to be ~1.6 cm/yr less than the sample mean (assuming at least 30 evaluable subjects) and ~1 cm/yr less than the sample mean (assuming at least 60 evaluable subjects) (i.e., the trial was powered with 30 patients per group to obtain a lower limit of confidence of the mean of ~1.6 cm/yr).

Secondary Outcome Measures

A paired t-test was used to evaluate the change in standardized height (standardized height after 6 months of therapy - baseline pre-treatment standardized height) in each dose group. Summary statistics for height age, bone age, change in height age minus change in bone age, and Bayley-Pinneau PAH are presented as well. Although these results were positive, the usefulness of these parameters over a 6 month period are limited and the sponsor chose not to discuss these findings in the submission.

Safety Analysis

Adverse events are tabulated by COSTART preferred term and body system for each dose group. Injection site-related adverse events are tabulated separately from non-injection site-related events. Laboratory and other safety values (including vital signs) are summarized with simple descriptive statistics for each dose group, including means and SD at baseline, after 3 and 6 months of therapy.

GH PK/IGF-I Analysis

A paired t-test was to used to evaluate the change in GH, IGF-I and IGFBP-3 from baseline to Month 3, baseline to Month 6, and Month 3 to Month 6 within each dose group.

Data Quality Assurance

Accurate, consistent, and reliable data were ensured through the use of standard practices and procedures.

8.2.2 Results

Subject Eligibility and Treatment Assignment

There were 79 randomizations during the study, including 4 subjects who replaced subjects who declined participation in the

study and were not dosed (n=3) and another subject who discontinued the study prior to 6 months. In total, 5 of the 79 randomized subjects were not dosed. Therefore, 74 subjects from 27 medical centers received Nutropin Depot: 36 subjects were assigned to 1.5 1x/mo and 38 subjects were assigned to 0.75 2x/mo.

Protocol Violations and Deviations

Three patients were allowed into the study with only 1 (rather than 2) abnormal GH stimulation test. Two female patients had a bone age >9 at study entry. Four subjects had a standardized height <2 SD below the normal mean for their age and sex. Four protocol deviations were reported in dosing during the study. The most significant deviation occurred in Subject 21-401 (0.75 2x/mo), who was deemed noncompliant with the dosing regimen and missed the last five doses.

8.2.2.1 Patient Disposition

Table 12 depicts the disposition of the 79 patients who were randomized. Five patients were not treated - 4 declined treatment and 1 was found not to have GHD. Of the 74 patients randomized and treated, 69 completed 6 months of Nutropin Depot therapy (53/69 had pre-study annualized growth rate data available).

Table 12. [redacted]03-004 - Patient Disposition*

	0.75 mg/kg twice a mo	1.5 mg/kg once a mo	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 [redacted]03-003	33	28	61

*Compiled by statistical reviewer

A total of 5/74 patients discontinued after being randomized and treated. Three of these patients withdrew because of injection site pain (1) or fear of injections (2). See Table 13.

Table 13. [redacted]03-004 - Reasons for Discontinuation*

	0.75 mg/kg twice a mo	1.5 mg/kg once a mo	Total
Randomized and treated	38	36	74
Discontinued	2	3	5
Reasons for discontinuation			
Injection related	1	2	3
--Injection site pain	1	0	1
--Fear of injection	0	2	2
Other adverse event - weak & dizzy	0	1	1
Entry criteria not met	1	0	1

*Compiled by statistical reviewer

8.2.2.2 Patient Characteristics

Most of the patients were male and Caucasian. More than 90% had idiopathic GHD; only 7 patients had an organic etiology. Chronological age ranged from 1.6 to 12.2 with pooled mean age ~7.5. Mean bone age was delayed ~1.3-1.6 years. Thirty out of 38 patients receiving 0.75 2x/mo and 26/36 patients receiving 1.5 1x/mo had acceptable pre-study growth rates. The mean pre-study annualized growth rates were 4.7 cm/yr (0.75 2x/mo) and 5.0 cm/yr (1.5 1x/mo). Mean standardized height was severely diminished and identical in the 2 dose groups (~-2.9). Overall, the subjects in the 2 dose groups had very similar baseline characteristics and were very similar to the naïve subjects in [redacted]03-002 as well! See Table 14.

Reviewer Comment:
In contrast to the inappropriately robust mean pre-study annualized growth rates in the naïve subjects in [redacted]03-002 (~5.6 cm/yr), the subjects in this trial had more appropriate and expected pre-study growth rates (4.7 to 5.0 cm/yr).

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Table 14. 03-004 - Patient Characteristics*

	0.75 mg/kg twice a mo (n=38)	1.5 mg/kg once a mo (n=36)
Male (%)	76%	58%
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)
Previous 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%	
Height (cm)	109.0(13.9)	106.6(17.4)
Standardized Height	-2.91(0.8)	-2.90(1.2)

*Compiled by statistical reviewer

Compliance

Subject 3-407 (1.5 1x/mo) discontinued treatment after Month 5. Subject 21-401 (0.75 2x/mo) was deemed noncompliant with injections, missing the last 5 doses. For other subjects, compliance with dosing, study procedures, and visit schedule was assessed to be adequate.

Concomitant Therapy

The most frequently used concomitant medication was EMLA cream applied prior to injection or venipuncture. Seven patients were treated with L-thyroxine therapy for central hypothyroidism and 3 patients (2 of whom were hypothyroid as well) were treated with replacement doses of hydrocortisone for central hypoadrenalism. Two patients were treated with desmopressin for diabetes insipidus. Other concomitant medications used by subjects were those used to treat pre-existing conditions or routine childhood ailments.

8.2.2.3 Efficacy Results

Primary Efficacy Endpoint: 6 Month Annualized Growth Rate

The primary efficacy endpoint for this study was the 6 month annualized growth rate after therapy with Nutropin Depot. The results are summarized in Table 15. Fifty three of the 69 subjects who completed 6 months of therapy had pre-study growth rates which met the protocol criteria described earlier. In this subset of patients (n=52), the on-study mean 6 month annualized growth rate was significantly greater than the pre-study mean annualized growth rate in both the 1.5 1x/mo and 0.75 2x/mo dose groups ($p<0.0001$ in each instance, paired t-test; see Figure 2). Moreover, the on-study mean 6 month annualized growth rates were very similar in the subset with 6 month annualized growth rates and pre-study growth rates, all subjects with 6 month annualized growth rates, and all subjects randomized and dosed with Nutropin Depot (ITT analysis) - in both dose groups.

Table 15. [redacted]03-004 - Annualized Growth Rates (cm/yr)*

	1.5 1x/Month	0.75 2x/Month	Doses Combined
Subjects with Pre-study and 6 Month Growth Rates	(n=25)	(n=28)	(n=53)
Pre-study			
Mean±SD	5.0±2.1	4.6±1.8	4.8±1.9
(Range)			
0 to 6 Months			
Mean±SD	8.5±1.7	8.6±2.4	8.6±2.0
(Range)			
95% CI	7.8 to 9.1	7.7 to 9.5	8.0 to 9.1
p-value for 0 to 6 months vs. pre-study	>0.0001	<0.0001	<0.0001
Subjects with 6-Month Growth Data			
0 to 6 Months	(n=33)	(n=36)	(n=69)
Mean±SD	8.3±1.7	8.4±2.4	8.4±2.1
(Range)			
95% CI	7.7 to 8.9	7.6 to 9.2	7.9 to 8.9
All Subjects (ITT)	(n=35)	(n=37)	(n=72)
Mean±SD	8.3±1.7	8.4±2.3	8.3±2.0*
95% CI	7.7 to 8.9	7.6 to 9.2	7.8 to 8.8

*Mean annualized growth rates based on 3 month data are similar to the 6 month rates (8.5 cm/yr, ITT, n=72); Compiled by statistical reviewer

Figure 2. [redacted]03-004 - Pre-study and 6 Month Annualized Growth Rate in 2 Dose Groups (Mean±SD)

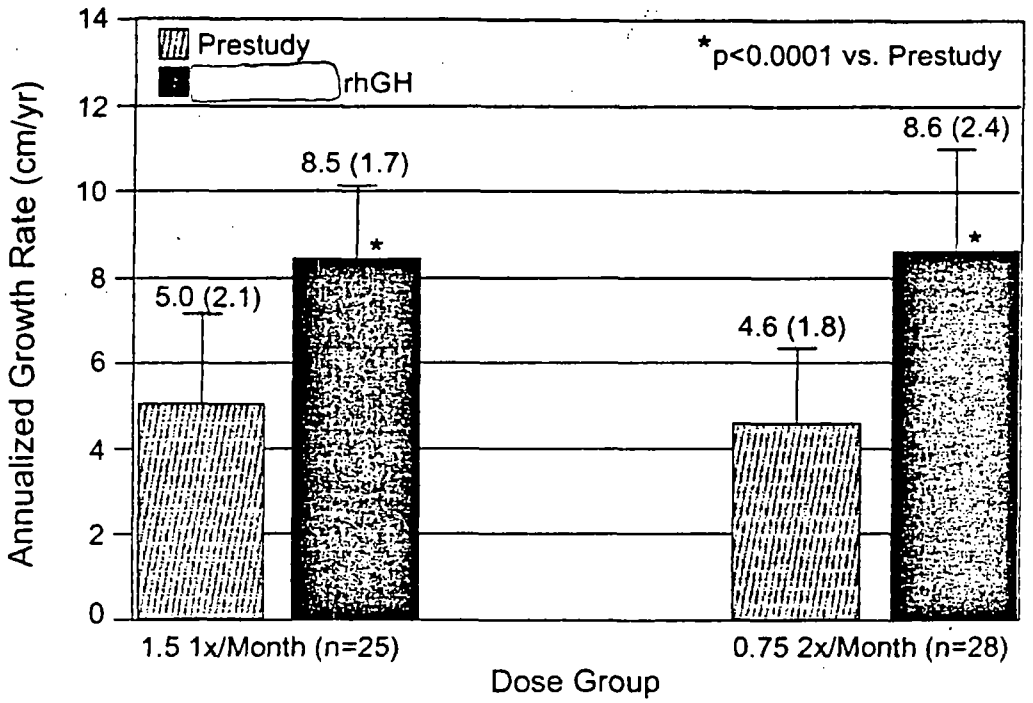

Figure 3 is a distribution plot (created by the Agency's statistical reviewer) comparing the distribution of the annualized growth rates in each dose group (all subjects are represented) in the cohort who completed 6 months of therapy (n=69). The similar growth rate responses to the 2 dosing regimens noted above are plainly evident. Interestingly, 6 patients treated with 0.75 2x/mo, as opposed to only 1 patient treated with 1.5 1x/mo, achieved growth rates ≥12 cm/yr!

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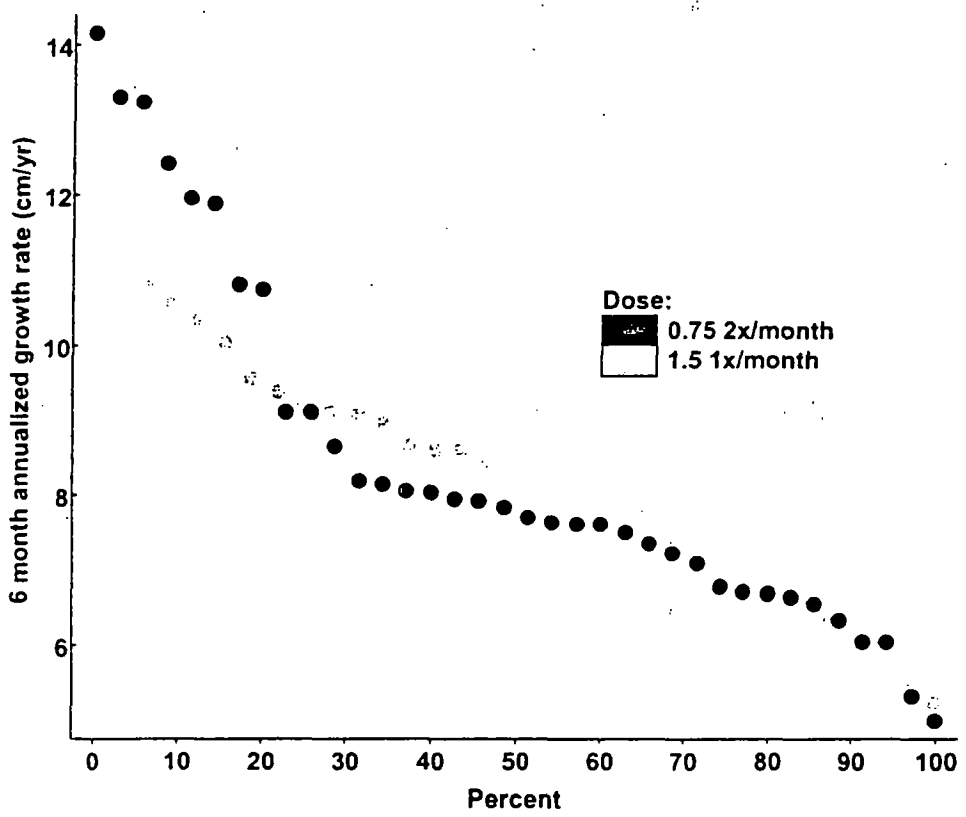
Figure 3. Comparison of Distribution of Annualized Growth Rates in Two Treatment Groups



is

In addition, the on-study mean annualized growth rates were not significantly different in the 2 dose groups (delta=0.1 in the ITT analysis, p=0.8). As noted by the Agency's statistical reviewer, the 95% CI for this difference is -0.9 to 1.1; therefore, a difference of ~1 cm/yr in favor of either dosing regimen is consistent with the observed data. See Table 15.

As per protocol, the data from the 2 dose groups were then pooled. Not surprisingly, in subjects with 6 month annualized growth rates and pre-study growth rates (n=53), the on-study mean 6 month annualized growth rate in the pooled population (8.6 cm/yr) was significantly greater than the pre-study mean annualized growth rate (4.8 cm/yr) (p<0.0001). See Table 15.

In [redacted]03-004, the sponsor did not propose a comparison with historical controls treated with daily injections of rhGH. However, the sponsor did provide summary data for the L0368g

study (Nutropin AQ, NDA 20-522). In Table 16 below, data for the naïve patients dosed with 0.75 2x/mo combined with data for the naïve patients treated with 1.5 1x/mo are compared with data from the L0368g study (see similar analysis performed in [redacted]03-002 review). As in the case of children treated with daily injections of rhGH in the L0368g study, and as shown in Table 15 earlier in this section, the mean annualized growth rate achieved in the patients treated with Nutropin Depot was significantly greater than the pre-study mean annualized growth rate ($p<0.0001$, Wilcoxon signed rank test). However, as in [redacted]03-002, the mean annual growth rate was significantly larger in the patients who received daily injections of rhGH compared with the group receiving Nutropin Depot (delta=2.7 cm/yr, $p<0.0001$, t-test).

Table 16. [redacted]03-004 - Comparison of Mean Annualized Growth Rate in Naïve Patients Receiving 1.5 mg/kg/month of Nutropin Depot in Single or Twice Monthly Injections with Mean Annual Growth Rate in Naïve Patients Receiving Daily Injections of rhGH*

	N	Age	Bone age	Pre-study growth rate	Dose (mg/kg/mo)	Annualized Growth Rate
[redacted]03-004 (SD)	72	7.5 (2.9)	6.0 (2.6)	4.7 (2.4)	1.5	8.3 (2.0)
L0368g (SD)	62	8.0 (3.4)	6.5 (3.1)	4.8 (2.3)	~1.3	11.0 (2.9)

*Table compiled by statistical reviewer
**Reflects data for 19 patients excluded by sponsor

Reviewer Comment:
As discussed earlier during review of efficacy results for [redacted]03-002, although [redacted]03-004 was not a prospective, actively controlled trial comparing Nutropin Depot with daily injections of rhGH in naïve patients, the use of the L0368g study as a historical control is reasonable in this instance because of the comparable demographics/baseline characteristics of the children in both trials. Review of the literature confirms the validity of the first year annual growth rate reported in the L0368g study (i.e., 10.7-11.9 cm/yr).

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Secondary Efficacy Results

Standardized Height/Height SDS

For subjects who completed 6 months of therapy, the mean baseline height SDS were -3.0±1.2 in the 1.5 1x/mo dose group and -3.0±0.7 in the 0.75 2x/mo dose group. After 6 months of Nutropin Depot therapy, the height SDS increased to -2.6 in both dose groups. Therefore, the mean changes in height SDS from baseline to the end of Month 6 were 0.35±0.31 in the 1.5 1x/mo dose group and 0.31±0.23 in the 0.75q2 dose group ($p<0.0001$ for each group).

Table 17. [redacted]03-004 - Heights Standardized for Age and Sex (Mean±SD)

	1.5 1×/Month (n=33)	0.75 2×/Month (n=36)
Baseline Mean±SD (Range)	-3.0±1.2 [redacted]	-3.0±0.7 [redacted]
Month 6 Mean±SD (Range)	-2.6±1.1 [redacted]	-2.6±0.8 [redacted]
Δ Baseline to Month 6 Mean±SD (Range)	0.35±0.31 [redacted]	0.31±0.23 [redacted]
p-value	<0.0001	<0.0001

Bone Age

The baseline bone age delay relative to chronological age was ~1.5 years in both dose groups. The mean changes in bone age after 6 months of Nutropin Depot therapy were 0.4±0.3 years in the 1.5 1x/mo dose group and 0.5±0.3 years in the 0.75 2x/mo dose group. These data demonstrate that the average rate of bone age advancement was appropriate, indicating that the improvements in growth rate were achieved without undue skeletal maturation.

Anti-GH Antibodies

Serum samples obtained at 3 month intervals were assayed for anti-GH antibodies, using Genentech's [redacted]

assay. None of the naïve subjects in this study had positive antibody titers at baseline. After the initiation of Nutropin Depot therapy, the prevalence of antibodies increased to 38% at Month 3, and 39% at Month 6 in the 1.5 1x/mo dose group, and 69% at Month 3, and 61% at Month 6 in the 0.75 2x/mo dose group. The mean titers were <2.0 at both timepoints in both dose groups, and only 1 subject had a titer of >3.0. Historically, antibodies suspected of being growth attenuating have not been observed with titers this low. All serum samples with positive antibody titers (>1.0) were assayed for binding capacity. No subject had a binding capacity value >2 mg/L. As expected when antibody titers are low, the majority of the samples with positive titers had binding capacities that were below assay limits.

Most importantly, the distribution of the 6 month annualized growth rates for antibody (+) and antibody (-) subjects were very similar in both dose groups (i.e., there was no evidence of a negative association between a positive antibody titer and growth rate). Interestingly, Subject 1-401, who had the highest titer (3.2 at Month 6), and the highest binding capacity (0.398 mg/L at Month 6) observed, had a very robust 6 month annualized growth rate of 12.0 cm/yr. It is therefore highly unlikely that anti-GH antibodies attenuated the efficacy of Nutropin Depot during this study.

8.2.2.4 Safety Results

Extent of Exposure

The 74 subjects who were enrolled and dosed in this study were treated for an average of 0.47 years for a total of 35 subject-years of exposure. Sixty-nine of the subjects (93%) who were enrolled and received at least one dose of Nutropin Depot completed the 6-month study.

Deaths

There were no deaths during the study.

Serious Adverse Events

Four serious adverse events were reported during the study - 2 episodes of decompensated diabetes insipidus in the same patient, viral syndrome-induced dehydration, and aggressive

behavior in a child with attention deficit-hyperactivity disorder, all requiring brief hospitalization. None of the events were considered to be related to treatment with Nutropin Depot, which continued uninterrupted for all 3 subjects.

Adverse Events Leading to Withdrawal

Three subjects discontinued from the study because of injection related reasons - pain during injection (n=1) and fear of injections (n=2). Another subject withdrew because of ill defined, periodic weakness and dizziness.

Adverse Events Associated with GH Therapy

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

2. Hypothyroidism - Seven patients were being treated with L-thyroxine at baseline. No additional cases of hypothyroidism were unmasked by Nutropin Depot therapy.

3. Allergy - No patients manifested allergy to the Nutropin Depot formulation.

4. Arthralgia probably related to Nutropin Depot therapy was reported by 2 subjects. One of these children (0.75 2x/mo dose group) required a temporary (2 dosings) 50% reduction in dosage. There were no reports of carpal tunnel syndrome.

5. Hyperglycemia - Patients with known diabetes mellitus were excluded from the study. Glucose metabolism was monitored by measurement of fasting and postprandial glucose and insulin levels, as well as hemoglobin A1C. As in [redacted]03-002, there were no significant changes in mean fasting or postprandial glucose or insulin levels, or mean hemoglobin A1C, noted after 6 months of Nutropin Depot therapy.

No subject developed diabetes mellitus during the study. De novo sporadic elevations of glucose and insulin levels were observed in individual subjects; however, these abnormalities did not persist.

In addition, several subjects had elevations of fasting and/or postprandial glucose levels at baseline that, in some cases, persisted during the study. Subject 22-402 (6 year old male in the 1.5 1x/mo dose group) and subject 9-403 ??(4.5 year old female in the 0.75 2x/mo dose group), both had elevated baseline pre-treatment postprandial glucose levels (118 mg/dl and ??mg/dl). During the course of the study, postprandial glucose values increased further (178 mg/dl-Month 3 and 165 mg/dl-Month 6 in subject 22-402, 145 mg/dl-Month 3 and 156-Month 6 in subject 9-403). Importantly, FBG and hemoglobin A1C remained normal throughout the study in both patients.

Adverse Events Related to Injection Site Reactions

Nutropin Depot was administered as a SC injection every 2 or 4 weeks. The very high incidence of injection site-related adverse events in [redacted]03-002 resulted in modification of drug administration procedures in [redacted]03-004 in an attempt to improve the tolerability of injections. Instead of 22 gauge, 1 inch needles, 21 gauge, ½ inch [redacted]needles were used in [redacted]03-004. Furthermore, extensive instructions were prepared for at-home injections as detailed earlier in the Dosage and Administration section of this review. Parents and subjects were instructed to record observations of the injection sites daily and to report these observations to the investigator during clinic visits. In addition, parents were given special instructions to assess pain during injection (see ahead).

Table 18 below was compiled by this reviewer using datasets supplied by the sponsor; it reports the number/percentage of patients experiencing a given injection site-related adverse event at least once during the study - for each dose group and for both dose groups combined. It is evident that the incidence of injection site reactions remained extremely high during this study with no meaningful differences between dose groups. Seventy three of the 74 subjects treated with Nutropin Depot reported adverse events related to the injection site. As noted earlier, 1 of the 74 subjects discontinued treatment because of pain during injection and 2 other subjects discontinued therapy because of fear of injections. The most frequent injection site reactions were pain during injection, nodules, erythema and pain post-injection with incidence rates of 93%, 86%, 85%, and 73% respectively (when both dose groups are combined). The incidence of lipoatrophy was 28% for the entire cohort. The great majority of these injection site reactions were rated as mild to moderate in intensity. In [redacted]03-002, pain during injection was the injection site reaction most frequently rated

as severe. As a result, the sponsor employed the Wong-Baker FACES pain rating scale in an attempt to more precisely gauge the severity of this particular injection site-related adverse event (see ahead).

Table 18. [redacted]03-004 - Number/% of Patients in Each Dose Group Experiencing Injection Site Reaction at Least Once

INJECTION SITE ADVERSE REACTION	Both dose groups combined n=74	1.5 1x/mo n=36	0.75 2x/mo n=38
PAIN DURING INJECTION*	69/93%	35/97%	34/92%
NODULES	64/86%	30/83%	34/92%
ERYTHEMA	63/85%	34/94%	29/78%
PAIN POST INJECTION	54/73%	29/81%	25/68%
BRUISING	47/64%	23/64%	24/65%
EDEMA	26/35%	14/39%	12/32%
ITCHINESS	23/31%	12/33%	11/30%
LIPOATROPHY	21/28%	14/39%	7/19%
REACTION	9/12%	3/8%	6/16%
WARMTH	8/11%	3/8%	5/14%
INDURATION	3/4	2/6%	1/3%

In order to better assess pain during injection, parents or guardians administering the injections were instructed in how to utilize the Wong-Baker FACES Pain Rating Scale. The scale is an adaptation of the picture-projection technique in which 6 faces are shown to a child. In this scale, Face 0 corresponds to "no hurt", Face 5 to "hurts worst", and Faces 1-4 to gradations of hurt between Face 0 and Face 5. The parent was instructed to ask the child following each dosing to choose the face that best described how he or she felt. At Month 1, 56 injections (40%) were reported as Face 5. At Month 6, 21 (16%) were reported as Face 5. The mean score decreased from 3.1 at Month 1 to 2.3 at Month 6, suggesting improved tolerability of Nutropin Depot injections over time.

As in [redacted]03-002, the total number of injection site reactions was compared with the total number of injections administered during the study. This is shown in Table 19. The ratio of total number of injection site reactions to total number of injections was ~3/1 (very similar to [redacted]03-002 results) - a

statistic which once again underscores the inordinately high incidence of injection site reactions after the administration of Nutropin Depot.

Table 19. [redacted]03-004 - Injection Site Reactions Compared with Total Number of Injections

TOTAL # OF INJCTNS	# OF INJCTN SITE REAX	# OF severe INJCTN SITE REAX
806	2553	28

As in [redacted]03-002, the total number of each specific type of injection site reaction was also compared with the total number of injections administered in the study. Notably, the percentage of injections with pain post-injection for all subjects irrespective of dose group was 40% in this study as opposed to 66% in [redacted]03-002. Downward trends were NOT observed for the other frequent injection site reactions (i.e., nodules, erythema, bruising and lipoatrophy) when the results of [redacted]03-004 were compared with [redacted]03-002.

Further issues regarding injection site reactions:

1) As in [redacted]03-002, review of Case Report Forms reveals no evidence that any of the subjects in this study elected to take more than the required number of injections to reduce the volume per injection and possibly the pain during injection.

2) In view of the remarkably high incidence of injection site-related adverse events after the administration of Nutropin Depot, the question arose as to whether there was a highly susceptible subgroup of GH deficient children sustaining the bulk of these adverse events. At the request of this reviewer, the sponsor recently performed an analysis of the naïve subjects who completed [redacted]03-004 (wherein injection procedures had been modified and optimized based on the experience obtained in [redacted]03-002).

Figure 4 shows 1) the overall mean number of injection site-related adverse events per injection was ~2.5 (range, [redacted] to [redacted] without bimodal clustering); and 2) both the mean and the range of adverse events per injection were similar for patients with smaller and larger number of injections (most of the subjects had received either 6 or 12 injections during the course of the study). In a similar vein, the mean number of injection site-related adverse events per injection in patients

receiving either 1, 2 or 3 injections per dosing were almost identical (~2.5) (see Table 20). Figure 4 also demonstrates a slight inverse correlation between the number of adverse events per injection and the number of injections when both dose groups were combined (r=-0.2 and p=0.03). When patients with event/injection ratios above and below the overall mean number of injection site-related adverse events per injection (~2.5) were compared (by the sponsor), no distinguishing characteristics were uncovered (see Table 21).

Figure 4. [redacted]03-004 - Events/Injection vs. Total Number of Injections in Study

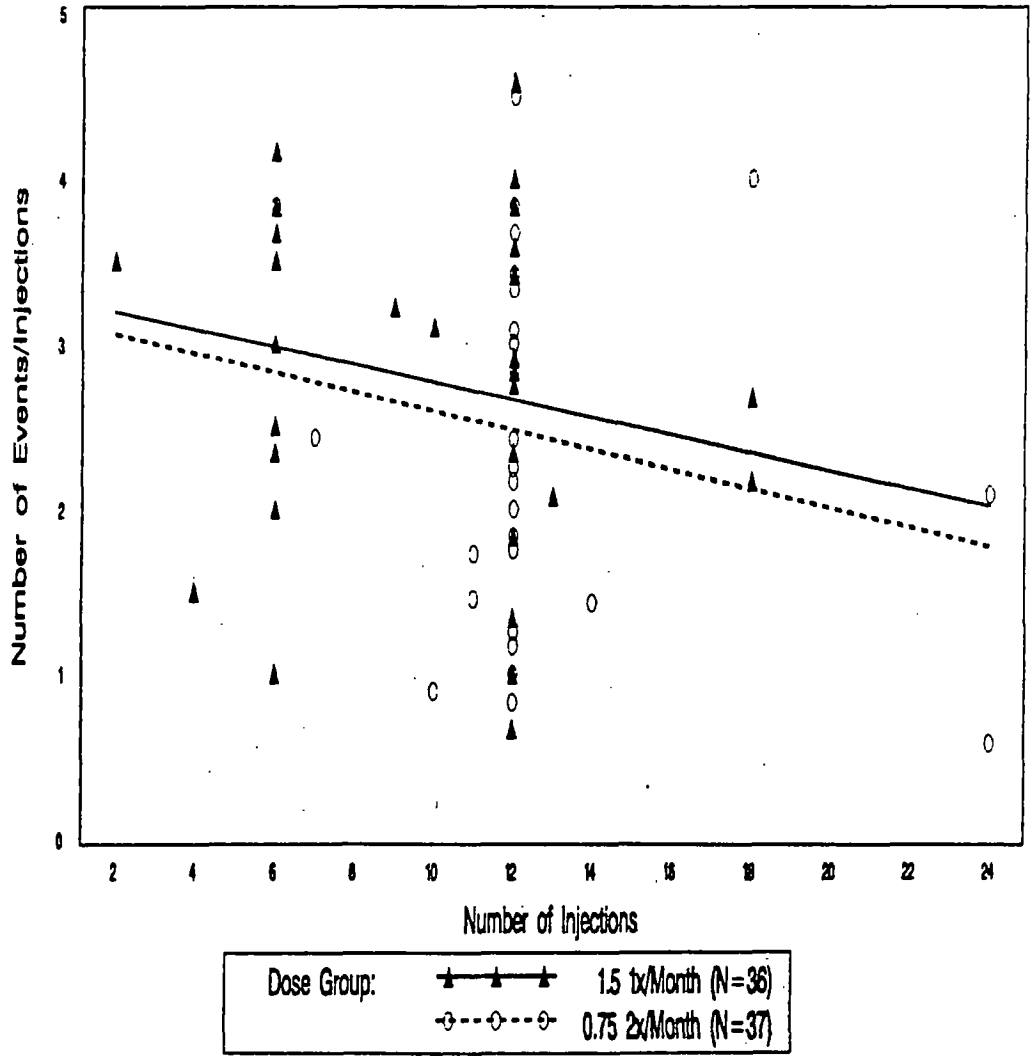

Table 20. [redacted]03-004 - Events/Injection vs. Number of Injections per Dosing

No. of Injections per Dosing	No. of Events (Erythema, Lipoatrophy, Nodules, Pain During Injection, Pain Post Injection)	No. of Injections	No. of Events per Injection
1	1224	473	2.6
2	720	294	2.4
3	93	39	2.4
Total	2037	806	2.5

Table 21. [redacted]03-004 - Baseline Characteristics

	≤ 2.5 events/injection (N=35)	> 2.5 events/injection (N=39)
Baseline Age (yrs)		
Mean	7.9	7.1
S.D.	2.6	3.2
Min-Max	3.5-11.8	1.6-12.2
Body Mass Index (kg/m²)		
Mean	16.0	16.2
S.D.	2.8	2.2
Min-Max	10.7-26.8	13.3-23.2
Sex (N)		
Male	26	24
Female	9	15

Other Adverse Events by Body System

Subjects were asked to report any adverse events or intercurrent illnesses at each monthly visit. Fifteen (20%) of the 74 subjects enrolled and treated reported the occurrence of "post-dosing" nausea, vomiting, headache or fever on at least one occasion during the study. Results of physical examination, including funduscopic examinations to rule out intracranial hypertension, were unrevealing. Similar observations were made during [redacted]03-002. Please refer to ISS for further incidence data generated by the sponsor at the request of this reviewer regarding this group of "post-dosing" adverse events (collectively and individually).

Physical examination and vital signs

No consequential changes occurred during the study.

Miscellaneous laboratory parameters

During the 6 month course of this study no consequential, clinically significant or consistent changes were observed in renal function, urinalyses, hematologic parameters, electrolytes, calcium, phosphate, lipids or liver function. Alkaline phosphatase increased from baseline as expected in children with GHD growing in response to rhGH therapy.

GH PK Data and IGF-I, IGFBP-3, and GHBP Data* (with implications for safety more than efficacy in this study) *See Biopharmaceutics Review for more detailed description and analysis

Trough serum concentrations of GH, IGF-I, and IGFBP-3 were measured at the end of the dosing cycle at Months 3 and 6 and compared with baseline values. Mean baseline GH levels were unremarkable and mean baseline IGF-I levels (104 to 120 ng/ml) were, as expected, at the lower end of the normal reference range for 7 to 11 year old males (88 to 110 ng/ml lower limit). No significant changes in trough GH or IGF-I concentrations were noted in the 1.5 1x/mo dose group at Month 3 or Month 6 compared with baseline. In the 0.75 2x/mo dose group, there were significant but extremely modest increases in trough GH and IGF-I concentrations at Month 3 and Month 6 (but Month 3 and Month 6 GH and IGF-I values were not different from each other). IGFBP-3 concentrations at Month 3 and Month 6 were not significantly elevated compared with baseline in either dose group. See Table 18.

Table 22. [redacted]03-004 - GH and IGF-I Results

	Baseline	Month 3	Month 6
0.75 2×/Month			
GH (ng/mL) (n)	1.7±2.0 (33)	3.1±2.2[A] (33)	3.1±2.7[A] (33)
IGF-I (ng/mL) (n)	104±73 (34)	127±70[A] (34)	125±64[A] (34)
IGFBP-3 (mg/L) (n)	2.2±0.9 (34)	2.4±0.9 (34)	2.3±1.0 (34)
1.5 1×/Month			
GH (ng/mL) (n)	2.2±3.7 (33)	3.1±4.0 (33)	2.2±1.9 (33)
IGF-I (ng/mL) (n)	120±78 (33)	111±77 (33)	129±73[B] (33)
IGFBP-3 (mg/L) (n)	2.1±0.9 (33)	2.2±1.0 (33)	2.3±0.9 (33)

Note: Results are based on subjects with baseline, Month 3, and Month 6 measurements.
[A]P<0.05 vs. baseline. [B]P<0.05 Month 3 vs. Month 6.

Reviewer Comment:
These data indicate no clinically significant accumulation of GH, IGF-I, or IGFBP-3 during 6 months of treatment with Nutropin Depot which could have resulted in acromegaloid adverse effects. The increases in GH and IGF-I levels from baseline in the 0.75 2x/mo dose group were very small.

8.2.3 Discussion

8.2.3.1 Efficacy Discussion

In this study, as in [redacted]03-002, the mean 6 month annualized growth rate of growth hormone deficient patients naïve to rhGH therapy treated with Nutropin Depot was significantly greater than the mean pre-study growth rate and similar in both dose groups. Mean standardized height improved significantly as well (~0.3 to 0.4 in both dose groups) and the rate of bone age advancement was appropriate in both dose groups, indicating that the improvements in growth were not accompanied by an undue advancement of bone age.

However, as in [redacted]03-002, the mean 6 month annualized growth rate was significantly less than the annual growth rate achieved by well matched historical controls treated with daily injections of rhGH (mean delta=2.7 cm/yr, p<0.0001). With the exception of 1 patient in particular, the sponsor noted that noncompliance was not an issue in this study, and, as noted

earlier, steps were taken to ensure optimal preparation and administration of the study drug. The mean age of the naïve patients who received Nutropin Depot (~7.5 cm/yr) was slightly less than the mean age of the naïve patients who were treated with daily rhGH in the L0368g study (~8 cm/yr). Therefore, noncompliance, problems with drug administration and selection of an older cohort are NOT likely explanations for this relative lack of efficacy. In addition, in contrast to [redacted]03-002, the baseline pre-treatment mean annualized growth rate in both treatment arms was much more appropriate (≤5 cm/yr), making it much less likely that patients who were not truly growth deficient and therefore less prone to respond to therapy were included in the study.

The observed relative lack of efficacy after treatment with Nutropin Depot compared with daily injections of rhGH more than likely relates to the GH PK profile and GH-induced IGF-I response following the administration of Nutropin Depot. As discussed in detail in the Efficacy Discussion section of [redacted]03-002, it is feasible that the markedly decreased rhGH bioavailability after Nutropin Depot administration compared with rhGH bioavailability after daily rhGH injections, unsustained normalization of serum GH and IGF-I levels following administration of Nutropin Depot (return to baseline levels ~2 weeks after dosing), and disproportionate maximal exposure to rhGH in the 2 days following injection may be explanatory factors. In addition, it is not clear whether the varying concentration of rhGH in the injectate utilized, injection site location or the number of injections per dosing (usually 1, 2, or 3) impacted the bioavailability of rhGH.

As in [redacted]03-002, 1.5 1x/mo and 0.75 2x/mo resulted in very similar mean annualized growth rates. However, as demonstrated in Figure 3 (a distribution plot comparing the annualized growth rates of all subjects in each dose group), 6 patients treated with 0.75 2x/mo, as opposed to only 1 patient treated with 1.5 1x/mo, achieved growth rates ≥12 cm/yr. This suggests that twice a month dosing may possibly be more efficacious than once a month dosing. The bioavailabilities of rhGH/$GH_{AUC0-28}$ after the administration of 1.5 1x/mo and 0.75 2x/mo have not been directly compared. Twice monthly injections produce 2 smaller bursts of rhGH (as opposed to one large burst after a single injection), and perhaps result in more days when GH (and IGF-I) blood levels remain above baseline (i.e., greater GH exposure and $GH_{AUC0-28}$). Hence, the sponsor should consider comparing the efficacy of twice- and once-monthly dosing in large numbers of patients during post-marketing studies.

8.2.3.2 Safety Discussion

The 74 subjects with GHD who were enrolled in this study were treated an average of 0.47 years for a total of 35 subject-years of exposure.

Analysis of GH PK and IGF-I trough levels at 3 and 6 indicates that GH and IGF-I did not accumulate inappropriately over time.

There were no deaths or serious adverse events related to study drug. None of the severe but unusual side effects associated with rhGH therapy were observed in this study. One patient developed severe protracted bilateral knee arthralgia which necessitated a transient (1 month) 50% reduction in dosage. No subject developed diabetes mellitus. Although transient elevations of glucose and insulin were occasionally observed in individual subjects. there were no significant changes in mean fasting or postprandial glucose or insulin levels, or mean hemoglobin A1C, noted after 6 months of Nutropin Depot therapy.

In contrast to the very small incidence of injection site-related adverse events associated with daily injections of rhGH, and in spite of modifications in study drug administration and the issuance of comprehensive instructional materials to the parents and guardians, the incidence of injection site reactions remained extremely high during this study with no meaningful differences between dose groups. The ratio of total number of injection site reactions to total number of injections 3/1 (compared with 2.5/1 in [redacted]03-002)! The most frequent injection site reactions were pain during injection, nodules, erythema and pain post-injection with incidence rates of 93%, 86%, 85%, and 73% respectively (when both dose groups are combined). The incidence of lipoatrophy was 28% for the entire cohort. The great majority of these injection site reactions were rated as mild to moderate in intensity (by the sponsor).

When both dose groups are combined, pain post-injection decreased from 91% in [redacted]03-002 to 75% in [redacted]03-004 (number of subjects experiencing at least 1 episode during study ÷ total number of subjects exposed) and from 66% to 40% (number of events ÷ total number of injections) - suggesting slightly better tolerability of Nutropin Depot in [redacted]03-004. However, there was no decrease in the incidence of erythema, nodules, bruising or lipoatrophy. Please refer to ISS for a comparative analysis of all studies with regard to these parameters.

The sponsor instructed parents and guardians how to utilize the Wong-Baker FACES pain rating scale to better assess the severity of **pain during injection**. The data collected suggests than during the 6 month course of therapy with Nutropin Depot, severe pain during injection diminished significantly. These findings suggest improved toleration of Nutropin Depot over time. On the other hand, the percentage of subjects experiencing at least 1 episode of pain during injection/total number of subjects exposed increased from 31% in [redacted]03-002 to 93% in [redacted]03-004. However, these data are significantly biased by the fact that the FACES scale was used in [redacted]03-004 to solicit adverse information and no pain instrument was utilized in [redacted]03-002. In addition, there was no evidence any of the subjects in this study elected to take more than the required number of injections to reduce the volume per injection and possibly the pain during injection.

The relative constancy of the mean number of injection site-related adverse events per injection (~2.5) irrespective of the number of injections administered, the lack of bimodal clustering when the range of events per injection is plotted, and the absence of characteristics which distinguish patients with event/injection ratios above and below the overall mean number of events per injection makes it unlikely that there is a subset of GH deficient patients more susceptible to injection site-related adverse events after treatment with Nutropin Depot. In addition, the slight inverse correlation between the number of adverse events per injection and the number of injections when both dose groups were combined suggests that an increased number of injections did not appear to predispose (sensitize) patients to more frequent adverse events.

As in [redacted]03-002, ~23% of subjects (both dose groups combined) reported transient headache, nausea, vomiting or fever at least once 1-2 days "post-dosing". This incidence contrasts with the rarity of similar post-dose phenomena in studies of similar children treated with daily injections of rhGH. Of course, since these latter children receive daily injections, it is much more difficult to discern what symptoms are possibly related to dosing. Please refer to ISS for a comparative analysis of all studies with regard to these parameters.

8.2.4 Conclusions

8.2.4.1 Efficacy

Nutropin Depot was clearly not as effective as daily injections of rhGH in stimulating growth in these children with GHD naïve to rhGH therapy. The mean annualized 6 month growth rate achieved after 6 months of Nutropin Depot therapy was significantly greater than the pre-study baseline annualized growth rate of these children, but was significantly less than the annual growth rate observed in a comparable group of children treated with daily injections of rhGH in an earlier pivotal study performed by the sponsor. As noted earlier, the administration of rhGH TIW (0.3 mg/kg/week) has also been shown to be not as effective as daily injections of rhGH (identical weekly dosage) in naïve patients with GHD; interestingly, the difference in growth rate after the first year of therapy in that trial (2.6 cm/yr) is quite similar to the difference in annualized growth rate observed when Nutropin Depot therapy and daily injections of rhGH are compared (2.3 cm/yr). In that 1.5 1x/mo and 0.75 2x/mo resulted in very similar mean annualized growth rates in these naïve subjects, the frequency of dosing does not appear to explain the decreased efficacy observed after Nutropin Depot therapy. However, the fact that more patients receiving 0.75 2x/mo had growth rates exceeding 14 cm/yr suggests that further comparison of these 2 dosing regimens should be considered. More than likely, the diminished efficacy observed after treatment of naïve patients with Nutropin Depot relates to the GH PK profile and the GH-induced IGF-I response observed after Nutropin Depot administration (i.e., in particular, the markedly decreased rhGH bioavailability after Nutropin Depot administration compared with rhGH bioavailability after daily rhGH injections). This reviewer agrees with the sponsor's decision at that point in time to further study

[redacted]

8.2.4.2 Safety

The overall safety of Nutropin Depot in this study was satisfactory. However, injection site-related adverse events were extremely common - as many as 3 events for every injection administered. This contrasts with the minimal incidence of injection site reactions after daily injections of rhGH. In

addition, 23% of the children in this study reported transient post-dose symptomatology (including headache, nausea, vomiting or fever) which contrasts as well with the minimal incidence of these phenomena after daily injections of rhGH. This reviewer agrees with the sponsor's decision at that point in time to further evaluate the

8.3 Study 03-003*

*This review is based on information in 1) 03-003 report in original NDA submission in 6/99, 2) 9/99 efficacy update for 03-003 and 3) 10/99 safety update for 03-003

8.3.1.1 Objectives

The objectives of this study were to determine the long-term safety and efficacy of a new sustained-release formulation of rhGH, Nutropin Depot.

8.3.1.2 Study Design

Study Design/Description of Study

03-003 is an ongoing, multicenter, open label, parallel group study designed to evaluate the long term safety and efficacy of Nutropin Depot administered as an SC injection. 03-002 is an extension study for 03-002 and 03-004. Subjects who completed 03-002 or 03-004 were eligible to enroll. Thirty five patients (20 naïve and 15 CT) who had completed 6 months of therapy in 03-002 (original enrollment 64 = 26 naïve and 38 CT) and (at a later date) 61 naive patients who had completed 6 months of therapy in 03-004 (original enrollment 74) were enrolled in this study. The initial doses employed in this study were essentially the same doses used in 03-002: 0.75q4, 1.5 1x/mo or 0.75 2x/mo. As stated earlier in this review, following a review of the data from 03-002, it was decided to utilize only the 2 larger doses in the Phase III study, 03-004, and for the remainder of 03-002. As a result, 10 subjects (5/20 naïve and 5/15 CT), who had been dosed with 0.75q4 in 03-002 and who had already been enrolled and treated with 0.75q4 in 03-003 (for 1 to 4 months!), were subsequently randomized to receive either 0.75 2x/mo or 1.5 1x/mo. Subjects who were dosed with either 0.75 2x/mo or 1.5 1x/mo in 03-002 and 03-004 continued those same doses in 03-003.

Subjects may continue in [redacted]03-003 as long as rhGH treatment is clinically indicated, until the product becomes commercially available, or until the study is discontinued by the sponsor. As in [redacted]03-004 (but unlike [redacted]03-002 where trained health care professionals administered injections), the SC injections in this extension study were administered usually at home by a parent or guardian. Evaluations performed at the final scheduled visit at the end of Month 6 for Studies [redacted]03-002 or [redacted]03-004 served as the baseline assessments for Study [redacted]03-003. However, throughout this report, baseline refers to the beginning of Study [redacted]03-002 and all timepoints are relative to this baseline.

8.3.1.3 Protocol

Protocol Amendments

The protocol was modified once in ways that do nor merit comment at this time.

Materials and Methods

Subjects

Subject Selection

Thirty five patients (20 naïve and 15 CT) who had completed 6 months of therapy in [redacted]03-002 and 61 naive patients who had completed 6 months of therapy in [redacted]03-004 (original enrollment 74) were enrolled in this study. See Study Design section above for a more detailed description.

Inclusion Criteria

The most consequential inclusion criteria for this study were completion of [redacted]03-002 or [redacted]03-004 with demonstrated compliance, use of acceptable contraception in females with childbearing potential and a commitment from the parent or guardian to administer the assigned dosage and monitor the injection site.

Exclusion Criteria

The most consequential exclusion criteria were demonstrated noncompliance in either of the feeder studies and unwillingness to continue in the extension study for whatever reason.

Method of Treatment Assignment

Please refer to the Study Design section above.

Study Treatment

Formulation

Nutropin Depot is a sustained-release formulation of somatropin (rhGH, Genentech). Please refer to reviews of [redacted]03-002 and [redacted]03-004 for a more detailed description.

Dosage and Administration

The dose for each subject was calculated according to the individual's weight (baseline weight was used for the first 3 months of the trial and then weight at 3 month visits were used for rest of trial), and was administered as a SC injection. Subjects received 0.75 mg/kg of Nutropin Depot twice monthly or 1.5 mg/kg of Nutropin Depot monthly. As noted above some subjects received 0.75 mg/kg of Nutropin Depot monthly for 1 to 4 months before being switched over to 1 of the 2 larger dosages. Five dosage units of Nutropin Depot were used in this study, 18 mg of deliverable rhGH + 1.5 ml of CMC solution diluent (concentration 13 mg/ml), 27 mg of deliverable rhGH + 1.5 ml of diluent (concentration 19 mg/ml), 22.5 mg of deliverable rhGH + 1.2 ml of CMC solution diluent (concentration 19 mg/ml), 22.5 mg of deliverable rhGH + 1.0 ml of CMC solution diluent (concentration 22 mg/ml), 22.5 mg of deliverable rhGH + 0.9 ml of CMC solution diluent (concentration 25 mg/ml). The very high incidence of injection site-related adverse events in [redacted]03-002 resulted in modification of drug administration procedures in [redacted]03-004 in an attempt to improve the tolerability of injections. These modifications are described in detail in review of [redacted]03-004.

****If the total volume for any dose exceeded 1.2 ml, the dose was divided and administered at more than 1 injection site.**

Dosage Modification

As already noted, 10 patients receiving 0.75q4 for 1 to 4 months were randomly switched to either 0.75 2x/mo or 1.5 1x/mo. Dosage for each individual subject was adjusted for change in weight at each 3 month visit.

Concomitant Therapy

Please refer to reviews of [redacted]03-002 and [redacted]03-004. The amendment to the protocol allowed the enrollment of patients ingesting cyproheptadine and methylphenidate which had not been permitted in the other 2 studies.

8.3.1.4 Study Assessments

Baseline Assessments

Comprehensive final assessments performed at the end of [redacted]03-002 and [redacted]03-004 constituted the baseline assessments for [redacted]03-003.

Assessments during Treatment

Efficacy Parameters

The primary efficacy endpoint was the 12 month annual growth rate.

Secondary efficacy endpoints included height age, standardized height (height SDS), bone age and Bayley-Pinneau predicted adult height (PAH). The titer and binding capacity of anti-GH antibodies were determined as well.

Standardized height, height age, bone age and anti-GH antibody titer/binding capacity were computed/determined as described for [redacted]03-002 and [redacted]03-004. Bayley-Pinneau PAH was calculated using the Bayley-Pinneau tables.

Height, weight, Tanner stage and anti-GH antibody measurements were performed every 3 months; bone age was reassessed after 6 months of therapy in [redacted]03-003.

Safety Parameters

Safety assessments were made based on adverse event reports, as well as interim histories and physical examinations, every 3 months, and laboratory studies after 6 months of therapy in [redacted]03-003.

PK Parameters and Biologic Markers (with both safety and efficacy implications)

Trough IGF-I and GH levels were determined every 3 months.

Subject Discontinuation

Criteria were identical to those described for [redacted]03-002 and [redacted]03-004 except for the addition of evidence of epiphyseal closure on bone age radiograph.

8.3.1.5 Statistical Analysis

Efficacy Analysis

Primary Outcome Measure

The 12 month annual growth rate (means and 95% CI) are presented by the sponsor for each dose group and both dose groups combined (the rates were similar) in naïve patients only. A paired t-test was used to evaluate the change in 12 month annual growth rate (i.e., the mean on-study 12 month annual growth rate minus the mean pre-study annualized growth rate) for each dose group and both dose groups combined. In addition, a post-hoc multiple regression analysis was performed to assess the importance of multiple variables as predictors of the response to Nutropin Depot therapy.

Secondary Outcome Measures

A paired t-test was used to evaluate the change in standardized height (standardized height after 12 months of therapy - baseline pre-treatment standardized height) in each dose group

for naïve patients only. Summary statistics for bone age, height age, change in height age minus change in bone age, and Bayley-Pinneau PAH are presented as well. The secondary endpoint of PAH (expressed in cm and as a SDS using normative data for adults) was added for [redacted]03-003 because the sponsor considered PAH a more valid measure after 12 months (as opposed to 6 months) of therapy.

Safety Analysis

Adverse events are tabulated by COSTART preferred term and body system for each dose group for all subjects. Injection site-related adverse events are tabulated separately from non-injection site-related events. Laboratory and other safety values (including vital signs) are summarized with simple descriptive statistics for each dose group, including means and SD, after 3 and 6 months of therapy in [redacted]03-003.

Data Quality Assurance

Accurate, consistent, and reliable data were ensured through the use of standard practices and procedures.

8.3.2 Results

Subject Eligibility and Treatment Assignment

Subjects who completed [redacted]03-002 or [redacted]03-004 were eligible to enroll. Thirty five patients (20 naïve and 15 CT) who had completed 6 months of therapy in [redacted]03-002 (6 month [redacted]03-002 completers = 53 = 24 naïve and 29 CT) and (at a later date) 61 naive patients who had completed 6 months of therapy in [redacted]03-004 (6 month [redacted]03-004 completers = 69 naive) were enrolled in this study. There was no interruption of therapy after enrollment. The initial doses employed in this study were essentially the same doses used in [redacted]03-002: 0.75q4, 1.5 1x/mo or 0.75 2x/mo. As stated earlier in this review, following a review of the data from [redacted]03-002, it was decided to utilize only the 2 larger doses in the Phase III study, [redacted]03-004, and for the remainder of [redacted]03-003. As a result, 10 subjects (5/20 naïve and 5/15 CT), who had been dosed with 0.75q4 in [redacted]03-002 and who had already been enrolled and treated with 0.75q4 in [redacted]03-003 (for 1 to 4 months!), were subsequently randomized to receive either 0.75 2x/mo or 1.5 1x/mo. Subjects who were dosed

with either 0.75 2x/mo or 1.5 1x/mo in [redacted]03-002 and [redacted]03-004 continued those same doses in [redacted]03-003.

Reviewer Comment:
Although 87% (81/93) of eligible naïve patients chose to enroll in [redacted]03-003, only 52% (15/29) of CT patients did so, more than likely related to dissatisfaction with the fall off in growth rate observed in [redacted]03-002 when the patients received Nutropin Depot therapy rather than daily injections of rhGH.

Protocol Violations and Deviations

No significant protocol violations were noted.

8.3.2.1 Subject Disposition

As noted above, 96 naïve and CT subjects who completed 6 months of treatment with Nutropin Depot [redacted]03-002 [n=35] or [redacted]03-004 [n=61] elected to enroll in the extension trial, [redacted]03-003. After 10 patients initially treated with 0.75q4 in [redacted]03-003 (5 naïve and 5 CT) were randomly switched over to 1 of the larger dosages, 45/96 were in the 1.5 1x/mo dose group and 51/96 were in the 0.75 2x/mo dose group. The 95 subjects who enrolled and received at least 1 dose of Nutropin are included in all evaluations of safety. The efficacy data presented by the sponsor for subjects completing 12 months of therapy with Nutropin Depot (6 months in the feeder study and 6 months in [redacted]03-003) is limited to the 69 rhGH-naïve patients (56 from [redacted]03-004 and 13 from [redacted]03-002) who were treated throughout the study with 0.75 2x/mo or 1.5 1x/mo, the dosages utilized in [redacted]03-004 and presently proposed for marketing. Data from 5 naïve patients treated initially in [redacted]03-003 for 1 to 4 months with 0.75q4 (a dosage considered by the sponsor to be less efficacious than the 2 higher dosages) were excluded when 12 month annual growth rates were determined in naïve patients. With regard to the CT patients, the sponsor presented preliminary 12 month annual growth rate data during [redacted]03-003 in the 6/99 original NDA submission, but chose not to update these results in the 9/99 efficacy update. The Agency's statistical reviewer did analyze this data and the results will be presented later in this review. See Table 23.

Table 23. [redacted]03-003 - Patient Disposition as of 6/99

	Naïve Subjects		CT Subjects		Total Subjects
	1.5 1x/mo[a] or 0.75 2x/mo[b] throughout study	0.75q4 initially	1.5 1x/mo[a] or 0.75 2x/mo[b] throughout study	0.75q4 initially	
Enrolled in [redacted]03-003:					
From [redacted]03-002	15 (a=6 and b=9)	5	10 (a=6 and b=4)	5	35
From [redacted]03-004	61 (a=28 and b=33)	0	0	0	61
Total	**76 (a=34 and b=42)**	5	**10 (a=6 and b=4)**	5	96
Completed 12 months In [redacted]03-003*:					
From [redacted]03-002	13	5	8 (a=5 and b=3)	5	31
From [redacted]03-004	56	0	0	0	56
Total	**69 (a=32 and b=37)**	5	**8 (a=5 and b=3)**	5	87
Completed 12 months in [redacted]03-003* and had pre-study growth rate data					
Total	**55 (a=24 and b=31)**	N/A	**8 (a=5 and b=3)**	N/A	N/A

*6 months in feeder study and 6 months in [redacted]03-003

One subject enrolled in [redacted]03-003 but did not return for scheduled visits and was not dosed. A total of 32 subjects had discontinued from the study as of 6/99, including 7 naïve patients (2 withdrew because of adverse events, 3 withdrew consent because of inadequate growth response and 2 were lost to followup) and 2 CT patients prior to completion of 12 months of therapy. The most common reason for discontinuation was inadequate growth response after Nutropin Depot therapy (resulting in withdrawal of parental consent or investigator-recommended withdrawal) in 24 of 32 patients (75%!). These 24 patients consisted of 15 of 81 naïve enrollees (19%) and 9 of 15 CT enrollees (60%). Three patients discontinued because of adverse events (pain during injection, lipoatrophy and "post-dosing" nausea and vomiting). See Table 24.

Table 24. [redacted]03-003 - Reasons for Discontinuation

		Dose Group	
	Overall	1.5 1x/Month	0.75 2x/Month
Number of subjects enrolled	96	45	51
Number of subjects dosed	95(99%)	45(100%)	50(98%%)
Number of subjects who discontinued	32(34%)*	18(40%)	14(28%)
Reasons for study termination:			
Adverse event	3(3%)	1(2%)	2(4%)
Protocol violation	0	0	0
Subject noncompliance	2(2%)	1(2%)	1(2%)
Subject withdrawal of consent**	12(13%)	7(16%)	5(10%)
Other***	15(16%)	9(20%)	6(12%)

*includes 7 naïve subjects and 2 CT subjects who discontinued prior to completion of 12 months of therapy
**withdrawal of consent because of inadequate growth response
***12 of these patients were discontinued by the investigator because of inadequate growth response

Reviewer Comment:
It is important to note that 75% of the patients who discontinued from [redacted]03-003 (60% of CT enrollees and 19% of naïve enrollees) did so because the growth response after Nutropin Depot therapy was considered to be inadequate.

8.3.2.2 Patient Characteristics

Demographic and baseline characteristics are presented for each dose group and both dose groups combined (the results for each dose group were very similar) for the 69 naïve subjects who completed 12 months of Nutropin Depot therapy (6 months in 1 of the feeder studies and 6 months in [redacted]03-003). Most of the patients were male and Caucasian. More than 90% had idiopathic GHD. Chronological age ranged from 1.6 to 12.2 with pooled mean age ~7.1. Mean bone age was delayed ~1.3-1.6 years. Thirty one out of 37 patients receiving 0.75 2x/mo and 24 out of 32 patients receiving 1.5 1x/mo had acceptable pre-study growth rates. The mean pre-study annualized growth rates were 4.9 cm/yr (0.75 2x/mo) and 5.3 cm/yr (1.5 1x/mo). Mean standardized height was severely diminished and very similar in the 2 dose groups (-2.9 in the 1.5 1x/mo dose group and -3.2 in the 0.75 2x/mo dose group). Overall, the subjects in the 2 dose groups had very similar baseline characteristics. Baseline characteristics were also very similar for each dose group in the 13 CT subjects who completed 12 months of Nutropin Depot therapy (results not shown). See Table 25.

Table 25. [redacted]03-003 - Demographic and Baseline Characteristics: Naïve Patients Completing 12 Months

	1.5 1x/Month (n=32)	0.75 2x/Month (n=37)	Pooled (n=69)
Sex, n (%)			
Male	18(56)	29(78)	47(68)
Female	14(44)	8(22)	22(32)
Etiology of GHD, n (%)			
Idiopathic	29(91)	35(95)	64(93)
Organic	3(9)	2(5)	5(7)
Chronological age (yr)			
Mean±SD	6.7±3.1	7.5±2.6	7.1±2.8
Range	1.6 to 12.2	3.2 to 11.9	1.6 to 12.2
Bone age (yr)			
Mean±SD	5.1±2.9	6.2±2.4	5.7±2.7
Range	0.2 to 11.1 (n=32)	2.1 to 10.4 (n=36)	0.2 to 11.1 (n=68)
Bone age delay (yr)			
Mean±SD	1.6±1.3	1.3±1.0	1.4±1.1
Range	-0.8 to 4.2 (n=32)	-1.9 to 3.4 (n=36)	-1.9 to 4.2 (n=68)
Previous growth rate (cm/yr)			
Mean±SD	5.3±2.1	4.9±1.6	5.1±1.8
Range	1.6 to 8.5 (n=24)	1.9 to 8.3 (n=31)	1.6 to 8.5 (n=55)
Standardized height			
Mean±SD	-2.9±1.2	-3.2±0.8	-3.0±1.0
Range	-6.7 to -0.6	-5.1 to -2.0	-6.7 to -0.6
Maximum stimulated GH (ng/mL)			
Mean±SD	5.3±2.7	6.0±2.9	5.7±2.8
Range	0.8 to 9.8 (n=27)	0.5 to 9.7 (n=29)	0.5 to 9.8 (n=56)

Compliance

Two patients were discontinued from [redacted]03-003 because of noncompliance and 1 other patient was discontinued because of problems with drug accountability. Otherwise, compliance with dosing, study procedures, and visit schedule were assessed to be adequate.

Concomitant Therapy

The most frequently used concomitant medication was EMLA cream applied prior to injection or venipuncture. As in [redacted]02-002 and [redacted]03-004, a number of patients were treated with L-thyroxine therapy for central hypothyroidism, replacement doses of hydrocortisone for central hypoadrenalism, and desmopressin for diabetes insipidus. Other concomitant medications used by

subjects were those used to treat pre-existing conditions or routine childhood ailments.

8.3.2.3 Efficacy Results

Naïve Subjects

Primary Efficacy Endpoint: 12 Month Annual Growth Rate

The primary efficacy endpoint for this study in naïve patients was the 12 month annual growth rate after therapy with Nutropin Depot. As stated earlier, the efficacy data presented by the sponsor for naïve subjects completing 12 months of therapy with Nutropin Depot is limited to the 69 naïve patients (56 from [redacted]03-004 and 13 from [redacted]03-002*) who were treated throughout the study with 0.75 2x/mo or 1.5 1x/mo, the dosages utilized in [redacted]03-004 and presently proposed for marketing. Data from 5 naïve patients treated initially in [redacted]03-003 for 1 to 4 months with 0.75q4 were excluded.
*Combining the data of the naïve patients from the 2 feeder studies is warranted based on the similarity of the demographics and inclusion criteria of those studies, and the similarity of the dose regimens for the 2 pivotal dose groups.

Fifty five of the 69 subjects who completed 12 months of therapy had pre-study growth rates which met the protocol criteria described earlier. In this subset of patients (n=55), the on-study mean 12 month annual growth rate was significantly greater than the pre-study mean annualized growth rate in both the 1.5 1x/mo and 0.75 2x/mo dose groups ($p<0.0002$ and $p<0.0001$, respectively, by paired t-test; see Figure 5 and Table 26). Moreover, the on-study mean 12 month annual growth rates for each dose group were very similar to each other, and also very similar in the subset with 12 month annual growth rates and pre-study growth rates, and all subjects with 12 month annual growth rates. See Table 26.

Table 26. [redacted]03-003 - Twelve Month Annual Growth Rates (cm/yr) by Dose Group for Naïve Subjects Completing 12 Months

	1.5 1X/Month	0.75 2X/Month	Pooled
Subjects with 12 month growth rates	(n=32)	(n=37)	(n=69)
12-Month growth rate			
Mean±SD	7.5±1.9	8.1±2.0	7.8±1.9
Range			
95% Confidence interval	6.9 to 8.2	7.4 to 8.7	7.4 to 8.3
Subjects with pre-study and 12 month growth rates	(n=24)	(n=31)	(n=55)
Pre-study growth rate			
Mean±SD	5.3±2.1	4.9±1.6	5.1±1.8
Range			
12 month growth rate			
Mean±SD	7.6±1.7	8.2±2.0	7.9±1.9
Range			
95% Confidence interval	6.9 to 8.4	7.5 to 8.9	7.4 to 8.4
p value: 12 month vs. pre-study	0.0002	<0.0001	<0.0001

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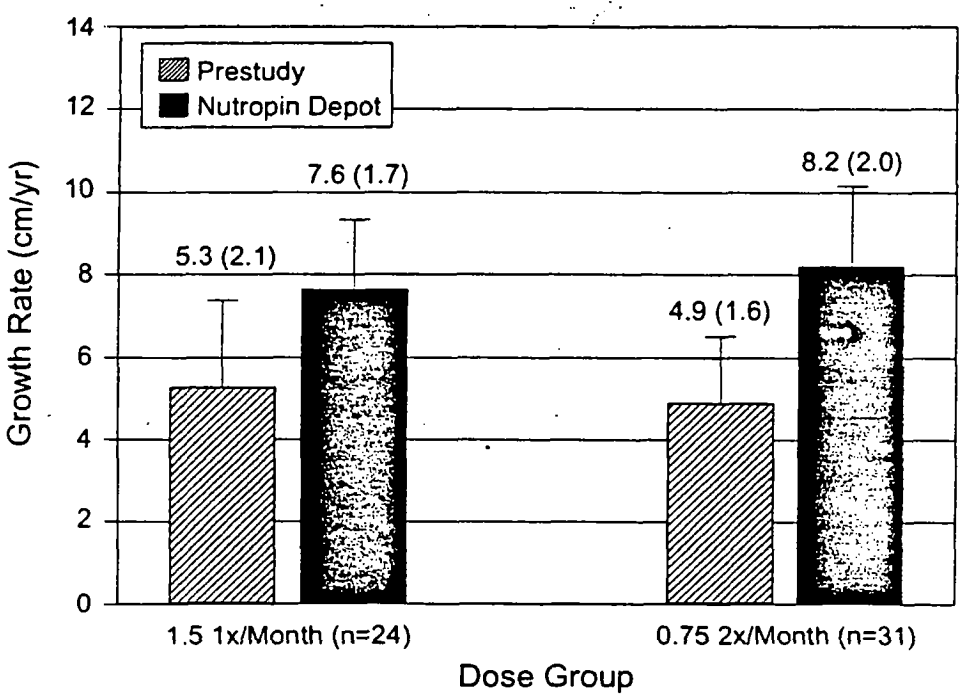
Figure 5. [redacted]03-003 - Twelve Month Annual Growth Rates (cm/yr) by Dose Group for Naïve Subjects with Pre-Study and 12 Month Values Mean (SD)



Reviewer Comment:
See Table 38 in the ISE for a comparison of the mean 12 month annual growth rates and the mean 6 month annualized growth rates of naïve subjects from [redacted]03-002 and [redacted]03-004 combined who completed 12 months in [redacted]03-003 (for each dose group and both dose groups combined). Interestingly, it shows that the mean 6 month annualized growth rates are ~1 cm greater than the mean 12 month annual growth rates of the same subjects.

Relationship of Baseline Characteristics to 12 Month Annual Growth Rates - Subgroup Analysis

The relationship between selected baseline characteristics and the 12 month annual growth rate after Nutropin Depot therapy was examined by the sponsor as well. This analysis was based on the pooled data of both dose groups for naïve subjects from [redacted]03-004 who had completed 12 months of therapy in [redacted]03-003 (n=56).

Based on a univariate analysis of discrete variables (i.e., a comparison of means between categories), no significant

relationships between 12 month growth rates and either sex (p=0.1756) or etiology (organic vs. idiopathic GHD; p=0.5783) were found. In addition, a univariate analysis of the correlation between selected continuous baseline characteristics and 12 month growth rate was performed. Two variables, maximum stimulated GH and chronological age, were negatively correlated with growth rate and significant (p<0.01). Bone age at baseline was also significant (p=0.0278) and negatively correlated with growth rate. Pre-study growth rate*, standardized height and bone age delay were not correlated with growth rate. See Table 27.

Table 27. Correlation between 12 Month Growth Rate and Selected Continuous Baseline Characteristics for Naïve Subjects from [redacted]03-004 Completing 12 Months of Therapy

Baseline Characteristic	N	Correlation Coefficient (r)	p value
Maximum stimulated GH level (ng/mL)	56	-0.3918	0.0028
Chronological age (yr)	56	-0.3502	0.0081
Bone age (yr)	55	-0.2967	0.0278
Standardized height	56	-0.1555	0.2523
Bone age delay (yr)	55	-0.1788	0.1916
Previous growth rate (cm/yr)	45	-0.0054	0.9719

A multiple regression analysis was also performed that included as independent variables the discrete and continuous baseline characteristics noted previously (excepting pre-study growth rate), and the 12 month annual growth rate as the dependent variable. Only maximum stimulated GH level and chronological age were identified by the multiple regression analysis as significantly (linearly) related to growth rate (at the p<0.05 level), after adjusting for baseline maximum stimulated GH level and chronological age.

Figure 6 shows the negative correlation between the 12 month annual growth rate and the maximum stimulated GH value (n=56). The mean annual growth rate for subjects with peak GH <5 mg/L (n=22) was 8.5±2.1 cm/yr compared with 7.3±1.4 cm/yr for subjects with peak GH >5 mg/L (n=34).

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Figure 6. [redacted]03-003 - Twelve Month Growth Rate vs. Maximum Stimulated Growth Hormone for Naive Subjects from [redacted]03-004 Completing 12 Months of Therapy (n=56)

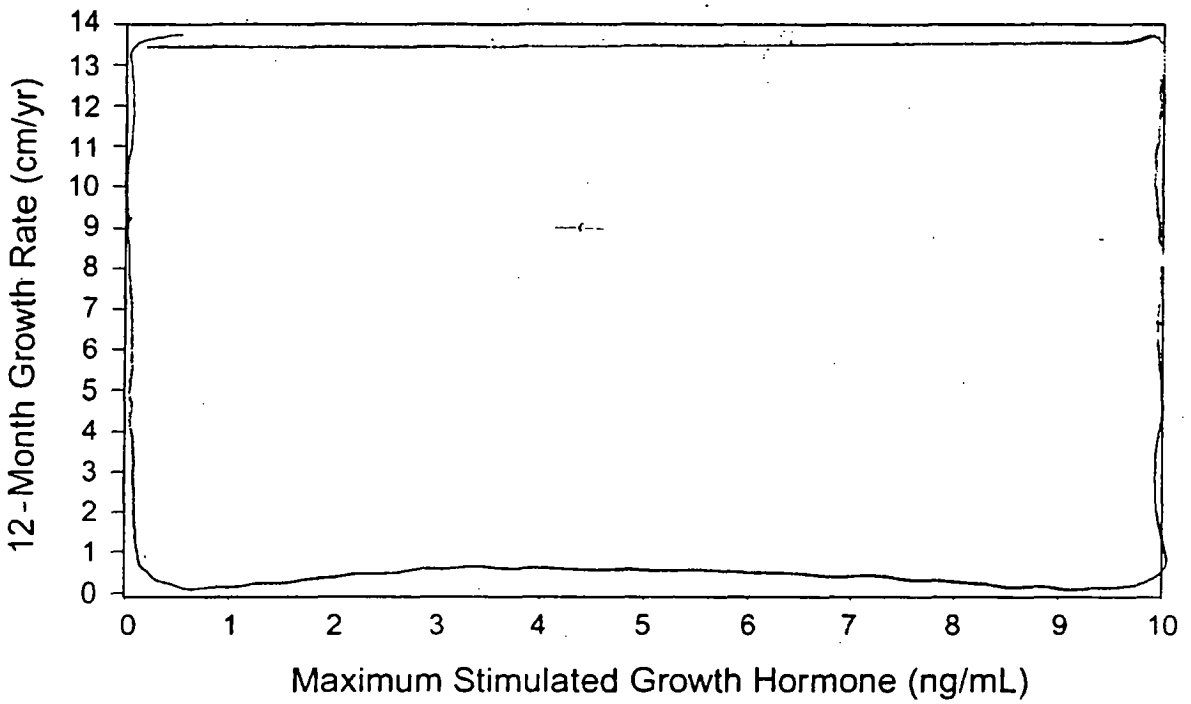

Figure 7 shows the negative correlation between the 12 month growth rate and the baseline chronological age (n=56). These data confirm the well known fact that younger children respond more robustly to rhGH therapy

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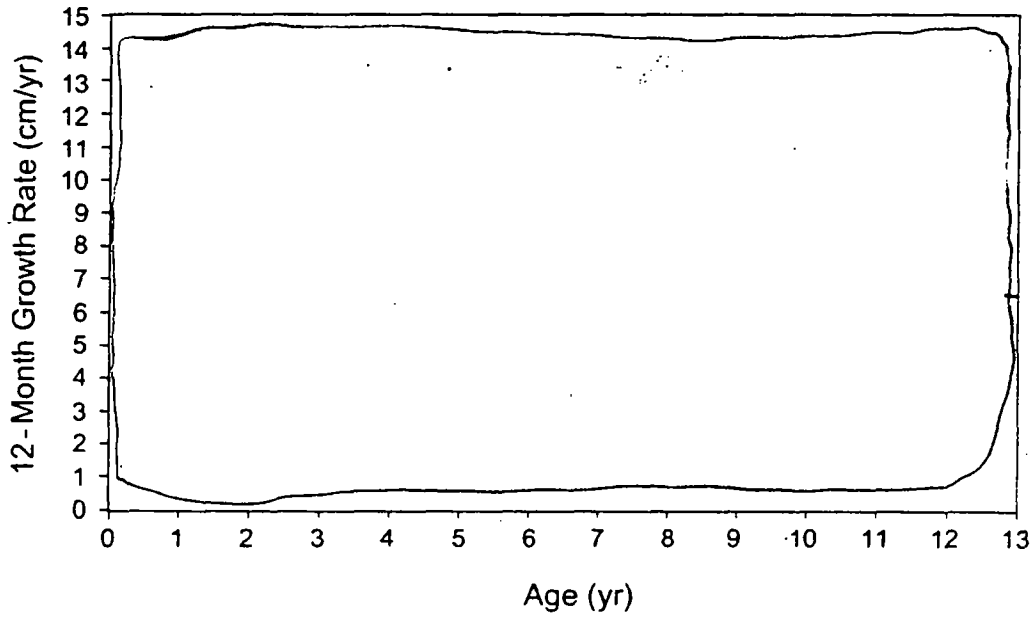
Figure 7. [redacted]03-003 - Twelve Month Growth Rate vs. Age for Naive Subjects from [redacted]03-004 Completing 12 Months of Therapy (n=56)



Secondary Efficacy Endpoints

Standardized Height/Height SDS

The mean baseline height SDS was markedly diminished (i.e., -2.93 in the 1.5 1x/month dose group [n=32] and -3.15 in the 0.75 2x/month dose group [n=37]). After 6 months of treatment with Nutropin Depot, the mean height SDS were -2.55 and -2.78, respectively, and after 12 months of therapy, the mean height SDS were further improved to -2.41 and -2.58, respectively. The change in height SDS was not significantly different for the 2 dose regimens ($p=0.6660$), and when data from the 2 dose groups were combined, the mean ($\pm$SD) change in height SDS from baseline to the end of Month 12 was 0.55 ± 0.39 with a range from [redacted] to [redacted] The change in height SDS was highly statistically significant in both dose groups and in the pooled data ($p<0.0001$). Thus, catch-up growth was evident after the first 6 months of therapy and continued improvement was observed after the second 6 months of treatment. See Table 28.

Table 28. [redacted]03-003 - Height Standardized for Age and Sex by Dose Group for Naïve Subjects Completing 12 Months, Mean±SD

	1.5 1x/Month	0.75 2x/Month	Pooled
	(n=32)	(n=37)	(n=69)
Baseline	-2.93±1.18	-3.15±0.77	-3.05±0.98
Month 6 (end of feeder study)	-2.55±1.01	-2.78±0.73	-2.68±0.87
Month 12	-2.41±1.03	-2.58±0.75	-2.50±0.89
Baseline to Month 6 change	+0.38±0.31	+0.37±0.23	+0.37±0.27
Baseline to Month 12 change	+0.53±0.43	+0.57±0.36	+0.55±0.39
Range			
p value	<0.0001	<0.0001	<0.0001

Bone Age

As noted earlier, the mean baseline bone age delay relative to chronological age was 1.4 years (see Table 24). The mean change in bone age after 12 months of Nutropin Depot therapy was 0.9±0.3 years in the 1.5 1x/month group (n=29) and 1.1±0.4 years in the 0.75 2x/month group (n=34); the difference between dose groups was not statistically significant (p=0.2016). When the dose groups were pooled, the mean change in bone age from 0 to 12 months was 1.0±0.4 years (n=63). These data demonstrate that the average rate of bone age advancement was normal and that the improvements in growth noted previously were not accompanied by an undue advancement of bone age. See Table 29.

Table 29. [redacted]03-003 - Bone Ages at Baseline and 12 Months by Dose Group for Naïve Subjects Completing 12 Months, Mean±SD

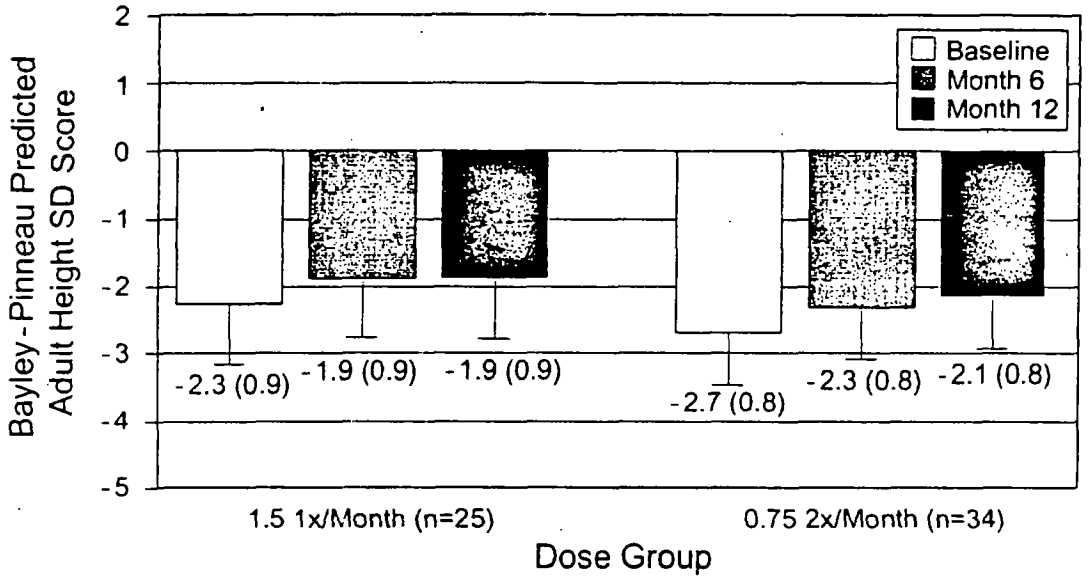
	1.5 1x/Month	0.75 2x/Month	Pooled
	(n=29)	(n=34)	(n=63)
Baseline	5.2±2.9	6.1±2.4	5.7±2.7
Month 12	6.2±2.9	7.2±2.4	6.7±2.6
Baseline to Month 12 change	0.9±0.3	1.1±0.4	1.0±0.4

Predicted Adult Height

The average baseline PAH SDS were markedly diminished (i.e., -2.3±0.9 for the subjects in the 1.5 1x/month group [n=25] and -2.7±0.8 in the 0.75 2x/month group [n=34]). After 12 months of Nutropin Depot therapy, the PAH SDS in the 2 dose groups improved to -1.9±0.9 and -2.1±0.8, respectively, demonstrating a

mean gain of 0.39±0.58 and 0.57±0.54, respectively (p=0.0026 and p<0.0001, respectively). The change was not significantly different in the 2 dose groups (p=0.1831). These positive changes in Bayley-Pinneau PAH suggest that the improvements in annual growth rate and height SDS achieved with Nutropin Depot therapy were accompanied by appropriate bone age advancement, and have resulted in improved adult height prognosis.

Figure 8. [redacted]03-003 - Bayley-Pinneau PAH SDS for Naïve Subjects Completing 12 Months of Therapy with Baseline, Month 6, and Month 12 Values



CT Subjects

Fifteen CT subjects completed 6 months of therapy in [redacted]03-002 and then enrolled in [redacted]03-003. The sponsor presented very preliminary 12 month annual growth rate data for these subjects during [redacted]03-003 in the original 6/99 NDA submission, but chose not to update these results in the 9/99 efficacy update. As of 6/99, 9 of the 15 patients had discontinued from the study because of unsatisfactory growth rates after switching to Nutropin Depot therapy from daily injections of rhGH. However, 12 month annual growth rate data is available for 13 of these 15 subjects. After excluding 5 of these 13 patients (because they were treated with 0.75q4 for 1 to 4 months in [redacted]03-003 before being randomly switched over to 1 of the larger doses proposed for marketing), the growth data for 8 subjects (5 assigned to 1.5 1x/mo and 3 assigned to 0.75 2x/mo) were analyzed by the Agency's statistical reviewer. The annual growth rates were as

follows (cm/yr; mean±SD): 4.8±2.4 for the subjects treated with 1.5 1x/mo (n=5); 5.2±0.3 for the subjects treated with 0.75 2x/mo (n=3); and 5.0±1.8 when the dose groups were pooled (n=8). The sample sizes are too small to perform a meaningful comparison with pre-study growth rates. Similar to what was observed in naïve patients, mean annual growth rates in this small group of CT patients were ~1 cm less than the mean 6 month annualized growth rates in the same patients. See Table 40 in the ISE.

Anti-GH Antibodies

As in [redacted]03-002 and [redacted]03-004, mean antibody titers in [redacted]03-003 continued to be very low and did not increase during the course of the study. All serum samples with positive antibody titers (>1.0) were assayed for binding capacity. No subject had a binding capacity value >2 mg/L. As expected when antibody titers are low, the majority of the samples with positive titers had binding capacities that were below assay limits.
It is therefore highly unlikely that anti-GH antibodies attenuated the efficacy of Nutropin Depot during this study.

8.3.2.4 Safety Results

Extent of Exposure

As of 6/99, the 95 subjects who were enrolled and dosed in this study have accrued a total of 74.3 subject-years of exposure.

Deaths

There were no deaths during the study.

Serious Adverse Events

Two serious adverse events have been reported during [redacted]03-003 - a traumatic skull fracture and an episode of laryngotracheitis, both requiring brief hospitalization. None of the events were considered to be related to treatment with Nutropin Depot, which continued uninterrupted for both subjects.

Adverse Events Leading to Withdrawal

Three subjects discontinued from the study because of adverse events - 1 subject with recurrent episodes of "post-dosing"

nausea, vomiting and diarrhea, 1 subject with injection site lipoatrophy and recurrent episodes of "post-dosing" headaches and 1 subject with severe pain during injection.

Adverse Events Associated with GH Therapy

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

2. Hypothyroidism - As in the earlier studies, a number of patients were being treated with L-thyroxine at baseline. No additional cases of hypothyroidism were unmasked by Nutropin Depot therapy.

3. Allergy - No patients manifested allergy to the Nutropin Depot formulation.

4. As in earlier studies, arthralgia probably related to Nutropin Depot therapy was reported by several subjects. There were no reports of carpal tunnel syndrome.

5. Hyperglycemia - Patients with known diabetes mellitus were excluded from the study. Glucose metabolism was monitored by measurement of fasting and postprandial glucose and insulin levels, as well as hemoglobin A1C. With the exception of a very minimal increase in mean FBG after 12 months of 0.75 2x/mo (mean FBG increased from 79.5 to 84.4 mg%), as in [redacted]03-002 and [redacted]03-004, there were no significant changes in mean postprandial glucose, mean fasting or postprandial insulin levels, or mean hemoglobin A1C, noted after 12 months of Nutropin Depot therapy (in either dose group).

No subject developed diabetes mellitus during the study. De novo sporadic elevations of glucose and insulin levels were observed in individual subjects; however, these abnormalities did not persist. One obese subject (11-402) with elevated fasting and postprandial insulin levels at baseline manifested more significant hyperinsulinemia and a postprandial glucose of 141 mg% after 12 months of therapy - the investigator on site thought the patient's increased insulin resistance was related to a 20 pound weight gain during the course of therapy. Hemoglobin A1C remained unchanged.

Adverse Events Related to Injection Site Reactions

Nutropin Depot was administered as a SC injection every 2 or 4 weeks. The very high incidence of injection site-related adverse events in [redacted]03-002 resulted in modification of drug administration procedures in [redacted]03-004 and the latter portion of [redacted]03-003 in an attempt to improve the tolerability of injections. These modifications have been previously outlined in the [redacted]03-004 review.

Tables 30 and 31 below were compiled by this reviewer using datasets supplied by the sponsor; they report the number/percentage of patients experiencing a given injection site-related adverse event at least once during the study - for each dose group and all dose groups combined for the entire duration of [redacted]03-003 and for the safety update period (6/98 to 6/99) only (the 2 Tables are remarkably similar). It is evident that the incidence of injection site reactions remained extremely high during [redacted]03-003 with no meaningful differences between dose groups. Ninety two of the 95 subjects treated with Nutropin Depot reported adverse events related to the injection site. As noted earlier, 2 of the 95 subjects enrolled and dosed in [redacted]03-003 discontinued treatment because of severe pain during injection and lipoatrophy, respectively. The most frequent injection site reactions were nodules, erythema, pain post-injection and pain during injection with incidence rates of 84%, 82%, 78%, and 66%, respectively (when both dose groups are combined). The incidence of lipoatrophy was 38% for the entire cohort. The great majority of these injection site reactions were rated as mild to moderate in intensity. As in [redacted]03-002 and [redacted]03-004, pain during injection was the injection site reaction most frequently rated as severe.

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Table 30. [redacted]03-003 (Total Cohort) - Number/% of Patients in Each Dose Group Experiencing Injection Site Reaction at Least Once

INJECTION SITE ADVERSE REACTION Mean months on-study	All 3 dose groups combined n=95 9.4	0.75q4 n=10 2.4	1.5 1x/mo n=45 9.3	0.75 2x/mo n=50 9.0
NODULES*	80/84%	8/80%	35/78%	45/90%
ERYTHEMA*	78/82%	9/90%	37/82%	40/80%
PAIN POST INJECTION*	74/78%	9/90%	34/76%	39/78%
PAIN DURING INJECTION*	63/66%	4/40%	29/64%	34/68%
BRUISING	58/61%	3/30%	28/62%	30/60%
LIPOATROPHY*	36/38%	4/40%	21/47%	14/28%
ITCHINESS	30/32%	2/20%	18/40%	12/24%
EDEMA	21/22%	0/0%	12/27%	9/18%
WARMTH	17/18%	1/10%	8/18%	9/18%
REACTION	10/11%	0/0%	4/9%	6/12%
INDURATION	2/2%	1/0%	1/2	1/2

Table 31. [redacted]03-003 (Update Only) - Number/% of Patients in Each Dose Group Experiencing Injection Site Reaction at Least Once

INJECTION SITE ADVERSE REACTION Mean months on-study	Both dose groups combined n=81 8.2	1.5 1x/mo n=37 8.2	0.75 2x/mo n=44 8.2
NODULES*	68/84%	29/78%	39/89%
ERYTHEMA*	68/84%	31/84%	37/84%
PAIN POST INJECTION*	60/74%	27/73%	33/75%
PAIN DURING INJECTION*	57/70%	25/68%	32/73%
BRUISING	51/63%	23/62%	28/64%
LIPOATROPHY*	30/37%	18/49%	12/27%
ITCHINESS	22/27%	13/35%	9/20%
EDEMA	21/26%	12/32%	9/20%
WARMTH	16/20%	8/22%	8/18%
REACTION	10/12%	4/11%	6/14%
INDURATION	1/1%	0/0%	1/2

As in [redacted]03-002 and [redacted]03-004, the total number of injection site reactions was compared with the total number of injections administered during the study. This is shown in Table 32. The ratio of total number of injection site reactions to total number of injections was ~2.5/1 (very similar to [redacted]03-002 and [redacted]03-004 results) - a statistic which once again underscores the inordinately high incidence of injection site reactions after the administration of Nutropin Depot. As noted earlier, pain during injection accounted for almost all of the 3% of injection site reactions rated as severe (by the investigator).

Table 32. [redacted]03-003 - Injection Site Reactions Compared with Total Number of Injections as of 6/99

TOTAL # OF INJCTNS	# OF INJCTN SITE REAX	# OF severe INJCTN SITE REAX
1832	4672	139(3%)*

*123/139 = pain during injection

As in [redacted]03-002 and [redacted]03-004, the total number of each specific type of injection site reaction was also compared with the total number of injections administered in the study. Notably, the percentage of injections with pain post-injection for all subjects irrespective of dose group was 34% during the update period only of [redacted]03-003 and 66% in [redacted]03-002. Downward trends were NOT observed for the other frequent injection site reactions (i.e., nodules, erythema, bruising and lipoatrophy) when the results of [redacted]03-003 (update period) were compared with [redacted]03-002 and [redacted]03-004. A comparison of the incidence of pain during injection in [redacted]03-003 with earlier studies is problematic because the FACES pain rating scale was used in [redacted]03-004 (see review) and probably has biased subsequent reporting of this event.

Further issues regarding injection site reactions:

1) As in [redacted]03-002 and [redacted]03-004, review of Case Report Forms reveals no evidence that a significant number of subjects in this study elected to take more than the required number of injections to reduce the volume per injection and possibly the pain during injection. One patient enrolled in [redacted]03-003 took 2 injections per dosing for 7 dosings when only 1 injection was necessary - and then reverted to single injections.

2) An analysis of the naïve subjects who completed [redacted]03-004 (wherein injection procedures had been modified and optimized based on the experience obtained in [redacted]03-002) did not reveal evidence for a subset especially at risk for injection site reactions. Therefore, this issue was not further assessed in [redacted]03-003.

Other Adverse Events by Body System

Subjects were asked to report any adverse events or intercurrent illnesses at each monthly visit. Approximately 15 (~16%) of the 95 subjects enrolled and treated reported the occurrence of "post-dosing" nausea, vomiting, headache or fever on at least one occasion during the study. Results of physical examination, including funduscopic examinations to rule out intracranial hypertension, were unrevealing. Similar observations were made during [redacted]03-002 and [redacted]03-004. Please refer to ISS for further incidence data generated by the sponsor at the request of this reviewer regarding this group of "post-dosing" adverse events (collectively and individually).

Physical examination and vital signs

No consequential changes occurred during the study.

Miscellaneous laboratory parameters

During the 6 month course of this study no consequential, clinically significant or consistent changes were observed in renal function, urinalyses, hematologic parameters, electrolytes, calcium, phosphate, lipids or liver function. Alkaline phosphatase increased from baseline as expected in children with GHD growing in response to rhGH therapy.

Trough Concentrations of GH and IGF-I

Table 33 below summarizes trough concentrations during [redacted]03-003. These trough levels indicate that no clinically significant accumulation of GH or IGF-I occurred during 12 months of treatment with Nutropin Depot in either dose group.

Table 33. [redacted]03-003 - Trough Serum GH and IGF-I Concentrations

			Mean±SD	
	Baseline	Month 6	Month 9	Month 12
GH (ng/mL)				
1.5 1x/Month (n=19)	2.2±3.0	1.5±1.6	2.4±2.9	1.8±2.7
0.75 2x/Month (n=26)	1.9±2.1	3.0±2.6	1.8±1.3	1.7±1.6
IGF-I (ng/mL)				
1.5 1x/Month (n=19)	106±89	102±71	103±82	98±89
0.75 2x/Month (n=26)	66±40	97±49	104±57	86±60

8.3.3 Discussion

8.3.3.1 Efficacy Discussion

Naïve Patients

The primary efficacy endpoint for this study was the 12 month annual growth rate after therapy with Nutropin Depot. Naïve patients who had successfully completed 6 months of Nutropin Depot therapy in [redacted]03-004 or [redacted]03-002 with either of the dosages to be marketed, and 6 more months of the same treatment in [redacted]03-003 were the focus of the study. In the subset of patients (n=55) with pre-study annualized growth rates meeting the criteria predefined in the protocol, the on-study mean 12 month annual growth rate was significantly greater than the pre-study mean annualized growth rate in both the 1.5 1x/mo and 0.75 2x/mo dose groups. However, just as in the case of the 6 month annualized growth rates achieved in naïve patients with Nutropin Depot therapy in the earlier trials, the study- and dose-pooled mean 12 month annual growth rate (7.8±1.9 cm/yr) after Nutropin Depot therapy was markedly less than the mean 12 month annual growth rates achieved by well matched historical controls treated with daily injections of the recommended amount of rhGH (i.e., MacGillivray et al [11.4 cm/yr], Study L0368g, Nutropin AQ, NDA 20-522 [11.0 cm/yr]).

The relative lack of efficacy after treatment with Nutropin Depot compared with daily injections of rhGH more than likely relates to the GH PK profile and GH-induced IGF-I response following the administration of Nutropin Depot, in particular the markedly decreased bioavailability of rhGH after Nutropin Depot administration (compared with rhGH bioavailability after daily rhGH injections for a month).

Interestingly, the study-pooled, mean 12 month annual growth rates of these 69 naïve patients after Nutropin Depot therapy were ~1 cm less than the mean 6 month annualized growth rates of the same cohort for each dose group and both dose groups combined. This finding is compatible with the clinical experience of many pediatric endocrinologists and the data published by MacGillivray et al. These investigators observed that the growth rate of children with GHD treated with rhGH diminishes over time (i.e., 11.4 cm/yr during the first year of therapy down to 9 cm/yr during the second year of therapy, etc). It would therefore not be surprising to see a decrease in absolute growth rate during the second 6 months of therapy compared with the first 6 months of therapy. Moreover, it provides a warning to investigators that annualizing 6 month growth rates may well overestimate the actual 12 month annual growth rates. Please see ISE for further comment.

Multiple regression analysis demonstrated that only chronological age and maximum stimulated GH response (and no other fixed or continuous variable) were inversely and significantly correlated with the growth rate response. This finding is consistent with the observations of other investigators (Ranke, 1999 and Blethen, 1993).

Mean height SDS after 1 year of Nutropin Depot therapy in naïve patients was significantly greater than pre-treatment values and further improved from 6 month values. The rate of bone age advancement was appropriate in both dose groups and PAH was significantly improved as well, indicating that the improvements in growth rate and standardized height were not accompanied by an undue advancement of bone age.

CT Patients

A very large percentage (60%) of CT patients discontinued from [redacted]03-003 because of clearcut dissatisfaction with the growth rate achieved after switching to Nutropin Depot therapy from daily injections of rhGH. More than likely, this is the primary reason that 48% of CT patients who completed [redacted]03-002 chose not to enroll in [redacted]03-003.

Meaningful comparison of the mean annual growth rates of the 8 patients who completed at least 6 additional months of therapy during [redacted]03-003 with pre-study growth rates is not possible because of the small sample size. As was the case in naïve patients, the mean 12 month annual growth rates of this small subset of patients was ~1 cm less than the mean 6 month

annualized growth rates of the same group of patients (see Table 40 in ISE).

8.3.3.2 Safety Discussion

As in the earlier trials, trough levels of GH and IGF-1 at 3 and 6 months indicate that GH and IGF-I did not accumulate inappropriately over time. Once again, there were no deaths or serious adverse events related to Nutropin Depot, and none of the severe but unusual side effects associated with rhGH therapy were observed in this study. No subject developed diabetes mellitus, although transient elevations of glucose and insulin were occasionally observed in individual subjects.

In spite of the procedural modifications made after [redacted]03-002 and previously discussed, the incidence of injection site reactions remained extremely high during [redacted]03-003 with no meaningful differences between dose groups. The ratio of total number of injection site reactions to total number of injections was once again ~2.5/1. The great majority of these injection site reactions were rated as mild to moderate in intensity (by the investigator). As in [redacted]03-002, pain during injection was the injection site reaction most frequently rated as severe (**123 out of 139 events rated as severe**). However, only 1 subject in this study elected to take more than the required number of injections to reduce the volume per injection and possibly the pain during injection.

When both dose groups are combined, the number of subjects experiencing at least 1 episode of pain post-injection decreased from 92% in [redacted]03-002 to 74% in [redacted]03-003 (safety update period only), and when pain post-injection is expressed as a percentage of the total number of injections administered, the incidence decreased from 66% in [redacted]03-002 to 34% in [redacted]03-003 (safety update period only) - suggesting slightly better tolerability of Nutropin Depot during the safety update period for [redacted]03-003. However, there was no decrease in the incidence of erythema, nodules, bruising or lipoatrophy. A comparison of the incidence of pain during injection between studies is problematic because of bias introduced by the use of the FACES Pain Rating Scale in [redacted]03-004. Please refer to ISS for a comparative analysis of all studies with regard to these parameters.

As per an analysis performed by the sponsor at this reviewer's request on the [redacted]03-004 cohort, there does not appear to be a subset of patients especially at risk for injection site

reactions and this issue was not explored further during [redacted]03-003.

As in [redacted]03-002 and [redacted]03-004, ~16% of subjects (both dose groups combined) reported at least 1 episode of transient headache, nausea, vomiting or fever (usually 1-2 days "post-dosing"). Please refer to ISS for a comparative analysis of both dose groups for all studies combined with regard to these "post-dosing" complaints.

8.3.4 Conclusions

8.3.4.1 Efficacy

In naïve patients, the mean 12 month annual growth rates achieved after Nutropin Depot therapy were significantly greater than the mean annualized pre-study growth rates, but significantly less than **(~3 cm/yr)** the annual growth rates reported for well matched cohorts in the literature treated with daily injections of the recommended amount of rhGH (just as was the case for the mean 6 month annualized growth rates attained after Nutropin Depot therapy in [redacted]03-002 and [redacted]03-004). The mean annual growth rates were ~1 cm less than the mean 6 month annualized growth rates; the explanation and implications of this finding will be discussed further in the ISE. Standardized height improved progressively during the course of a year's worth of therapy without undue advancement of bone age. The relative lack of efficacy of Nutropin Depot is more than likely directly related to the relative decrease in bioavailability of rhGH after the administration of Nutropin Depot. Multiple regression analysis confirmed earlier reports that chronological age and maximum stimulated GH response (a reflection of the severity of the GHD) are the only consistent predictors of the first year growth response to any form of rhGH therapy. Sample size was too small (n=8) to make meaningful comparisons of the annual growth rate achieved in CT patients after 1 year of Nutropin Depot therapy.

8.3.4.2 Safety

The primary safety issue with Nutropin Depot remained the very large incidence of injection site reactions - 2.5 reactions for every injection administered. Fortunately, most reactions continued to be rated as mild to moderate. Pain during injection continued to be the reaction most often rated as severe - in this study 123 of the 129 injection site events