

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER: 21-075**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**



**CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW**

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<b>NDA 21-075 / N-000</b>	<b>SUBMISSION DATE:</b>	<b>14-DEC-99</b>
<b>BRAND NAME:</b>	<b>Nutropin Depot</b>	
<b>GENERIC NAME:</b>	<b>Somatropin (rDNA origin) for injectable suspension</b>	
<b>REVIEWER:</b>	<b>Robert M. Shore, Pharm.D.</b>	
<b>SPONSOR:</b>	<b>Genentech, Inc., South San Francisco, CA</b>	

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**SYNOPSIS:**

The sponsor has submitted (via Email and FAX) a proposal for the [redacted] along with a Phase 4 commitment to submit a revised method and/or specification within one year (this was agreed upon in a T/con on 13-DEC-99; See Appendix).

This is acceptable to The Office of Clinical Pharmacology and Biopharmaceutics.

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Robert M. Shore, Pharm.D.  
Division of Pharmaceutical Evaluation II  
Office of Clinical Pharmacology and Biopharmaceutics

[redacted] /S/

14-DEC-99

RD/FT initialed by Hae-Young Ahn, Ph.D., Team Leader

[redacted] /S/

12/14/99

CC: NDA 21-075/N-000 (orig.,1 copy), HFD-510(King, Malozowski, MooreS), HFD-870(Ahn, HuangSM), CDR (Barbara Murphy).

Code: AP

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## CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW

NDA 21-075 / N-000	SUBMISSION DATE:	25-JUN-99, 22-OCT-99(BZ)
BRAND NAME:	Nutropin Depot	
GENERIC NAME:	Somatropin (rDNA origin) for injectable suspension	
REVIEWER:	Robert M. Shore, Pharm.D.	
SPONSOR:	Genentech, Inc., South San Francisco, CA	
TYPE OF SUBMISSION:	Original application; Code: 3P	

### TERMS AND ABBREVIATIONS:

AUCa-b ..... Area under the plasma-concentration-time curve from time a to time b  
DMEDP ..... Division of Metabolic and Endocrine Drug Products  
GH ..... Growth hormone; somatropin; rhGH  
GHBP ..... Growth hormone binding protein  
GHD ..... Growth hormone deficient  
IGF-1 ..... Insulin-like growth factor-1  
IGFBP-3 ..... Insulin-like growth factor-1 binding protein-3  
OCPB ..... Office of Clinical Pharmacology and Biopharmaceutics  
ProLease ..... Old name for Nutropin Depot  
SC ..... Subcutaneous

### SYNOPSIS:

Nutropin Depot is an extended release formulation of somatropin supplied as 13.5, 18, and 22.5 mg single-use vials. The formulation consists of micronized particles of somatropin embedded in a biodegradable poly D/L-lactide-co-glycolide (PLG) matrix which has been used in another depot product. It is suspended in aqueous Diluent for Nutropin Depot (supplied in Nutropin Depot kit), the volume of which depends on the vial size; the resulting suspension is 19 mg/mL for each vial. The proposed dosage is 1.5 mcg/kg SC once each month or 0.75 mg/kg SC twice each month. The sponsor claims bioactive somatropin is released from the microspheres initially by diffusion followed by both diffusion and polymer degradation, with the polymer undergoing hydrolysis to lactic and glycolic acid and ultimately to carbon dioxide and water. The sponsor's proposed indication for Nutropin Depot is the long-term treatment of growth failure due to lack of adequate endogenous growth hormone secretion.

Nutropin Depot is not currently marketed in any country. Lyophilized Nutropin is approved for treatment of 1) growth failure due to lack of endogenous growth hormone, 2) growth failure associated with chronic renal insufficiency, 3) short stature associated with Turner syndrome and 4) adult growth hormone deficiency (AGHD).

Genentech is responsible for manufacturing the rhGH as well as labeling, packaging, final release and distribution of Nutropin Depot final vial product and the kit, and [ ] is responsible for manufacturing and testing the Nutropin Depot final product microspheres.

The sponsor conducted neither absolute nor relative bioavailability studies with Depot and daily somatropin. However, when compared with historic healthy adult single dose GH AUC<sub>0-24hr</sub> data, the relative bioavailability of a single dose of Nutropin Depot in GHD children (AUC<sub>0-28days</sub>) is calculated to be about 35%. Of the total Depot AUC<sub>0-28days</sub> observed in children, about 50-60% of the exposure occurs in the first 2 days after injection. This may contribute to the poor efficacy of the Depot product to promote

growth in GHD children as compared to historic daily SC Nutropin growth data.

Three principal studies are discussed in this NDA: a Phase I safety and pharmacokinetic study in GHD adults (03-001), a dose ranging Phase I/II pharmacokinetic study in GHD children (03-002), and a Phase III efficacy study (03-004) with limited pharmacokinetics in GHD children. In addition, an extension study (03-003) for long term follow up is included. Only one formulation was used in these studies, although lots produced at different scales of manufacture were used. The adult study was a pilot study to assess the pharmacokinetics of Nutropin Depot after a single SC dose.

Elevated GH, IGF-I, and IGFBP-3 levels were observed following SC injection of Nutropin Depot in the Phase 2/3 GHD pediatric studies. Serum levels of GH, IGF-I, and IGFBP-3 generally returned to baseline before the next dose and no progressive accumulation was seen over 6 months of dosing for the 3 dose groups in the Phase 2/3 pediatric studies. The hGH peak level and AUC<sub>0-28</sub> days were approximately dose proportional in the pediatric studies. In the pediatric studies, IGF-I and IGFBP-3 levels were increased at all 3 doses compared to baseline. These increases were neither dose nor hGH concentration proportional. Generally reproducible pharmacokinetic and pharmacodynamic responses were obtained within subjects over 6 months of treatment.

The sponsor has proposed an [ ] and [ ] specification for quality control.

**RECOMMENDATION:**

The following recommendation should be forwarded to the sponsor:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPE-2) has reviewed NDA 21-075/N-000 submitted 25-JUN-99 and 22-OCT-99. The overall Human Pharmacokinetic Section is acceptable to OCPB. However, it is suggested that the [ ]

[ ] is acceptable.

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*(Appendices and/or Attachments available from DMEDP filing room or DFS, if not included)*

**STUDY SUMMARY INDEX**

<b>Protocol Number</b>	<b>Title</b>	<b>Page</b>
03-001	AN OPEN-LABEL PHARMACOKINETIC STUDY OF [REDACTED] hGH IN ADULT PATIENTS WITH GROWTH HORMONE DEFICIENCY	p. 39
03-002	A PHASE I/II, MULTICENTER, OPEN-LABEL STUDY OF THE SAFETY AND EFFICACY OF [REDACTED] rhGH ADMINISTERED MONTHLY IN CHILDREN WITH GROWTH FAILURE DUE TO GROWTH HORMONE DEFICIENCY	p.41
03-004	A PHASE III, MULTICENTER, OPEN-LABEL STUDY OF THE SAFETY AND EFFICACY OF [REDACTED] rhGH ADMINISTERED IN CHILDREN WITH GROWTH FAILURE DUE TO GROWTH HORMONE DEFICIENCY	p. 51
03-003	AN OPEN-LABEL, LONG-TERM EXTENSION STUDY OF THE SAFETY AND EFFICACY OF [REDACTED] rhGH IN CHILDREN WITH GROWTH FAILURE DUE TO GROWTH HORMONE DEFICIENCY	p. 62

**DRUG FORMULATION:**

The Nutropin Depot microspheres are packaged in sterile vials as a sterile, dry, free-flowing powder. Before administration, the microspheres are hydrated by suspending them in an aqueous diluent. After subcutaneous injection of the suspension, the protein is released from the microspheres into the subcutaneous space and absorbed. Ultimately, the microspheres undergo hydrolysis into small, naturally

occurring molecules (lactic acid and glycolic acid), which are completely metabolized by the body.

Drug product vial:

Quantitative Composition Including Overage

Ingredient	Specification	Microsphere Composition*	Quantitative Composition per Dosage Unit*		
			13.5 mg rhGH	18 mg rhGH	22.5 mg rhGH
rhGH					
Zinc Acetate					
Zinc Carbonate					
PLG					

\* Nutropin Depot Final Product is supplied as 13.5, 18, and 22.5 mg dosage units; vials are overfilled to ensure delivery of labeled amount of somatotropin.

\* NC = Noncompendial; specification sheet provided in Section 4.A.3.a.

\* Nutropin Depot Microsphere composition, % (w/w).

Diluent vial:

Quantitative Composition

Component	Compendial Reference	Amount/mL
Carboxymethylcellulose sodium	USP	30.0 mg
Polysorbate 20	USP	1.0 mg
Sodium chloride	USP	9.0 mg
Water for Injection	USP	

The commercial manufacturing scale will be [redacted] of microspheres; lots of this size were used in studies [redacted] 03-002, [redacted] 03-003 and [redacted] 03-004. The adult study ([redacted] 03-001) used small lots and, thus, the data from this study are less reliable.

• DISSOLUTION:

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**ANALYTICAL METHODOLOGY:**

The submission includes acceptable validation data for all assays.

**HUMAN PHARMACOKINETICS AND BIOAVAILABILITY STUDIES:**

- I. **Bioavailability**
- A. *Absolute/Relative Bioavailability*

The sponsor did not conduct an absolute bioavailability ( $F_{abs}$ ) study. Instead, the relative bioavailability ( $F_{rel}$ ) of single SC doses of Nutropin Depot based on comparisons with historical data from Genentech studies in normal adult males that received somatotropin formulated for daily administration as a single IV or SC bolus was estimated to be 44% in adults and 33%-38% in children. The estimated absolute bioavailability of Nutropin Depot was approximately 36% in adults and 27%-32% in children as compared to 83% for Nutropin AQ. The relative bioavailability after chronic treatment ( $F_{rel,Chron}$ ) was also calculated using an GH AUC adjusted for chronic dosing per Kearns et al. 1991. These authors found an approximate 30% decrease in serum hGH AUC following 4-6 weeks of daily dosing (0.043 mg/kg/day). However, the sponsor has only corrected the daily AUC value and not the Depot AUC value; this seems biased and, if the AUC of GH does change (perhaps due to body changes) then these changes should be evident after either daily or Depot somatotropin. When compared to the daily AUC value adjusted for chronic dosing, the relative bioavailability of Nutropin Depot was 63% in adults and 48%-55% in children.

Summary of Bioavailability Estimates for rhGH and Nutropin Depot in Humans

Parameter	Treatment Groups					
	Somatropin IV Single Bolus in Normal Adult Males	Nutropin AQ SC Single Bolus in Normal Adult Males	Nutropin AQ SC Single Bolus Adjusted for Chronic Treatment	Nutropin Depot SC Single Dose in GHD Adults	Nutropin Depot SC Single Dose in GHD Children	Nutropin Depot SC Single Dose in GHD Children
rhGH Dose (mg/kg)	0.02	0.10	0.10	0.75	0.75	1.50
Mean Body Weight (kg)	73.2	73.8	73.8	87.4	27.1	20.0
Data Source Final Report No.	GNE M0019g	GNE L0560g	GNE L0560g (Kearns et al) <sup>a</sup>	03-001	03-002 <sup>b</sup>	03-002 <sup>b</sup>
AUC <sub>0-24h</sub> (ng • hr/mL)	162 ± 26.3 <sup>c</sup> 156 ± 25.3 <sup>d</sup>	673 ± 88.1	462 ± 60.5	2150 ± 623	1840 ± 1170	3310 ± 832
AUC <sub>0-24h</sub> or AUC <sub>0-12h</sub> (ng • hr/mL)	163 ± 26.4 <sup>c</sup> 156 ± 25.4 <sup>d</sup>	677 ± 88.2	465 ± 60.6	2210 ± 613	1930 ± 1150	3330 ± 833
$F_{abs}$ (%)	100	83 ± 11	Not Applicable	36 ± 10	32 ± 19	27 ± 7
$F_{rel}$ (%)	Not Applicable	100	Not Applicable	44 ± 12	38 ± 23	33 ± 8
$F_{rel,Chron}$ (%)	Not Applicable	Not Applicable	100	63 ± 18	55 ± 33	48 ± 12

<sup>a</sup> Kearns GL, Kemp SF, Frindik JP. Single and multiple dose pharmacokinetics of methionyl growth hormone in children with idiopathic growth hormone deficiency. J Clin Endocrinol Metab 1991;72:1148-56.

<sup>b</sup> From the intensively-sampled subject group.

<sup>c</sup> Dose-normalized by the ratio of the nominal protein content per vial (5.0 mg) to the actual reported value (4.8 mg).

<sup>d</sup> Original AUC values.

## II. Pharmacokinetics/Pharmacodynamics

### A. Single vs. Multiple Dose Administration

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**Analyses of Pharmacokinetic and Pharmacodynamic Parameters for Clinical Studies**

Study	Dose Group	Observations	hGH Pharmacokinetic Parameters <sup>a</sup>	IGF-I Pharmacodynamic Parameters <sup>a</sup>
03-001	0.75 mg/kg	hGH, IGF-I, IGFBP-2, IGFBP-3, GHBP	C <sub>max</sub> , T <sub>max</sub> , AUC <sub>0-1d</sub> , AUC <sub>0-2d</sub> , AUC <sub>0-27d</sub> , AUC <sub>0-55</sub> , days above baseline	C <sub>max</sub> , T <sub>max</sub> , AUC <sub>0-27d</sub> baseline corrected, days above baseline
03-002	0.75 mg/kg intensive	hGH, IGF-I	C <sub>max</sub> , T <sub>max</sub> , AUC <sub>0-1d</sub> , AUC <sub>0-2d</sub> , AUC <sub>0-27d</sub> , days above 1 ng/mL	T <sub>max</sub> , days above 1 ng/mL, baseline corrected C <sub>max</sub> , AUC <sub>0-1d</sub> , AUC <sub>0-2d</sub> , AUC <sub>0-27d</sub>
	1.5 mg/kg intensive	hGH, IGF-I		
	0.75 mg/kg q4	hGH, IGF-I, IGFBP-3, GHBP		
03-004	1.5 mg/kg q4	hGH, IGF-I, IGFBP-3, GHBP	Baseline and trough levels at Months 3 and 6	Baseline and trough levels at Months 3 and 6
	0.75 mg/kg q2	hGH, IGF-I, IGFBP-3, GHBP		
03-003 <sup>b</sup>	0.75 mg/kg q4	hGH, IGF-I, IGFBP-3, GHBP	Baseline and trough levels every 3 months	Baseline and trough levels every 3 months
	1.5 mg/kg q4	hGH, IGF-I, IGFBP-3, GHBP		
	0.75 mg/kg q2	hGH, IGF-I, IGFBP-3, GHBP		

<sup>a</sup> Major parameters estimated.

<sup>b</sup> Subjects who completed Study 03-002 or Study 03-004 and agreed to participate in Study 03-003.

The table above summarizes the pharmacokinetic and pharmacodynamic parameters that were characterized in the submitted studies. Study 03-002 provides the only intensive pharmacokinetic and pharmacodynamic data and this is in a small subset of patients.

The tables below include some demographic data on the patients as well as sampling times from the studies.

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Summary Study Design for Nutropin Depot ( ) rhGH) Clinical Pharmacokinetic Studies

Study	Group	N (m/f)	Mean (Range) Age (yrs)	Mean (Range) BW (kg)	Dose (mg/kg)	Schedule	Sample Observations	Timepoints
03-001	1	13 (8/5)	48 (27-67) <sup>a</sup>	88 (65-132)	0.75	Single	hGH, IGF-I, GHBP, IGFBP-2, IGFBP-3	Every 2 hours for 0-48 hours, twice a week for Days 2-27, and Days 41, 55
03-002	1	Naive 9 (7/2) CT 10 (8/2)	9.3 (2.7-13.7) 9.3 (6.1-11.2)	23.2 (11.3-35.3) 29.1 (20.5-46.7)	0.75	Multiple, once every 4 weeks for 6 months	hGH, IGF-I, GHBP, IGFBP-3	Days 1, 7, 14, 21, 28 after each dose
	Subset <sup>b</sup>	13 (10/3) Naive 6 CT 7	9.7 (2.7-13.7)	27.6 (11.3-46.7)	0.75	After first or second dose <sup>c</sup>	hGH, IGF-I	Every 6 hours for 0-48 hours, twice a week for Days 2-28
	2	Naive 8 (5/3) CT 17 (11/6)	6.3 (3.6-11.4) 9.9 (7.3-14.1)	15.6 (11.7-23) 28.2 (17.4-43.6)	1.5	Multiple, once every 4 weeks for 6 months	hGH, IGF-I, GHBP, IGFBP-3	Days 1, 7, 14, 21, 28 after each dose
	Subset <sup>b</sup>	9 (3/6) Naive 6 CT 3	7.5 (3.6-14.1)	20.0 (11.7-36.4)	1.5	After first dose	hGH, IGF-I	Every 6 hours for 0-48 hours, twice a week for Days 2-28
	3	Naive 9 (7/2) CT 11 (6/5)	7.4 (5.5-11.1) 9.4 (4.3-13)	17.6 (14-26) 30.3 (14-69.2)	0.75	Multiple, once every 2 weeks for 6 months	hGH, IGF-I, GHBP, IGFBP-3	Days 1, 7, 14 after each dose

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Summary Study Design for Nutropin Depot [redacted] rhGH) Clinical Pharmacokinetic Studies (cont'd)

Study	Group	N (m/f)	Age (yrs)	BW (kg)	Dose (mg/kg)	Schedule	Sample Observation	Timepoints
03-004	1	Naive 36 (21/15)	7.3 (1.6-12.2) <sup>a</sup>	18.3 (5.9-34.2)	1.5	Multiple, once every month for 6 months	hGH, IGF-I, GHBP, IGFBP-3	Baseline, trough levels at Month 3 and Month 6
	2	Naive 38 (21/15)	7.6 (3.2-11.9)	20.1 (8.8-43)	0.75	Multiple, twice every month for 6 months	hGH, IGF-I, GHBP, IGFBP-3	Baseline, trough levels at Month 3 and Month 6
03-003	1	Naive & CT 10 (9/1)	9.3 (2.7-13.7)	24.9 (11.3-35.3)	0.75	Multiple, once every month for 6 months	hGH, IGF-I, GHBP, IGFBP-3	Baseline, trough levels every 3 months
	2	Naive 12 (7/5)	7.8 (3.6-11.4)	20.1 (11.7-32)	1.5	Multiple, once every month for 6 months	hGH, IGF-I, GHBP, IGFBP-3	Baseline, trough levels every 3 months
	3	Naive 12 (9/3)	7.4 (4.5-11.1)	17.8 (14-26.5)	0.75	Multiple, twice every month for 6 months	hGH, IGF-I, GHBP, IGFBP-3	Baseline, trough levels every 3 months

m/f = male/female.

Naive = Subjects not previously treated with hGH.

CT = Subjects previously treated with daily hGH administration before enrollment for this study.

<sup>a</sup> Minimum-maximum values.

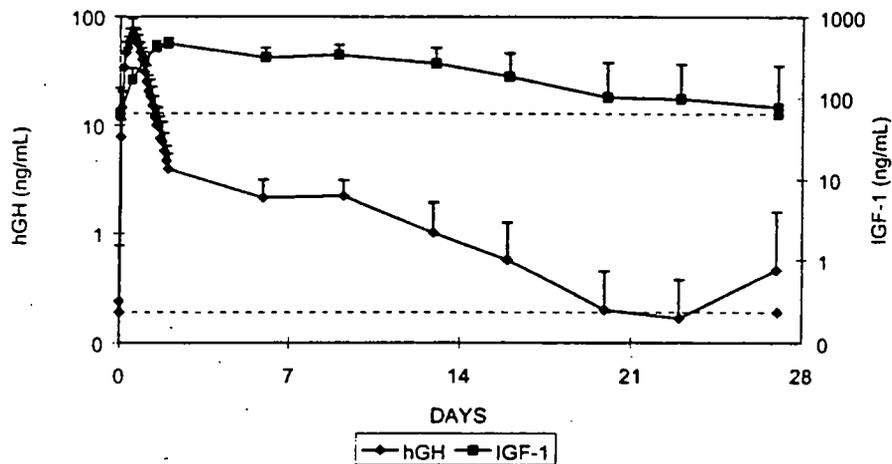
<sup>b</sup> Subjects assigned to take samples more frequently after a first or second dose in multiple-dose regimens.

<sup>c</sup> The second dose data were used in the analyses for subjects that received their first dose of Nutropin Depot using [redacted] diluent because of incomplete dose administration with this diluent.

The first dose of Nutropin Depot tested in humans was 0.75 mg/kg GH administered as a single SC injection to GHD adults (Study 03-001). This dose was approximately equivalent to the total maximum monthly dose in use for adult GHD patients at the time of the study (25 mg/kg/day x 30 days) and represents approximately 60% of the total monthly dose currently recommended for GHD children (43 mg/kg/day x 30 days). Serum GH and the GH-related biologic response markers (IGF-I, IGFBP-3, and GHBP) were measured. Based on the GH serum profile, IGF-I response, and tolerability data from Study 03-001, 0.75 mg/kg every 4 weeks (0.75Q4) was chosen as the initial dose for the Phase 1/2 study in pediatric GHD patients (Study 03-002). The problem with this is the assumption that 100% of the GH in the depot will be fully systemically available – it seems this is not the case (as noted in the bioavailability section).

The pharmacokinetic portion of the adult study characterized somatotropin release from the Depot product from the time of SC injection out to 56 days from administration. According to the sponsor, this Phase 1 study in GHD adults showed that a single dose of Nutropin Depot elicited initial high somatotropin concentrations within 2 days of administration followed by sustained levels of both somatotropin and IGF-I for approximately 3 to 4 weeks postdose.

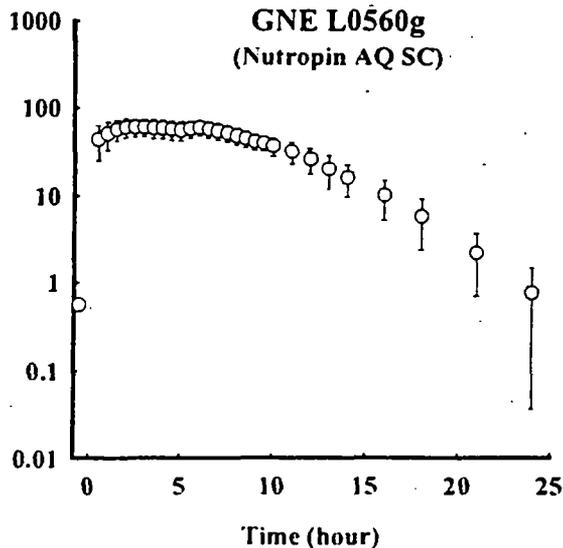
Mean (N=13) ± SD Serum Profiles of hGH and IGF-I following Single-Dose (0.75 mg/kg) Administration of Nutropin Depot in GHD Adults: Study 03-001



Dotted lines represent baseline values for each curve.

From an old study, the plot below represents the mean ±SD GH plasma concentration-time curve for SC Nutropin AQ (i.e., the formulation used for daily injection) in healthy adults (These data were used in the relative bioavailability calculation).

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Following the 3-month data evaluation in [redacted] 03-002, 2 dose groups were added: 1.5 mg/kg every 4 weeks (1.5Q4) and 0.75 mg/kg every 2 weeks (0.75Q2). The objective of this Phase 1/2 study was to evaluate the safety and efficacy of Nutropin Depot in children with repeated dosing up to 24 weeks. The study investigated previously-treated subjects and naive subjects. A small subset of subjects was intensively sampled after the first or second dose of Nutropin Depot to characterize pharmacokinetics and pharmacodynamics (Note: second dose data were used in the analysis for subjects that received Nutropin Depot as a first dose using a dextran diluent because of incomplete dose administration with this diluent). According to the sponsor, a single dose of Nutropin Depot produced initially high somatotropin concentrations followed by a sustained elevation of both somatotropin and IGF-I levels which lasted between 2 and 3 weeks in GHD children. Overall, somatotropin, IGF-I, GHBP, and IGFBP-3 levels following Nutropin Depot SC administration in GHD children were reproducible at each cycle, and there was no evidence of progressive accumulation during the course of the study period. The somatotropin was released from Nutropin Depot in a generally dose-proportional manner based on C<sub>max</sub> and AUC<sub>0-28days</sub>. Previous somatotropin history (previously treated vs. naive) had little effect on the somatotropin pharmacokinetic profile after Nutropin Depot administration.

The tables below summarize the mean±SD data from [redacted] 03-002, the pediatric study.

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Pharmacokinetic and Pharmacodynamic Summary for  
Intensively Sampled Subjects in Study 03-002

Parameters	0.75q4		1.5q4	
	CT (n=7)	Naive (n=5 <sup>a</sup> )	CT (n=2 <sup>a</sup> )	Naive (n=6)
<b>hGH</b>				
Baseline, ng/mL	1.5±2.1	2.1±3.7	0.21±0.23	1.6±1.0
C <sub>max</sub> , ng/mL	43±32	54±13	122±9	80±15
T <sub>max</sub> , days	0.57±0.19	0.45±0.11	0.50±0.00	0.58±0.20
AUC <sub>0-28</sub> , ng·d/mL	83±65	83±6.5	144±7.6	139±41
Days above 1 ng/mL	10±2	13±9	11±2	15±4
<b>IGF-I</b>				
Baseline, ng/mL	170±107	92±76	52±2.1	55±43
C <sub>max/corr</sub> , ng/mL	301±124	228±200	435±90	124±60
T <sub>max</sub> , days	1.6±0.45	1.9±0.22	2.0±0	3.4±2.4
AUC <sub>0-28/corr</sub> , ng·d/mL	1851±2068	1262±1133	2322±778	760±582
Days above baseline	17±8	18±9	16±1	20±9

C<sub>max</sub> and T<sub>max</sub> values are observed values based on 0, 0.25, 0.5, 1, 1.5, 2, 7, 10, 14, 17, 21, and 24 days of timepoints.

<sup>a</sup> After excluding outliers (Subjects 06-002 and 11-003); these 2 subjects had hGH concentrations with several values that appeared markedly inconsistent with the rest of data.

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Mean ± SD Baseline and 24-Hour  
hGH, IGF-I, GHBP, and IGFBP-3 Concentrations following  
Multiple-Dose Administration of Nutropin Depot in Study [ ] 03-002

Dose Group	0.75q4		1.5q4		0.75q2	
	CT (n=6)	Naive (n=7)	CT (n=12)	Naive (n=7)	CT (n=11)	Naive (n=9)
<u>hGH (ng/mL)</u>						
Baseline	1.7±2.2	0.90±0.90	1.2±2.8	1.4±1.0	0.27±0.34	0.48±0.40
Cycle 1	14±7	33±24	44±27	42±17	17±11	39±41
Cycle 6	15±11	43 <sup>a</sup> ±22	51±32	39±19	27±22	28±20
<u>IGF-I (ng/mL)</u>						
Baseline	203±93	102 <sup>a</sup> ±67	101±70	54±40	191±107	70 <sup>a</sup> ±55
Cycle 1	472±21 <sup>b</sup>	255±197	257±98	131 <sup>a</sup> ±92	453±255	160 <sup>a</sup> ±121
Cycle 6	469±142	244 <sup>a</sup> ±189	271±97	129 <sup>a</sup> ±95	382±277	181 <sup>a</sup> ±118
<u>GHBP (pmol/L)</u>						
Baseline	1002±386	946±300	847±313	642±87	981±389	842±404
Cycle 1	1287±366 <sup>b</sup>	663 <sup>a</sup> ±162	865±215	532 <sup>a</sup> ±277	861±103	794±293
Cycle 6	1015±483	665±238	662±327	499±175	758±467	573±328
<u>IGFBP-3 (µg/mL)</u>						
Baseline	3.2±0.75	2.3±0.85	1.8±0.83	1.4±0.27	2.9±1.3	1.7 <sup>a</sup> ±1.1
Cycle 1	3.4±0.6 <sup>b</sup>	2.8±0.8	2.4±0.8	1.8±0.5	3.1±1.0	2.0 <sup>a</sup> ±1.0
Cycle 6	3.9±1.0	2.6 <sup>a</sup> ±0.8	2.5±0.8	1.8±0.5	3.2±1.2	2.4±1.2

Concentrations were not corrected for the baseline values.

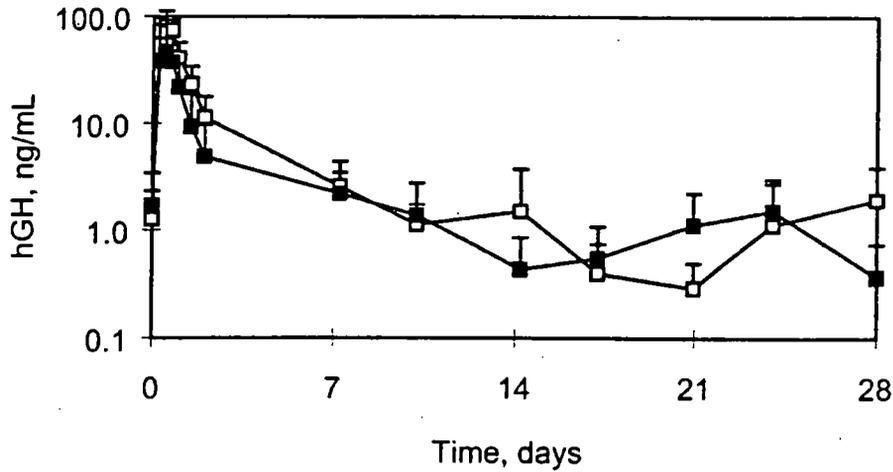
<sup>a</sup> Statistically significant difference when compared to the CT group within the same dose group.

<sup>b</sup> N=2 due to exclusion of subjects who received [ ] diluent in Cycle 1.

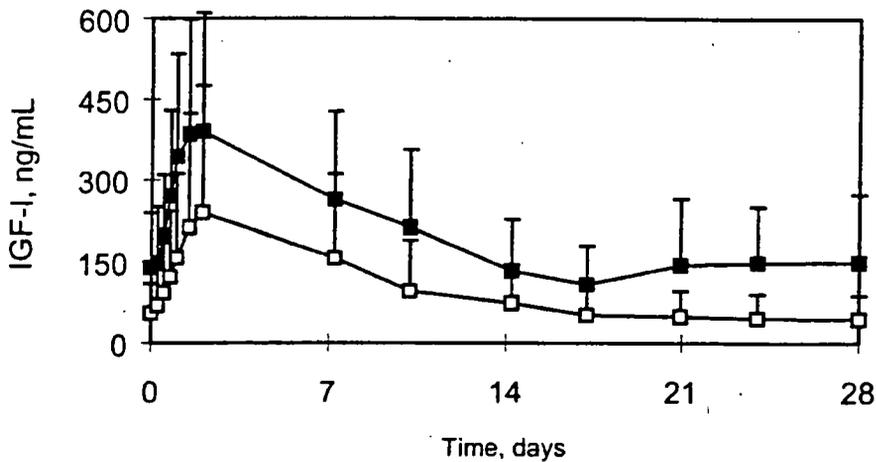
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Mean hGH (a) and IGF-I (b) Serum Profiles  
of 0.75 mg/kg (N=12) and 1.5 mg/kg (N=8) Dose Groups following  
First or Second Dose Administration of Nutropin Depot in Naive and CT GHD Children

(a)



(b)

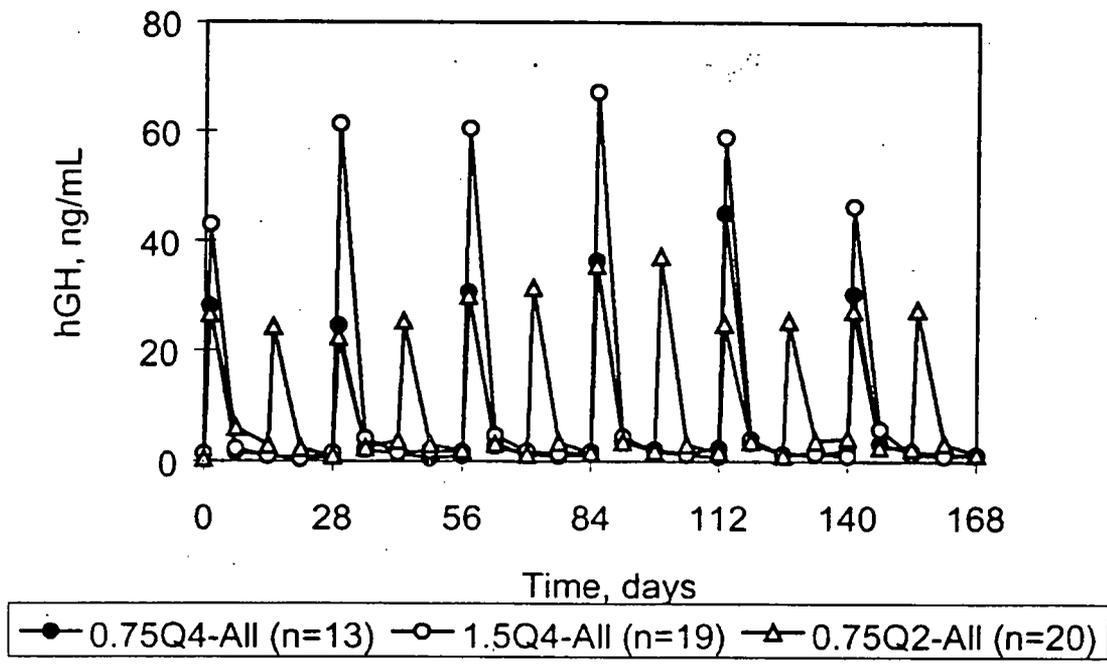


■=0.75Q4, □=1.5Q4.

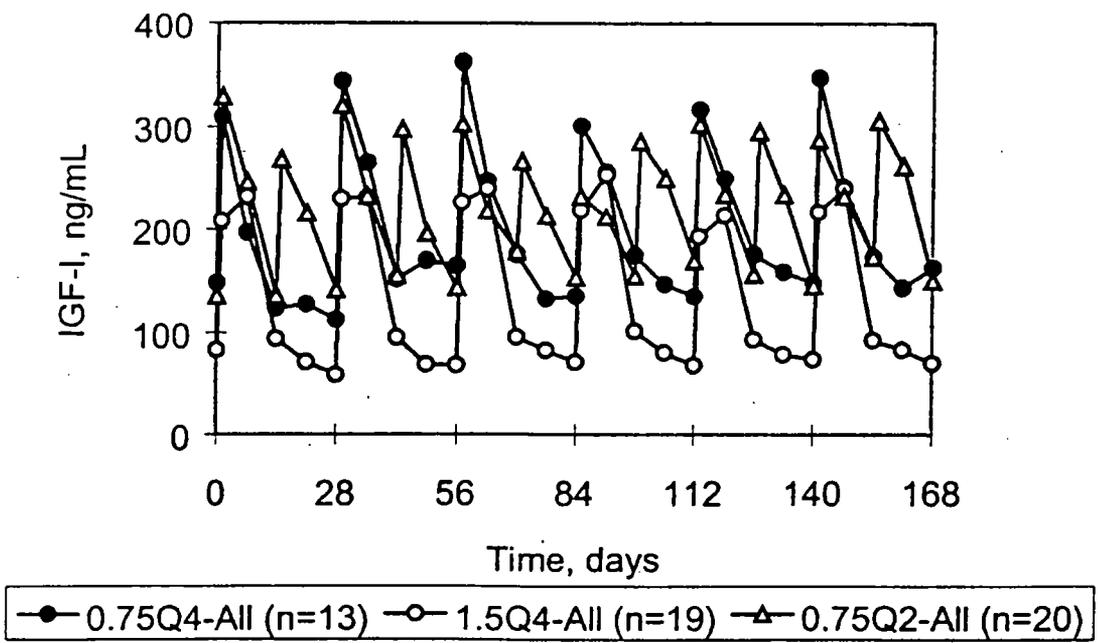
Note in the plot above that the lower dose (0.75Q4) appears to cause a greater IGF-1 response; the reason is unknown.

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Mean hGH Serum Profiles following Multiple Doses of Nutropin Depot at Various Doses in Naive and CT GHD Children (03-002)



Mean IGF-I Serum Profiles following Multiple Doses of Nutropin Depot at Various Doses in Naive and CT GHD Children (03-002)



Note, again, that the 1.5Q4 dose appears to elicit a lower peak and lower trough for IGF-1 as compared to the 0.75Q4 or 0.75Q2.

03-004 was a Phase 3, multicenter, open-label, 6-month study designed to demonstrate the safety and efficacy of two doses of Nutropin Depot in the treatment of children with growth failure due to GHD. Seventy-four prepubertal subjects with GHD who had not been previously treated with GH (naive) were enrolled and treated at 27 medical centers. Subjects were randomized centrally to one of the following two treatment groups: 1.5 mg/kg Nutropin Depot administered once a month or 0.75 mg/kg Nutropin Depot administered twice a month. According to the sponsor, there was no significant increase in trough hGH and IGF-I, IGFBP-3 levels for the 1.5q4 group. For the 0.75q2 group, the trough level of hGH at Month 3 was increased from the baseline value but the level did not change significantly from Month 3 to Month 6, indicating no progressive drug accumulation. With the exception of the IGF-I level in the 0.75q2 group at Month 3, IGF-I and IGFBP-3 levels at Months 3 and 6 for all 3 dose groups were not apparently different from those at baseline supporting no accumulation in pharmacodynamic marker levels.

Mean  $\pm$  SD Trough Serum hGH, IGF-I, and IGFBP-3 Concentrations in Study 03-004

	Baseline	Month 3	Month 6
<u>0.75 mg/kg 2x/mo</u>			
hGH (ng/mL)	1.7 $\pm$ 2.0	3.1 $\pm$ 2.2 <sup>a</sup>	3.1 $\pm$ 2.7 <sup>a</sup>
(n)	(33)	(33)	(33)
IGF-I (ng/mL)	104 $\pm$ 73	127 $\pm$ 70 <sup>a</sup>	125 $\pm$ 64 <sup>a</sup>
(n)	(34)	(34)	(34)
IGFBP-3 ( $\mu$ g/mL)	2.2 $\pm$ 0.9	2.4 $\pm$ 0.9	2.3 $\pm$ 1.0
(n)	(34)	(34)	(34)
<u>1.5 mg/kg 1x/mo</u>			
hGH (ng/mL)	2.2 $\pm$ 3.7	3.1 $\pm$ 4.0	2.2 $\pm$ 1.9
(n)	(33)	(33)	(33)
IGF-I (ng/mL)	120 $\pm$ 78	111 $\pm$ 77	129 $\pm$ 73 <sup>b</sup>
(n)	(33)	(33)	(33)
IGFBP-3 ( $\mu$ g/mL)	2.1 $\pm$ 0.9	2.2 $\pm$ 1.0	2.3 $\pm$ 0.9
(n)	(33)	(33)	(33)

<sup>a</sup> p < 0.05 vs. baseline.

<sup>b</sup> p < 0.05 Month 3 vs. Month 6.

III. Special Populations

Not performed.

IV. Retrospective Analysis

A retrospective analysis of the data obtained from the phase 1/2 GHD pediatric study 03-002 was conducted. The following manufacturing and drug delivery variables were analyzed for their effect on the relevant pharmacokinetic and pharmacodynamic parameters (day 1, 7, and 14 GH or IGF-1

concentrations) include: manufacturing scale; dose level; dose frequency; dose cycle; site of injection; and injection concentration. The effect of patient demographic variables such as race and gender were also evaluated. Analysis was also done to describe the change in serum marker concentration with repeat administration and the presence or extent of accumulation with repeat dose cycles. Finally, estimates of intra- and inter-subject variability were obtained using analysis of variance for subject and cycle (replicate dosing). It should be noted that study 03-002 was not designed with this retrospective analysis in mind and the data included in this analysis are too small to draw any firm conclusions.

The analysis failed to show a significant difference between scales of manufacture (clinical, small or intermediate scale) for hGH levels (days 1, 7 & 14), although the small scale day 1 concentrations were larger than intermediate scale (to-be-marketed scale) values. Day 7 and 14 GH values were comparable between the scales as were all mean IGF-I and IGFBP-3 levels.

From the limited data available from 5 subjects who were administered a 16 mg/mL dosing suspension on their first dose and 22 mg/mL dosing suspensions on all other doses, there was no apparent difference in GH or IGF-I levels resulting from the two different dosing solution concentrations.

For the six paired sets of data for abdomen and thigh and 20 paired data sets for arm and thigh, analysis of the results failed to show a statistically significant difference at any day for any of the sites of injection compared.

Analysis of variance was used to estimate within and between subject variation (coefficient of variation) for hGH levels at day 1, 7 and 14 for all subjects and all doses. Both the within and between subject variabilities are summarized in the following table.

Dose	Source of variation	CV for baseline levels	CV for day 1 levels	CV for day 7 levels	CV for day 14 levels
0.75 mg/kg q4	Between subject	151%	55%	52%	57%
	Within subject	-	57%	52%	97%
0.75 mg/kg q2	Between subject	103%	52%	39%	66%
	Within subject	-	67%	151%	281%
1.5 mg/kg q4	Between subject	171%	71%	86%	114%
	Within subject	-	36%	52%	127%

Mean values for day 1, 7 and 14 GH, IGF-I and IGFBP-3 were determined for each subject. The only finding was higher day 1 GH levels for females as compared to males. The female hGH levels were approximately 50% higher at day 1 for both doses and were statistically significant. However, analysis of IGF-I and IGFBP-3 data show no consistent relationship between gender and pharmacodynamic marker levels.

Due to the limited number of non-caucasian subjects (90% white), no definitive conclusions could be drawn from this analysis.

GH trough levels at Month 3 and 6 were not markedly changed as compared to those at baseline except for those in the 0.75 mg/kg q2 dose group. In 0.75 mg/kg q2 group, the trough level of hGH at Month 3 was increased from the baseline value but the level remained almost unchanged at Month 6, indicating no progressive drug accumulation. IGF-I and IGFBP-3 levels at Months 3 and 6 for all three dose groups were not apparently different from those at baseline.

**COMMENTS FROM THE MEDICAL OFFICER:**

- 1) Compared with historic data, it seems the Nutropin Depot product does not promote growth to the same extent as daily SC somatropin.

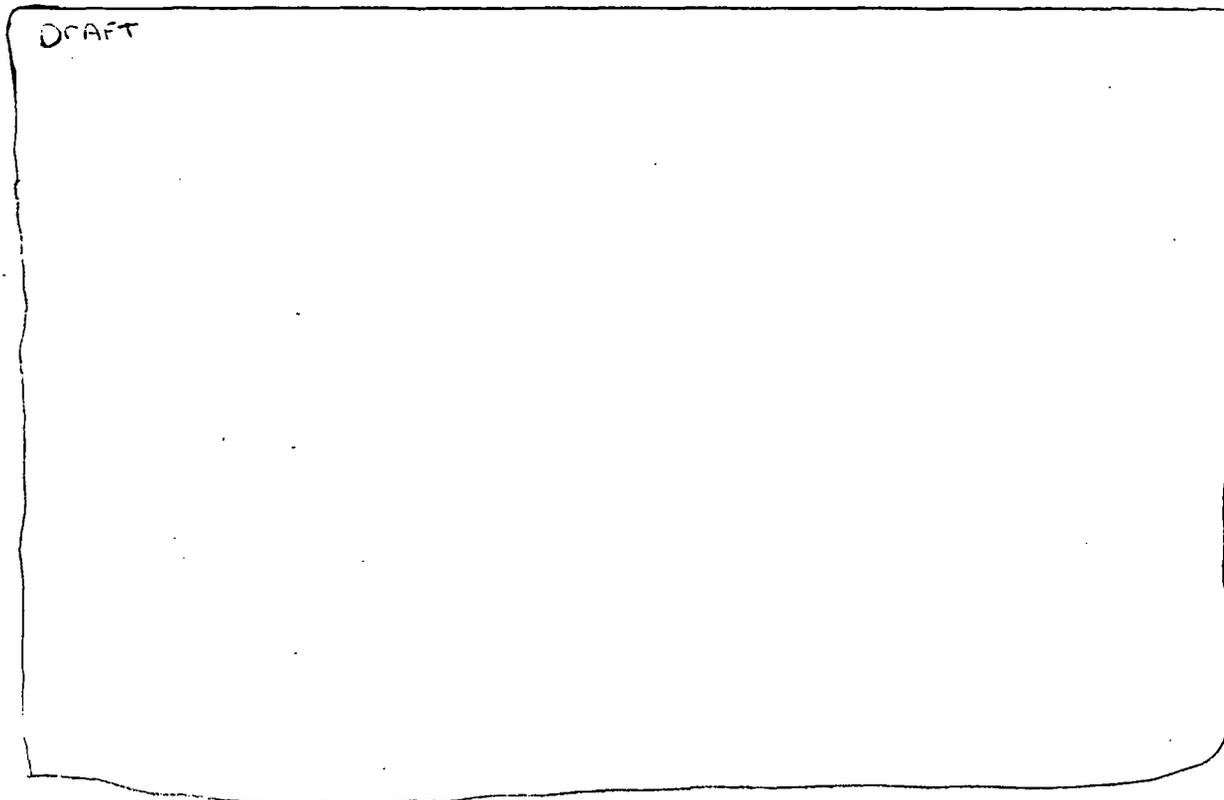
**COMMENTS TO BE SENT TO MEDICAL OFFICER:**

- 1) The systemic bioavailability of the Nutropin Depot seems to be only about 35% of daily SC somatropin, with a large portion (50-60%) of the exposure occurring in the first 2 days after injection of the Depot.

**LABELING COMMENTS:**

(Where applicable, ~~strikeout text~~ should be removed from labeling; Double underlined text should be added to labeling; ☞ indicates an explanation only and is not intended to be included in the labeling)

- 1) The following plot should be added to the labeling in a section titled pharmacodynamics following the pharmacokinetics section. The format should be the same as the GH plot (i.e., include N after symbol designation, and include 'Mean  $\pm$ SD' on plot). Also, include in this section any references to IGF-1 and/or IGFBP-3 rather than including these parameters in the pharmacokinetics section.



- 2) In the proposed 'Absorption' section the sponsor wishes to exclude the  $AUC_{0-2days}$  data. Two other labels from similar products (Lupron Depot and Sandostatin LAR) have no such 'initial' AUC

estimate yet both have an initial burst. However, those products are not GH and the inclusion of the burst AUC in the Nutropin Depot labeling may be relevant to the clinical effects seen. Thus, this AUC<sub>0-28days</sub> should remain in the labeling.

3) The sponsor wishes to include a wider range of relative bioavailability ( $F_{rel}$ ) estimates (Depot vs daily SC). According to a publication (Kearns et al., J Clin. Endocrinol & Met., 72:1148-56, 1991), the sponsor claims "chronic treatment with daily or TIW rhGH may result in an apparent reduction in total AUC. Kearns et al. reported an apparent reduction in GH AUC of 31% after 4-6 weeks of dosing with daily or TIW rhGH. This chronic treatment AUC may be a more representative reference AUC than an acute single dose AUC."

How does this effect the relative bioavailability estimate? Well, simplified, the estimate is the dose-normalized AUC<sub>total</sub> after a single Depot injection compared to the dose-normalized AUC<sub>total</sub> after a single daily injection (See equation below). This estimate, without any correction for 'chronic treatment' as per Kearns, is  $0.38 \pm 0.23$  for the 0.75mg/kg dose and  $0.33 \pm 0.08$  for the 1.5mg/kg dose (Note: this is a comparison of a single dose of Depot in GHD children and a single dose of SC Nutropin AQ in healthy adults). However, the sponsor has applied the 'chronic treatment' correction to **only** the daily injection AUC estimate and, thus, this daily AUC estimate is reduced. So, according to the equation below, the denominator decreases but the numerator remains the same and thus the  $F_{rel}$  increases to  $0.55 \pm 0.33$  for the 0.75mg/kg dose and  $0.48 \pm 0.12$  for the 1.5mg/kg dose.

However, it is this reviewer's opinion that this 'chronic treatment' correction cannot be **only** applied to the daily injection AUC estimate - this is biased. Why would GH exposure from daily injections but not from a Depot injection lead to a decrease in GH AUC? If the GH AUC changes, perhaps because of some physiological changes to the body, wouldn't those changes be expected to occur from **both** daily as well as Depot GH? If this is true, then the changes would 'cancel' each other out and the estimates of  $F_{rel}$  would go back to 0.38 and 0.33.

$$F_{rel} = \frac{\frac{AUC_{0-28}}{Dose_{0.75 \text{ or } 1.50}}}{\frac{AUC_{0-\infty, SC}}{Dose_{SC}}}$$

In conclusion, the labeling should exclude potentially biased estimates of GH AUC after chronic treatment when estimating  $F_{rel}$ . The section should read as follows:

Absorption-In a study of Nutropin Depot in pediatric patients with GHD, an SC dose of 0.75 mg/kg (n=12) or 1.5 mg/kg (n=8) was administered. The mean±SD hGH C<sub>max</sub> values were 48±26 and 90±23 µg/L, respectively, at 12-13 hours postdose. The corresponding AUC<sub>0-28 days</sub> values were 83±49 and 140±34 µg·day/L, respectively, for the two doses. For the 0.75mg/kg and 1.5mg/kg doses, the AUC<sub>0-28days</sub> accounted for 52±16 and 61±10 percent of the total AUC<sub>0-28days</sub>, respectively.

Draft

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Robert M. Shore, Pharm.D.  
Division of Pharmaceutical Evaluation II  
Office of Clinical Pharmacology and Biopharmaceutics

/S/

02-DEC-99

RD initialed by Hae-Young Ahn, Ph.D., Team Leader 01-DEC-99

CPB Briefing 02-DEC-99

Attendees: Rob Perlstein, Mike Fossler, Hung Truong, Steve Johnson, John Hunt, Mei-Ling Chen, Ajaz Hussain, Saul Malozowski, Shiew-Mei Huang, John Lazor, Hae-Young Ahn, Peter Lee.

FT initialed by Hae-Young Ahn, Ph.D., Team Leader

/S/

12/2/99

CC: NDA 21-075/N-000 (orig., 1 copy), HFD-510(KIRG, Perlstein, Malozowski, MooreS), HFD-340 (Viswanathan), HFD-870(Ahn, ChenME), HFD-850(Lesko, Huang) CDR (Barbara Murphy).

Code: AE

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**Appendix 1. Draft labeling with comments**

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Labeling

**Appendix 2. Study summaries**

## 0.0 EXECUTIVE SUMMARY

This Phase I study using a single dose of [ ] hGH [0.75 mg/kg somatropin (5 mg/kg [ ] hGH)] administered subcutaneously (SC) was conducted in growth hormone deficient adults. A total of 13 growth hormone deficient adults from two centers were dosed and completed the study. Safety was assessed by clinical laboratory measurements, patient signs and symptoms, and adverse events. There were two primary pharmacokinetic endpoints: 1) characterization of the initial release of hGH during the first 48 hours after administration, with intensive sampling for hGH and IGF-I levels, and 2) the sustained release of hGH and subsequent pharmacodynamic effect was evaluated by biweekly determination of hGH and IGF-I levels until Day 28. Weekly determinations continued until Day 56.

There were 8 males and 5 females with a mean age of 47.5 years (range 27 - 67) and a mean weight of 87.4 kg (range 64.8 - 132.3). The pre-dose hGH mean level was 0.2 ng/mL (s.d. 0.5); predose IGF-I mean level was 64.4 ng/mL (s.d. 65.9).

After the administration of [ ] hGH, hGH levels increased and reached a peak mean of 70 ng/mL (s.d. 26 ng/mL) at 12 hours post dose. The median time for growth hormone to return to the baseline level was 23 days (95% CI 19.9 - 54.9).

IGF-I levels rose to a mean peak of 463 ng/mL at 48 hours post dose. The median time to return to baseline was 54.9 days (95% CI 26.9 - 54.9).

The maximum concentration of IGFBP-3 was  $3.8 \pm 1.2$  mg/L. The median time for IGFBP-3 levels to return to the baseline value was 26.9 days (95% CI 19.9 to > 41).

Mean GHBP levels remained relatively constant throughout the study. Changes in mean IGFBP-3 levels essentially paralleled changes noted in IGF-I levels throughout the study. IGFBP-2 mean levels remained relatively constant during the study period.

Overall, laboratory studies did not reveal any untoward abnormal trends. No subjects formed detectable antibodies to growth hormone during the study. The most frequent adverse events reported by patients consisted of injection site reactions (site erythema, itchiness, warmth, swelling and pain), peripheral edema, arthralgias and headache. Two patients experienced serious adverse events (prolonged hospitalization) consisting of nausea and vomiting, which were considered to be related by the investigator to the study drug. One patient with nausea and vomiting also experienced abdominal pain, which was considered to be probably related to study drug.

A single dose of [ ] hGH (0.75 mg/kg hGH, 5 mg/kg [ ] hGH) in growth hormone deficient adults elicited elevated levels of growth hormone and IGF-I levels

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which were sustained. [redacted] hGH was well tolerated with no detectable immunogenicity.

These results demonstrate that [redacted] is a potentially useful method of growth hormone delivery in adults, and other patient populations, including children.

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## SYNOPSIS

**TITLE:** A PHASE I/II, MULTICENTER, OPEN-LABEL STUDY OF THE SAFETY AND EFFICACY OF [REDACTED] rhGH ADMINISTERED MONTHLY IN CHILDREN WITH GROWTH FAILURE DUE TO GROWTH HORMONE DEFICIENCY

**REPORT NUMBER:** [REDACTED] 03-002

**PHASE:** I/II

**INDICATION:** Growth hormone deficiency

**SPONSORS:**

[REDACTED]

Genentech, Inc.  
1 DNA Way  
South San Francisco, CA 94080-4990 U.S.A.

**REPORT DATE:** 2 March 1999

**PERIOD OF STUDY:** Initiation: 11 November 1996  
Completion: 7 April 1998

**PUBLICATIONS:** None

### INVESTIGATORS

The list of investigators is in Appendix A (Module I).

### OBJECTIVES

The objective of this study was to demonstrate the safety and efficacy of a new sustained-release formulation of recombinant human growth hormone (rhGH) in the treatment of growth failure in children with growth hormone deficiency (GHD).

### STUDY DESIGN

This was a Phase I/II, multicenter, open-label, 6-month study of a new formulation of rhGH, [REDACTED] rhGH, in prepubertal subjects with GHD. Thirty-eight subjects with GHD and currently treated (CT) with daily rhGH and 26 subjects with GHD and naive to rhGH treatment were enrolled at 12 medical centers in the United States. The first 6 subjects enrolled were currently treated with daily rhGH and were assigned to receive 0.75 mg/kg rhGH every 4 weeks as a subcutaneous (SC) injection. This dose represents ~60% of the total conventional daily rhGH dose (0.043 mg/kg/day) given over 30 days.

After two treatments with [redacted] rhGH, the insulin-like growth factor I (IGF-I) levels and adverse experience profiles of the 6 CT subjects were assessed prior to dosing the naive subjects. Six naive subjects were subsequently given the same dose. Based on the assessment of IGF-I levels and the adverse event profiles of these subjects, two higher doses were added and additional subjects were recruited. The dose of [redacted] rhGH was assigned as follows: 4 CT and 3 naive subjects received 0.75 mg/kg every 4 weeks (0.75q4), and 17 CT and 8 naive subjects received 1.5 mg/kg rhGH every 4 weeks (1.5q4). The third dose group, consisting of 11 CT and 9 naive subjects, received 0.75 mg/kg rhGH every 2 weeks (0.75q2).

The pharmacokinetic profiles of GH released from [redacted] rhGH and IGF-I levels were investigated in all subjects. In addition, a subset of subjects at each dose (0.75 mg/kg and 1.5 mg/kg) underwent intensive pharmacokinetic sampling for GH and IGF-I levels.

### PROTOCOL AMENDMENTS

The protocol was amended six times. The first amendment, dated 20 November 1996, specified a time window for laboratory assessments to occur between baseline and the first day of dosing, revised the procedure for study drug preparation, and added administrative changes to improve the clarity of the protocol. The second amendment, dated 4 December 1996, changed the [redacted] diluent from a solution of [redacted] to one of carboxymethylcellulose, increased the diluent volume from [redacted] mL to 1.5 mL, and revised the study drug preparation and administration procedures. The third amendment, dated 6 February 1997, increased the number of subjects to be enrolled. The fourth amendment, dated 4 March 1997, added a third dose group of 12 CT and 8 naive subjects who received 0.75q2. The fifth amendment, dated 8 April 1997, removed the requirement for the review of data in the subset of subjects undergoing intensive pharmacokinetic sampling prior to dosing the entire group. The sixth amendment, dated 13 August 1997, reduced the number of CT subjects from 6 to 3 who were to undergo intensive pharmacokinetic sampling in the 1.5q4 dose group.

### SUBJECT SELECTION CRITERIA

CT and naive subjects had to have documented GHD by a maximum GH response of  $<10 \mu\text{g/L}$  on at least two prior standard pharmacologic tests of GH secretory capacity, a bone age of  $\leq 9$  years for girls or  $\leq 10$  years for boys, and prepubertal Tanner Stage 1 for breasts (girls) or genitalia (boys). Subjects with multiple hormone deficiencies had to have been stabilized on L-thyroxine or hydrocortisone for at least 6 months prior to enrollment. The height of naive subjects had to have been  $\leq 2$  standard deviations (SD) below the normal mean for their age and sex. CT subjects had to have been on continuous rhGH therapy for at least 1 year prior to study entry at an average dose of 0.25–0.35 mg/kg/week administered 6 or 7 times/week and have height data available for at least 6 months prior to the study.

Subjects were excluded from participation in the study if they had diabetes mellitus or growth failure due to reasons other than GHD. Treatment with anabolic agents or current treatment with methylphenidate or cyproheptadine were exclusions. Hypothalamic-pituitary tumors diagnosed or treated within the past year, known bleeding disorders, or known allergy or sensitivity to any components of the [redacted] rhGH formulation were also exclusions.

### STUDY DRUG AND FORMULATION

[redacted] is a depot-drug delivery system developed to provide sustained release of macromolecules, including peptides and proteins. The system consists of biocompatible, biodegradable microspheres formulated from poly D/L lactide co-glycolide (PLG) co-polymers. [redacted] rhGH is a sustained-release formulation of Genentech, Inc.'s somatotropin intended for administration every 2 weeks (0.75 mg/kg dose level) or every 4 weeks (0.75 or 1.5 mg/kg dose level).

[redacted] diluent is composed of carboxymethylcellulose sodium salt, polysorbate 20, sodium chloride, and water for injection.

#### **DRUG AND DILUENT LOT NUMBERS**

The drug and diluent lot numbers appear in Appendix B (Module I).

#### **DOSE, ROUTE, AND REGIMEN**

The dose for each subject was calculated according to the individual's weight at each visit and was administered as an SC injection. Subjects received 0.75 mg/kg somatropin or 1.5 mg/kg somatropin.

Administration of all doses of [redacted] rhGH in this study was done by a trained health care professional. Injections were performed taking care to ensure that the dose was delivered in a single, smooth motion.

If the total volume for any dose exceeded 1 mL, the dose was divided into two or more injections of equal volume.

#### **DURATION OF THERAPY**

[redacted] rhGH was administered as an SC injection every 2 weeks (0.75 mg/kg dose level) or every 4 weeks (0.75 or 1.5 mg/kg dose level) for 6 months.

#### **CONCOMITANT THERAPY**

Subjects with adrenocorticotrophic hormone deficiency could have received hydrocortisone at a dose that did not interfere with growth (physiologic replacement dose). Dosage must have been stable for 6 months prior to the study.

Subjects with hypothyroidism could have received L-thyroxine. Dosage must have been stable for 6 months prior to the study. One dose adjustment during the study was allowed as determined by the investigator.

Other medications that were considered necessary for the subject's welfare and for which there was no evidence of interference with the study medication or effect on growth were given at the discretion of the investigator.

#### **PRIMARY EFFICACY OUTCOME MEASURES**

The primary efficacy outcome measures were the annualized growth rates at 3 and 6 months. Efficacy was supported by data for change in standardized height, height age, and bone age.

#### **SAFETY OUTCOME MEASURES**

The safety and tolerability of [redacted] rhGH were assessed by physical examination, including inspection of injection sites, measurement of vital signs, clinical laboratory evaluations, measurement of anti-GH antibodies, and reports of adverse events.

#### **STATISTICAL METHODS**

Demographic and baseline physical examination results, vital signs, and clinical laboratory evaluations were summarized with descriptive statistics and subject listings as appropriate.

##### **Efficacy Analysis**

The planned primary analysis of growth rate was based on performing an analysis of covariance in which the 6-month annualized growth rates of naive subjects among the dose groups would be

compared with those of age-matched controls treated with daily rhGH in Genentech Study L0368g, using age as a covariate. Instead, because of the small sample sizes in each dose group, the 6-month annualized growth rate estimates along with the corresponding confidence intervals (CI) are presented for each dose group.

Summary statistics for height, standardized height, and height age are presented at prestudy and Month 3 for subjects who completed 3 months, and at prestudy and Months 3 and 6 for subjects who completed the study. These were done by dose group and subject group. Summary statistics for bone age (Fels Institute method) are presented at prestudy and Month 6 for subjects who completed the study. In addition, the change in bone age minus the change in height age at Month 6 is presented. Although the results were positive, the usefulness of these parameters over a 6-month period are limited and thus are not discussed in this report.

Standardized height (SD score) was computed as follows:

$$\frac{\text{Actual height} - \text{mean height of normal subjects of same age and sex}}{\text{Height SD of normal subjects of same age and sex}}$$

The prestudy growth rate was determined based on the subject's height measured closest to 1 year prior to study start. For CT subjects, several height measurements at least 6 months prior to the start of the study were prospectively collected. The height used for the prestudy growth rate had to be at least 6 months prior to study start and no more than 425 days (i.e., ~1 year and 2 months prior to study start). For naive subjects, several height measurements at least 6 months prior to the start of the study were retrospectively collected. The height used for the prestudy growth rate was that obtained at least 153 days prior to study start and no more than 425 days (i.e., ~1 year and 2 months) prior to study start. Any prestudy growth rates based on heights outside of these boundaries were considered unreliable estimates of prestudy growth rate and were not used.

#### Pharmacokinetic Analysis

The pharmacokinetics of rhGH as well as the changes in concentrations of the related biological markers of GH activity (IGF-I, GH binding protein [GHBP], and IGFBP-3) were investigated in 52 subjects at regular intervals throughout the study. In addition, a subset of subjects who received doses of 0.75q4 (n=13; 7 CT and 6 naive) and 1.5q4 (n=9; 3 CT and 6 naive) underwent intensive blood sampling for GH and IGF-I levels following the first dose and for some subjects following the second dose as well. Serum samples were analyzed for GH, IGF-I, GHBP, and IGFBP-3 concentrations by  procedures.

For subjects who underwent intensive blood sampling, pharmacokinetic parameters of the maximum observed concentration ( $C_{max}$ ), the time of  $C_{max}$  ( $T_{max}$ ), area under the curve (AUC) from 0 to 28 days ( $AUC_{0-28d}$ ), the fractional AUC for 0-2 days ( $\%AUC_{0-2d/0-28d}$ ), 2-7 days, 7-14 days, and 14-28 days, and baseline values were estimated for GH. The number of days that GH concentrations were above 1 ng/mL and the number of days that IGF-I levels were above baseline were also estimated. For all subjects, mean concentrations of GH, IGF-I, GHBP, and IGFBP-3 at predose, and at 1, 7, 14 (and 15 for 0.75q2 only), and 21 days of each cycle for each treatment group were determined.

#### Safety Analysis

Tabulations were performed to examine key parameters such as adverse events, change in vital signs, and change in laboratory parameters. Adverse events were tabulated by COSTART preferred term and body system for each dose group for CT, naive, and all subjects. Injection-site adverse events were tabulated separately from non-injection-site events. The number of injection-site events is also presented for each dose group for CT, naive, and all subjects.

Laboratory and other safety values were summarized with simple descriptive statistics, including means and SD at baseline, 24 hours postdose, and at the end of Months 3 and 6 by subject group and by dose group.

The percentage of subjects with positive anti-GH antibody results and the antibody titer levels were summarized at baseline and at Months 3 and 6 for each dose group, CT, naive, and all subjects. All samples with a titer of  $\geq 1.0$  were assayed for binding capacity and the results summarized.

### SUBJECT ELIGIBILITY AND DISPOSITION

Sixty-four prepubertal subjects with GHD were enrolled at 12 medical centers in the United States. Thirty-eight subjects were currently being treated with daily rhGH for an average of 2.9 years (range [redacted] years), and 26 subjects were rhGH naive. Subjects were assigned to receive one of the following regimens of [redacted] rhGH:

- Group 1: 0.75q4 (10 CT and 9 naive subjects)
- Group 2: 1.5q4 (17 CT and 8 naive subjects)
- Group 3: 0.75q2 (11 CT and 9 naive subjects)

	All Subjects	Dose Group		
		0.75q4	1.5q4	0.75q2
Subjects dosed	64	19	25	20
Subjects who completed study (%)	52 (81)	13 (68)	19 (76)	20 (100)
Subjects who discontinued study (%)	12 (19)	6 (32)	6 (24)	0 (0)
Reason for study termination:				
Adverse event (%)	7 (11)	4 (21)	3 (12)	0 (0)
Subject withdrew consent (%)	4 (6)	1 (5)	3 (12)	0 (0)
Other (%)	1 (2)	1 (5)	0 (0)	0 (0)

### DEMOGRAPHIC AND BASELINE CHARACTERISTICS OF STUDY POPULATION

There was a predominance of males in both groups. The etiology of GHD was largely idiopathic, with only 4 CT subjects enrolled with a history of organic GHD. All 38 CT subjects and 18 of 26 naive subjects had prestudy growth rates available that met the criteria described above. Baseline bone age determinations were available for 35 of the 38 CT subjects.

### EFFICACY RESULTS

#### Primary Efficacy Results

##### a. Growth Rate

**CT Subjects:** Mean prestudy growth rates in the CT subjects ranged from 7.4 to 8.6 cm/yr in the three dose groups. In the first 3 months of treatment, the mean growth rates ranged from 6.0 to 7.5 cm/yr and the mean 0- to 6-month growth rates ranged from 5.0 to 5.2 cm/yr.

In CT subjects, the growth response to [redacted] rhGH was less than that achieved with the prior daily rhGH therapy in many of the subjects. Some subjects increased or maintained their previous growth rates, whereas others decreased their growth rates compared with prestudy.

**Naive Subjects:** Among the 16 subjects with prestudy and 6-month data, the mean prestudy growth rates ranged from 5.6 to 6.1 cm/yr. At Month 3, mean growth rates increased and ranged from 9.6 to 10.8 cm/yr; at Month 6, mean growth rates ranged from 8.8 to 9.3 cm/yr. Among the 24 subjects with 6-month data, the mean 6-month growth rate was 7.6, 8.3, and 8.9 cm/yr in the

0.75q4, 1.5q4, and 0.75q2 dose groups, respectively. The mean growth rate on treatment was greater than the mean prestudy growth rates in all three dose groups.

### **Secondary Efficacy Results**

#### **a. Standardized Height**

**CT Subjects:** Mean prestudy height SD scores ranged from  $-1.3$  to  $-1.5$  in the higher dose groups, and was  $-0.3$  in the lower dose group. The mean change in height SD scores from baseline to Month 6 was 0.0 in all groups.

**Naive Subjects:** Mean prestudy height SD scores ranged from  $-2.8$  to  $-3.5$  in the three dose groups. Mean height SD scores increased by 0.1 to 0.2 in all groups by Month 3 and had increased by  $0.2 \pm 0.3$  in the lower dose group (0.75q4), by  $0.3 \pm 0.2$  in the 1.5q4 dose group, and by  $0.4 \pm 0.3$  in the 0.75q2 dose group by Month 6.

#### **b. Bone Age**

**CT Subjects:** Bone age at baseline was moderately delayed by an average of  $\sim 1$  year relative to chronological age. The mean change in bone age after 6 months of treatment was 0.7 years in all dose groups.

**Naive Subjects:** Bone age at baseline was markedly delayed by an average of  $\sim 2.0$  years relative to chronological age. The mean change in bone age after 6 months of treatment was 0.6 years in the 0.75q4 dose group, 0.6 in the 1.5q4 dose group, and 0.5 in the 0.75q2 dose group.

For both CT and naive subjects, the average rate of bone age advancement was appropriate, indicating that the improvements in growth rate were not accompanied without undue skeletal maturation.

### **PHARMACOKINETIC RESULTS**

In the intensively sampled group, Cycle 2 data were used for subjects who received [redacted] rhGH in the [redacted] diluent in Cycle 1 because of incomplete administration of dose with this diluent. Data for 2 subjects were excluded from the mean data analysis for the intensively sampled group. These 2 subjects had GH concentrations with several values that appeared markedly inconsistent with the rest of the data. For data analysis of all subjects, the values from subjects who completed all six cycles, including those of these 2 subjects were used. However, the first cycle of GH values from 2 subjects were excluded from the all subject group analysis.

#### **a. Intensively Sampled Subjects**

In the intensively sampled subjects, the mean GH serum concentration-time profiles were similar for the CT and naive subjects following [redacted] rhGH administration. The GH serum profiles of the 0.75q4 and 1.5q4 dose groups were similar over 10 to 15 days and proportional to dose.

The  $C_{max}$ ,  $T_{max}$ , and area under the curve (AUC) values of GH were similar among the CT and naive subjects at either dose level, except for the  $C_{max}$  in the 1.5q4 group, which was higher in CT subjects, although  $n=2$ . Both the GH  $C_{max}$  and AUC values were approximately proportional to dose. The percent contribution of Day 0 to 2 to total GH AUC ranged from 50% to 70% and was not markedly different by dose or treatment history (CT vs. naive). These data indicate that more than half of the observed serum GH exposure occurred during the initial-release phase of [redacted] rhGH.

Mean maximal total IGF-I levels ( $C_{max}$ ) increased  $\sim 2$ - to 8-fold from baseline values. The increases were variable among individual subjects and not proportional to dose. Increases in total IGF-I were generally larger in the CT than in the naive subjects. The larger IGF-I response could be

due in part to the difference in baseline status among the CT vs. naive subjects and/or an increased capacity for IGF-I response in the CT subjects as a result of their prior rhGH treatment.

#### **b. All Completed Subjects**

The mean GH serum concentration-time profiles for the 0.75q4, 1.5q4, and 0.75q2 dose groups were similar among the CT and naive subjects, approximately dose proportional, and reproducible at each cycle. The serum GH profiles from Day 0 to 14 postdose after 0.75q2 administration were very similar to those GH profiles after 0.75q4 administration. The final GH concentrations at the end of Cycle 6 from all three dose groups had returned to the baseline values of Cycle 1. There was no decreasing or increasing trend in observed GH levels at 24 hours postdose over the 6-month study period. In addition, the 24-hr postdose GH levels were not generally different by GH treatment history (CT or naive) or by cycle and were dose proportional within the dose levels tested. These results indicate that the initial-release phase from [redacted] rhGH after repeated SC administration was reproducible in children with GHD and that GH disposition during the initial phase was not affected substantively by previous rhGH exposure (CT vs. naive) nor by repeated dosing over 6 months.

As expected, the biological response markers IGF-I and IGFBP-3 (-Day 7) increased with [redacted] rhGH treatment. Increases were variable among subjects and not proportional to the rhGH dose administered. GHP levels remained unchanged or declined during [redacted] rhGH treatment. Observed peak concentrations (24-hr postdose) of all response variables were consistent over the six dosing cycles and had returned to baseline values at the end of the study, indicating no accumulation or elevation to unacceptable levels over the 6-month study period.

### **SAFETY RESULTS**

#### **Extent of Exposure**

The 64 subjects with GHD who were enrolled in this study were treated an average of 0.42 years for a total of 27 subject-years of exposure.

#### **Adverse Events**

##### **a. Deaths**

There were no deaths during the study.

##### **b. Serious Adverse Events**

One serious adverse event was reported during the study. A 3.7-year-old naive male in the 1.5q4 dose group was admitted to the hospital for 24 hours with acute dehydration as the result of vomiting and diarrhea associated with a viral gastroenteritis. The investigator considered the event related to viral illness and unrelated to [redacted] rhGH. [redacted] rhGH was continued for the remainder of the study period.

##### **c. Adverse Events Leading to Withdrawal**

Seven subjects discontinued treatment because of an adverse event. Two CT subjects in the 0.75q4 group, both with a history of hypoglycemia, experienced worsening of hypoglycemia during the study. One subject discontinued because of an allergic reaction. Four subjects reported adverse events associated with injection-site pain and discontinued from the study.

##### **d. Adverse Events Associated with GH Therapy**

**Hyperglycemia.** No subject developed diabetes during the study. One naive subject in the 0.75q4 dose group was reported to have glycosuria on one occasion at Month 1 and hyperglycemia at Month 2. The investigator noted the events to be probably related to treatment with [redacted] rhGH. [redacted] rhGH was continued with no additional occurrences of hyperglycemia or glycosuria throughout the remainder of the study.

**Hypothyroidism.** Hypothyroidism is often associated with GHD. Nine CT subjects were being treated with L-thyroxine at baseline. No additional subjects began treatment during the study.

**Allergic Reaction.** There was one allergic reaction associated with rhGH treatment. Two other subjects reported allergic reactions, however, they were not associated with GH treatment.

**Arthralgia.** Arthralgia or myalgia was reported by 8 subjects.

**e. Adverse Events Related to Injection Sites**

Sixty-three of the 64 subjects reported events related to the injection site; 7 subjects rated the events as severe. Four of the 64 subjects discontinued treatment because of injection-site events.

Twenty-one subjects reported lipoatrophy, which was generally mild to moderate in severity and did resolve. Lipoatrophy was reported as severe for 1 naive subject and was listed as a secondary reason for discontinuation from the study for another subject.

Pain was reported in two ways: during injection and postinjection. The pain postinjection was generally rated as mild or moderate and occurred when the injection site was inadvertently touched. Application of EMLA<sup>®</sup> cream or ice was used to minimize the discomfort during injection.

**f. Other Adverse Events by Body System**

Many of the events were those associated with usual childhood complaints: nausea, vomiting, diarrhea, flu syndrome, headache, etc.

**Body as a Whole/Digestive System.** Events often related to childhood ailments such as fever, flu syndrome, headache, nausea, and vomiting were reported by 31 subjects on at least one occasion. The following case studies listed according to dose group detail these events:

- In the 0.75q4 dose group, events were reported by 5 CT and 4 naive subjects
- In the 1.5q4 dose group, events were reported by 7 CT and 4 naive subjects
- In the 0.75q2 dose group, events were reported by 6 CT and 5 naive subjects

**Cardiovascular System.** Two subjects reported pallor; one case was considered unrelated to [redacted] rhGH by the investigator, and the other was considered possibly related.

**Hemic/Lymphatic System.** Lymphadenopathy was reported by 6 subjects that was often associated with an intercurrent upper respiratory infection. Another subject was reported to have cervical lymphadenopathy at Month 3 that continued and was determined to be possibly related to [redacted] rhGH by the investigator.

**Metabolic/Nutritional System.** Hypoglycemia was reported as possibly/probably related to [redacted] rhGH by 3 subjects. Two CT subjects discontinued treatment. A third subject experienced hypoglycemia on one occasion at Month 3. [redacted] rhGH was not interrupted, and the subject completed the study with no additional episodes.

One subject reported glycosuria on one occasion at Month 1, 24 hours postdose and hyperglycemia 24 hours after the Month 2 dose. The investigator noted both events were probably related to treatment with [redacted] rhGH. Hyperbilirubinemia was reported by 1 subject and was considered possibly related to treatment on one occasion by the investigator.

**Musculoskeletal System.** Five subjects reported arthralgia, which has been often reported by individuals receiving treatment with rhGH. The investigators noted the events to be possibly related to [redacted] rhGH in 3 of the 5 subjects.

**Nervous System.** One subject was reported to have a limp at Month 1 that was thought to be probably related to study drug by the investigator. The limp resolved without intervention, and the subject completed the study without subsequent complaint.

Two subjects experienced seizures during the study. [redacted] rhGH was discontinued in 1 subject because the seizure was associated with hypoglycemia. A second subject also had a pre-existing seizure disorder but not hypoglycemia. The subject continued the study without additional episodes.

**Respiratory System.** Respiratory events, including exacerbations of pre-existing asthma, cough, laryngitis, pharyngitis, sinusitis, and rhinitis occurred. The investigators determined that most of these events were unrelated to treatment with [redacted] rhGH. However, one event of rhinitis was determined to be possible related to [redacted] rhGH by the investigator.

**Skin and Appendages.** Six subjects were reported to have a rash during the study. In most cases, the rashes were related to eczema or insect bites. One subject was reported to have an allergic reaction.

### **Laboratory Results**

Other than those changes that were generally expected in children with GHD and those known to be associated with GH therapy, there were no clinically relevant or sustained changes in laboratory parameters.

Glucose metabolism was monitored carefully throughout the 6 months, and no clinically significant abnormalities were noted because of treatment. Hb A<sub>1c</sub> levels remained well within the normal range. A mean increase in serum glucose was seen at the 24-hour timepoint following administration of [redacted] rhGH, with a return to baseline levels noted before the next dose. Among individual subjects there were no persistent changes in any of the assessed parameters of glucose homeostasis.

### **Anti-GH Antibodies**

A single CT subject had antibodies in the 0.75q4 dose group. This subject had antibodies at baseline as well as at Month 3, but the antibody status was unknown at Month 6. In the 1.5q4 dose group, 2 CT subjects had antibodies at baseline and thereafter, and 1 CT subject developed antibodies after baseline. In the 0.75q2 dose group, 1 CT subject had antibodies at baseline and thereafter; 5 CT subjects developed antibodies after baseline.

No naive subject was antibody positive at baseline. Four of the 9 subjects in the 0.75q4 dose group developed antibodies at Month 3. Three of the 8 subjects in the 1.5q4 dose group had antibodies at either Month 3 or Month 6. Seven of the 9 subjects in the 0.75q2 dose group had antibodies at either Month 3 or Month 6. The distribution of the growth rates for antibody-negative and antibody-positive subjects was similar.

### **Vital Signs and Physical Findings**

There were no clinically significant changes in vital signs or results of physical examination other than those previously discussed in relation to adverse events.

### **CONCLUSIONS**

[redacted] rhGH was shown to produce a positive growth response in naive subjects with GHD at the doses used, resulting in catch-up growth. In subjects currently treated with daily rhGH, [redacted] rhGH resulted in growth rates appropriate for age and maintenance of standardized height.

No clinically significant adverse events or laboratory changes clearly attributable to treatment were identified. Injection-site reactions occurred; injections were generally well tolerated, but some subjects did discontinue therapy for this reason.

These data enabled selection of two doses of [redacted] rhGH for the Phase III trial.

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## SYNOPSIS

**TITLE:** A PHASE III, MULTICENTER, OPEN-LABEL STUDY OF THE SAFETY AND EFFICACY OF [REDACTED] rhGH ADMINISTERED IN CHILDREN WITH GROWTH FAILURE DUE TO GROWTH HORMONE DEFICIENCY

**REPORT NUMBER:** [REDACTED] 03-004

**PHASE:** III

**INDICATION:** Growth hormone deficiency

**SPONSORS:**



Genentech, Inc.  
1 DNA Way  
South San Francisco, CA 94080-4990 U.S.A.

**REPORT DATE:** 11 February 1999

**PERIOD OF STUDY:** Initiation: 4 December 1997  
Completion: 6 September 1998

**PUBLICATIONS:** None

### INVESTIGATORS

The list of investigators is in Appendix A (Module I).

### OBJECTIVES

The objective of this study was to demonstrate the safety and efficacy of two doses (1.5 mg/kg once a month and 0.75 mg/kg twice a month) of a new sustained-release formulation of growth hormone (GH) in the treatment of growth failure in children with growth hormone deficiency (GHD). Efficacy was assessed using 6-month annualized growth rates.

### STUDY DESIGN

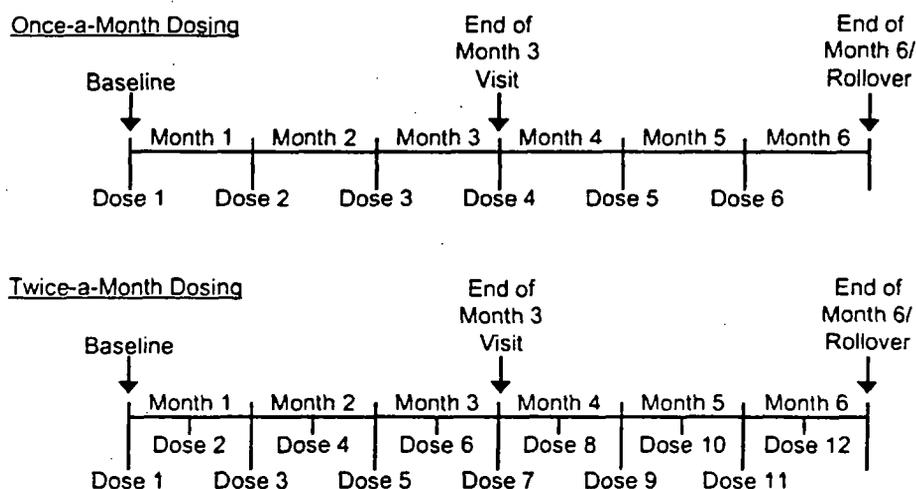
This was a Phase III, multicenter, open-label, 6-month study of [REDACTED] recombinant human (rh)GH. Seventy-four prepubertal subjects with GHD who had not been previously treated with GH (naive) were enrolled and treated at 27 medical centers. Subjects were randomized centrally to one of the following two treatment groups: 1.5 mg/kg [REDACTED] rhGH administered

once a month or 0.75 mg/kg [redacted] rhGH administered twice a month. Subjects were dosed at home, usually by a parent or guardian.

Subjects were seen in the clinic at three timepoints during the study: at baseline, at the end of 3 months, and at the end of 6 months (see Figure 1). At the end of this 6-month study, subjects had the option of participating in the ongoing, open-label study [redacted] 03-003) to assess the long-term safety and efficacy of [redacted] rhGH.

Figure 1

Study Visit Schematic



### PROTOCOL AMENDMENTS

The protocol was amended once. The amendment, dated 19 November 1997 (Serial No. 024 submitted to IND [redacted]), revised the study procedures to collect trough samples for GH, insulin-like growth factor I (IGF-I), and IGF-binding protein 3 (IGFBP-3) at the end of Months 3 and 6 no more than 48 hours prior to the next dose rather than 24 hours post dose. The entry criteria regarding prior use of anabolic agents and the standardized height requirement were clarified, and the definitions of serious adverse events were updated to be consistent with the new guidelines. A Medical Monitor at Genentech, Inc. was also identified. Other administrative changes were included to improve the clarity and consistency of the protocol.

### SUBJECT SELECTION CRITERIA

Subjects had to have documented GHD by a maximum GH response of  $<10 \mu\text{g/L}$  on at two prior standard pharmacologic tests of GH secretory capacity, a bone age of  $\leq 9$  years for girls or  $\leq 10$  years for boys, and prepubertal Tanner Stage 1 for breasts (girls) or genitalia (boys). Subjects with multiple hormone deficiencies had to have been stabilized on L-thyroxine and/or hydrocortisone for at least 3 months prior to enrollment. Height had to have been at least 2 standard deviations (SD) below the normal mean for age and sex. All subjects had to have a consent form signed by parent or legal guardian and a willingness and ability to participate in study assessments.

Subjects were excluded from participation in the study if they had panhypopituitarism with documented hypoglycemia, diabetes mellitus, or growth failure due to other reasons, including disorders of genitourinary, gastrointestinal, cardiopulmonary, or nervous system; nutritional/vitamin deficiency; chromosomal abnormality; or osteochondrodystrophy. Treatment

with anabolic agents >30 days during the 24 months prior to study entry or prior treatment for GHD was an exclusion. Hypothalamic-pituitary tumors diagnosed or treated within the past year or known allergy or sensitivity to any components of [redacted] rhGH were also exclusions.

### STUDY DRUG AND FORMULATION

[redacted] is a depot drug delivery system developed to provide sustained release of macromolecules, including peptides and proteins. The system consists of biocompatible, biodegradable microspheres formulated from poly D/L lactide co-glycolide (PLG) co-polymers. [redacted] rhGH is a sustained-release formulation of Genentech, Inc.'s somatropin intended for administration twice a month (0.75 mg/kg dose level) or once a month (1.5 mg/kg dose level).

[redacted] diluent is composed of carboxymethylcellulose sodium salt, polysorbate 20, sodium chloride, and water for injection.

[redacted] rhGH is stored at 2°C–8°C. [redacted] diluent is stored at [redacted].

### DRUG AND DILUENT LOT NUMBERS

The drug and diluent lot numbers appear in Appendix B (Module I).

### DOSE, ROUTE, AND REGIMEN

The dose for each subject was calculated according to the individual's weight at baseline and again at the 3-month visit and was administered as a subcutaneous (SC) injection. Subjects received 1.5 mg/kg somatropin 1x/month or 0.75 mg/kg somatropin 2x/month.

Two dosage units of [redacted] rhGH were used in this study, an 18-mg vial and a 27-mg vial.

The dose group of [redacted] rhGH remained the same for each subject during the study. The dosage for each individual subject was adjusted for change in body weight at the Month 3 visit.

### CONCOMITANT AND EXCLUDED THERAPY

Subjects with adrenocorticotrophic hormone (ACTH) deficiency could have received hydrocortisone in a dose that did not interfere with growth. Dosage had to be stable for 3 months prior to enrollment.

Subjects with hypothyroidism could have received L-thyroxine. Dosage had to be stable for 3 months prior to enrollment.

Other medications that were considered necessary for the subject's welfare and that were thought not to interfere with the study medication or affect growth were given at the discretion of the investigator. Administration of all such drugs was recorded in the appropriate section of the Case Report Form.

### PRIMARY AND SECONDARY EFFICACY ENDPOINTS

The primary efficacy endpoint for this study was the 6-month annualized growth rate. Secondary efficacy endpoints included standardized height and bone age (Fels Institute method) summarized at 6 months.

### STATISTICAL METHODS

All heights reported during the study were an average of three heights collected on the Case Report Form, with the exception of the prestudy height for which only one height measurement was required.

The height used for the prestudy growth rate must have been obtained at least 130 days prior to study start and no more than 425 days (i.e., ~1 year and 2 months prior to study start). The prestudy growth rates that met the criteria above are presented in tables with the on-study growth rates. Any prestudy growth rates based on heights outside of these boundaries were considered unreliable estimates and were not used. A paired t-test was used to evaluate the change in growth rate (i.e., the 6-month annualized growth rate minus the prestudy annualized growth rate) within each dose group.

Additional efficacy parameters (standardized height and bone age [Fels Institute method]) were summarized at 6 months.

Standardized height (SD score) was computed as follows:

$$\frac{\text{Actual height} - \text{Mean height of normal subjects of same age and sex}}{\text{Height SD of normal subjects of same age and sex}}$$

The means and SD of height for age and sex for normal subjects were derived from the percentiles published by the National Center for Health Statistics (2). A paired t-test was used to evaluate the change in standardized height.

Predicted adult heights were calculated using the Bayley-Pinneau tables (3) and a revised Bayley-Pinneau predicted adult height method ([redacted] personal communication) for children with bone ages of 3-6 years.

Height age was also calculated. The height age of a subject is equal to the age at which the mean height of normal children of the same sex is equal to the subject's height. For example, a girl who is 138.3 cm tall at any age has a height age of 10.0 years because the average height of a normal 10.0-year-old girl is 138.3 cm. Calculations of height age, change in height age minus change in bone age, and Bayley-Pinneau predicted adult height were made. Although these results were positive, the usefulness of these parameters over a 6-month period are limited and thus are not discussed in this report.

Assessments of the safety and tolerability of [redacted] rhGH were also objectives of this study. Subject listings of all data that address these assessments are presented.

Tabulations were performed to examine key parameters such as adverse events, change in vital signs, and change in laboratory parameters. Adverse events were tabulated by COSTART preferred term and body system. The incidence of adverse events that occurred was summarized by dose group.

Vital signs and hematology and serum chemistry laboratory values were summarized for all subjects at each timepoint. A paired t-test was used to evaluate the change in GH, IGF-I, IGFBP-3 from baseline to Month 3, baseline to Month 6, and Month 3 to Month 6 within each dose group. This analysis was based on subjects with measurements at all three timepoints.

Results for anti-GH antibody determinations by Genentech's [redacted] assay are presented at all timepoints by dose group. Assays for antibody binding capacity were performed for all samples with a titer of  $\geq 1.0$ .

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## SUBJECT ELIGIBILITY AND DISPOSITION

Subject Eligibility and Disposition

	All Subjects	1.5 1x/Month	0.75 2x/Month
Subjects enrolled	74	36	38
Completed study	69	33	36
Discontinued study	5	3	2
Adverse event	2	1	1
Protocol violation	1	0	1
Subject withdrew consent	2	2	0

## DEMOGRAPHIC AND BASELINE CHARACTERISTICS OF STUDY POPULATION

Selected Demographic and Baseline Characteristics

Characteristic	1.5 1x/Month (n=36)	0.75 2x/Month (n=38)
Sex (n, %)		
Male	21 (58)	29 (76)
Female	15 (42)	9 (24)
Etiology of GHD (n, %)		
Idiopathic	32 (89)	35 (92)
Organic	4 (11)	3 (8)
Chronological age (yr)		
Mean±SD	7.3±3.2	7.6±2.7
(Range)	(1.6–12.2)	(3.2–11.9)
Bone age (yr)		
Mean±SD	5.7±2.8	6.3±2.4
(Range)	(0.2–11.1)	(2.1–10.4)
(n=37)		
Previous growth rate (cm/yr)		
Mean±SD	5.0±2.1	4.7±1.9
(Range)	(1.6–8.5)	(1.4–9.2)
(n=26)		(n=30)
Standardized height		
Mean±SD	-2.9±1.2	-2.9±0.8
(Range)	(-6.7 to -0.6)	(-5.1 to -0.8)
Maximum stimulated GH (ng/mL)		
Mean±SD	5.7±2.6	6.0±2.8
(Range)		

SD = Standard deviation.

## EFFICACY RESULTS

The primary efficacy endpoint for this study was the 6-month annualized growth rate. Of the 69 subjects who completed 6 months of therapy, 53 had prestudy growth rates available. The mean±SD prestudy growth rate for subjects in the 1.5 1x/month group was 5.0±2.1 cm/yr (n=25).

The mean 6-month annualized growth rate for this subset of subjects was  $8.5 \pm 1.7$  cm/yr ( $p < 0.0001$  vs. prestudy growth rate). The mean 6-month annualized growth rate for the entire dose group ( $n=33$ ) was  $8.3 \pm 1.7$  cm/yr.

Similar results were obtained for subjects in the 0.75 2×/month group. The mean  $\pm$ SD prestudy growth rate was  $4.6 \pm 1.8$  cm/yr ( $n=28$ ). The mean 6-month annualized growth rate for this subset of subjects was  $8.6 \pm 2.4$  cm/yr ( $p < 0.0001$  vs. prestudy growth rate). The mean 6-month annualized growth rate for the entire dose group ( $n=36$ ) was  $8.4 \pm 2.4$  cm/yr.

As per the protocol, because the growth rates were not significantly different between the two dose groups ( $p=0.8$ ), the data were pooled. The mean 6-month annualized growth rate for the pooled population was  $8.4 \pm 2.1$  cm/yr ( $n=69$ ), with a 95% confidence interval of 7.9 to 8.9. For subjects with both prestudy and 6-month data available, the pooled annualized growth rates were  $4.8 \pm 1.9$  cm/yr prestudy and  $8.6 \pm 2.0$  cm/yr on [redacted] rhGH ( $n=53$ ), with a 95% confidence interval of 8.0 to 9.1 cm/yr. The growth rates ranged from [redacted] cm/yr.

Height standardized for age and sex (i.e., z-score or SD score) allows for comparisons of subjects' heights with normal children of the same chronological age and sex (2). Based on all subjects dosed, the mean baseline height SD score in both dose groups was  $-2.9$ , indicating that the subjects had significant short stature, which is typical of this prepubertal GH-deficient population. For subjects who completed 6 months of therapy, the mean baseline height SD scores were  $-3.0 \pm 1.2$  in the 1.5 1×/month group and  $-3.0 \pm 0.7$  in the 0.75 2×/month group. By Month 6, the height SD score increased to  $-2.6$  in both groups. The mean changes in height SD scores from baseline to the end of Month 6 were  $0.35 \pm 0.31$  in the 1.5 1×/month group and  $0.31 \pm 0.23$  in the 0.75 2×/month group and were highly statistically significant in both groups ( $p < 0.0001$ ). The positive change in standardized height indicated that catch-up growth, an important goal of the first year of GH therapy, was achieved.

The change in bone age was used to assess the effect of [redacted] rhGH therapy on the rate of skeletal maturation. The baseline bone age delay relative to chronological age was  $\sim 1.5$  years. The mean changes in bone age after 6 months of therapy were  $0.4 \pm 0.3$  years in the 1.5 1×/month group and  $0.5 \pm 0.3$  years in the 0.75 2×/month group. These data demonstrate that the average rate of bone age advancement was appropriate and that the improvements in growth noted above were not accompanied by an undue advancement of bone age.

## 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 35.0 subject-years of exposure. Sixty-nine of the subjects (93%) who were enrolled and received at least one dose of [redacted] rhGH completed the 6-month study.

### Adverse Events

#### a. All Adverse Events

[redacted] rhGH was generally well tolerated. There were no serious adverse events related to study drug and 93% of subjects completed the study.

#### b. Deaths

There were no deaths during the study.

#### c. Serious Adverse Events

There were a total of four serious adverse events reported during the study; two of which were experienced by 1 subject. None of the events were considered to be related to treatment with [redacted] rhGH, which continued uninterrupted for all 3 subjects. One subject (0.75 2×/month group) with a history of panhypopituitarism receiving multiple-hormone replacement, was hospitalized on two occasions for dehydration related to inadequate desmopressin acetate

(DDAVP<sup>®</sup>) replacement for diabetes insipidus during a viral respiratory illness. Another subject (0.75 2×/month group) with a history of attention deficit-hyperactivity disorder treated with Prozac<sup>®</sup> and Dexedrine<sup>®</sup>, required hospitalization for an acute episode of aggressive behavior after the third dosing. The third subject (0.75 2×/month group) was hospitalized and given intravenous antibiotics following diagnosis of a viral syndrome, otitis media with fever and vomiting, resulting in dehydration after his tenth dose of [ ] rhGH.

#### d. Adverse Events Leading to Withdrawal

Two subjects discontinued from the study because of adverse events. One subject (1.5 1×/month group) reported multiple events, including buttock and groin pain, dizziness, weakness, increased thirst, and nausea. Physical examination findings were normal and laboratory values were within the normal ranges. The subject discontinued from the study after the third dosing because of periodic weakness and dizziness.

The other subject (0.75 2×/month group) discontinued after six doses of study drug because of pain during injections.

#### e. Adverse Events Associated with GH Therapy

There were no reports of the following events, which have been reported to be associated with treatment with GH: hyperglycemia, hypothyroidism, leukemia, intracranial hypertension, or slipped capital femoral epiphysis. Occurrences of arthralgia and allergic reaction were reported; however, only arthralgia was considered possibly/probably related to [ ] rhGH.

Mild to moderate arthralgia was reported by 3 subjects during the study and was considered possibly/probably related to [ ] rhGH for 2 subjects in the 0.75 2×/month group. One subject reported achiness in both knees on four occasions, with the onset following the ninth dosing of [ ] rhGH; similar symptoms were reported in the wrists on two occasions. The symptoms were treated with Tylenol<sup>®</sup> Liquid. The other subject reported intermittent pain and swelling of knees and feet that occurred 1 week after the initial dosing of [ ] rhGH and continued ~15 weeks. The dose was reduced to 0.375 mg/kg twice a month for two dosings by the Medical Monitor, resulting in resolution of symptoms. The subject then resumed dosing at 0.75 2×/month. The symptoms resolved prior to the last four doses of [ ] rhGH.

Six subjects reported allergic reactions. However, the events were generally associated with environmental allergies or exacerbations of pre-existing asthma and were not attributed to treatment with [ ] rhGH by the investigators. One subject (1.5 1×/month group) had an allergic reaction (periorbital swelling) attributed to EMLA<sup>®</sup> cream when he inadvertently rubbed his eye after touching the injection site.

#### f. Adverse Events Related to Injection Sites

Adverse events related to injection sites were reported by the majority of subjects in the study, although injections were generally well tolerated. Injections were administered at home, usually by a parent or guardian. The most common injection-site reactions were pain during injection, nodules, erythema, bruising, and pain postinjection; all of which occurred in more than 50% of subjects. However, improvement in tolerability was seen over time. Itchiness and edema were less common. Lipoatrophy occurred with 28% of subjects and was likely the result of transient loss of local subcutaneous fat.

To assess pain during injection, parents or guardians administering the injections were instructed to utilize the Wong-Baker FACES Pain Rating Scale (4) and to record the results with each dosing. The scale is an adaptation of the picture-projection technique in which six faces are shown to a child.

The rater (parent or guardian) was instructed to explain to the child that each face represented a person who either was happy because he or she had no pain (hurt) or sad because he or she had some or a lot of pain. Using a scale from 0 to 5, in which Face 0 corresponds to "no hurt," Face 1 "hurts a little bit," Face 2 "hurts little more," Face 3 "hurts even more," Face 4 "hurts whole lot,"

and Face 5 "hurts worst," 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, indicating improvement in tolerability of administration of [redacted] rhGH over time.

**g. Adverse Events Reported as Possibly, Probably, or Definitely Related to Treatment by Body System**

**Body as a Whole.** Headache was reported by 2 subjects (6%) in the 1.5 1×/month group and 3 subjects (8%) in the 0.75 2×/month group. The headaches generally resolved with either no intervention or with administration of a mild analgesic. Results from funduscopic examinations conducted at 3-month intervals did not show any changes from baseline.

Abdominal pain was reported by 3 subjects (1 in the 1.5 1×/month group and 2 in the 0.75 2×/month group).

Other events in this body system reported by the investigators as possibly or probably related to treatment with study drug, including accidental injury, asthenia, fever, neck pain, pelvic pain, and decreased tolerance to cold occurred in either 1 or 2 subjects per dose group and did not result in discontinuation from the study for any subject. In addition, 2 subjects both with a history of migraine headaches and 1 in each dose group, reported a migraine headache during the study.

**Cardiovascular System.** Two subjects reported migraine headaches during the study; both subjects had a history of migraine headaches.

**Digestive System.** Seven subjects in the 1.5 1×/month group (19%) and 6 subjects in the 0.75 2×/month group (16%) reported events in this system. The most frequently reported event was nausea, which was reported by 6 subjects in the 1.5 1×/month group (17%) and 2 subjects in the 0.75 2×/month group (5%). Vomiting sometimes associated with nausea was reported by 2 subjects in the 1.5 1×/month group (6%) and 3 subjects in the 0.75 2×/month group (8%). In total, 6 subjects in the 1.5 1×/month group and 4 in the 0.75 2×/month group reported nausea or vomiting.

**Hemic/Lymphatic System.** Two subjects, 1 in each dose group, reported events in this category.

**Metabolic/Nutritional System.** Four subjects in the 1.5 1×/month group (11%) and 1 subject in the 0.75 2×/month group (3%) reported events in this category. Two subjects in the 1.5 1×/month group (6%) reported increased thirst on one occasion each during the study.

**Musculoskeletal System.** Two subjects in the 0.75 2×/month group (5%) reported arthralgia during the study that the investigators considered possibly related to [redacted] rhGH.

**Nervous System.** Four subjects in the 1.5 1×/month group (11%) and 5 subjects in the 0.75 2×/month group (13%) reported events in this category.

Two subjects in the 1.5 1×/month group reported dizziness. Two subjects, 1 from each dose group, reported agitation and a third subject in the 0.75 2×/month group reported tremor and somnolence. Other events in this category, including insomnia, sleep disorder, hyperkinesia, and emotional lability, although considered possibly related to study drug by the investigators, occurred generally in 1 subject on one occasion and did not result in discontinuation from study.

**Skin and Appendages.** One subject reported the occurrence of rash and a second subject reported diaphoresis.

**Urogenital System.** Two subjects reported events related to the urogenital system during the study.

## Laboratory Results

**Renal Function.** Renal function was assessed by measurement of BUN and creatinine. There were no clinically significant changes at Months 3 or 6 compared with baseline. Mean levels of both BUN and creatinine remained within the normal ranges during the study.

**Bone Metabolism.** Parameters of bone metabolism measured in this study included calcium, inorganic phosphorus, and alkaline phosphatase. No clinically significant changes occurred in calcium concentration for any subject. As expected with GH therapy, there was a slight increase in mean levels of inorganic phosphorus during treatment. Mean alkaline phosphatase levels were elevated at Months 3 and 6 compared with baseline as expected in children with GHD treated with GH.

**Glucose Metabolism.** Glucose metabolism was monitored by measurement of fasting glucose and insulin, postprandial glucose and insulin, and hemoglobin A<sub>1c</sub> (Hb A<sub>1c</sub>) levels. There were no clinically significant changes in mean fasting or postprandial glucose or insulin levels noted after 6 months. There were also no clinically significant changes in Hb A<sub>1c</sub> levels after 6 months.

Several subjects had elevations in fasting and/or postprandial glucose levels at baseline that in some cases persisted during the study. One subject (1.5 1×/month group) had postprandial glucose levels of 178 mg/L and 165 mg/L at the end of Months 3 and 6, respectively; however, he had a postprandial glucose level of 118 mg/L at baseline. His fasting glucose and Hb A<sub>1c</sub> levels remained within normal ranges during the study. One subject (0.75 2×/month group) had elevated postprandial glucose levels of 145 mg/L and 156 mg/L at the end of Months 3 and 6, respectively, with normal or low fasting glucose levels. Her Hb A<sub>1c</sub> level remained within the normal range. Sporadic elevations of both glucose and insulin levels were noted in other subjects; however, these changes were not sustained and no individuals had symptoms associated with hyperglycemia.

**Lipid Metabolism.** There were no clinically significant changes noted in levels of cholesterol during 6 months of treatment with [redacted] rhGH. Individual subjects had elevated levels of cholesterol at baseline that persisted throughout the study. Most subjects had levels within the normal range.

**Thyroid Function.** Thyroid function was monitored by measurement of free T<sub>4</sub>, total T<sub>4</sub>, and thyroid-stimulating hormone (TSH). Mean values remained within the normal ranges during the study. Individual subjects had sporadic elevations of T<sub>4</sub>. There was a small decrease in mean T<sub>4</sub> during the 6-month study period in the 1.5 1×/month group from 10.2 µg/dL at baseline to 9.6 µg/dL at Month 6. There was essentially no change in mean levels in the 0.75 2×/month group. One subject (1.5 1×/month group) had an elevated TSH level of 12.0 µU/mL at baseline and was subsequently diagnosed with Hashimoto thyroiditis. There were no cases of new onset hypothyroidism observed during the study.

**Liver Function.** Several subjects had elevations in AST (SGOT) at baseline that persisted during the study and were not thought to be associated with administration of [redacted] rhGH. There was no trend toward an increase in levels. Mean values AST, ALT (SGPT), and GGT remained within the normal ranges.

**Hematology.** There were no clinically significant changes in hematology parameters measured during the study. Individual subjects had levels of hemoglobin, hematocrit, and platelet counts outside the normal ranges sporadically during the study. One subject (0.75 2×/month group) with a history of abnormal platelet morphology, hemolytic anemia, and thrombocytopenia, had decreased platelet and white blood counts at baseline that persisted. One subject (1.5 1×/month group) had a decreased platelet count at the end of Month 3 that resolved by the end of Month 6. Another subject (1.5 1×/month group) with a normal platelet count ( $286 \times 10^3/\mu\text{L}$ ) at baseline, had decreased platelet counts at the end of Months 3 and 6 ( $146$  and  $94 \times 10^3/\mu\text{L}$ , respectively). Other hematology parameters remained within the normal ranges. There were no clinically significant

changes in physical examination findings or reports of associated adverse events for this subject. Concurrent medications included Ritalin®, imipramine, and Paxil®.

#### **Other Laboratory Parameters**

Changes in laboratory values for other serum chemistries and urinalysis were not clinically significant.

#### **Anti-GH Antibodies**

Serum samples obtained at 3-month intervals were assayed for anti-GH antibodies using Genentech's [redacted] assay. A titer from this assay equals the base-10 logarithm of the dilution factor result from the assay.

In these naive subjects, the prevalence of antibodies was 0% at baseline, 38% at Month 3, and 39% at Month 6 in the 1.5 1x/month group and 0% at baseline, 69% at Month 3, and 61% at Month 6 in the 0.75 2x/month group. The mean titers were <2.0 at both timepoints in both dose groups, and only 1 subject had a titer of >3.0. The titers were generally low and in a range that historically has not been associated with growth attenuation. One subject, who had the highest titer (3.2 at Month 6), had a 6-month annualized growth rate of 12.0 cm/yr.

There was no evidence of negative association between antibody titer and growth rate. These data suggest that the antibodies were not associated with attenuation of the growth response.

All serum samples with positive antibody titers ( $\geq 1.0$ ) were assayed for binding capacity and these data are shown in Appendix E. No subject had a binding capacity value greater than 2.0 mg/L and most values (23 of 26 in the 1.5 1x/month group and 32 of 47 in the 0.75 2x/month group) were below the assay limit of detection [redacted] mg/L. The highest value observed was 0.398 mg/L that occurred for 1 subject at Month 6. The value corresponded to the largest observed titer (3.2) and coincided with a 6-month annualized growth rate of 12.0 cm/yr, as noted above. The data suggest that binding capacities were not associated with attenuation of growth response.

#### **GH, IGF-I, IGFBP-3, and GHBP Results**

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. No significant change in trough GH concentrations were noted in the 1.5 1x/month group at Month 3 or Month 6 compared with baseline, although the Month 3 value was slightly greater than the Month 6 value.

No significant changes in trough IGF-I concentrations were seen in the 1.5 1x/month group at either Month 3 or Month 6 compared with baseline, although the Month 6 value was slightly greater than the Month 3 value. In the 0.75 2x/month group, there were significant but modest increases in IGF-I trough concentrations at Month 3 and Month 6 associated with increased GH concentrations. However, Month 3 and Month 6 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, suggesting a return to baseline concentrations between doses.

Together, these data indicate no clinically significant accumulation of GH, IGF-I, or IGFBP-3 during 6 months of treatment with [redacted] rhGH and only slight increases in GH and IGF-I from baseline in the 0.75 2x/month group.

#### **Vital Signs and Physical Findings**

There were no clinically significant changes in vital signs or physical examination findings except as discussed in the report of adverse events.

**CONCLUSIONS**

[redacted] rhGH is safe and effective therapy for the treatment of growth failure due to growth hormone deficiency.

**APPEARS THIS WAY  
ON ORIGINAL**

## SYNOPSIS

**TITLE:** AN OPEN-LABEL, LONG-TERM EXTENSION STUDY OF THE SAFETY AND EFFICACY OF [REDACTED] rhGH IN CHILDREN WITH GROWTH FAILURE DUE TO GROWTH HORMONE DEFICIENCY

**REPORT NUMBER:** [REDACTED] 03-003

**PHASE:** III

**INDICATION:** [REDACTED]

**SPONSOR:** [REDACTED]

Genentech, Inc.  
1 DNA Way  
South San Francisco, CA 94080-4990 U.S.A.

**REPORT DATE:** 24 February 1999

**PERIOD OF STUDY:** 28 April 1997-present

**PUBLICATIONS:** None

### INVESTIGATORS

The list of investigators is provided in Appendix A (Module I).

### OBJECTIVES

The objectives of this study were to determine the long-term safety of a new sustained-release formulation of rhGH ([REDACTED] rhGH) and to determine the long-term efficacy of a new sustained-release formulation of rhGH ([REDACTED] rhGH).

### STUDY DESIGN

This is an ongoing, multicenter, open-label, parallel-group pediatric study designed to evaluate the long-term safety and efficacy of [REDACTED] rhGH administered as an subcutaneous (SC) injection. The initial doses used in this study were the following: 0.75 mg/kg once a month (0.75q4), 1.5 mg/kg once a month, or 0.75 mg/kg twice a month. At the time of dose selection for Phase III, all subjects in this study were assigned to receive one of the two doses selected for Phase III, i.e., 0.75 mg/kg twice a month or 1.5 mg/kg once a month (hereafter referred to as 0.75 2x/month and 1.5 1x/month, respectively).

This study is being conducted as an extension to Studies [REDACTED] 03-002 (begun in November 1996) and [REDACTED] 03-004 (begun in December 1997). Subjects who completed Studies [REDACTED] 03-002 or [REDACTED] 03-004 were eligible to enroll. This interim report includes data available as of 25 May 1998 for 34 subjects from Study [REDACTED] 03-002 who chose to participate in this extension study and who

had at least one visit prior to 17 February 1998. At the time of this interim report, data were not yet available for any subjects from Study [redacted] 03-004 and are therefore not included. Subjects may continue on Study [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 Sponsors. Data from all subjects enrolled in Study [redacted] 03-003 will be included in a final report after completion of the trial.

A goal of Study [redacted] 03-002 was the selection of the dose(s) and regimen(s) to be used in Phase III. Following a review of the data and a decision regarding the dose and regimen to be used in Phase III, 10 subjects who were dosed at 0.75q4 in Study [redacted] 03-002 and who had already enrolled in Study [redacted] 03-003 were randomized to receive either 0.75 2x/month or 1.5 1x/month. Subjects who were dosed at either 0.75q2 or 1.5q4 in Study [redacted] 03-002 continued at the originally assigned dose and schedule in Study [redacted] 03-003. Unlike Study [redacted] 03-002 in which 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.

#### PROTOCOL AMENDMENTS

The protocol was amended once (13 February 1998, Serial No. 031 submitted to IND [redacted]). Entry criteria were revised to include subjects from Study [redacted] 03-004 and subjects treated with methylphenidate or cyproheptadine. An additional criterion was added, stipulating that sexually active female subjects of childbearing potential had to agree to use medically acceptable contraception. Based on a review of the safety experience with [redacted] rhGH, the study procedures were revised to reduce the frequency of study visits and the number of laboratory assessments, and the pediatric safety experience with [redacted] rhGH was updated. A Medical Monitor at Genentech, Inc. was identified. Other administrative changes were included to improve the clarity and consistency of the protocol.

#### SUBJECT SELECTION CRITERIA

The investigator performed the final physical examination, bone age X-ray, laboratory measurements, and evaluation of the subject's compliance in Studies [redacted] 03-002 or [redacted] 03-004 prior to enrolling the subject in [redacted] 03-003 and determined the subject's eligibility for continuation in this extension study using the criteria below.

Fifty-two subjects who completed Study [redacted] 03-002 were eligible to enroll in this extension study, and 35 subjects agreed to participate. Follow-up data were available for 34 subjects from Study [redacted] 03-003 for this interim report (25 May 1998) and are the basis of this report. The 35th subject had not yet reached the first scheduled visit at the time of the database closure for this interim analysis and data were not available for this report. Data for all subjects enrolled in this study will be included in periodic updates and in the final report of the study.

#### Inclusion Criteria

Subjects had to fulfill the following criteria to be eligible for entry in the study:

- Completed Studies [redacted] 03-002 or [redacted] 03-004 and demonstrated compliance
- Volunteered to participate in the extension study and agreed to return for scheduled clinic visits

- Females of childbearing potential agreed to use medically acceptable contraception if sexually active

Parents or guardians had to agree to do the following:

- Administer regularly scheduled SC injections to their child at home as instructed by the study staff
- Adhere to the dosing regimen prescribed by the investigator
- Complete injection-site worksheets during the entire study period
- Provide informed consent prior to any study procedures

### Exclusion Criteria

Subjects who met any of the following criteria were excluded from the study:

- Completed Studies [redacted] 03-002 or [redacted] 03-004 and did not wish to continue in the extension study
- Were deemed noncompliant with visit schedule and/or protocol procedures
- Participated in another investigational study with an investigational drug

### **STUDY DRUG AND FORMULATION**

[redacted] is a depot drug delivery system developed to provide sustained release of macromolecules, including peptides and proteins. The system consists of biocompatible, biodegradable microspheres formulated from poly D/L lactide co-glycolide (PLG) co-polymers.

[redacted] rhGH is a sustained-release formulation of rhGH (Genentech Inc.'s somatropin) intended for administration once or twice a month.

[redacted] diluent is composed of carboxymethylcellulose sodium salt, polysorbate 20, sodium chloride, and water for injection.

### **DRUG AND DILUENT LOT NUMBERS**

The drug and diluent lot numbers are listed in Appendix B of this report.

### **DOSE, ROUTE, AND REGIMEN**

The dose for each subject was calculated according to the individual's weight at each 3-month visit and was administered as an SC injection. Subjects received 0.75 mg/kg [redacted] rhGH or 1.5 mg/kg [redacted] rhGH.

[redacted] rhGH was suspended with the supplied [redacted] diluent before each administration by SC injection. The initial instructions were to suspend the microspheres with [redacted] mL of diluent and inject with a 22-gauge, 1-inch needle; however, needle clogging occurred with the first subject dosed. The suspension was then made with 1.5 mL of diluent also using a 22-gauge needle to inject. This procedure was used by 6 subjects for 2 months. It was determined that a larger gauge needle was required to avoid needle clogging. The suspension was subsequently prepared using [redacted] mL of diluent and injected with a 21-gauge, ½-inch needle.

The final procedure used for the majority of subjects and dosings was as follows: 1.0 mL of [redacted] diluent was withdrawn and injected into the vial of [redacted] rhGH microspheres. The sides of the vial were tapped to ensure that any microspheres adhering to the glass went into suspension. The vial was then inverted several times over 90 seconds to produce a homogeneous suspension of microspheres. The vial was shaken to ensure that the particles were

well mixed. The vial was inspected visually and if any clumps of unsuspended particles were observed, the mixing procedures were continued until all the particles were resuspended.

The calculated dose of suspended microspheres was then withdrawn into a new 3-mL syringe with a 21-gauge, ½-inch, thin-wall needle. The dose was injected immediately, taking care to ensure that the dose was delivered in a single, smooth motion.

If the total volume for any dose exceeded 1.2 mL, the dose was divided into two or more injections of equal volume. The dose was administered into the SC tissue of the upper arms, thighs, or abdomen as instructed by the investigator.

#### **DURATION OF THERAPY**

The average length of treated with [redacted] rhGH in the combined study period of Studies [redacted] 03-002 and [redacted] 03-003 was 12.3 months. The maximum duration of exposure to [redacted] rhGH was 18 months.

#### **CONCOMITANT AND EXCLUDED THERAPY**

No subject was allowed to participate in another study with an investigational drug during the course of this study. If a question arose regarding the propriety of a medication during the study, the parent or guardian was instructed to contact the study staff. No other concomitant medications were specifically restricted.

#### **PRIMARY AND SECONDARY OUTCOME MEASURES**

##### **Safety Outcome Measures**

The safety and tolerability of [redacted] rhGH were assessed by physical examination, inspection of injection sites, measurement of vital signs, clinical laboratory evaluations, measurement of anti-GH antibodies, and reports of adverse events.

##### **Efficacy Outcome Measures**

The primary efficacy outcome measure is the annualized growth rate. Efficacy is supported by data for change in standardized height, height age, and bone age.

#### **STATISTICAL METHODS**

Demographics, physical examination findings, vital signs, and clinical laboratory evaluations were summarized with descriptive statistics and subject listings as appropriate.

All heights reported during the study were an average of three heights collected on the Case Report Form (CRF), with the exception of the prestudy height for which only one height measurement was required.

#### **SUBJECT ELIGIBILITY AND DISPOSITION**

Fifty-two subjects who completed Study [redacted] 03-002 were eligible to enroll in this extension study, of whom 29 were currently treated (CT) and 23 were naive subjects. Thirty-four subjects, 14 CT subjects (41%) and 20 naive subjects (59%), are the focus of this report. Eight of the CT subjects (57%) and 5 of the naive subjects (25%) had discontinued from the study as of this report. Of the 34 subjects for whom data were available, 21 (6 CT subjects and 15 naive) remained in the study at the time of the database closure for this report.

	All Subjects	Dose Group	
		1.5 1x/Month	0.75 2x/Month
Enrolled, n	34	17	17
Discontinued study, n (%)	13 (38)	8 (47)	5 (29)
Reason for study termination, n (%):			
Adverse event	1 (3)	0 (0)	1 (6)
Subject withdrew consent	7 (21)	4 (24)	3 (18)
Other	5 (15)	4 (24)	1 (6)

## DEMOGRAPHIC AND BASELINE CHARACTERISTICS OF STUDY POPULATION

Baseline characteristics present at baseline in Study [redacted] 03-002 were used for subjects who agreed to participate in Study [redacted] 03-003. Fourteen subjects were currently being treated with daily rhGH at the time of original enrollment in Study [redacted] 03-002, and 20 had not received any prior treatment with GH (naive). There was a predominance of males in both groups. The etiology of GHD was largely idiopathic, with only 2 CT subjects and no naive subjects enrolled with a diagnosis of organic GHD. All 14 CT subjects and 15 of 20 naive subjects had prestudy growth rates that met the efficacy analysis criteria.

## SAFETY RESULTS

### Extent of Exposure

The 34 subjects discussed in this report were treated with [redacted] rhGH in the combined study period of Studies [redacted] 03-002 and [redacted] 03-003 for an average of 12.3 months or 34.3 subject-years of exposure. The maximum duration of exposure to [redacted] rhGH was 18 months.

### Adverse Events

#### a. Deaths

There were no deaths during the reporting period.

#### b. Serious Adverse Events

There were no serious adverse events during the reporting period.

#### c. Adverse Events Leading to Withdrawal

One subject, an 11.1-year-old CT male (0.75 2x/month), reported moderate pain during injection and discontinued from the study at the Month 9 visit.

#### d. Adverse Events Associated with GH Therapy

Certain expected adverse events have been commonly reported to be possibly associated with rhGH treatment, including hyperglycemia, hypothyroidism, allergic reaction, leukemia, intracranial hypertension, slipped capital femoral epiphysis, and arthralgia. There were no reports of any of these events during the reporting period.

#### e. Adverse Events Related to Injection Sites

Thirty-one of the 34 subjects reported an adverse event related to injection site. The majority of the events were mild or moderate; the event was rated as severe in 4 subjects. One subject discontinued because of pain with injection.

Fourteen subjects reported lipoatrophy associated with injection sites. The events were generally mild and resolved spontaneously.

Nodules were reported at the injection site for 28 subjects, and for 1 subject, the nodule was noted to be severe. However, in most cases the nodule resolved by the time of the next administration of [redacted] rhGH.

Pain was reported in two ways: during injection and postinjection. Pain during injection was reported for 13 subjects, with 3 subjects reporting pain as severe. Mild or moderate pain postinjection was reported for 29 subjects. Application of EMLA® cream or ice was used to minimize discomfort with injection.

**f. Other Adverse Events**

A summary of adverse events that occurred during or after administration of the first dose of [redacted] rhGH in Study [redacted] 03-003 and that were reported by investigators as possibly, probably, or definitely related to treatment (excluding injection-site events) and the total number of subjects with those events reported (whether or not causality to treatment with rhGH was suspected) are presented in the table below.

Body System/Primary Term	Relationship	
	Possible/Probable/Definite	Total
No. of subjects dosed		34
No. of subjects with an adverse event		24
Body as a whole		
Fever	1 (3%)	5 (15%)
Headache	5 (15%)	7 (21%)
Digestive system		
Vomiting	1 (3%)	5 (15%)
Nervous system		
Nervousness	1 (3%)	1 (3%)
Skin and appendages		
Skin disorder	1 (3%)	1 (3%)

**Body as a Whole.** Headache was reported by 7 subjects. Headache occurred on more than one occasion in 4 subjects and was thought to be possibly or probably related to treatment with [redacted] rhGH in 5 subjects. The complaints were generally mild to moderate and resolved either spontaneously or with the use of analgesics. Fever was thought to be possibly related to [redacted] rhGH on one occasion.

**Digestive System.** Five subjects reported vomiting on one occasion each. One subject, a 4.3-year old naive female in the 1.5 1x/month group, reported vomiting on the day of the Month 10 dosing. A second subject, a 6.1-year-old naive male in the 0.75 2x/month group, reported vomiting 3 days after the Month 8A dosing. Two subjects (a 9.8-year-old CT male and a 14.2-year-old naive male) in the 1.5 1x/month group each reported vomiting 2-3 weeks following the Month 18 dosing. Except for the vomiting experienced by 1 subject, all the other events were attributed to usual childhood illnesses and considered unrelated to [redacted] rhGH by the investigators.

**Nervous System.** One subject in the 0.75 2x/month group (previously treated with 0.75q4) reported occurrences of occasional "shaky spells" during the study. There was no documentation of abnormal glucose levels or other symptoms associated with these episodes. The onset of symptoms relative to dosing was unknown. The investigator considered the events to be possibly related to [redacted] rhGH.

**Skin and Appendages.** One subject in the 1.5 1x/month group was noted to have a change in the appearance of a mole on the right side of his chest at Month 12. The investigator noted the event to be possibly related to [redacted] rhGH.

**g. Adverse Events Ongoing at the End of Study [redacted] 03-002**

Some adverse events considered possibly related to treatment with [redacted] rhGH by the investigators were ongoing at the end of Study [redacted] 03-002. With the exception of knee pain reported by 1 subject, the events resolved during the study period of Study [redacted] 03-003. These events are discussed in the following sections.

**Body as a Whole.** Eight subjects reported lipoatrophy or nodules subsequent to their final dose of [redacted] rhGH in Study [redacted] 03-002 that resolved during Study [redacted] 03-003.

**Hemic/Lymphatic System.** One subject in the 1.5 1x/month group was reported to have right cervical lymphadenopathy prior to any treatment with [redacted] rhGH in Study [redacted] 03-002 that continued through Month 12 in Study [redacted] 03-003. The investigator considered the event to be possibly related to treatment with [redacted] rhGH, and the condition resolved without intervention.

**Metabolic/Nutritional System.** Hyperbilirubinemia was reported as possibly related to treatment for a 9.0-year-old CT male subject (1.5 1x/month group). Review of the data revealed that he had a mildly elevated bilirubin level prior to any treatment with [redacted] rhGH and sporadic elevations throughout the study.

**Musculoskeletal System.** A 6.1-year-old naive male (0.75 2x/month group) subject reported intermittent bilateral knee pain throughout the study that the investigator thought was possibly related to [redacted] rhGH.

**h. Other Adverse Events**

Other adverse events reported during the study were those associated with pre-existing childhood conditions or those associated with GHD.

**Laboratory Results**

**a. Laboratory Tests**

**Bone Metabolism.** No clinically significant changes occurred in mean levels of either calcium or inorganic phosphorus during the study. Mildly elevated levels of inorganic phosphorus were observed in several subjects at baseline that persisted during the study. Low levels of calcium were noted for some subjects but were sporadic and not clinically significant. The mean level of alkaline phosphatase did not change during treatment with [redacted] rhGH as assessed by measurements prior to dosing.

**Glucose Metabolism.** No clinically significant changes in mean fasting or postprandial glucose or insulin levels were noted after 12 months. There were also no clinically significant changes in hemoglobin A<sub>1c</sub> (Hb A<sub>1c</sub>) levels after 12 months. Sporadic elevations of both glucose and insulin levels were noted; however, no persistent elevations in either glucose or insulin levels occurred for individual subjects.

**Thyroid Function.** Thyroid function was monitored by measurement of free T<sub>4</sub>, T<sub>4</sub>, and T<sub>3</sub> levels. Mean values remained within the normal ranges. Individual subjects had sporadic elevations of T<sub>4</sub>. No new cases of hypothyroidism in individual subjects were observed during the study.

**Liver Function.** Several subjects had elevations in AST values prior to treatment with [redacted] rhGH that persisted during the study and were not thought to be associated with administration of [redacted] rhGH. Mean values of ALT and GGT remained within the normal

ranges. One subject (10-005) had elevated AST and bilirubin levels prior to treatment with [redacted] rhGH that resolved without intervention.

#### b. Anti-GH Antibodies

Seventeen of the 34 subjects had a positive titer during the combined study period, including 1 CT subject who had a positive titer prior to treatment with [redacted] rhGH. The maximum titer for any subject was 2.6. Historically, antibodies with titers of this level have not been associated with growth attenuation.

One CT subject who had a positive titer at baseline in Study [redacted] 03-002 prior to treatment with [redacted] rhGH became negative after 9 months. A second CT subject became positive at the Month 6 visit, as did a third CT subject at the Month 9 visit.

All naive subjects had negative antibody titers prior to treatment with [redacted] rhGH. Fourteen naive subjects developed a positive titer. Titers for 5 of these subjects became negative after 3-6 months and 9 remained positive.

Six subjects, 1 CT subject who had a positive titer at baseline and 5 naive who developed a positive titer during treatment with [redacted] rhGH, had negative titers after varying periods of time.

All serum samples with positive antibody titers ( $\geq 1.0$ ) were assayed for binding capacity. No subject had a binding capacity of  $\geq 2$  mg/L and most values (38 of 46) were below the assay limit [redacted]

Of the 3 CT subjects with a total of 8 positive antibody titers, there was only one binding capacity value above assay limits. This occurred for 1 subject at baseline, prior to treatment with [redacted] rhGH. The binding capacity value was 0.075 mg/L and decreased below assay limits at Months 3 and 6.

Of the 14 naive subjects with a total of 38 positive antibody titers from Month 3 through Month 18, there were only 3 subjects with a total of seven binding capacity values above assay limits. These 3 subjects were dosed at 0.75 2x/month. The first subject had binding capacity values below assay limits at Months 3 and 12, and values of 0.049 and 0.036 mg/L at Months 6 and 9, respectively. The second subject had binding capacity values below assay limits at Months 3, 6, and 12, and values of 0.031 and 0.061 mg/L at Months 9 and 15, respectively. The third subject had binding capacity values below assay limits at Month 6 and values of 0.040, 0.050, and 0.061 mg/L at Months 3, 9, and 12 respectively.

As noted above, there was no growth attenuation in any subject due to antibody formation. These data suggest that binding capacities were not associated with attenuation of growth response.

#### c. GH, IGF-I, IGFBP-3, and GHBP Results

GH levels were elevated at 24 hours following administration of [redacted] rhGH. Trough levels for GH drawn predose at the clinic visits every 3 months showed a return to near predosing levels in both treatment arms.

At Month 12, the mean ( $\pm$ SD) GH trough concentration for 15 subjects with levels measured at both baseline and Month 12 increased from  $1.3 \pm 1.5$  to  $2.6 \pm 3.3$  ng/mL. Further review showed that 1 subject had a GH level of 11.0 ng/mL at his final visit. Although he was to restart daily rhGH treatment, it is not clear whether the subject had already begun daily injections prior to the sample being drawn. Trough GH levels for the other 14 subjects were  $1.2 \pm 1.5$  ng/mL at baseline and  $1.9 \pm 2.4$  ng/mL at Month 12.

Trough levels of IGF-I increased slightly with treatment. A greater response was seen in subjects receiving 0.75 2x/month compared with those receiving 1.5 1x/month. After 12 months of treatment, mean ( $\pm$ SD) levels for 27 subjects had increased from  $94.7 \pm 84.8$  ng/mL to

118.3±114 ng/mL. One subject, a CT male in the 0.75 2x/month group with Tanner Stage 2 pubertal development at baseline, had an elevated IGF-I level at baseline (365 ng/mL) that persisted throughout the study. The trough IGF-I sample for this subject at Month 12 was 555 ng/mL. With the exception of this subject, trough samples did not exceed the normal range for age. Trough levels of IGFBP-3 did not change with treatment. GHBP levels declined over time.

### Vital Signs and Physical Findings

There were no clinically significant changes in vital signs or physical examination findings except as discussed in the report of adverse events.

## **EFFICACY RESULTS**

### Primary Efficacy Results

**CT Subjects.** The mean prestudy growth rate for 10 subjects who completed 12 months in combined Studies [redacted] 03-002 and [redacted] 03-003, including 5 subjects who were treated with 0.75q4 for 7–10 months was 7.1±2.3 cm/yr (range [redacted] cm/yr). The mean 12-month growth rate was 4.8±2.6 cm/yr (range [redacted] cm/yr). The mean prestudy growth rate for 5 subjects with 12-month data who did not change dose was 6.5±1.6 cm/yr (range [redacted] cm/yr). After 12 months, the mean growth rate for these 5 subjects was 4.5±2.2 cm/yr (range [redacted] cm/yr).

**Naive Subjects.** The mean prestudy growth rate for 12 naive subjects with prestudy and 12-month growth rates available, including 3 subjects who had received 0.75q4 in Study [redacted] 03-002 for 7–9 months, was 5.8±1.5 cm/yr (range [redacted] cm/yr). After 12 months of treatment, the mean growth rate was 8.5±1.9 cm/yr (range [redacted] cm/yr). The mean prestudy growth rate for 9 naive subjects who did not change doses was 5.7±1.4 cm/yr (range, [redacted] cm/yr). After 12 months, the mean growth rate increased to 8.8±1.9 cm/yr (range, [redacted] cm/yr).

Similar results were seen for subjects without sufficient height data available for calculation of the prestudy growth rates. The mean 12-month growth rate for 12 subjects who did not change dose groups, including 3 subjects without prestudy growth rate data was 8.1±2.4 cm/yr (range, [redacted] cm/yr). The mean 12-month growth rate for all naive subjects with 12-month growth rates available, including an additional 5 subjects without prestudy growth rate data was 7.9±2.2 cm/yr (range [redacted] cm/yr).

### Secondary Efficacy Results

#### **a. Standardized Height**

**CT Subjects.** The mean prestudy height SD score for 10 subjects who completed 12 months in the combined study period, including those who changed dose, was -1.1±1.3. After 12 months the height SD score was -1.2±1.2. The mean prestudy SD score for 5 CT subjects who did not change dose was -1.6±1.4 prior to any treatment with [redacted] rhGH. The mean height SD score after 12 months was similar at -1.7±1.3. Thus, standardized height was maintained during 1 year of treatment with [redacted] rhGH in CT subjects.

**Naive Subjects.** The mean baseline height SD score for 17 subjects who completed 12 months in the combined study period, including 5 subjects who changed dose after 7–9 months, was well below the normal range at -3.3±0.7. After 12 months of treatment, the mean height SD score had increased by 0.5±0.4. The mean baseline height SD score was -3.4±0.8 for the 12 naive subjects who did not change dose groups and who completed 12 months of treatment with [redacted] rhGH. The mean height SD score increased by 0.6±0.4 after 12 months of treatment, demonstrating improvement in standardized height and suggest continued catch-up growth beyond 6 months in these subjects treated with [redacted] rhGH.

**b. Bone Age**

Data are presented for 4 CT subjects and 7 naive subjects for whom bone ages were available at baseline and 12 months (i.e., subjects who did not change dose groups).

**CT Subjects.** During 12 months of treatment, the mean change in bone age for 4 CT subjects was  $0.9 \pm 0.3$  years.

**Naive Subjects.** Bone age was markedly delayed relative to chronological age for naive subjects at baseline prior to treatment with [redacted] rhGH. During 12 months of treatment, the mean change in bone age was  $1.2 \pm 0.3$  years. This change in bone age was appropriate for the degree of catch-up growth. Therefore, the improvements in growth noted above were achieved without undue advancement in skeletal maturation.

**CONCLUSIONS**

These data demonstrate that [redacted] rhGH is safe in the treatment of childhood GHD for up to 18 months.

No clinically significant study drug-related adverse events or laboratory changes were identified. Injection-site events occurred, leading to discontinuation from the study for 1 subject, although injections were generally well tolerated when given by parents at home.

Treatment with [redacted] rhGH demonstrated improvement in growth rates in naive subjects, resulting in catch-up growth. In subjects who had received previous treatment with daily rhGH (CT subjects), the growth rates were generally less than had been seen with their prior therapy; however, there was no change in standardized height, indicating that growth appropriate for age was maintained.

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### Appendix 3. Assay performance

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#### Appendix 4. Formulation

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Test Material<sup>a</sup> Summary for Nutropin Depot ( ) rhGH)  
Clinical Pharmacokinetic Studies

Study	Nutropin Depot Lot No.	Diluent Lot No.
03-001	0137, 0217	0218b
03-002	0217, 0354, 0356, 0381, 0389, 0410, 0490, 0493	0218b, A01A7, D03A7, J05A6 <sup>a</sup>
03-004	0494, 0495, 0497, 0502	D03A7
03-003	0354, 0356, 0381, 0389, 0410, 0490, 0493, 0494, 0497	D03A7
<u>Major Formulation Components<sup>b</sup></u>		<u>Nominal Composition</u>
Nutropin Depot	rhGH Zinc acetate Zinc carbonate PLG polymer	)
Diluent for Nutropin Depot (per mL)	Carboxymethylcellulose sodium Polysorbate 20 Sodium chloride Water for Injection	

PLG = polylactide-coglycolide polymer.

<sup>a</sup> Formulation components: ( ); polysorbate 20: ( ); sodium chloride (9.0 mg), Water for Injection: ( )

<sup>b</sup> Major components of the formulation and diluent are the same for the lots used except for the ( ) diluent used in Study 03-002. The data from the subjects receiving the ( ) vehicle were excluded for PK/PD analyses.

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### Scale of Manufacture of Test Material

Study	Lot	Scale
03-001	0137	CS
	0217	CS
03-002	0217	CS
	0354	SS
	0356	SS
	0381	SS
	0389	SS
	0410	SS
	0490	IS
	0493	IS
03-004	0494	IS
	0495	IS
	0497	IS
	0502	IS
03-003	0354	SS
	0356	SS
	0381	SS
	0389	SS
	0410	SS
	0490	IS
	0493	IS
	0494	IS
	0497	IS

CS= Clinical scale.

SS= Small scale.

IS= Intermediate scale.