CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: 020522, S09

Trade Name: NUTROPIN AQ

Generic Name: SOMATROPIN [rDNA ORIGIN] FOR INJECTION

Sponsor: GENETECH, INC.

Approval Date: 12/1/99

INDICATION(s): LONG TERM TREATMENT OF CHILDREN WHO HAVE GROWTH FAILURE DUE TO LACK OF ENDOGENOUS GROWTH HORMONE SECRETION AND TREATMENT OF CHILDREN WHO HAVE GROWTHFAILURE

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION for: 020522, S09

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	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
Tenative Approval Letter			X	
Approvable Letter			X	
Final Printed Labeling			X	
Medical/Statistical Review(s)	X			
Chemistry Review(s)	X			
EA/FONSI			X	
Pharmacology Review(s)	X			
Statistical Review(s)	(Combined with Medical Review)			
Microbiology Review(s)			X	
Clinical Pharmacology Biopharmaceutics Review(s)			X	
Bioequivalence Review(s)			X	
Administrative Document(s)/ Correspondence	X			

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Application Number: 020522, S09

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

NDA 20-522/S-009

Food and Drug Administration
Rockville MD 20857

Genentech, Inc.
Attention: Robert L. Garnick, Ph.D.
Vice President, Regulatory Affairs
1 DNA Way
South San Francisco, CA 94080

DEC 1 1999

Dear Dr. Garnick:

Please refer to your supplemental new drug application dated January 29, 1999, received February 1, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Nutropin AQ (somatropin [rDNA origin] injection).

We acknowledge receipt of your submissions dated August 11, October 29, and November 5, 1999.

This supplemental new drug application provides for the following additions to the CLINICAL PHARMACOLOGY section of the labeling: (1) improvement in spine bone mineral density observed in childhood-onset adult growth hormone deficient patients; and (2) increases in serum alkaline phosphatase.

We have completed the review of these supplemental applications, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text. Accordingly, these supplemental applications are approved effective on the date of this letter.

You are not required to complete a pediatric assessment for this application because it is not covered by the Pediatric Rule (21 CFR 314.55(a)).

The final printed labeling (FPL) must be identical to the submitted draft labeling (package insert submitted November 5, 1999).

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed to each application. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, these submissions should be designated "FPL for approved supplement NDA 20522/S-009." Approval of these submissions by FDA is not required before the labeling is used.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, contact Crystal King, P.D., M.G.A., Regulatory Project Manager, at (301) 827-6423.

Sincerely,

/S/

Solomon Sobel, M.D.
Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER for: 020522, S09

MEDICAL/STATISTICAL REVIEW(S)

Date: November 1, 1999 /S/

From: Saul Malozowski
Medical Officer

Subject: NDA 20-522 S/009, Nutropin AQ; BMD label changes

To: The file

The review performed by Joy Mele and I of NDA 19-676 SE1-013 supports the sponsor's claim under this NDA. All pertinent information on NDA 20-522 S/009 was cross-referenced from NDA 19-676 SE1-013. A copy of the original review is attached for the file.

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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:

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

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Background

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

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.

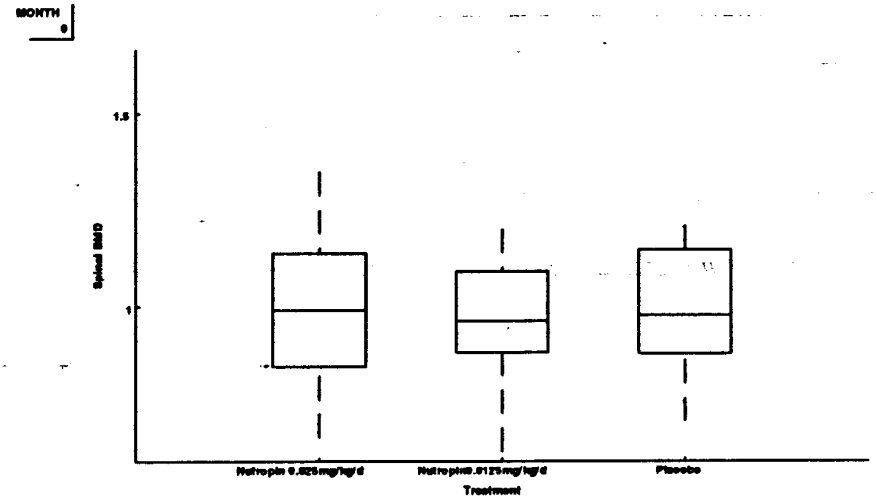
The three treatment groups were comparable at baseline for spinal BMD with a mean value of about 1 gm/cm^2 (Table 5 and Figure 1). A transient decrease in spinal BMD was seen in all treatment groups at Month 6; 87% of patients treated with Nutropin 0.025 had a decrease. Statistically significant treatment 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

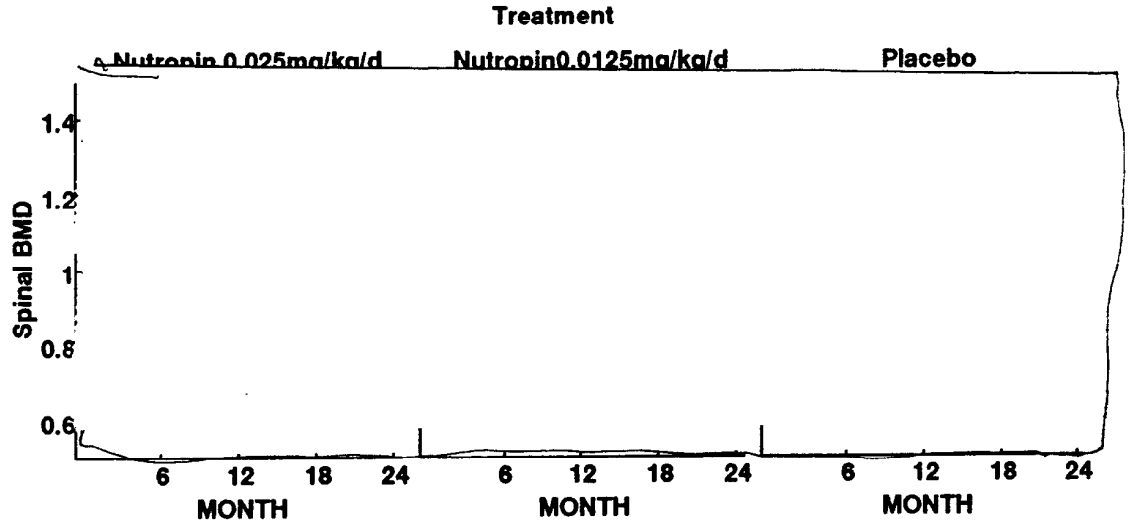
[1] P-values are results of Wilcoxon Rank Sum tests performed by FDA statistician.
[2] ANCOVA adjusting for baseline BMD yielded a p-value of .05.

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.

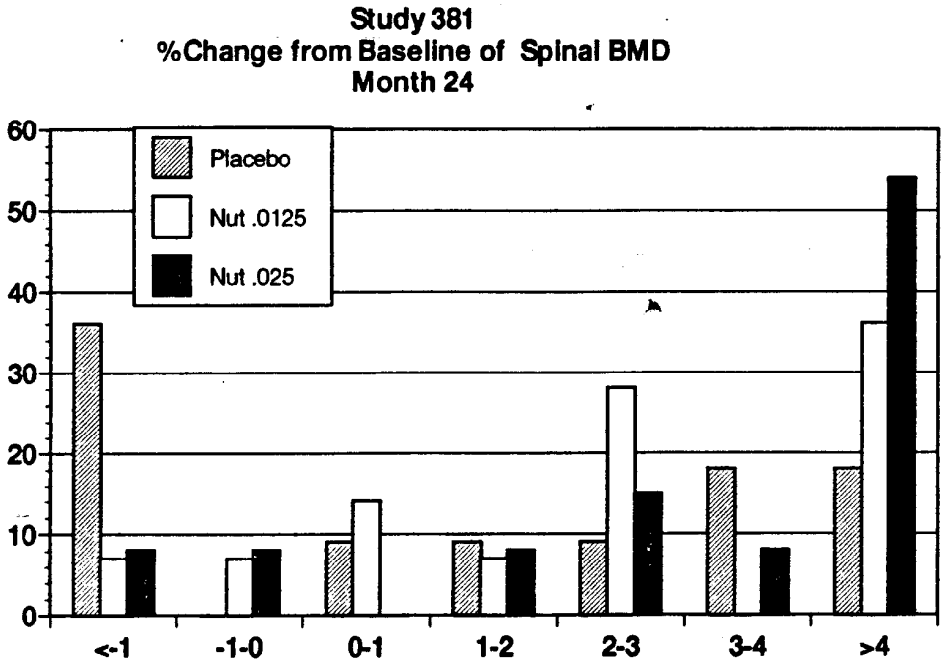
Figure 2. Individual Patient Spinal BMD Results



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.

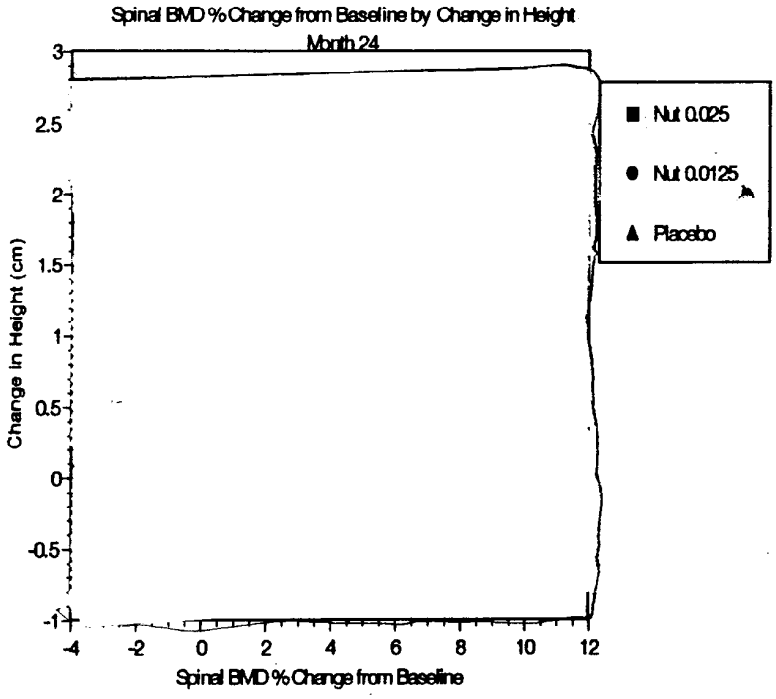
Medical Reviewer's Comments

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.

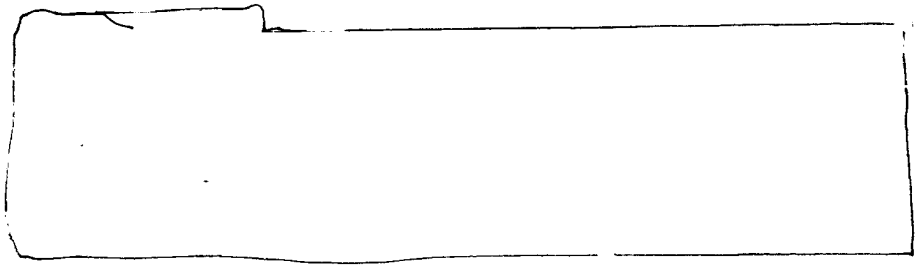
These observations bring into question the use of AGHD as an umbrella denomination. Clearly these two patient populations are quite distinct, although the causes of the disorder or the deficiencies may be identical. AGHD should be defined as adult onset or childhood onset to better depict the population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

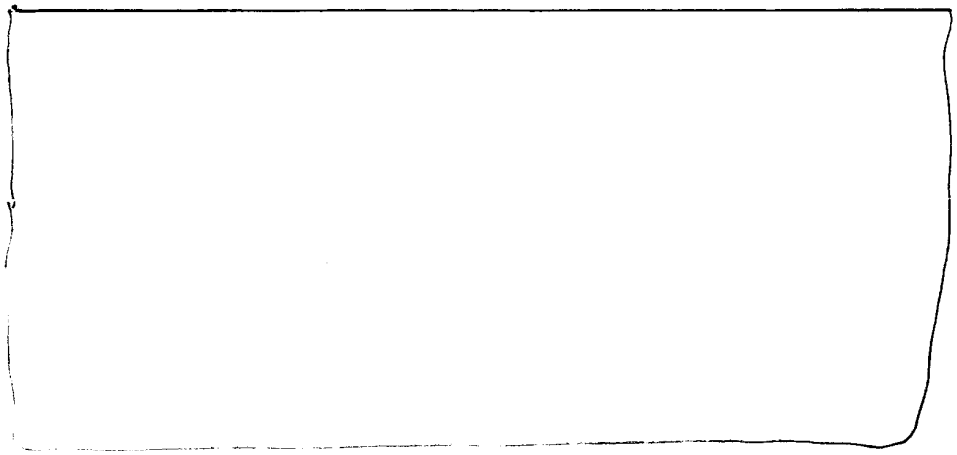
Comments regarding labeling

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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/S/ 11-4-99

Solomon Sobel, M.D.
Director, DMEDP

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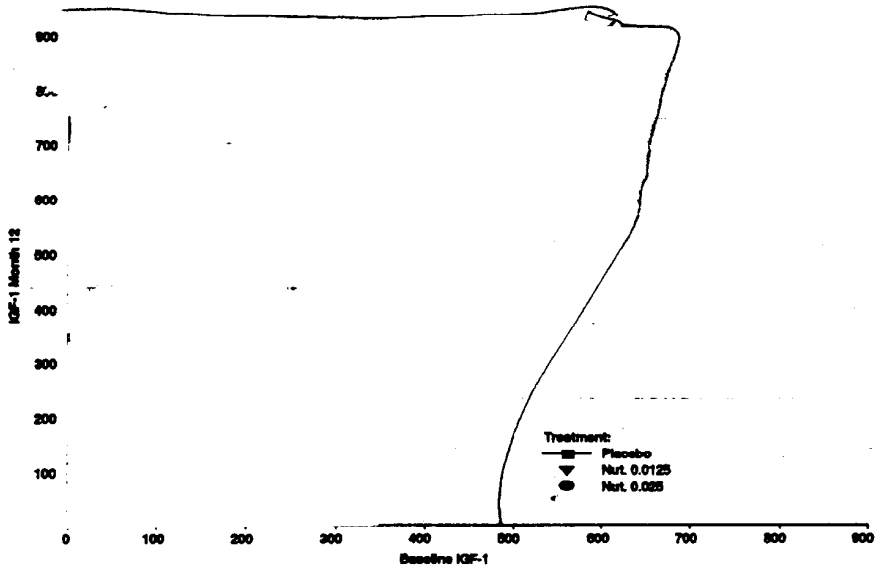
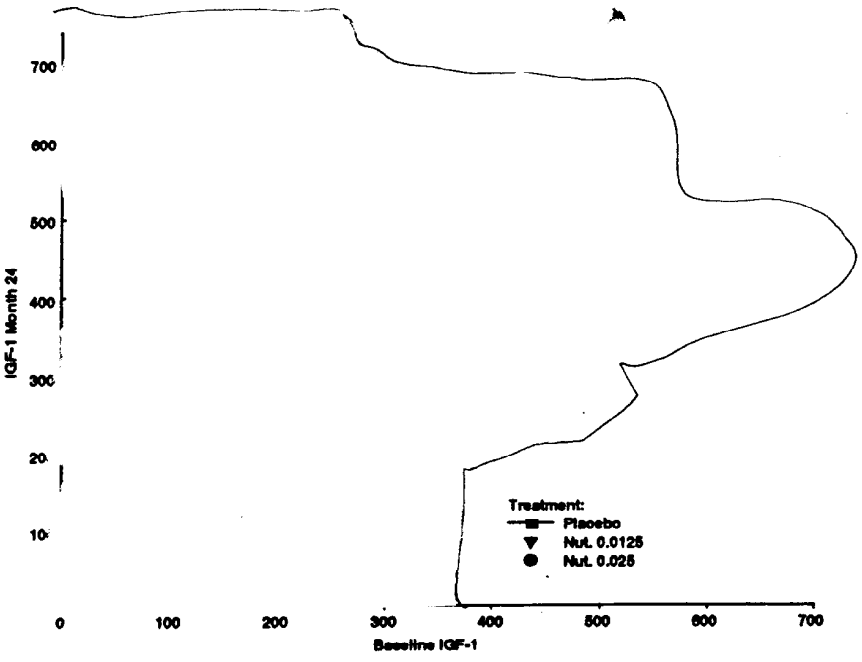
Appendix 1. IGF-1 levels at Months 12 and 24 by baseline IGF-1 for each treatment group.[1]

MONTH 12

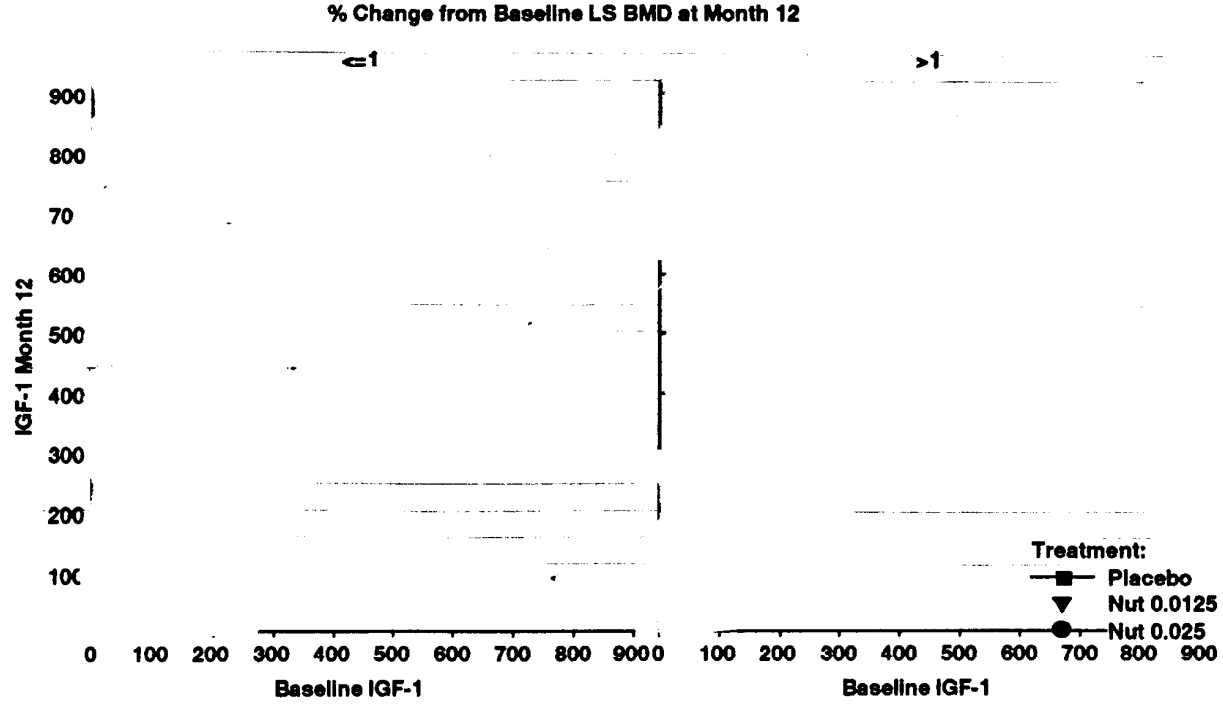


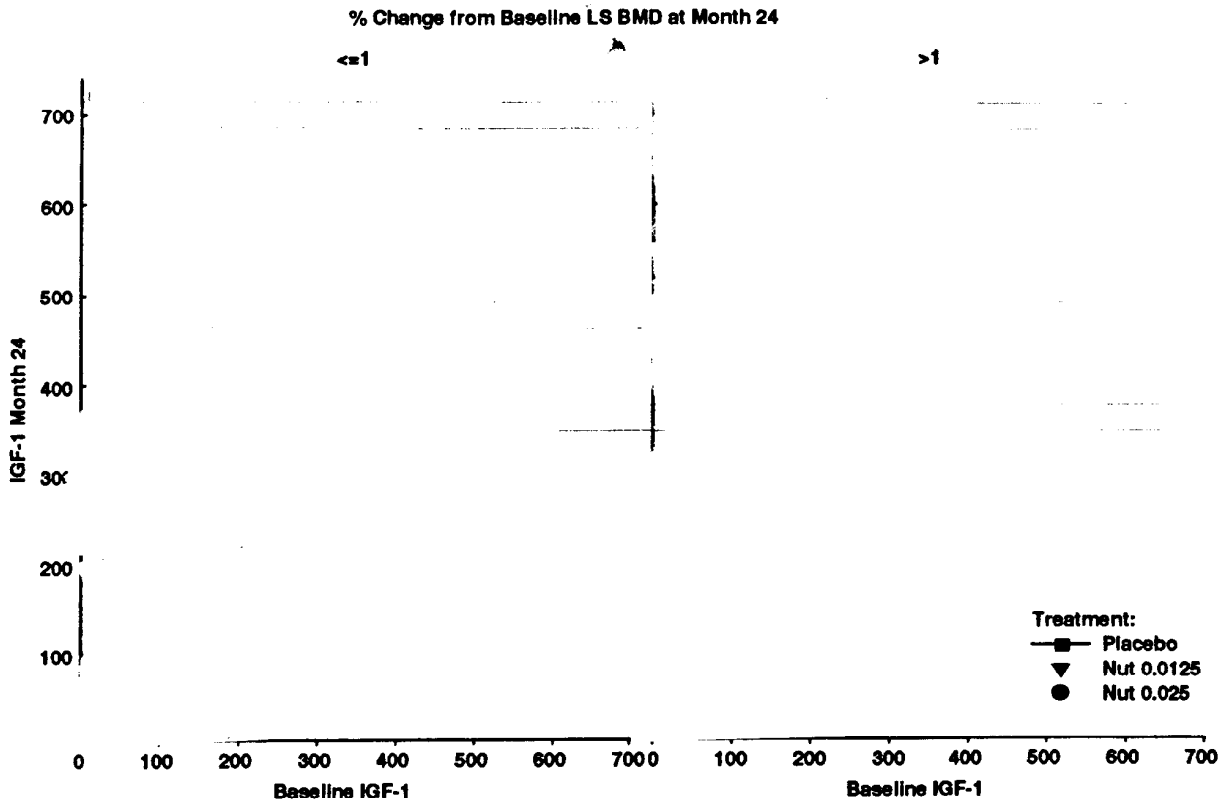
MONTH 24



[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%).





CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER for: 020522, S09

CHEMISTRY REVIEW(S)

CHEMISTS REVIEW	1. ORGANIZATION	2. NDA NUMBER
	DMEDP II, HFD-510	20-522
3. NAME AND ADDRESS OF APPLICANT		4. SUPPLEMENT NUMBER, DATE
Genentech Inc. 1 DNA Way South San Francisco, CA 94080		SE8-009, 29-JAN-1999
5. PROPRIETARY NAME	6. NAME OF THE DRUG	7. AMENDMENTS, REPORT, DATE
Nutropin AQ	Somatropin (rDNA origin) injection	

8. SUPPLEMENT PROVIDES FOR

Labeling changes including improved bone-mineral density with Nutropin AQ treatment in adult patients with childhood-onset growth-hormone deficiency under the "Efficacy Studies" section of the package insert.

9. PHARMACOLOGICAL CATEGORY	10. HOW DISPENSED	11. RELATED IND, NDA, DMF
Growth hormone	Rx	
12. DOSAGE FORM	13. POTENCY	
Solution for injection	5, 10 mg	

14. CHEMICAL NAME AND STRUCTURE

15. COMMENTS

The applicant proposes labeling changes, to be supported by clinical data supplied with an amendment to NDA 19-676/S013 (dated 14-MAY-1999). Curiously, the applicant's proposed change to the Nutropin AQ label, while consistent in tone, is not at all consistent in text with that proposed for the Nutropin PI, for which the clinical data was supplied (see chemists review of N 19-676/S013). As far as CMC review is concerned, however, the proposed change is acceptable, and as there is no new indication provided for, there is no need for a request for a waiver from the requirement to prepare an EA in support of this efficacy supplement.

16. CONCLUSION AND RECOMMENDATION

There are no CMC issues with the proposed labeling changes, and there is no requirement for an EA nor is an EA waiver request necessary. The application may be Approved based on CMC review.

17. NAME	18. REVIEWERS SIGNATURE	19. DATE COMPLETED
WILLIAM K. BERLIN	/S/	20-SEP-1999

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10/1/99

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER for: 020522, S09

PHARMACOLOGY REVIEW(S)

NDA 20-522/S-009 23 June 1999

Genentech Inc.
460 Point San Bruno Blvd.
South San Francisco, CA 94080-4990

Submission: 29 Jan, 1 Feb 99

PHARMACOLOGY REVIEW OF NDA SUPPLEMENT
Supplement to NDA 20-522 #009

DRUG: Nutropin AQ (somatropin [rDNA origin] for injection)

CATEGORY: Growth hormone.

INDICATION: This submission provides a clinical data supplement to support an additional label claim for improved bone mineral density (BMD) with Nutropin treatment in the adult patient population.

PHARMACOLOGY COMMENTS: There were no preclinical data submitted under supplement S-009 and none is deemed to be needed. Thus, no pharmacology review is necessary for this supplement. There were no labeling changes made to the previously approved preclinical sections of the label.

RECOMMENDATION: AP

/S/
David H. Hertig
Pharmacologist

cc: NDA 20-522 Orig
HFD-510 Division File
HFD-510 RSteigerwalt
HFD-510 DHertig
HFD-510 CKing

I Concur:
/S/
6/24/99

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER for: 020522, S09

ADMINISTRATIVE DOCUMENTS and CORRESPONDENCE

13. PATENT INFORMATION ON ANY PATENT WHICH CLAIMS THE DRUG

21 U.S.C. 355 (b): The applicant shall file with the application the patent number and the expiration date of any patent which claims the drug for which the applicant submitted the application or which claims a method of using such drug and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use or sale of the drug.

Nutropin AQ® [somatropin (rDNA origin) injection] falls within the scope of the claims of Patent Number 5,763,394. A copy of the patent is included in this section.

US005763394A

United States Patent [19]

O'Connor et al.

[11] Patent Number: 5,763,394

[45] Date of Patent: Jun. 9, 1998

[54] **HUMAN GROWTH HORMONE AQUEOUS FORMULATION**

[75] Inventors: **Barbara H. O'Connor**, San Carlos; James Q. Oeswein, Moss Beach, both of Calif.

[73] Assignee: Genentech, Inc., South San Francisco, Calif.

[21] Appl. No.: 117,156

[22] PCT Filed: Jul. 29, 1993

[86] PCT No.: PCT/US93/07139

§ 371 Date: Sep. 14, 1993

§ 102(e) Date: Sep. 14, 1993

[87] PCT Pub. No.: WO94/03198

PCT Pub. Date: Feb. 17, 1994

Related U.S. Application Data

[63] Continuation of Ser. No. 923,401, Jul. 31, 1992, abandoned, which is a continuation-in-part of Ser. No. 751,424, Aug. 28, 1991, abandoned, which is a continuation of Ser. No. 182,262, Apr. 15, 1988, Pat. No. 5,096,885.

[51] Int. Cl.[6] A61K 38/27; C07K 14/61

[52] U.S. Cl. 514/12; 530/324

[58] Field of Search 514/12

[56] References Cited

U.S. PATENT DOCUMENTS

3,929,147	12/1975	Monte et al.
4,297,568	10/1981	Schwarz et al.
4,333,920	11/1982	Chan et al.
4,623,717	11/1986	Fernandez et al.
4,789,441	11/1988	Thurow.
4,812,557	3/1989	Yamada et al.
4,816,568	3/1989	Hamilton, Jr. et al.
4,852,506	8/1989	Tyle
4,917,685	4/1990	Viswanathan et al.
5,005,244	4/1991	Miller et al.
5,009,885	3/1992	Pearlman et al.
5,125,324	6/1992	Clark et al.
5,182,258	1/1993	Chow.
5,317,012	5/1994	Kudsk.
5,374,620	12/1994	Clark et al.
5,567,677	10/1996	Cassanova et al.
5,597,892	1/1997	Clark et al.

FOREIGN PATENT DOCUMENTS

A-59771/39	9/1989	Australia.
AUA30771/8	9/1989	Australia.
164459B	4/1989	Denmark
0 131 864	1/1985	European Pat. Off.
0 193 917	9/1986	European Pat. Off.
0 211 401	2/1987	European Pat. Off.
0211601	2/1987	European Pat. Off.
0 303 746	2/1989	European Pat. Off.
0303746	2/1989	European Pat. Off.
0 406 856	1/1991	European Pat. Off.
0 433 713	6/1991	European Pat. Off.
72359	7/1983	Israel.
1076238	12/1959	Israel.
8906655	7/1989	WIPO.
WO8906655	7/1989	WIPO.
WO9115509	10/1991	WIPO.
WO9118623	12/1991	WIPO.
WO9217209	10/1992	WIPO.
WO9306861	4/1993	WIPO.
WO9312811	7/1993	WIPO.
WO9319776	10/1993	WIPO.
WO9322335	11/1993	WIPO.
WO9403198	2/1994	WIPO.

OTHER PUBLICATIONS

Skottner et al., "Growth Responses in a Mutant Dwarf Rat to Human Growth Hormone and Recombinant Human Insulin-Like Growth Factor I" *Endocrinology* 124 (5): 2519–2526 (1989).

Becker, et al., *Biotechnology & Applied Biochemistry* 9:478–487 (1987).

Pearlman, et al., *Current Communications in Molecular Biology*, eds. D. Marshak, D. Liu, pp. 25–30 (1989).

Physician's Desk Reference, Medical Economics Co., Orawell, NJ pp. 1193–1194 (1988).

Physician's Desk Reference, Medical Economics Co., Orawell, NJ pp. 1059–1350 (1992).

Physician's Desk Reference, Medical Economics Co., Orawell, NJ pp. 1256–1267 (1992).

The Merck Index, Merck & Co. Inc., Rahway, NJ p. 983, entry No. 7342 (1976).

The Merck Index, Merck & Co. Inc., Rahway, NJ p. 1203, entry No. 7537 (1989).

Merck Manual, Eleventh Ed., Merck & Co., 1989, pp. 1203–1207.

Primary Examiner—Paula K. Hutzell
Assistant Examiner—Bene: Prickril
Attorney, Agent, or Firm—Diane L. Marschang

[57] **ABSTRACT**

A stable pharmaceutically acceptable aqueous formulation containing human growth hormone, a buffer, a non-ionic surfactant, and, optionally, a neutral salt, mannitol, or, a preservative, is disclosed. Also disclosed are associated means and methods for preparing, storing, and using such formulations.

23 Claims, 5 Drawing Sheets

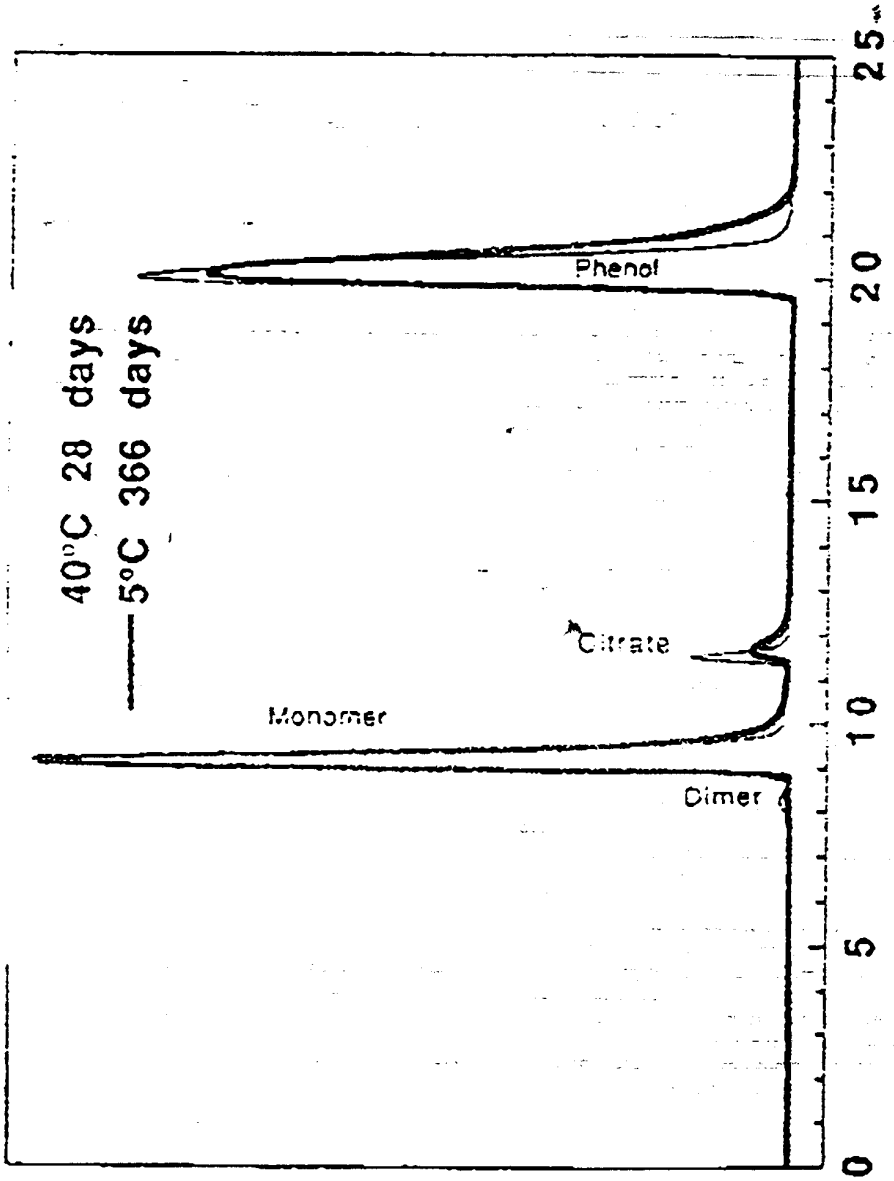

FIG. 1

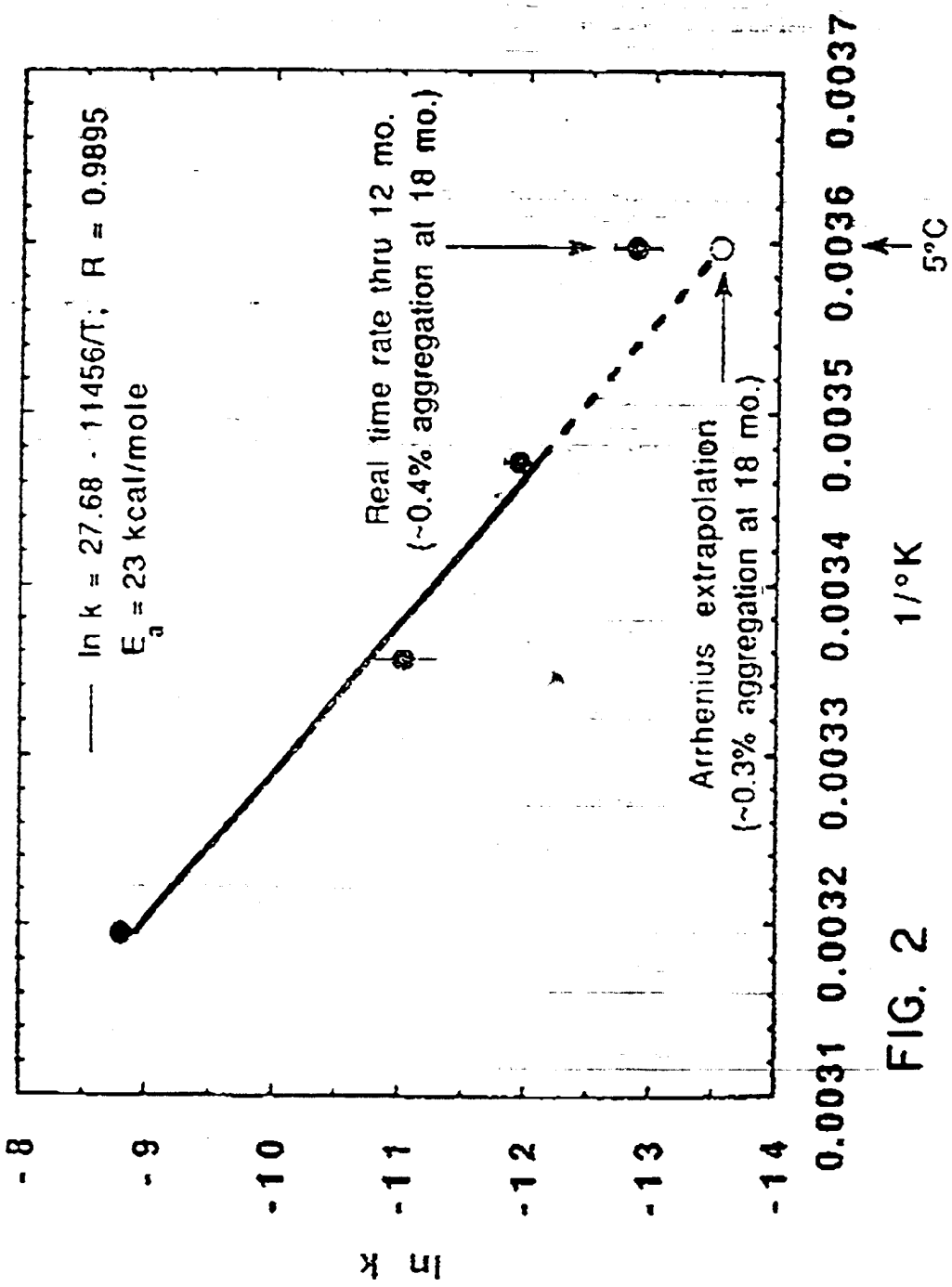

FIG. 2

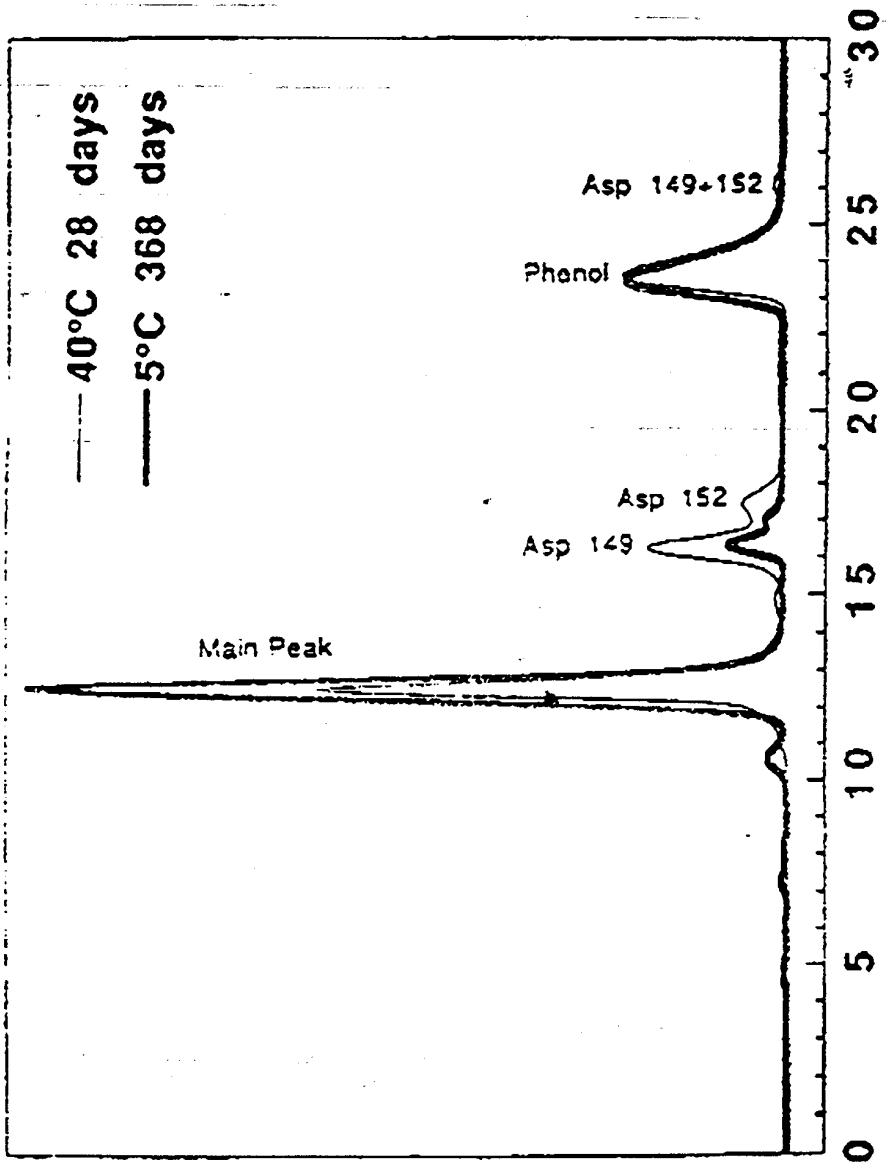

FIG. 3

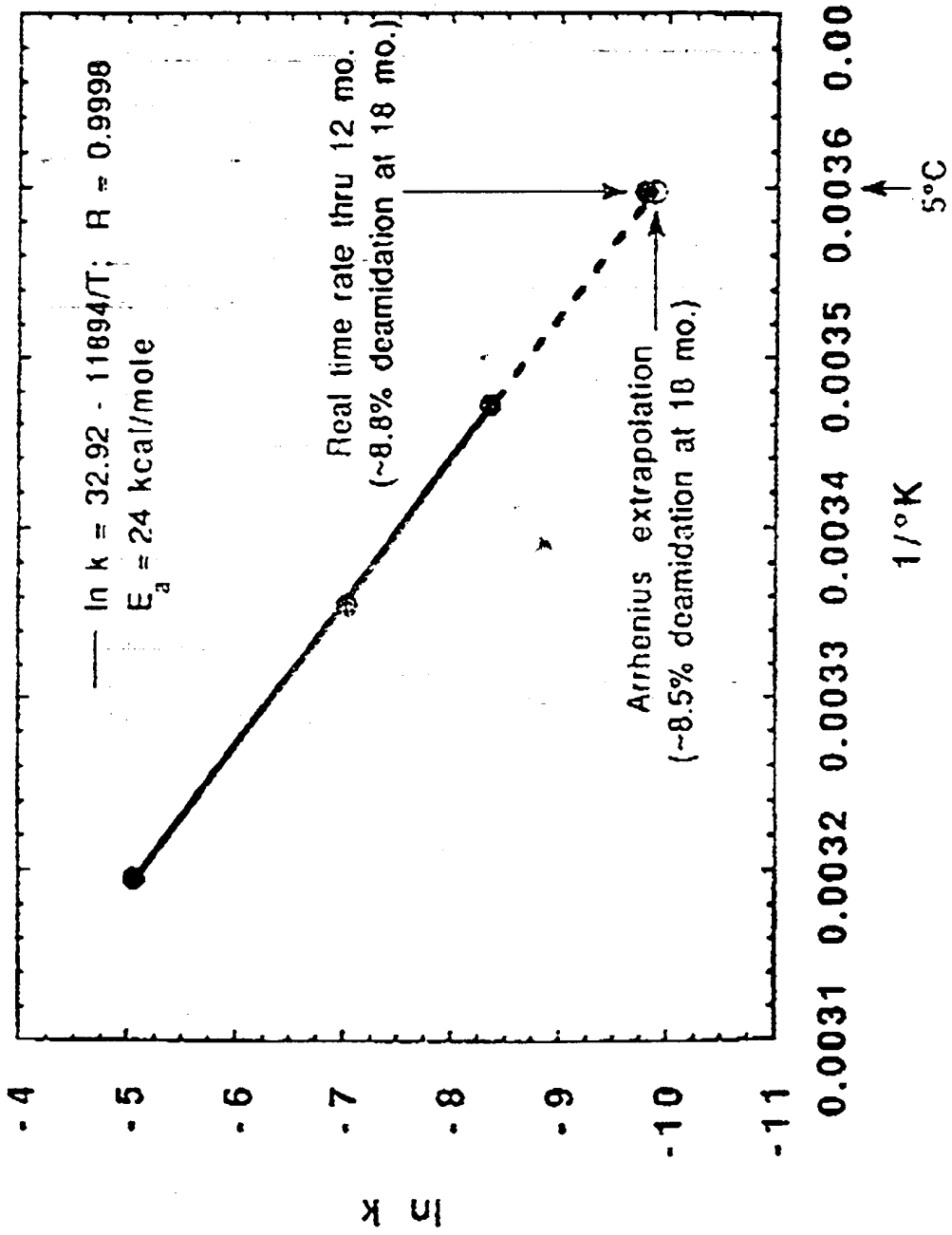

FIG. 4

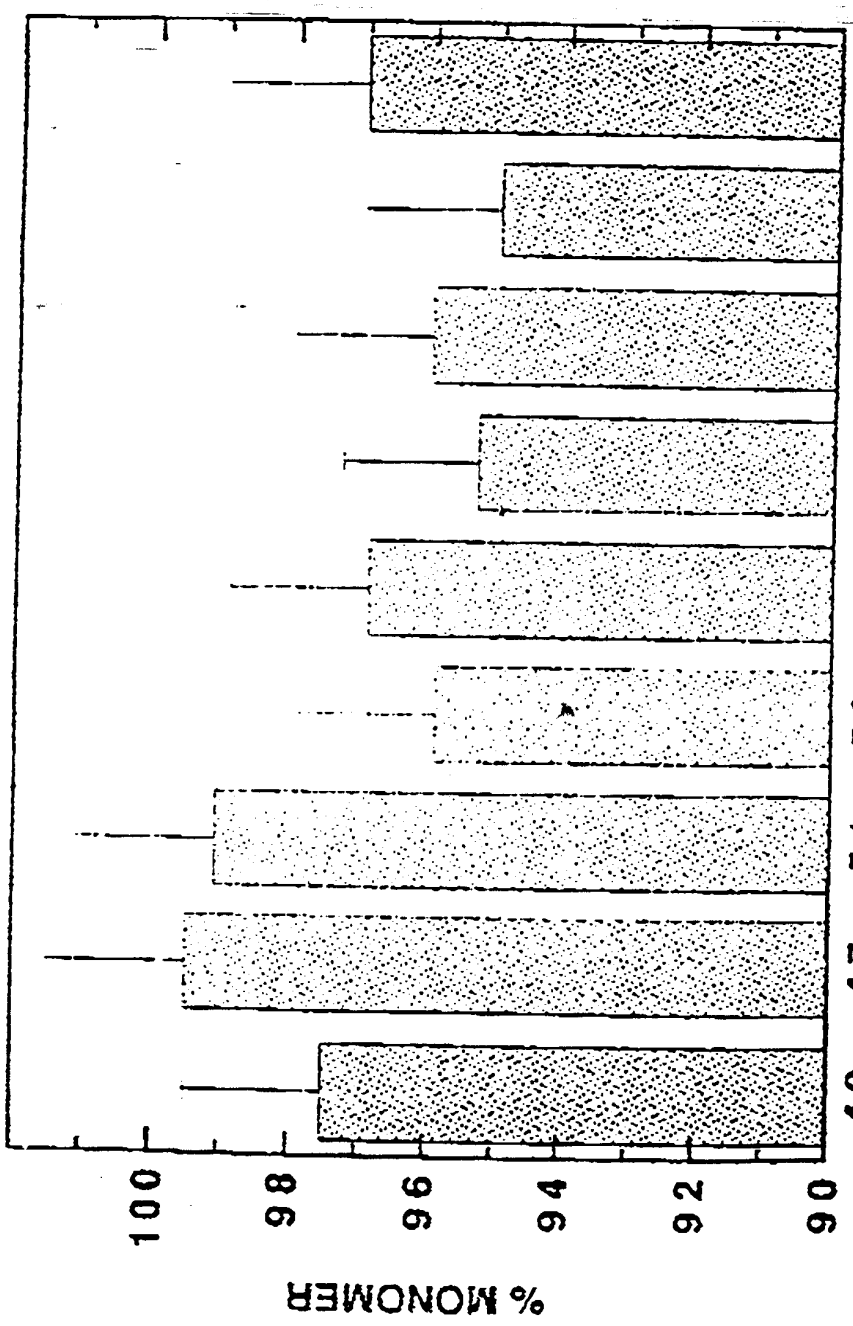

FIG. 5

HUMAN GROWTH HORMONE AQUEOUS FORMULATION

CROSS REFERENCE TO RELATED APPLICATIONS

This case is a U.S. national stage application of PCT/US93/07149, filed Jul. 29, 1993, which is a continuation of U.S. patent application Ser. No. 07/923,401, filed Jul. 31, 1992, now abandoned, which is a continuation-in-part of U.S. patent application Ser. No. 07/751,424, filed Aug. 28, 1991, now abandoned, which is a continuing application of U.S. patent application Ser. No. 07/182,262, filed Apr. 15, 1988, now U.S. Pat. No. 5,096,885.

FIELD OF THE INVENTION

The present invention is directed to pharmaceutical formulations containing human growth hormone (hGH) and to methods for making and using such formulations. More particularly, this invention relates to such pharmaceutical formulations having increased stability in aqueous formulation.

BACKGROUND OF THE INVENTION

Human growth hormone formulations known in the art are all lyophilized preparations requiring reconstitution. Per vial, Protropin® hGH consists of 5 mg hGH, 40 mg mannitol, 0.1 mg monobasic sodium phosphate, 1.6 mg dibasic sodium phosphate, reconstituted to pH 7.8 (*Physician's Desk Reference*, Medical Economics Co., Oradell N.J., p. 1049, 1992). Per vial, Humatrope® hGH consists of 5 mg hGH, 25 mg mannitol, 5 mg glycine, 1.13 mg dibasic sodium phosphate, reconstituted to pH 7.5 (*Physician's Desk Reference*, p. 1266, 1992).

For a general review for growth hormone formulations, see Pearlman et al., *Current Communications in Molecular Biology*, eds. D. Marshak and D. Liu, pp. 23–30, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 1989. Other publications of interest regarding stabilization of proteins are as follows.

U.S. Pat. No. 4,297,344 discloses stabilization of coagulation factors II and VIII, antithrombin III, and plasminogen against heat by adding selected amino acids such as glycine, alanine, hydroxyproline, glutamine, and aminobutyric acid, and a carbohydrate such as a monosaccharide, an oligosaccharide, or a sugar alcohol.

U.S. Pat. No. 4,783,441 discloses a method for the prevention of denaturation of proteins such as insulin in aqueous solution at interfaces by the addition of up to 500 ppm surface-active substances comprising a chain of alternating, weakly hydrophilic and weakly hydrophobic zones at pH 6.8–8.0.

U.S. Pat. No. 4,812,557 discloses a method of stabilization of interleukin-2 using human serum albumin.

European Patent Application Publication No. 0 303 746 discloses stabilization of growth promoting hormones with polyols consisting of non-reducing sugars, sugar alcohols, sugar acids, pentaerythritol, lactose, water-soluble dextrans, and Ficoll, amino acids, polymers of amino acids having a charged side group at physiological pH, and choline salts.

European Patent Application Publication No. 0 211 601 discloses the stabilization of growth promoting hormones in a gel matrix formed by a block copolymer containing polyoxyethylene-polyoxypropylene units and having an average molecular weight of about 1,100 to about 40,000.

European Patent Application Publication No. 0 193 917 discloses a biologically active composition for slow release

characterized by a water solution of a complex between a protein and a carbohydrate.

Australian Patent Application No. AU-A-30771/89 discloses stabilization of growth hormone using glycine and mannitol.

U.S. Pat. No. 5,096,885 (which is not prior art) discloses a formulation of hGH for lyophilization containing glycine, mannitol, a non-ionic surfactant, and a buffer. The instant invention provides an unexpectedly stabilized aqueous formulation in the absence of glycine.

hGH undergoes several degradative pathways, especially deamidation, aggregation, clipping of the peptide backbone, and oxidation of methionine residues. Many of these reactions can be slowed significantly by removal of water from the protein. However, the development of an aqueous formulation for hGH has the advantages of eliminating reconstitution errors, thereby increasing dosing accuracy, as well as simplifying the use of the product clinically, thereby increasing patient compliance. Thus, it is an objective of this invention to provide an aqueous hGH formulation which provides acceptable control of degradation products, is stable to vigorous agitation (which induces aggregation), and is resistant to microbial contamination (which allows multiple use packaging).

SUMMARY OF THE INVENTION

One aspect of the invention is a stable, pharmaceutically acceptable, aqueous formulation of human growth hormone comprising human growth hormone, a buffer, a non-ionic surfactant, and optionally, a neutral salt, mannitol, and a preservative.

A further aspect of the invention is a method of preventing denaturation of human growth hormone aqueous formulations comprising mixing human growth hormone and a non-ionic surfactant in the range of 0.1–5% (w/v) (weight/volume). In yet another aspect of the invention, this stabilized formulation is stored for 6–18 months at 2°–8° C.

DESCRIPTION OF THE FIGURES

FIG. 1 is a size exclusion chromatogram of aqueous growth hormone formulation stored for 28 days at 40° C. (i.e., thermally stressed) and for one year at 5° C. (i.e., recommended conditions for storage).

FIG. 2 is a plot of Arrhenius rate analysis of growth hormone aggregation in aqueous formulation.

FIG. 3 is an anion exchange chromatogram comparing a thermally stressed (40° C.) aqueous formulation hGH sample with an aqueous formulation hGH sample stored under recommended conditions (2°–8° C.) for one year.

FIG. 4 is a plot of Arrhenius rate analysis of hGH deamidation in aqueous formulation.

FIG. 5 is a graph of the percentage monomer present in the various formulations where mannitol has been substituted with a neutral salt.

DETAILED DESCRIPTION OF THE INVENTION

A. Definitions

The following terms are intended to have the indicated meanings denoted below as used in the specification and claims.

The terms "human growth hormone" or "hGH" denote human growth hormone produced by methods including natural source extraction and purification, and by recombi-

nant cell culture systems. Its sequence and characteristics are set forth, for example, in *Hormone Drugs*, Guerriguian et al., U.S.P. Convention, Rockville, Md. (1982). The terms likewise cover biologically active human growth hormone equivalents, e.g., differing in one or more amino acid(s) in the overall sequence. Furthermore, the terms used in this application are intended to cover substitution, deletion and insertion amino acid variants of hGH, or posttranslational modifications. Two species of note are the 191 amino acid native species (somatropin) and the 192 amino acid N-terminal methionine (met) species (somatrem) commonly obtained recombinantly.

The term "pharmaceutically effective amount" of hGH refers to that amount that provides therapeutic effect in an administration regimen. The compositions hereof are prepared containing amounts of hGH at least about 0.1 mg/ml, upwards of about 10 mg/ml, preferably from about 1 mg/ml to about 20 mg/ml, more preferably from about 1 mg/ml to about 5 mg/ml. For use of these compositions in administration to human patients suffering from hypopituitary dwarfism, for example, these compositions contain from about 0.1 mg/ml to about 10 mg/ml, corresponding to the currently contemplated dosage regimen for the intended treatment. The concentration range is not critical to the invention, and may be varied by the clinician.

B. General Methods

The instant invention has no requirement for glycine. Glycine is an optional component of the aqueous formulation, although with less advantage in the aqueous formulations hereof compared with those formulations that are lyophilized for later reconstitution. Amounts of glycine will range from 0 mg/ml to about 7 mg/ml.

Non-ionic surfactants include a polysorbate, such as polysorbate 20 or 80, etc., and the poloxamers, such as poloxamer 184 or 188, Pluronic® polyols, and other ethylene/polypropylene block polymers, etc. Amounts effective to provide a stable, aqueous formulation will be used, usually in the range of from about 0.1% (w/v) to about 5% (w/v), more preferably, 0.1% (w/v) to about 1% (w/v). The use of non-ionic surfactants permits the formulation to be exposed to shear and surface stresses without causing denaturation of the protein. For example, such surfactant-containing formulations are employed in aerosol devices such as those used in pulmonary dosing and needleless jet injector guns.

Buffers include phosphate, Tris, citrate, succinate, acetate, or histidine buffers. Most advantageously, the buffer is in the range of about 2 mM to about 50 mM. The preferred buffer is a sodium citrate buffer.

A preservative is included in the formulation to retard microbial growth and thereby allow "multiple use" packaging of the hGH. Preservatives include phenol, benzyl alcohol, meta-cresol, methyl paraben, propyl paraben, benzalconium chloride, and benzethonium chloride. The preferred preservatives include 0.2–0.4% (w/v) phenol and 0.7–1% (w/v) benzyl alcohol.

Suitable pH ranges, adjusted with buffer, for aqueous hGH formulation are from about 4 to 8, more preferably about 5.5 to about 7, most advantageously 6.0. Preferably, a buffer concentration range is chosen to minimize deamidation, aggregation, and precipitation of hGH.

Mannitol may optionally be included in the aqueous hGH formulation. The preferred amount of mannitol is about 5 mg/ml to about 50 mg/ml. As an alternative to mannitol, other sugars or sugar alcohols are used, such as lactose, trehalose, stachiose, sorbitol, xylitol, ribitol, myoinositol, galactitol, and the like.

Neutral salts such as sodium chloride or potassium chloride are optionally used in place of sugars or sugar alcohols. The salt concentration is adjusted to near isotonicity, depending on the other ingredients present in the formulation. For example, the concentration range of NaCl may be 50–200 mM, depending on the other ingredients present.

In a preferred embodiment, the formulation of the subject invention comprises the following components at pH 6.0.

Ingredient	Quantity (mg)
hGH	5
Sodium Chloride	9.8
Polysorbate 20	20
Sorbitol (mannitol)	25
Phenol	25
Sterile water	1 ml

It will be understood that the above quantities are somewhat flexible within ranges, as set forth in more detail above, and that the materials are interchangeable within the component categories. That is, polysorbate 80, or a poloxamer, may be substituted for polysorbate 20, a succinate or acetate buffer could instead be employed, and alternative preservatives and different pHs could be used. In addition, more than one buffering agent, preservative, sugar, neutral salt, or non-ionic surfactant may be used. Preferably, the formulation is isotonic and sterile.

In general, the formulations of the subject invention may contain other components in amounts not detracting from the preparation of stable forms and in amounts suitable for effective, safe pharmaceutical administration. For example, other pharmaceutically acceptable excipients well known to those skilled in the art may form a part of the subject compositions. These include, for example, various bulking agents, additional buffering agents, chelating agents, antioxidants, cosolvents and the like; specific examples of these could include trimethylamine salts ("Tris buffer"), and disodium edetate.

EXPERIMENTAL EXAMPLES

A. Assay Methods

Anion exchange chromatography (HPIEC) was run on a TSK DEAE 5PW column (1.0×7.5 cm) at 45° C. with a flow rate of 0.5 ml/min. The column was equilibrated in 50 mM potassium phosphate, pH 5.5, containing 10% (w/v) acetonitrile.

Elution was performed using a 25 minute gradient from 50–100 mM potassium phosphate, pH 5.5 with constant 10% (w/v) acetonitrile. The column load was 83 μg of protein. Detection was at 230 nM.

Nondenaturing size exclusion chromatography was run on a TSK 2000 SWXL column in 50 mM sodium phosphate, pH 7.2 containing 150 mM sodium chloride. The flow rate was 1 ml/min, with a 50–75 μg column load and detection at either 214 and 280 nm.

Denaturing size exclusion chromatography was run on a Zorbax GF250 column in 200 mM sodium phosphate, pH 6.8–7.2/0.1% SDS. The flow rate was 1.0 ml/minute, with a with a 50–75 μg column load and detection at either 214 and 280 nm.

B. Formulation Preparation

In general, aqueous hGH formulation samples for analysis in these experimental examples were prepared by buffer exchange on a gel filtration column. The elution buffer contained either sodium chloride or mannitol, buffer and the non-ionic surfactant in their final ratios. This resulting

solution was diluted to a desired hGH concentration and the preservative was added. The solution was sterile filtered using a sterilized membrane filter (0.2 micron pore size or equivalent) and filled into sterile 3 cc type I glass vials, stoppered and sealed with aqueous-type butyl rubber stoppers and aluminum flip-off type caps.

The aqueous hGH formulation used in the experimental examples consisted of 5.0 mg somatropin (Genentech, Inc.), 45.0 mg mannitol, 2.5 mg phenol, 2.0 mg polysorbate 20, and 2.5 mg sodium citrate, pH 6.0, per ml of solution. The lyophilized formulation used as a reference for comparison in the examples consisted of 5.0 mg somatropin, 1.7 mg glycine, 45.0 mg mannitol, 1.7 mg sodium phosphate, 9 mg benzyl alcohol per ml sterile solution after reconstitution.

C. Example I

Chemical Stability of the Aqueous Formulation

Vials of the hGH aqueous formulation (lots 12738/55-102 and 12738/55-105) were incubated at either recommended storage temperatures of 2°–8° C., or elevated storage temperatures of 15° C., or 25° C., and then removed at various time points and assayed for changes in pH, color and appearance, and protein concentration. In addition, samples were incubated at 40° C. in order to study degradation patterns under extreme stress conditions. Degradation patterns for the aqueous formulation were also compared to the known degradation patterns for lyophilized growth hormone.

After storage at 2°–8° C. for up to one year, the aqueous formulation showed insignificant changes in pH, color and appearance, and protein concentration. Nondenaturing size exclusion HPLC performed on samples stored for up to one year at 2°–8° C. showed no significant aggregation of the drug product (FIG. 1). This result is unexpected in light of the teaching of U.S. Pat. No. 5,096,885 that glycine contributes to preventing aggregation in the lyophilized preparation.

At temperatures above 8° C., little or no changes in pH or protein concentration were observed over time. Visual inspection revealed an increase in opalescence with time for samples stored at 40° C. This change was minimal during storage at 15°–25° C. and has not been observed during 2°–8° C. storage.

The amount of degradation product was calculated as an area percentage of the total hGH area of the chromatogram. The rate constant for each reaction was then calculated by subtracting the percentage of degradation product from 100%, taking the $\log_{10}$ and plotting against the time in days. The slope of a straight line to fit these data was used as the reaction constant (k). Arrhenius analysis was done by plotting the natural logarithm (ln) of the absolute value of each calculated reaction rate constant at 15°, 25°, and 40° C. as a function of the inverse absolute temperature and then extrapolating to 5° C. Arrhenius and real time rate analysis (FIG. 2) of data from the size exclusion HPLC indicate that the amount of growth hormone aggregation after 18 months of storage will be less than 1% (w/v).

Anion exchange HPLC analysis performed on the aqueous hGH formulation stored at 40° C. indicated an increase in acidic peaks over 28 days (FIG. 3). Three of these peaks, eluting at about 16, 17.5, and 26 minutes, were produced by hGH deamidation at positions 149, 152, and 149 plus 152. Arrhenius and real time rate analysis (FIG. 4) of data from this method, were plotted as described above, and indicate that the amount of deamidated hGH in these lots after 18 months of storage at 2°–8° C. will be about 9% (w/v). This includes an initial amount of about 2.4% (w/v) deamidated hGH at time zero. Values as high as 15% (w/v) deamidation have been reported for other hGH products (Larhammar, H., et al., (1985) *Int. J. Pharmaceutics* 23:13–23). Although the rate of deamidation is faster in the aqueous state, this rate is minimized at pH 6.0 and below.

D. Example II

Physical Stability of the Aqueous Formulation

Each of six vials of lyophilized growth hormone were reconstituted with 1 ml bacteriostatic water for injection (BWFI) U.S.P. After dissolving, the contents were transferred to 3 cc vials, stoppered, and capped to provide the same configuration as that for the aqueous formulation. The six vials of the hGH aqueous formulation and six vials of reconstituted lyophilized hGH were vigorously shaken top to bottom in a horizontal fashion on a Glas-Col Shaker-in-die-Round at 240 jolts per minute using a stroke setting of 2.5, giving a horizontal displacement of 8±1 cm for up to 24 hours at room temperature to assess the effects of agitation on physical stability of the hGH aqueous formulation. All twelve samples were placed in a straight line on the shaker to assure that they were all exposed to the same force for each formulation. Two vials were removed for assays at 30 minutes, 6 hours, and 24 hours.

The results are displayed in Table I. Agitation produced very little change in the visual clarity of the aqueous formulation. There was no change in the content of total growth hormone monomer as detected by a nondenaturing size exclusion HPLC assay. This assay detects noncovalent aggregates, which are completely dispersed by SDS in a denaturing size exclusion HPLC assay.

By comparison, these results also demonstrated that the reconstituted lyophilized product was more sensitive to treatment, even after only 30 minutes of shaking. This sensitivity is typical for all currently available formulations of hGH, other than the aqueous formulation of the instant invention. The inclusion of the non-ionic surfactant is the most important factor in preventing this phenomenon from occurring.

TABLE I

Effects of Agitation at Room Temperature on hGH Aqueous Formulation vs. Reconstituted Lyophilized Formulation

Sample	Color/Appearance	% HPSEC Monomer	% Soluble Protein	% Total[1] Monomer
Unshaken				
Aqueous	clear/colorless	99.7	ND	ND
Aqueous	clear/colorless	99.8	ND	ND
Lyophilized	clear/colorless	99.6	100	99.0
Lyophilized	clear/colorless	ND	ND	ND
Shaken 0.5 hr				
Aqueous	very slightly opalescent/colorless	99.9	100	99.9
Aqueous	very slightly opalescent/colorless	100.0	100	100.0
Lyophilized	slightly opalescent/colorless	99.6	100	99.6
Lyophilized	clear/colorless	92.8	100	92.8

TABLE I-continued

Effects of Agitation at Room Temperature on hGH Aqueous Formulation vs Reconstituted Lyophilized Formulation

Sample	Color/Appearance	% HPSEC Monomer	% Soluble Protein	% Total Monomer
Shaken 6 hr				
Aqueous	slightly opalescent/ colorless	99.9	100	99.9
Aqueous	opalescent/colorless	99.4	100	99.4
Lyophilized	very opalescent/yellow to brown	87.5	79	69.1
Lyophilized	very opalescent/yellow to brown	92.7	91.7	84.9
Shaken 24 hr				
Aqueous	slightly opalescent/ colorless	99.8	100	99.8
Aqueous	clear/colorless	99.8	ND	ND
Lyophilized	very cloudy/yellow to brown	80.6	21.5	13.9
Lyophilized	very cloudy/yellow to brown	93.7	14.8	9.4

"Total monomer" = % monomer × % soluble protein/100

E. Example III

Preservative Effectiveness in the Aqueous Formulation

Samples of hGH aqueous formulation were subjected to bacterial challenge according to an abbreviated challenge using the standard U.S.P. test. In this test, a suspension of either *E. coli* or *S. aureus* was added to an aliquot of hGH aqueous formulation to give a final concentration of bacteria between 10^5 to 10^6 CFU/ml. Viable bacteria remaining in the tubes were counted immediately and after 4 and 24 hours incubation at 20°–25° C. The percentage change in the concentration of the microorganisms during the challenge was calculated according to the following equation:

$$\% \text{ initial titer} = \frac{\text{titer at } T = X \text{ hours} \times 100}{\text{titer at } T = 0}$$

The results of this experiment indicated that for two species of bacteria, concentrations of viable bacteria were reduced to less than 0.01% of the initial concentrations after 24 hours.

F. Example IV

Substitution of Mannitol with Salt

In this experiment aqueous formulations of hGH were compared that varied in concentrations of salt, mannitol, and non-ionic surfactant. All formulations contained 5 mg/ml hGH/0.25% (w/v) phenol/10 mM sodium citrate, pH 6.0. Samples were stored 3–4 months at 2°–8° C. FIG. 5 indicates the percentage monomer present in the indicated formulations. The Table below indicates the composition of each formulation. These results demonstrate the unexpected stability of hGH in a formulation in which mannitol has been substituted with a neutral salt in the presence of a surfactant.

TABLE 3

Formulations Tested in FIG. 5

Formulation #	Composition
42	0.1% (w/v) polysorbate 20 50 mM mannitol
49	0.1% (w/v) poloxamer 188 0.1M NaCl
51	0.5% (w/v) polysorbate 20 50 mM mannitol
52	0.1% (w/v) poloxamer 188 50 mM mannitol
53	0.1% (w/v) poloxamer 184 50 mM mannitol
60	0.2% (w/v) polysorbate 20 0.1M NaCl
61	0.2% (w/v) polysorbate 20 0.05M NaCl
62	0.2% (w/v) polysorbate 20 0.15M NaCl
63	0.2% (w/v) polysorbate 20 50 mM mannitol

We claim:

1. A human growth hormone formulation comprising:

a) 1 mg/ml to 20 mg/ml human growth hormone,

b) buffer system providing pH 5.5 to pH 7,

c) 0.1% w/v to 1% w/v nonionic surfactant, and

d) 50 mM to 200 mM of neutral salt

in a sterile injectable aqueous vehicle,

wherein said formulation is a long term cold temperature storage stable for 6 to 18 months at 2° to 8° C., directly injectable, pharmaceutically acceptable liquid, free of glycine and mannitol.

2. The formulation of claim 1 wherein the nonionic surfactant is a poloxamer.

3. The formulation of claim 2 wherein the poloxamer is poloxamer 188 or poloxamer 184.

4. The formulation of claim 1 wherein the nonionic surfactant is a polysorbate.

5. The formulation of claim 4 wherein the polysorbate is polysorbate 20 or polysorbate 80.

6. The formulation of claim 1 wherein the neutral salt is sodium chloride or potassium chloride.

7. The formulation of claim 1 wherein the buffer buffers the formulation to about pH 6.

8. The formulation of claim 1 wherein the buffer is selected from the group consisting of citrate, phosphate, Tris, succinate, acetate, and histidine buffers.

9. A human growth hormone formulation consisting essentially of:

a) 1 mg/ml to 20 mg/ml human growth hormone,

b) buffer system providing pH 5.5 to pH 7,

c) 0.1% w/v to 1% w/v nonionic surfactant,

d) 50 mM to 200 mM of neutral salt and

e) a preservative,

in a sterile injectable aqueous vehicle,

wherein said formulation is a long term cold temperature storage stable for 6 to 18 months at 2° to 8° C. directly injectable, pharmaceutically acceptable liquid free of glycine and mannitol

10. The formulation of claim 9 wherein the nonionic surfactant is a poloxamer.

11. The formulation of claim 10 wherein the poloxamer is poloxamer 188 or poloxamer 184.

12. The formulation of claim 9 wherein the nonionic surfactant is a polysorbate.

13. The formulation of claim 12 wherein the polysorbate is polysorbate 20 or polysorbate 80.

14. The formulation of claim 9 wherein the neutral salt is sodium chloride or potassium chloride.

15. The formulation of claim 9 wherein the buffer buffers the formulation to about pH 6.

16. The formulation of claim 9 wherein the buffer is selected from the group consisting of citrate, phosphate, Tris, succinate, acetate, and histidine buffers.

17. The formulation of claim 9 wherein the preservative is selected from the group consisting of phenol, benzyl alcohol, meta-cresol, methyl paraben, propyl paraben, benzalkonium chloride, and benzethonium chloride.

18. A directly injectable aqueous human growth hormone formulation consisting of

5 mg/ml human growth hormone,

8.8 mg/ml sodium chloride,

2.0 mg/ml polysorbate 20,

2.5 mg/ml sodium citrate, and

0.5 mg/ml phenol

in a pH 6 buffered aqueous vehicle;

wherein said formulation is a long term cold temperature storage stable for 6 to 18 months at 2° to 8° C., directly injectable, pharmaceutically acceptable liquid, free of glycine and mannitol.

19. The formulation of claim 18 packaged in stoppered and capped sterile glass vials.

20. A method for using human growth hormone comprising the steps of

A) formulating said human growth hormone into an aqueous liquid formulation comprising:

a) 1 mg/ml to 20 mg/ml human growth hormone,

b) buffer system providing pH 5.5 to pH 7,

c) 0.1% w/v to 1% w/v non-ionic surfactant, and

d) 50 mM to 200 mM of neutral salt

in a pharmaceutically acceptable, injectable sterile aqueous vehicle, said formulation being free of glycine and mannitol;

B) storing said formulation as an aqueous liquid for from six to 18 months at 2° C. to 8° C. thereby forming a stored formulation; and

C) directly injecting said stored formulation into a patient in need of human growth hormone therapy.

21. A method for using human growth hormone comprising the steps of

A) formulating said human growth hormone into an aqueous liquid formulation consisting essentially of:

a) 1 mg/ml to 20 mg/ml human growth hormone,

b) buffer system providing pH 5.5 to pH 7,

c) 0.1% w/v to 1% w/v nonionic surfactant,

d) 50 mM to 200 mM of neutral salt and

e) a preservative,

in a pharmaceutically acceptable, injectable sterile aqueous vehicle said formulation being free of glycine and mannitol;

B) storing said formulation as an aqueous liquid for from six to 18 months at 2° C. to 8° C. thereby forming a stored formulation; and

C) directly injecting said stored formulation into a patient in need of human growth hormone therapy.

22. The method of claim 21 wherein in the aqueous liquid formulation

the human growth hormone is present at 5 mg/ml,

the buffer system is a sodium citrate buffer providing pH 6,

the polysorbate nonionic surfactant is 2.0 mg/ml polysorbate 20,

the neutral salt is 8.8 mg/ml sodium chloride and

the preservative is 0.5 mg/ml phenol.

23. A method for using human growth hormone comprising the steps of

A) formulating said human growth hormone into an aqueous liquid formulation comprising:

a) 1 mg/ml to 20 mg/ml human growth hormone,

b) buffer system providing pH 5.5 to pH 7,

c) 0.1% w/v to 1% w/v non-ionic surfactant, and

d) 50 mM to 200 mM of neutral salt

in a pharmaceutically acceptable, injectable sterile aqueous vehicle;

B) storing said formulation as an aqueous liquid for from six to at least 18 months at 2° C. to 8° C. thereby forming a stored formulation; and

C) directly injecting said stored formulation into a patient in need of human growth hormone therapy.

* * * * *

14. PATENT CERTIFICATION WITH RESPECT TO ANY PATENT WHICH CLAIMS THE DRUG

All investigations in this application were conducted by or for the applicant; hence, this section is not applicable.

Exclusivity Checklist

NDA: 20-522-S009				
Trade Name: Nutropin AQ				
Generic Name: (somatropin [rDNA origin] injection)				
Applicant Name: Genentech, Inc.				
Division: DMEDP, HFD-510				
Project Manager: Celyssa King				
Approval Date:				
PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?				
1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.				
a. Is it an original NDA?	Yes		No	✓
b. Is it an effectiveness supplement?	Yes	✓	No	
c. If yes, what type? (SE1, SE2, etc.)	SE-8			
Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")	Yes	✓	No	
If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.				
Explanation:				
If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:				
Explanation: TO add CLIN PHARM regarding IMPROVEMENT in spine BMD.				
d. Did the applicant request exclusivity?	Yes		No	✓
If the answer to (d) is "yes," how many years of exclusivity did the applicant request?				
IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS.				
2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?	Yes		No	✓
If yes, NDA #				
Drug Name:				
IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE				

BLOCKS.				
3. Is this drug product or indication a DESI upgrade?	Yes		No	✓
IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS (even if a study was required for the upgrade).				
PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES				
(Answer either #1 or #2, as appropriate) NOT APPLICABLE				
1. Single active ingredient product.	Yes		No	
Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.	Yes		No	
If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).				
Drug Product				
NDA #				
Drug Product				
NDA #				
Drug Product				
NDA #				
2. Combination product.	Yes		No	
If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)	Yes		No	
If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).				
Drug Product				
NDA #				
Drug Product				
NDA #				
Drug Product				
NDA #				

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS. IF "YES," GO TO PART III.				
PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS				
To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."				
1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.	Yes	✓	No	
IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS.				
2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application. For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.				
a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?	Yes	✓	No	
If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCKS.**				
Basis for conclusion: —				
b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?	Yes		No	✓
1) If the answer to 2 b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.	Yes		No	
If yes, explain:				

2) If the answer to 2 b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?	Yes		No	✓
If yes, explain:				
c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:				
Investigation #1, Study #: M0381g	IND			
Investigation #2, Study #:				
Investigation #3, Study #:				
3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.				
a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")				
Investigation #1	Yes		No	✓
Investigation #2	Yes		No	
Investigation #3	Yes		No	
If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:				
Investigation #1 -- NDA Number				
Investigation #2 -- NDA Number				
Investigation #3 -- NDA Number				
b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?				
Investigation #1	Yes		No	✓
Investigation #2	Yes		No	
Investigation #3	Yes		No	
If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:				
Investigation #1 -- NDA Number				
Investigation #2 -- NDA Number				
Investigation #3 -- NDA Number				
If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):				
Investigation #1 M038[g - updated information				

Investigation #2				
Investigation #3				

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a. For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 M038 1a	Yes	✓	No	
IND#:				
Explain:				
Investigation #2	Yes		No	
IND#:				
Explain:				
Investigation #3	Yes		No	
IND#:				
Explain:				

b. For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	Yes		No	
IND#:				
Explain:				
Investigation #2	Yes		No	
IND#:				
Explain:				
Investigation #3	Yes		No	
IND#:				
Explain:				

c. Notwithstanding an answer of "yes" to (a) or (b), are there

other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)	Yes		No	✓
If yes, explain:				

BACK TO TOP

/S/

Signature of PM/CSO

Date: 11/16/99

/S/

Signature of Division Director

Date: 11/30/99

APPEARS THIS WAY
ON ORIGINAL

cc: 20-522
Original NDA
Division File
HFD-93 Mary Ann Holovac

BACK TO TOP

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

BLA # 20-522 Supplement # 009 Circle one (SE1) SE2 SE3 SE4 SE5 SE6 (SE8)

Nutropin AQ (somatropin [rDNA origin])

HFD-510 Trade and generic names/dosage form: ~~_____~~ injection) Action: (AP) AE NA

Applicant Genentech Therapeutic Class growth hormones

Pediatric patients: (1) long-term Tx of growth failure due to lack of adequate endogenous GH secretion;

Indication(s) previously approved (2) Tx of growth failure associated with chronic renal insufficiency; (3) Tx of short stature for Turner syndr

Pediatric information in labeling of approved indication(s) is adequate ✓ inadequate ___ Adult patients: replacement of endogenous GH who me specified criteri

Proposed indication in this application no change

FOR SUPPLEMENTS, ANSWER THE FOLLOWING QUESTIONS IN RELATION TO THE PROPOSED INDICATION.

IS THE DRUG NEEDED IN ANY PEDIATRIC AGE GROUPS? ___Yes (Continue with questions) ✓No (Sign and return the form)

WHAT PEDIATRIC AGE GROUPS IS THE DRUG NEEDED? (Check all that apply)

___Neonates (Birth-1month) ___Infants (1month-2yrs) ___Children (2-12yrs) ___Adolecents(12-16yrs)

___ 1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

___ 2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

___ 3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

___ a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

___ b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.

___ c. The applicant has committed to doing such studies as will be required.

___ (1) Studies are ongoing,

___ (2) Protocols were submitted and approved.

___ (3) Protocols were submitted and are under review.

___ (4) If no protocol has been submitted, attach memo describing status of discussions.

___ d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

___ 4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

___ 5. **If none of the above apply, attach an explanation, as necessary.**

ARE THERE ANY PEDIATRIC PHASE IV COMMITMENTS IN THE ACTION LETTER? ___Yes ✓No

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

This page was completed based on information from Medical team leader (e.g., medical review, medical officer, team leader)

/S/ 11/5/99

Signature of Preparer and Title Date

Orig NDA/~~BLA~~ # 20-522-S 009

HFD-510 /Div File

NDA/~~BLA~~ Action Package

HFD-006/ KRoberts

(revised 10/20/97)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, KHYATI ROBERTS, HFD-6 (ROBERTSK)

16. DEBARMENT CERTIFICATION

[Section 306(k)(1) of the Act (21 U.S.C. 335a(k)(1)]

This is to certify that Genentech, Inc. has not and will not use, in any capacity, the services of any person debarred under subsections (a) or (b) [Section 306(a) or (b)], in connection with this Supplemental New Drug Application (NDA).

Signed by: _____

Robert L. Garnick, Ph.D

Title: Vice President, Regulatory Affairs

Date: 11/5/99

Date: November 1, 1999

54

From: Saul Malozowski
Medical Officer

Subject: NDA ~~20252~~ 20522 S009, Nutropin AQ changes in bone mineral density; Team Leader Memo

To: The file

I concur with the contents of this NDA review and with the recommendations proposed by the reviewers.

I concur 11-30-99

/S/

Division of Metabolic and Endocrine Drug Products, HFD-510

Review of Draft Labeling

Application Number: 20-522/S-009

Name of Drug: Nutropin AQ® (somatropin [rDNA origin] injection)

Sponsor: Genentech, Inc.

Material Reviewed

Submission Date: November 5, 1999

Receipt Date: November 8, 1999

Review

The draft labeling submitted on November 5, 1999 has been reviewed. This labeling has been compared to the FPL submitted on April 30, 1999, as (Supplement-011), approved by the Agency on November 24, 1999. The changes to the draft labeling for S-009 are as follows:

1. Page 18. In the **CLIN PHAM** section, under the **Mineral Metabolism** subsection, there is an additional statement regarding increases in serum alkaline phosphatase.

2. Page 28. In the **CLIN PHARM** section, under the subsection **Adult Growth Hormone Deficiency (GHD)**, there is an additional paragraph regarding an increase in spine bone mineral density.

The above changes are highlighted and attached to this review and are acceptable.

/S/ 11/24/99
Dwayne Keels

/S/ 11/24/99
Crystal King, P.D., M.G.A.

/S/ 11/29/99
Enid Galliers, CPMS

/S/ 11/30/99
Saul Malozowski, M.D.

/S/ 11/30/99
Joy Mele, Statistician

/S/ 11/30/99
Todd Sahlroot, Statistical TL

cc:
HFD-510/DivFile
HFD-510/Keels

RECORD OF TELEPHONE CONVERSATION/MEETING	Date: November 1, 1999
At 12:00 noon, EST, I left a voice message for Shawn requesting that a NEW final draft label amendment be submitted. The final draft label submitted on 10/29/99 contained two errors to be corrected to: (1) (2) in Contraindications: Further, I requested that the debarment statement and patent information and statement be submitted. APPEARS THIS WAY ON ORIGINAL /S/ 11/1/99 **Crystal King, P.D., M.G.A.,** **Regulatory Project Manager**	**NDA#: 19-676-013** **20-522-009** **Telecon/Meeting initiated by:** ○ Applicant/Sponsor ● FDA **By:** Telephone **Product Name:** Nutropin **Firm Name:** Genentech **Name and Title of Person with whom conversation was held:** Shawn McLaughlin **Phone:** 650-225-1915

cc: NDA 19-676
NDA 20-522
Div Files

Genentech, Inc.
Genentech, Inc.
Genentech, Inc.
Genentech, Inc.
Genentech, Inc.

1 DNA Way
South San Francisco, CA 94080-4990 USA
Phone: (650) 225-2631
Fax: (650) 225-3117
E-mail: kma@gene.com

October 12, 1999

Saul Malozowski, MD, PhD, Medical Team Leader
Division of Metabolic and Endocrine Drug Products, HFD-510
Center for Drug Evaluation and Research, Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Subject: Nutropin NDA 19-676, S-013, Bone Mineral Density Label

Dear Dr. Malozowski:

Please see the attached revised PI proposal based on our discussion today. You can respond via FAX to the regulatory department at 650-225-1397. Thank you for your careful consideration of this.

Sincerely,

Ken Attie

Kenneth M. Attie, MD
Sr. Clinical Scientist, Genentech, Inc

Genentech, Inc.
Genentech, Inc.
Genentech, Inc.
Genentech, Inc.
Genentech, Inc.

1 DNA Way
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Phone: (650) 225-2631
Fax: (650) 225-3117
E-mail: kma@gene.com

October 8, 1999

Saul Malozowski, MD, PhD, Medical Team Leader
Division of Metabolic and Endocrine Drug Products, HFD-510
Center for Drug Evaluation and Research, Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Subject: Nutropin NDA 19-676, S-013, Bone Mineral Density Label

Dear Dr. Malozowski:

Thank you for sending to us the proposed wording for the BMD data to be added to the adult GHD section of the Nutropin label. Please see the attached proposal we have come up with after some internal discussions. We have performed some statistical calculations where you had blanks for data. In general, the p-values are derived from Wilcoxon sign rank (within group) and rank sum (between groups) tests. We have tried to include all of the major points you want to make, while revising the wording to add clarification. Please send your comments to me directly via FAX at 650-225-3117 (work) or 415-664-4494 (home). Feel free also to call at home at 415-664-4550.

Sincerely.

Ken Attie

Kenneth M. Attie, MD
Sr. Clinical Scientist, Genentech, Inc

KMS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-522/S-009

FEB 17 1999

Genentech, Inc.
1 DNA Way
South San Francisco, CA 94080

Attention: Robert L. Garnick, Ph.D.
Vice President, Regulatory Affairs

Dear Dr. Garnick:

We acknowledge receipt of your supplemental application for the following:

Name of Drug:	Nutropin AQ® (somatropin (rDNA) injection)
NDA Number:	20-522
Supplement Number:	S-009
Date of Supplement:	January 29, 1999
Date of Receipt:	February 1, 1999

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on April 2, 1999, in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Attention: Document Control Room 14B-19
5600 Fishers Lane
Rockville, MD 20857

Sincerely

/S/

Enid Galliers
Chief, Project Management Staff
Division of Metabolic and Endocrine
Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Genentech, Inc.

1 DNA Way
South San Francisco, CA 94080-4990
(650) 225-1000
FAX: (650) 225-6000

November 5, 1999

Solomon Sobel, M.D.
Director
Division of Metabolic and
Endocrine Drug Products, HFD-510
Center for Drug Evaluation and Research
Food and Drug Administration
Attn: Document Control Room, 14B-03
5600 Fishers Lane
Rockville, MD 20857

Subject: **NDA 20-522, S-009**
Nutropin AQ® [somatropin (rDNA origin) injection]
Supplement—Additional Label Claim
Bone Mineral Density
Information Amendment

Dear Dr. Sobel:

Reference is made to our Supplemental New Drug Application, NDA 20-522, S-009 for Nutropin AQ® [somatropin (rDNA origin) injection], to provide an additional label claim of improved bone mineral density (BMD) in adults with growth hormone deficiency. The original supplement was submitted on January 29,1999 and final draft labeling was submitted October 29, 1999.

This submission provides revised final draft labeling to correct two minor typographical errors that were noted by the Agency in our October 29 submission and communicated by Ms. Crystal King.

- (Page 13 of label, 2nd paragraph, 3rd sentence): [redacted] has been corrected to be [redacted]
- (Page 15, CONTRAINDICATIONS, 1st paragraph, 2nd sentence): [redacted] has been corrected to be "non-growth

[redacted] (Please note that this error appeared in the draft labeling submitted to this supplement, but the wording is correct in our current FPL for Nutropin AQ)

In addition, this submission provides the following items requested by Ms. King on November 1, 1999 that were not included in the original supplement:

- Patent information
- Patent certification
- Debarment certification
- Categorical exclusion statement for Environmental Assessment

Please note that this supplement is based on established bioequivalence to lyophilized Nutropin [redacted]

Should you have any further questions regarding this submission please contact Mr. Shawn McLaughlin of my staff at (650) 225-1915.

Sincerely,

Robert L. Garnick, Ph.D.
Vice President
Regulatory Affairs

Genentech, Inc.

[illegible]

October 29, 1999

Solomon Sobel, M.D.
Director
Division of Metabolic and
Endocrine Drug Products, HFD-510
Center for Drug Evaluation and Research
Food and Drug Administration
Attn: Document Control Room, 14B-03
5600 Fishers Lane
Rockville, MD 20857

Subject: **NDA 20-522, S-009**
Nutropin AQ® [somatropin (rDNA origin) injection]
Supplement: Additional Label Claim
Bone Mineral Density
Final Draft Labeling

Dear Dr. Sobel:

Reference is made to our Supplemental New Drug Application, NDA 20-522, S-009 for Nutropin AQ® [somatropin (rDNA origin) injection], to provide an additional label claim of improved bone mineral density (BMD) in adults with growth hormone deficiency. Specifically, we refer to the draft package insert (PI). The first draft PI was submitted with the original supplement on January 29, 1999. This submission supersedes that earlier version.

Included in this submission is an annotated (the new change is indicated by underlined text), as well as a clean version of the final draft labeling.

Please note that this supplement is based on established bioequivalence to lyophilized Nutropin.

[redacted]

Should you have any questions regarding this submission please contact Mr. Shawn McLaughlin of my staff at (650) 225-1915.

Sincerely,

Robert L. Garnick, Ph.D.
Vice President
Regulatory Affairs

20522-097 sub rer

Genentech, Inc.

1 DNA Way
South San Francisco, CA 94080-4990
(650) 225-1000
FAX (650) 225-6000

NDA SUPP AMEND
SE8-009-00
SNC
DUPLICATE

August 11, 1999

Solomon Sobel, M.D.
Director
Division of Metabolic and
Endocrine Drug Products, HFD-510
Center for Drug Evaluation and Research
Food and Drug Administration
Attn: Document Control Room, 14B-03
5600 Fishers Lane
Rockville, MD 20857

Subject: **NDA 20-522, S-009**
Nutropin AQ® [somatropin (rDNA origin) injection]
Supplement - Additional Label Claim
Bone Mineral Density
Request for Waiver of Requirement to Conduct Pediatric Studies
[21CFR 201.23(a)]

Dear Dr. Sobel:

Reference is made to our Supplemental New Drug Application, NDA 20-522, S-009, for Nutropin AQ® [somatropin (rDNA origin) injection], submitted on January 29, 1999 for an additional label claim of improved bone mineral density (BMD) with Nutropin AQ treatment in adults with growth hormone deficiency.

Further to a telephone conversation with Crystal King of your office, and in regard to the FDA Final Rule: Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients, we are requesting a waiver from the requirements of 21CFR 201.23(a), under subpart (c)(1), on the basis that adequate pediatric studies have already been performed with Nutropin AQ and Nutropin® [somatropin (rDNA origin) for injection].

20522-095 sub ss

The studies already performed in pediatrics include:

- Study L0368g in NDA 20-522, and studies 86-061 and 87-070 in NDA 19-676, for pediatric growth hormone deficiency.
- Studies 87-069 and M0079g in NDA 20-168, for growth failure associated with chronic renal insufficiency.
- Study 85-044 in NDA 20-656, for short stature associated with Turner syndrome.
- Study M0380g in IND [redacted], for pubertal dosing in pediatric growth hormone deficiency.
- Phase IV study P0583n, and on-going National Cooperative Growth Study.

Should you have any further questions regarding this submission please contact Mr. Shawn McLaughlin of my staff at (650) 225-1915.

Sincerely,

Robert L. Garnick, Ph.D.
Vice President
Regulatory Affairs

20522-095 sub ss

ORIGINAL

Genentech, Inc.

1 DNA Way
South San Francisco, CA 94080-4990
(650) 225-1000
FAX (650) 225-6000

NDA NO. 20-522 REF NO. 009
NDA SUPPL FOR SLR

January 29, 1999

Solomon Sobel, M.D.
Director
Division of Metabolic and
Endocrine Drug Products, HFD-510
Center for Drug Evaluation and Research
Food and Drug Administration
Attn: Document Control Room, 14B-03
5600 Fishers Lane
Rockville, MD 20857

REVIEWS COMPLETED	
CSO ACTION: ☐ LETTER ☐ N.A.I. ☐ MEMO	
CSO INITIALS	DATE

Subject: **NDA 20-522**
Nutropin AQ® [somatropin (rDNA origin) injection]
Supplement - Additional Label Claim
Bone Mineral Density

Dear Dr. Sobel:

Reference is made to our New Drug Application, NDA 20-522, for Nutropin AQ® [somatropin (rDNA origin) injection], initially approved on December 29, 1995. As is reflected in the currently approved labeling, Nutropin AQ has been determined to be bioequivalent to lyophilized Nutropin®, based on the statistical evaluation of AUC and C_{max}.

A supplement describing additional data regarding the positive effect of Nutropin treatment on spine bone mineral density in adult growth hormone deficient patients is being submitted to NDA 19-676. This Nutropin supplement is therefore cross-referenced and the data contained therein is considered to be applicable to Nutropin AQ, based on the established bioequivalence of the two products. This revised labeling for Nutropin AQ is being submitted concurrently with the labeling supplement for lyophilized Nutropin in order to make possible a simultaneous review of the BMD claim for both Nutropin and Nutropin AQ.

Enclosed is a revised package insert for Nutropin AQ® [somatropin (rDNA origin) injection] with the bone mineral density claim added. The new change is indicated by underlined text.

20522-087 sub ss

This submission contains no preclinical data and the labeling change is not under the purview of Pharmacology; thus, we would have no objection to filing of this labeling change supplement. No review necessary. /S/ 2/9

Should you have any questions regarding this submission please contact Ms. Fiona Cameron of my staff at (650) 225-1818.

Sincerely,

Robert L. Garnick, Ph.D.
Vice President
Regulatory Affairs

20522-087 sub ss

Date: November 1, 1999 /S/

From: Saul Malozowski
Medical Officer

Subject: NDA ~~20252~~ 20522-S009, Nutropin AQ changes in bone mineral density; Biopharm review

To: The file

This NDA supplement was an extension of the original studies that composed this NDA. The original NDA review covered all relevant biopharmaceutical issues. Thus, it was determined that a biopharm review was not required for this supplement.

APPEARS THIS WAY
ON ORIGINAL