CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-075

STATISTICAL REVIEW(S)

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STATISTICAL REVIEW AND EVALUATION
CLINICAL STUDIES

NDA #: 21-075

Drug: Nutropin Depot (somatropin)

Class: 3P

Sponsor: Genentech, Inc.

Indication: Treatment of growth failure due to lack of adequate endogenous growth hormone secretion

Date of Submission: June 25, 1999

Volume Numbers in Statistical Section: Volumes 1-6

Medical Input: Robert Perlstein, M.D. (HFD-510)

Introduction

The sponsor has submitted the results of two clinical trials (03-002 and 03-004, Table 1) and one extension study (03-003) to demonstrate the efficacy of Nutropin Depot for the treatment of growth failure due to lack of adequate endogenous growth hormone secretion. Nutropin Depot is a sustained-release formulation of somatropin administered once- or twice-monthly.[1]

Table 1. Brief Summary of Clinical Trials

Study Number	# of Sites	Design	Treatment Arms (N)	Duration of Treatment	Patients
03-002	12	Open label, Phase I/II	0.75 1xmonth (19) 0.75 2xmonth (20) 1.5 1xmonth (25) Total N=64	6 months	Naïve and currently treated patients
03-004	27	Open label, Randomized, Phase III	0.75 2xmonth (38) 1.5 1xmonth (36) Total N=74	6 months	Naïve patients only

After completion of 6 months in Study 03-002 or Study 03-004, patients could continue on Nutropin Depot in extension Study 03-003.

[1] Marketed formulations of somatropin presently are administered daily or 3-6 times per week.

Study [redacted]03-002 (conducted 11/96 to 7/98)

Study [redacted]03-002 is a Phase I/II, open-label, uncontrolled, non-randomized multicenter study of Nutropin Depot. A total of 64 patients (38 currently treated (CT) and 26 naïve patients) were treated at 12 centers and followed for 6 months. CT patients were switched from daily GH therapy to Depot. The primary efficacy variable was the 6-month annualized growth rate.

Patient Disposition

Table 2 depicts the number of patients assigned to the three dosage levels for CT and naïve patients separately. Nineteen patients were assigned to 0.75 mg/kg once a month, 20 to 0.75 mg/kg twice a month and 25 to 1.5 mg/kg once a month. The 19 patients dosed with once a month doses of 0.75mg/kg were entered in the trial during the first 4 months at 7 sites; based on those results, all subsequent patients that entered the trial were placed on the other two higher doses. Enrollment was complete in 11 sites when enrollment at a twelfth site began; 11 CT patients were enrolled at this 12th site. About 83% (53/64) of enrolled patients completed six months on therapy; 66% (35/53) of completers opted to continue therapy under extension Study [redacted]03-003.

Table 2. Study [redacted]03-002 Patient Disposition

	0.75 mg/kg once a month		0.75 mg/kg twice a month		1.5 mg/kg once a month	
	CT	Naïve	CT	Naïve	CT	Naive
Entered	10	9	11	9	17	8
Completed 3 months	9	9	11	9	13	8
Completed 6 months	6	7	11	9	12	8
Completed 6 months and had pre-study growth rate	6	3	11	8	12	5
Completed 12 months in [redacted]03-003	5	5	3	8	5	5

There were more dropouts among CT patients (9/38, 24%) than among naïve patients (3/26, 12%). There were no dropouts in the 0.75 mg/kg twice a month dose group. The primary reason for dropout for both CT and naïve patients was pain at injection site (Table 3).

Table 3. Study [redacted]03-002 Reasons for Discontinuation

	0.75 mg/kg once a month		0.75 mg/kg twice a month		1.5 mg/kg once a month	
	CT	Naïve	CT	Naïve	CT	Naive
Entered	10	9	11	9	17	8
Discontinued	4	2	0	0	5	1
Reasons for discontinuation						
Hypoglycemia	2	0	0	0	0	0
Injection site pain	1	2	0	0	4	0
Allergic reaction	0	0	0	0	0	1
Subject request (no reason given)	1	0	0	0	1	0

Patient Characteristics

Most of the patients were males and Caucasian; more than 90% had idiopathic GHD (Table 4). Patients' ages ranged from 3 to 14. The average age for CT patients was 9.6 years with bone-age of 8.2; the average age for naive patients was 7.7 years with bone-age of 5.6.

Table 4. Study 03-002 Patient Characteristics

	0.75 mg/kg once a month		0.75 mg/kg twice a month		1.5 mg/kg once a month	
	CT (n=10)	Naïve (n=9)	CT (n=11)	Naïve (n=9)	CT (n=17)	Naive (n=8)
Male (%)	80%	78%	55%	78%	65%	63%
Etiology (%)						
Idiopathic	90%	100%	82%	100%	94%	100%
Organic	10%	0%	18%	0%	6%	0%
Age (years)	9.3	9.3	9.4	7.4	9.9	6.3
Range	6-11	3-14	4-13	6-11	7-14	4-11
Bone Age (years)	8.1	6.9	7.9	5.5	8.5	4.0
Pre-Study Growth Rate (cm/yr)	8.3 (n=10)	5.2 (n=5)	8.6 (n=11)	5.6 (n=8)	7.9 (n=17)	5.6 (n=5)
Race (%)						
White	90%	89%	100%	78%	82%	100%
Height (cm)	131	117	126	105	128	101
Standardized Height	-0.57	-2.75	-1.51	-3.50	-1.49	-3.02

The pre-study growth rate was based on the subject's height measured closest to 1 year prior to study start; the date of measurement needed to be between about 5 months and 425 days of entrance into the study. This definition of pre-study growth rate was not included in the protocol. The NDA stated that "any pre-study growth rates based on heights outside of these boundaries were considered unreliable estimates of pre-study growth rate and were not used." Based on these criteria, all CT patients and 18 of 26 naïve patients had pre-study growth rates. The average pre-study growth rate for all CT patients was about 8 cm/yr and for the 18 naïve patients, 5.5 cm/yr. Pre-study growth rates outside of the sponsor-defined window were available for the other 8 naive patients. This reviewer included the values for those 8 naive patients that most closely met the sponsor's criteria[1] and recomputed the mean pre-study growth rate for the naive patients producing the following results:

	0.75X1	0.75X2	1.5
Pre-study growth rate	6.8	5.3	5.5

All analyses using pre-study growth rates for naive patients performed by this reviewer included the aforementioned data of the 8 naive patients.

[1] The time since baseline for the heights used in the calculations of the pre-study growth rates for these 8 patients were 86, 91, 102, 120, 154, 432, 457 and 1054 days. For 7 of these patients, these times were within 2½ months of the time range specified by the sponsor.

Sponsor's Planned Statistical Methods

For CT patients, a paired t-test was proposed in the protocol to compare the 6 month growth rate prior to entry into the study (while on a daily treatment regimen) to the 6 month growth rate on the depot. With 10 currently-treated patients, the trial was powered to detect a 2.2 cm/yr difference in 6 month growth rates prior to the study and on study.

For naïve patients, an ANCOVA with age as a covariate was planned to compare 6 month growth rates of subjects in this study to age-matched controls treated with daily GH in Genentech Study L0368g. With 21 naive patients, the trial was powered to detect a 2.7 cm/yr difference in growth rate between the 6 month growth rate of the naïve subjects in this study and the 6 month growth rate of the control subjects from Genentech Study L0368g.

Efficacy Results

Primary Efficacy Results: 6-month Annualized Growth Rate

The mean 6-month annualized growth rates for patients with 6-month data and for all patients with the last observed rate carried forward are shown in Table 5 for each group of patients. The rates for naïve patients are clearly larger than the rates observed for the CT patients for all dose levels; this would be expected since GHD patients generally show the greatest increase in growth rate during the first year of treatment.

It is interesting to note that there are no statistically significant differences among the doses (Kruskal-Wallis p-value>0.5) particularly since the 0.75 mg/kg/month dose was dropped in subsequent trials due to lack of efficacy. A comparison of 3-month annualized growth rates revealed a similar relationship among the doses.

Table 5. Study [redacted]03-002 6-month annualized growth rates

	0.75 mg/kg once a month		0.75 mg/kg twice a month		1.5 mg/kg once a month	
	CT	Naïve	CT	Naïve	CT	Naive
Pts with 6-month data						
N	6	7	11	9	12	8
Mean cm/yr (SD)	**5.2** (3.7)	**7.6** (2.3)	**5.2** (1.3)	**8.9** (3.2)	**5.0** (2.5)	**8.3** (2.6)
95% CI	(1.7, 8.7)	(5.5, 9.7)	(4.2, 6.0)	(6.5, 11.3)	(3.4, 6.6)	(6.2, 10.4)
All Pts						
N	10	9	11	9	15[1]	8
Mean cm/yr (SD)	**5.1** (3.0)	**8.0** (2.1)	**5.2** (1.3)	**8.9** (3.2)	**4.8** (2.6)	**8.3** (2.6)
95% CI	(3.0, 7.2)	(6.3, 9.6)	(4.2, 6.0)	(6.5, 11.3)	(3.4, 6.2)	(6.2, 10.4)

[1] Two patients had no height data on study.

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According to the protocol, rates for naïve patients were to be compared to rates of age-matched naïve patients treated with daily GH in Genentech Study L0368g. The sponsor states that the latter was not done due to the small sample sizes in each treatment group. (The trial was powered based on 21 naïve patients; 17 naïve patients were given the dose proposed for marketing.) The sponsor did provide summary data for Study L0368g; this data is shown below with data for the naïve patients dosed with Depot 0.75 mg/kg twice a month or 1.5 mg/kg once a month (Table 6). The samples are comparable regarding age and pre-study growth rates (p>.2, t-test) but not bone age (p=.04, t-test). The mean annualized growth rate is significantly larger in the daily dosing group than the Depot group (p=.005, t-test) with a difference of 2.3 cm/yr . The 95% confidence interval for the treatment difference is 0.7 to 3.9, so differences in favor of daily dosing could be as large as 3.9 cm/yr.

Table 6. Comparison of Results for Naive Patients in Study [redacted]03-002 to Study L0368g

	N	Age	Bone age	Pre-study growth rate	Dose (mg/kg/mo)	Annualized Growth Rate
[redacted]03-002	17	6.9 (2.4)	4.8 (2.3)	5.4 (2.6)	1.5	8.7 (2.9)
L0368g	62	8.0 (3.4)	6.5 (3.1)	4.8 (2.3)	~1.33	11.0 (2.9)

According to the protocol, on-study growth rates for CT patients were to be compared to pre-study growth rates using a paired analysis; these results were not presented in the NDA. This reviewer's results (Table 7) show for all treatment groups that the mean depot rates are less than the mean daily rates by more than 2 cm/yr (range of [redacted]). For the ITT sample, paired differences for each treatment group are either statistically significant or borderline significant (p≤.06). Since the trial was powered to find a paired difference of 2.2, one might assume that these differences are clinically relevant; however, it is left to the medical reviewer to make this judgement.

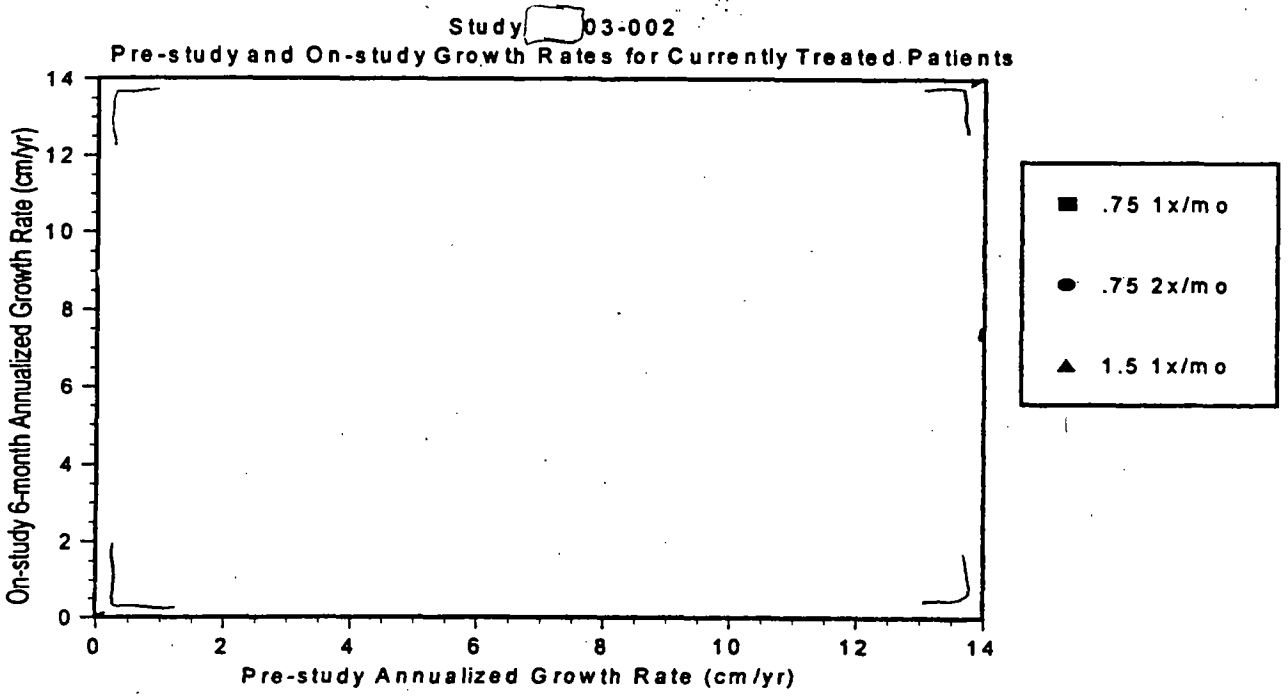
Table 7. Pre-study and On-study Growth Rates for Currently Treated Patients

	0.75 mg/kg once a month	0.75 mg/kg twice a month	1.5 mg/kg once a month	0.75 2x/mo + 1.5 1x/mo combined
Pts with 6-month data				
N	6	11	12	23
Pre-study rate	7.7 (2.5)	8.6 (2.2)	7.4 (3.4)	8.0 (2.9)
On-study rate	5.2 (3.7)	5.2 (1.3)	5.0 (2.5)	5.0 (2.0)
Paired difference[1]	-2.5 (5.8)	-3.4 (1.9)	-2.4 (5.2)	-2.9 (3.9)
Paired test p-value[2]	.31	.001	.15	.002
All Pts (LOCF data)				
N	10	11	15	26
Pre-study rate	8.3 (2.9)	8.6 (2.2)	7.9 (3.4)	8.2 (2.9)
On-study rate	5.1 (3.0)	5.2 (1.3)	4.8 (2.6)	5.0 (2.1)
Paired difference	-3.2 (4.5)	-3.4 (1.9)	-2.9 (5.1)	-3.1 (4.0)
Paired test p-value	.06	.001	.05	.0003

[1] On-study rate minus previous rate. Positive values favor Nutropin Depot.
[2] Results for Wilcoxon signed rank test for paired difference

Figure 1 of all CT patients shows that only 5 patients had an improvement in growth rate over the rate observed for daily dosing. About ⅓ of the CT patients had an on-study growth rate within 2.2 cm/yr of their pre-study growth rate.

Figure 1



Secondary Efficacy Results

In the study report, the results for standardized height and bone age are presented as secondary efficacy results; no secondary efficacy variables were named in the protocol. Minimal changes in standardized height were observed for all dose groups; very small mean decreases were seen for CT patients and increases of 0.2 to 0.4 for naive patients. There were small consistent increases in bone age in all groups with values of 0.7 years or less.

Table 8. Standardized height and bone age for patients with 6-month data

	0.75 mg/kg once a month		0.75 mg/kg twice a month		1.5 mg/kg once a month	
	CT	Naïve	CT	Naïve	CT	Naive
Standardized Height	n=6	n=7	n=11	n=9	n=12	n=8
Baseline	-0.3 (1.1)	-2.8 (0.5)	-1.5 (1.0)	-3.5 (0.9)	-1.3 (2.1)	-3.0 (0.7)
Mean change from baseline (SD)	-0.03 (0.3)	+0.2 (0.3)	-0.02 (0.1)	+0.4 (0.3)	-0.01 (0.2)	+0.3 (0.2)
Bone Age	n=5	n=7	n=11	n=8	n=11	n=6
Baseline	8.6 (1.3)	7.0 (2.7)	7.9 (2.7)	5.0 (1.8)	8.4 (1.8)	3.4 (2.0)
Mean change from baseline (SD)	+0.7 (0.5)	+0.6 (0.2)	+0.7 (0.4)	+0.5 (0.3)	+0.7 (0.4)	+0.6 (0.3)

Reviewer's comments on Study [redacted]03-002

Study [redacted]03-002 is an open-label uncontrolled study designed to assess the efficacy of 3 treatment regimens of Nutropin Depot; 0.75 mg/kg once a month, 0.75 mg/kg twice a month and 1.5 mg/kg once a month. Both currently treated (CT) and naive patients were entered in this study. The growth rates for these two groups of patients are expected to differ since GHD patients generally have a growth spurt during the first year of GH therapy and then rates gradually decline in subsequent years. The data from this study clearly illustrates the difference between these two groups of patients; for CT patients, the mean annualized growth rates were 4.8 to 5.2 and for naive patients, 8.0 to 8.9 with the highest mean rate observed for the 0.75 mg/kg twice a month group. No statistically significant differences were observed among the three treatment groups, nevertheless the sponsor decided that the efficacy for the 0.75 mg/kg once a month dose was inadequate and hence that dose was not studied in the subsequent Phase III study, [redacted]03-004.

Two analyses were proposed in the protocol; 1) for CT patients, a comparison of pre-study growth rates to on-study growth rates and 2) for naive patients, a comparison of on-study growth rates to rates observed in Genentech Study L0368g (a study of naive patients on daily dosing). The protocol did not state whether the depot was expected to be comparable to or better than the comparator so no criteria for efficacy were predefined. These analyses were not performed by the sponsor but they were performed by this reviewer.

For the CT patients, the on-study rate was significantly lower than the pre-study rate by a mean of about 3 cm/yr for patients treated with 1.5 mg/kg/month (once and twice a month dosing combined). Power calculations performed by the sponsor suggest that a difference of 2.2 cm/yr would be considered clinically important so it appears that these differences are clinically and statistically important. However, interpretation of these results may be clouded by the measurement of the pre-study rate and the selection of patients. Patients needed to be on GH therapy for at least one year before the study and the pre-study growth rate was to be computed based on growth in that year. One might postulate that patients less compliant on daily therapy may be more likely candidates for this uncontrolled trial and their pre-study growth rates may be less than what is normally observed for patients on daily GH therapy but no data was collected on compliance with daily GH therapy so this can not be ascertained. Assessment of the pre-study growth rate may also be confounded by the time since onset of GH therapy; growth rates on GH therapy are generally higher during the first year of therapy and decline thereafter, plateauing after a few years on therapy. There were 3 patients who had been only treated for one year; about 50% of the patients had been treated for 3 or more years. It seems then that the pre-study growth rate is not inflated due to timing and the decline in the rate due to Depot therapy is significant.

For the naive patients, the on-study growth rate was significantly less than what was observed for naive patients on a daily regimen in Study L0368g by about 2.3 cm/yr; the trial was powered to detect a difference of 2.7 compared to the historical data. The major problem with this comparison is that the groups being compared are not randomized groups so they may not be well matched at baseline. The limited data provided suggests that the groups do not differ significantly with regard to age or pre-study growth rate but a difference in bone age was noted; other differences may exist. Comparisons of results for naive patients to historical data is further discussed in a separate section of this review found on pages 15-16.

Study 03-004 (conducted 12/97 to 9/98)

Study 03-004 is a Phase III, open-label, randomized, uncontrolled, multicenter study of 2 doses of Nutropin depot; 0.75 mg/kg twice a month and 1.5 mg/kg once a month. Naïve patients were randomized to dose and followed for 6 months with visits at baseline, Month 3 and Month 6. The primary efficacy measure was the 6-month annualized growth rates.

Patient Disposition

A total of 79 patients were randomized to treatment (Table 9); 41 to 0.75 mg/kg twice a month and 38 to 1.5 mg/kg once a month at 27 sites. Five patients (3 randomized to 0.75 and 2 to 1.5) were not treated; 4 declined treatment and 1 was found not to be growth hormone deficient. Of the 74 patients randomized and treated, 69 completed six months on therapy.

Table 9. Study 03-004 Patient Disposition

	0.75x2	1.5x1	Total
Randomized	41	38	79
Not Treated	3	2	5
Randomized and treated	38	36	74
Completed 3 months	37	35	72
Completed 6 months	36	33	69
Completed 6 months and had pre-study growth rate data	28	25	53
Continued into 03-003	33	28	61
Completed 12 months	29	27	56

A total of 10 patients discontinued after being randomized to treatment (Table 10); 5 before treatment (patient choice (4) and entry criteria not met (1)) and 5 during treatment. The primary reason for discontinuation among patients dosed was injection related.

Table 10. Study 03-004 Reasons for Discontinuation

	0.75x2	1.5x1	Total
Randomized	41	38	79
Discontinued	5	5	10
Reasons for discontinuation			
Injection related (pain or fear)	1	2	3
Entry criteria not met	2	0	2
Patient withdrew before dosing	2	2	4
ADE (weak and dizzy)	0	1	1

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Patient Characteristics

Table 11 summarizes baseline patient characteristics for the randomized and treated patients in the two treatment groups; the groups were comparable on these characteristics. Most of the patients were males and Caucasian; about 90% had idiopathic GHD. The average age of patients was about 7 years (range of 1.6 to 12.2) with a bone age of about 6.

Table 11. Study [redacted]03-004 Baseline Patient Characteristics

	0.75x2 (n=38)	**1.5x1** (n=36)
M/F (%)	76%/24%	58%/42%
Etiology		
Idiopathic	92%	89%
Organic	8%	11%
Age (years)	7.6 (2.7)	7.3 (3.2)
Range	(3.2-11.9)	(1.6-12.2)
Bone Age (years)	6.3 (2.4)	5.7 (2.8)
Pre-study Growth Rate (cm/yr)	4.7 (1.9) (n=30)	5.0 (2.1) (n=26)
Race		
White	76%	92%
Hispanic	16%	8%
Other	3%	0%
Height (cm)	109.0 (13.9)	106.6 (17.4)
Standardized Height	-2.91 (0.8)	-2.90 (1.2)
Max stim. GH (ng/ml)	6.0 (2.8)	5.7 (2.6)

Pre-treatment growth rates were calculated using a height measurement taken at least 130 days prior to study start and no more than 425 days from start. Using this definition, pre-study growth rates were available for 30 (79%) 0.75 patients and 26 (72%) 1.5 patients. As for Study [redacted]03-002, pre-study growth rates outside of the sponsor-defined window were available for the remaining 18 naive patients. This reviewer included the values for 18 patients that most closely met the sponsor's criteria[1] and recomputed the mean pre-study growth rate producing the following results:

	0.75x2 (n=38)	1.5x1 (n=36)	Doses combined (n=74)
Pre-study growth rate	4.6 (2.5)	5.0 (2.3)	4.8 (2.4)

Sponsor's Proposed Statistical Methods

The trial was powered with 30 patients per group to obtain a lower limit of about 1.6 cm/yr less than the mean. The original protocol stated that the intention was to show

[1] The time since baseline for the heights used in the calculations of the pre-study growth rates for these 18 patients ranged from 28 to 470 days. For 12 of these 18 patients, these times are within 1 month of the time range specified by the sponsor.

a growth rate of 9 cm/yr; this objective was removed with the first amendment prior to the start of the trial.

The protocol states that means and 95% confidence intervals for the 6-month annualized growth rate will be presented for each dose group. If the estimates are similar, the data for the doses will be combined to produce an overall estimate. No criteria for similarity were specified and no statistical comparisons were planned.

In the study report, 95% confidence intervals and the results of paired t-tests comparing pre-study annualized growth rates to on-treatment 6-month annualized growth rates were presented.

Efficacy Results

Primary Efficacy Results: 6-month Annualized Growth Rate

The 6-month annualized growth rate was the primary efficacy measure[1]. The results for patients with 6-month data (completers) and for all patients with on-therapy data[2] (LOCF data) are shown in Table 12. The rates for the two dosing regimens appear to be comparable with a small difference of 0.1 cm/yr. The 95% confidence interval for this difference is –0.9 to 1.1; so a difference of about 1 cm/yr in favor of either dosing regimen is consistent with the observed data.

Table 12. Study 03-004 6-month Annualized Growth Rates

	0.75 x 2	1.5 x1	Doses Combined
Pts with 6-month data	n=36	n=33	n=69
Mean cm/yr (SD)	8.4 (2.4)	8.3 (1.7)	8.4 (2.1)
95% CI	(7.6, 9.2)	(7.7, 8.9)	(7.9, 8.9)
All Pts (LOCF)	n=37	n=35	n=72
Mean cm/yr (SD)	8.4 (2.3)	8.3 (1.7)	8.3 (2.0)
95% CI	(7.6, 9.2)	(7.7, 8.9)	(7.8, 8.8)

Annualized rates based on 3-month data are similar to the 6-month rates with a rate of 8.5 for the doses combined.

Figure 2 on the following page further illustrates the similarity of the annualized growth rates for the two dosing regimens with a plot of the growth rate for each patient with 6-month data.

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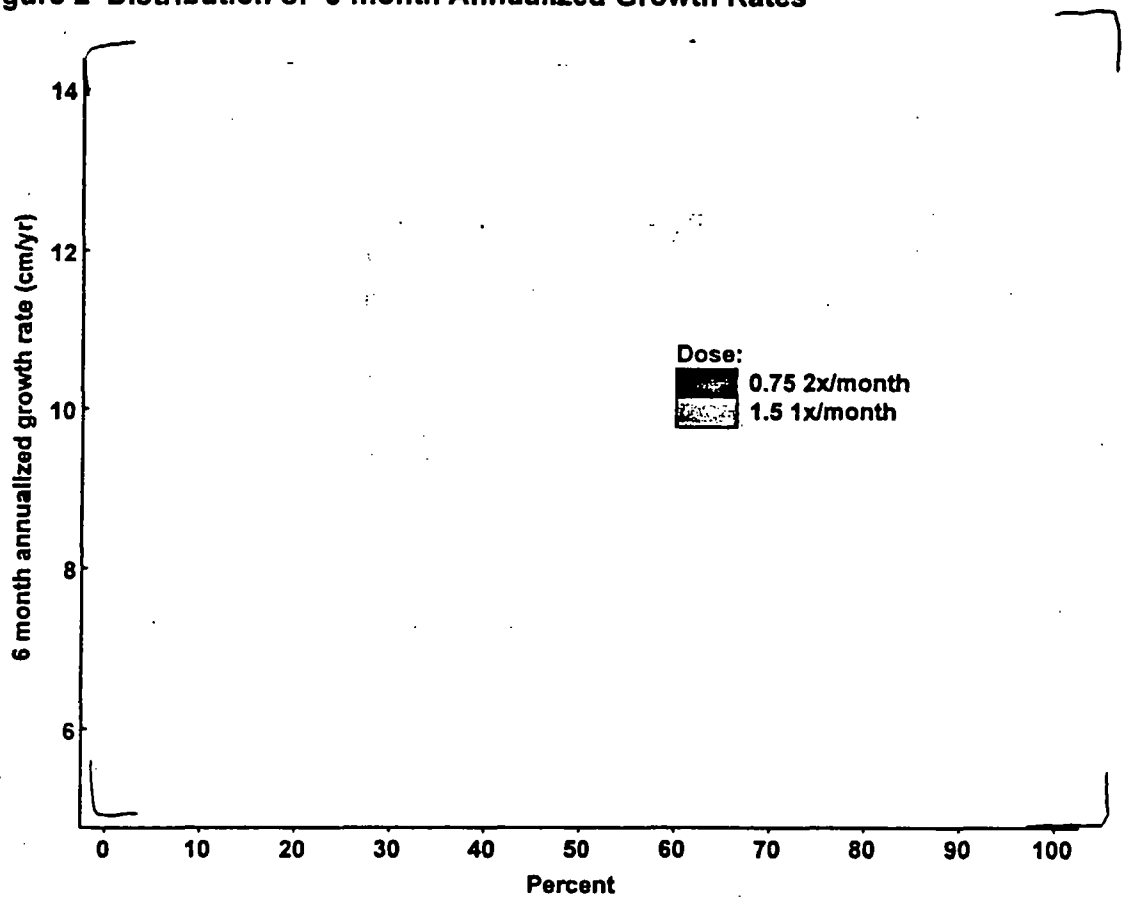
[1] Annualized rates are computed as follows:{(Height at visit – Baseline Height) / (Date at visit – Baseline Date)} * 365

[2] Two patients who were treated for one month are not included in the data for Table 12. One patient had no height data after therapy. The other patient had height data but is excluded here because the data is based on only one month of therapy and, also, the patient was discontinued by the investigator due to lack of GHD (i.e. the patient did not satisfy entry criteria).

Figure 2 Distribution of 6-month Annualized Growth Rates



*The values on the x-axis represent the percentiles of patient responses.

It is worth noting that 6 patients on twice a month dosing had rates of 12 cm/year or greater while only one patient on once a month dosing had a rate that high.

For a comparison of the pre-study growth rates to the on-study growth rates, this reviewer included the 72 patients with both pre-study (as described on Page 9) and on-study growth rates. With both dose groups combined, the mean pre-study growth rate was 4.7 cm/yr (SD 2.4, range of [redacted]); the mean rate after 6 months of treatment for these patients was 8.3 cm/yr (SD 2.0, p<.0001, paired t-test).

Secondary Efficacy Results

In the study report, the results for standardized height[1] and bone age are presented as secondary efficacy results; no secondary efficacy variables were named in the protocol.

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[1] Standardized height is computed as follows:

$$\frac{\text{Actual Height - Mean Height of Normal Subjects of Same Age and Sex}}{\text{Height SD of Normal Subjects of Same Age and Sex}}$$

The results for the 2 dose groups are comparable (Table 13). The changes from baseline for standardized height are consistent with what was observed for naive patients in Study [redacted]03-002; the clinical relevance of these changes is left to the judgement of the medical reviewer. The changes in bone age are less than the changes seen in Study [redacted]03-002 by about 0.15 years; the baseline bone age is higher by about 2 years than what was observed in 002.

Table 13. Standardized height and bone age for patients with 6-month data

	0.75 x 2 (n=36)	1.5 x1 (n=33)	Combined (n=69)
Standardized Height			
Baseline	-3.0 (0.7)	-3.0 (1.2)	-3.0 (1.0)
Mean change from baseline (SD)	+0.3 (0.2)	+0.35 (0.3)	+0.3 (0.3)
Bone Age			
Baseline	6.5 (2.4)	5.6 (2.9)	6.1 (2.7)
Mean change from baseline (SD)	+0.5 (0.3)	+0.4 (0.3)	+0.4 (0.3)

Reviewer's Comments on Study ALK03-004

The data clearly show that the annualized growth rate after 6 months of Depot treatment is significantly increased over the baseline no-treatment rate for naive patients.

Interpretation of the results of this study is limited by the lack of a concurrent control group. The inclusion of a treatment arm of patients treated with daily administration of Nutropin would have greatly enhanced the quality of the data from this study. In lieu of concurrent control data, historical data can be used to put the results of this trial in perspective. A discussion of a comparison of the data from this study and Study [redacted]03-002 to historical data is provided on pages 15-16 of this review.

Subgroup Efficacy Results for Naive Patients in Studies 002 and 004 Combined

To examine the consistency of the primary efficacy response to Nutropin Depot, this reviewer looked at subgroups based on pre-study rate (by median of 4.9 cm/yr), gender, etiology, age (by median of 7 years) and maximum stimulated growth hormone level (by median of 5.8 ng/ml). The results for naive patients in Studies [redacted]03-002 and [redacted]03-004 were combined and are presented in Table 14. Consistent subgroup differences by dose and for doses combined was seen for both age and maximum stimulated growth hormone level [1]. The sponsor also found these baseline characteristics to be correlated strongly with outcome. Growth rate was negatively correlated with age (R=-0.36, p=.0005) and with maximum stimulated GH level (R=-0.47, p=.0003).

Table 14. 6-Month Annualized Growth Rates for Naive Patients in Studies 002 and 004

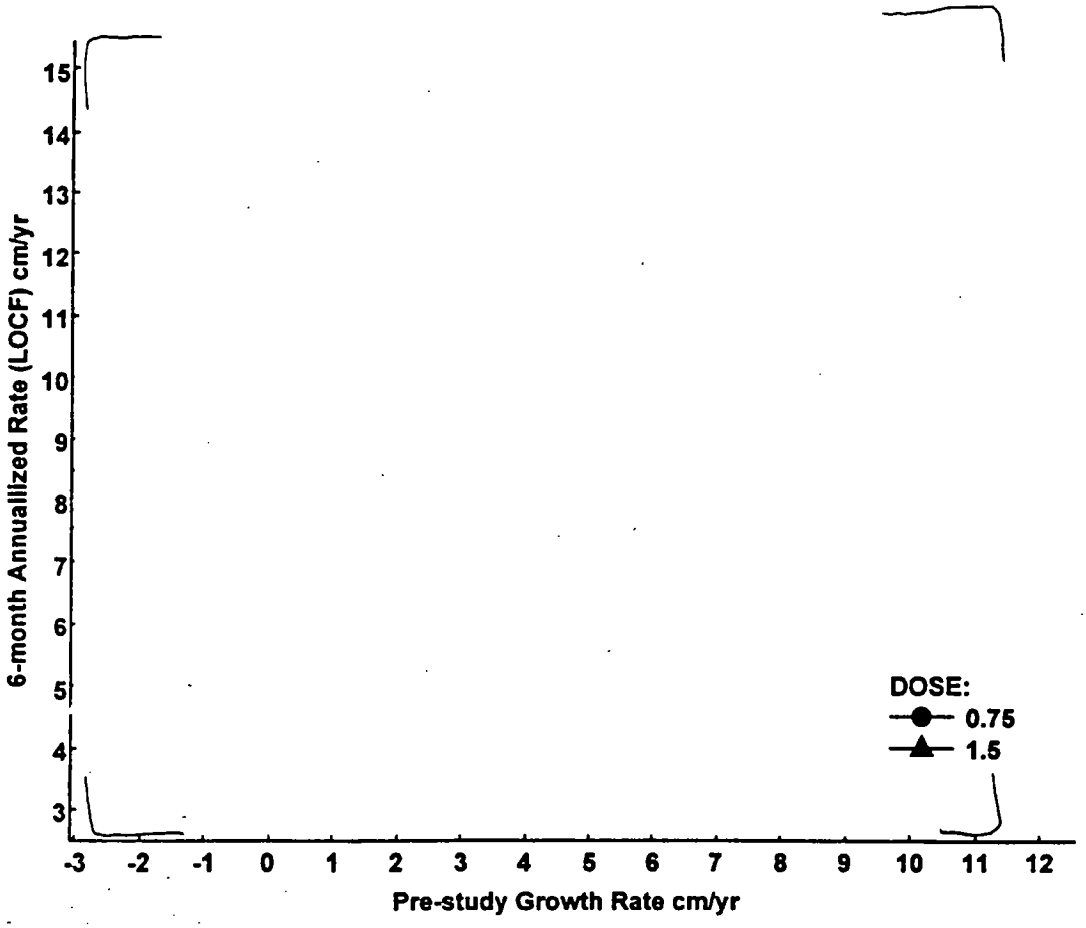
	0.75 x 2	1.5 x1	Doses Combined
All patients	8.5 (2.5) (n=46)	8.3 (1.9) (n=43)	8.4 (2.2) (n=89)
Pre-study Rate			
≤4.9 cm/yr	9.0 (2.2) (n=24)	8.2 (1.9) (n=21)	8.6 (2.1) (n=45)
>4.9 cm/yr	8.0 (2.7) (n=22)	8.3 (1.8) (n=22)	8.2 (2.3) (n=44)
Gender			
Male	8.3 (2.3) (n=36)	7.9 (1.7) (n=26)	8.1 (2.1) (n=62)
Female	9.5 (2.9) (n=10)	8.9 (1.9) (n=17)	9.1 (2.3) (n=27)
Etiology			
Idiopathic	8.6 (2.5) (n=43)	8.2 (1.9) (n=39)	8.4 (2.2) (n=82)
Organic	6.7 (1.5) (n=3)	8.8 (1.1) (n=4)	7.9 (1.6) (n=7)
Age			
≤7 years	8.9 (2.8) (n=19)	9.1 (1.5) (n=25)	9.0 (2.2) (n=44)
>7 years	8.2 (2.2) (n=27)	7.1 (1.7) (n=18)	7.8 (2.1) (n=45)
Max. Stim GH level (ng/ml)[2]			
≤5.8	10.6 (2.7) (n=12)	8.9 (1.3) (n=17)	9.6 (2.2) (n=29)
>5.8	7.6 (0.9) (n=17)	8.1 (2.0) (n=10)	7.8 (1.4) (n=27)

[1] There also appears to be a gender difference however the data is limited for females. It is possible that gender is confounded with age or maximum stimulated GH level but due to limited data and time this reviewer did not examine this further.

[2] Maximum stimulated growth hormone data was only available to this reviewer for patients in 004 who completed 12 months in 003. No data was available for patients in 002 and the other 004 patients.

There is a suggestion of a relationship between pre-study rate and on-study rate for the 0.75 twice a month dose using a cutpoint of 4.9 cm/yr. This difference did not hold-up when lower cutpoints were used (see Appendix 1). Figure 3 below further illustrates the lack of a relationship between the two measures (for the doses combined, R=0.05, p=.63).

Figure 3. Six-month annualized growth rate by pre-study growth rate for naive patients in Studies [redacted]03-002 and [redacted]03-004



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Comparisons of Growth Rates for Naive Patients to Historical Data

The protocols for Studies [redacted]03-002 and [redacted]03-004 did not provide criteria for assessing the efficacy of Nutropin Depot; that is, no statistical methods were defined to determine whether the estimates of the 6-month annualized growth rates (the primary efficacy variable) represented important (statistically and clinically) improvements in growth. Without concurrent controls, one is dependent on predefined levels of efficacy to meet (for example, an accepted range of growth rates) or historical data to assess efficacy. The former was not done so then one is dependent on historical data. For Study [redacted]03-002, the protocol did specify that data for the naive patients would be compared to data from Study L0368g (Ref#10 in Table 16 below); however, as mentioned earlier in this review, no criteria for assessing comparability was provided.

Table 15. Pre-study and on-study growth rates for naive patients in Studies [redacted]03-002 and [redacted]03-004

	0.75 2x/month	1.5 1x/month	Doses Combined
Study [redacted]/03-002	(n=9)	(n=8)	(n=17)
Pre-study rate	5.3 (1.5)	5.5 (3.6)	5.4 (2.6)
On-study rate	8.9 (3.2)	8.3 (2.6)	8.7 (2.9)
95% CI	(6.8, 11.0)	(6.5, 10.1)	(7.3, 10.1)
Study [redacted]/03-004	(n=37)	(n=35)	(n=72)
Pre-study rate	4.5 (2.4)	4.9 (2.3)	4.7 (2.4)
On-study rate	8.4 (2.3)	8.3 (1.7)	8.3 (2.0)
95% CI	(7.7, 9.1)	(8.0, 8.6)	(7.8, 8.8)

To determine how the results for Nutropin Depot (Table 15) fit into the available armamentarium for the treatment of growth hormone deficiency, this reviewer has compiled historical data (Table 16, below and continued on following page) from a literature review by this reviewer (Appendix 2) and from references provided by the sponsor (Appendix 3). Studies were chosen that best matched Studies [redacted]03-002 and [redacted]03-004 based on baseline patient characteristics (age, maximum stimulated growth hormone level (where available), bone age, height SD and pre-study growth rate).

An examination of the annualized growth rates and the 95% confidence intervals presented in Tables 15 and 16 clearly shows that the rates on Nutropin Depot are significantly lower than the historical rates, particularly when looking at the daily dosing regimens. The Depot rates are closer in comparabilty to low doses of Nutropin (Ref#2) or 3 times a week dosing (MacGillivray study).

Table 16. Selected historical control data compiled by this reviewer

Study (Source)	Patient Population	Nutropin Dose[1]	Sample Size	First Year Annualized Growth Rate (cm/yr)	95% CI (calculated by reviewer)
85-041 (Orig NDA)	Naïve Bone age=5.1 yrs Height=106 cm	0.1 mg/kg 3x/week	44	Base=4.0 (1.6) 6 mo=11.9 (4.0)	(10.7, 13.1)
MacGillivray et al (J Clin Endocrin + Metabol, 1996)	Naïve Bone age=6.7 Height=112.4 Ht SD=-2.8	0.1 mg/kg 3x/week	28	Base=4.2 (1.7) 12 mo=8.8 (1.8)	(8.1, 9.5)
	Bone age=5.9 Height=113.3	0.05 mg/kg 6x/week	23	Base=4.2 (1.7) 12 mo=11.4 (2.5)	(10.4, 12.4)

[1] A Nutropin dose of 43 µg/kg/day is equivalent to a weekly dose of 0.3 mg/kg, the recommended dose.

Study (Source)	Patient Population	Nutropin Dose[1]	Sample Size	First Year Annualized Growth Rate (cm/yr)	95% CI (calculated by reviewer)
	Ht SD=-2.7				
National Cooperative Growth Study (provided by sponsor)	Naïve/ idiopathic Bone age=5.3 Ht SD=-3.1	Protropin or Nutropin	1909	Base=4.5 (2.4) **6 mo=10.7 (3.6)**	**(10.5, 10.9)**
	Naïve/ organic Bone age=5.3 Ht SD=-3.1		384	Base=4.2 (2.6) **6 mo=11.4 (4.1)**	**(11.0, 11.8)**
Ref#2 Blethen, 1993	Naive/IGHD Age=8 Bone age=5.7 Ht SD=-3.1	37 µg/kg/day 3-7x/week	523	Base=4.5 (2.8) **12 mo=9.2 (2.4)**	**(9.0, 9.4)**
Ref#3 De Muinck, 1994	Naive Age=6.8 Bone age=5.4 Ht SD=-3.6	19 µg/kg/day daily	10	Base=4.5 (2.8) **12 mo=11 (3.0)**	**(9.1, 12.9)**
Ref#4 De Muinck, 1994	Naive Age=6.9 Bone age=5.6 Ht SD=-3.3	38 µg/kg/day daily	11	Base=5.3 (2.2) **12 mo=13.3 (3.9)**	**(11, 15.6)**
Ref#10 L0368g, 1994	Naive Age=8 Bone age=6.5 Ht SD=-2.7	43 µg/kg/day daily	62	Base=4.8 (2.3) **12 mo=11 (2.9)**	**(10.3, 11.7)**

Even though comparisons to historical controls may be problematic due to patient selection bias, the comparisons here are clear given the quantity of historical data and the consistency of estimates across the historical studies.

Study [redacted]03-003 Extension Study (started 4/97, ongoing)

Compliant patients in Studies [redacted]03-002 and [redacted]03-004.were eligible to volunteer for continued treatment in extension study [redacted]03-003. Of the 143 patients enrolled in Studies [redacted]03-002 and [redacted]03-004, 96 (67%) were continued into [redacted]03-003 (Table 17).

Table 17. [redacted]3-003 Patient Disposition by Previous Study and Dose

	Naive Patient			CT Patients		
Randomized Treatment	0.75 mg/kg 1x month	0.75 mg/kg 2x month	1.5 mg/kg 1x month	0.75 mg/kg 1x month	0.75 mg/kg 2x month	1.5 mg/kg 1x month
[redacted]03-002						
Enrolled	9	9	8	10	11	17
Completed 002	7	9	8	6	11	12
Entered 003	5	9	6	5	4	6
Completed 12 mos	5	8	5	5	3	5
[redacted]03-004						
Enrolled		41	38			
Completed 004	NA	36	33	NA	NA	NA
Entered 003		33	28			
Completed 12 mos		29	27			
[redacted]03-003 (Total)						
Completed 12 mos	5	37	32	5	3	5

A higher percentage of naive patients opted to continue treatment in 003 (81/93, 87%) than CT patients (15/29, 52%). At the request of FDA, data for patients who had completed 12 months of therapy was submitted and is reviewed here.

Patients assigned to 0.75 mg/kg once a month in Study [redacted]03-002, were randomized to either 0.75 mg/kg twice a month or 1.5 mg/kg once a month in this extension study. For all patients completing 12 months of therapy on Study [redacted]03-003, the 6-month dose and extension dose is shown in Table 18. This reviewer included the data from all the patients when summarizing the extension data; the inclusion of the patients that switched doses did not change the estimates by an appreciable amount.

Table 18. Treatment Assignment in [redacted]03-003 extension study

	Naive Patient		CT Patients	
	0.75 mg/kg 2x month	1.5 mg/kg 1x month	0.75 mg/kg 2x month	1.5 mg/kg 1x month
Completed 12 months	39	35	6	7
6 month dose				
Same	37	32	3	5
0.75/month	2	3	3	2

The pre-study and on-study annualized growth rates for all patients completing the extension study [redacted]03-003 are presented in Table 19. For all groups, the 12-month annualized growth rate is less than the 6-month annualized growth rate by about 1 cm/yr. Comparing these 12 month rates to the 12 month rates from historical controls (Table 16), it is clear that these rates are considerably lower.

Table 19. Annualized growth rates for all patients completing 12 months in [redacted]03-003 extension study

	Naive Patient		CT Patients	
	0.75 mg/kg 2x month	1.5 mg/kg 1x month	0.75 mg/kg 2x month	1.5 mg/kg 1x month
N	39	35	6	7
Pre-study Rate	4.6 (2.2)	5.2 (2.9)	8.3 (2.9)	6.7 (2.8)
Month 6 Rate	9.0 (2.4)	8.4 (1.8)	7.1 (2.3)	4.9 (2.7)
Month 9 Rate	8.4 (2.1)	7.7 (1.8)	5.7 (2.2)	4.1 (2.6)
Month 12 Rate	8.1 (1.9)	7.4 (1.8)	5.6 (2.5)	4.4 (2.2)

Overall Summary and Comments

The sponsor has submitted the results of two 6-month uncontrolled studies, [redacted]03-002 and [redacted]03-004, to establish the efficacy and safety of Nutropin Depot for the treatment of GHD in children. In Study [redacted]03-002, 38 CT patients (patients treated for at least one year with daily Nutropin prior to entering this study) and 26 naive patients were assigned to one of three doses; 0.75 mg/kg once a month, 0.75 mg/kg twice a month or 1.5 mg/kg once a month. In Study [redacted]03-004, 74 naive patients were randomized to 0.75 mg/kg twice a month or 1.5 mg/kg once a month. In both studies, the primary efficacy variable was the 6-month annualized growth rate; annual rates based on 12 months of data from the extension study [redacted]03-003 were available for about 67% of the total enrolled patients.

The sponsor concludes that Nutropin Depot "is a viable alternative to daily rhGH." Direct comparisons to a daily regimen were only available for CT patients. The data for these patients shows a statistically significant decrease in growth rate ($p<.05$, paired Wilcoxon signed rank test) when switching from daily dosing to monthly dosing with Depot (Table 20) in Study [redacted]03-002; the drop from pre-study using 12-month data is nearly significant with the doses combined ($n=13$, $p=.06$). In spite of the limited data provided for CT patients, there is strong evidence that the growth rate decreases when switching from a daily regimen to once or twice a month dosing with Depot (for a more detailed discussion see pages 5-7 of this review).

Table 20. Annualized growth rates for CT patients in Study [redacted]03-002 and extension Study [redacted]03-003

	0.75 mg/kg twice a month	1.5 mg/kg once a month
Study [redacted]03-002	(n=11)	(n=15)
Pre-study rate	8.6 (2.2)	7.9 (3.4)
6-month rate	**5.2** (1.3)	**4.8** (2.6)
Study [redacted]03-003	(n=6)	(n=7)
Pre-study rate	8.3 (2.9)	6.7 (2.8)
6-month rate	7.1 (2.3)	4.9 (2.7)
12-month rate	**5.6** (2.5)	**4.4** (2.2)

For naive patients, the efficacy data is more difficult to interpret due to the lack of a concurrent control on daily regimen and the absence of pre-defined criteria for establishing efficacy. Historical control data compiled by this reviewer and the sponsor can be used to assess the comparability of Depot to a daily regimen. The drawback to the latter approach is that the comparison groups are not randomized groups so that the baseline comparabilty cannot be assured. This reviewer attempted to choose for comparison historical trials of naive patients that most closely matched naive patients in [redacted]03-002 and [redacted]03-004 on several baseline characteristics (age, maximum

stimulated growth hormone level (where available), bone age, height SD and pre-study growth rate). The annualized rates for Nutropin Depot are less than those observed for daily GH in the historical studies (Table 21) by about 3 cm/yr. It is left to the medical reviewer to determine the clinical significance of this difference.

Table 21. Annualized growth rates for naive patients in Studies [redacted]03-002 and [redacted]03-004 and extension Study [redacted]03-003

	0.75 mg/kg twice a month		1.5 mg/kg once a month	
	Mean	95% CI	Mean	95% CI
Study [redacted]03-002 **6-month rate**	(n=9) **8.9** (3.2)	**(6.8, 11.0)**	(n=8) **8.3** (2.6)	**(6.5, 10.1)**
Study [redacted]03-004 **6-month rate**	(n=37) **8.4** (2.3)	**(7.7, 9.1)**	(n=35) **8.3** (1.7)	**(8.0, 8.6)**
Study [redacted]03-003 **12-month rate**	(n=39) **8.1** (1.9)	**(7.5, 8.7)**	(n=35) **7.4** (1.8)	**(6.8, 8.0)**
Historical Studies (daily dosing) [1]				
6-month rate				
Study 85-041	11.9 (4.0)	(10.7, 13.1)	NA	
NCGS	10.7 (3.6)	(10.5, 10.9)		
12-month rate				
MacGillivray	11.4 (2.5)	(10.4, 12.4)		
Ref#3	11.0 (3.0)	(9.1, 12.9)		
Ref#4	13.3 (3.9)	(11.0, 15.6)		
Ref#10	11.0 (2.9)	(10.3, 11.7)		

The 6-month annualized growth rates with 002 and 004 combined and the doses combined ranged from [redacted] cm/yr to [redacted] cm/yr with a mean of 8.4 cm/yr and a median of 8 cm/yr. About 80% of the patients had a growth rate on-study of 7 cm/yr or greater (Table 22).

Table 22. Percentage of Naive Patients by 6-month Annualized Growth Rate

6-month Annualized Growth Rate (cm/yr)	0.75 mg/kg twice a month (n=46)	1.5 mg/kg once a month (n=43)	Doses Combined (n=89)
<5	4.4%	2.3%	3.4%
5-<7	19.6%	20.9%	20.2%
7-<9	45.7%	41.9%	43.8%
9-<11	15.2%	27.9%	21.3%
≥11	15.2%	7.0%	11.2%

In summary, the lack of concurrent controls or pre-defined statistical criteria for establishing efficacy precludes drawing any definitive conclusions regarding efficacy from a statistical viewpoint. Interpretation of the data from these studies would have been greatly enhanced by the inclusion of a treatment arm of naive patients treated with

[1] See pages 15-16 and Appendices 2 and 3 of this review for further information regarding these historical studies.

daily Nutropin. Nevertheless, it is clear from comparing historical data on daily dosing to the Depot data for the naive patients and from comparing pre-study rates on daily dosing to Depot rates for previously treated (CT) patients that the efficacy of Nutropin Depot was notably less than what has been observed for a daily regimen of GH therapy. Due to the less frequent dosing, there may be some patients who are willing to compromise some efficacy and therefore this product may be a useful addition to the GH therapy armamentarium. The label should reflect the drawbacks to Nutropin Depot over usual GH therapy.

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Joy D. Mele, M.S.
Mathematical Statistician

Concur:

for
Todd Sahlroot, Ph.D. /S/ 11-12-99
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cc:
Archival NDA#21,075
HFD-510
HFD-510/RPerlstein, SMalozowski, SSobel, CKing
HFD-715/Division 2 File, Chron, JMele

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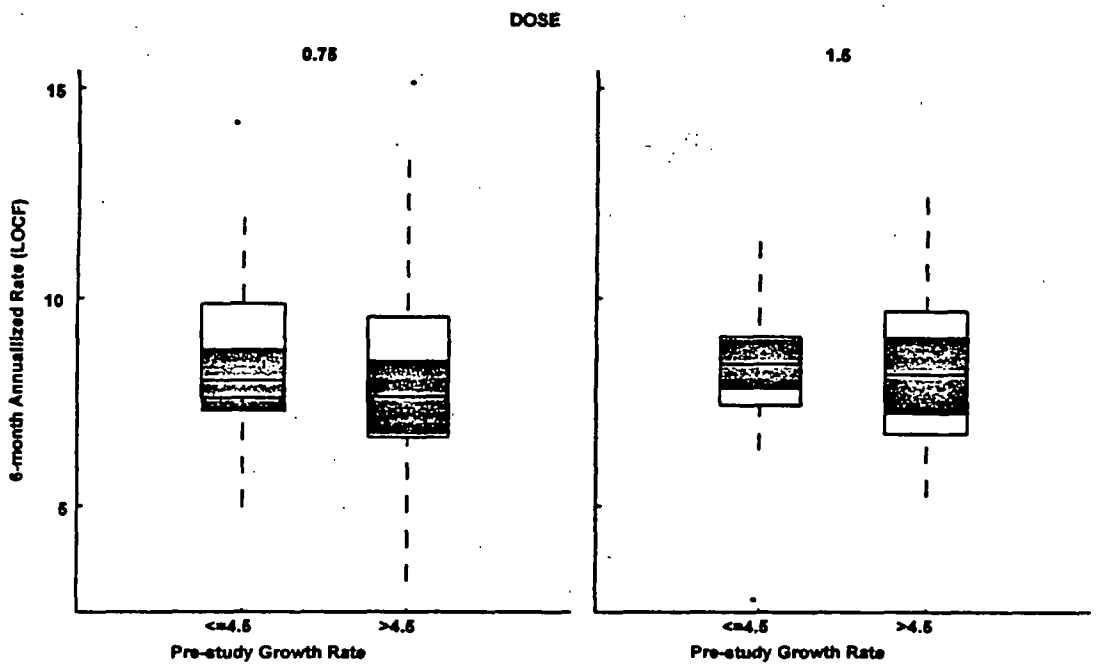
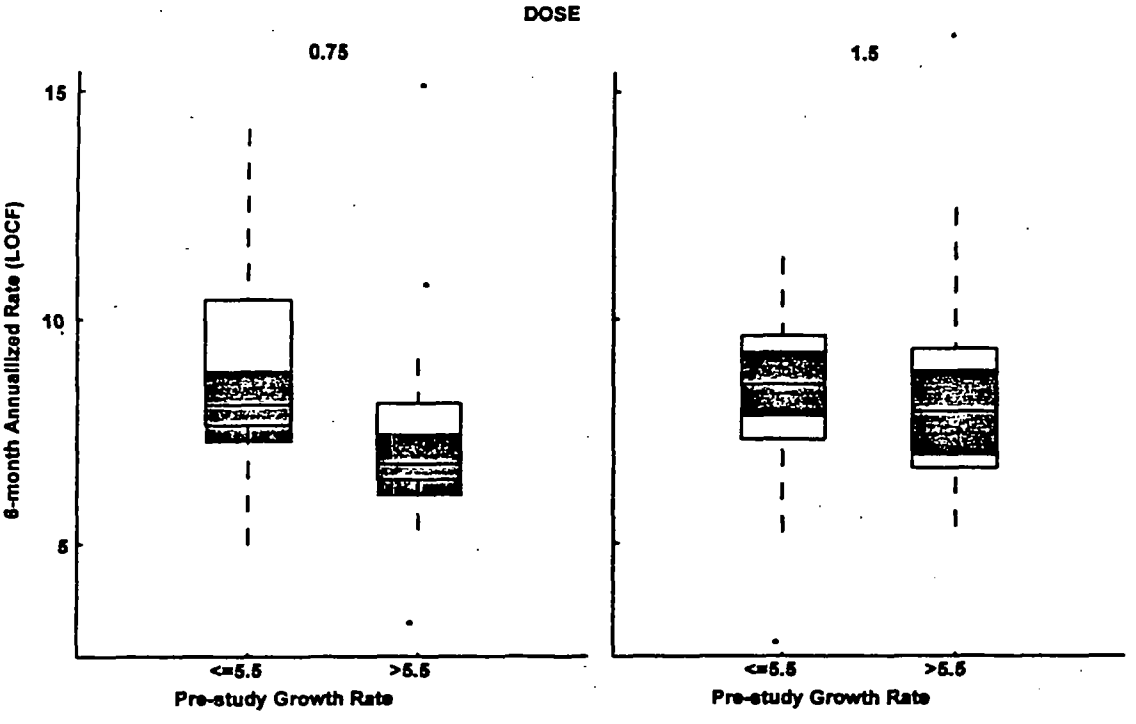
Appendix 1. 6-month annualized growth rates by pre-study growth rates using different cutpoints





Appendix 2. Historical control data compiled by this reviewer

Table 16. Historical data compiled by this reviewer

Study (Source)	Patient Population	Nutropin Dose	Sample Size	Nutropin Rate Cm/yr (annualized)
85-041 (Orig NDA)	Naïve Bone age=5.1 yrs Height=106 cm	0.2 mg/kg 3x/week	44	Base=4.0 (1.6) 6 mo=**11.9 (4.0)**
85-042 (Orig NDA)	Prev. Treated Bone age=7.7 Height=117	0.1 mg/kg 3x/week	44	Base=3.2 (1.7) 6 mo=10.4 (2.4)
Kaplan et al (The Lancet; 1986)	Naïve Bone age=5.4 Ht SD=-3.7	0.1 mg/kg 3x/week	22	Base=3.2 (1.0) 12 mo=10.5 (2.2) 24 mo=7.2 (1.9) 36 mo=7.2 (1.9)
Gunnarrson (Acta Paediatr Scand Suppl, 1987)	NA	Genotropin	149	Base=3.3 (1.4) 12 mo=9.3 (2.6)
Shi et al (Acta Paediatr Scand Suppl, 1988)	NA	0.5 –0.7 IU/kg/week	59	Base=2.8 (1.0) 12 mo=13.1 (2.5)
MacGillivray et al (J Clin Endocrin + Metabol, 1996)	Naïve Bone age=6.7 Height=112.4 Ht SD=-2.8 Bone age=5.9 Height=113.3 Ht SD=-2.7	0.2 mg/kg 3x/week 0.05 mg/kg 6x/week	28 23	Base=4.2 (1.7) 12 mo=**8.8 (1.8)** Base=4.2 (1.7) 12 mo=**11.4 (2.5)**
National Cooperative Growth Study (provided by sponsor)	Naïve/ idiopathic Bone age=5.3 Ht SD=-3.1 Naïve/ organic Bone age=5.3 Ht SD=-3.1	Protropin or Nutropin	1909 384	Base=4.5 (2.4) 6 mo=**10.7 (3.6)** Base=4.2 (2.6) 6 mo=**11.4 (4.1)**

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Appendix 3. Historical control data provided by the sponsor and copied directly from the NDA

Table 1: First Year Annualized Growth Rates and Associated Treatment Information for Naïve, GHD Children in Cited References

Ref No.	Study/ Reference	n (M/F)	Dose [a] (µg/kg/day)	Dose Frequency	Annualized Growth rate (cm/yr)
1	Anhalt, 1994	12	25	daily	6.6 ± 4.0
1	Anhalt,1994	18	50	daily	10.7 ± 4.2
2	Blethen, 1993	523 (389/134)	37.14	3-7x/week	9.2 ± 2.4
2	Blethen, 1993	109 (69/40)	34.29	3-7x/week	8.8 ± 2.6
3	De Muinck, 1994	10(8/2)	19.2	daily	11.0 ± 3.00
3	De Muinck, 1994	11 (8/3)	38.5	daily	13.3 ± 3.9
4	Frasier, 1981	27	6.43	3x/week	5.59 ± 2.30
4	Frasier, 1981	38	12.86	3x/week	7.31 ± 1.75
4	Frasier, 1981	12	17.14	3x/week	7.22 ± 3.12
4	Frasier, 1981	16	21.43	3x/week	8.94 ± 1.19
5	Kaplan[b], 1986	22 (12/10)	42.86	3x/week	10.5 ± 2.2
5	Kaplan[b], 1986	14 (8/6)	42.86	3x/week	10.1 ± 3.0
5	Kaplan[b], 1986	10 (6/4)	42.86	3x/week	10.1 ± 1.6
6	Rosenbloom, 1989	26	25.71	3x/week	9.3 ± 1.8
6	Rosenbloom, 1989	116	42.86	3x/week	10.3 ± 2.6
7	Soliman, 1996	20	35.71	daily	9.11 ± 2.25
7	Soliman, 1996	10	17.86	daily	8.1 ± 1.52
7	Soliman, 1996	9	17.86	daily	8.4 ± 1.4
8	Tauber, 1993	10 (6/4)	38.46	daily	8.2 ± 1.5
9	Vassilopoulou-Sellin, 1995	20 (15/5)	42.86	daily	8.6 ± 2.65
10	L0368g, 1994	62	42.86	daily	11.0 ± 2.9

Data are mean ± SD unless otherwise indicated.

[a] Doses converted from original units. See dose conversions in Appendix A.

[b] GH administered by intramuscular injections.

Table 3: Demographic Data for Naïve GHD Children in Cited References

Ref No.	Reference	n (M/F)	Age (yr)	Height Age (yr)	Height SDS	Bone Age (yr)	Bone Age SDS	Max Stimulated GH (ng/mL)	Pretreatment Growth Rate (cm/yr)	Pre-Pubertal %	Tanner Stage	Diagnosis[a]
1	Anhalt, 1994	12	12.2 ± 4.7	ND[b]	ND	ND	ND	ND	ND	ND	ND	GHD
1	Anhalt, 1994	18	11.1 ± 5.2	ND	ND	ND	ND	ND	ND	ND	ND	GHD
2	Blethen, 1993	523 (389/134)	8.0 ± 3.7	ND	-3.1 ± 1.0	5.7 ± 3.4	-3.3 ± 1.6	5.1 ± 2.7	4.5 ± 2.8	100	ND	IGHD
2	Blethen, 1993	109 (69/40)	8.7 ± 3.5	ND	-2.4 ± 1.3	6.8 ± 3.2	-2.7 ± 1.7	2.5 ± 2.0	3.5 ± 2.6	100	ND	Organic
3	De Muinck, 1994	10 (8/2)	6.8[c] (1.5 – 11.6)	ND	-3.6 ± 0.88	5.4[c] (0.7 – 9.4)	ND	ND	5.5 ± 2.2	ND	ND	IGHD Organic MPHD
3	De Muinck, 1994	11 (8/3)	6.9[c] (1.5 – 13.8)	ND	-3.26 ± 1.52)	5.6[c] (0.8 – 11.6)	ND	ND	5.3 ± 2.2	ND	ND	IGHD Organic MPHD
4	Frasier, 1981	27	13.03 ± 4.06	ND	ND	7.46 ± 3.00	ND	ND	3.04 ± 1.18	100	ND	GHD
4	Frasier, 1981	38	10.52 ± 4.5	ND	ND	6.62 ± 3.57	ND	ND	3.30 ± 1.40	100	ND	GHD
4	Frasier, 1981	12	9.86 ± 5.80	ND	ND	6.85 ± 4.45	ND	ND	3.60 ± 1.91	100	ND	GHD
4	Frasier, 1981	16	9.16 ± 3.34	ND	ND	5.09 ± 2.53	ND	ND	3.25 ± 0.39	100	ND	GHD
5	Kaplan[d], 1986	22 (12/10)	9.1[c] (3.3 – 14.5)	ND	-3.7[c] (-1.5 – -5.0)	5.4[c] (1.6 – 10.7)	ND	ND	3.2 ± 1.1	100	ND	GHD
5	Kaplan[e], 1986	14 (8/6)	8.6[c] (3.1 – 13.9)	ND	-3.6[c] (-1.8 – -4.7)	6.6[c] (2.1 – 11.0)	ND	ND	3.2 ± 1.0	100	ND	GHD
5	Kaplan[e], 1986	10 (6/4)	6.1[c] (4.1 – 12.2)	ND	-3.7[c] (-2.1 – -5.5)	5.0[c] (1.5 – 11.4)	ND	ND	3.8 ± 1.0	100	ND	GHD

Table 3 Continued: Demographic Data for Naïve GHD Children in Cited References

Ref No.	Reference	n (M/F)	Age (yr)	Height Age (yr)	Height SDS	Bone Age (yr)	Bone Age SDS	Max Stimulated GH (ng/mL)	Pretreatment Growth Rate (cm/yr)	Pre-Pubertal %	Tanner Stage	Diagnosis[a]
6	Rosenbloom[f], 1989	26	8.5 ± 3.8	ND	ND	ND	ND	ND	3.8 ± 1.3	ND	ND	GHD
6	Rosenbloom[f], 1989	116	7.8 ± 3.6	ND	ND	ND	ND	ND	3.7 ± 1.4	ND	ND	GHD
7	Soliman, 1996	20	6.9 ± 1.5	ND	-3.3 ± 1.2	ND	ND	4.3 ± 2.3[g]	3.45 ± 1.23	100	ND	GHD
7	Soliman, 1996	10	7.5 ± 2.1	ND	-2.85 ± 1.2	ND	ND	3.9 ± 2.6[g]	3.44 ± 1.27	100	ND	GHD
7	Soliman, 1996	9	7.1 ± 1.9	ND	-3.4 ± 0.8	ND	ND	6.6 ± 1.1[g]	3.65 ± 1.10	100	ND	Partial GHD
8	Tauber, 1993	10 (6/4)	9.0 ± 3.3	ND	-2.6 ± 0.4	7.2 ± 3.0	ND	5.0 ± 2.0	4.0 ± 0.8	ND	ND	Partial IGHD
9	Vassilopoulou-Sellin, 1995	20 (15/5)	11.0 ± 2.7	ND	-1.7 ± 1.38	9.7 ± 3.2	ND	2.1 ± 1.6[h]	3.1 ± 1.4	ND	ND	GHD
10	L0368g, 1994	67[i] (48/19)	8.0 ± 3.4	5.6 ± 2.8	-2.7 ± 1.0	6.5 ± 3.1	ND	4.8 ± 2.9	4.8 ± 2.3	ND	1.1 ± 0.4	IGHD Organic

Data are mean ± SD unless indicated otherwise.

[a] MPHD = Multiple pituitary hormone deficiencies
IGHD = Idiopathic growth hormone deficiency
ISS = Idiopathic short stature
Organic = Organic growth hormone deficiency

[b] ND = No Data

[c] Mean (minimum-maximum)

[d] IM injections

[e] Median (minimum-maximum)

[f] IM or SC injections

[g] GH peak after clonidine administration

[h] Peak serum GH level during stimulation test with insulin hypoglycemia, L-dopa, clonidine or arginine.

[i] Only 62 children completed 12 months on study.