

rated as severe were pain during injection! Although there was a modest trend downward in the incidence of pain post-injection during [redacted]03-003, the incidence of the other frequent injection site reactions did not change, and it does not appear that the changes made in injection preparation and administration after [redacted]03-002 have impacted substantially on the occurrence of these injection site-related adverse events. The incidence of "post-dosing" headache, nausea, vomiting or fever when dose groups are combined remained in the same range (15 to 25%).

9 Integrated Summary of Efficacy (ISE) and Integrated Summary of Safety (ISS)/Overview

Description of Studies

This ISE/ISS consolidates data from 3 clinical studies of Nutropin Depot, a formulation of Genentech's somatropin, designed to provide sustained release of rhGH for up to 1 month in the treatment of pediatric GHD: [redacted]03-002 (a Phase I/II, PK/PD, dose-ranging and safety study in naïve and CT children with GHD), [redacted]03-004 (a Phase III, pivotal efficacy and safety study in naïve subjects only), and [redacted]03-003 (a long term efficacy and safety extension study which enrolled successful completers of 6 months of therapy with Nutropin Depot in the 2 other studies). See Table 34.

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Table 34. Summary of Clinical Trials of Nutropin Depot in Pediatric GHD

	Studies		
	03-002 Phase I/II	03-004 Phase III	03-003 Extension Study
Design	Open label	Open label, randomized	Open Label
Duration of treatment	6 mo	6 mo	Ongoing
<ul style="list-style-type: none"> • No of subjects enrolled • CT • Naïve 	<ul style="list-style-type: none"> • 64 • 38 • 26 	<ul style="list-style-type: none"> • 74 • N/A • 74 	<ul style="list-style-type: none"> • 96 • 15 • 81
Subject eligibility criteria	<ul style="list-style-type: none"> • Prepubertal • Maximum stimulated GH <10 ng/ml • Bone ≤9 yr (girls) and ≤10 yrs (boys) • Height ≤-2 SD for age and sex (naïve and idiopathic only) • Naïve subjects • CT subjects on continuous rhGH for at least 1 yr prior to enrollment 	<ul style="list-style-type: none"> • Prepubertal • Maximum stimulated GH <10 ng/ml • Bone ≤9 yr (girls) and ≤10 yrs (boys) • Height ≤-2 SD for age and sex (naïve and idiopathic only) • Naïve subjects • No prior rhGH treatment 	<ul style="list-style-type: none"> • Completion of 6 mo in 03-002 or 03-004
Dose (mg/kg) and regimen	0.75q4, 1.5q4, 0.75q2	1.5 1x/mo, 0.75 2x/mo	0.75q4, 1.5 1x/mo, 0.75 2x/mo

Overall Disposition

Table 35 summarizes the overall disposition of patients in all 3 studies. Of note, 81 of 93 naïve subjects who completed 03-004 and 03-002, and were therefore eligible for 03-003, enrolled in 03-003, and 69 of 76 naïve subjects who received the 2 dosages proposed for marketing throughout 03-003 completed 12 months in 03-003. However, only 15 of 29 eligible CT subjects from 03-002 chose to enroll in 03-003 - more than likely because of the poor growth response achieved

after the switch to Nutropin Depot therapy and perhaps because of the high incidence of injection site reactions as well.

Table 35
Subject Disposition for Studies [redacted] 03-002, [redacted] 03-003, and [redacted] 03-004

	Naive Subjects		CT Subjects ^a	Pooled
	1.5 1x/mo or 0.75 2x/mo Throughout	0.75q4 in Study [redacted] 03-002		
Enrolled in Study [redacted] 03-002	17	9	38	64
Enrolled in Study [redacted] 03-004	74	0	0	74
Total enrollment ^b	91	9	38	138
Complete 6 months in				
Study [redacted] 03-002	17	7	29	53
Study [redacted] 03-004	69	0	0	69
Enrolled in Study [redacted] 03-003 from				
Study [redacted] 03-002	15	5	15	35
Study [redacted] 03-004	61	0	0	61
Total enrolled in [redacted] 03-003	76	5	15	96
Completed 12 months in Study [redacted] 03-003 from				
Study [redacted] 03-002	13	5	13	31
Study [redacted] 03-004	56	0	0	56
Completed 12 months total	69	5	13	87

^a Treatment groups consisted of 1:5 1x/mo, 0.75 2x/mo, or 0.75q4.

^b One subject (12003) was enrolled but never treated and is therefore not included.

The following observations not shown in Table 34 also merit comment: 1) Nine of the 14 patients who discontinued from all 3 studies combined because of an adverse event did so because of an injection site reaction, in particular pain during injection; 2) Twenty four of 32 patients who discontinued from [redacted] 03-003 (enrollment 96; 15 of 81 naive and 9 of 15 CT) did so because of dissatisfaction of the parents or investigators with the growth responses after Nutropin Depot therapy.

9.1 ISE

Naïve Patients

Overall Demographics of Naïve Patients

The pooled demographics of 86 naïve subjects who completed 6 months of Nutropin Depot therapy in [redacted] 03-002 and [redacted] 03-004 receiving 1.5 mg/kg/month of Nutropin Depot in single or twice monthly injections are presented in Table 36. The similar demographics of the subsets who chose to enroll in [redacted] 03-003 (n=76) or who completed at least 6 additional months in [redacted] 03-003 (n=69), and the 7 naïve subjects who completed 6 months of therapy in [redacted] 03-002 receiving 0.75q4 are not included in this table. Most patients were males with idiopathic GHD with a mean age of 7.4, a mean height SDS of -3.0, a mean delay in bone age of 1.5, a mean pre-study growth rate of 5.0 cm/yr, and a mean maximum stimulated GH of 5.8 ng/ml.

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Table 36. ISE - Study-Pooled Selected Demographic and Baseline Characteristics of 86 Naïve Subjects Who Completed 6 months in []03-002 or []03-004 Receiving 1.5 mg/kg/month of Nutropin Depot in Single or Twice Monthly Injections by Dose Group and for Both Dose Groups Combined

	1.5 1x/Month (n=41)	0.75 2x/Month (n=45)	Pooled (n=86)
Sex, n (%)			
Male	25 (61)	35 (78)	60 (70)
Female	16 (39)	10 (22)	26 (30)
Etiology of GHD, n (%)			
Idiopathic	37 (90)	42 (93)	79 (92)
Organic	4 (10)	3 (7)	7 (8)
Chronological age (yr)			
Mean±SD	7.0±3.1	7.7±2.6	7.4±2.9
Range	1.6 to 12.2	3.2 to 11.9	1.6 to 12.2
Bone age (yr)			
Mean±SD	5.3±2.9	6.3±2.4	5.8±2.7
Range	0.2 to 11.1 (n=40)	2.1 to 10.4 (n=44)	0.2 to 11.1 (n=84)
Bone age delay (yr)			
Mean±SD	1.6±1.2	1.4±1.0	1.5±1.1
Range	-0.8 to 4.2 (n=40)	-1.9 to 3.4 (n=44)	-1.9 to 4.2 (n=84)
Previous growth rate (cm/yr)			
Mean±SD	5.1±2.0	4.8±1.7	5.0±1.8
Range	1.6 to 8.5 (n=30)	1.4 to 8.3 (n=36)	1.4 to 8.5 (n=66)
Standardized height			
Mean±SD	-3.0±1.2	-3.1±0.8	-3.0±1.0
Range	-6.7 to -0.6	-5.1 to -1.8	-6.7 to -0.6
Maximum stimulated GH (ng/mL) ^a			
Mean±SD	5.5±2.6	6.0±2.8	5.8±2.7
Range	0.8 to 9.8 (n=33)	0.5 to 9.7 (n=36)	0.5 to 9.8 (n=69)

^a Note: Baseline maximum stimulated GH levels were not recorded for subjects in Study []03-002.

Primary Efficacy Endpoints - 6 Month Annualized Growth Rate and 12 Month Annual Growth Rate

6 Month Annualized Growth Rate

Treatment of naïve subjects with Nutropin Depot in []03-004 and []03-002 resulted in mean 6 month annualized growth rates which were very similar in the 1.5 lx/mo and 0.75 2x/mo dose groups.

(Note: In []03-004, a distribution plot demonstrated that 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.) When the responses for each dose group were pooled, the mean 6 month annualized growth rate in each study was significantly greater than the mean pre-study annualized growth rate, but significantly less than the mean annual growth rate of well matched historical controls receiving daily injections of rhGH (Study L0368g, Nutropin AQ, NDA 20-522).

The demographics and baseline characteristics, as well as the mean 6 month annualized growth rates observed after Nutropin Depot therapy, of the naïve patients in 1) [redacted] 03-004 compared with [redacted] 03-002 pooling dose groups and 2) each dose group for both studies combined were similar (males with idiopathic GHD, mean chronological age 6.9 to 7.7, mean bone age delay 1.4 to 2.1, mean height SDS -2.9 to -3.3, mean maximum stimulated GH 5.5 to 6.0 ng/ml, mean pre-study annualized growth rate 4.7 to 5.4 cm/yr and mean 6 month annualized growth rate after therapy with Nutropin Depot 8.3 to 8.7 cm/yr). It is therefore reasonable to pool the study results as well as the results for each dose group. In Table 37 below, pooled dose and study data for naïve patients treated with Nutropin Depot are compared with data from the L0368g study. Not surprisingly, the results are quite similar to the analyses performed for each individual study. As in the case of children treated with daily injections of rhGH in the L0368g study, the mean annualized growth rate achieved in the naïve patients treated with Nutropin Depot was significantly greater than the mean pre-study annualized growth rate ($p < 0.0001$, Wilcoxon signed rank test). However, the mean annual growth rate was significantly larger in the patients who received daily injections of rhGH compared with the group receiving Nutropin Depot ($\Delta = 2.6$ cm/yr, $p < 0.0001$, t-test).

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Table 37. [redacted]03-004 and [redacted]03-002 Combined - 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 in Historical Control Study*

	n	Age	Bone age	Pre-study growth rate	Dose (mg/kg/mo)	Annualized Growth Rate
[redacted]03-002 (SD)	17	6.9 (2.4)	4.8 (2.3) n=13	5.4** (2.6)	1.5	8.7 (2.9)
[redacted]03-004 (SD)	72	7.5 (2.9)	6.0 (2.6)	4.7*** (2.4)	1.5	8.3 (2.0)
[redacted]03-002 & [redacted]03-004 combined	89	7.4 (2.8)	5.8 (2.6)	4.8**** (2.4)	1.5	8.4 (2.2)
L0368g (SD)	62	8.0 (3.4)	6.5 (3.1)	4.8 (2.3)	-1.3	11.0 (2.9)

*Data compiled by statistical reviewer - ITT analyses

**Reflects data for 4 patients excluded by sponsor

***Reflects data for 19 patients excluded by sponsor

****Reflects data for 23 patients excluded by sponsor

12 Month Annual Growth Rate

Sixty nine naïve patients who had completed 6 months of treatment in [redacted]03-004 and [redacted]03-002 received at least 6 additional months of Nutropin Depot therapy with either 1.5 1x/mo or 0.75 2x/mo throughout the study in [redacted]03-003. The mean 12 month annual growth rates observed in these patients were very similar in the 2 dose groups. In the subset of patients with both on-study and valid pre-study growth rates (n=55), the mean on-study 12 month annual growth rate was significantly greater than the mean pre-study annualized growth rate in each dose group and both dose groups combined (7.9 cm/yr vs. 5.1 cm/yr; see Figure 5 and Table 25), but clearly less than the 12 month annual growth rate achieved with optimal amounts of rhGH administered daily (11.4 cm/yr; MacGillivray et al, 1996).

Table 38 compares the mean 12 month annual growth rates and the mean 6 month annualized growth rates of 69 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.

Table 38. Naïve Subjects: Comparison of 6 Month Annualized Growth Rates with 12 Month Annual Growth Rates in 69 Subjects from []03-004 and []03-002 Combined Who Completed 12 Months in []03-003

All data expressed as mean±SD	1.5 1x/mo	0.75 2x/mo	0.75 2x/mo + 1.5 1x/mo combined
6 month annualized growth rates for naïve subjects from []03-002 and []03-004 combined (ITT)	8.3±1.9 n=43	8.4±2.5 n=46	8.4±2.2 n=89
6 month annualized growth rates for naïve subjects from []03-002 and []03-004 combined who completed 12 months in []03-003*	8.5±1.9 n=32	9.0±2.4 n=37	8.8±2.2 n=69*
12 month annual growth rates for naïve subjects from []03-002 and []03-004 combined who completed 12 months in []03-003*	7.5±1.9 n=32	8.1±2.0 n=37	7.8±1.9 n=69*

*5 patients were excluded who were treated for several months with 0.75q4 during the initial stages of []03-003 before being randomized to 1 of the larger doses

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

The sponsor performed a univariate analysis of discrete variables and the correlation between selected continuous baseline characteristics and the study- and dose-pooled 12 month annual growth rate, as well as a multiple regression analysis that included the same variables. Only the maximum stimulated GH level and chronological age were identified by the multiple regression analysis as significantly related to and inversely correlated with annual growth rate ($p < 0.05$). Similar analyses by the Agency's statistical reviewer using 6 month annualized growth rates from []03-004 and []03-002 combined, and by the sponsor using 6 month annualized growth rates from []03-004 alone in the 6/99 ISE produced identical correlations. (Note: The Agency's statistical reviewer did find that pre-study growth rate was inversely correlated with the on-study growth rate when a cut off of 4.9 cm/yr was used, but not when 4.5 cm/yr was used; therefore, she concluded this finding had questionable

significance.) Lastly, please refer to Biopharmaceutics Review for a discussion of the very weakly positive, if any, correlation of $GH_{AUC2-28}$ and 6 month annualized growth rate in the subset of patients intensively sampled in [redacted] 03-002 (especially CT patients). Not surprisingly, there was clearly no correlation of any measured or calculated IGF-I parameter and the 6 month annualized growth rate in this subset of patients in [redacted] 03-002.

Secondary Efficacy Endpoints

Height SDS (Standardized Height), Bone Age, PAH

Results from 1) [redacted] 03-004 and [redacted] 03-002 considered separately, 2) both studies combined, and 3) [redacted] 03-003 all reflect a similar statistically significant improvement in height SDS accompanied by an appropriate advancement of bone age. In [redacted] 03-003, when data from the 2 dose groups were combined, baseline height SDS was markedly diminished at -3.05, the mean change in height SDS from baseline to the end of Month 6 was +0.37 and the mean change from baseline to Month 12 was +0.55 - indicating an improvement in height SDS during the first 6 months of therapy which continued during the second 6 months of treatment. The mean change in bone age from baseline to Month 12 was 1 year and Bayley-Pinneau PAH improved significantly as well. **This positive change in height SDS without undue advancement of bone age reflects catch-up growth.**

CT Subjects

Overall Demographics of CT Patients

The demographics of 38 CT subjects from [redacted] 03-002 who enrolled in [redacted] 03-002 and were assigned to receive 1.5q4, 0.75q2 and 0.75q4 of Nutropin Depot are presented in Table 39. The similar demographics of the subsets who completed 6 months of Nutropin Depot therapy in [redacted] 03-002 (n=29), who chose to enroll in [redacted] 03-003 (n=15), or who completed at least 6 additional months in [redacted] 03-003 (n=13), are not presented in this table. The pooled dose group results reveal that most patients were Caucasian males with idiopathic GHD with a mean age of 9.6, a mean height SDS of -1.3, a mean delay in bone age of 1.4 and a mean pre-study growth rate of 8.2 cm/yr (while receiving daily injections of rhGH).

Table 39. Selected Demographic and Baseline Characteristics of 38 CT Subjects Who Enrolled in [redacted] 03-002 by Dose Group

CT Patients	All Doses Combined	0.75q4	0.75q2	1.5q4
	n=38	n=10	n=11	N=17
Male (%)	66%	80%	55%	65%
Etiology (%)				
Idiopathic	89%	90%	82%	94%
Organic	11%	10%	18%	6%
Age (years)	9.6	9.3	9.4	9.9
Range	4-14	6-11	4-13	7-14
Bone Age (years)	8.2 n=35	8.1	7.9	8.5
Previous Growth Rate (cm/yr)	8.2	8.3	8.6	7.9
Range	3-14			
Race (%)				
White	91%	90%	100%	82%
Weight (kg)	29			
Height (cm)	128	131	126	128
Standardized Height	-1.3	-0.6	-1.5	-1.5

Primary Efficacy Endpoints - 6 Month Annualized Growth Rate and 12 Month Annual Growth Rate

6 Month Annualized Growth Rate

As discussed in the review of [redacted] 03-002, Nutropin Depot did not prove to be an efficacious therapy when CT subjects were switched to Nutropin Depot from daily injections of rhGH (0.25 to 0.35 mg/kg/week). The mean annualized pre-study growth rates exceeded the mean annualized on-study growth rates by 3.1 cm/yr in the ITT sample (see Table 8). In the ITT sample, paired differences for all treatment groups were either highly statistically significant or borderline significant. Only 4 patients achieved an improved growth rate when on-study growth rates were plotted against pre-study growth rates for individual patients in the CT cohort (see Figure 1), and only 1/3 of the CT patients had an on-study annualized growth rate within 2.2 cm/yr of their pre-study annualized growth rate (the study had been powered to detect a 2.2 cm/yr difference in the on-study and pre-study annualized growth rates).

12 Month Annual Growth Rate

Only 8 CT patients from []03-002 who received the 2 doses of Nutropin Depot to be marketed throughout the study (1.5 1x/mo, n=5 and 0.75 2x/mo, n=3) completed at least 6 more months of Nutropin Depot therapy in []03-003. As a result, meaningful comparisons of 12 month annual growth rates with pre-study annualized growth rates are not possible.

Table 40 compares the mean 12 month annual growth rates and the mean 6 month annualized growth rates of 8 CT subjects from []03-002 who completed 12 months in []03-003 (for each dose group and both dose groups combined). As was the case in naïve patients, 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.

Table 40. CT Subjects: Comparison of 6 Month Annualized Growth Rates with 12 Month Annual Growth Rates in 8 Subjects from []03-002 Who Completed 12 Months in []03-003

All data expressed as mean±SD	1.5 mg/kg once a mo	0.75 mg/kg twice a mo	0.75 2x/mo +1.5 1x/mo combined
6 month annualized growth rates for []03-002	4.8±2.6 n=15	5.2±1.3 n=11	5.0±2.1 n=26
6 month annualized growth rates for subjects from []03-002 who completed 12 months in []03-003*	5.8±2.7 n=5	6.2±0.9 n=3	6.0±2.1 n=8*
12 month annual growth rates for subjects from []03-002 who completed 12 months in []03-003*	4.8±2.4 n=5	5.2±0.3 n=3	5.0±1.8 n=8*

*5 patients were excluded who were treated for several months with 0.75q4 during the initial stages of []03-003 before being randomized to one of the larger doses

Secondary Efficacy Endpoints

Height SDS (Standardized Height)

In []03-002, mean pre-study height SDS ranged from -1.3 to -1.5 in the 2 higher dose groups, and did not change after 6 months of Nutropin Depot therapy.

Bone Age

In [redacted] 03-002, bone age at baseline in CT patients was moderately delayed by an average of ~1 year relative to chronological age in all dose groups. The mean change in bone age after 6 months of Nutropin Depot treatment was 0.7 years in all dose groups. Therefore, in CT subjects, the decrement in growth rate after switching to Nutropin Depot therapy was not accompanied (as one would have expected) by inappropriate skeletal maturation.

Anti-GH Antibodies in Naïve and CT Patients

Approximately 40 to 60% of naïve patients developed de novo positive antibody titers (≥ 1.0) to rhGH after 3 months of exposure to Nutropin Depot. Approximately 10% of CT patients had positive antibody titers present at baseline, and the prevalence of positive antibody titers increased to ~50% after 6 months of exposure to Nutropin Depot. In both naïve and CT patients, antibody titers were very low at all times (usually not exceeding 2.5), and did not increase further after prolonged exposure to Nutropin Depot. All serum samples with positive antibody titers were assayed for binding capacity. No subject had a binding capacity value > 2 mg/L. In fact, as expected when antibody titers are low, the majority of the samples with positive titers had binding capacities that were below assay limits ([redacted]). There was no evidence of a negative association between the presence of positive anti-GH antibody titers and growth rate in any of the 3 studies. **It is therefore highly unlikely that anti-GH antibodies attenuated the efficacy of Nutropin Depot during any of these studies.**

Discussion of ISE for Naïve Patients

1. Issue of historical controls (i.e., which historical controls should be used in that these were not randomized, actively controlled studies?):

a. In the first place, a prospective, randomized trial comparing Nutropin Depot with daily injections of the recommended dose of rhGH (43 ug/kg/day) would have been preferred (rather than an open label study powered to obtain a result within 2.7 cm/yr (-1 SD) of the L0368g mean growth rate response).

b. Sponsor's comment:

i. Since 1981, a large number of studies have been performed in naïve patients with GHD which assessed the first year growth rate response after the administration of different regimens of rhGH. The amount and dosing frequency of rhGH varied considerably in these studies (i.e., 17 to 50 ug/kg/day administered daily; 0.05 to 0.3 mg/kg/week administered in 3 equal injections TIW). Although the currently recommended regimen is 43 ug/kg/day administered daily, the sponsor contends that many of the less optimal regimens noted above are still being utilized by many pediatric endocrinologists in the "real world". The mean first year growth rate response in the majority of the abovementioned studies ranged from 7 to 11 cm/yr. Therefore, the mean dose-pooled 6 month annualized growth rate observed after Nutropin Depot therapy in [redacted] 03-004 and [redacted] 03-002 combined (~8.4 cm/yr) falls within that range. See Tables 1, 2 and 2 (continued) in the Appendix.

ii. The sponsor also believes that it is important to compare the Nutropin Depot results with a well matched cohort derived from the massive NCGS Phase IV post-marketing surveillance effort who initiated daily rhGH therapy subsequent to 1993 (n=1909) (see ahead to discussion of relative lack of efficacy). The experience from the NCGS with respect to the "real world" effectiveness of rhGH has recently been reported (Root et al, 1998).

c. Medical reviewer comment:

i. The children in Study L0368g (n=62) and the MacGillivray study (n=33) (where the presently recommended dosage of rhGH was injected daily) were very well matched with the subjects treated with Nutropin Depot with regard to demographic and baseline characteristics. With regard to the well established variables which predict the response to rhGH therapy, the mean maximum stimulated GH responses were comparable (4.8 ng/ml in the L0368g study and 5.8 ng/ml in the Nutropin Depot studies [pooled dose groups for [redacted] 03-004 and [redacted] 03-002 combined]) and, in fact, the mean chronological ages in the L0368g study (8.0 years) and the MacGillivray study (8.4 years) were greater than the Nutropin Depot subjects (7.4 years). Nonetheless, the children in these 2 historical control studies achieved significantly better first year results (i.e., the mean annual growth rates [L0368g and MacGillivray, 1996] were 11 and 11.4 cm/yr, respectively) than the children treated with Nutropin Depot (8.4 cm/yr, pooled study and dose group results). [redacted]

[REDACTED]

2. Why was Nutropin Depot less efficacious than daily injections of the recommended dosage of rhGH in Study L0368g, the MacGillivray study and the matched NCGS cohort:

a. Sponsor comment:

i. In the cohort derived from the NCGS (n=1909), whose demographic and baseline characteristics (mostly males, all with idiopathic GHD, age, bone age, height SDS, maximum stimulated GH, pre-study growth rate) were similar to the GH deficient patients enrolled and treated in [REDACTED] 03-004 (and [REDACTED] 03-002), and who had been and are still being treated with daily injections of rhGH, the mean 6 month annualized growth rate was 10.7 ± 3.6 cm/yr (as opposed to 8.4 ± 2.2 in the Nutropin Depot studies [ITT, n=89, [REDACTED] 03-004 and [REDACTED] 03-002 combined with pooling of dose groups]), the mean baseline to 6 month change in height SDS was $+0.5 \pm 0.4$ and the mean baseline to 12 month change in bone age was 1.4 ± 1.0 years. The sponsor attempts to explain the difference in efficacy between the matched NCGS cohort and the children treated with Nutropin Depot by suggesting that the NCGS cohort were more responsive to rhGH therapy because they were more severely GH deficient (bone age delay slightly greater, pre-study growth rate slightly less, height SDS minimally less). In addition, the sponsor notes that bone age advancement was minimally greater after 1 year of therapy in the NCGS cohort (1.4 years in NCGS as opposed to 1.2 years after Nutropin Depot), and therefore suggests that the ultimate adult height of these 2 groups of GH deficient children may not differ. (Note:

[REDACTED]

b. Medical reviewer explanation for lesser efficacy:

There are several good reasons for the relative lack of efficacy of Nutropin Depot in naïve subjects compared with appropriate historical control data where the recommended dosage of rhGH was administered daily.

With regard to GH PK and IGF-I data (please see Biopharmaceutics Review):

----the monthly bioavailability of rhGH after an injection of Nutropin Depot is 33% of the bioavailability of rhGH after daily injections administered for a month

----50% of GH exposure occurs within 2 days of dosing resulting in relatively little GH exposure for the following 13 or 28 days prior to the next dosing

----2 weeks after dosing, GH (and IGF-I) levels have returned to baseline

----it remains unclear (as per the Agency's biopharmaceutics reviewer) if the varying concentrations of rhGH in the injectates used in the various Nutropin Depot studies impacted the bioavailability of rhGH (see Table 3 in Appendix)

----the effect of utilizing different injection sites and the effect of the varying number of injections per dosing (usually 1 to 3) on the bioavailability of Nutropin Depot remains unknown

It is probably more than coincidence that the response to Nutropin Depot was almost identical to the first year response observed by MacGillivray et al when the recommended dose of rhGH (0.3 mg/kg/week) was administered TIW (a regimen she clearly demonstrated to be significantly inferior to the recommended dose administered daily). More than likely, the TIW regimen, analogous to therapy with Nutropin Depot, resulted in decreased GH exposure/GH_{AUC} and therefore decreased bioavailability of rhGH.

With regard to factors known to predict responsivity to rhGH (Blethen and mathematical model ref), age was not a factor (as stated, the L0368g subjects were in fact older than the Nutropin Depot cohort and still grew better), and the maximum stimulated GH response was similar in Study L0368g subjects and the Nutropin Depot patients.

The pre-study annualized growth rate was inappropriately robust in the subjects enrolled in []03-002 and therefore this reviewer was concerned that children without true GHD and therefore less likely to respond to rhGH may have been enrolled (Vance et al recently recommended including growth velocity <25th percentile in the diagnostic criteria for GHD to diminish false positive diagnoses of GHD when only peak GH response to provocation <10 ng/ml is utilized.) However, this reviewer now considers this an unlikely explanation for the decreased efficacy of Nutropin Depot because 1) the 6 month annualized growth rates observed in []03-002 were very similar to the growth rates seen in []03-004 ([]03-004 subjects had more appropriately decreased pre-study growth rates) and 2) multiple subgroup analyses by both the sponsor and the Agency's statistical reviewer did not reveal a meaningful correlation between pre-study and on-study growth rates.

3. Comment on the difference between the mean 6 month annualized growth rates and the mean 12 month annual growth rates for subjects from []03-004 and []03-002 combined who completed 12 months in []03-003:

There was a 1 cm/yr drop off for each dose group and both dose groups combined when 12 month annual growth rates were compared with 6 month annualized growth rates in 69 pooled naïve subjects from []03-004 and []03-002 who completed 12 months in []03-003. This is not surprising in view of the long term MacGillivray study which demonstrated that annual growth rates decreased from 11.5 cm/yr to 9 cm/yr to 8 cm/yr to 7.5 cm/yr during 4 years of therapy with daily injections of rhGH. In other words, a 4.4 cm absolute growth rate after the first 6 months of Nutropin Depot therapy (half of 8.8 cm/yr, the 6 month annualized rate) may well decrease to 3.4 cm (7.8 cm [annual growth rate] - 4.4 cm) during the second 6 months of therapy. This observation should also be a warning to investigators that annual growth rates may be overestimated when 6 month annualized growth rates are utilized.

4. Comment about possible greater efficacy of 0.75 2x/mo compared with 1.5 1x/mo observed in []03-004:

In []03-004, a distribution plot demonstrated that 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. In that the mean responses in the 2 dose groups were almost identical, the significance, if any, of this finding is unclear at this time. The bioavailability of 0.75 2x/mo and 1.5 1x/mo were not compared in the NDA submission. The sponsor might consider performing []

Phase IV post-marketing study.

5. Comment on the multiple regression subgroup analyses performed by the sponsor and the Agency's statistical reviewer:

These analyses verify that chronological age and maximum stimulated GH response to provocation are the most important predictors of the first year growth rate response of GH deficient children treated with any form of rhGH therapy. This has been previously reported (Ranke, 1999 and Blethen, 1993).

6. Comment on discontinuation of naïve patients from []03-003:

The most common reason for discontinuation (15 of 81 naïve enrollees) was dissatisfaction of family members or

investigators with the growth response achieved with Nutropin Depot. On the other hand, the sponsor correctly points out that 81 of 93 eligible patients from [redacted] 03-004 and [redacted] 03-002 chose to enroll in [redacted] 03-003 and that 69 of 76 completed 12 months of therapy in [redacted] 03-003.

7. Comment regarding anti-GH antibodies:

Although there was a substantial prevalence of positive anti-GH antibodies after 3 months of therapy, the titers of these antibodies were very low and the antibodies possessed minimal binding capacity. There was no evidence in any of these studies that the presence of anti-GH antibodies interfered with the efficacy of Nutropin Depot in naïve patients.

Discussion of ISE for CT Patients

1. Comment regarding study design:

A prospective, randomized trial comparing Nutropin Depot with continued daily injections of the recommended dose of rhGH (43 ug/kg/day) would have been preferred (rather than an open label study powered to obtain a result within 2.2 cm/yr (~1 SD) of the pre-study growth rate).

2. Why was Nutropin Depot less efficacious than daily injections of rhGH in the treatment of CT children?

a. Sponsor comment:

i. The sponsor suggests that the decreased efficacy of Nutropin Depot compared with daily injections of rhGH was related to the expected waning effect of rhGH therapy which is known to occur over time. The sponsor also notes that the CT subjects, although growing at a lesser rate after switching to Nutropin Depot therapy, grew at the expected rate for normal children matched for age and sex.

b. Medical reviewer comment:

i. The mean duration of daily rhGH therapy prior to entry into [redacted] 03-002 was ~3 years and the dose was 0.25 to 0.35 mg/kg/week. As reported in the MacGillivray study, the growth rate between year 3 and year 4 should have dropped to 7.5 cm/yr - not 5 cm/yr. These GH deficient children are still "catching up" at that point. This reviewer, therefore, does not accept the explanation offered above by the sponsor.

ii. It is problematic to apply growth rate data from children with GHD (before and certainly after therapy) to normative curves.

iii. There are several good reasons for the lack of efficacy of Nutropin Depot in CT subjects when pre-study and on-study growth rates are compared:

As discussed several pages ago in the "Discussion of ISE for Naïve Patients", the most likely explanation for the lack of efficacy of Nutropin Depot relates to the markedly diminished bioavailability of rhGH after the administration of Nutropin Depot compared with the bioavailability of rhGH after daily injections for a month.

With regard to the factors which are known to predict responsivity to rhGH, neither chronological age nor maximum stimulated GH response are explanatory factors in that each child served as his/her own control in this study.

3. Comment on the difference between the mean 6 month annualized growth rates and the mean 12 month annual growth rates for CT subjects from []03-002 who completed 12 months in []03-003:

i. There was a 1 cm/yr drop off for each dose group and both dose groups combined when 12 month annual growth rates were compared with 6 month annualized growth rates in 8 CT subjects from []03-002 who completed 12 months in []03-003. This is identical to the decrement observed in naïve patients and not surprising in view of the data from the MacGillivray study presented earlier. In other words, a 3 cm absolute growth rate during the first 6 months of the ~fourth year of Nutropin Depot therapy (half of 6 cm/yr, the 6 month annualized rate) may well decrease to 2 cm (5 cm [annual growth rate] - 3 cm) during the second 6 months of therapy.

4. Comment regarding disposition and discontinuation of CT subjects:

i. Only 52% of CT subjects who completed []03-002 elected to enroll in []03-003 - more than likely related to dissatisfaction of family members or investigators with the growth response after switching to Nutropin Depot.

ii. Five of 15 CT patients enrolled in []03-003 have discontinued from this ongoing study because of dissatisfaction

of family members or investigators with the growth response after switching to Nutropin Depot.

5. Comment regarding anti-GH antibodies:

Prior to switching to Nutropin Depot therapy, ~10% of CT patients had positive anti-GH antibodies. The prevalence of positive anti-GH antibodies increased substantially after 3 to 6 months of Nutropin Depot therapy. However, the titers of these antibodies were very low and the antibodies possessed minimal binding capacity. There was no evidence in [redacted] 03-002 or [redacted] 03-003 that the presence of anti-GH antibodies interfered with the efficacy of Nutropin Depot in CT patients.

9.2 ISS

Exposure Data

One hundred and thirty eight patients were exposed for 135.9 patient years (including 1.5 lx/mo for 61.2 patient-years and 0.75 2x/mo for 65.1 patient-years). Mean exposure was 11.8 months and maximum exposure was ~28 months.

Deaths and Serious Adverse Events

No deaths and no serious adverse events related to Nutropin Depot occurred during these studies.

Adverse Events Leading to Withdrawal

Nine of 14 (~65%) patients who discontinued from [redacted] 03-002, [redacted] 03-004, and [redacted] 03-003 because of adverse events did so due to injection site-related adverse events. Of the 5 remaining patients who discontinued because of other adverse events, 1 patient did so because of recurrent "post-dosing" nausea and vomiting, 1 patient because of weakness, dizziness and multiple somatic complaints, 1 patient because of "apparent" allergy to some component of the Nutropin Depot formulation, and 2 patients because of exacerbation of pre-existing hypoglycemic episodes which had been present when GHD was first diagnosed.

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 any of these trials. In addition, no cases of leukemia were reported.

2. Hypothyroidism - In all 3 of the studies a number of patients were being treated with L-thyroxine at baseline for central hypothyroidism. No additional cases of hypothyroidism were unmasked by Nutropin Depot therapy.

3. Allergy - No patient manifested documented allergy to the Nutropin Depot formulation. One patient appeared to allergic to some component of the Nutropin Depot formulation, but this could not be confirmed by extensive testing and the naïve patient (1.5q4) completed 6 months of therapy in []03-002.

4. Arthralgia probably related to Nutropin Depot therapy was reported by at least 10 subjects during the 3 studies. One of these children (0.75 2x/mo dose group in []03-004) required a temporary (2 dosings) 50% reduction in dosage before the symptoms abated. 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. There were no clinically significant changes in mean fasting or postprandial glucose or insulin levels, or mean hemoglobin A1C, noted in any of the studies with the exception of a very minimal increase in mean FBG after 12 months of 0.75 2x/mo in []03-003 (mean FBG increased from 79.5 to 84.4 mg%). 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 or increased during the study. In []03-004, 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 107 mg/dl, respectively). 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.

Injection Site-Related Adverse Events

1. Incidence

a. Quantification in all studies combined

Injection site reactions were by far and away the most common adverse event associated with Nutropin Depot therapy in all 3 studies. The most common reactions were erythema, nodules, pain post-injection, pain during injection, bruising, itchiness and lipoatrophy. The remarkably high incidence of these various injection site reactions is demonstrated in the next 4 tables. Table 41 demonstrates that whether one tabulates these injection site reactions as a percentage of the total number of injections administered or as the number of subjects experiencing at least 1 injection site reaction divided by the total number of subjects dosed with Nutropin Depot for all 3 studies combined, the incidence figures were extremely high and rank ordered almost identically (although a lower incidence was observed for any given injection site reaction when the reactions are expressed as a percentage of the total number of injections administered).

Table 41. ISS - Injection Site Reactions in Studies []03-002, []03-003 (including update) and []03-004 Combined

Injection-Site Adverse Event	Percent of Total Injections	Percent of Subjects Experiencing ≥1 reaction
	3459 Injections	138 Subjects
Erythema	53%	89%
Nodules	61%	88%
Pain Post-Injection	47%	88%
Pain During Injection	43%	73%
Bruising	20%	66%
Itchiness	13%	49%
Lipatrophy	13%	38%
Edema	8%	30%
Warmth	5%	17%
Injection-Site Reaction	2%	12%
Induration	2%	4%

b. Comparison between dose groups

Tables 42 and 43 demonstrate that the incidence of these injection site reactions (expressed in the 2 ways noted above) was not meaningfully different across dose groups when the results of all 3 studies are combined.

Table 42. ISS

Number of Injection Site Adverse Events as a Percentage of Total Number of Injections by Dose Group: Studies 03-002, 03-003 (including update) and 03-004 Combined				
Body System/Primary Term	All Subjects	0.75q4	1.5q4 or 1.5 1x/mo	0.75q2 or 0.75 2x/mo
Number of Injections	3459	529	1265	1665
Inj Site Erythema	1824 (53%)	153 (29%)	751 (59%)	920 (55%)
Inj Site Nodules	2111 (61%)	163 (31%)	872 (69%)	1076 (65%)
Inj Site Pain Post Injection	1642 (47%)	176 (33%)	739 (58%)	727 (44%)
Inj Site Pain During Injection	1501 (43%)	53 (10%)	582 (46%)	866 (52%)
Inj Site Bruising	697 (20%)	41 (8%)	266 (21%)	390 (23%)
Inj Site Itchiness	457 (13%)	38 (7%)	236 (19%)	183 (11%)
Inj Site Lipoatrophy	455 (13%)	59 (11%)	173 (14%)	223 (13%)
Inj Site Edema	260 (8%)	6 (1%)	114 (9%)	140 (8%)
Inj Site Warmth	165 (5%)	5 (1%)	61 (5%)	99 (6%)
Inj Site Reaction	68 (2%)	1 (0%)	18 (1%)	49 (3%)
Inj Site Induration	59 (2%)	2 (0%)	33 (3%)	24 (1%)

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Table 43. ISS

Number of Subjects with ≥1 Injection Site Adverse Event by Dose Group: Studies 03-002, 03-003, (including update) and 03-004 Combined				
Body System/Primary Term	All Subjects	0.75q4	1.5q4 or 1.5 1x/mo	0.75q2 or 0.75 2x/mo
Number Of Subjects Dosed	138	19	66	63
Any Inj Site Event	136 (99%)	19 (100%)	65 (98%)	61 (97%)
Inj Site Erythema	123 (89%)	17 (89%)	61 (92%)	53 (84%)
Inj Site Nodules	121 (88%)	18 (95%)	55 (83%)	57 (90%)
Inj Site Pain Post Injection	121 (88%)	19 (100%)	57 (86%)	54 (86%)
Inj Site Pain During Injection	101 (73%)	9 (47%)	45 (68%)	51 (81%)
Inj Site Bruising	91 (66%)	9 (47%)	41 (62%)	45 (71%)
Inj Site Itchiness	68 (49%)	10 (53%)	35 (53%)	27 (43%)
Inj Site Lipoatrophy	53 (38%)	8 (42%)	29 (44%)	20 (32%)
Inj Site Edema	41 (30%)	3 (16%)	19 (29%)	19 (30%)
Inj Site Warmth	23 (17%)	2 (11%)	10 (15%)	12 (19%)
Inj Site Reaction	17 (12%)	1 (5%)	5 (8%)	11 (17%)
Inj Site Induration	5 (4%)	1 (5%)	3 (5%)	1 (2%)

c. Multiple reactions in the same patient

Table 43 further demonstrates that 136 of 138 patients (99%) treated with Nutropin Depot experienced at least 1 event. In fact, many patients reported various reactions on multiple occasions. In support of this observation, Table 44 demonstrates that in every study performed the ratio of total number of injection site reactions to total number of injections administered was ~2.5-3/1.

Table 44. ISS - Ratio of Total Injection Site Reactions to Total Number of Injections by Study

Study	Total Inj	Total Reax	Ratio	Rated as Severe Reax
002	821	2034	2.5	47 (44 pain during inj)
003 (pre-update)	470	1200	2.6	14 (13 pain during inj)
004	806	2533	3.1	*
003 (update)	1362	3472	2.5	139 (123 pain during inj)
Total	3459	9239	2.7	*

*FACES Pain Rating Scale used in 03-004

d. Severity

Table 44 also demonstrates that only 1-4% of these injection site reactions were rated as severe in intensity (as assessed by the investigator). In fact, most of these injection site adverse events were rated as mild to moderate in intensity. The most common injection site reaction rated as severe was pain during injection.

e. Comparison across sequential studies following modifications in injection preparation and administration

After []03-002 was completed and the sponsor became aware of the very high incidence of injection site-related adverse events, injection preparation and administration procedures were modified including a change to 21 gauge ½ inch [] needles from 22 gauge 1 inch needles and intensive education of the family members who would be giving future injections. It is therefore appropriate to compare the incidence of these injection site reactions in the studies which followed []03-002 (i.e., []03-004 and the latter part of []03-003 [safety update period]) with the original incidence data reported for []03-002. Table 45 (percentage of subjects experiencing at least 1 adverse event/total patients exposed), Table 46 (pain post-injection expressed as a percentage of total number of injections administered) and Table 47 (5 other frequent injection site reactions expressed as a percentage of total number of injections administered) compare the incidence of these various injection site events across sequential studies combining the data for all dose groups. It is evident that excepting a trend downward in pain post-injection (an apparent 40 to 50% decrease in Table 46 and a more modest 20% decrease in Table 45), there was no meaningful change in the incidence of the other injection site reactions in the studies performed subsequent to []03-002.

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Table 45. ISS - Comparison of Number/% of Patients Experiencing Injection Site Reaction at Least Once Across All Studies (Dose Groups Combined)

INJECTION SITE ADVERSE REACTION	03-002 N=63	03-003 (Pre-Update) n=34	03-004 n=74	03-003 (Update Only) n=81
PAIN POST-INJECTION*	58/92%*	29/85%	54/73%	60/74%*
ERYTHEMA	56/89%	26/76%	63/85%	68/84%
NODULES	55/87%	28/82%	64/86%	68/84%
ITCHINESS	32/51%	14/41%	23/31%	22/27%
BRUISING	28/44%	17/50%	47/64%	51/63%
LIPOATROPHY	21/33%	14/41%	21/28%	30/37%
PAIN DURING INJECTION	20/32%	13/38%	69/93%**	57/70%
EDEMA	8/13%	1/3%	26/35%	21/26%
WARMTH	8/13%	2/6%	8/11%	16/20%
REACTION	2/3%	0/0%	9/12%	10/12%
INDURATION	2/3%	1/3%	4%	1/1%

*Trend downward in pain post-injection

**FACES Pain Rating Scale used in 03-004

Table 46. ISS - Comparison of Pain Post-Injection (% of Total Injections) Across All Studies (Dose Groups Combined)

Injection-Site Adverse Event	03-002	03-003 (Pre-Update)	03-004	03-003 (Update Only)
Pain post injection*				
All subjects	66%*	67%	40%	34%*
0.75q4*	80%	59%	-	-
1.5q4 or 1.5 1x/mo*	55%*	79%	52%	39%*
0.75q2 or 0.75 2x/mo*	69%*	57%	31%	31%*

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Table 47. ISS - Comparison of Pain During Injection, Erythema, Nodules, Bruising and Lipoatrophy (% of Total Injections) Across All Studies (Dose Groups Combined)

Injection-Site Adverse Event	03-002	03-003 (Pre-Update)	03-004	03-003 (Update Only)
No of Injections	821	470	806	1362
Erythema	50%	53%	56%	52%
Nodules	61%	62%	63%	59%
Pain During Injection	16%	18%	81%*	46%
Bruising	15%	17%	24%	22%
Lipoatrophy	13%	17%	12%	12%

*FACES Pain Rating Scale used in 03-004

2. Pain during injection

a. As noted earlier, pain during injection was the injection site reaction most often rated as severe by the investigator (see Table 44). Of the 14 patients who discontinued from the 3 studies because of an adverse event, 6 of these subjects complained of severe pain during injection (4 in 03-002 and 1 each in 004 and 03-003) and 2 other patients dropped out because of fear associated with Nutropin Depot injections (both in 03-004). Pain during injection may also be part of the reason (aside from lack of efficacy) that ~50% of CT patients who completed 6 months of therapy in 03-002 chose not to enroll in 03-003 (on the other hand, 81 of 96 naïve patients who completed either 03-002 or 03-004 did choose to enroll in 03-003 and the majority of these patients did

complete at least 6 additional months of Nutropin Depot therapy in [redacted]03-003.

b. In [redacted]03-004, the sponsor taught parents to utilize the Wong-Baker FACES Pain Rating Scale to better assess pain during injection. As discussed in the [redacted]03-004 review, these results suggested decreased severity of pain during injection and increased tolerability of Nutropin Depot injections during the course of the study. At the end of Month 1, 40% of injections were reported as FACE 5 ("worst pain"), whereas at the end of Month 6, only 16% of injections were reported as FACE 5. It should be further noted at this point that a comparison of the incidence of pain during injection across sequential studies is problematic because of the bias introduced by the utilization of the FACES Pain Rating Scale in [redacted]03-004 - which resulted in the aggressive solicitation of feedback about this particular injection site-related adverse event. Finally, review of Case Report Forms for all 3 studies revealed only 1 patient (in [redacted]03-003) who transiently elected to receive more than the required number of injections per dosing to reduce the volume per injection and possibly the pain during injection.

3. Apparent lack of a subset of patients especially susceptible to injection site reactions

At the request of this reviewer, the sponsor performed a detailed analysis of data from the [redacted]03-004 cohort to discern whether a subset of patients at particular risk for injection site reactions existed. This analysis revealed 1) the mean number of injection site-related adverse events per injection (~2.5) remained constant irrespective of the number of injections administered, 2) the absence of bimodal clustering when the range of events per injection is plotted, and 3) the absence of characteristics which distinguish patients with event/injection ratios above and below the overall mean number of events per injection.

4. "Post-dosing" headache, nausea, vomiting and fever

During [redacted]03-002, [redacted]03-004 and [redacted]03-003, approximately 45 of 234 subjects (20%; -15 of 64 in [redacted]03-002, -15 of 75 in [redacted]03-004 and -15 of 95 in [redacted]03-003; dose groups combined) reported the occurrence of "post-dosing" headache, nausea, vomiting or fever on at least 1 occasion (usually 1 to 3 days after dosing with Nutropin Depot). At the request of this reviewer, the sponsor determined the number of subjects experiencing at least 1 episode of any of these symptoms divided by the total number

of subjects exposed to Nutropin Depot and the number of dosings (irrespective of the number of injections per dosing) associated with at least 1 episode of any of these symptoms divided by the total number of dosings for all 3 studies combined for each of the dose groups separately and then pooled. If one examines the "dosings" data, there is a suggestion that 1.5 1x/mo causes more headaches. However, if one then looks at the "subject" data in the lower half of the table, it is clear that none of these complaints is more common in any given dose group. Overall, headache (~10%) and nausea (~10%) appear to be the more frequent "post-dosing" complaints. Finally, the finding (for each dose group and after dose group data has been pooled) that ~20% of patients experience at least 1 episode of "post-dosing" headache and/or nausea and/or vomiting and/or fever matches up very closely with the ~20% incidence reported for each individual study.

Table 48. ISS - Studies []03-002, []03-003 (including update) and []03-004 Combined: Subjects or Dosings With at Least 1 Episode of Headache, Nausea, Vomiting or Fever Within 3 Days of Dosing and Possibly, Probably or Definitely Related to Study Drug

	All Subjects	0.75q4	1.5q4 or 1.5 1x/mo	0.75q2 or 0.75 2x/mo
Total Number of Dosings	2435	124	745	1566
Number of Dosings with ≥1 episode of:				
Headache	42 (2%)	3 (2%)	28 (4%)	11 (<1%)
Nausea	18 (<1%)	2 (2%)	11 (1%)	5 (<1%)
Vomiting	17 (<1%)	2 (2%)	7 (<1%)	8 (<1%)
Fever	7 (<1%)	1 (<1%)	2 (<1%)	4 (<1%)
Any of the above adverse events	68 (3%)	6 (5%)	39 (5%)	23 (1%)
Total Number of Subjects	138	19	66	63
Number of Subjects with ≥1 episode of:				
Headache	13 (9%)	2 (11%)	7 (11%)	5 (8%)
Nausea	11 (8%)	2 (11%)	7 (11%)	2 (3%)
Vomiting	7 (5%)	1 (5%)	3 (5%)	3 (5%)
Fever	7 (5%)	1 (5%)	2 (3%)	4 (6%)
Any of the above adverse events	28 (20%)*	4 (21%)	13 (20%)	12 (19%)

GH PK parameters and IGF-I levels with safety implications (see Biopharmaceutics Review and more detailed discussion of this data in the study-specific reviews)

In [] 03-002, GH levels peaked 24 hours post-dose in a dose proportional manner (associated with a transient, clinically insignificant increase in FBG 24 hours post-dose) and returned to baseline values ~2 weeks after dosing. IGF-I levels (which as expected were at the low end of the age- and sex-matched normal reference range at baseline) increased 2-8 fold ~1.5 days post-dose in a non-dose proportional manner and also returned to baseline ~2 weeks after dosing. The GH and IGF-I serum concentration-time profiles were very similar during each treatment cycle in both naïve and CT patients indicating that both the exaggerated initial-release (0-2 days) and sustained-release (2-28 days) phases of rhGH (as well as the IGF-I response) after repeated SC administration of Nutropin Depot were reproducible in children with GHD. Trough levels of GH and IGF-I obtained in all 3 studies at Months 3 and 6 were not meaningfully different from baseline values. Taken together, these data indicate that there was no clinically significant accumulation of GH or IGF-I (or sustained inappropriately elevated GH or IGF-I levels) after 6 to 12 months of treatment with Nutropin Depot which could have resulted in acromegaloid and metabolic adverse effects.

Discussion of ISS

With the exception of the bother and discomfort of a very large amount of injection site-related adverse events and occasional "post-dosing" headache and/or nausea in ~20% of patients, Nutropin Depot was a safe and well tolerated drug. GH and IGF-I did not accumulate after repeated administration and there were no serious adverse events related to Nutropin Depot. None of the severe but unusual consequences of rhGH therapy occurred during any of the studies and the effects on glucose tolerance were minimal and sporadic. Mild arthralgia probably related to rhGH therapy occurred in some patients but in 1 patient was quite severe until the dosage was transiently lowered.

Three sequelae merit some additional comments:

1. During [] 03-003, 2 CT patients receiving 0.75q4 had an exacerbation of pre-existing hypoglycemic episodes originally related to hypopituitarism/GH insufficiency. It was thought by

the investigator and the sponsor that the 0.75q4 dosage was not supplying sufficient rhGH to act as a counterregulatory hormone and therefore these patients were discontinued. For this safety-related reason (as well as apparent lesser efficacy compared with the larger doses), this dosage was not continued in the later trials. Moreover, the sponsor appropriately has added a "precaution" to the proposed label (i.e., patients with symptomatic hypoglycemia related to GHD should be monitored carefully while receiving Nutropin Depot).

2. The enormous incidence of injection site-related reactions remains a significant problem. For every injection administered, 2-3 reactions occur! As discussed at length in the review of [] 03-004, these does NOT appear to be subset more prone to injection site reactions. Fortunately, 90-95% of these reactions are rated mild to moderate in intensity. In spite of the countermeasures undertaken after [] 03-002, the incidence of these various injection site reactions has not diminished in the later trials - with the exception possibly of a downward trend in pain post-injection.

Pain during injection was consistently the most frequent cause of a "severe" injection site reaction (including 123 patients in the safety update period!) and the reason for discontinuation in 9 of the 14 patients who left one of the studies due to an adverse event. The utilization of the FACES Pain Rating Scale during [] 03-004 suggested that pain during injection may diminish during a six month exposure to Nutropin Depot - this should be explored further.

Lastly, the huge incidence of injection site reactions after the injection of Nutropin Depot dwarfs the minimal incidence of injection site reactions after the daily administration of rhGH.

3. The reason for the periodic occurrence of "post-dosing" headache and/or nausea and/or vomiting and/or fever in up to 20% of patients is not known. Fortunately, the complaints are self-limited and easily treated when they do occur. These kinds of complaints have NOT been associated with daily injections of rhGH - but it is obviously much harder to assess the relationship of dosing to non-specific "everyday" complaints like headache and nausea when the child is being injected daily.

Labeling Revisions

Significant labeling revisions were made by this reviewer, the team leader and the Agency's statistical reviewer in 3 sections of the proposed label submitted by the sponsor. Discussions with the sponsor regarding the label will begin on Monday 22 November 1999.

The labeling revisions are as follows:

1. Efficacy Studies Section

a. Sponsor's proposal:

Efficacy Studies

Pediatric Growth Hormone Deficiency (GHD)

DRAFT

b. Reviewer's revision:

The entire section has been rewritten as follows:

Efficacy Studies

Pediatric Growth Hormone Deficiency (GHD)

In two multicenter, open-label clinical studies (Study 1 and Study 2) in prepubertal children with idiopathic or organic GHD previously untreated with rhGH, 91 patients were treated with Nutropin Depot at 1.5 mg/kg once monthly or 0.75 mg/kg twice monthly by subcutaneous injection for 6 months.

[Redacted]

The dose-pooled, mean 6-month annualized growth rate on Nutropin

Depot therapy was 8.4 cm/yr (n=89).

[Redacted]

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Labeling

2. Indications and Usage Section

a. Sponsor's proposal:

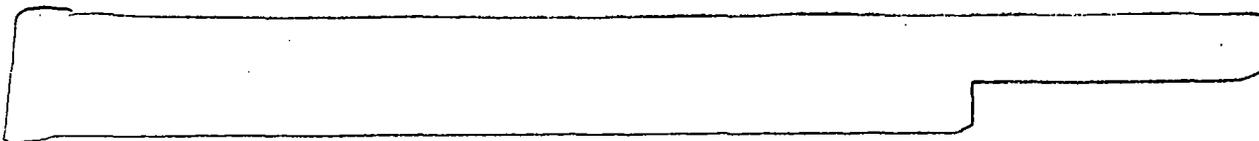
Indications and Usage

Nutropin Depot [somatropin (rDNA origin) for injectable suspension] is indicated for the long-term treatment of growth failure due to a lack of adequate endogenous GH secretion.

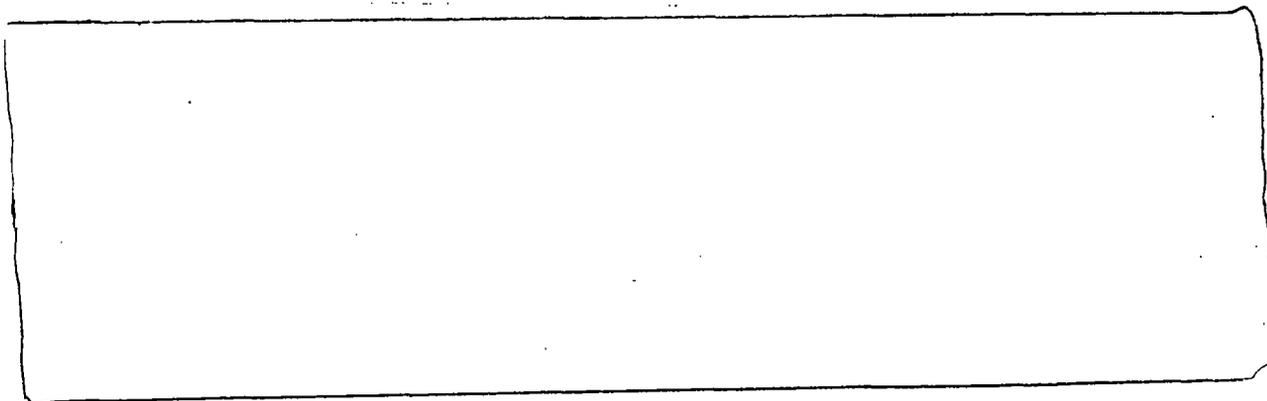
c. Reviewer's revision:

The section has been rewritten.

Indications and Usage



Considerations in the Use of Nutropin



4. Adverse Reactions Section

a. Sponsor's proposal:

Adverse Reactions

As with all protein pharmaceuticals, patients may develop antibodies to the protein. GH antibody-binding capacities below 2 mg/L have not been associated with growth attenuation. In some cases when binding capacity exceeds 2 mg/L, growth attenuation has been observed. In clinical studies of pediatric patients who were treated with Nutropin Depot, 0/138 patients with GHD screened for antibody production developed antibodies with binding capacities ≥ 2 mg/L at any time during a treatment period of up to 17.4 months.

In addition to an evaluation of compliance with the prescribed treatment program and thyroid status, testing for antibodies to GH should be carried out in any patient who fails to respond to therapy.

In studies involving 138 pediatric patients treated with Nutropin Depot, the most frequent adverse events were injection-site reactions, which occurred in [redacted] patients. [redacted] erythema, injection-site discomfort, nodules, bruising, itching, lipoatrophy, and swelling or puffiness. [redacted]

Events observed less frequently in the Nutropin Depot studies that were considered possibly, probably, or definitely related to the drug by the treating physician included: headache, lower extremity pain, nausea, fever, and vomiting. One patient experienced a generalized body rash [redacted] an allergic reaction to Nutropin Depot.

Leukemia has been reported in a small number of GHD patients treated with GH. It is uncertain whether this increased risk is related to the pathology of GH deficiency itself, GH therapy, or other associated treatments such as radiation therapy for intracranial tumors. On the basis of current evidence, experts cannot conclude that GH therapy is responsible for these occurrences.

Other adverse drug reactions that have been reported in GH-treated patients include the following: 1) Metabolic: Mild, transient peripheral edema. 2) Musculoskeletal: Arthralgia, carpal tunnel syndrome. 3) Skin: Rare increased growth of pre-existing nevi; patients should be monitored for malignant transformation. 4) Endocrine: Gynecomastia. Rare pancreatitis. Of these reactions, only edema (<1% of patients) and arthralgia (4%) were reported in the Nutropin Depot studies.

Reviewer's revision:

The third and fourth paragraphs have been rewritten and a Table was added. A minimal change was made to the last paragraph as well.

Adverse Reactions

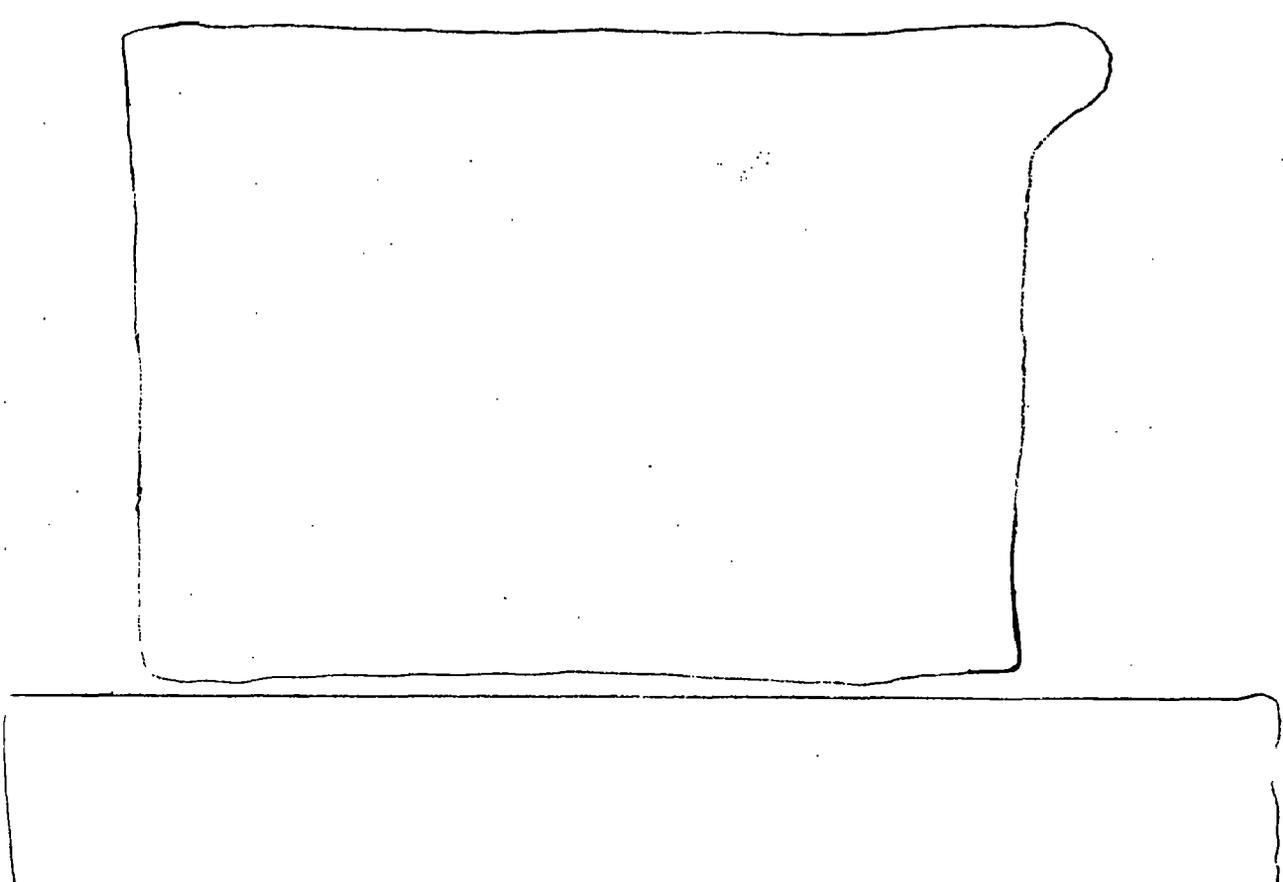
As with all protein pharmaceuticals, patients may develop antibodies to the protein. GH antibody-binding capacities below 2 mg/L have not been associated with growth attenuation. In some cases when binding capacity exceeds 2 mg/L, growth attenuation has been observed. In clinical studies of pediatric patients who were treated with Nutropin Depot, 0/138 patients with GHD screened for antibody production developed antibodies with binding capacities ≥ 2 mg/L at any time during a treatment period of up to 17.4 months.

In addition to an evaluation of compliance with the prescribed treatment program and thyroid status, testing for antibodies to GH should be carried out in any patient who fails to respond to therapy.

The most frequent adverse events were injection-site reactions

[REDACTED]

[REDACTED]



Leukemia has been reported in a small number of GHD patients treated with GH. It is uncertain whether this increased risk is related to the pathology of GH deficiency itself, GH therapy, or other associated treatments such as radiation therapy for intracranial tumors. On the basis of current evidence, experts cannot conclude that GH therapy is responsible for these occurrences.

Other adverse drug reactions that have been reported in GH-treated patients include the following: (1) metabolic: mild, transient peripheral edema; (2) musculoskeletal: arthralgia, carpal tunnel syndrome; (3) skin: rare increased growth of pre-existing nevi; patients should be monitored for malignant transformation; (4) endocrine: gynecomastia; (5) rare pancreatitis. Of these reactions, only edema (<1% of patients) and arthralgia (4%) were reported in the Nutropin Depot studies.

Conclusions

Efficacy

1. When Nutropin Depot was administered to children with GHD previously untreated with rhGH, it is clear that the mean 12 month annual growth rate and the mean 6 month annualized growth rate were significantly greater (by ~3 cm/yr) than the baseline, pretreatment annualized growth rate of these children. However, it is also clear that the response to Nutropin Depot was significantly inferior to the mean 12 month annual growth rate and mean 6 month annualized growth rate achieved when demographically similar naïve children were treated with daily injections of the currently recommended dosage of rhGH (43 ug/kg/day). Whereas Nutropin Depot produced a mean response of ~8 to 8.5 cm/yr (~70% of patients grew <9 cm/yr), mean growth rates of 10.5 to 12 cm/yr were achieved with an optimal therapeutic regimen. The growth response after Nutropin Depot closely resembled the response seen when children with GHD were treated with the currently recommended dosage administered TIW, a documented second line, suboptimal therapeutic regimen.
2. The increase in standardized height in naïve patients after Nutropin Depot therapy was not accompanied by inappropriate advancement of the bone age, indicating that catchup growth had occurred.
3. The mean annual growth rate was ~1 cm less than the mean 6 month annualized growth rate in naïve (and very small sample of CT) patients. This is more than likely explained by the well known natural decline in growth rate response to rhGH over time. Investigators should be aware that 6 month annualized growth rates can overestimate the true annual growth rate.
4. In [redacted] 03-004, although the mean 6 month annualized growth rates were very similar in the 2 dose groups being marketed, a distribution plot suggested that 0.75 2x/mo may be more advantageous.
5. Multiple regression analyses by the sponsor and the Agency's statistical reviewer confirm that chronological age and maximum stimulated GH response are the best predictors of first year growth response to rhGH therapy.

6. When CT patients were switched from daily therapy with optimal amounts of rhGH to Nutropin Depot, the mean 6 month annualized growth rate attained was clearly inferior to the pre-switch mean annualized growth rate on daily injections (by ~3 cm).

7. Nutropin Depot was clearly less efficacious than daily therapy in naïve and CT patients more than likely because of its markedly reduced bioavailability compared with daily injections of rhGH.

8. This reviewer believes it is remarkable that as of 6/99, ~20% of naïve patients and 60% of CT patients had discontinued from 03-003 specifically because the family and/or the on-site investigator were dissatisfied with the growth response.

Safety

1. The administration of Nutropin Depot to 138 patients for ~1 year was not associated with life-threatening or serious sequelae. None of the severe but unusual side effects associated with rhGH therapy were reported during these trials. Although transient and sporadic elevations of glucose and insulin levels were noted in individual subjects, the mean levels of glucose, insulin and hemoglobin A1C did not change during any of the studies. A small percentage of patients reported arthralgias - an expected consequence of rhGH administration in any form. **Ironically, the reduced bioavailability of this formulation of rhGH (which resulted in reduced efficacy) more than likely disallowed more rhGH-associated adverse sequelae.** One patient may have manifested allergy to an unknown component of the Nutropin Depot formulation.

2. Trough levels of GH ^{IGF-I} revealed no evidence of inappropriate accumulation.

3. The most consequential adverse effect associated with Depot Nutropin therapy were local injection site reactions including pain during and after injection, nodules, erythema, bruising and lipoatrophy:

---The incidence of these injection site adverse events was extremely high (70-100%) and about the same in the different dose groups - **and contrasts with the minimal incidence of injection site reactions associated with daily injections of rhGH**

---The ratio of injection site reactions to total number of injections approached 2.5-3/1 in every study performed

---Fortunately, 95% of these reactions were mild to moderate in intensity

---Pain during injection was the injection site reaction most often rated as severe. A small number of subjects discontinued because of injection site pain. In [] 03-004, quantification of pain using a pain rating scale suggested less severe pain and improved injection tolerance during the course of the study

---Changes in injection administration and preparation procedures after the first study did not have a significant impact on the incidence of these reactions in the subsequent studies excepting a mild trend downward in pain post-injection

---An analysis of the naïve cohort in [] 03-004 did not reveal evidence of a subset more susceptible to injection site reactions

4. Approximately 20% of all subjects in the 3 studies reported at least 1 episode of "post-dosing" headache, nausea, vomiting or fever. The etiology of this phenomenon is unknown. Similar "post-dosing" symptoms after daily injections of rhGH seem to be unusual.

Recommendations

Efficacy

1. The drug is approvable pending substantial modification of the label proposed by the sponsor. The revised label has been returned to the sponsor and interactive discussion will begin very soon.

2. Nutropin Depot should only be used in previously untreated patients (as a second line alternative therapy in children who refuse to take daily injections). If the initial response is suboptimal (or if the initial response is satisfactory but wanes inappropriately subsequently), and a careful investigation does not reveal a reason, the patient should be encouraged to switch to daily injections of the currently recommended dose.

3. The sponsor should consider further comparing the efficacy of 1.5 lx/mo and 0.75 2x/mo in a post-marketing study. It would be of interest as well to compare the bioavailabilities of these 2 dose regimens in a subset of patients.

Safety

1. There are no safety issues which impact the approvability of Nutropin Depot for marketing.
2. Patients should be advised of the high likelihood of injection site reactions and the less likely possibility of "post-dosing" complaints prior to the initiation of therapy with Nutropin Depot.
3. Sponsor should continue to look for ways to minimize the incidence of these very common and bothersome injection site reactions.

/S/

11/22/99

Robert S. Perlstein MD, FACP, FACE
Medical Review Officer

CC: Original NDA 21-075; HFD-510 NDA 21-075
Original IND [redacted] HFD-510 IND [redacted]
HFD-510 SSobel, SMalozowski, RPerlstein, JMele, RShore,
DHertig, SMOore, CKing

/S/

11/23/99

Saul Malozowski MD, PhD
Acting Team Leader

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Relevant Literature/References (Review of literature)

1. Anhalt H, Wilson DM, Bachrach LK, Hintz RL, Olney RC, Eckert KL et al. A prospective randomized trial of growth response to two dosages of rhGH. *Pediatr Res* 1994;35:93A.
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APPENDIX

Appendix 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.

^b GH administered by intramuscular injections.

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Appendix Table 2. 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
	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 ^e (3.3 - 14.5)	ND	-3.7 ^e (-1.5 - 5.0)	5.4 ^e (1.6 - 10.7)	ND	ND	3.2 ± 1.1	100	ND	GHD
5	Kaplan ^d , 1986	14 (8/6)	8.8 ^e (3.1 - 13.9)	ND	-3.6 ^e (-1.8 - 4.7)	6.6 ^e (2.1 - 11.0)	ND	ND	3.2 ± 1.0	100	ND	GHD
5	Kaplan ^d , 1986	10 (6/4)	6.1 ^e (4.1 - 12.2)	ND	-3.7 ^e (-2.1 - 5.5)	5.0 ^e (1.5 - 11.4)	ND	ND	3.8 ± 1.0	100	ND	GHD

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Appendix Table 2 (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 ¹ , 1989	26	8.5 ± 3.8	ND	ND	ND	ND	ND	3.6 ± 1.3	ND	ND	GHD
6	Rosenbloom ¹ , 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	^c 3.9 ± 2.6	3.44 ± 1.27	100	ND	GHD
7	Soliman, 1996	9	7.1 ± 1.9	ND	-3.4 ± 0.8	ND	ND	8.6 ± 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 ± 1.39	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

^a are mean ± SD unless indicated otherwise.

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.

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References for Appendix Tables 1 and 2

1. Anhalt H, Wilson DM, Bachrach LK, Hintz RL, Olney RC, Eckert KL et al. A prospective randomized trial of growth response to two dosages of rhGH. *Pediatr Res* 1994;35:93A.
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Appendix Table 3. Vial Configurations and Diluent Volumes Used in Pediatric Studies

Study	Vial Size (mg rhGH)	Actual Fill (mg rhGH)	Diluent Volume (mL)	Conc. (mg rhGH/mL)
03-002	22.5	26.3	0.9	25
	22.5	26.3	1.5 CMC	16*
	22.5	26.3	1.0 CMC	22*
03-003	22.5	26.3	1.2 CMC	19
	22.5	26.3	1.0 CMC	22
	22.5	26.3	0.9 CMC	25
	18	21.7	1.5 CMC	13
	27	32.0	1.5 CMC	19
03-004	18	21.7	1.5 CMC	13
	27	32.0	1.5 CMC	19

*Concentrations of 22 mg/mL and 16 mg/mL used in the NDA analysis of the effect of dose concentration on PK (Item 6.F, Study Report 03-002a, page 13)

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