD" to maximize statistical power. To produce the p-values presented in Tables 5, 6 and 7, FDA used the Wilcoxon rank sum test. Analyses using ANCOVA also were performed by FDA and produced results consistent with the Wilcoxon results.

Statistical Reviewer's Comments

A test for trend does not provide sufficient evidence to establish the efficacy of each Nutropin dose compared to placebo. A positive trend just indicates that the drug has activity and that increasing the dose increases the effect; a positive trend does not indicate that each dose tested is significantly more effective than placebo (or the next lowest dose). To show that each dose is effective at increasing BMD, the results for each dose must be significantly different from the results for placebo.

Efficacy Results

Spinal BMD

BMD was assessed at each center with different DEXA machines. All determinations for each subject were made with the same apparatus.

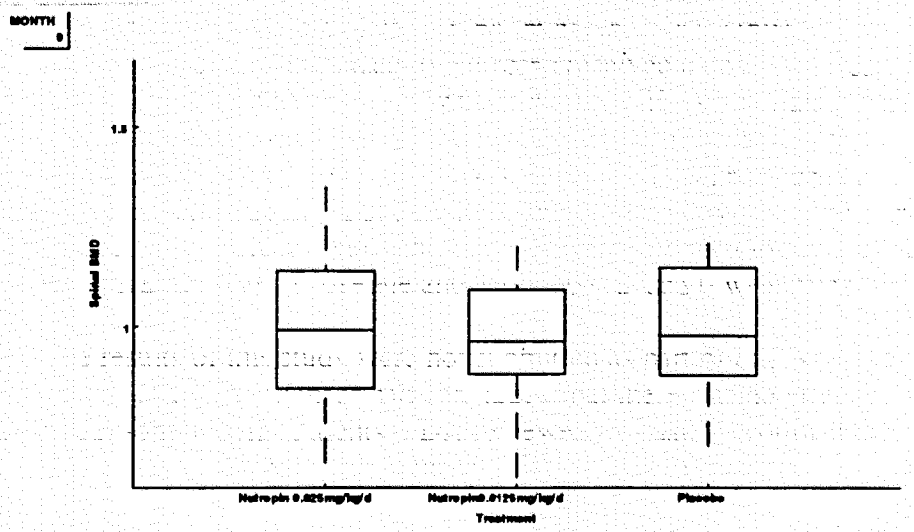
The three treatment groups were comparable at baseline for spinal BMD with a mean value of about 1 gm/cm^2 (Table 5 and Figure 1). A transient decrease in spinal BMD was seen in all treatment groups at Month 6; 87% of patients treated with Nutropin 0.025 had a decrease. Statistically significant treatment effects for percent change from baseline and z-score change from baseline were seen in the highest dose group (Nutropin 0.025) at Month 24 for the observed cases and for the last-observation-carried-forward (LOCF) data compared to placebo (Table 5). Results for the 0.0125 group were only significant at the .05 level at Month 18; an adjustment for multiple comparisons would render those results non-significant. Note that no post-hoc adjustments for multiple comparisons are made here. It is clear that any adjustment for multiple comparisons due to multiple endpoints and multiple treatment groups would yield, most likely, non-significant results; so the results here are not robust.

Table 5. Study M0381g Results[1] for Spinal BMD

	Placebo	Nutropin .0125	Nutropin .025	p-value Plac vs .0125	p-value Plac vs. .025
Spinal BMD Gm/cm^2					
Baseline	1.01 (0.1)	0.97 (0.2)	1.0 (0.2)	.61	.93
Month 24	1.06 (0.2)	0.97 (0.1)	1.07 (0.3)		
% Change					
Month 12	+0.4% (2.3)	+1.3% (3.6)	+1.9% (4.1)	.46	.34
Month 18	+1.2% (2.2)	+3.2% (2.8)	+3.1% (5.1)	.05	.37
Month 24	+1.3% (2.9)	+3.3% (3.9)	+4.3% (3.6)	.29	.04[2]
LOCF	+1.0% (2.9)	+3.2% (3.8)	+4.6% (4.9)	.17	.03
Z score					
Baseline	-1.03 (1.4)	-1.26 (1.3)	-1.16 (1.3)	.91	.76
Change					
Month 12	+0.03 (0.2)	+0.02 (0.2)	+0.2 (0.4)	1.0	.32
Month 18	+0.1 (0.2)	+0.2 (0.2)	+0.2 (0.5)	.19	.69
Month 24	+0.1 (0.3)	+0.3 (0.3)	+0.3 (0.3)	.14	.10
LOCF	+0.1 (0.3)	+0.3 (0.3)	+0.4 (0.4)	.06	.03

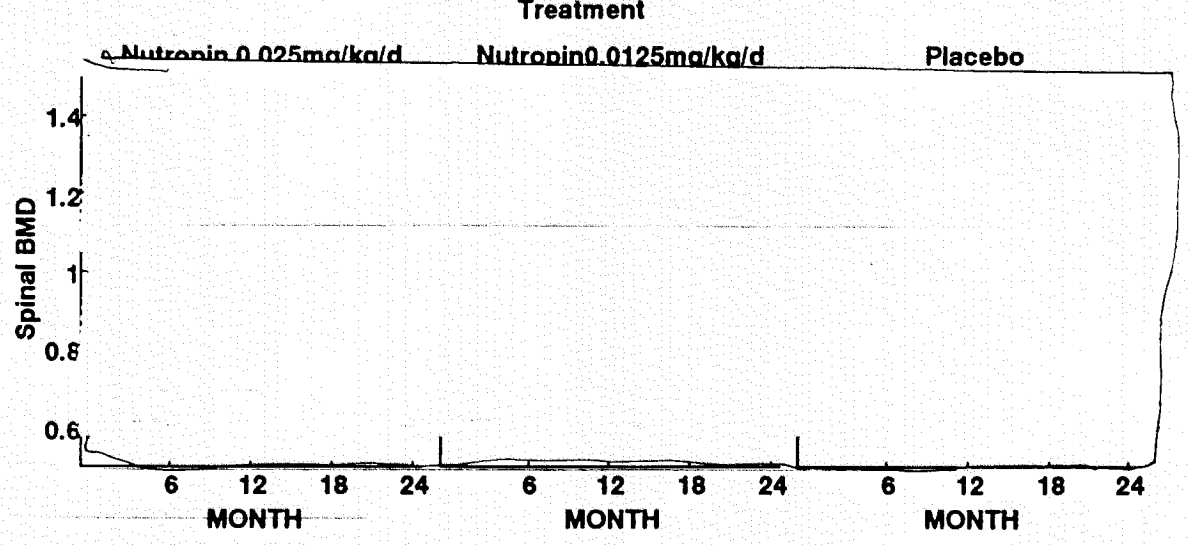
[1] P-values are results of Wilcoxon Rank Sum tests performed by FDA statistician.
[2] ANCOVA adjusting for baseline BMD yielded a p-value of .05.

Figure 1. Boxplot of Baseline Spinal BMD



Spinal BMD data for each patient is plotted in Figure 2; in all groups some patients decreased, increased or did not show any changes in BMD. Note for the Nutropin 0.025 group, the changes in BMD are small and these changes appear to be unrelated to baseline. Further analyses by FDA failed to show a relationship between baseline BMD and BMD change from baseline. The lack of correlation between baseline BMD and response is puzzling and counterintuitive.

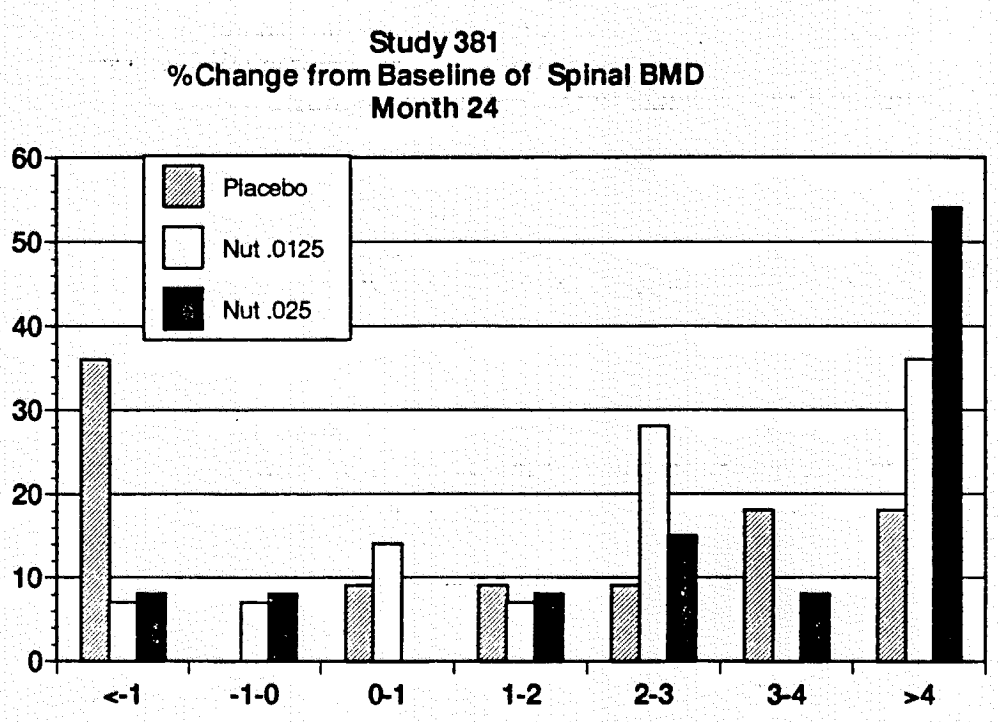
Figure 2. Individual Patient Spinal BMD Results



From Figure 2, also it can be seen that positive results were not restricted to only a few patients; this point is further illustrated in Figure 3 on the following page. About 55% of the patients in the Nutropin 0.025 group showed an increase of 4% or greater in

spinal BMD compared to 18% in the placebo group. About 35% of placebo patients had a decrease in BMD by Month 24 compared to 15% and 16% in the Nutropin 0.0125 and 0.025 groups, respectively. This data is quite valuable suggesting that the magnitude of BMD increase was large for 55% of the patients receiving the 0.025 kg/dose. Conversely, it also shows that lack of treatment seems to be deleterious to the ability to accrue BMD, because 35% of these subjects were below baseline at Month 24, in contrast to only 15% in the high GH dose. This data also suggests that not all patients benefit and that not all doses are effective at increasing BMD. Significant BMD increments are only seen in the spine and only seen with the higher GH dose.

Figure 3



Analyses of subgroups defined by age or gender produced results consistent with the overall results.

Secondary Efficacy Results

The results for secondary endpoints are summarized in Table 6. GH appears not to have any substantial effects on total BMD. Nutropin 0.025 significantly increased height, inorganic phosphorus and alkaline phosphatase compared to placebo at Month 24.

Table 6. Study M0381g Results for Secondary Variables at Month 24

	Placebo	Nutropin .0125	Nutropin .025	p-value Plac vs. .025
Whole body BMD				
Baseline	1.01 (0.13)	0.94 (0.12)	0.99 (0.16)	
% Change	+1.4% (1.9)	+1.8% (4.2)	+2.2% (2.6)	.41
Baseline Z score	-1.2 (1.4)	-1.8 (1.3)	-1.4 (1.6)	
Change	+0.2 (0.2)	+0.2 (0.4)	+0.2 (0.4)	.95
BMI				
Baseline	26	28	27	
Change	+1.3	+0.7	+0.8	.95
Height (cm)				
Baseline	166	157	165	
Change	+0.01 (0.5)	+0.5 (0.7)	+1.0 (1.0)	.003
Weight				
Baseline	74	77	67	
Change	+3.8	+3.4	+2.6	.81
Weight by dexa				
Baseline	74	64	67	
Change	+2.9	+1.2	+2.6	.52
Calcium				
Baseline	9.1	9.2	9.1	
Change	+0.1	+0.2	+0.3	.34
Inorg Phosphorus				
Baseline	3.7	3.9	3.9	
Change	+0.3	+0.2	+0.8	.04
Alkaline Phosphatase				
Baseline	65.6 (22)	77.7 (31)	78.0 (23)	.03
Change	-3 (11)	+2 (14)	+21 (21)	.002

FDA looked at the relationship of changes in height and changes in alkaline phosphatase to change in spinal BMD. For the Nutropin 0.025 group, changes in alkaline phosphatase were not correlated with changes in spinal BMD (R=.02, p=.94) while changes in height were correlated with changes in spinal BMD (R=.59, p=.03). Neither measure was correlated with spinal BMD for the other two treatment groups.

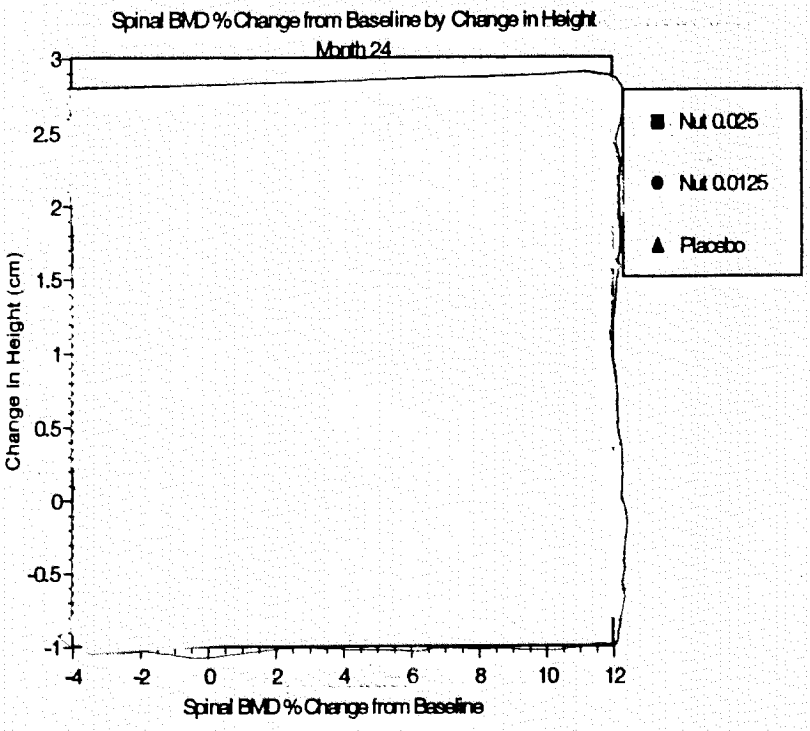
Medical Reviewer's Comments

The secondary endpoint results are consistent with all previous studies using GH. Metabolic markers such as alkaline phosphatase increase due to GH administration. Bone metabolic markers have not been allowed to be used to claim efficacy for drugs with action at the bone level. Moreover, bone markers and even BMD have not been accepted alone as adequate endpoints for indications for drugs to treat osteoporosis. No

correlation between changes in these bone markers and BMD have been established, thus, no claims can be made of either a correlation or an association between these markers and BMD. ***The claim of increments of alkaline phosphatase as a result of GH treatment is substantiated by these results and should be granted.***

Figure 4 below illustrates the relationship between height change from baseline and spinal BMD change from baseline. About one-third of the variation in spinal BMD can be explained by increase in height in the Nutropin 0.025 group. An ANCOVA with change in height as a covariate produced a p-value of .21 for the comparison of Nutropin 0.025 to placebo.

Figure 4



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Medical Reviewer's Comments

These results suggest that patients that benefited the most were those with insufficient baseline bone maturation. As stated before, two main events are seen in the skeleton: one is final height achievement that occurs in the late teens or mid twenties, and two, peak BMD that occurs later in that decade. Thus, patients that have not achieved final height and still have growth potential are probably the ones with more opportunity to accrue BMD. This was seen in this study in patients receiving the highest GH dose and only in the spine.

IGF-I Results

IGF-I levels were measured at baseline and at Months 3, 6, 9, 12, 18 and 24 on study. Means and medians for both observed and standardized values of IGF-I at baseline and Months 12, 18 and 24 are displayed in Table 7. The groups are comparable at baseline. No changes are noted in the placebo group while dose-related changes are seen in the Nutropin treatment groups.

Table 7. Study M0381g IGF-I Results

	Placebo (n=13)		Nutropin .0125 (n=14)		Nutropin .025 (n=13)	
	Mean (SD)	Median	Mean (SD)	Median	Mean (SD)	Median
ng/mL						
Baseline	94 (81)	77	84 (97)	41	83 (60)	69
Month 12	115 (147)	52	252 (146)	232	562 (226)	570
Month 18	77 (56)	47	252 (162)	222	495 (278)	449
Month 24	81 (60)	60	291 (110)	266	425 (214)	333
Change (ng/mL)						
Month 12	+17 (61)	-9	+187 (107)	+200	+477 (227)	+450
Month 18	-24 (56)	-16	+191 (159)	+148	+431 (271)	+405
Month 24	-26 (45)	-21	+214 (93)	+180	+336 (224)	+299
Adult SDS						
Baseline	-4.2 (2.0)	-4.7	-4.6 (2.3)	-5.4	-4.4 (1.6)	-4.5
Month 12	-4.0 (3.0)	-5.3	-0.7 (2.8)	-0.5	+3.6 (3.2)	+4.0
Month 18	-4.6 (1.6)	-5.1	-0.7 (3.0)	-1.0	+2.6 (3.8)	+2.6
Month 24	-4.4 (1.7)	-4.7	+0.3 (1.8)	+0.1	+2.0 (3.0)	+1.1

Based on upper limit of normal values provided by the sponsor [1], FDA computed the percentage of patients with abnormally elevated IGF-1 levels at Months 6, 12, 18 and 24 and at anytime during therapy (Table 8). These sex and age adjusted values show that GH administration resulted in IGF-I levels above the upper limit of normal in 6% of

[1] Upper limit of normal IGF-1 values

Age (yrs)	Male	Female
12-16	957	1096
16-26	841	726
26+	470	460

patients at the lower dose, and 35% of the subjects at the higher dose (p=.009 compared to placebo) at any time during the study. The group receiving the 0.025 mg/kg/day dose, had mean IGF-I levels at month 12 (562 ± 226 ng/mL), at month 18 (495 ± 278 ng/mL). and at month 24 (425 ± 214 ng/mL) near the upper limit of normal; values are particularly elevated for the patients of 26 years or older (about half the patients).

Table 8. Percent of Patients with Above Normal IGF-1 Levels

	Placebo (n=13)	Nutropin .0125 (n=14)	Nutropin .025 (n=13)
Baseline	0%	0%	0%
Month 6	0%	0%	24%
Month 12	0%	6%	13%
Month 18	0%	6%	15%
Month 24	0%	7%	0%
Any Month	0%	6%	35%

No correlation of endpoint IGF-1 with baseline IGF-1 or with percent change in lumbar spine BMD was noted. Graphs in Appendices 1 and 2 illustrate these relationships.

Medical Reviewer's Comments

Current trends in the AGHD field suggests that GH doses should be adjusted to target IGF-I values at the mean levels. This practical approach is the result of more than 10 years experience in this patient population that suggest that most of the adverse reactions of GH excess are associated with higher IGF-I levels.

Increasing information is emerging suggesting that higher levels of IGF-I (within the normal range) are associated with an increase risk for prostate cancer (Science 279:563, 1998, J Nat Cancer Inst. 90:911, 1998), lung cancer (J Nat Cancer Inst. 91:151, 1998), colorectal cancer (J Nat Cancer Inst. 91:620, 1999) and breast cancer (Breast Cancer Res Treat, 47:111, 1998, Lancet 351:1393, 1998.) These epidemiological studies strongly indicate that subjects with IGF-I levels in the upper quartiles are at increased risk for many of these tumors.

The elevated IGF-1 levels suggest that the high dose is not a replacement dose that will lead to normalization of IGF-I levels, but a phrmacologic dose that may result in IGF-I levels above the upper limit of normal. Because the long-term effects of these elevated IGF-I levels are unknown, the use of this compound at this dose should be weighted against the potential risks for adverse reactions.

It appears that this intervention at replacement doses (0.0125 mg/kg/day) that normalize IGF-I levels, does not achieve the desired increase in spinal BMD and that in order to accelerate this process and probably to allow patients to overcome the spinal BMD deficit necessitate pharmacological GH doses.

It appears that the IGF-I levels are not good predictors of changes in spinal BMD (Appendix 2). The reasons for a lack of a relationship between these two measures remains unknown.

Study M0431g

Study M0431g is a double-blind randomized placebo-controlled multicenter Phase II study. Patients randomized to Nutropin received a dose of 0.0125 mg/kg/day SC. Adults with acquired (adult-onset) growth hormone (GH) were eligible for this study. Entry criteria included aged 18 to 70 and no previous GH therapy. The primary endpoints in this study were percent lean body mass, physical performance (strength and endurance) and quality of life. Bone mineral density (BMD) was measured but not named in the protocol as an efficacy endpoint. Patients were followed for 2 years; BMD was measured by DEXA scan at baseline and Months 6, 12, and 3 weeks post-study.

The results of this study were not submitted as part of this NDA but were requested by FDA. The sponsor had concluded that there was no effect of GH therapy on BMD in adult-onset GHD patients. FDA reviewed this data to confirm the sponsor's conclusions and to explore the data further. Only the BMD data is presented here.

BMD Results

A total of 166 patients were randomized to treatment; 82 to placebo and 84 to Nutropin. Two patients in each group had no baseline BMD data. About 20% of the patients had no BMD data at Month 12. The results in Table 9 below show no statistically significant differences between Nutropin and placebo at Month 12 for whole body and spinal BMD. The results for whole body BMD are borderline significant with p-values less than 0.1; however, these results favor placebo. Subgroup analyses defined by baseline levels, age or gender produced results consistent with the overall results.

Table 9. Study M0431g Results at Month 12

	Placebo	Nutropin .0125	p-value[1]
Whole body BMD			
Baseline	1.0 (0.1)	1.0 (0.1)	.47
% Change	-0.1% (2.6)	-0.9% (3.1)	.09
	n=65	n=62	
Baseline Z score	-0.7 (1.4)	-0.6 (1.3)	.79
Change	+0.05 (0.2)	-0.03 (0.3)	.06
	n=50	n=48	
Spinal BMD			
Baseline	1.0 (0.2)	1.1 (0.2)	.53
% Change	+0.2% (3.9)	+1.0% (4.5)	.38
	n=68	n=64	
Baseline Z score	-0.1 (1.5)	-0.002 (1.4)	.54
Change	+0.1 (0.4)	+0.1 (0.4)	.37
	n=65	n=63	

[1] Results of Wilcoxon rank sum tests

Medical Reviewer's Comments

Data from this study are very important because they give greater insight as to the relevance of the sponsor's claims to AGHD patients overall. Two main differences exist between these studies. One, patients in this study became GHD during adulthood. The mean age of these patients was 48 years (range of 20 to 70 years). The onset of GHD probably occurred in most after peak BMD was achieved. In that sense the baseline BMD was less affected by GHD than in the previous study. Nevertheless, in the CO-GHD study, the baseline BMD, was not found to be a predictor of response.

Two, the dose of GH, (i.e. 0.0125 mg/kg/day) used was shown to be ineffective in Study M0381g. This dose selection is the result of the inability of this patient population to tolerate greater GH doses. Patents at the selected dose or higher have acute adverse reactions when therapy is initiated. With time, most patients can tolerate the 0.0125 dose, but it has been quite difficult to administer doses in excess of 0.0125 mg/kg/day to AO-GHD individuals. So, the larger doses of GH needed to improve BMD, as for the younger CO-GHD patients, are not tolerated by these subjects. This would preclude extension for this indication or inclusion of this claim for this population of AO-GHD patients.

In addition, although it did not reach statistical significance, patients with AO-GHD receiving placebo did better than those receiving GH. Further, it appears that the degree of BMD loss in the patients receiving placebo was not as dramatic as the loss seen in the CO placebo-treated patients, where 38 % had a decrease in BMD after two years of treatment.

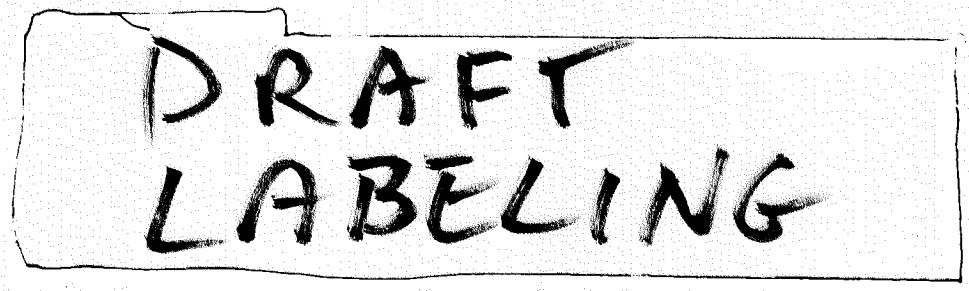
These observations bring into question the use of AGHD as an umbrella denomination. Clearly these two patient populations are quite distinct, although the causes of the disorder or the deficiencies may be identical. AGHD should be defined as adult onset or childhood onset to better depict the population differences as well as to define what and how these subjects should be treated.

Safety

The safety of this NDA was previously reviewed for S-009 in 1997. All pertinent information was taken into consideration and it was incorporated into the current GH label.

Comments regarding labeling

The sponsor has proposed the following change to the ***Clinical Pharmacology*** section of the label for Nutropin:



The proposed label is not satisfactory. It provides information comparing changes from baseline to endpoint and it does not present comparisons between the placebo group and the different treatment arms. The dose response information is not important or relevant and should not be included. In addition, the proposed labeling focuses only on the changes that favor the drug, failing to show that these were the only positive changes among a long list of variables studied that did not improve as a result of GH therapy. Moreover, the potential beneficial changes occurred only at the largest dose; the lower dose of GH did not induce significant spinal BMD accretion compared to placebo. No changes were seen in AO GHD patients that underwent similar evaluations; this should be disclosed in the labeling. Finally, the explanation stating that "..A transient decrease was seen at Month 6 in the high dose group, consistent with expansion of the remodeling space...", is inappropriate and speculative because no information was provided to substantiate this claim.

After discussions with the sponsor, FDA agreed to the following labeling:

The May 14th 1999 amendment "GH therapy stimulates bone formation and results in increases in serum alkaline phosphatase" is not properly substantiated because although increases in serum alkaline phosphatase were seen, it is difficult to state that this was accompanied by "bone formation" particularly since no correlation between change in BMD and alkaline phosphatase was observed. Hence, we can accept a statement regarding the increased serum alkaline phosphatase only.

Overall Comments

This study offers information suggesting that GH plays a role in spinal bone accretion during the transition from adolescence to adulthood and during young adulthood. It seems that GH replacement at lower doses could induce linear growth but not activate bone accretion in the spine. This can be achieved with higher GH doses that increase mean IGF-I levels above normal levels. This bone accretion property, that was previously hypothesized to occur as a result of GH administration, happens in this study only in patients receiving the higher GH dose. Therefore, it can be hypothesized that any patient with CO-GHD properly replaced with GH could reach the end of puberty with adequate spinal density. If GH treatment using the higher Nutropin dose continues once final height is achieved the process of spinal bone accretion will occur as desired. In contrast, lack of GH administration or lower GH doses could affect the tempo of BMD spinal accretion. Whether absence of GH at this time will be deleterious to these patients' spine remains unknown, and whether additional spinal bone accretion may occur with more time in the absence of GH or at lower GH doses also remains unsolved.

Of concern are the consistent higher IGF-I levels with the higher GH dose. CO GHD subjects are able to tolerate this dose with little if not absent acute adverse reactions, so commonly seen in AO GHD patients at much lower dosages. The long term effects of elevated IGF-I levels pose theoretical increased risk for the development of malignancies at later times in life.

Hence, a balance between the theoretical risk posed by a decrease in spinal BMD in the long term with emerging data that associate elevated IGF-I levels with numerous tumors, should be reached when prescribing and using this medication at this dose.

/S/

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Recommendation code: AP

cc:
Archival NDA# 19-676 SE1-013
HFD-510
HFD-510/SMalozowski, SSobel, CKing
HFD-715/Biometrics Division 2 File, Chron, JMele

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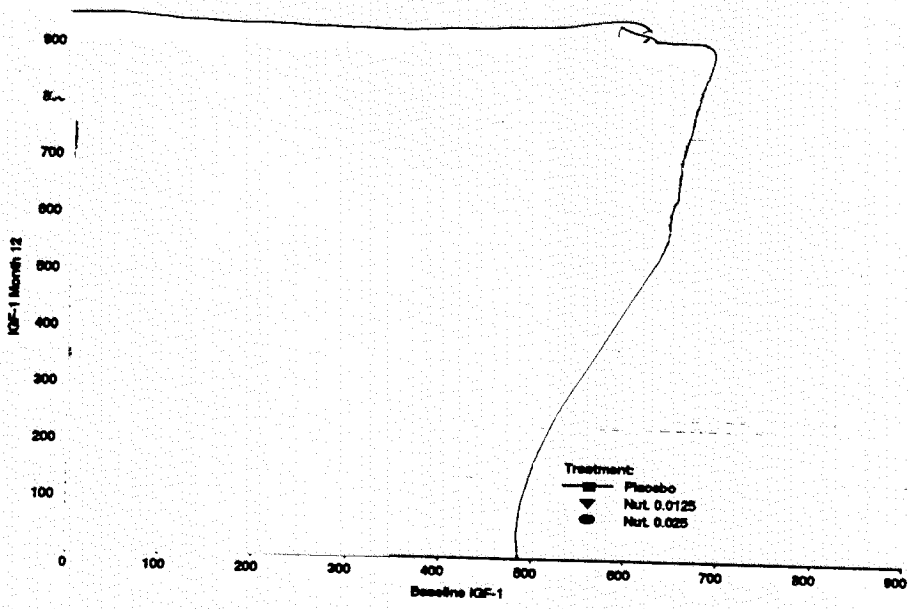
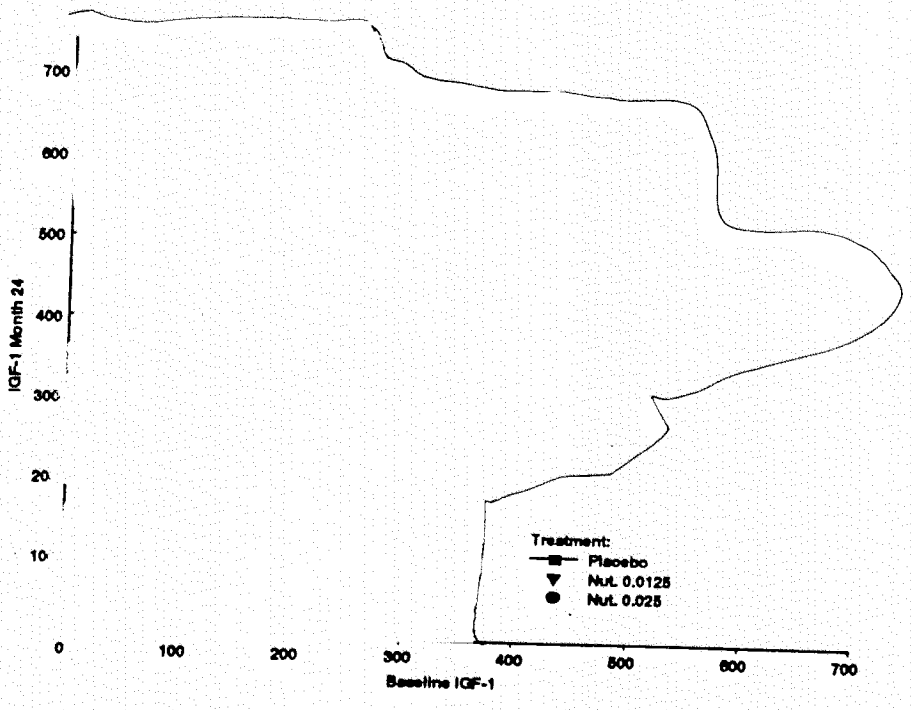
Appendix 1. IGF-1 levels at Months 12 and 24 by baseline IGF-1 for each treatment group.[1]

MONTH 12



MONTH 24



[1] Only a fitted line for the placebo group is shown because the fit for the treatment groups is poor. Also the placebo line is close to the identity line since IGF-1 did not essentially change; the placebo line then provides a good reference line with all values above it indicating an increase from baseline.

Appendix 2. IGF-1 levels at Months 12 and 24 by baseline IGF-1 for each treatment group by subgroups defined by % change in lumbar spine BMD (≤1% versus >1%).