

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 19-640/S-033

Trade Name: Humatrope

Generic Name: Somatropin, rDNA origin for injection

Sponsor: Eli Lilly and Company

Approval Date: July 25, 2003

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 19-640S-033

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	X
Approvable Letter	
Final Printed Labeling	X
Medical Review(s)	X
Chemistry Review(s)	X
EA/FONSI	X
Pharmacology Review(s)	
Statistical Review(s)	X
Microbiology Review(s)	
Clinical Pharmacology/ Biopharmaceutics Review(s)	
Administrative and Correspondence Document(s)	X

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 19-640/S-033

APPROVAL LETTER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 19-640/S-033

Eli Lilly and Company
Attention: Jeffery T. Fayerman, PhD
Senior Regulatory Research Scientist, US Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Fayerman:

Please refer to your new drug application (NDA) dated and received on September 26, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Humatrope (somatropin [rDNA origin] for injection) 5, 6, 12, 24 mg vials and cartridges.

We acknowledge receipt of your submissions dated January 6, February 17, March 5, April 2, June 17 and 19, and July 14 and 21, 2003.

This supplemental new drug application provides for the use of Humatrope for the long-term treatment of idiopathic short stature, also called non-growth hormone-deficient short stature, defined by height $SDS < -2.25$, and associated with growth rates unlikely to permit attainment of adult height in the normal range, in pediatric patients whose epiphyses are not closed and for whom diagnostic evaluation excludes other causes associated with short stature that should be observed or treated by other means.

We completed our review of this application, as amended and it is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling (package insert submitted July 21, 2003). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved NDA 19-640/S-033.**" Approval of this submission by FDA is not required before the labeling is used.

We encourage the continuation of your ongoing global postmarketing observational research program, entitled "The Genetics and Neuroendocrinology of Short Stature International Study (GeNeSIS-Protocol GDFC). GeNeSIS includes a neoplasia substudy protocol and a growth-predictors substudy protocol as described in your submissions dated September 26, 2002 and March 25 and June 19, 2003. The goal of GeNeSIS is to evaluate further the long-term efficacy and safety of Humatrope treatment

in pediatric patients receiving the drug for short stature, including idiopathic short stature. This program gathers information on adverse event frequencies by documenting, at each visit, the presence or absence of protocol-identified adverse events that have been associated with growth hormone use. Additionally, the program collects auxological data and laboratory data on carbohydrate metabolism, thyroid function, as well as IGF-1 and IGF binding protein-3 (IGFBP-3) levels, whenever these tests are obtained by the patient's physician. Updated GeNeSIS information will be reported to the FDA on a regular basis. Submit the protocols related to GeNeSIS to your IND for this product. We also remind you of the risk management plan related to the use of Humatrope for idiopathic short stature that you plan to implement as outlined in your submissions dated September 26, 2002 and March 25 and June 19, 2003. Elements of that plan include:

- Restrictive Humatrope labeling for idiopathic short stature
- Physician education
- Limited marketing to (pediatric) endocrinologists
- Limited sales force
- No direct-to-consumer advertising
- Controlled distribution process

We request that you provide FDA with information about any changes to this plan at the time the changes are made and periodically report to FDA data on the extent of use of Humatrope for idiopathic short stature.

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Monika Johnson, Regulatory Project Manager, at (301) 827-9087.

Sincerely,

{See appended electronic signature page}

David G. Orloff, M.D.
Director
Division of Metabolic and Endocrine Drug
Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation Research

Enclosure: Draft package insert

A4.0 NL1641 AMP

HUMATROPE[®]
SOMATROPIN (rDNA ORIGIN) FOR INJECTION
VIALS
and
CARTRIDGES FOR USE WITH THE

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

David Orloff
7/25/03 04:14:42 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 19-640/S-033

APPROVED LABELING

HumatroPen™ INJECTION DEVICE

DESCRIPTION

Humatrope® (Somatotropin, rDNA Origin, for Injection) is a polypeptide hormone of recombinant DNA origin. Humatrope has 191 amino acid residues and a molecular weight of about 22,125 daltons. The amino acid sequence of the product is identical to that of human growth hormone of pituitary origin. Humatrope is synthesized in a strain of *Escherichia coli* that has been modified by the addition of the gene for human growth hormone.

Humatrope is a sterile, white, lyophilized powder intended for subcutaneous or intramuscular administration after reconstitution. Humatrope is a highly purified preparation. Phosphoric acid and/or sodium hydroxide may have been added to adjust the pH. Reconstituted solutions have a pH of approximately 7.5. This product is oxygen sensitive.

VIAL — Each vial of Humatrope contains 5 mg somatotropin (15 IU or 225 nanomoles); 25 mg mannitol; 5 mg glycine; and 1.13 mg dibasic sodium phosphate. Each vial is supplied in a combination package with an accompanying 5-mL vial of diluting solution. The diluent contains Water for Injection with 0.3% Metacresol as a preservative and 1.7% glycerin.

CARTRIDGE — The cartridges of somatotropin contain either 6 mg (18 IU), 12 mg (36 IU), or 24 mg (72 IU) of somatotropin. The 6, 12, and 24 mg cartridges contain respectively: mannitol 18, 36, and 72 mg; glycine 6, 12, and 24 mg; dibasic sodium phosphate 1.36, 2.72, and 5.43 mg. Each cartridge is supplied in a combination package with an accompanying syringe containing approximately 3 mL of diluting solution. The diluent contains Water for Injection; 0.3% Metacresol as a preservative; and 1.7%, 0.29%, and 0.29% glycerin in the 6, 12, and 24 mg cartridges, respectively.

CLINICAL PHARMACOLOGY

General

Linear Growth — Humatrope stimulates linear growth in pediatric patients who lack adequate normal endogenous growth hormone. In vitro, preclinical, and clinical testing have demonstrated that Humatrope is therapeutically equivalent to human growth hormone of pituitary origin and achieves equivalent pharmacokinetic profiles in normal adults. Treatment of growth hormone-deficient pediatric patients and patients with Turner syndrome with Humatrope produces increased growth rate and IGF-I (Insulin-like Growth Factor-I/Somatomedin-C) concentrations similar to those seen after therapy with human growth hormone of pituitary origin.

In addition, the following actions have been demonstrated for Humatrope and/or human growth hormone of pituitary origin.

A. Tissue Growth — 1. **Skeletal Growth**: Humatrope stimulates skeletal growth in pediatric patients with growth hormone deficiency. The measurable increase in body length after administration of either Humatrope or human growth hormone of pituitary origin results from an effect on the growth plates of long bones. Concentrations of IGF-I, which may play a role in skeletal growth, are low in the serum of growth hormone-deficient pediatric patients but increase during treatment with Humatrope. Elevations in mean serum alkaline phosphatase concentrations are also seen. 2. **Cell Growth**: It has been shown that there are fewer skeletal muscle cells in short-statured pediatric patients who lack endogenous growth hormone as compared with normal pediatric populations. Treatment with human growth hormone of pituitary origin results in an increase in both the number and size of muscle cells.

B. Protein Metabolism — Linear growth is facilitated in part by increased cellular protein synthesis. Nitrogen retention, as demonstrated by decreased urinary nitrogen excretion and serum urea nitrogen, follows the initiation of therapy with human growth hormone of pituitary origin. Treatment with Humatrope results in a similar decrease in serum urea nitrogen.

C. Carbohydrate Metabolism — Pediatric patients with hypopituitarism sometimes experience fasting hypoglycemia that is improved by treatment with Humatrope. Large doses of human growth hormone may impair glucose tolerance. Untreated patients with Turner syndrome have an increased incidence of glucose intolerance. Administration of human growth hormone to normal adults or patients with Turner syndrome resulted in increases in mean serum fasting and postprandial insulin levels although mean values remained in the normal range. In addition, mean fasting and postprandial glucose and hemoglobin A_{1c} levels remained in the normal range.

D. Lipid Metabolism — In growth hormone-deficient patients, administration of human growth hormone of pituitary origin has resulted in lipid mobilization, reduction in body fat stores, and increased plasma fatty acids.

E. Mineral Metabolism — Retention of sodium, potassium, and phosphorus is induced by human growth hormone of pituitary origin. Serum concentrations of inorganic phosphate increased in patients with growth hormone deficiency after therapy with Humatrope or human growth hormone of pituitary origin. Serum calcium is not significantly altered in patients treated with either human growth hormone of pituitary origin or Humatrope.

Pharmacokinetics

Absorption — Humatrope has been studied following intramuscular, subcutaneous, and intravenous administration in adult volunteers. The absolute bioavailability of somatropin is 75% and 63% after subcutaneous and intramuscular administration, respectively.

Distribution — The volume of distribution of somatropin after intravenous injection is about 0.07 L/kg.

Metabolism — Extensive metabolism studies have not been conducted. The metabolic fate of somatropin involves classical protein catabolism in both the liver and kidneys. In renal cells, at least a portion of the breakdown products of growth hormone is returned to the systemic circulation. In normal volunteers, mean clearance is 0.14 L/hr/kg. The mean half-life of intravenous somatropin is 0.36 hours, whereas subcutaneously and intramuscularly administered somatropin have mean half-lives of 3.8 and 4.9 hours, respectively. The longer half-life observed after subcutaneous or intramuscular administration is due to slow absorption from the injection site.

Excretion — Urinary excretion of intact Humatrope has not been measured. Small amounts of somatropin have been detected in the urine of pediatric patients following replacement therapy.

Special Populations

Geriatric — The pharmacokinetics of Humatrope has not been studied in patients greater than 65 years of age.

Pediatric — The pharmacokinetics of Humatrope in pediatric patients is similar to adults.

Gender — No studies have been performed with Humatrope. The available literature indicates that the pharmacokinetics of growth hormone is similar in both men and women.

Race — No data are available.

Renal, Hepatic insufficiency — No studies have been performed with Humatrope.

Table 1
Summary of Somatropin Parameters in the Normal Population

	C_{max} (ng/mL)	$t_{1/2}$ (hr)	$AUC_{0-\infty}$ (ng•hr/mL)	Cl _s (L/kg•hr)	$V\beta$ (L/kg)
0.02 mg (0.05 IU*)/kg					
iv					
MEAN	415	0.363	156	0.135	0.0703
SD	75	0.053	33	0.029	0.0173
0.1 mg (0.27 IU*)/kg					
im					
MEAN	53.2	4.93	495	0.215	1.55
SD	25.9	2.66	106	0.047	0.91
0.1 mg (0.27 IU*)/kg					
sc					
MEAN	63.3	3.81	585	0.179	0.957
SD	18.2	1.40	90	0.028	0.301

Abbreviations: C_{max} =maximum concentration; $t_{1/2}$ =half-life; $AUC_{0-\infty}$ =area under the curve; Cl_s=systemic clearance; $V\beta$ =volume distribution; iv=intravenous; SD=standard deviation; im=intramuscular; sc=subcutaneous.

* Based on previous International Standard of 2.7 IU=1 mg.

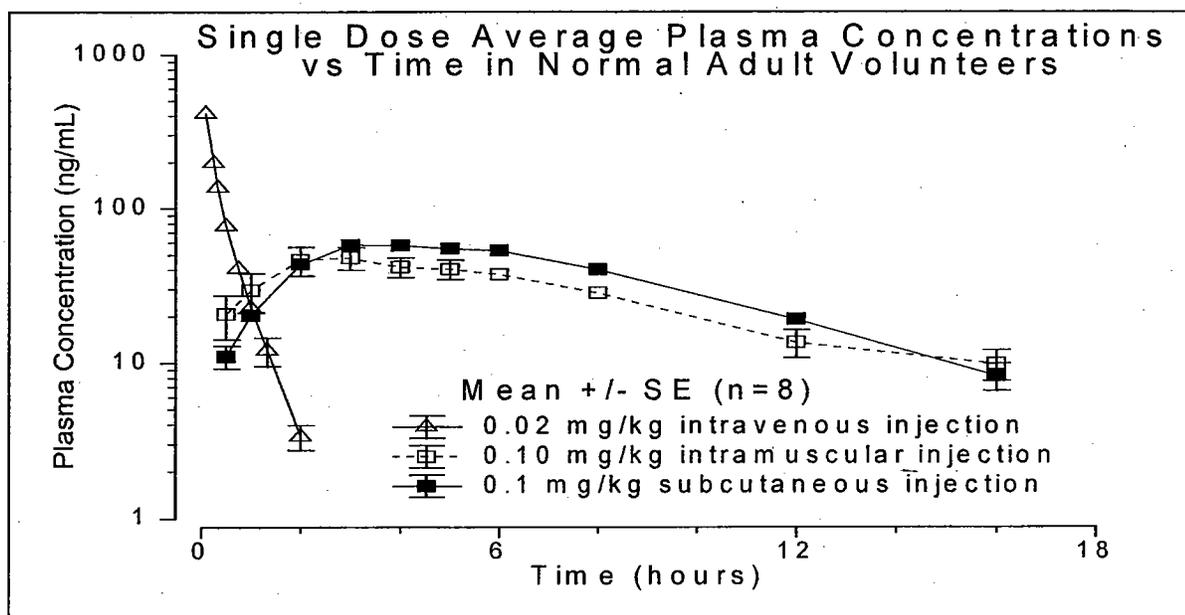


Figure 1

CLINICAL TRIALS

Effects of Humatrope Treatment in Adults with Growth Hormone Deficiency

Two multicenter trials in adult-onset growth hormone deficiency (n=98) and two studies in childhood-onset growth hormone deficiency (n=67) were designed to assess the effects of replacement therapy with Humatrope. The primary efficacy measures were body composition (lean body mass and fat mass), lipid parameters, and the Nottingham Health Profile. The Nottingham Health Profile is a general health-related quality of life questionnaire. These four studies each included a 6-month randomized, blinded, placebo-controlled phase followed by 12 months of open-label therapy for all patients. The Humatrope dosages for all studies were identical: 1 month of therapy at

0.00625 mg/kg/day followed by the proposed maintenance dose of 0.0125 mg/kg/day. Adult-onset patients and childhood-onset patients differed by diagnosis (organic vs. idiopathic pituitary disease), body size (normal vs. small for mean height and weight), and age (mean=44 vs. 29 years). Lean body mass was determined by bioelectrical impedance analysis (BIA), validated with potassium 40. Body fat was assessed by BIA and sum of skinfold thickness. Lipid subfractions were analyzed by standard assay methods in a central laboratory.

Humatrope-treated adult-onset patients, as compared to placebo, experienced an increase in lean body mass (2.59 vs. -0.22 kg, $p < 0.001$) and a decrease in body fat (-3.27 vs. 0.56 kg, $p < 0.001$). Similar changes were seen in childhood-onset growth hormone-deficient patients. These significant changes in lean body mass persisted throughout the 18-month period as compared to baseline for both groups, and for fat mass in the childhood-onset group. Total cholesterol decreased short-term (first 3 months) although the changes did not persist. However, the low HDL cholesterol levels observed at baseline (mean=30.1 mg/mL and 33.9 mg/mL in adult-onset and childhood-onset patients) normalized by the end of 18 months of therapy (a change of 13.7 and 11.1 mg/dL for the adult-onset and childhood-onset groups, $p < 0.001$). Adult-onset patients reported significant improvements as compared to placebo in the following two of six possible health-related domains: physical mobility and social isolation (Table 2). Patients with childhood-onset disease failed to demonstrate improvements in Nottingham Health Profile outcomes.

Two additional studies on the effect of Humatrope on exercise capacity were also conducted. Improved physical function was documented by increased exercise capacity (VO_2 max, $p < 0.005$) and work performance (Watts, $p < 0.01$) (J Clin Endocrinol Metab 1995; 80:552-557).

Table 2
Changes^a in Nottingham Health Profile Scores^b in Adult-Onset Growth Hormone-Deficient Patients

Outcome Measure	Placebo (6 Months)	Humatrope Therapy (6 Months)	Significance
Energy level	-11.4	-15.5	NS
Physical mobility	-3.1	-10.5	$p < 0.01$
Social isolation	0.5	-4.7	$p < 0.01$
Emotional reactions	-4.5	-5.4	NS
Sleep	-6.4	-3.7	NS
Pain	-2.8	-2.9	NS

^a An improvement in score is indicated by a more negative change in the score.

^b To account for multiple analyses, appropriate statistical methods were applied and the required level of significance is 0.01.

NS=not significant.

Effects of Growth Hormone Treatment in Patients with Turner Syndrome

One long-term, randomized, open-label multicenter concurrently controlled study, two long-term, open-label multicenter, historically controlled studies and one long-term, randomized, dose-response study were conducted to evaluate the efficacy of growth hormone for the treatment of patients with short stature due to Turner syndrome.

In the randomized study, GDCT, comparing growth hormone-treated patients to a concurrent control group who received no growth hormone, the growth hormone-treated patients who received a dose of 0.3 mg/kg/wk given 6 times per week from a mean age of 11.7 years for a mean duration of 4.7 years attained a mean near final height of 146.0 ± 6.2 cm ($n=27$, mean \pm SD) as compared to the control

group who attained a near final height of 142.1 ± 4.8 cm (n=19). By analysis of covariance*, the effect of growth hormone therapy was a mean height increase of 5.4 cm (p=0.001).

In two of the studies (85-023 and 85-044), the effect of long-term growth hormone treatment (0.375 mg/kg/wk given either 3 times per week or daily) on adult height was determined by comparing adult heights in the treated patients with those of age-matched historical controls with Turner syndrome who never received any growth-promoting therapy. The greatest improvement in adult height was observed in patients who received early growth hormone treatment and estrogen after age 14 years. In Study 85-023, this resulted in a mean adult height gain of 7.4 cm (mean duration of GH therapy of 7.6 years) vs. matched historical controls by analysis of covariance.

In Study 85-044, patients treated with early growth hormone therapy were randomized to receive estrogen replacement therapy (conjugated estrogens, 0.3 mg escalating to 0.625 mg daily) at either age 12 or 15 years. Compared with matched historical controls, early GH therapy (mean duration of GH therapy 5.6 years) combined with estrogen replacement at age 12 years resulted in an adult height gain of 5.9 cm (n=26), whereas patients who initiated estrogen at age 15 years (mean duration of GH therapy 6.1 years) had a mean adult height gain of 8.3 cm (n=29). Patients who initiated GH therapy after age 11 (mean age 12.7 years; mean duration of GH therapy 3.8 years) had a mean adult height gain of 5.0 cm (n=51).

In a randomized blinded dose-response study, GDCI, patients were treated from a mean age of 11.1 years for a mean duration of 5.3 years with a weekly dose of either 0.27 mg/kg or 0.36 mg/kg administered 3 or 6 times weekly. The mean near final height of patients receiving growth hormone was 148.7 ± 6.5 cm (n=31). When compared to historical control data, the mean gain in adult height was approximately 5 cm.

In some studies, Turner syndrome patients (n=181) treated to final adult height achieved statistically significant average height gains ranging from 5.0 to 8.3 cm.

Table 3
Summary Table of Efficacy Results

Study/ Group	Study Design ^a	N at Adult Height	GH Age (yr)	Estrogen Age (yr)	GH Duration (yr)	Adult Height Gain (cm) ^b
GDCT	RCT	27	11.7	13	4.7	5.4
85-023	MHT	17	9.1	15.2	7.6	7.4
85-044:	A*	29	9.4	15	6.1	8.3
	B*	26	9.6	12.3	5.6	5.9
	C*	51	12.7	13.7	3.8	5
GDCI	RDT	31	11.1	8-13.5	5.3	~5 ^c

^a RCT: randomized controlled trial; MHT: matched historical controlled trial; RDT: randomized dose-response trial.

^b Analysis of covariance vs. controls.

^c Compared with historical data.

* A: GH age <11 yr, estrogen age 15 yr.

B: GH age <11 yr, estrogen age 12 yr.

C: GH age >11 yr, estrogen at month 12.

* Analysis of covariance includes adjustments for baseline height relative to age and for mid-parental height.

Effect of Humatrope treatment in pediatric patients with idiopathic short stature

Two randomized, multicenter trials, 1 placebo-controlled and 1 dose-response, were conducted in pediatric patients with idiopathic short stature, also called non-growth hormone-deficient short stature. The diagnosis of idiopathic short stature was made after excluding other known causes of short stature,

as well as growth hormone deficiency. Limited safety and efficacy data are available below the age of 7 years. No specific studies have been conducted in pediatric patients with familial short stature or who were born small for gestational age (SGA).

The placebo-controlled study enrolled 71 pediatric patients (55 males, 16 females) 9 to 15 years old (mean age 12.38 ± 1.51 years), with short stature, 68 of whom received study drug. Patients were predominately Tanner I (45.1%) and Tanner II (46.5%) at baseline.

In this double-blind trial, patients received subcutaneous injections of either Humatrope 0.222 mg/kg/wk or placebo. Study drug was given in divided doses 3 times per week until height velocity decreased to ≤ 1.5 cm/year ("final height"). Thirty-three subjects (22 Humatrope, 11 placebo) had final height measurements after a mean treatment duration of 4.4 years (range 0.11-9.08 years).

The Humatrope group achieved a mean final height Standard Deviation Score (SDS) of -1.8 (Table 4). Placebo-treated patients had a mean final height SDS of -2.3 (mean treatment difference = 0.51 , $p=0.017$). Height gain across the duration of the study and final height SDS minus baseline predicted height SDS were also significantly greater in Humatrope-treated patients than in placebo-treated patients (Table 4 and 5). In addition, the number of patients who achieved a final height above the 5th percentile of the general population for age and sex was significantly greater in the Humatrope group than the placebo group (41% vs. 0%, $p<0.05$), as was the number of patients who gained at least 1 SDS unit in height across the duration of the study (50% vs. 0%, $p<0.05$).

Table 4
Baseline Height Characteristics and Effect of Humatrope on Final Height^a

	Humatrope (n=22) Mean (SD)	Placebo (n=11) Mean (SD)	Treatment Effect Mean (95% CI)	p-value
Baseline height SDS	-2.7 (0.6)	-2.75 (0.6)		0.77
BPH SDS	-2.1 (0.7)	-2.3 (0.8)		0.53
Final height SDS ^b	-1.8 (0.8)	-2.3 (0.6)	0.51 (0.10, 0.92)	0.017
FH SDS - baseline height SDS	0.9 (0.7)	0.4 (0.2)	0.51 (0.04, 0.97)	0.034
FH SDS - BPH SDS	0.3 (0.6)	-0.1 (0.6)	0.46 (0.02, 0.89)	0.043

^a For final height population.

^b Between-group comparison was performed using analysis of covariance with baseline predicted height SDS as the covariate. Treatment effect is expressed as least squares mean (95% CI).

Abbreviations: FH = final height. SDS = standard deviation score. BPH = baseline predicted height. CI = confidence interval.

The dose-response study included 239 pediatric patients (158 males, 81 females), 5 to 15 years old, (mean age 9.8 ± 2.3 years). Mean baseline characteristics included: a height SDS of $-3.21 (\pm 0.70)$, a predicted adult height SDS of $-2.63 (\pm 1.08)$, and a height velocity SDS of $-1.09 (\pm 1.15)$. All but 3 patients were Tanner I. Patients were randomized to one of three Humatrope treatment groups: 0.24 mg/kg/wk; 0.24 mg/kg/wk for 1 year, followed by 0.37 mg/kg/wk; and 0.37 mg/kg/wk.

The primary hypothesis of this study was that treatment with Humatrope would increase height velocity during the first 2 years of therapy in a dose-dependent manner. Additionally, after completing the initial 2-year dose-response phase of the study, 50 patients were followed to final height.

Patients receiving 0.37 mg/kg/wk had a significantly greater increase in mean height velocity after 2 years of treatment than patients receiving 0.24 mg/kg/wk (4.04 vs. 3.27 cm/year, $p=0.003$). The mean difference between final height and baseline predicted height was 7.2 cm for patients receiving 0.37 mg/kg/wk and 5.4 cm for patients receiving 0.24 mg/kg/wk (Table 5). While no patient had height

above the 5th percentile in any dose group at baseline, 82% of the patients receiving 0.37 mg/kg/wk and 47% of the patients receiving 0.24 mg/kg/wk achieved a final height above the 5th percentile of the general population height standards (p=NS).

Table 5
Final Height Minus Baseline Predicted Height: Idiopathic Short Stature Trials

	Placebo-controlled Trial 3x per week dosing		Dose Response Trial 6x per week dosing		
	Placebo (n=10)	Humatrope 0.22 mg/kg (n=22)	Humatrope 0.24 mg/kg (n=13)	Humatrope 0.24/0.37 mg/kg (n=13)	Humatrope 0.37 mg/kg (n=13)
FH – Baseline PH Mean cm (95% CI)	-0.7 (-3.6, 2.3)	+2.2 (0.4, 3.9)	+5.4 (2.8, 7.9)	+6.7 (4.1, 9.2)	+7.2 (4.6, 9.8)
Mean inches (95% CI)	-0.3 (-1.4, 0.9)	+0.8 (0.2, 1.5)	+2.1 (1.1, 3.1)	+2.6 (1.6, 3.6)	+2.8 (1.8, 3.9)

Abbreviations: PH= predicted height; FH=final height; CI = confidence interval

INDICATIONS AND USAGE

Pediatric Patients — Humatrope is indicated for the long-term treatment of pediatric patients who have growth failure due to an inadequate secretion of normal endogenous growth hormone.

Humatrope is indicated for the treatment of short stature associated with Turner syndrome in patients whose epiphyses are not closed.

Humatrope is indicated for the long-term treatment of idiopathic short stature, also called non-growth hormone-deficient short stature, defined by height SDS ≤ -2.25 , and associated with growth rates unlikely to permit attainment of adult height in the normal range, in pediatric patients whose epiphyses are not closed and for whom diagnostic evaluation excludes other causes associated with short stature that should be observed or treated by other means.

Adult Patients — Humatrope is indicated for replacement of endogenous growth hormone in adults with growth hormone deficiency who meet either of the following two criteria:

1. Adult Onset: Patients who have growth hormone deficiency either alone, or with multiple hormone deficiencies (hypopituitarism), as a result of pituitary disease, hypothalamic disease, surgery, radiation therapy, or trauma;

or

2. Childhood Onset: Patients who were growth hormone-deficient during childhood who have growth hormone deficiency confirmed as an adult before replacement therapy with Humatrope is started.

CONTRAINDICATIONS

Humatrope should not be used for growth promotion in pediatric patients with closed epiphyses.

Humatrope should not be used or should be discontinued when there is any evidence of active malignancy. Anti-malignancy treatment must be complete with evidence of remission prior to the institution of therapy.

Humatrope should **not** be reconstituted with the supplied Diluent for Humatrope for use by patients with a known sensitivity to either Metacresol or glycerin.

Growth hormone should not be initiated to treat patients with acute critical illness due to complications following open heart or abdominal surgery, multiple accidental trauma or to patients having acute respiratory failure. Two placebo-controlled clinical trials in non-growth hormone-deficient adult patients (n=522) with these conditions revealed a significant increase in mortality (41.9% vs. 19.3%) among somatropin-treated patients (doses 5.3 to 8 mg/day) compared to those receiving placebo (*see* WARNINGS).

WARNINGS

If sensitivity to the diluent should occur, the vials may be reconstituted with Bacteriostatic Water for Injection, USP or, Sterile Water for Injection, USP. When Humatrope is used with Bacteriostatic Water (Benzyl Alcohol preserved), the solution should be kept refrigerated at 2° to 8°C (36° to 46°F) and used within 14 days. **Benzyl alcohol as a preservative in Bacteriostatic Water for Injection, USP has been associated with toxicity in newborns.** When administering Humatrope to newborns, use the Humatrope diluent provided or if the patient is sensitive to the diluent, use Sterile Water for Injection, USP. When Humatrope is reconstituted with Sterile Water for Injection, USP in this manner, use only one dose per Humatrope vial and discard the unused portion. If the solution is not used immediately, it must be refrigerated [2° to 8°C (36° to 46°F)] and used within 24 hours.

Cartridges should be reconstituted only with the supplied diluent. Cartridges should not be reconstituted with the Diluent for Humatrope provided with Humatrope Vials, or with any other solution. Cartridges should not be used if the patient is allergic to Metacresol or glycerin.

See CONTRAINDICATIONS for information on increased mortality in patients with acute critical illnesses in intensive care units due to complications following open heart or abdominal surgery, multiple accidental trauma or with acute respiratory failure. The safety of continuing growth hormone treatment in patients receiving replacement doses for approved indications who concurrently develop these illnesses has not been established. Therefore, the potential benefit of treatment continuation with growth hormone in patients having acute critical illnesses should be weighed against the potential risk.

PRECAUTIONS

General — Therapy with Humatrope should be directed by physicians who are experienced in the diagnosis and management of patients with growth hormone deficiency, Turner syndrome, idiopathic short stature, or adult patients with either childhood-onset or adult-onset growth hormone deficiency.

Patients with preexisting tumors or with growth hormone deficiency secondary to an intracranial lesion should be examined routinely for progression or recurrence of the underlying disease process. In pediatric patients, clinical literature has demonstrated no relationship between somatropin replacement therapy and CNS tumor recurrence. In adults, it is unknown whether there is any relationship between somatropin replacement therapy and CNS tumor recurrence.

Patients should be monitored carefully for any malignant transformation of skin lesions.

For patients with diabetes mellitus, the insulin dose may require adjustment when somatropin therapy is instituted. Because human growth hormone may induce a state of insulin resistance, patients should be observed for evidence of glucose intolerance. Patients with diabetes or glucose intolerance should be monitored closely during somatropin therapy.

In patients with hypopituitarism (multiple hormonal deficiencies) standard hormonal replacement therapy should be monitored closely when somatropin therapy is administered. Hypothyroidism may develop during treatment with somatropin and inadequate treatment of hypothyroidism may prevent optimal response to somatropin.

Pediatric Patients (see General Precautions) — Pediatric patients with endocrine disorders, including growth hormone deficiency, may develop slipped capital epiphyses more frequently. Any pediatric patient with the onset of a limp during growth hormone therapy should be evaluated.

Growth hormone has not been shown to increase the incidence of scoliosis. Progression of scoliosis can occur in children who experience rapid growth. Because growth hormone increases growth rate, patients with a history of scoliosis who are treated with growth hormone should be monitored for progression of scoliosis. Skeletal abnormalities including scoliosis are commonly seen in untreated Turner syndrome patients.

Patients with Turner syndrome should be evaluated carefully for otitis media and other ear disorders since these patients have an increased risk of ear or hearing disorders (*see Adverse Reactions*). Patients with Turner syndrome are at risk for cardiovascular disorders (e.g., stroke, aortic aneurysm, hypertension) and these conditions should be monitored closely.

Patients with Turner syndrome have an inherently increased risk of developing autoimmune thyroid disease. Therefore, patients should have periodic thyroid function tests and be treated as indicated (*see General Precautions*).

Intracranial hypertension (IH) with papilledema, visual changes, headache, nausea and/or vomiting has been reported in a small number of pediatric patients treated with growth hormone products. Symptoms usually occurred within the first 8 weeks of the initiation of growth hormone therapy. In all reported cases, IH-associated signs and symptoms resolved after termination of therapy or a reduction of the growth hormone dose. Funduscopic examination of patients is recommended at the initiation and periodically during the course of growth hormone therapy. Patients with Turner syndrome may be at increased risk for development of IH.

Adult Patients (see General Precautions) — Patients with epiphyseal closure who were treated with growth hormone replacement therapy in childhood should be re-evaluated according to the criteria in INDICATIONS AND USAGE before continuation of somatropin therapy at the reduced dose level recommended for growth hormone-deficient adults.

Experience with prolonged treatment in adults is limited.

Geriatric Use — The safety and effectiveness of Humatrope in patients aged 65 and over has not been evaluated in clinical studies. Elderly patients may be more sensitive to the action of Humatrope and may be more prone to develop adverse reactions.

Drug Interactions — Excessive glucocorticoid therapy may prevent optimal response to somatropin. If glucocorticoid replacement therapy is required, the glucocorticoid dosage and compliance should be monitored carefully to avoid either adrenal insufficiency or inhibition of growth promoting effects.

Limited published data indicate that growth hormone (GH) treatment increases cytochrome P450 (CP450) mediated antipyrine clearance in man. These data suggest that GH administration may alter the clearance of compounds known to be metabolized by CP450 liver enzymes (e.g., corticosteroids, sex steroids, anticonvulsants, cyclosporin). Careful monitoring is advisable when GH is administered in combination with other drugs known to be metabolized by CP450 liver enzymes.

Carcinogenesis, Mutagenesis, Impairment of Fertility — Long-term animal studies for carcinogenicity and impairment of fertility with this human growth hormone (Humatrope) have not been performed. There has been no evidence to date of Humatrope-induced mutagenicity.

Pregnancy — Pregnancy Category C — Animal reproduction studies have not been conducted with Humatrope. It is not known whether Humatrope can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Humatrope should be given to a pregnant woman only if clearly needed.

Nursing Mothers — There have been no studies conducted with Humatrope in nursing mothers. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Humatrope is administered to a nursing woman.

Information for Patients — Patients being treated with growth hormone and/or their parents should be informed of the potential risks and benefits associated with treatment. Instructions on appropriate use should be given, including a review of the contents of the patient information insert. This information is intended to aid in the safe and effective administration of the medication. It is not a disclosure of all possible adverse or intended effects.

Patients and/or parents should be thoroughly instructed in the importance of proper needle disposal. A puncture resistant container should be used for the disposal of used needles and/or syringes (consistent with applicable state requirements). Needles and syringes must not be reused (*see* Information for the Patient insert).

ADVERSE REACTIONS

Growth Hormone-Deficient Pediatric Patients

As with all protein pharmaceuticals, a small percentage of patients may develop antibodies to the protein. During the first 6 months of Humatrope therapy in 314 naive patients, only 1.6% developed specific antibodies to Humatrope (binding capacity ≥ 0.02 mg/L). None had antibody concentrations which exceeded 2 mg/L. Throughout 8 years of this same study, two patients (0.6%) had binding capacity > 2 mg/L. Neither patient demonstrated a decrease in growth velocity at or near the time of increased antibody production. It has been reported that growth attenuation from pituitary-derived growth hormone may occur when antibody concentrations are > 1.5 mg/L.

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

In studies with growth hormone-deficient pediatric patients, injection site pain was reported infrequently. A mild and transient edema, which appeared in 2.5% of patients, was observed early during the course of treatment.

Leukemia has been reported in a small number of pediatric patients who have been treated with growth hormone, including growth hormone of pituitary origin as well as of recombinant DNA origin (somatrem and somatropin). The relationship, if any, between leukemia and growth hormone therapy is uncertain.

Turner Syndrome Patients

In a randomized, concurrent controlled trial, there was a statistically significant increase in the occurrence of otitis media (43% vs. 26%), ear disorders (18% vs. 5%) and surgical procedures (45% vs. 27%) in patients receiving Humatrope compared with untreated control patients (Table 6). Other adverse events of special interest to Turner syndrome patients were not significantly different between treatment groups (Table 6). A similar increase in otitis media was observed in an 18-month placebo-controlled trial.

Table 6

Treatment-Emergent Events of Special Interest by Treatment Group in Turner Syndrome

Adverse Event	Overall	Treatment Group		Significance
		hGH ¹	Untreated ²	
Total Number of Patients	136	74	62	
Surgical procedure	50 (36.8%)	33 (44.6%)	17 (27.4%)	$p \leq 0.05$
Otitis media	48 (35.3%)	32 (43.2%)	16 (25.8%)	$p \leq 0.05$
Ear disorders	16 (11.8%)	13 (17.6%)	3 (4.8%)	$p \leq 0.05$
Bone disorder	13 (9.6%)	6 (8.1%)	7 (11.3%)	NS
Edema				

Conjunctival	1 (0.7%)	0	1 (1.6%)	NS
Non-specific	3 (2.2%)	2 (2.7%)	1 (1.6%)	NS
Facial	1 (0.7%)	1 (1.4%)	0	NS
Peripheral	6 (4.4%)	5 (6.8%)	1 (1.6%)	NS
Hyperglycemia	0	0	0	NS
Hypothyroidism	15 (11.0%)	10 (13.5%)	5 (8.1%)	NS
Increased nevi ³	10 (7.4%)	8 (10.8%)	2 (3.2%)	NS
Lymphedema	0	0	0	NS

¹ Dose=0.3 mg/kg/wk.

² Open-label study.

³ Includes any nevi coded to the following preferred terms: melanosis, skin hypertrophy, or skin benign neoplasm.

NS=not significant.

Patients with Idiopathic Short Stature

In the placebo-controlled study, the adverse events associated with Humatrope therapy were similar to those observed in other pediatric populations treated with Humatrope (Table 7). Mean serum glucose level did not change during Humatrope treatment. Mean fasting serum insulin levels increased 10% in the Humatrope treatment group at the end of treatment relative to baseline values but remained within the normal reference range. For the same duration of treatment the mean fasting serum insulin levels decreased by 2% in the placebo group. The incidence of above-range values for glucose, insulin, and HbA_{1c} were similar in the growth hormone and placebo-treated groups. No patient developed diabetes mellitus. Consistent with the known mechanism of growth hormone action, Humatrope-treated patients had greater mean increases, relative to baseline, in serum insulin-like growth factor-I (IGF-I) than placebo-treated patients at each study observation. However, there was no significant difference between the Humatrope and placebo treatment groups in the proportion of patients who had at least one serum IGF-I concentration more than 2.0 SD above the age- and gender-appropriate mean (Humatrope: 9 of 35 patients [26%]; placebo: 7 of 28 patients [25%]).

Table 7
Nonserious Clinically Significant Treatment-Emergent Adverse Events by Treatment Group in Idiopathic Short Stature

Adverse Event	Treatment Group	
	Humatrope	Placebo
Total Number of Patients	37	31
Scoliosis	7 (18.9%)	4 (12.9%)
Otitis media	6 (16.2%)	2 (6.5%)
Hyperlipidemia	3 (8.1%)	1 (3.2%)
Gynecomastia	2 (5.4%)	1 (3.2%)
Hypothyroidism	0	2 (6.5%)
Aching joints	0	1 (3.2%)
Hip pain	1 (2.7%)	0
Arthralgia	4 (10.8%)	1 (3.2%)
Arthrosis	4 (10.8%)	2 (6.5%)
Myalgia	9 (24.3%)	4 (12.9%)
Hypertension	1 (2.7%)	0

The adverse events observed in the dose-response study (239 patients treated for 2 years) did not indicate a pattern suggestive of a growth hormone dose effect. Among Humatrope dose groups, mean fasting blood glucose, mean glycosylated hemoglobin, and the incidence of elevated fasting blood

glucose concentrations were similar. One patient developed abnormalities of carbohydrate metabolism (glucose intolerance and high serum HbA_{1c}) on treatment.

Adult Patients — In clinical studies in which high doses of Humatrope were administered to healthy adult volunteers, the following events occurred infrequently: headache, localized muscle pain, weakness, mild hyperglycemia, and glucosuria.

In the first 6 months of controlled blinded trials during which patients received either Humatrope or placebo, adult-onset growth hormone-deficient adults who received Humatrope experienced a statistically significant increase in edema (Humatrope 17.3% vs. placebo 4.4%, $p=0.043$) and peripheral edema (11.5% vs. 0%, respectively, $p=0.017$). In patients with adult-onset growth hormone deficiency, edema, muscle pain, joint pain, and joint disorder were reported early in therapy and tended to be transient or responsive to dosage titration.

Two of 113 adult-onset patients developed carpal tunnel syndrome after beginning maintenance therapy without a low dose (0.00625 mg/kg/day) lead-in phase. Symptoms abated in these patients after dosage reduction.

All treatment-emergent adverse events with $\geq 5\%$ overall incidence during 12 or 18 months of replacement therapy with Humatrope are shown in Table 8 (adult-onset patients) and in Table 9 (childhood-onset patients).

Adult patients treated with Humatrope who had been diagnosed with growth hormone deficiency in childhood reported side effects less frequently than those with adult-onset growth hormone deficiency.

Table 8
Treatment-Emergent Adverse Events with $\geq 5\%$ Overall Incidence in Adult-Onset Growth Hormone-Deficient Patients Treated with Humatrope for 18 Months as Compared with 6-Month Placebo and 12-Month Humatrope Exposure

Adverse Event	18 Months Exposure [Placebo (6 Months)/hGH (12 Months)] (N=46)		18 Months hGH Exposure (N=52)	
	n	%	n	%
Edema ^a	7	15.2	11	21.2
Arthralgia	7	15.2	9	17.3
Paresthesia	6	13.0	9	17.3
Myalgia	6	13.0	7	13.5
Pain	6	13.0	7	13.5
Rhinitis	5	10.9	7	13.5
Peripheral edema ^b	8	17.4	6	11.5
Back pain	5	10.9	5	9.6
Headache	5	10.9	4	7.7
Hypertension	2	4.3	4	7.7
Acne	0	0	3	5.8
Joint disorder	1	2.2	3	5.8
Surgical procedure	1	2.2	3	5.8
Flu syndrome	3	6.5	2	3.9

Abbreviations: hGH=Humatrope; N=number of patients receiving treatment in the period stated; n=number of patients reporting each treatment-emergent adverse event.

^a $p=0.04$ as compared to placebo (6 months).

^b $p=0.02$ as compared to placebo (6 months).

Table 9

Treatment-Emergent Adverse Events with $\geq 5\%$ Overall Incidence in Childhood-Onset Growth Hormone-Deficient Patients Treated with Humatrope for 18 Months as Compared with 6-Month Placebo and 12-Month Humatrope Exposure

Adverse Event	18 Months Exposure [Placebo (6 Months)/hGH (12 Months)] (N=35)		18 Months hGH Exposure (N=32)	
	n	%	n	%
Flu syndrome	8	22.9	5	15.6
AST increased ^a	2	5.7	4	12.5
Headache	4	11.4	3	9.4
Asthenia	1	2.9	2	6.3
Cough increased	0	0	2	6.3
Edema	3	8.6	2	6.3
Hypesthesia	0	0	2	6.3
Myalgia	2	5.7	2	6.3
Pain	3	8.6	2	6.3
Rhinitis	2	5.7	2	6.3
ALT increased	2	5.7	2	6.3
Respiratory disorder	2	5.7	1	3.1
Gastritis	2	5.7	0	0
Pharyngitis	5	14.3	1	3.1

Abbreviations: hGH=Humatrope; N=number of patients receiving treatment in the period stated; n=number of patients reporting each treatment-emergent adverse event; ALT=alanine amino transferase, formerly SGPT; AST=aspartate amino transferase, formerly SGOT.

^a p=0.03 as compared to placebo (6 months).

Other adverse drug events that have been reported in growth hormone-treated patients include the following:

- 1) Metabolic: Infrequent, mild and transient peripheral or generalized edema.
- 2) Musculoskeletal: Rare carpal tunnel syndrome.
- 3) Skin: Rare increased growth of pre-existing nevi. Patients should be monitored carefully for malignant transformation.
- 4) Endocrine: Rare gynecomastia. Rare pancreatitis.

OVERDOSAGE

Acute overdosage could lead initially to hypoglycemia and subsequently to hyperglycemia. Long-term overdosage could result in signs and symptoms of gigantism/acromegaly consistent with the known effects of excess human growth hormone. (See recommended and maximal dosage instructions given below.)

DOSAGE AND ADMINISTRATION

Pediatric Patients

The Humatrope dosage and administration schedule should be individualized for each patient. Therapy should not be continued if epiphyseal fusion has occurred. Response to growth hormone therapy tends to decrease with time. However, failure to increase growth rate, particularly during the

first year of therapy, should prompt close assessment of compliance and evaluation of other causes of growth failure such as hypothyroidism, under-nutrition and advanced bone age.

Growth hormone-deficient pediatric patients — The recommended weekly dosage is 0.18 mg/kg (0.54 IU/kg) of body weight. The maximal replacement weekly dosage is 0.3 mg/kg (0.90 IU/kg) of body weight. It should be divided into equal doses given either on 3 alternate days, 6 times per week or daily. The subcutaneous route of administration is preferable; intramuscular injection is also acceptable. The dosage and administration schedule for Humatrope should be individualized for each patient.

Turner Syndrome — A weekly dosage of up to 0.375 mg/kg (1.125 IU/kg) of body weight administered by subcutaneous injection is recommended. It should be divided into equal doses given either daily or on 3 alternate days.

Patients with idiopathic short stature — A weekly dosage of up to 0.37 mg/kg of body weight administered by subcutaneous injection is recommended. It should be divided into equal doses given 6 to 7 times per week.

Adult Patients

Growth hormone-deficient adult patients — The recommended dosage at the start of therapy is not more than 0.006 mg/kg/day (0.018 IU/kg/day) given as a daily subcutaneous injection. The dose may be increased according to individual patient requirements to a maximum of 0.0125 mg/kg/day (0.0375 IU/kg/day).

During therapy, dosage should be titrated if required by the occurrence of side effects or to maintain the IGF-I response below the upper limit of normal IGF-I levels, matched for age and sex. To minimize the occurrence of adverse events in patients with increasing age or excessive body weight, dose reductions may be necessary.

Reconstitution

Vial — Each 5-mg vial of Humatrope should be reconstituted with 1.5 to 5 mL of Diluent for Humatrope. The diluent should be injected into the vial of Humatrope by aiming the stream of liquid against the glass wall. Following reconstitution, the vial should be swirled with a GENTLE rotary motion until the contents are completely dissolved. DO NOT SHAKE. The resulting solution should be inspected for clarity. It should be clear. If the solution is cloudy or contains particulate matter, the contents MUST NOT be injected.

Before and after injection, the septum of the vial should be wiped with rubbing alcohol or an alcoholic antiseptic solution to prevent contamination of the contents by repeated needle insertions. Sterile disposable syringes and needles should be used for administration of Humatrope. The volume of the syringe should be small enough so that the prescribed dose can be withdrawn from the vial with reasonable accuracy.

Cartridge — Each cartridge of Humatrope should only be reconstituted using the diluent syringe and the diluent connector which accompany the cartridge **and should not be reconstituted with the Diluent for Humatrope provided with Humatrope Vials.** (See WARNINGS section.) See the **HumatroPen™ User Guide for comprehensive directions on Humatrope cartridge reconstitution.**

The reconstituted solution should be inspected for clarity. It should be clear. If the solution is cloudy or contains particulate matter, the contents MUST NOT be injected.

The HumatroPen allows the somatropin dosage volume to be dialed in increments of 0.048 mL per click of dosage knob, and the maximum dosage volume that can be injected is 0.576 mL (based on a 12-click maximum). (See Table 10 for additional information.)

Table 10
Concentration of Reconstituted Humatrope Solutions, Incremental Dosage and
Maximum Injectable Dose for Each Cartridge

Cartridge	Somatropin Concentration	Dose Per Click of Dosage Knob	Maximum Injectable Dose
6 mg	2.08 mg/mL	0.1 mg	1.2 mg
12 mg	4.17 mg/mL	0.2 mg	2.4 mg
24 mg	8.33 mg/mL	0.4 mg	4.8 mg

This cartridge has been designed for use only with the HumatroPen. A sterile disposable needle should be used for each administration of Humatrope.

STABILITY AND STORAGE

Vials

Before Reconstitution — Vials of Humatrope and Diluent for Humatrope are stable when refrigerated [2° to 8°C (36° to 46°F)]. Avoid freezing Diluent for Humatrope. Expiration dates are stated on the labels.

After Reconstitution — Vials of Humatrope are stable for up to 14 days when reconstituted with Diluent for Humatrope or Bacteriostatic Water for Injection, USP and stored in a refrigerator at 2° to 8°C (36° to 46°F). Avoid freezing the reconstituted vial of Humatrope.

After Reconstitution with Sterile Water, USP — Use only one dose per Humatrope vial and discard the unused portion. If the solution is not used immediately, it must be refrigerated [2° to 8°C (36° to 46°F)] and used within 24 hours.

Cartridges

Before Reconstitution — Cartridges of Humatrope and Diluent for Humatrope are stable when refrigerated [2° to 8°C (36° to 46°F)]. Avoid freezing Diluent for Humatrope. Expiration dates are stated on the labels.

After Reconstitution — Cartridges of Humatrope are stable for up to 28 days when reconstituted with Diluent for Humatrope and stored in a refrigerator at 2° to 8°C (36° to 46°F). Store the HumatroPen without the needle attached. Avoid freezing the reconstituted cartridge of Humatrope.

HOW SUPPLIED

Vials

5 mg (No. 7335) — (6s) NDC 0002-7335-16, and 5-mL vials of Diluent for Humatrope (No. 7336)

Cartridges

Cartridge Kit (MS8089) NDC 0002-8089-01
 6 mg cartridge (VL7554), and prefilled syringe of Diluent for Humatrope (VL7557)

Cartridge Kit (MS8090) NDC 0002-8090-01
 12 mg cartridge (VL7555), and prefilled syringe of Diluent for Humatrope (VL7558)

Cartridge Kit (MS8091) NDC 0002-8091-01
 24 mg cartridge (VL7556), and prefilled syringe of Diluent for Humatrope (VL7558)

Literature revised July 18, 2003

Eli Lilly and Company, Indianapolis, IN 46285, USA

www.lilly.com

A4.0 NL1641 AMP

PRINTED IN USA

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 19-640/S-033

MEDICAL REVIEW(s)

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: July 25, 2003

FROM: David G. Orloff, M.D.
Director, Division of Metabolic and Endocrine Drug Products

TO: NDA 19-640/S-033
Humatrope (somatropin [rDNA origin] for injection)
Proposed new indication: for the treatment of children with "non-GH-deficient short stature"

SUBJECT: sNDA review issues and recommended action

Background

In September, 1987, the endocrine and metabolic drugs advisory committee met to discuss methodologic approaches to and endpoints of a study of the safety and efficacy of GH in pediatric patients with idiopathic short stature. Leading up to that meeting, in 1983 NICHD held a consensus conference on uses and possible abuses of hGH looking toward the imminent availability of large supplies of recombinant hGH, once products were approved by FDA. That conference concluded that there was an "urgent need for therapeutic trials to determine the effect of hGH in short children who do not have GHD." Indeed, over the 20 years since 1983, there seems to have been general agreement in the pediatric endocrinologic community on the need for data on clinical safety and efficacy in idiopathic, non-syndromic, short stature to inform recommendations on the use of GH in these children.

At the 1987 meeting, the AC further concluded that data on final height in the context of a randomized, blinded, placebo-controlled trial were needed to provide insight into the ultimate effects of GH therapy in this population.

With this application, Lilly has submitted the results of two studies of GH in idiopathic short stature. One, study GDCH, is the blinded, placebo-controlled trial the AC recommended. The second is a larger, parallel-group dose-ranging study using higher doses and a daily (as opposed to thrice weekly) injection schedule.

The use of GH in children with short stature not attributable to GH deficiency is controversial, though the discussion has evolved over time as data on safety and efficacy have been brought forward. In the last 5-6 years, hGH (specific products; there are no generics) has been approved to augment height in children with Prader-Willi syndrome, chronic renal insufficiency, and Turner syndrome (gonadal dysgenesis), and most recently, a GH product has been approved by FDA for the treatment of children born small for gestational age (SGA; height greater than 2 standard deviations below the mean for chronological age) who fail to exhibit catch up growth

NDA #
Drug:
Proposal:
07/25/03

by age 2. To some degree, the documented effects of GH in these populations of children with short stature may serve as the reference for the definition of "meaningful" height augmentation in children with idiopathic non-syndromic short stature.

The current proposal targets a broad and presumably heterogeneous population of short children (height greater than 2.25 SD below the mean) who are expected to achieve final adults heights well short of target height (biparental height; a function of gender and parental height) and at the very low end of the population distribution. The target population is intended to exclude patients with syndromic short stature as well as those born SGA. At least some of these children likely have some form of GH secretory abnormality, or potentially poorly active endogenous GH. Some may have abnormalities in GH responsiveness; whether any of these would be expected to respond to exogenous GH is unclear.

A central problem in this area of clinical research and practice is the diagnosis of GH deficiency. While criteria for the diagnosis of classic GH deficiency in children are not argued, it is not clear that these criteria necessarily capture all those with clinically significant GH deficiency who might benefit from GH replacement or supplementation. Furthermore, the criteria ignore the large population of extremely short, non-syndromic children who have reasons other than classic GHD for their short stature and who may respond to GH with an augmentation in final height relative to predicted height, as the results of the studies submitted indicate. As discussed in the American Academy of Pediatrics statement "Considerations Related to the Use of Recombinant Human Growth Hormone in Children" (Pediatrics 1997; 99: 122-129), the decision to treat children other than those with classical GHD with GH requires an understanding of benefits, particularly related to final height relative to predicted height, and risks. The goals of such therapy also must be defined, specifically what constitutes a meaningful degree of height augmentation.

This last point is, in many respects, the crux of the issue, and unfortunately the most difficult to address, if an answer is even possible. Short stature is clearly not itself a disease, though, depending on the severity, it may for some, though again clearly not all, be a disability or significant challenge. More on the basis of anecdote than on any other forms of data, short stature can impair social function, achievement, employment, quality of life, and activities of daily living. Again, on the basis of anecdote, height augmentation can, for some, ease these burdens, though even patient by patient, the magnitude of height augmentation required for improvement in the aforementioned parameters is known at best in retrospect.

The endocrine and metabolic drugs advisory committee was convened on June 9, 2003, to discuss the data from the Lilly application. The sponsor presented the results of GDCH and E001. Dr. Harvey Guyda, from McGill University in Montreal made a presentation essentially against the use in children without GHD based on what he perceives as modest efficacy, unproven safety, and great societal economic cost.

The committee was asked to discuss and respond to a list of questions. The quick minutes of the meeting are appended to Dr. Roman's review. A majority of the committee ultimately recommended approval of the application.

NDA #
Drug:
Proposal:
07/25/03

Clinical efficacy and safety

The reviews by Dr. Roman (medical officer) and by Joy Mele (biostatistician) present the data analyses in detail. Trial GDCH enrolled 71 patients among whom 33 contributed final height data. In this study, patients received a relatively low dose of GH (0.222 mg/kg/wk) in 3 divided doses, a regimen now known to be suboptimal for efficacy of GH (as confirmed by the second study, E001, in which GH was dosed daily and at higher doses). The mean baseline height SDS in this trial across treatment groups was 2.75 to -2.81 (close to the 1st percentile for age and sex). Importantly, the baseline predicted height (based on baseline height, gender, bone age, age) in all but a handful of patients was well below the target height (based on gender and parental heights), with an average difference of about 3 inches. Furthermore, for most, the target height SDS was below zero, with the majority between -1 and -2 SD below the mean. Therefore, these children were predicted at baseline to be shorter still than their short parents. The primary endpoint was change from baseline to time of attainment of final height (growth velocity < 1.5 cm/year for the final height population) in height SDS.

At the end of an average 4.4 years of follow up in the final height cohort, the difference between drug and placebo groups was 0.51 SDS units favoring drug. The sponsor "translated" this difference in SDS scores to a linear difference of 3.7 cm. The FDA analysis concludes a difference of 3.2 cm, discussed in what follows, which summarizes additional analyses by Ms. Mele.

The GH treatment effect on the difference between baseline height and final height (i.e., the linear growth during the period of observation) was 5.7 cm (2.25 inches) relative to placebo. With regard to absolute final height obtained (because the groups were of slightly different mean heights at baseline), the difference between the least square means for the two treatment groups was 3.2 cm (1.25 inches), favoring GH. This corresponds to the difference in height SDS that the sponsor "translated" to 3.7 cm of height. Ms. Mele further includes a number of analyses in her review that contribute to the understanding of the effect of this relatively low dose of GH relative to placebo. The first is purely descriptive, though compelling, and is shown in figure 5 of her review. It shows for each patient in the final height cohort, the height SDS score at baseline and endpoint. It is first notable that the highest final height SDS scores are in GH treated patients. Furthermore, the greatest changes from baseline to endpoint are also in the GH-treated patients. It is also notable that 15/22 (68%) of GH-treated patients had increases in height SDS from baseline to endpoint, while this was the case for only 4/11 (36%) of placebo-treated patients. And, in the final height population, Humatrope patients on average exceeded predicted height by 2.9 cm (1.1 inch) relative to placebo. Similarly, Humatrope treated patients came closer to their target heights by approximately 1 inch on average, though they still fell short by an average of almost 2 inches.

On balance, based on the data from this trial, we must conclude that GH augments final height in these patients.

NDA #
Drug:
Proposal:
07/25/03

In study E001, 239 patients were enrolled and randomized to three treatment groups: 0.24 mg/kg/wk, 0.24 mg/kg/wk for 1 year followed by 0.37 mg/kg/wk, 0.37 mg/kg/wk. Final height data are available on approximately 20% of patients (16 to 17 in each group by original randomization). The average treatment duration in the final height cohort in this study was nearly 6.5 years, substantially longer than in GDCH, related to a younger mean age at enrollment.

In this cohort, even more dramatically than in GDCH, predicted height at baseline fell well short of target height.

Results showed a dose-response with regard to final height SDS and a categorical analysis shows that 94% of patients in the high dose group with final height data had final height SDS of greater than -2 while ~50% has final height SDS greater than -1.

Consistent with the results of GDCH, and to a greater degree with increasing dose, in E001, final height exceeded predicted height. Overall, this was the case in all but 3 patients in the study. Final height exceeded predicted height by 10 or more centimeters in some patients. In the high-dose group, final height exceeded baseline predicted height by a mean of 7.2 cm, or nearly 3 inches. Again consistent with GDCH, the gain in final height relative to target height was less "successful" than the effect relative to predicted height (target height exceeds predicted height in these children, despite GH therapy), though the effect on this parameter (target height minus predicted height) was also dose-related.

The following table is reproduced from Joy Mele's review and summarizes the data on final height relative to predicted height and target height, the analysis that addresses the goal of GH therapy in these children; that is, the degree to which GH therapy affords linear growth beyond that predicted at the time of initial diagnostic evaluation for extreme short stature revealing no syndromic or organic cause, without a history of being small for gestational age, and in the absence of a diagnosis of GHD.

	GDCH		E001		
	Placebo	Humatrope 0.22	Humatrope 0.24	Humatrope 0.24/0.37	Humatrope 0.37
FH-baseline PH SDS	-0.18	+0.33	+0.83	+1.1	+1.3
cm	-0.9	+2.3	+5.4	+6.5	+7.3
(95% CI for cm)	(-3.3, 1.5)	(0.6, 3.9)	(2.9, 8.0)	(3.9, 9.1)	(4.7, 9.8)
FH-target height SDS	-0.96	-0.68	-0.46	-0.64	-0.26
cm	-7.0	-4.8	-3.3	-4.8	-1.9
(95% CI for cm)	(-11.3, -2.6)	(-7.6, -2.0)	(-7.7, 1.0)	(-9.2, -0.4)	(-6.3, 2.4)

Finally, the sponsor presented the results of a published meta-analysis of trials of GH in children with idiopathic short stature. The estimate for an effect on final adult height from these studies is 4-6 cm (1.6-2.4 inches). This is consistent with the results of Lilly's trials.

NDA #
Drug:
Proposal:
07/25/03

Safety

The safety profile of Humatrope as observed in the trials submitted with this sNDA is essentially the same as that for Humatrope and for GH generally for the other pediatric uses for which it is indicated. The adverse effects known to be associated with GH therapy in other studies and postmarketing include reversible disturbances in carbohydrate and salt and water metabolism, articular and musculoskeletal abnormalities and symptoms, and rare reversible effects such as pseudotumor cerebri. There were two malignancies diagnosed during treatment in patients on GH, one in E001 and the other in GDCH. One patient had a rare desmoplastic small round cell tumor of the abdomen, which ultimately proved fatal. Another patient was diagnosed with Hodgkin's disease early in the course of therapy. In retrospect, the disease was present at enrollment. His pre-study chest X-ray had shown a widened mediastinum, labeled as "residual thymus." Based on nearly 40 years of experience, there is general consensus among experts in the field that GH therapy does not increase the risk of malignancy in children or adults, with the possible exception of secondary malignancies in patients predisposed due to underlying genetic disease and/or previous radiation or chemotherapy for malignancy. The labeling for the use of GH recommends against use in individuals with active malignancy.

Dr. Roman's review contains an exhaustive discussion of safety.

Risk Management

The aspects of the sponsor's proposed program include: restrictive labeling and pharmacovigilance, physician education, limited marketing, controlled distribution, and post-marketing research.

Physician education will include CME programs and physician-to-physician educational programs. Sale specialists will only call on pediatric endocrinologists for this indication, and there will be no direct-to-consumer marketing. A statement of medical necessity will be required for new patient diagnoses and Humatrope for this indication as well as for all others is shipped only through Lilly-approved closed specialty pharmacies. Lilly also intends to monitor prescribing behavior for this indication as they do for other approved indications for GH.

The GeNeSIS program (genetics and neuroendocrinology of short stature international study) is ongoing in 30 countries and with a goal of establishing > 400 study sites. Additional sites are enrolled on a progressive basis. Enrollment is voluntary, but there are incentives to do so. And all Humatrope-treated patients are offered enrollment.

The GeNeSIS sites collect data on history, diagnosis, and efficacy, as well as comprehensive safety data, including reports of neoplasia. In addition, laboratory data are collected. Data are analyzed and reported annually to investigators.

While GeNeSIS is an imperfect tool in many respects (it is not a registry), it has the potential to reveal information on the safety of this intervention, as well as to yield data on use patterns for this and other GH indications.

NDA #
Drug:
Proposal:
07/25/03

The FDA had expressed concerns that with an approval to treat idiopathic short stature with GH, it could obviate the need to fully evaluate the etiology of short stature. In short, the sponsor argued persuasively that labeling, education, restriction of prescribing to pediatric endocrinologists would assure that this would not occur.

With regard to "opening the floodgates" to inappropriate use of GH and a vast increase in the number of patients on GH, the sponsor re-emphasized the restricted height criterion for this indication, the pediatric endocrine community as gatekeepers, insurance companies as gatekeepers, as well as other aspects of the limited distribution and promotion program.

Finally, Lilly's estimate of use are that after 5 years a total US cohort of 30,000 – 40,000 patients will be treated with GH under this indication, approximately 10% of the eligible population because of selective referral, conservative treatment recommendations and family choice, and limited reimbursement.

Labeling

The labeling relative to this indication will exclude from the indication those children born small for gestational age, as Humatrope is not approved for this use. Additionally, in order to distinguish this target population from others in which GH is indicated, this will be the only GH indication with a height criterion for eligibility.

Labeling is discussed in detail in Dr. Roman's review. The final labeling is included in the action package and in DFS.

Biopharmaceutics

No issues

Pharmacology/Toxicology

No issues

Chemistry/ Microbiology

No issues

DSI/Data Integrity

No audits were requested or conducted.

Financial disclosure

The financial disclosure information is in order. The sponsor has certified that no investigator received outcome payments, that no investigator disclosed a proprietary interest in the product or an equity interest in the company, and that no investigator was the recipient of significant payments of other sorts.

Summary and conclusions

The efficacy observed in these trials is, on average, modest, and some patients clearly benefit more than others. The average height gain in idiopathic short stature is consistent with the effects of GH in children with Turner syndrome. While the clinical significance of this height augmentation cannot be reliably assessed, the advisory committee agreed that efficacy was demonstrated. There were no novel safety findings in this development program. The safety of GH is presumed to be no different in this population than in other in which it is indicated. The division and the committee concur that the balance of risk and benefit for this proposed use is

NDA #

Drug:

Proposal:

07/25/03

favorable, and that individual patient decisions regarding use of GH in idiopathic short stature should be up to the patient, his or her family, and the physician based on assessment of risk versus benefit. The information submitted in the application permits labeling adequate to convey expected benefits and risks in this population to guide safe and effective use.

Recommendation

This sNDA may be approved.

NDA #
Drug:
Proposal:
07/25/03

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

David Orloff
7/25/03 03:10:43 PM
MEDICAL OFFICER

MEDICAL OFFICER REVIEW

Division of Metabolic and Endocrine Drug Products (HFD-510)

APPLICATION #:	19-640	APPLICATION TYPE:	sNDA
SPONSOR:	Eli Lilly and Company	PROPRIETARY NAME:	Humatrope
CATEGORY OF DRUG:	Growth hormone	GENERIC NAME:	Somatropin
		ROUTE:	Injectable (subcutaneous)
MEDICAL REVIEWER:	Dragos Roman, MD	REVIEW DATE	07-17-2003
		PDUFA DATE:	07-26-2003

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date:	CDER Stamp Date:	Submission Type:	Comments:
09/26/2002	12/08/2000	Supplemental NDA	
11/20/2002		Amendment to sNDA	
01/06/2003		Amendment to sNDA	
02/17/2003		Amendment to sNDA	
03/25/2003		Amendment to sNDA	
04/02/2003		Amendment to sNDA	
06/17/2003		Amendment to sNDA	
06/19/2003		Amendment to sNDA	
07/14/2003		Amendment to sNDA	

RELATED APPLICATIONS

Document Date:	APPLICATION Type:	Comments:
----------------	-------------------	-----------

Overview of Application/Review: Humatrope (somatropin) is recombinant human growth hormone (GH). This application provides evidence that Humatrope treatment is efficacious in increasing final height in patients with non-growth hormone deficient short stature (NGHDSS), a new proposed indication. NGHDSS patients represent a heterogeneous group that includes, among others, (1) patients with growth hormone deficiency not captured by the current diagnostic criteria for GH insufficiency and (2) children with normal variants of linear growth. On average, Humatrope treatment increases final height by 3.7 cm over placebo (about 0.5 SD unit) if started at the beginning of puberty as a 0.22 mg/kg/wk regimen given three times a week. A higher dose regimen (0.37 mg/kg/week) given daily and started before puberty adds on average about 3 more cm (or a little less than 0.5 SD unit) to a 0.24 mg/kg/wk daily regimen.

These two observations combined suggest an overall mean height benefit > 6 cm relative to placebo for the 0.37 mg/kg/week regimen. This degree of efficacy is consistent with a benefit of 7.2 cm in final height over the baseline predicted adult height recorded for the 0.37 mg/kg/wk Humatrope regimen. Despite a mean benefit on final height, the benefit to individual patients is variable, with some patients responding no better than placebo and others having significant improvement in final height.

The safety profile of Humatrope in this patient population is similar to that observed in other approved pediatric indications. The safety of GH in general has been characterized in 200,000 patients (>500,000 patient-years) including 100,000 pediatric patients during the last 4 decades. NGHDSS patients represent a significant segment of the overall pediatric exposure because of the current off-label use of GH in this patient population. Our current understanding of GH is that it has a favorable safety profile in pediatric patients.

Approval of Humatrope for NGHDSS patients will result in a substantial increase in the number of pediatric patients who will be treated with GH (as many as 400,000 patients are currently estimated to become candidates for GH therapy under this new indication). On June 10, 2003 the Endocrinologic and Metabolic Drugs Advisory Committee has recommended approval of Humatrope treatment in NGHDSS.

Recommended Regulatory Action: Approval

Signed: _____ Medical Reviewer: Dragos Roman M.D.

Date: 07/17/2003

Medical Team Leader: _____

Date: _____

Table of Contents

Executive Summary	1
I. Recommendations	1
A. Recommendation on Approvability	1
B. Recommendation on Phase 4 Studies and Risk Management Steps	1
II. Summary of Clinical Findings	1
A. Background and Brief Overview of Clinical Program	1
B. Efficacy Conclusions	1
C. Safety Conclusions	1
D. Dosing	1
E. Special Populations	1
F. General Comments on Non-growth Hormone Deficient Short Stature	1
Clinical Review	1
I. Introduction and Background	1
A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups	1
B. State of Armamentarium for Indication	1
C. Important Milestones in Product Development	1
D. Other Relevant Information/Foreign Marketing History	1
E. Important Issues with Pharmacologically Related Agents	1
II. Clinically Relevant Findings From Chemistry, Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews	1
III. Human Pharmacokinetics and Pharmacodynamics	1
IV. Description of Clinical Data and Sources	1
A. Overall Data	1
B. Tables Listing the Clinical Trials	1
C. Postmarketing Experience	1
D. Literature Review	1
V. Clinical Review Methods	1
A. Overview of Materials Consulted in Review /How the Review was Conducted	1
B. Ethics Review/ Ethical Conduct of the Study	1
C. Financial Disclosure	1
D. Data Quality and Integrity	1
VI. Integrated Review of Efficacy	1
A. Efficacy Conclusions	1
B. General Approach to Review of the Efficacy of the Drug	1
C. Detailed Review of Trials by Indication	1
C.1. Pivotal Clinical Study GDCH	1
C.1.1 Objective	1
C.1.2 Study Design	1
C.1.3 Main Inclusion and Exclusion Criteria	1
C.1.4. Protocol amendments	1
C.1.5. Data and Safety Monitoring Board	1
C.1.6 Patient Disposition	1
C.1.7. Protocol violations	1
C.1.8 Treatment compliance	1
C.1.9 Baseline Patient Characteristics	1
C.1.10. Efficacy	1

C.1.10.1. Data sets analyzed	1
C.1.10.2 Efficacy variables – definitions	1
C.1.10.4 Statistical plan	1
C.1.10.5. Efficacy Results	1
C.2. Supportive Clinical Study E001	1
C.2.1 Objective	1
C.2.2 Study Design	1
C.2.3 Main Inclusion and Exclusion Criteria	1
C.2.5 Patient Disposition	1
C.2.6. Protocol violations	1
C.2.7. Treatment compliance	1
C.2.8 Baseline Patient Characteristics	1
C.2.6. Efficacy evaluation	1
C.2.6.1. Data sets analyzed	1
C.2.6.2 Efficacy variables	1
C.2.6.3. Planned Analyses	1
C.2.6.3. Efficacy Results	1
C.4. Comparison of Efficacy Findings in Trials GDCH and E001	1
C.5. Supportive Studies from Peer-Reviewed Literature	1
D. Efficacy Conclusions	1
VII. Integrated Review of Safety	1
A. Brief Statement of Conclusions	1
B. Description of Patient Exposure	1
C. Methods and Specific Findings of Safety Review	1
C.1. Deaths	1
C.2. Serious Adverse Events	1
C.3. Patient Discontinuations Due to Adverse Events	1
C.4. Treatment-Emergent Adverse Events	1
C.5. Clinically Significant Treatment-Emergent Adverse Events	1
C.6. Clinical Laboratory Data	1
C.6.1. Carbohydrate Metabolism	1
C.6. 2. Thyroid Function	1
C.6.3 Insulin-Like Growth Factor-I	1
C.6.4. Other Laboratory Parameters – study GDCH	1
C.7 Vital Signs	1
C.8 Additional Safety Studies	1
D. Adequacy of Safety Testing	1
E. Summarize Critical Safety Findings and Limitations of Data	1
VIII. Dosing, Regimen, and Administration Issues	1
IX. Use in Special Populations	1
A. Gender Effects Analyses	1
B. Age, Race, or Ethnicity Effects on Safety or Efficacy	1
C. Pediatric Program	1
D. Special Populations	1
X. Overall Conclusions, Recommendations, and Labeling	1
A. Conclusions Regarding Safety and Efficacy/Risk Benefit Analysis	1
B. Recommendations	1
C. Labeling	1
XI. Appendix	1
A. Additional Safety Data	1
A.1 Study GDCG	1
A. 2. Study GDCP	1
A.3. Study (Protocol) GDFC (GENESIS)	1

B. References	1
C. Quick Minutes of the June 10, 2003, Endocrinologic and Metabolic Drugs Advisory Commeeting Meeting	1

Executive Summary

I. Recommendations

A. Recommendation on Approvability

Given that pharmacological treatment with Humatrope is effective in increasing final (adult) height in children with severe short stature who do not meet the current definition criteria of growth hormone deficiency and given that the safety profile of Humatrope in this patient population is similar to that of other approved growth hormone indications, Humatrope treatment for children with non-growth hormone deficient short stature (NGHDSS) should be approved from a clinical perspective. This recommendation is consistent with the recent recommendation of the June 10th, 2003, Endocrinologic and Metabolic Drugs Advisory Committee. It is also consistent with the fact that all but one prior pediatric indications for growth hormone (GH) use are for pharmacological treatment of short stature in children.¹ For a detailed risk/benefit analysis of Humatrope use in children with NGHDSS, please refer to section X.A.

B. Recommendation on Phase 4 Studies and Risk Management Steps

The following Phase 4 commitments are recommended:

- The applicant should attempt to capture the final height data on the 21 patients (11 Humatrope, 10 placebo) who were still growing at a height velocity >1.5 cm/y at the end of study GDCH and therefore could not be included in the final analysis.
- During the postmarketing phase, the applicant should conduct studies that will: (1) demonstrate that the post approval safety profile of Humatrope is not different from the safety profile observed during drug development (this is particularly important since Humatrope use in NGHDSS is anticipated to be substantial and it may unmask serious adverse events previously not recognized and, therefore, not labeled); (2) identify predictors of efficacy in this patient population (small clinical trials have failed to find such predictors but this may change in the context of a large postmarketing patient exposure). The postmarketing study GeNeSIS, proposed by the sponsor, appears to be an appropriate vehicle for these goals.
- The applicant should implement an active surveillance program for bone tumors (osteosarcoma, osteochondroma) /

The applicant has implemented a similar program for a recently approved recombinant PTH (Forteo) in the treatment of adult osteoporosis. A similar program can serve the same purpose in patients with NGHDSS treated with Humatrope.

¹ Chronic renal insufficiency (1993), Turner syndrome (1996), Prader-Willi syndrome (2000), and small for gestational age (SGA) children without catch up growth by 2 years of age (2001). The first approved GH indication was growth hormone deficiency in 1985.

indication (1200 patient years) are similar to the other two approved pediatric Humatrope indications (GHD and Turner syndrome).

B. Efficacy Conclusions

This application provides evidence that Humatrope treatment is efficacious in increasing final height in patients with NGHDSS. Trials GDCH and E001 have different designs, use different dose regimens, and show different effects on final height.

Trial GDCH demonstrates that Humatrope is superior to placebo in increasing final height. This NIH conducted clinical trial shows that patients who received 0.222 mg/kg/wk of Humatrope in three equally divided doses for a mean duration of 4.62 years achieved greater mean final height than those who received placebo for a similar period of time (4.06 years). The magnitude of the Humatrope effect was 0.51 ± 0.20 standard deviation score (SDS) ($p=0.017$) in the primary efficacy analysis of 33 patients who contributed final height data. Individual efficacy showed marked variability (95% CI: 0.1-0.92 SD). The primary analysis is supported by an intent-to-treat analysis of height SDS that shows a similar magnitude of treatment effect (0.52 ± 0.15 ; $p=0.001$). Additional analyses support the primary and the intent-to-treat analyses. These efficacy observations are made in the context of a clinical trial with multiple dropouts. However, it does not appear that the patients who discontinued the trial had different initial responses to treatment when compared to patients who remained on trial.

Trial E001 establishes that a Humatrope regimen of 0.37 mg/kg/week given in six daily injections (high-dose regimen) is superior to a Humatrope regimen of 0.24 mg/kg/week administered in the same fashion (low-dose regimen). This was observed during short-term Humatrope use (effect on two-year height velocity) and during long-term Humatrope treatment (effect on final height on a subgroup of patients with available final height data). The high-dose Humatrope regimen resulted in a final height that exceeded baseline predicted adult height by an average of 7.2 cm (7.21 ± 5.97 cm or 1.9 height SDS; $p=0.001$), whereas the low-dose Humatrope regimen had a smaller treatment effect of 5.4 cm (5.36 ± 3.20 cm or 1.6 SDS; $p<0.001$) for the same endpoint. Intent-to-treat analyses and several other analyses confirm a dose-related treatment effect on final height.

Of note is that the mean difference between final height and baseline predicted adult height for the low-dose regimen noted in trial E001 (5.4 cm) is higher than that observed in trial GDCH (2.2 cm) for an almost identical Humatrope dose (0.24 mg/kg/week in trial E001 vs. 0.22 mg/kg/week in GDCH). Differences in trial duration (patients were treated longer in trial E001), and in particular differences in Humatrope regimen (daily vs. three times a week) may account for a larger magnitude of treatment effect in trial E001. The combined data from studies GDCH and E001 suggest that a larger treatment effect can be achieved if a larger dose is used (0.37 mg/kg/week) and if Humatrope is given daily.

Both trial GDCH and E001 enrolled a few patients who were small for gestational age (SGA). At the time of initiation of both trials (1988) short stature in SGA patients was not an FDA approved indication.

Additional evidence of favorable effect of growth hormone therapy on final height in patients with NGHDSS is provided from published literature. A recent meta-analysis of 38 clinical trials (10 controlled and 28 uncontrolled) estimates a benefit on adult height of 4-6 cm (range of 2.3 to 8.7 cm) (Finkelstein B S et al., 2002).

C. Safety Conclusions

The safety profile of Humatrope in patients with NGHDSS appears to be similar to the safety profile of Humatrope in other pediatric indications in which its use is indicated.

There were no deaths recorded during the clinical trials. Two Humatrope-receiving patients, however, were diagnosed with malignancies during follow up. One patient in study E001 had an abdominal desmoplastic small round cell tumor diagnosed six years in the clinical trial, discontinued the trial and died four years later (desmoplastic small round cell tumors have not been described in association with GH therapy). One patient in trial GDCH was diagnosed with stage 3B Hodgkin disease approximately 4-5 months on treatment (this patient had evidence of subclinical disease not recognized at enrollment).

There were few patient discontinuations due to adverse events in patients receiving Humatrope. In addition to the two patients who developed malignancies, two patients discontinued treatment in trial E001 due to slipped capital femoral epiphysis and glucose intolerance/elevated HbA1c, respectively. There were no distinct or new patterns of treatment-emergent adverse events (TEAEs) associated with Humatrope use in patients with NGHDSS. Small imbalances in TEAEs between the Humatrope treated group and the placebo treated group were observed for adverse events related to the musculoskeletal system such as bone disorder, arthrosis, arthralgia, back pain, neck pain, myalgia. Evaluation of carbohydrate metabolism in patients with NGHDSS treated with Humatrope during trial GDCH showed findings consistent with the observed effects of GH therapy in previous trials for other pediatric indications (i.e. an increase in mean serum fasting insulin levels in the presence of normal mean fasting serum glucose levels and mean HbA1c levels). In trial E001, there was no distinct, dose-related pattern of abnormalities related to carbohydrate metabolism in the two variables assessed (fasting serum glucose and HbA1c). Data on serum insulin concentration was not available for this trial.

At the request of the agency the applicant submitted a comprehensive safety comparison of Humatrope use across patients with NGHDSS, GHD and Turner syndrome. No major differences in safety profile were noted across the three patient populations.

D. Dosing

Clinical trial GDCH establishes an effective dose regimen for Humatrope in patients with NGHDSS. This dose regimen is 0.22 mg/kg/week of Humatrope given three times a week (TIW) in equally divided doses. This dose regimen has been demonstrated to be superior to placebo in enhancing final height and was not associated with unexpected safety signals.

Clinical trial E001 provides evidence that a weekly dose of 0.37 mg/kg given in equally divided daily injections is more effective than a similar regimen of 0.24 mg/kg/week. The 0.37 mg/kg/week regimen is superior both as short-term treatment (as judged by superior height velocity over a 2-year period), as well as long-term treatment (as judged by greater final height than baseline predicted adult height and greater height gain on treatment among a subgroup of patients with final height).

The daily Humatrope regimen in trial E001 (0.24 mg/kg/week) resulted in a larger magnitude of treatment effect than a TIW³ regimen of almost identical dose in trial GDCH (0.22 mg/kg/week). The two regimens were not compared side by side in the same trial and the two trials differed in duration (trial E001 was longer). However, superiority of daily regimens over TIW regimens is well established.

The dosage and the regimen established in this application for patients with NGHDSS is within the range of GH dose regimens approved for other pediatric indications and is consistent with GH regimens currently used in clinical practice (Tanaka et al., 2002). The approved range of GH doses varies between 0.16 mg/kg/week (GH deficiency) and 0.48 mg/kg/week (SGA patients). For patients with GH deficiency entering puberty, a regimen as high as 0.7 mg/kg/week is currently labeled.

The dose-related Humatrope effect on efficacy was not clearly associated with a dose-dependent pattern of adverse events. The strength of this statement is limited by the relatively small database (236 patients) and by the lower level of ascertainment of adverse events and analytes in trial E001.

E. Special Populations

The two clinical studies GDCH and E001 enrolled exclusively pediatric patients. The ages studied (immediately prepubertal and pubertal) are consistent with the expected ages of GH treatment initiation in this patient population (Finkelstein BS, 1998). Enrollment of boys exceeded enrollment of girls by a 2:1 to 3:1 ratio. This reflects the gender bias that exists in the diagnosis and treatment of short stature in children in general and NGHDSS in particular (Hintz RL et al., 1999). Since the number of patients with final height was small in both studies, gender-specific efficacy analyses, although performed, were not always informative (overall no gender effect was noted). The most important gender-specific safety analysis was the effect of Humatrope therapy on the time of attainment of different stages of puberty (no detrimental effect is seen in either boys or girls).

The vast majority of patients in study GDCH were Caucasians (79.7%). Minorities (such as African Americans, Hispanics, and "other") totaled approximately 20%. This seems to roughly represent the US ethnic/racial distribution. In the presence of such small numbers of patients, no ethnic/racial efficacy or safety analyses were done. Study E001, was done in Europe and, not surprisingly, included overwhelmingly Caucasians.

³ TIW = three times a week

F. General Comments on Non-growth Hormone Deficient Short Stature

All the previous approvals for GH treatment in pediatric patients have been based primarily on improvement in linear growth. GH therapy has been approved as replacement therapy in patients with deficient or absent endogenous GH secretion (growth hormone deficiency), or as pharmacological treatment in patients with Turner syndrome, chronic renal failure prior to renal transplantation, Prader-Willi syndrome, and in SGA patients. For some indications (e.g. Prader-Willi) the metabolic benefit of GH on body composition complemented the linear growth benefit.

While NGHDSS is not the first indication for a treatment regimen that uses pharmacological doses of GH in patients without growth hormone deficiency, it is different from previously approved pediatric GH indications in several respects:

(1) The currently approved GH indications in children target patients with defined clinical/pathological entities associated with short stature. By contrast, NGHDSS is not a single clinical entity with a known "cause" but rather a group of pathologic and non-pathologic entities or conditions producing a common clinical outcome: short stature. Under the NGHDSS term one includes: (1) some forms of GH deficiency or GH secretory dysfunction not captured by the current GH diagnostic standards for GH deficiency; (2) growth retardation due to mutations of other growth promoting genes (e.g. partial GH receptor defects, SHOX gene mutations); (3) normal variations in linear growth patterns such as familial/genetic short stature or constitutional delay of growth and puberty (Godard AD et al, 1995; Rosenfeld RG, 2001, Rappold GA et al., 2002).

(2) Approval of GH use in patients with NGHDSS will have important public health implications. Currently, GH use is restricted to a limited number of orphan indications. The overall pediatric GH experience accumulated over the last four decades encompasses approximately 100,000 patients (GH Research Society Consensus statement, 2001). GH treatment for patients with NGHDSS could add up to 400,000 patients under the current restricted indication (height SDS ≤ -2.25).

Clinical Review

I. Introduction and Background

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

Humatrope (somatropin) is recombinant human growth hormone (GH). Humatrope use is approved for both pediatric and adult indications. The pediatric indications are: (1) long-term treatment of pediatric patients who have growth failure due to an inadequate secretion of normal endogenous growth hormone and (2) treatment of short stature associated with Turner syndrome. The approved adult indication is replacement of endogenous growth hormone in adults with growth hormone deficiency of adult or childhood onset. Additional approved indications for GH products other than Humatrope are AIDS wasting and cachexia (in adults), children with Prader Willi syndrome, children born small for gestational age who fail to manifest spontaneous catch-up growth by age 2 years, and children with growth failure associated with chronic renal insufficiency up to the time of renal transplantation. Human GH has been used therapeutically since 1958, recombinant methionyl-GH (somatrem) since 1985, and recombinant GH (somatropin) since 1987.

In this application, Lilly proposes a new indication for Humatrope: _____

The applicant proposes a weekly Humatrope regimen of "_____". The patient population to be treated under this indication is exclusively pediatric. The applicant does not propose a specific age of treatment initiation. Thus, patients are candidates for GH therapy as long as their epiphyses are not closed. Although most pediatric patients are evaluated for short stature at around the age of 8-10 years, much younger patients may be candidates for Humatrope treatment under this new indication (3-4 years and above).

The rationale proposed by the applicant for using GH therapy in children with NGHDSS is based on the following arguments:

- growth failure is equivalent to that in other growth disorders
- untreated patients do not achieve their adult height prediction
- children with NGHDSS respond to GH
- short children may face psychological stress, social stigma, reduced school achievement, impaired socialization, and may be at a disadvantage when compared with peers of normal

⁴ Height SDS (= height standard deviation score) is the calculated number of standard deviations from the mean for age and gender.

B. State of Armamentarium for Indication

Non-growth hormone deficient short stature is a new indication and, therefore, there are no approved products for the indication. There is, however, considerable off label use of GH in patients with NGHDSS (Hilken et al.2001;Guyda HJ, 1999; Cuttler L et al.1996).

C. Important Milestones in Product Development

The following product development chronology and regulatory history is provided in this application:

The 1983 International Conference on Uses and Abuses of Growth Hormone recognized a need for studies in "short children who do not have growth hormone deficiency."

8 June 1986: Lilly submitted an IND application (28,574) to support studies of Humatrope in conditions other than hypopituitary dwarfism.

07 July 1987: Lilly submitted the protocol for Study B9R-MC-GDCH (referred to as Study GDCH in this review) to the IND. This study was initiated in 1988 by Lilly and the National Institutes of Health (NIH) as a double-blind, randomized, parallel, placebo-controlled clinical study of Humatrope to final height in pediatric patients with NGHDSS.

28 September 1987: An Endocrinologic and Metabolic Drugs Advisory Committee met to provide guidance regarding studies of GH treatment in pediatric patients with non-GH deficient forms of short stature. The committee unanimously agreed that the critical endpoint was final height and that such studies should include a control group.

1992: In response to a third party challenge who asserted that the study was being conducted contrary to the principles that should be followed when using children in medical research., the NIH convened an external advisory panel, the Human Growth Hormone Protocol Review Committee. The committee concluded that the protocol addressed an important public health need and did not violate any of the applicable Department of Health and Human Services (HHS) regulations cited in the challenge (45 Code of Federal Regulations [CFR] Part 46). It was recommended that a Data and Safety Monitoring Board (DSMB) be convened to conduct an independent review of the study on a regular basis.

05 June 2000: The DSMB recommended unanimously that the placebo-controlled study be terminated, that active patients be offered the option to receive open-label treatment, and that the results be published as soon as possible. The DSMB concluded that the study was not maturing sufficiently to justify the maintenance of a placebo injection control group. Subsequently, Lilly submitted a statistical analysis plan, reviewed and approved by the NIH Institutional Review Board, before the study was unblinded.

26 September, 2002: Lilly submitted a supplemental NDA for Humatrope for non-growth deficient short stature.

10 June 2003: The Endocrinologic and Metabolic Drugs Advisory Committee met and recommended that Humatrope should be approved by the agency for the treatment of NGHDS (see quick minutes of the meeting in Appendix C.)

D. Other Relevant Information/Foreign Marketing History

Humatrope is an approved GH product in 75 countries. The approved indications vary from country to country. In addition to the US approved indications, in some countries, Humatrope is approved for treatment in achondroplasia and chronic renal insufficiency. There is no listed indication for children with non-growth hormone deficient short stature.

E. Important Issues with Pharmacologically Related Agents

Recombinant human growth hormone (somatropin) is the major form of growth hormone currently on the market. There are no other chemically related approved or investigational compounds relevant to this application.

II. Clinically Relevant Findings From Chemistry, Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

This application does not provide any new information concerning chemistry, animal toxicology, microbiology or clinical pharmacology. Overall, the efficacy conclusions of the statistical review are consistent with the efficacy conclusion of the applicant (see statistical review for details).

III. Human Pharmacokinetics and Pharmacodynamics

The pharmacokinetics (PK) and pharmacodynamics (PD) of Humatrope (and growth hormone in general) are well characterized and appropriately labeled. No additional PK/PD information is provided in this submission.

The Humatrope label indicates that the PK characteristics of the product have been studied following intramuscular, subcutaneous, and intravenous administration in adult volunteers. The absolute bioavailability of somatropin is 75% and 63% after subcutaneous and intramuscular administration, respectively. The PK characteristics of Humatrope in pediatric patients are similar to adults. The metabolic fate of somatropin involves classical protein catabolism in both the liver and kidneys. The mean half-life of subcutaneously administered somatropin is 3.8 hours. The clinical pharmacology section of the label describes the Humatrope actions on tissue growth, protein, carbohydrate, lipid and mineral metabolism.

IV. Description of Clinical Data and Sources

A. Overall Data

This clinical review has been conducted from the electronic NDA submission (dated September 26, 2002) and subsequent submissions dated October 11, 2002, January 6, 2003, February 17, 2003, March 25, 2003, April 2, 2003, June 17, 2003, and June 19, 2003. The NDA contains efficacy data from one placebo-controlled study of Humatrope (trial GDCH) and one dose-range trial of Humatrope (trial E001). In addition, it contains literature review of efficacy clinical trials conducted with other growth hormone drug products in patients with NGHDSS. For safety analysis, the applicant provided the following additional data: (1) a comparison of the safety profile of Humatrope in patients with NGHDSS, Turner syndrome and growth hormone deficiency and (2) supportive safety data from two other trials of Humatrope, previously reported to the agency.

B. Tables Listing the Clinical Trials

The two major efficacy clinical trials that constitute the basis for this supplemental NDA are summarized in table 1. The trials that provide additional supportive safety information are presented in the Integrated Review Section of this clinical review and in Appendix B..

Table 1: Summary of Lilly Efficacy Studies of Humatrope in Patients with Non-Growth Hormone Deficient Short Stature

Study Name	Design	Clinical study characteristics				
		No. and age of patients	Main inclusion criteria	Duration of treatment	Regimen	Criteria for evaluation
GDCH (USA)	Multicenter, double-blind, randomized, parallel, placebo-controlled	Enrolled: 71 patients (55 males 16 females) Ages: 9.2- 15.2 y (mean age: 12.4 y)	Pubertal stage I or II males and females with NGHDSS and height SDS or predicted height SDS ≤ -2.5 or ≤ -2.25 (amended)	Until HV fell below 0.5 cm/ y, or 1.5 cm/ y (amended) Mean duration: 3.5 \pm 1.8 y	Humatrope 0.074 mg/ kg, given TIW by sc injection (0.222 mg/ kg/ wk) Placebo given TIW by sc injection	Final height SDS for the <i>Final Height Population*</i>
E001 (Europe)	Open- label, randomized, parallel, dose-response	Enrolled: 239 patients (158 males 81 females) Ages: 5.1- 15.2 y (mean age: 9.8 y)	Prepubertal males and females with NGHDSS, height SDS ≤ -2.0 , and HV $< 25^{\text{th}}$ percentile	Initial 2-y dose-response and extension until HV fell below 2.0 cm/ y. Mean duration: 4.5 \pm 2.4 y	Humatrope D1=0.24 mg/ kg/ wk, D2=0.24 mg/ kg/ wk for 1 y, and then 0.37 mg/ kg/ wk thereafter, D3=0.37 mg/ kg/ wk, given 6 times/ wk by sc injection	Change in HV from pre-treatment to two-year endpoint.* Final height SDS for the <i>Final Height Population**</i>

--	--	--	--	--	--	--

Source: Table 3. H. 1. HV = height velocity.

*Primary efficacy analysis.

**Secondary analysis.

C. Postmarketing Experience

Postmarketing efficacy and safety data on Humatrope use in patients with NGHDSS are currently collected by the applicant in a phase IV, multicenter, open-label, observational study named GeNeSIS. An interim safety analysis on 23 patients with NGHDSS enrolled in GeNeSIS is provided in this application and presented in detail in Appendix B. In summary, this analysis does not identify any deaths, serious adverse events, patient dropouts, or unusual/unexpected treatment-emergent adverse events.

Postmarketing experience with GH in general is extensive. It is estimated that close to 100,000 children have been treated with recombinant human GH (Consensus, 2001). A significant number of these patients have NGHDSS and are treated off label. Postmarketing pharmacovigilance data from several sources are published and continuously scrutinized (Wilton P, 1999, Maneatis T, 2000, Consensus, 2001, Lawson Wilkins Pediatric Endocrine Society 2003). In general, GH therapy has been safe, although long-term effects of GH therapy in children are not known.

D. Literature Review

A large number of studies have been undertaken over the last two decades that investigated growth hormone treatment in patients with NGHDSS. A recent meta-analysis of 38 studies (10 controlled, 28 uncontrolled) provides a comprehensive analysis of recombinant GH treatment in patients with NGHDSS (Finkelstein et al, "Effect of growth hormone therapy on height in children with idiopathic short stature. A meta-analysis" *Arch Pediatr Adolesc Med*, 2002). This study was submitted by the applicant as supportive evidence of efficacy and is summarized next.

The objective of the study was to determine the effect of GH on short- and long-term growth in patients with idiopathic short stature. The study design consisted in a systematic review of controlled and uncontrolled studies of GH use in patients with idiopathic short stature. Data sources included, among many, a comprehensive MEDLINE search for the period 1985-2000 (1985 was the year of approval of GH by the agency and, at the same time, it was the year when biosynthetic GH became widely available). Studies were included in the meta-analysis if they met several criteria including the following:

- the topic was short stature (height below the 10th percentile for age)
- the patients presented as GH-naïve patients and had an absence of classic GH deficiency (peak GH levels were ≥ 10 mcg/L on ≥ 1 standard stimulation test)
- there were no comorbid conditions that impair growth (e.g. Turner syndrome, renal failure, intrauterine growth retardation, GH insensitivity)
- the treatment was biosynthetic (not pituitary-derived) GH in a range of 0.14 to 0.40 mg/kg/week for a minimum of 6 months

- the study presented primary data and included appropriate height outcome measures (growth velocity or height)

The primary outcome measures were growth velocity and height SDS at baseline and after 1 year for short-term effect of GH treatment. Adult height was analyzed to evaluate the long-term effect of GH. Thirty eight studies met the inclusion criteria and were further analyzed. The controlled and the uncontrolled trials were analyzed separately. They were ten controlled trials (controlled meant an available concurrent control group; 6 were randomized, 4 non-randomized, 434 patients total) and 28 uncontrolled trials (655 patients).

Two types of analyses were performed: aggregate and paired. Aggregate analyses calculated pooled estimates across all studies reporting each growth variable. Paired analyses provided pooled estimates of baseline growth variables across those studies reporting that variable as an outcome.

Adult height was measured in four controlled studies. Across these four studies, the mean duration of treatment was 5.3 years. The weighted average GH dosage for the children in these studies was 0.31 mg/kg/wk. For the controlled studies, the dose was administered six times per week. While no significant differences between treatment and control groups were noted at baseline, the mean between-group difference in adult height SDS between the treatment group and the control group ranged from 0.78 (paired analysis) to 0.84 (aggregate analysis), which corresponds to 5 to 6 cm (range, 2.3 to 8.7 cm).

In addition to comparing adult height of GH-treated and control groups, the authors also compared adult height achieved with that predicted at baseline. In this analysis, the adult height SDS achieved by the GH-treated patients exceeded baseline predicted height SDS by 0.54 (aggregate analysis) to 0.65 (paired analysis), which corresponds to 3.6 to 4.6 cm. Figure 1 illustrates this comparison of the mean difference in height SDS between treatment and control groups for baseline predicted adult height and achieved adult height. The GH effect on final height is reflected by the significantly greater difference between treatment and control groups for achieved adult height SDS over baseline predicted height SDS.

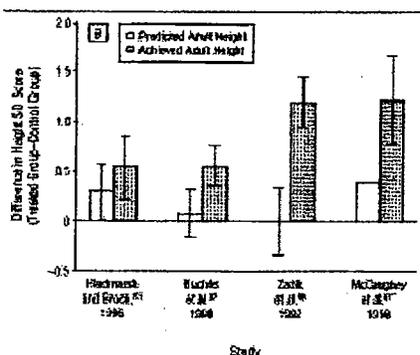
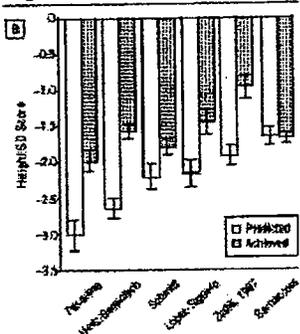


Figure 1: Difference in height standard deviation score for controlled studies

Source: Figure 3.H.9. reproduced from Finkelstein et al. (2002).

In uncontrolled trials, the assessment of effect of GH on adult height was based on comparison of adult height achieved with that predicted at baseline. The mean duration of treatment was 4.7 years, and the weighted average GH dosage was 0.27 mg/kg/wk. The dose was administered six times per week. The baseline mean predicted adult height was -2.18 SDS. In the aggregate analysis, the adult height attained was -1.62 SDS. Similarly, in the paired analysis, the predicted adult height at baseline was -2.25 SDS, whereas the height actually achieved after GH therapy was greater (-1.62 SDS). The difference between achieved adult height SDS and baseline predicted height SDS ranged from 0.56 (aggregate analysis) to 0.63 (paired analysis), which corresponds to 3.8 to 4.5 cm. These results are similar to those for the controlled trials. Figure 2 presents the paired analysis comparison of baseline predicted height SDS versus achieved adult height SDS for the uncontrolled studies.

Figure 2: Height standard deviation score for uncontrolled studies



Source: Table 3.H.10 reproduced from Finkelstein et al. (2002).

In all but one study the GH-treated patients achieved a significantly greater adult height SDS than was predicted at baseline. In summary, the studies in this meta-analysis suggest an average gain in adult height of approximately 4 to 6 cm (range 2.3 to 8.7 cm for controlled studies) following GH treatment of patients with NGHDSS.

V. Clinical Review Methods

A. Overview of Materials Consulted in Review /How the Review was Conducted

This clinical review has been conducted from the electronic submission and, to a lesser extent, paper copies of this NDA. All the clinical studies submitted in this application were reviewed. Original data and tables were re-formatted in order to follow the structure of this clinical review (the NDA source for each re-formatted table is listed at the bottom of the table). Extensive data in table format are included in the clinical review to serve as references for future inquires by primary, secondary, and tertiary reviewers.

B. Ethics Review/ Ethical Conduct of the Study

The application summary states that, for U.S. study GDCH, all protocol amendments, informed consent documents, assent forms, clinical investigator's brochure (with subsequent updates), and any relevant curricula vitae were provided to the Ethics Review Board as required. Informed consent/assent documents were clear and complete.

The European study E001 was initiated in 1987, prior to the 1996 implementation of the International Conference on Harmonization (ICH) guidelines. The protocol and informed consent documents were approved by the Institutional Review Board (IRB) or Ethics Review Board (ERB) at each hospital or university, if the hospital or university had a duly constituted IRB. For sites that did not have an IRB, approval was obtained either from another site's IRB or from the European Ethics Review Committee, an Independent Ethics Committee that was created in 1977 to review multicenter, transnational protocols for clinical studies carried out in Europe and associated states.

On the basis of the submitted information, this reviewer does not find any ethical violations.

Study GDCH deserves additional comments since it has been the subject of intense ethical scrutiny. In 1987, an Endocrinologic and Metabolic Drugs Advisory Committee met to provide guidance for growth hormone manufacturers regarding studies of GH treatment in pediatric patients with non-GH deficient forms of short stature. The committee unanimously agreed that the critical endpoint was final height and that such studies should include a control group. Although there were concerns about the type and feasibility of the control, the committee recommended that "...the control group should be a placebo-treated, parallel, randomized group of patients..." and that "...the subjects should be followed until their ultimate height is reached..." Study GDCH was initiated in January 1988. In 1992 there was a challenge to the study by a third party who asserted that the study was being conducted contrary to the principles that should be followed when using children in medical research. In response to this challenge, the NIH convened an external advisory panel, the Human Growth Hormone Protocol Review Committee. The committee concluded that the protocol addressed an important public health need and did not violate any of the applicable Department of Health and Human Services regulations cited in the challenge (45 Code of Federal Regulations [CFR] Part 46). It was recommended, however, that a Data and Safety Monitoring Board (DSMB) be convened to conduct an independent review of the study on a regular basis and to evaluate the appropriateness of continuing the study in the context of these data and any other relevant published data. The DSMB was convened for the first time in 1993, then annually through 1999. Each time it recommended continuation of the study. In June, 2000, the DSMB met and recommended that the placebo-controlled study be terminated, that active patients be offered the option to receive open-label treatment, and that the results be published as soon as possible. At that time, patients were reaching final height at a rate of 2 per year, and it would have required approximately 5 additional years before the remaining patients reached final height, during which time there likely would have been further dropouts. The DSMB, therefore, unanimously concluded that the study was not maturing sufficiently to justify the maintenance of a placebo injection. The sponsor followed the recommendations of the DSMB.

C. Financial Disclosure

Financial disclosure documents are provided for U.S. pivotal study GDCH. They contain a signed statement from Dr. Gordon Cutler, Eli Lilly Medical Adviser, stating that there was no financial arrangement with the listed clinical investigators, that none of the listed (20) investigators disclosed any proprietary interest or significant equity in the product, and that no listed investigator was a recipient of significant payments of other sorts as defined in 21 CFR 54.2 (I). Six subinvestigators failed to report financial certification and disclosure information despite, reportedly, repeated attempts by the applicant to do so; none of them were principal investigators.

No financial disclosure documents are provided for the supportive study E001, which was conducted in Europe.

D. Data Quality and Integrity

There was no DSI audit. The submitted data appeared complete and no inconsistencies or errors were identified between tables and text in different sections of the submission.

The following summarizes the data on the conduct of the clinical trials provided in the application. Study GDCH took place primarily at the National Institutes of Health. Dr. Gordon B. Cutler, Jr, the initial PI for the study left NIH and joined Eli Lilly in 1997 as the medical director for the Humatrope Product Team. At Lilly, Dr Cutler, reportedly, was excluded from all direct management of the study and from data analysis conducted for the internal Data Monitoring Board review. He was blinded to all data until the data lock was completed and the locked study database was unblinded. The study was originally managed by Lilly. During the period between 1988 and 1995, clinical research monitors conducted annual or more frequent monitoring visits.

included regular monitoring visits at the study sites, collection and maintenance of clinical site regulatory documents, and data transfer to Lilly.

Study E001 was conducted by 28 endocrinologists at 28 study sites in 10 countries. The coordinating investigator for this study was

The study was monitored throughout by Lilly. The data management for the study was transferred to several CROs.

VI. Integrated Review of Efficacy

A. Efficacy Conclusions

This application provides evidence that Humatrope treatment is efficacious in increasing final height in patients with non-growth hormone deficient short stature (NGHDSS). In a placebo-controlled clinical trial, a Humatrope regimen of 0.22 mg/kg/week increased final height by 3.7 cm. or approximately 0.5 SD over placebo. Individual efficacy showed marked variability (95% CI: 0.1-0.92 SD). In a dose-response clinical trial of Humatrope in which a subgroup of patients has been followed to final height, a 0.37 mg/kg/week regimen of Humatrope added on the average 3 cm or a little less than 0.5 SD to a Humatrope regimen of 0.24 mg/kg/week (individual responses were variable). This implies a mean treatment effect of approximately 6 cm or 1 SD over placebo. This magnitude of treatment effect is consistent with published observations in other clinical trials. There are no major differences in the interpretation of efficacy data between this reviewer and the sponsor.

B. General Approach to Review of the Efficacy of the Drug

The efficacy of Humatrope treatment in improving final height in patients with NGHDSS is based on evidence provided by two Lilly clinical studies and published literature. The two Lilly clinical studies are study GDCH (double-blind, randomized, placebo-controlled) and study E001 (randomized, open-label, dose-response). These two studies are presented in detail in the next section of the clinical review along with supportive efficacy data from peer-reviewed medical literature. For each trial, the objective, trial design, inclusion/exclusion criteria, clinical endpoints, baseline patient characteristics and planned analyses will be described prior to presenting the efficacy analyses. In a pre-NDA meeting the agency waived the request of an integrated summary of efficacy on the basis of the fact that clinical trials GDCH and E001 have different designs.

C. Detailed Review of Trials by Indication

C.1. Pivotal Clinical Study GDCH

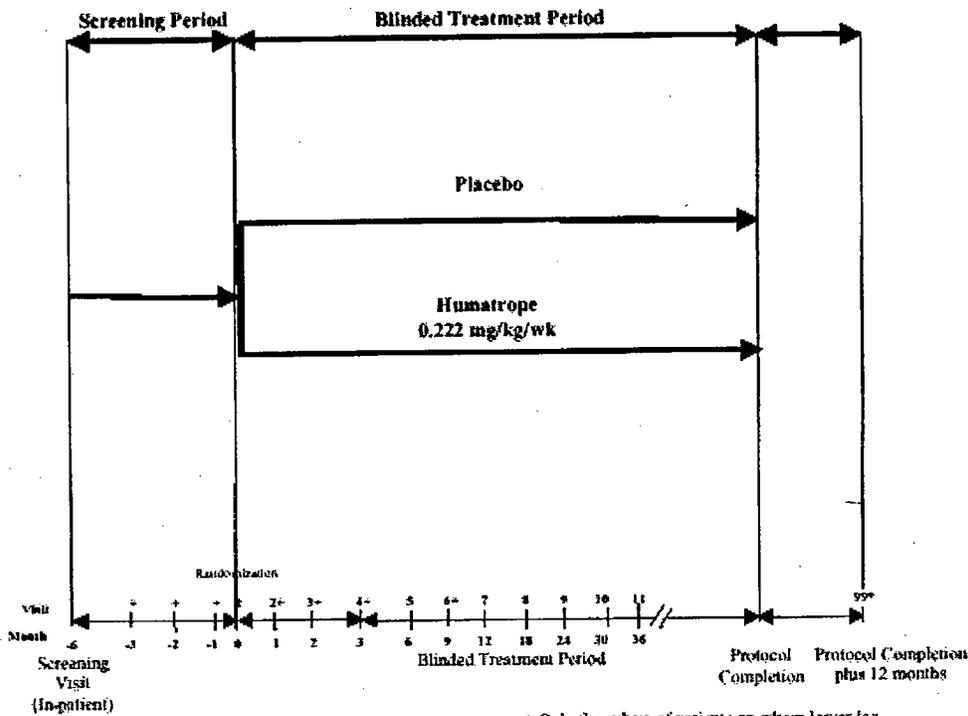
C.1.1 Objective

The primary objective of this study was to test the hypothesis that Humatrope treatment would improve final height when compared to placebo in pediatric patients with NGHDSS. Final height was defined as the height following a measured height velocity < 0.5 cm/y (later amended to < 1.5 cm/y)

C.1.2 Study Design

This clinical trial is a two-center, double-blind, randomized, parallel group, placebo-controlled study conducted between January 1988 and February 2001 in U.S.A. Figure 3 presents the study design. The study included of a screening period and a blinded treatment period. During the screening period each patient underwent an inpatient screening visit. The patients who met inclusion/exclusion criteria were randomized 1:1 to Humatrope and placebo. In addition, patients were stratified according to baseline predicted adult height. During the blinded period, patients received injections of placebo or Humatrope (0.222 mg/kg/wk). Patients were evaluated every 6 months until they reached final height. Patients who completed the study were asked to return for a final height measurement 1 year after protocol completion. Patients who discontinued the study prior to protocol completion were asked to return for a final height measurement after height velocity, measured locally, had fallen below 1.5 cm/y. Humatrope was administered subcutaneously in divided doses given 3 days per week.

Figure 3: Study design of trial B9R-MC-GDCH



+ Only the subset of patients on whom lower leg measurements were obtained attended study Visits 2 to 4 and 6.
 * Poststudy Summary Visit (Visit 99): 1 year after protocol completion, for patients completing the protocol; at final height, for patients who discontinued the study before protocol completion.

*Source: Figure GDCH.9.1.

C.1.3 Main Inclusion and Exclusion Criteria

The main inclusion criteria are listed in Table 2.

Table 2: Inclusion Criteria – Trial GDCH

Height	Height or predicted adult height (Bayley-Pinneau) had to be ≤ -2.5 (amended to ≤ -2.25 then back to ≤ -2.5) standard deviations (SD) below the mean within the 12 months prior to treatment initiation.
Chronological age	9 to 15 years (females) and 10 to 16 years (males).
Bone age	≤ 11 years in females and ≤ 13 years in males
Tanner stage	$\leq II$
Criterion for growth hormone sufficiency	Peak GH response > 7 ng/mL to arginine-insulin or levo-dopa, and/or other accepted GH-stimulation tests.
Thyroid function	Normal or stable on replacement therapy.
Karyotype	Normal for all females and in selected males where indicated

Height velocity was not an inclusion criterion. Exclusion criteria were: prior growth hormone therapy, chronic illnesses, malignancies, CNS trauma, psychiatric risk, unbalanced home environment, prior hormone therapy (GH, estrogens, androgens, glucocorticoids), or therapy with drugs that may interfere with GH secretion or action.

C.1.4. Protocol amendments

There were seven protocol amendments. They are summarized in Table 3 below:

Table 3: Summary of Protocol Amendments

Name/time of Amendment	Content of Amendment	Patients enrolled
B9R-MC-GDCH(a), September 1987	<ul style="list-style-type: none"> added fasting glucose, insulin and lipid assessments performed at baseline and every 6 months* added an oral glucose tolerance test with insulin measurements, performed in those patients found to have abnormally high fasting glucose and/or HbA1c concentrations* 	0
B9R-MC-GDCH(b) February 1988	<ul style="list-style-type: none"> clarified required GH stimulation tests added the Lilly Quality Assurance personnel to the list of individuals not blinded to treatment group assignment added measurements of arm span, head circumference and lower leg lengths, and added thyroid function tests blocked randomization was added, with patients grouped by gender and predicted adult height* enrolment criterion changed (height or predicted height at least 2.25 SD below the mean instead of 2.5 SD below the mean) 	3
B9R-MC-GDCH(c), January 1993.	<ul style="list-style-type: none"> frequencies of patient visits and study procedures in the first year were reduced height and predicted height enrollment criterion changed back to original (height or predicted height at least 2.5 SD below the mean) 	40
B9R-MC-GDCH(d),	<ul style="list-style-type: none"> added final visit (Visit 99) changed the criterion for protocol completion to height velocity < 1.5 	45

January 1994	cm/y instead of height velocity <0.5 cm/y, based on measurements made at 12-month intervals	
B9R-MC-GDCH(e), May 1995.	<ul style="list-style-type: none"> reduced the number of laboratory tests E. Coli Protein (ECP) antibody data collection discontinued (negative titers) 	54
B9R-MC-GDCH(f), April 1998.	<ul style="list-style-type: none"> TRH-stimulated TSH and diurnal TSH concentrations at the 6-month inpatient visit were deleted (no effect noted on treatment). 	68
B9R-MC-GDCH(g), January 2001.	<ul style="list-style-type: none"> In response to a recommendation by the DSMB on 5 June 2000, this amendment terminated the blinded treatment period of the study and added an open-label extension phase to provide Humatrope-treated patients the opportunity to continue on Humatrope and to allow placebo patients the option to receive Humatrope treatment a detailed analysis plan, reviewed and approved by the NIH Institutional Review Board (IRB), was added. 	71

*FDA suggested according to applicant submission.

C.1.5. Data and Safety Monitoring Board

At the recommendation of an NIH advisory panel, which met in 1992, an external Data Safety Monitoring Board (DSMB) was established. It reviewed blinded interim safety and efficacy data on an annual basis from 1993 to 2000. In 2000, the DSMB recommended that the placebo-controlled study be terminated and that the results of the study should be published. Active patients were offered the option to receive open-label treatment.

C.1.6 Patient Disposition

The information on patient disposition is summarized in Table 4. A total of 71 patients were randomized (38 to Humatrope and 33 to placebo). Of the 71 randomized patients, 68 patients received study drug and were included in the Safety Population (3 patients discontinued the study prior to receiving any study drug; two in the placebo group because they did not meet protocol entry criteria, and one in the Humatrope treatment group due to physician decision).

The intent-to-treat population was defined as any patient who received study drug and had height velocity recorded at 6 months. The applicant called this population the "Efficacy Evaluable Population." It included 64 patients. Three patients discontinued without a height measurement at 6 months, one in the placebo group and two in the Humatrope group (all three discontinuations were due, reportedly, to patient decisions). One additional placebo patient (008/1201) was excluded from the Efficacy Evaluable Population because he/she received GH outside the study.

The 25 patients who completed the protocol were the Protocol Complete Population. These 25 patients along with 8 patients from the Efficacy Evaluable Population who had discontinued the study prior to protocol completion but returned for a final height measurement while still blinded to treatment assignment were included in the Final Height Population. Therefore, there were 33 patients in the Final Height Population (placebo, n = 11; Humatrope, n = 22).

Table 4: Patient Disposition

Population	Humatrope N (%)	Placebo N (%)	Total N (%)
All randomized	38 (100%)	33 (100%)	71 (100%)
Safety	37 (97%)	31 (94%)	68 (96%)
Efficacy Evaluable	35 (92%)	29 (88%)	64 (90%)
Protocol complete	16 (42%)	9 (27%)	25 (35%)
Final Height*	22 (58%)	11 (33%)	33 (46%)

N=number of patients. % is percentage of patients within each group (column).

*Includes protocol completers and 8 additional patients who returned for final height measurements.

Source: Table GDCH.11.1

The reasons for patient discontinuation for the All Randomized Population are displayed in Table 5. Most discontinuations were due to patients' decision: 17 patients (44.7%) in the Humatrope group and 12 patients (36.4%) in the placebo group. Four patients (12.1%) were lost to follow-up (all in the placebo group). One patient in each treatment group discontinued due to an adverse event (for the patient in the placebo group the adverse event occurred after trial discontinuation). Eight patients (three in the Humatrope group and five in the placebo group) were discontinued ("sponsor's decision") after the DSMB recommended the termination of the blinded period of the trial, at which time all remaining patients were given the option to receive open-label Humatrope.

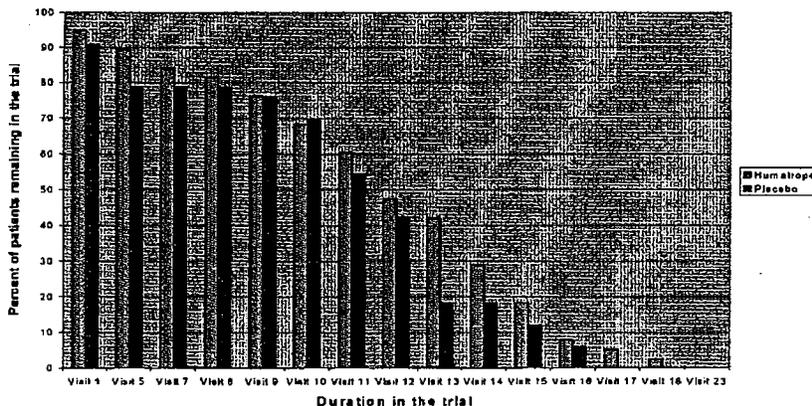
Table 5: Reasons for Study Discontinuation (All Randomized Population)

Reasons for Discontinuation	Humatrope N=38	Placebo N=33	Total N=71
Protocol completed	16 (42.1%)	9(27.3%)	25(35.2%)
Adverse event	1 (2.6%)	1 (3.0%)	2(2.8%)
Lost to follow-up	0	4 (12.1%)	4(5.6%)
Entry criteria violation	0	2 (6.1%)	2(2.8%)
Sponsor's decision	3(7.9%)	5(15.2%)	8(11.3%)
Patient decision	17(44.7%)	12(36.4%)	29(40.8%)
Physician decision	1(2.6%)	0	1(1.4%)

Source: Tables GDCH.10.1., GDCH.10.2., and GDCH.10.3.

Figure 4 displays the number of patients in each treatment arm who remained in the trial as a function of time. A steady decline of patients in the trial occurred over time. Although a larger proportion of patients discontinued in the placebo group, overall, the number of patients per treatment group was comparable for most of the trial duration.

Figure 4: Patient Retention in Trial GDCH



Source: Table GDCH.10.5. Visit 1 is the time of randomization; all subsequent visits are 6 months apart.

C.1.7. Protocol violations

Significant protocol violations are defined as deviations from the protocol that could have had an impact on patient safety, data integrity, or conclusions drawn from the study. A list of all protocol violations is presented in Table 6.

Table 6: Significant Protocol Violations All Randomized Patients

Violation Category	Humatrope	Placebo	Overall
	N=38 n (%)	N=33 n (%)	N=71 n (%)
Entry Criteria Not Met	0 (0.0)	2 (6.1)	2 (2.8)
Informed Consent/Assent Issues	1 (2.6)	3 (9.1)	4 (5.6)
Incorrect Study Drug Administered	0 (0.0)	1 (3.0)	1 (1.4)
Received Excluded Concomitant Medications	2 (5.3)	2 (6.1)	4 (5.6)
Study Procedure Not Performed Correctly	6 (15.8)	3 (9.1)	9 (12.7)

Abbreviations: N = number of patients enrolled, n = number of patients with protocol violation.

Source: Table GDHC.10.7.

Entry criteria violations: Two patients enrolled in the placebo group did not meet the study entry criteria. They were discontinued prior to receiving study drug.

Informed consent/assent: One patient in the Humatrope group and 3 patients in the placebo group had violations related to the signing of informed consent/assent documents (all violations were relatively minor).

Study drug: Incorrect study drug was administered to Patient 007/1601, who was enrolled in the placebo group. Due to errors in study drug handling, this patient received Humatrope instead of placebo during two 6-month periods. The patient was allowed to continue the study (blinding was maintained). The patient experienced a substantial increase in height velocity during the first period of Humatrope administration which coincided with puberty and transition from Tanner stage III to Tanner stage IV of puberty (approximately 14.4 to 15 years of age) during this time. During the second period of Humatrope administration, the patient was at Tanner stage V of puberty (approximately 16.4 to 16.9 years of age), and no effect on height velocity was observed (the patient was included in the Final Height Population and was counted in the placebo group).

Excluded medications: Four patients received excluded medications. Patient 008/1060 (placebo, Final Height Population) received 10 mg/day of Ritalin (methylphenidate) for 1 month beginning at 16 years of age. Patient 008/1066 (placebo) received 15 mg/day of Ritalin for less than 1 year beginning at approximately 13.1 years of age. Patient 008/1082 (Humatrope) received 10 mg/day of Ritalin for 6 months) at approximately 12.5 years of age; a decline in this patient's height velocity was observed during this time. Patient 008/1203 (Humatrope, Final Height Population)

received Cylert (pemoline) for approximately 2.9 years (19 to 93.75 mg/day), between approximately 12.4 and 15.3 years of age, and Ritalin-SR for at least 1 year while active in the study (1 tablet of unidentified dosage per day). This patient experienced some variability in height velocity during the time she received the excluded medications.

Study procedures: There were nine instances where study procedures were performed incorrectly. In the Humatrope group, five patients fasted for less than 5 hours prior to obtaining samples for blood glucose and for one patient the fasting status at one visit is unknown. In the placebo group, one patient fasted for less than 5 hours on several occasions and two patients had unknown fasting status one occasion each.

Three of the above-mentioned violations had the potential to influence the primary efficacy analysis: a placebo patient who received GH (this would bias against the drug, however) and two Humatrope patients who received GH-suppressing medications. The exposure to Ritalin was very short for the placebo patient (1 month) and the exposure for the Humatrope-receiving patient would bias against the drug.

C.1.8 Treatment compliance

A study patient was considered compliant if he/she/ received $\geq 80\%$ of expected injections. Table 7 summarizes the number and percent of compliant patients for the Efficacy Evaluable Population and the Final Height Population. Compliance was slightly higher in the Humatrope-treated group when compared to placebo. Patients in the Final Height Population showed better compliance than patients in the Efficacy Evaluable Population.

Table 7: Study Compliance

Patients who received $\geq 80\%$ of expected injections	Efficacy Evaluable Population		Final Height Population	
	Humatrope (N=35) n (%)	Placebo (N=29) n (%)	Humatrope (N=22) n (%)	Placebo (N=11) n (%)
Yes	26 (74.3)	20 (69.0)	19 (86.4)	9 (81.8)
No	9 (25.7)	9 (31.0)	3 (13.6)	2 (18.2)

Source: Table GDCH.11.7. and GDH.11.8.

Overall, patients in the Humatrope-treated group received a larger proportion of the expected injections (mean=88.3%) than the placebo-treated group (mean=84.1%) among the Efficacy Evaluable Population. This was barely the case in the Final Height Population, where the Humatrope-treated group received 89.3% of expected injections while the placebo-treated group received 88.7% of the expected injections.

C.1.9 Baseline Patient Characteristics

The main growth-related parameters recorded at baseline are presented in Table 8. The mean height SDS was -2.78 ± 0.48 . The mean predicted adult height SDS at the initiation of treatment was higher (-2.09 ± 0.79). The mean bone age was delayed (bone age/chronological age ratio was 0.84 ± 0.12). The target height SDS (-1.08 ± 0.88) was below the population mean. Patients were predominantly Tanner stage I (47.4% Humatrope vs. 42.4% placebo) or Tanner 2 stage of

sexual development (47.4 % Humatrope vs. 45.5% placebo). A few patients were Tanner stage III (5.3% Humatrope and 12.1% placebo).

Table 8: Growth Characteristics at Baseline-All Randomized Patients

Variable	Humatrope (N=38) Mean (SD)	Placebo (N=33) Mean (SD)	Total (N=71) Mean (SD)
Weight (kg)	30.33 (5.12)	30.24 (6.03)	30.29 (5.52)
BMI (kg/m ²)	17.09 (1.70)	17.53 (2.64)	17.29 (2.18)
Height (cm)	132.84 (8.19)	131.00 (7.74)	131.98 (7.98)
Height SDS	-2.75 (0.49)	-2.81 (0.49)	-2.78 (0.48)
Height Velocity (cm)	4.81 (1.80)	4.77 (2.07)	4.79 (1.92)
Height Velocity (SDS)	-0.6 (1.1)	-0.8 (1.2)	-0.7 (1.2)
Chronological Age (CA)	12.50 (1.61)	12.25 (1.40)	12.38 (1.51)
Bone Age (yrs)*	10.45 (1.86)	10.36 (1.72)	10.41 (1.79)
BA/CA Ratio*	0.84 (0.12)	0.84 (0.11)	0.84 (0.12)
Predicted Height (cm)**	159.34 (8.25)	156.90 (8.12)	158.26 (8.22)
Predicted Height (SDS)**	-1.96 (0.75)	-2.26 (0.83)	-2.09 (0.79)
Target Height (cm)***	165.94 (8.40)	165.13 (8.34)	165.59 (8.32)
Target Height (SDS)***	-1.00 (0.97)	-1.19 (0.74)	-1.08 (0.88)
IFG-I (ng/ml)****	189.57 (74.11)	225.58 (100.3)	N/A
IFG-I SDS****	-1.93(1.11)	-1.39 (1.56)	N/A

*Calculated from 36 patients in Humatrope Group and 28 patients in placebo group.

** Calculated from 35 patients in Humatrope Group and 28 patients in placebo group. BPH was assessed for only those patients who were in the study for >6 months. Some baseline bone age assessments from the central reader were missing, for unknown reasons.

*** Calculated from 38 patients in Humatrope Group and 29 patients in placebo group.

****Includes baseline data for the 68 patients that constitute the safety population instead of the 71 all randomized patients. N/A = not available

Source: Table GDH.11.2. and Table A4

Gender and racial baseline characteristics are presented in Table 9. There were three times more male patients enrolled in the trial when compared to female patients in either treatment group. Most patients enrolled were Caucasian, with a small Hispanic subgroup. There were only one African American and one Asian patient enrolled in the trial (both in the placebo treatment group).

Table 9: Baseline Gender and Racial/Ethnic Characteristics-All Randomized Patients

Variable	Humatrope (N=38)	Placebo (N=33)	Total (N=71)
Gender	Male	29 (76.3%)	55 (77.5%)
	Female	9 (23.7%)	16 (22.5%)
Origin	African	0	1 (1.4%)
	Asian	0	1 (1.4%)
	Caucasian	30 (78.9%)	55 (77.5%)
	Hispanic	7 (18.4%)	11 (15.5%)
	Other	1 (2.6%)	2 (6.1%)

Source: Table GDCH.11.2.

Baseline growth characteristics for the patients in the Final Height Population were similar to those recorded for the randomized patients. They are listed in Table 10.

Table 10: Growth Characteristics at Baseline–“Final Height” Patients

Variable Mean (SD)	Humatrope (N=22)	Placebo (N=11)	Total (N=33)
Weight (kg)	30.14 (5.01)	31.95 (5.38)	30.74 (5.13)
BMI (kg/m ²)	17.01 (1.78)	17.50 (2.15)	17.17 (1.89)
Height (cm)	132.82 (7.95)	134.88 (6.74)	133.51 (7.52)
Height SDS	-2.69 (0.55)	-2.75 (0.57)	-2.71 (0.55)
Height Velocity (cm)	5.20 (1.81)	5.63 (2.35)	5.35 (1.98)
Chronological age (CA)	12.49 (1.61)	12.90 (1.06)	12.63 (1.44)
Bone Age (yrs)*	10.40 (1.89)	10.67 (1.15)	10.48 (1.68)
BA/CA Ratio*	0.84 (0.13)	0.81 (0.07)	0.83 (0.11)
Predicted Height (cm)**	158.96 (7.49)	157.43 (7.82)	158.48 (7.50)
Predicted Height (SDS)**	-2.08 (0.69)	-2.26 (0.80)	-2.14 (0.72)
Target Height (cm)**	165.83 (8.16)	164.30 (8.40)	165.35 (8.13)
Target Height (SDS)**	-1.11 (1.00)	-1.32 (0.69)	-1.18 (0.91)

*Calculated from 21 patients in Humatrope Group and 9 patients in placebo group.

** Calculated from 22 patients in Humatrope Group and 10 patients in placebo group. BPH was assessed for only those patients who were in the study for >6 months. Some baselining bone age assessments from the central reader were missing, for unknown reasons.

Source: Table GDH.11.4.

An inspection of historical diagnoses (medical conditions that resolved prior to study entry) and secondary conditions at the time of trial initiation did not identify any interpretable imbalances between the two treatment groups. Several patients (6 out of 71) were small for gestational age (SGA). SGA was not an approved GH indication at the time of initiation of the GDCH clinical trial. Five SGA patients were in the Humatrope group and one in the placebo group. All but one (patient 1081, Humatrope group) were part of the Final Height Population. A list of SGA patients is provided in Table 11 (a patient was determined to have been born SGA if his or her birth weight SDS was <-2). In addition, seventeen patients did not have complete birth data (birth weight, gestational age, or both) and a determination as whether they were SGA or not cannot be made.

Table 11: Small for Gestational Age Patients in Study GDCH (All patients)

Patient number	Treatment group	Gestational age (weeks)	Birth Weight (kg)	Birth weight (SDS)
1003	Humatrope	37	1.11	-4.69
1055	Humatrope	33	1.09	-3.24
1061	Placebo	38	2.30	-2.08
1069	Humatrope	40	2.41	-2.33
1081	Humatrope	38	2.16	-2.43
1106	Humatrope	39	2.39	-2.26

Source: AS.1.1.

C.1.10. Efficacy

C.1.10.1. Data sets analyzed

The applicant conducted efficacy data analysis in three patient populations of study participants:

- The Efficacy Evaluable Population. It includes all patients who had a height measurement at Visit 5 (approximately 6 months). This population serves as the intent-to-treat population for this study (64 patients).
- The Final Height Population. It includes patients in the Efficacy Evaluable Population on whom a final height measurement was obtained, either at protocol completion or after discontinuation from the study at a poststudy follow-up visit. Because final height was the predefined endpoint of this study, analysis of efficacy data for the Final Height Population represents the primary efficacy analysis (33 patients).
- The Protocol Complete Population comprises all patients who continued the study until height velocity fell below 1.5 cm/y (25 patients).

Of note is patient 008/1201 (placebo) who was excluded from the Efficacy Evaluable and Final Height Populations because she received growth hormone therapy for approximately 4 to 5 years after discontinuing the study. She was included though in the Safety Population for the placebo group (see the statistical review's modified ITT analysis for a discussion on this patient's lack of significant effect on efficacy analyses and conclusions).

C.1.10.2 Efficacy variables – definitions

C.1.10.2.1. Primary efficacy variable

Final height SDS was the primary efficacy variable. Final height was defined as the last height obtained after the height velocity fell below 1.5 cm/y (either at protocol completion or at a poststudy follow-up visit). Height SDS was calculated from the US growth charts published in the year 2000 by the NCHS/CDC.

C.1.10.2.2 Secondary efficacy variables

The secondary efficacy variables were:

- (1) Height velocity (cm/y). Height velocity was calculated from the difference between two height measurements divided by the time interval (years) between measurements.
- (2) Height velocity SDS. Height velocity SDS was derived by subtracting the age and gender-matched population mean height velocity (cm/y) from the patient's height velocity (based on measurements obtained 12 months apart) then dividing this value by the age and gender-matched population height velocity SD.

C.1.10.5. Efficacy Results

This section summarizes the relevant analyses provided by the applicant. At the end of this section data that define the magnitude of Humatrope treatment effect is highlighted. Due to the small size of the clinical trial, emphasis is placed on both mean and individual measures of efficacy.

The primary analysis was prespecified. Of the secondary analyses, some were prespecified, some were not.

C.1.10.5.1. Primary Analysis-Final Height

The primary efficacy variable was final height SDS. The primary efficacy analysis was a Humatrope-to-placebo comparison of final height SDS for the patients with final height data. Between-group comparisons were performed using analysis of covariance (ANCOVA), with baseline predicted height SDS as the covariate. The two-sided significance level for this analysis was set at $\alpha=0.05$. The results of this analysis are presented in Table 12. The Humatrope effect of 0.51 SDS (which corresponds to a mean 3.7 cm difference between groups) was statistically significant ($p=0.017$). The mean age at assessment of final height was 18.6 years for Humatrope-treated patients and 19.1 years for placebo-treated patients.

Table 12: Final Height SDS (Analysis of Covariance-Final Height Population)

	Humatrope (n=22)	Placebo (n=10) ^a	Effect ^b	p-value
Final height SDS	-1.81 ± 0.11	-2.32 ± 0.17	0.51 ± 0.20	0.017

Note: Data are expressed as least squares mean (LSM) ± standard error of the mean (SEM) using analysis of covariance (ANCOVA) with BPH SDS as covariate.

Abbreviations: BPH = baseline predicted height; n = number of patients; SDS = standard deviation score.

^a Only 10 patients were used in this analysis, as 1 patient was missing the baseline predicted height measurement.

^b Value represents the difference in the final height SDS between the Humatrope-treated group and the placebo-treated group.

Source: Table GDCH.11.9.

C.1.10.5.2. Secondary and Other Analyses

Endpoint Height SDS for the Efficacy Evaluable Population and Final Height for the Protocol Complete Population

The results of an intent-to-treat (ITT) analysis of height SDS for the Efficacy Evaluable Population and of final height SDS for the Protocol Complete Population are presented Table #13 They both indicate a similar magnitude of treatment effect as the primary analysis (about 0.5

standard deviations). The intent-to-treat analysis of height SDS was statistically significant ($p=0.001$). The final height SDS for the small number of patients (25) who completed the protocol showed a trend toward statistical significance ($p=0.061$). Both analyses use the baseline predicted height SDS as a covariate.

Table 13: ANCOVA of Endpoint Height SDS (for the Efficacy Evaluable Population) and Final Height (for the Protocol Complete Population)

Population	Humatrope	Placebo	Effect ^a	p-value
Efficacy Evaluable				
n	35	27 ^b		
Endpoint height SDS ^c	-1.89 ± 0.10	-2.40 ± 0.11	0.52 ± 0.15	0.001
Protocol Complete				
n	16	9		
Final height SDS	-1.86 ± 0.14	-2.32 ± 0.18	0.46 ± 0.23	0.061

Note: Values represent least squares mean (LSM) ± standard error (SE).

Abbreviations: n = number of patients in the analysis; SDS = standard deviation score.

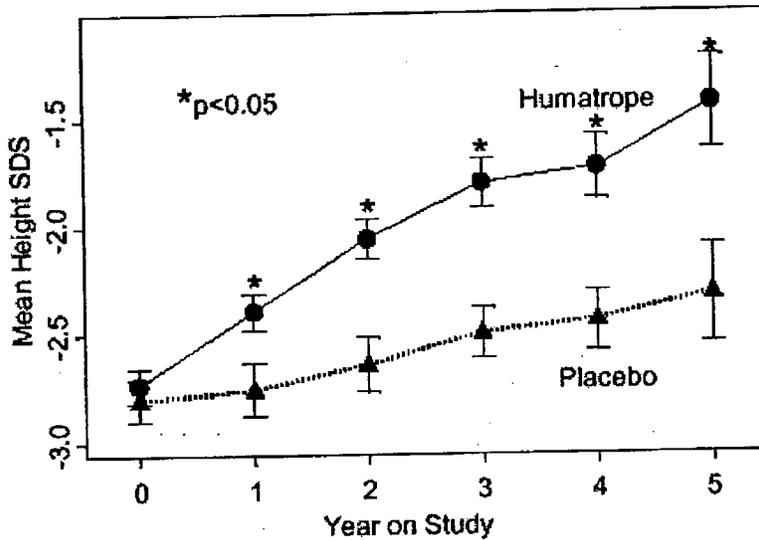
- ^a Values represent the difference in endpoint or final height SDS between the Humatrope-treated group and the placebo-treated group.
- ^b Two of the 29 patients in the placebo group did not have a baseline predicted height, due to missing bone age x-rays, and therefore could not be included in this analysis.
- ^c Endpoint height represents the last measured height.

Source: Table 3.H.6.

Height SDS by Year on Study (Efficacy Evaluable Population)

The height SDS changes by years on the study for the Efficacy Evaluable Population are presented in Figure 5. Starting from a similar baseline height SDS, the two treatment groups display a divergence in measured height SDS. To this end, the Humatrope-treated patients experienced a larger height SDS increase. The difference between the two treatments reaches statistical significance by the end of the first year of treatment ($p=0.02$). It augments and persists in subsequent years. It should be noted that error bars represent 1 SD. This analysis incorporated patients with final height and patients without final height. This analysis was not prespecified.

Figure 5: Height SDS by Year on Study-Efficacy Evaluable Population



Source: Figure 3.H.3. This population includes all patients who received ≥ 6 months study drug, whether or not they achieved final height. Data are cross-sectional.

Additional Final Height Analyses for the Patients with Final Height Data

Additional efficacy analyses for patients with final height data are presented in Table 14. Compared with placebo-treated patients, Humatrope-treated patients had a significantly greater difference in final height SDS minus baseline predicted height SDS (prespecified in cm and not as SDS), final height SDS, and height gain (both SDS and cm).

Table 14: Final Height Characteristics Final Height Population

PARAMETER	HUMATROPE (n=22)	PLACEBO (n=11)	EFFECT	F Value
FHSDS - PFHSDS*	0.22 (0.55)	-0.14 (0.59)	0.46	0.043
Final height SDS	-1.77 (0.78)	-2.34 (0.55)	0.57	0.029
Height gain (SDS)**	0.53 (0.73)	0.42 (0.23)	0.51	0.034
Height gain (cm)**	28.30 (7.38)	22.58 (6.90)	5.73	0.046

Note: Data are expressed as mean (standard deviation).
 Abbreviations: n = number of patients; SDS = standard deviation score
 FHSDS = final height standard deviation score
 PFHSDS = baseline predicted height standard deviation score
 * n=10 for placebo, as one patient did not have a baseline predicted height due to missing bone age X-ray.
 ** Height gain is from start of treatment to final height.

Source: Table 3. H. 8.

Repeated Measures Analysis

This analysis was not prespecified. It was performed by the applicant with the purpose of "addressing the potential bias that may have resulted from missing final data." This analysis (Table 15) shows a mean treatment effect of Humatrope on height SDS at age 18 years of 0.69

± 0.13 ($p < 0.0001$), which corresponds to 5.0 cm (higher than the 3.7 cm recorded by the primary analysis. See the statistical review for a critical look at this analysis.

Table 15: Repeated Measures Analysis: Height SDS at Age 18 Years in Efficacy Evaluable Population

Source: Table 3.H.7.

Variable	Humatrope (n=35)	Placebo (n=27)	Effect ^a	p-value
Height SDS	-1.52 \pm 0.11	-2.20 \pm 0.12	0.69 \pm 0.13	<0.0001

Note: Data are expressed as least squares mean (LSM) \pm standard error of the mean (SEM) from repeated measures analysis.

Abbreviations: n = number of patients; SDS = standard deviation score.

^a Value represents the difference in the height SDS at age 18 years between the Humatrope-treated group and the placebo-treated group.

Proportion of Patients who Achieved 5th and 10th Percentiles for Height

Table 16 shows the proportion of patients with final height data whose height exceeded the 5th or 10th percentile of the standard growth curve at baseline and at the end of treatment. Nine (41%) of the Humatrope-treated patients achieved a final height above the 5th percentile. In contrast, none of the placebo-treated patients achieved final heights above this threshold ($p=0.015$). Additionally, 27% of Humatrope-treated patients had final height above the 10th percentile compared with none of the placebo-treated patients. This last comparison did not reach statistical significance. None of these analyses were specified in the protocol.

Table 16: Patients with Final Height Above 5th or 10th Percentile -Final Height Population

Number of Patients Above	Humatrope (n=22)	Placebo (n=11)	p-value ^a
Baseline			
5th percentile	0 (0%)	0 (0%)	
10th percentile	0 (0%)	0 (0%)	
Final height			
5th percentile	9 (41%)	0 (0%)	0.015
10th percentile	6 (27%)	0 (0%)	0.077

Abbreviation: n = number of patients.

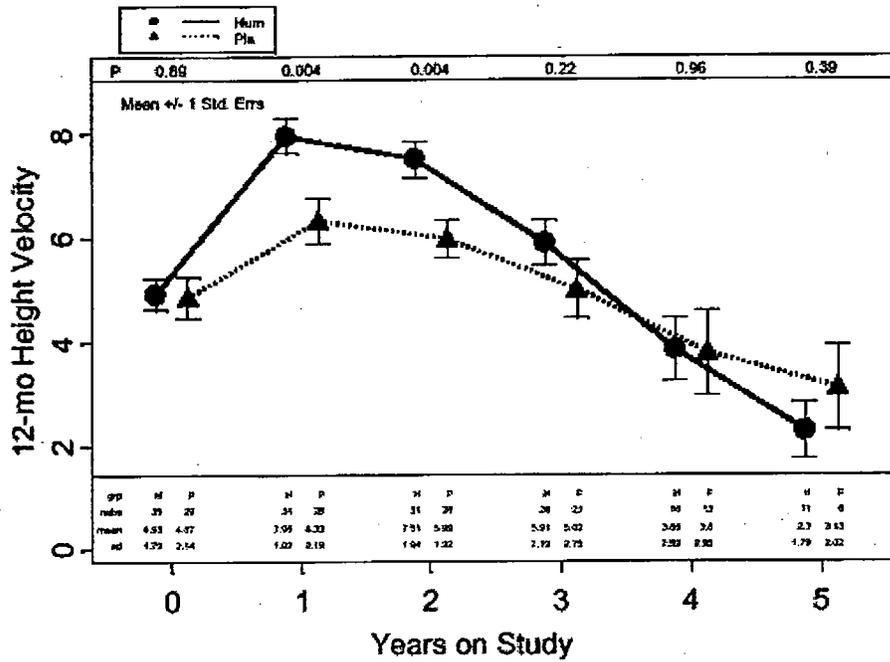
^a Fisher's exact test for between-group differences.

Source: Table 3.H.9.

Twelve-Month Height Velocity for the Efficacy Evaluable Population

The 12-month height velocity by years on study for the ITT (Efficacy Evaluable) population is presented in Figure 6. Both treatment groups had similar baseline mean height velocities. Humatrope-treated patients had significantly greater mean height velocity than placebo-treated patients at Year 1 and Year 2 of the study. Error bars represent 1 SD.

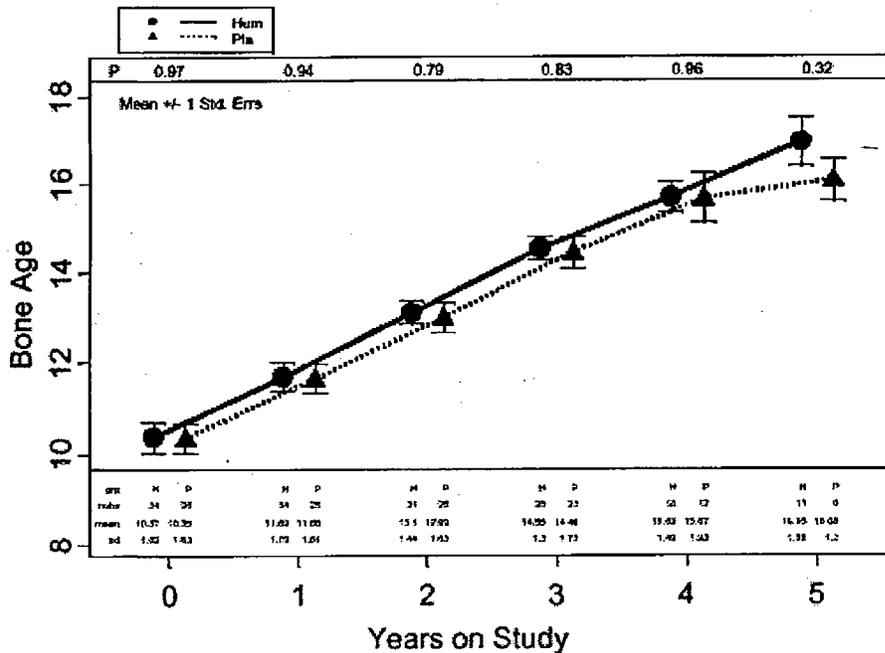
Figure 6: Twelve-month Height Velocity by Year on Study



Source: Figure GDCH.11.4.

The increase in height velocity and height in general associated with Humatrope treatment were not associated with an undue acceleration of bone age advancement. (Figure 7). There were no statistically significant differences in bone age between Humatrope treatment and placebo for the duration of the trial.

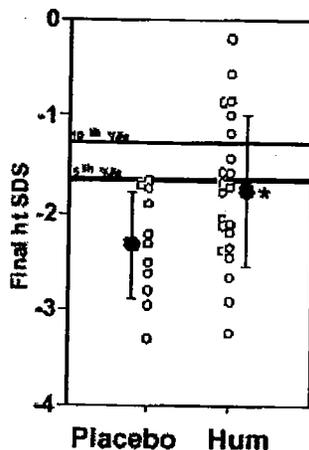
Figure 7: Greulich-Pyle Bone Age (Years) by Year on Study



C.1.10.5.3. Individual Patient Responses

The distribution of final height standard deviation scores for the Humatrope-treated and the placebo-treated patients are displayed in Figure 8. The 5th and the 10th percentiles are highlighted. The 5th percentile corresponds to -1.64 SDS (5 feet, 4.7 inches or 164.2 cm in males, and 5 feet, 0 inches or 152.5 cm in females). Although patients in both treatment groups had similar baseline distribution of height SD scores (not shown), by the end of the trial the distribution of height SD scores was different. Thus, about half of the Humatrope-treated patients had a height distribution almost identical to the placebo-receiving patients, while another half had height SD scores higher than placebo (and above the 5th percentile).

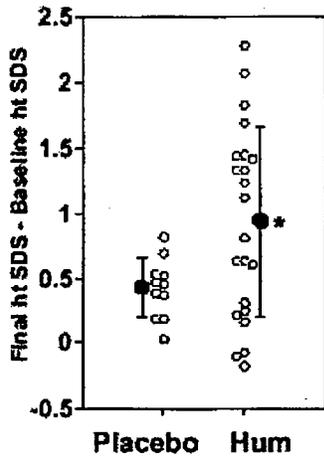
Figure 8: Final height SDS: By-patient Display



Source: Figure GDCH.11.3. Note: * represents a statistically significant difference between treatment group means. Abbreviations: ht = height, Hum = Humatrope, SDS = standard deviation score.

Individual height SDS gain (defined as final height SDS minus baseline height SDS) is displayed in Figure 9. The mean height SDS gain was almost 1 SD for the Humatrope group and 0.5 SD for the placebo group. Fifty percent (11 out of 22) of the Humatrope patients gained more than 1 SD in height versus none of the placebo patients (p=0.005). Considerable variability of individual responses is noted.

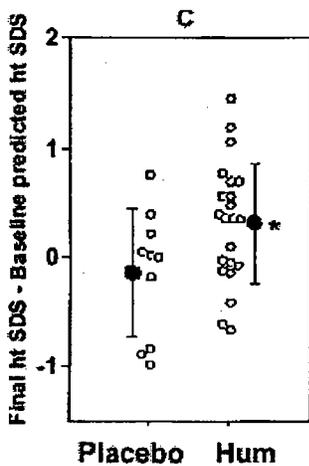
Figure 9: Final Height SDS- Baseline Height SDS: By-patient Display



Source: Figure GDCH.11.3. Note: * represents a statistically significant difference between treatment group means. Abbreviations: ht = height; Hum = Humatrope, SDS = standard deviation score.

Figure 10 illustrates the mean and individual values for the difference between final height SDS and baseline predicted height (BPH) SDS for the two treatment groups. The negative mean FH-BPH for the placebo group (-0.14 SDS) is due to the fact that baseline predicted height overestimates final height (Hintz RL et al., 1999). The mean FH-BPH was positive for the Humatrope group (0.32 SDS). Only 10 patients are analyzed in the placebo group because one did not have baseline bone age measured.

Figure 10: Final Height SDS- Baseline Predicted Height SDS: By-patient Display



Source: Figure GDCH.11.3. Note: * represents a statistically significant difference between treatment group means. Abbreviations: ht = height; Hum = Humatrope, SDS = standard deviation score.

C.1.10.5.4. Humatrope Treatment Effect in Trial GDCH

Table 17 highlights efficacy data that describes the magnitude of the Humatrope treatment effect. In addition to data presented in the NDA, it incorporates additional data provided in the applicant's June 10th Endocrinologic and Metabolic Advisory Committee Briefing Document. Whenever available, data are presented as SD score and in centimeters with 95 % confidence intervals. Despite methodological differences, these analyses support a mean treatment effect of approximately 0.5 SD or 3.7 cm., with a wide range of possible clinical responses (from 0.1 SDS to almost 1 SDS as indicated by the calculated 95 % confidence intervals).

Table 17: Treatment Effect – Trial GDCH
(updated from the applicant's draft Briefing Document)

Analysis and Population	Treatment group		Treatment effect		P-value
	Humatrope	Placebo	SDS	cm	
Final height SDS (ANCOVA using BPH SDS as covariate)-Primary analysis - FH*	-1.81 ± 0.11	-2.32 ± 0.17	0.51 ± 0.20 (CI: 0.10-0.92)	3.7	0.017
Final height SDS (ANCOVA using BPH SDS as covariate using imputed data for missing BPH in 1 patient -FH *	NA	NA	0.48 ± 0.19 (CI: 0.09-0.88)	NA	0.017
Final height SDS (ANCOVA using BPH SDS as covariate) - PC**	-1.86 ± 0.14	-2.32 ± 0.18	0.46 ± 0.23	3.3	0.06
Last observed height SDS (ANCOVA using BPH SDS as covariate)- EE***	-1.89 ± 0.10	-2.40 ± 0.11	0.52 ± 0.15 (CI: 0.22-0.82)	NA	0.001
Last observed height SDS (ANCOVA using BPH SDS as covariate)- AR****	-1.96 ± 0.10	-2.36 ± 0.11	0.40 ± 0.15	NA	0.011
Last observed height SDS (ANOVA no covariate)- AR****	-1.90 ± 0.11	-2.42 ± 0.12	0.52 ± 0.17	NA	0.003
Repeated measures analysis (Height SDS at age 18) - EE***	-1.52 ± 0.11	-2.20 ± 0.12	0.69 ± 0.13 (CI: 0.43-0.94)	5	<0.001
Final height minus BPH (cm)-(t-test)- FH*	2.2 ± 0.8	-0.7 ± 1.3 cm	NA	2.8 ± 1.3	0.07

Highlighted areas = protocol specified analyses

*FH = final height population

** PC = protocol complete population

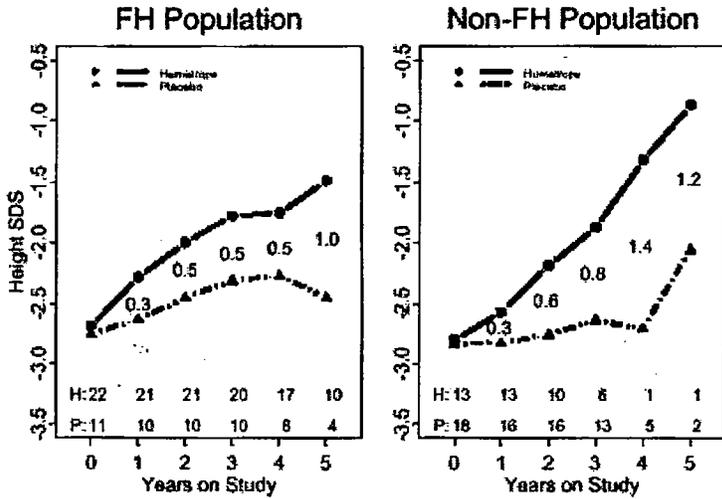
***EE = efficacy evaluable population

****AR = all randomized population

CI = confidence interval. NA not available. BPH = baseline predicted height. Prespecified analyses are grayed out.

This treatment effect was established in a trial with multiple dropouts (only 42% of Humatrope-treated patients and 27% of placebo-treated patients completed the trial). However, it does not appear that the patients who discontinued the trial had different initial responses to treatment when compared to patients who remained on trial (Figure 11) since both groups of patients indicate a similar (and superior) effect of Humatrope on height SDS when compared to placebo. (See also the statistical review which analyzes efficacy in final height and non-final height populations in detail).

Figure 11: Mean Height SDS for the Final Height Population and for the Non-final Height Subgroup of the Efficacy Evaluable Population by Year on Study



Source: Figure GDCH. 11. 2. Abbreviations: FH = final height; H = Humatrope; P = Placebo.

This magnitude of therapeutic effect has been achieved without evidence of undue acceleration of bone age (Figure #) and without change in the time of attainment of pubertal stages (Table 18). It should be also noted that this treatment effect was established with a Humatrope regimen of three injections per week. This is no longer the standard of care since daily GH regimens replaced three times a week regimens because of increased efficacy.

Table 18: Age at Attainment of Tanner Stage II, III, IV, and V (Males and Females) – Efficacy Evaluable Population

Variable	Males		Females	
	Humatrope (n=27)	Placebo (n=23)	Humatrope (n=8)	Placebo (n=6)
Age of Tanner stage II				
No. of Patients	12	6	4	1
Mean	13.17	12.89	11.35	12.40
Median	13.12	13.07	11.35	12.40
Standard Dev.	1.71	0.97	0.40	
Unspecified	15	17	4	5
Age of Tanner stage III				
No. of Patients	20	10	6	5
Mean	14.17	13.85	12.43	12.81
Median	14.12	13.82	12.66	12.89
Standard Dev.	1.39	1.27	0.73	0.33
Unspecified	7	13	2	1
Age of Tanner stage IV				
No. of Patients	23	17	7	5
Mean	14.80	14.52	13.24	13.18
Median	14.46	14.26	13.53	13.19

Standard Dev.	1.35	1.01	0.66	0.95
Unspecified	4	6	1	1
Age of Tanner stage V				
No. of Patients	19	13	3	4
Mean	16.09	16.16	13.76	14.33
Median	16.12	16.02	14.00	14.41
Standard Dev.	1.24	1.17	1.13	1.29
Unspecified	8	10	5	2

Source: Tables GDCH.11.16. and GDCH.11.17.

C.2. Supportive Clinical Study E001

C.2.1 Objective

The primary objective of this study was to assess whether a higher dose of Humatrope (0.37 mg/kg/week) would result in a greater increase in height velocity over pre-treatment height velocity at the end of 2 years of treatment, when compared to a lower Humatrope dose of 0.24 mg/kg/week. The secondary objectives relevant to final height were: (1) to determine whether the higher dose of Humatrope (0.37 mg/kg/wk) would result in a greater final height compared to the lower dose (0.24 mg/kg/wk) and (2) to determine any difference in the rate of adverse events among the different dosing regimens.

C.2.2 Study Design

This clinical trial was a multinational, multicenter (28 study centers), randomized, open-label, three-arm, parallel, dose-response study conducted in Europe. The study consisted of a screening phase, during which patients were assessed for study eligibility, followed by a three-arm, randomized, open-label, 2-year "core dose-response phase". Patients were randomly assigned (without stratification) to one of three Humatrope treatment groups:

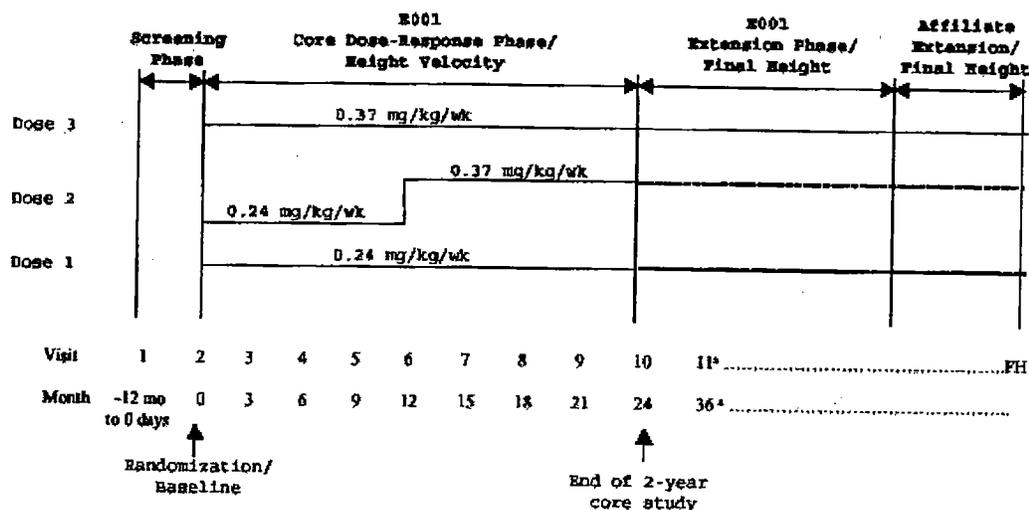
- Dose 1: 0.24 mg/kg/wk
- Dose 2: 0.24 mg/kg/wk for 1 year, followed by 0.37 mg/kg/wk
- Dose 3: 0.37 mg/kg/wk

Humatrope was administered subcutaneously in divided doses given 6 days per week in the evening.

After completion of the 2-year "core dose-response phase" of the study, patients were to be followed to final height in a long-term extension phase, with the intent of determining the impact of GH dose on final height. Patients were to remain on the same dose of Humatrope as that received during the last year of the core dose-response phase. In 1996 the multinational E001 extension phase was stopped. Thereafter, four Lilly affiliates (France, Germany, Spain, and Netherlands) elected to continue the study under local extensions, with the aim of obtaining as

much final height data as possible during an “affiliate-specific extension phase.” Figure 12 presents the study design for clinical trial E001.

Figurer 12: Study Design for Trial E001



Source: FigureE001.9.1. FH = final height.

C.2.3 Main Inclusion and Exclusion Criteria

A total of 239 patients with NGHDSS were randomized. The main inclusion criteria are listed in Table 19:

Table 19: Inclusion Criteria – Study E001

Height	Height < 2.0 standard deviation (SD) below the mean for age for British standards
Height velocity	below the 25 th percentile for age before the age of 10 years for girls and 12 years for boys; above these age limits, the height velocity was required to be below the 25 th percentile for bone age.
Chronological age	5 years of age or older
Bone age	less than 10 years in girls and less than 12 years in boys (TW2-RUS method)
Tanner stage	Stage I
Growth hormone diagnostic sufficiency criteria	Peak GH response of greater than 20 mU/L (approximately 10 ng/mL) in one standard stimulation test.
Thyroid function	Normal or stable on replacement therapy.

Exclusion criteria were: previous GH treatment, endocrine or metabolic disorders, chronic or nutritional diseases, any sign of puberty, genetic syndromes except Russell-Silver syndrome, drug treatment that could interfere with response to GH, psychosomatic problems, family

circumstances that could negatively influence the outcome of the patient's participation in the study.

C.2.5 Patient Disposition

Two hundred sixty-one patients were screened for entry into this study. Twenty-two of the 261 patients either failed inclusion/exclusion criteria, decided not to participate in the study, or were lost to follow-up. The remaining 239 patients qualified for the study and were randomized into one of three treatment groups (Dose 1, n = 78; Dose 2, n = 78; Dose 3, n = 83). All 239 patients were included in the All Randomized Patients dataset.

Of the 239 patients in the All Randomized Patient Population, 30 patients discontinued between baseline and end of the 2-year core study. The remaining 209 patients (Dose 1, n = 70; Dose 2, n = 67; Dose 3, n = 72) were included in the Two-Year Height Velocity Population (efficacy dataset for height velocity endpoint).

Fifty of the 239 patients randomized to therapy had final height measurements available and were included in the Final Height Population (Dose 1, n = 17; Dose 2, n = 16; Dose 3, n = 17). Some reached final height on trial, some post-study (Table 20). Of the 50 patients who reached final height, almost half (22 patients) were from one center in the Netherlands. They were patients who had discontinued the study prior to reaching final height but had subsequently been followed to final height post-study.

Table 20: Final Height Attainment (Final Height Population)

Variable	Dose 1 (N=17)	Dose 2 (N=16)	Dose 3 (N=17)	Total (N=50)
Final Height Attained				
No. Patients	17	16	17	50
On Study	8 (47.1)	10 (62.5)	10 (58.8)	28 (56.0)
Post study	9 (52.9)	6 (37.5)	7 (41.2)	22 (44.0)

Source: Table E001.10.1. "On Study" = patients who attained the final height criterion of height velocity <2.0 cm/ y while still receiving Humatrope. "Post Study" = patients who discontinued Humatrope before attainment of final height and were followed to final height by Investigator 601.

There were similar numbers and percentages of patients who discontinued due to adverse events, protocol entry criteria violations, sponsor's decision, physician's decision or were lost to follow-up, in all three treatment arms (Table 21). More patients in the high dose arm discontinued due to patient decision than in the low dose arm (38 patients or 45.8% vs. 22 patients or 28.2 %).

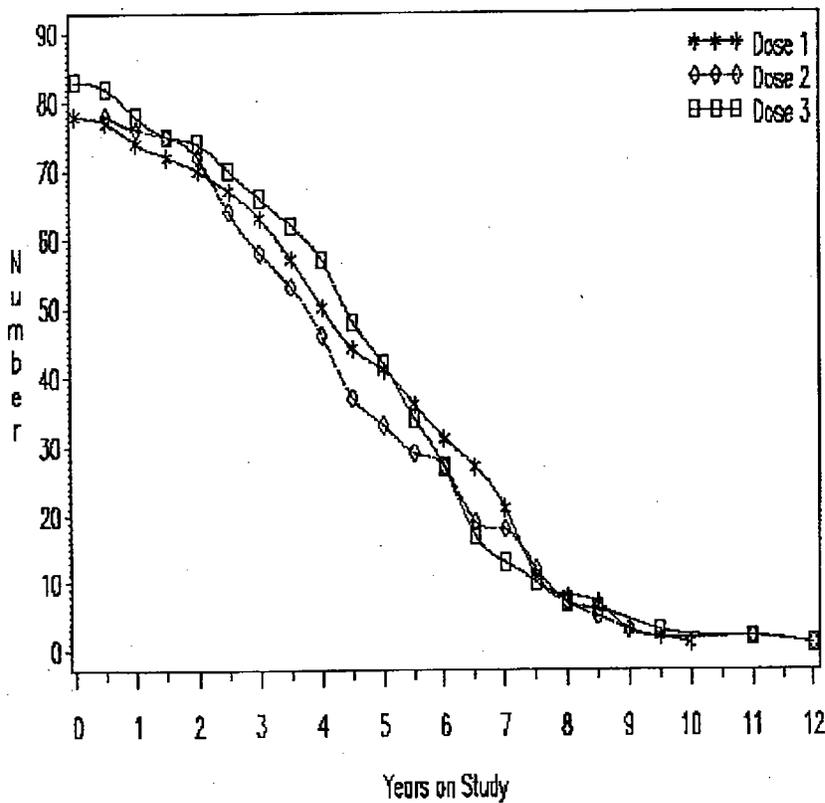
Table 21: Primary Reasons for Study Discontinuation All Randomized Patients

Primary Reasons for Discontinuation	Dose 1	Dose 2	Dose 3	Total
	(N=78) n (%)	(N=78) n (%)	(N=63) n (%)	(N=219) n (%)
Protocol completed	18 (23.1)	11 (14.1)	14 (16.9)	43 (18.0)
Adverse event	2 (2.6)	0	1 (1.2)	3 (1.3)
Unable to contact patient (lost to follow-up)	4 (5.1)	2 (2.6)	3 (3.6)	9 (3.8)
Protocol entry criteria not met	7 (9.0)	9 (11.5)	8 (9.6)	24 (10.6)
Sponsor's decision	6 (7.7)	7 (9.0)	5 (6.0)	18 (7.8)
Patient decision	22 (28.2)	31 (39.7)	38 (45.8)	91 (38.1)
Physician decision	10 (12.8)	7 (9.0)	8 (9.6)	25 (10.5)

Source: Table E001.10.2. Dose 1 = 0.24 mg/ kg/ wk, Dose 2 = 0.24- 0.37 mg/ kg/ wk, Dose 3 = 0.37 mg/ kg/ wk

Figure 13 shows the patient retention during trial E001 as a function of time. The pattern is similar for all three treatment groups and resembles that seen in trial GDCH: a steady decline of patients remaining in the trial was noticed over time.

Figure 13: Patient Retention In Trial E001



Source: Figure E001.10.2.

C.2.6. Protocol violations

There were few protocol violations (protocol violations were defined as deviations from the protocol that could have had an impact on patient safety, data integrity, or conclusions drawn from the study). One patient, in the Dose 1 treatment arm, received methylphenidate (a drug that may interfere with growth hormone secretion) at the time of screening and enrollment. Thirteen (5.4%) patients were not discontinued although they missed > 14 consecutive injections (the length of time patients did not receive treatment ranged from 2 weeks to 6 months). They were evenly distributed among the three treatment arms: 6 (77%) for Dose 1 group, 6 (77%) for the Dose 2 group, and 2 (24%) for the Dose 3 group.

C.2.7. Treatment compliance

Treatment compliance was not analyzed since the number of injections administered was not recorded on the clinical report forms (CRFs).

C.2.8 Baseline Patient Characteristics

The main growth-related parameters recorded at baseline are presented in Table 22. The mean height SDS of -3.21 ± 0.70 was lower than the mean height SDS recorded at baseline in trial GDCH (-2.78 ± 0.48). The mean predicted adult height SDS of -2.63 ± 1.08 was also lower (-2.09 ± 0.79 in trial GDCH). The degree of delay in bone age was almost identical (bone age/chronological age ratio was 0.82 ± 0.15 vs. 0.84 ± 0.12 in trial GDCH). Similar to trial GDCH, the target height SDS (-1.23 ± 0.90) was below the population mean. Most patients were Tanner stage I (98% in each arm); only one patient in each treatment group was Tanner stage II and none was Tanner stage III.

Table 22: Growth Characteristics at Baseline-All Randomized Patients

Variable	Dose 1 (N=78) Mean (SD)	Dose 2 (N=78) Mean (SD)	Dose 3 (N=83) Mean (SD)	Total (N=239) Mean (SD)
Weight (kg)	21.33(5.86)	22.40(5.27)	22.78(5.37)	22.18(5.51)
BMI (kg/m ²)	15.30(1.77)	15.43(1.61)	15.40(1.68)	15.38(1.68)
Height (cm)	116.83(12.79)	119.47(11.25)	120.70(10.70)	119.03(11.66)
Height SDS	-3.37(0.81)	-3.21(0.69)	-3.04(0.54)	-3.21(0.70)
Height Velocity (cm/y)**	4.29(1.08)	4.39(1.26)	4.31(1.12)	4.33(1.15)
Height Velocity (SDS)	-1.19 (1.14)	-0.97 (1.17)	-1.11 (1.13)	-1.09 (1.15)
Chronological age (CA)	9.43 (2.40)	9.88 (2.16)	9.95(2.25)	9.76 (2.28)
Bone Age (yrs)*	7.40(2.56)	8.09(2.28)	8.01(2.06)	7.84(2.31)
BA/CA Ratio*	0.80(0.15)	0.83(0.15)	0.83(0.14)	0.82(0.15)
Predicted Height (cm)***	156.40(9.02)	155.08(10.18)	158.72(9.49)	156.70(9.70)
Predicted Height (SDS)***	-2.69(1.00)	-2.84(1.05)	-2.36(1.13)	-2.63(1.08)
Target Height (cm)****	163.71(8.08)	165.05(8.75)	165.86(8.02)	164.90(8.29)
Target Height (SDS)****	-1.34(0.88)	-1.17(0.95)	-1.17(0.86)	-1.23(0.90)
IFG-I (ng/ml)	N/A	N/A	N/A	N/A
IFG-I SDS	N/A	N/A	N/A	N/A

Source: Table E001.14.12 and B1

- *One patient in "Dose 1" and "Dose 3" arm, respectively did not have a specified bone age at baseline.
- **Two patients in the "Dose 1" and "Dose 2" arms, and one patient in the "Dose 3" arm did not have height velocity data.
- *** Only 44 patients in "Dose 1" arm, 60 patients in "Dose 2" arm, 55 patients in "Dose 3 arms", and 159 patients overall had predicted height calculated.
- ****Two patients in the "Dose 1" arm, four patients in the "Dose 2" arm, one patient in the "Dose3" arm, and seven patients overall had unspecified target heights.

Gender and racial baseline characteristics are presented in Table 23. There were twice as many male patients (66.1%) than female patients (33.9%). Almost all patients enrolled were Caucasian (the study was done in Europe).

Table 23: Baseline Gender and Racial/Ethnic Characteristics-All Randomized Patients

Variable		Dose 1 (N=78)	Dose 2 (N=78)	Dose 3 (N=83)	Total (N=239)
Gender	Male	49 (62.8%)	50 (64.1%)	59 (71.1%)	158 (66.1%)
	Female	29 (37.2%)	28 (35.9%)	24 (28.9%)	81 (33.9%)
Origin	Asian	0	2 (2.6%)	0	2 (0.8%)
	Caucasian	78 (100%)	76 (97.4%)	83 (100%)	237 (99.2%)

Source: Table E001.14.12

Baseline growth characteristics for the Final Height Population are presented in Table 24. Overall, the baseline growth characteristics for the three treatment groups were comparable to the All Randomized Population. All patients were Tanner stage I.

Table 24: Growth Characteristics at Baseline-Final Height Population

Variable Mean (SD)	Dose 1 (N=17)	Dose 2 (N=16)	Dose 3 (N=17)	Total (N=50)
Weight (kg)	22.59(5.12)	23.15(5.45)	23.46(5.49)	23.06(5.26)
BMI (kg/m ²)	15.05(1.43)	15.22(1.82)	15.42(1.99)	15.23(1.73)
Height (cm)	121.73(11.29)	122.34(11.37)	122.41(9.51)	122.15(10.53)
Height SDS	-3.26(0.77)	-3.08(0.77)	-2.88(0.62)	-3.08(0.72)
Height Velocity (cm/yr)*	4.71(1.43)	5.13(2.03)	4.39(1.49)	4.73(1.65)
Bone Age (yrs)*	8.47(2.10)	8.52(2.13)	8.91(1.85)	8.63(2.00)
BA/CA Ratio*	0.82(0.08)	0.83(0.13)	0.88(0.10)	0.84(0.11)
Predicted Height (cm)**	157.96(8.96)	155.72(9.50)	157.51(6.86)	157.06(8.35)
Predicted Height (SDS)**	-2.51(1.07)	-2.62(0.90)	-2.31(0.85)	-2.48(0.93)
Target Height (cm)	165.21(8.73)	166.75(11.01)	166.79(8.09)	166.24(9.16)
Target Height (SDS)	-1.16(1.05)	-0.78(1.14)	-0.91(0.87)	-0.95(1.02)

Source: Table E001.11.3.

- * One patient in the "Dose 2" and "Dose 3" arm, respectively, and two patients overall, had "unspecified" baseline height velocity measurements.
- **One patient in the "Dose 1" and "Dose 3" arm, respectively, and two patients overall, had "unspecified" baseline bone age measurements.
- ***Four patients in the "Dose 1" arm, three patients in the "Dose 2" arm, four patients in the "Dose 3" arm, and 11 patients, overall, did not have the predicted height specified.

An inspection of historical diagnoses (medical conditions that resolved prior to study entry) and secondary conditions at the time of trial initiation did not identify any interpretable imbalances between the treatment groups. There were 4 patients (Patients 001-0017, 001-0018, 201-2001, and 601-6007) who had Russell-Silver syndrome listed as a secondary condition. Patients with this diagnosis were allowed in the clinical trial according to protocol. One such patient (601-6007) was included in the Final Height Population.

At the request of the agency, the applicant provided a list of patients enrolled in study E001 who were small for gestational age (SGA). A patient was determined to have been born SGA if his or her birth weight SDS was <-2 . There were 13 SGA patients in Dose 1 treatment arm, 8 SGA patients in the Dose 2 arm, and 12 SGA patients in the Dose 3 arm. For six additional patients the information necessary to determine whether they were SGA was missing. No subgroup analyses were performed, due to the small number of patients (only 33 of 239 patients were born SGA). The final height population included 5 SGA patients and one patient with unknown SGA status in the Dose 1 treatment arm, four SGA patients in the Dose 2 treatment arm, and two SGA patients plus two patients with unknown SGA status in the Dose 3 treatment arm.

C.2.6. Efficacy evaluation

C.2.6.1. Data sets analyzed

The applicant conducted data analysis in three patient populations of study participants:

- The All Randomized Patient Population is defined as those patients who were randomized at Visit 2 (239 patients). Safety analyses were performed on data from this patient population.
- The Two-Year Height Velocity Population comprises all patients who had a height measurement at 2 years (209 patients). Analysis of efficacy data for the Two-Year Height Velocity Population is the primary efficacy analysis.
- The Final Height Population comprises patients on whom a final height measurement was obtained (after height velocity had fallen below 2.0 cm/y), either at protocol completion (28 patients) or after discontinuation from the study (22 patients from the Netherlands), 50 patients in total. Analysis of efficacy for the Final Height Population is the secondary efficacy analysis.

Table 25 provides the number of patient for each population and treatment arm.

Table 25: Number of Patients in Data Analysis Populations

Population	Dose 1	Dose 2	Dose 3	Total
All Randomized Patients	78	78	83	239
Two-Year Height Velocity	70	67	72	209
Final Height	17	16	17	50

Dose 1 = 0.24 mg/kg/wk, Dose 2 = 0.24 mg/kg/wk for the first year, then 0.37 mg/kg/wk, Dose 3 = 0.37 mg/kg/wk

Source: Table E001.11.1

C.2.6.2 Efficacy variables

Primary efficacy variable

The primary efficacy variable for this study was height velocity. The primary efficacy analysis was the change in height velocity (cm/y) from pretreatment to 2-year endpoint. Height velocity (cm/y) was defined as the rate of linear growth calculated by the

difference between two height measurements, divided by the time interval (years) between those measurements.

Secondary efficacy variable

The secondary efficacy variables were:

- Final height standard deviation score (SDS);
- Final height minus baseline height (centimeters and SDS);
- Final height minus baseline predicted height (BPH) (centimeters and SDS);
- Final height minus target height (centimeters and SDS).

These variables were defined as follows:

- **Height SDS:** This was derived by subtracting the age-and-gender-matched population mean height from the patient's height and then dividing this value by the age-and-gender-matched population height SD. For patients greater than 18 years of age, the gender-matched population mean and SD of 18-year-olds were used in the calculation.
- **Final height:** The last height obtained after the height velocity fell below 2 cm per year.
- **Final height SDS:** The final height expressed as a SDS using the method described above for calculating height SDS.
- **Baseline predicted height (BPH):** Greulich-Pyle bone age (converted from TW2-RUS bone age), chronological age, gender, and height at Visit 1 (screening) or Visit 2 (randomization), were used to calculate the BPH using the method of Bayley and Pinneau. A BPH was calculated only if a bone age assessment was available within 120 days of Visit 1 or Visit 2.
- **Target height:** This represents the approximate adult height that the patient could be expected to attain, based on the heights of her/his parents (that is, the patient's "genetic target" height). This is a gender-adjusted, average height of the patient's parents' heights calculated in centimeters, modified from the method of Tanner et al. (1975).
- **Target height SDS:** Target height expressed as a height SDS value, based on the patient's gender, compared to the Swiss reference population (Prader et al. 1989) at age 18 years.

C.2.6.3. Planned Analyses

The prespecified primary analysis was that of change in height velocity during treatment compared to pretreatment height velocity. The protocol did not prespecify analyses for final height data.

C.2.6.3. Efficacy Results

C.2.6.3.1. Primary Analysis

The primary efficacy analysis was the change in height velocity (cm/y) from pretreatment to the two-year endpoint for the Two-Year Height Velocity Population. It is presented in Table 26.

Table 26: Height Velocity Changes from Pretreatment to Two-Year Endpoint (Two-Year Height Velocity Population)

Therapy		Baseline	Endpoint	Change
Dose 1	N	68	68	68
	Mean	4.23	7.49	3.27
	Std	1.07	1.21	1.32
	Median	4.24	7.39	3.32
	Min	1.66	5.43	-0.07
	Max	6.46	10.18	6.05
Dose 2	N	66	66	66
	Mean	4.45	7.61	3.16
	Std	1.33	1.47	1.53
	Median	4.39	7.63	3.02
	Min	0.93	4.87	0.45
	Max	10.93	11.28	7.74
Dose 3	N	71	71	71
	Mean	4.35	8.39	4.04
	Std	1.10	1.32	1.66
	Median	4.32	8.38	3.95
	Min	0.92	5.79	0.20
	Max	7.26	11.27	7.25

Source: Table E001.11.6. Dose 1 = 0.24 mg/kg/wk, Dose 2 = 0.24- 0.37 mg/kg/wk, Dose 3 = 0.37 mg/kg/wk.

By analysis of variance (ANOVA), the patients who received 0.37 mg/kg/wk Humatrope (Dose 3) achieved a significantly greater pretreatment to two-year endpoint change in height velocity than the patients who received 0.24 mg/kg/wk Humatrope (Dose 1, $p=0.003$) or 0.24 mg/kg/wk Humatrope for the first year and 0.37 mg/kg/wk Humatrope thereafter (Dose 2, $p=0.001$). There was no statistically significant difference in height velocity change between Dose 1 and Dose 2 regimens ($p=0.672$). There was no evidence of a differential effect of Humatrope on height velocity change from pretreatment to two-year endpoint for investigator, country, or country group (tests of interaction provided by the applicant).

As expected, the height velocity changes for the first year of treatment were higher than the 2-year changes (Table 27). By ANOVA, the patients who received 0.37 mg/kg/wk Humatrope (Dose 3) achieved a significantly greater pretreatment to one-year endpoint change in height velocity than the patients who received 0.24 mg/kg/wk Humatrope (Dose 1, $p=0.005$) or 0.24 mg/kg/wk Humatrope for the first year and 0.37 mg/kg/wk Humatrope thereafter (Dose 2, $p<0.001$). There was no statistically significant difference in height velocity change between Dose 1 and Dose 2 regimens ($p=0.238$).

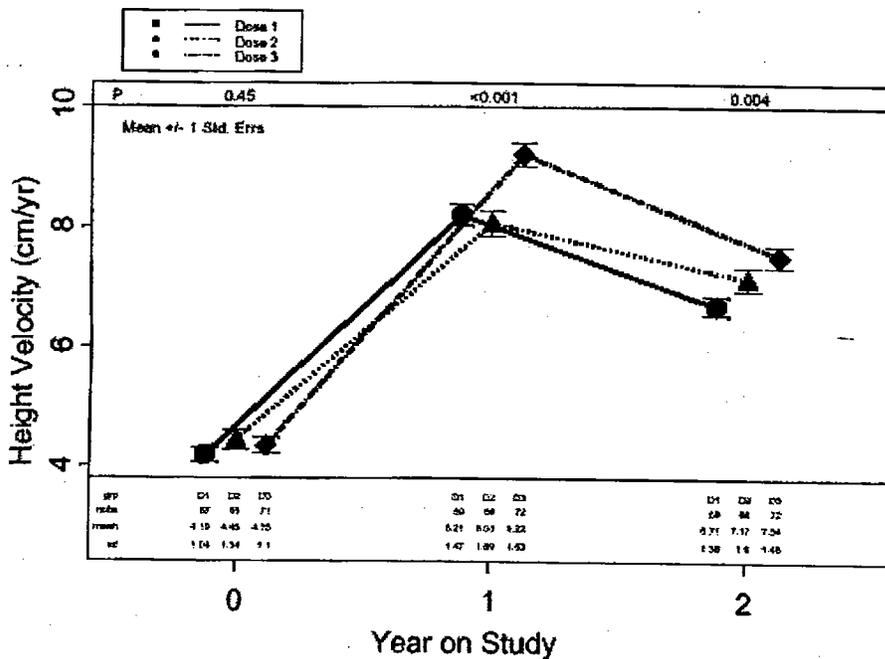
Table 27: Height Velocity Changes from Pretreatment to One-Year Endpoint (Two-Year Height Velocity Population)

Therapy		Baseline	Endpoint	Change
Dose 1	N	67	67	67
	Mean	4.19	8.21	4.02
	Std	1.04	1.48	1.66
	Median	4.24	8.20	3.99
	Min	1.46	5.06	-0.00
	Max	6.30	11.30	8.00
Dose 2	N	65	65	65
	Mean	4.45	8.10	3.66
	Std	1.34	1.69	1.76
	Median	4.37	8.04	3.64
	Min	0.93	5.15	0.27
	Max	10.53	13.02	10.02
Dose 3	N	71	71	71
	Mean	4.35	8.23	3.88
	Std	1.10	1.63	1.87
	Median	4.32	8.08	3.73
	Min	0.92	6.31	0.62
	Max	7.26	14.14	10.36

Source: Table E001.11.7.

Figure 14 summarizes descriptively the on-study mean height velocities for all three treatment groups. It includes only patients with height velocity determinations at one year and two years of study. During the second year of treatment there was a decrease in height velocity in all three treatment groups. This decline in height velocity was slower in the Dose 2 group, in which the Humatrope dose was increased from 0.24 mg/kg/wk to 0.37 mg/kg/wk at the end of the first year,

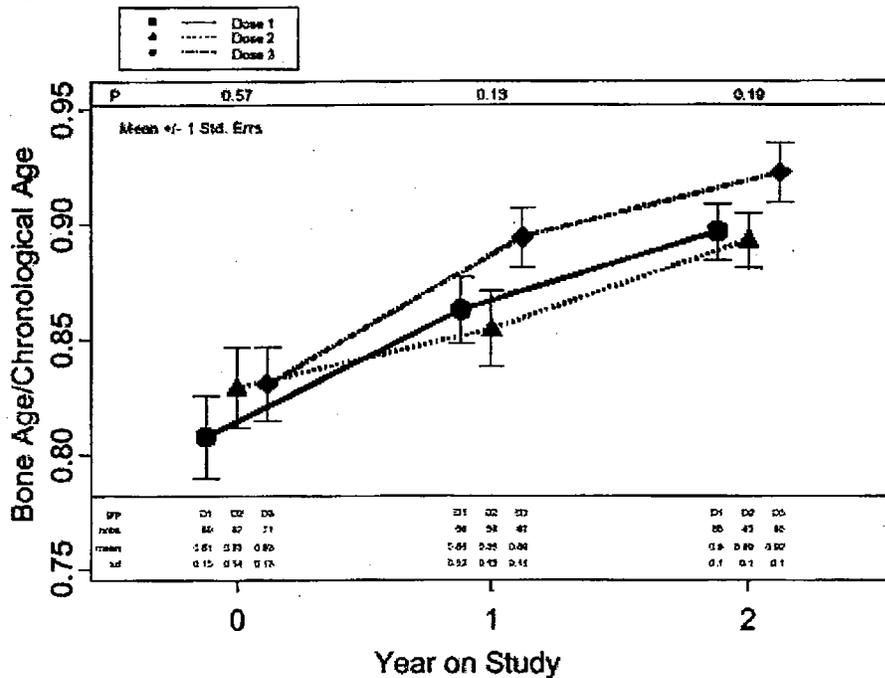
Figure 14: Height Velocity by Time on Study in the Two-year Height Velocity Population.



Source: Figure E001.11.1. Dose 1 = 0.24 mg/kg/wk, Dose 2 = 0.24-0.37 mg/kg/wk, Dose 3 = 0.37 mg/kg/wk.

The changes in height velocity were not associated with a dose-dependent acceleration in bone maturity. To this end, the ratio of bone age to chronological age by time on study in the Two-Year Height Velocity Population is presented in Figure 15. No statistically significant differences between treatment groups at baseline, 1 year, or 2 years are reported. Overall, the mean value of bone age over chronological age stayed below 1. Error bars represent 1 SD. Bone age accelerated faster than chronological age but was similar for all treatment groups and remained below 1.

Figure 15: Bone Age/ Chronological Age by Time on Study in the Two-year Height Velocity Population



Source: Figure E001.11.2.

C.2.6.3.2. Final Height-Related Efficacy Analyses

The Final Height Population comprises patients on whom a final height measurement was obtained after height velocity had fallen below 2 cm/year either at protocol completion (28 patients) or after the discontinuation from the study (22 patients from the Netherlands). A summary of several final height analyses for the Final Height Population is provided in Table 28. The mean duration of treatment was 6.1, 6.3, and 7.0 years for the Dose 1, Dose 2, and Dose 3 groups, respectively. The treatment effect (measured as final height minus baseline predicted height) ranged from a mean of 5.4 cm (Dose 1) to a mean of 7.2 cm (Dose 3). The on-study height gain (final height minus baseline height) ranged from 1.55 SD (Dose 1) to 1.85 SD (Dose 3). Patients who received the highest Humatrope dosage (0.37 mg/kg/wk, Dose 3) reached a final height that was closer to target height (gender-adjusted midparental height). A dose-response was noted across all above mentioned analyses when Dose 1 and Dose 3 regimens were compared. However, the Dose 2 regimen, which is expected to show intermediate level of

efficacy between Dose 1 and Dose 2 provided inconsistent results for height gain and for target height minus final height.

Table 28: Final Height Analyses - Final Height Population

Variable	Dose 1	Dose 2	Dose 3
Number of patients	13	13	13
FH - BPH (cm) ^a	5.36 ± 3.20	6.66 ± 4.12	7.21 ± 5.97
p-value ^b	<0.001	<0.001	0.001
Number of patients	17	16	17
FH SDS - BH SDS ^a	1.55 ± 0.58	1.52 ± 1.07	1.85 ± 0.82
p-value ^b	<0.001	<0.001	<0.001
Number of patients	17	16	17
TH - FH (cm) ^a	3.78 ± 7.34	5.31 ± 9.68	1.33 ± 5.01
p-value ^b	0.050	0.045	0.288

Note: Dose 1 = 0.24 mg/kg/wk; Dose 2 = 0.24 mg/kg/wk for the first year, and then 0.37 mg/kg/wk thereafter; Dose 3 = 0.37 mg/kg/wk.

Abbreviations: BH = baseline height; BPH = baseline predicted height; FH = final height; SDS = standard deviation score; TH = target height.

^a Data are expressed as mean ± standard deviation (SD).

^b p-values refer to a within-group *t* test of the null hypothesis that mean value equals zero.

Source: Table 3.H.12.

Intent-to-treat Analysis of Height SDS for the Two-Year Height Velocity Population and Repeated Measures Analysis

An intent-to-treat analysis (endpoint height SDS) for the Two-Year Height Velocity Population and a repeated measures analysis of height SDS at age 18 are presented in Table 29. Patients who received 0.37 mg/kg/wk of Humatrope (Dose 3) had a higher endpoint height SDS than those who received 0.24 mg/kg/wk (Dose 1) (p=0.006). Similarly, patients in the Dose 3 treatment group had a higher height SDS at age 18 than the patients in the Dose 1 treatment group (repeated measures analysis). The Humatrope dose effect (Dose 1 versus Dose 3) for these analyses was similar (0.51 versus 0.45 SDS, respectively).

Table 29: Endpoint Height SDS and Height SDS at Age 18 Years

Variable	Dose 1	Dose 2	Dose 3	Effect	p-value (Dose 1 vs Dose 3)
ANCOVA					
n	39	52	48		
Endpoint height SDS ^a	-1.95 ± 0.13	-1.87 ± 0.12	-1.45 ± 0.12	0.51 ± 0.18 ^b	0.006
Repeated measures					
n	39	52	47		
Height SDS at age 18 years ^c	-1.26 ± 0.16	-1.56 ± 0.15	-0.82 ± 0.14	0.44 ± 0.17 ^d	0.012

Note: Dose 1 = 0.24 mg/kg/wk; Dose 2 = 0.24 mg/kg/wk for the first year, and then 0.37 mg/kg/wk thereafter; Dose 3 = 0.37 mg/kg/wk.

Abbreviations: ANCOVA = analysis of covariance; n = number of patients who had a baseline predicted height measurement; SDS = standard deviation score; vs = versus.

^a Data are expressed as least squares mean (LSM) ± standard error of the mean (SEM) from ANCOVA, with baseline predicted height (BPH) SDS as the covariate.

^b Value represents the difference in the endpoint height SDS between the Dose 1 group and the Dose 3 group.

^c Data are expressed as least squares mean (LSM) ± standard error of the mean (SEM) from repeated measures linear model for measured or estimated height SDS at age 18 years. Section E001.16.1.6 provides additional details of this model.

^d Value represents the difference in the height SDS at age 18 years between the Dose 1 group and the Dose 3 group.

Source: Table 3.H.13.

ANCOVA of Final Height SDS

ANCOVA of final height SDS for the Final Height Population (using baseline predicted final height SDS as the covariate) is provided. A dose effect of 0.45 is recorded when Dose 3 regimen is compared with Dose 1 regimen but it does not reach statistical significance (p=0.086).

Proportion of Patients who Achieved 5th and 10th Percentiles for Height

Table 30 shows the proportion of patients in the Final Height Population whose final height exceeded the 5th or 10th percentile on standard growth curves. Although the difference between treatment groups did not reach statistical significance, a trend favoring the Dose 3 treatment group is noticeable. Overall, a considerable percentage of patients attained heights within the normal range following Humatrope treatment.

Table 30: Patients With Final Height Above 5th or 10th Percentile (Final Height Population)

Number of Patients Above	Dose 1 (n=17)	Dose 2 (n=16)	Dose 3 (n=17)	Total (n=50)	p-value * (Dose 1 vs Dose 3)
Baseline					
5 th percentile	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
10 th percentile	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Final Height					
5 th percentile	8 (47.1%)	8 (50%)	14 (82.4%)	30 (60%)	0.071
10 th percentile	5 (29.4%)	6 (37.5%)	11 (64.7%)	22 (44%)	0.084

Abbreviations: n = number of patients.

* Fisher's exact test.

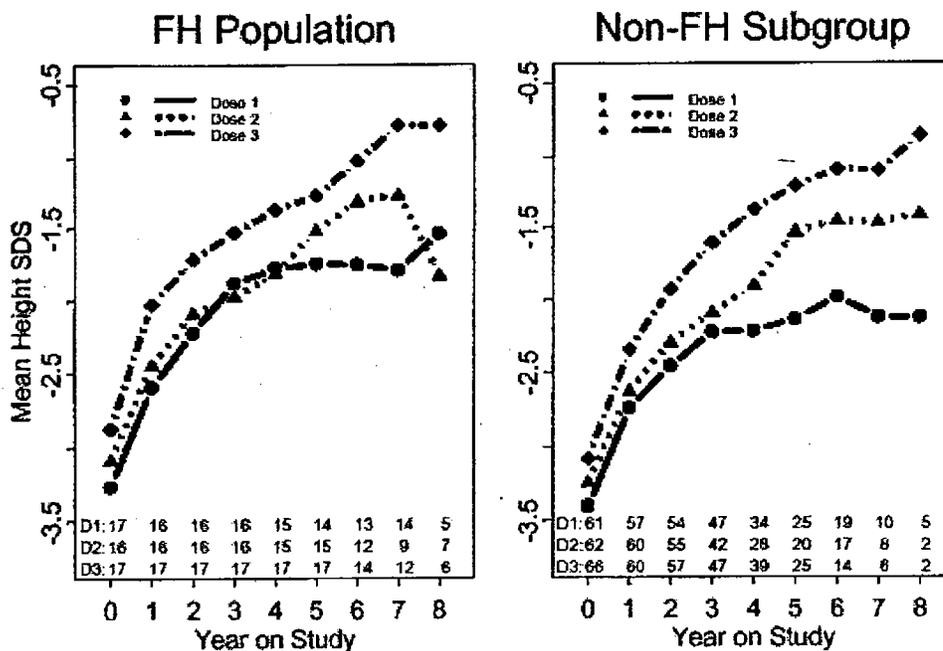
Source: Table E001.11.12.

Efficacy Comparison of Final Height Patients and Non-Final Height Patients

Final height measurements were not available for a number of randomized patients either because they discontinued prior to study completion or because they were not enrolled in the extension phase of the study. These patients are referred to by the applicant as the Non-Final Height subgroup of All Randomized Patients (n = 189). The Final Height Population (n = 50) and the Non-Final Height subgroup (n = 189) comprise All Randomized Patients (n = 239). Figure 16 presents descriptively the mean changes in height SDS as a function of time for both populations. Qualitative similarities are noted between the Final Height Population and the Non-Final Height subgroup..

Figure 16 : Mean Height SDS for the Final Height Population and Non-Final Height subgroup of All Randomized Patients by year on study

Source: Figure 3.H.8.



C.2.6.3.3. Individual data responses

The applicant does not provide individual efficacy data for patients enrolled in trial E001.

C.2.6.3.4. Humatrope Dose Effect During Trial E001

Table 31 lists efficacy data that describes the dose-effect for the Humatrope treatment (Dose 3 vs. Dose 1). In addition to data presented in the sNDA it incorporates additional data provided in the applicant's briefing document. A dose-effect is noticed during short-term Humatrope treatment (effect on two-year height velocity) as well as during long-term treatment (effect on final height in a subgroup of patients with available final height data). The dose-effect on final height is relatively consistent among the different analyses and measures approximately 0.5 SD or a little over 3 cm. The 95 % confidence interval ranges between 0.1 SD and 0.87 SD.

Table 31: Dose-Effect – Trial E001
(updated from the applicant's draft Briefing Document)

Analysis and Population	Treatment group			Dose effect (Dose 3 vs. Dose 1)		P-value
	Dose 1	Dose 2	Dose 3	SDS	cm	
Final height SDS (ANCOVA using BPH SDS as covariate)- FH*	-1.63±0.18	-1.38±0.18	-1.19±0.26	0.45±0.26	3.1	0.086
Last observed height SDS (ANCOVA using BPH SDS as covariate)- HV**	-1.95±0.13	-1.87±0.12	-1.45±0.12	0.51±0.18 (CI: 0.15-0.87)	3.6	0.006
Repeated measures analysis (Height SDS at age 18) - HV**	-1.26±0.16	-1.56±0.15	-0.82±0.14	0.44±0.17 (CI: 0.10-0.78)	3.1	0.012
Height velocity changes from pretreatment to 2-year in cm/y (ANOVA)	3.27±0.18	3.16±(0.19)	4.04±(0.18)	NA	0.78±0.26 (CI: 0.3-1.3) [#]	0.003

Highlighted areas = protocol specified analyses

*FH = final height population

** HV = 2-year height velocity population

[#] Dose 3 minus Dose 1 (difference of least square means).

CI = confidence interval. BPH = baseline predicted height. Grayed out areas are pre-specified analyses.

C.4. Comparison of Efficacy Findings in Trials GDCH and E001

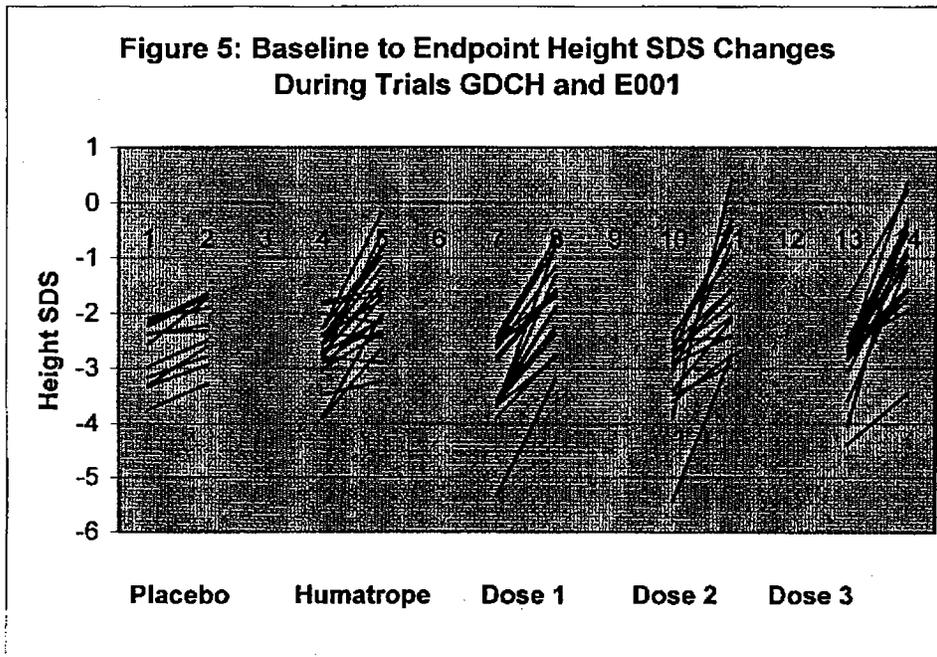
In an attempt to integrate some of the efficacy data from trial E001 with those from trial GDCH, Table 32 summarizes the efficacy analyses reported for final height minus baseline predicted height (FH-BPH) and target height minus final height (TH-FH) from both clinical trials. Patients in the Humatrope treatment arm of trial GDCH and patients in the Dose 1 arm of trial E001 received similar weekly doses of GH (0.22 mg/kg TIW vs. 0.24 mg/kg daily). Other differences between the trials should be noted: patients in trial E001 were enrolled at an earlier age, were shorter at baseline and were treated longer.

Table 32: Efficacy comparisons across trials
(updated from the applicant's draft Briefing Document)

Analysis and Population	Study GDCH		Study E001		
	Placebo	Humatrope	Dose 1	Dose 2	Dose 3
Final height minus BPH (cm)	-0.7 ± 1.3 (p=0.62)	2.2 ± 0.8 (p=0.02)	5.4 ± 0.9 (p<0.001)	6.66 ± 1.14 (<0.001)	7.2 ± 1.7 (p= 0.001)
Final height minus BPH (SDS)	-0.14 ± 0.19	0.32 ± 0.12	1.55 ± 0.14 (p<0.001)	1.52 ± 0.27 (p<0.001)	1.85 ± 0.20 (p<0.001)
Target height minus final height (cm)	7.10 ± 1.81	4.71 ± 1.37	3.78 ± 1.78 (p=0.050)	5.31 ± 2.42 (p=0.045)	1.33 ± 1.21 (p=0.228)
Target height minus final height (SDS)	1.02 ± 0.25	0.66 ± 0.19	NA	NA	NA

P = within group p-value where available. BPH = baseline predicted height.

Figure 17 presents a descriptive comparison of individual height SDS values at the beginning and the end of the treatment for patients with final data in each treatment arm in trials GDCH and E001. "Placebo" and "Humatrope" are the respective treatment arms in trial GDCH. "Dose 1", "Dose 2", and "Dose 3" are the respective treatment arms in trial E001.



C.5. Supportive Studies from Peer-Reviewed Literature

This evidence is presented in the Literature Review section of the Clinical Review.

D. Efficacy Conclusions

This application provides evidence that Humatrope treatment is efficacious in increasing final height in patients with NGHDSS. Trials GDCH and E001 have different designs, use different dose regimens, and show a different effect on final height.

Trial GDCH demonstrates that Humatrope is superior to placebo in increasing final height. This NIH conducted clinical trial shows that patients who received 0.222 mg/kg/wk of Humatrope in three equally divided doses for a mean duration of 4.62 years achieved greater mean final height than those who received placebo for a similar period of time (4.06 years). The magnitude of the Humatrope effect was 0.51 ± 0.20 standard deviation score (SDS) ($p=0.017$) in the primary efficacy analysis of 33 patients who contributed final height data. Individual efficacy showed marked variability (95% CI: 0.1-0.92 SD). The primary analysis is supported by an intent-to-treat analysis of height SDS that shows a similar magnitude of treatment effect (0.52 ± 0.15 ; $p=0.001$). Additional analyses support the primary and the intent-to-treat analyses. These efficacy observations are made in the context of a clinical trial with multiple dropouts. However, it does not appear that the patients who discontinued the trial had different initial responses to treatment when compared to patients who remained on trial.

Trial E001 establishes that a Humatrope regimen of 0.37 mg/kg/week given in six daily injections (high-dose regimen) was superior to a Humatrope regimen of 0.24 mg/kg/week administered in the same fashion (low-dose regimen). This was observed during short-term Humatrope use (effect on two-year height velocity) and during long-term Humatrope treatment (effect on final height in a subgroup of patients with available final height data). The high-dose Humatrope regimen resulted in a final height that exceeded baseline predicted adult height by an average of 7.2 cm (7.21 ± 5.97 cm or 1.9 height SDS; $p=0.001$), whereas the low-dose Humatrope regimen had a smaller treatment effect of 5.4 cm (5.36 ± 3.20 or 1.6 SDS; $p<0.001$) for the same endpoint. Intent-to-treat analyses and several other analyses confirm a dose-related treatment effect on final height.

Of note is that the mean difference between final height and baseline predicted adult height for the low-dose regimen noted in trial E001 (5.4 cm) is higher than that observed in trial GDCH (2.2 cm) for an almost identical Humatrope dose (0.24 mg/kg/week in trial E001 vs. 0.22 mg/kg/week in GDCH). Differences in trial duration (patients were treated longer in trial E001), as well as differences in Humatrope regimen (daily vs. three times a week) may account for a larger magnitude of treatment effect in trial E001. The combined data from studies GDCH and E001 suggest that a larger treatment effect can be achieved if a larger dose is used (0.37 mg/kg/week) and if Humatrope is given daily.

Both trial GDCH and E001 enrolled a few patients who were small for gestational age (SGA). At the time of initiation of both trials (1988) short stature in SGA patients was not an FDA approved indication.

Additional evidence of favorable effect of growth hormone (GH) therapy on final height in patients with NGHDSS is provided from published literature. A recent meta-analysis of 38

clinical trials (10 controlled and 28 uncontrolled) estimates a benefit on adult height of 4-6 cm (range of 2.3 to 8.7 cm) (Finkelstein B S et al., 2002).

VII. Integrated Review of Safety

A. Brief Statement of Conclusions

The safety profile of Humatrope in patients with NGHDSS appears to be similar to the safety profile of Humatrope in two other approved pediatric indications (growth hormone deficiency and Turner syndrome). No new safety signals, no unexpected treatment-emergent adverse events and no distinct dose-dependent adverse events were identified in patients with NGHDSS. During the clinical trials a small number of serious adverse events and patient withdrawals were due to conditions known to be associated with GH use (slipped capital, femoral epiphysis, glucose intolerance, and arthralgia). No new adverse events was identified in this patient population. Two malignancies occurred during treatment with Humatrope (one in each clinical trial); causality is difficult to establish due to the small number of patients.

B. Description of Patient Exposure

The overall exposure to Humatrope in patients with NGHDSS was similar to that of two previously approved Humatrope pediatric indications: GHD and short stature in Turner syndrome (approximately 1200 patient years of exposure each). The mean duration the NGHDSS clinical trials was between 3.7 years and 4.5 years. Table 33 presents the descriptive statistics of Humatrope exposure for NDHDSS subjects who participated in trials GDCH and E001.

Table 33: Study drug exposure in studies GDCH and E001

Exposure (years on study)	Study GDCH			Study E001			
	GH* N=37	Placebo N=31	Total N=68	GH Dose 1 N=78	GH Dose 2 N=78	GH Dose 3 N=83	Total N=239
Mean	3.7	3.3	3.5	4.7	4.4	4.5	4.5
Median	3.6	3.5	3.6	4.6	4.0	4.7	4.2
SD	1.9	1.6	1.8	2.4	2.4	2.4	2.4
Minimum	0.0	0.0	0.0	0.0	0.3	0.0	0.0
Maximum	9.1	6.1	9.1	10.0	11.8	11.7	11.8

Source: AS 4.4 and 4.5. Exposure was defined as the number of years from the first visit to the last recorded on-study visit. N = number of patients in safety analysis.

* Dose = 0.222 mg/kg/wk.

Dose 1 = 0.24 mg/kg/wk. Dose 2 = 0.24 mg/kg/wk for the first year, and then 0.37 mg/kg/wk thereafter. Dose 3 = 0.37 mg/kg/wk.

C. Methods and Specific Findings of Safety Review

This safety review was conducted from the electronic submission of NDA 19-640. After detailed analysis, the applicant's datasets and tables were selectively re-formatted in order to better integrate into the structure of this review. Whenever a table was re-formatted, references to the original table or dataset were made at the bottom of the table. Selected datasets submitted in JMP were also reviewed.

The sponsor did not present an integrated summary of safety (ISS). Instead, safety information was provided separately for the pivotal study GDCH, the supportive study E001, and for three additional studies (two of them previously presented to the agency: study GDCG and GDFC). The requirement for an ISS was waived by the agency at the July 31, 2001 pre-NDA meeting. At the same meeting the agency requested an additional analysis comparing the safety profile of GH use in patients with NGHDSS against the safety profile of GH in two currently approved pediatric indications. To this end, the sponsor submitted a safety analysis of Humatrope use in patients with GHD and Turner syndrome.

This safety review presents data in the following order:

1. Safety information from the pivotal study GDCH.
2. Safety information from the supportive study E001.
3. Comparative safety analysis of Humatrope use across different indications (NGHDSS vs. GHD vs. Turner syndrome).

Table 34 summarizes the main features of the GHD, Turner syndrome, and NGHDSS clinical trials included in this comparison.

Table 34: Clinical Studies Included in the Safety Comparison

Condition	Study	N	Age and Gender	
			Entry Criteria	Design
GHD	GDAB	333	Males and females, age ≥ 2 y	
TS	GDCT	136	Females, age ≥ 7 y	
TS	GDCI	230	Females, age ≥ 5 y	
NGHDSS	GDCH	68	Males, ages 10 to 16 y Females, ages 9 to 15 y	
NGHDSS	E001	239	Males and females, age ≥ 5 y	

Abbreviations: GHD = growth hormone deficiency; N = number of patients in safety analysis;
NGHDSS = non-growth hormone deficient short stature; TS = Turner syndrome.

Source: table 3.H.17.

Although a comparison of Humatrope safety profile across indications is important, several limitations need to be highlighted:

- different dictionaries were used to code adverse events during different studies (e.g. ELECT for studies GDAB and E001, COSTART for studies GDCT, GDCl, and GDCH)
- patients with GHD, Turner syndrome have different background rates of disease-specific illnesses, congenital malformations, surgical procedures
- clinical trials were different in design, dose, duration, patient age at enrollment; some had a control group, other were open-label

A standard presentation plan is followed in this safety review. It includes the following: deaths, serious adverse events (SAEs), clinical trial dropouts, treatment emergent adverse events (TEAEs), laboratory findings. Additional safety data for studies previously presented to the agency (GDCG and GDCP) are presented in Appendix 2.

C.1. Deaths

C.1.1 Deaths in study GDCH

There were no patient deaths reported during this study.

C.1.2 Deaths in study E001

There were no patient deaths reported during this study. However, a 12-year-old male who had received 0.24 mg/kg/wk Humatrope for approximately 6.4 years died approximately 4 years after discontinuing the study due to a malignant tumor (a desmoplastic small round cell tumor). The tumor was diagnosed while the patient was on study medication (Humatrope).

C.1.3 Deaths: Comparison Across Studies for Different Indications

Table 35 summarizes the patient deaths recorded during and after clinical studies.

Table 35: Patient Deaths During and After Study

Condition	Study	N	Humatrope	Control
GHD	GDAB	333	3 ^a	NA
TS	GDCT	136	0	1 ^b
TS	GDCl	230	0	0
NGHDSS	GDCH	68	0	0
NGHDSS	E001	239	1 ^c	NA

Source: Table # 3.H.20. GHD = growth hormone deficiency; N = number of patients in safety analysis; NA = not applicable; NGHDSS = non-growth hormone deficient short stature; TS = Turner syndrome.

^a One patient death (due to aspiration) occurred during the study. Two additional deaths (one due to apnea and one due to surgical complications) were reported after patients discontinued from the study.

^b Death due to ruptured aortic aneurysm.

^c This patient, who had been diagnosed with a desmoplastic small round cell tumor and died approximately 4 years after discontinuation from the study.

In Study GDAB, a 6-year-old male who had GHD and cerebral palsy died due to aspiration during an afternoon nap. Two additional deaths were reported after study discontinuation: (1) a 5-year-old male, was hospitalized for flu symptoms, hypoglycemia, severe

dehydration, and respiratory arrest approximately 4.5 months after discontinuation from study; (2) the second patient, a 20-year-old male who had a history of craniopharyngioma had been hospitalized for surgery to remove a suprasellar cyst and died following vascular complications during surgery.

In Study GDCT, a 13-year-old with Turner syndrome died due to a ruptured aortic aneurysm during hospitalization for chest pain. She was in the control group receiving ethinyl estradiol but no growth hormone.

In Study E001, as mentioned above, a 12-year-old male with NGHDSS who had received 0.24 mg/kg/wk of Humatrope for approximately 6.4 years died due to a desmoplastic small round cell tumor approximately 4 years after discontinuing from the study. The applicant states that this tumor has not been previously identified in GH-treated patients. This reviewer has not found any published literature that shows an association between this tumor and GH treatment.

The incidence of deaths in GH-treated patients with NGHDSS is the lowest among all GH-treated pediatric subpopulations reported in GH registries. It represents 3.4% of all recorded deaths in the National Cooperative Growth Study (Maneatis et al, 2000) and is lower than Turner syndrome (4.21%), idiopathic growth hormone deficiency (12.8%), organic growth deficiency (35.1%), and chronic renal failure (12.2%).

C.2. Serious Adverse Events

C.2.1 Serious Adverse Events in study GDCH

A total of seven serious adverse events (SAEs) were reported for seven patients: five (13.5%) in the Humatrope treated group and two (6.5%) in the placebo-treated group.

Of particular interest is patient ~~1103~~, an 11-year-old male who was diagnosed with Stage 3B Hodgkin disease after 4 months of Humatrope treatment. The applicant states that "the short duration of Humatrope treatment prior to the diagnosis of lymphoma makes causality unlikely". Hodgkin lymphoma is not a common neoplasm noted to be associated with GH therapy. In the KIGS pharmacoepidemiological survey there is a single case of de novo Hodgkin lymphoma recorded in a patient with idiopathic growth hormone deficiency (a 9-year-old treated for 3.2 years with GH) (Wilton P et al., 1999). In addition, it appears that the patient had subclinical disease not recognized at the time of enrollment (enlarged mediastinum on chest X-ray and elevated LDH).

All four remaining SAEs in the Humatrope group involved trauma and resulted in hospitalization. They were: (1) alcohol ingestion and a dislocated fourth left finger in a 15-year-old male (patient 008/1071); (2) skull fracture, right crushed orbit, eye hemorrhage, intracerebral hemorrhage, increased right eye pressure, and broken left femur and wrist, all resulting from a fall from a tree (patient 008/1070, an 18-year old male); (3) left leg fracture in a sports-related accident in a 16-year-old male (patient 008/1076); (4) right tibia and fibula fracture in a sports-related accident in a 15-year-old male (patient 008 1103).

The two SAEs in the placebo control group were: (1) motor vehicle accident in a 17-year-old male (patient 008/1073); (2) black widow spider bite in a 14-year-old male (patient 008/1075).

C.2.2 Serious Adverse Events in study E001

Overall, 31 patients (13%) experienced at least one SAEs and a total of 38 SAEs. The Dose 1 treatment arm had 11 (14.1%) patients with SAEs, the Dose 2 treatment arm had 4 (5.1%) patients with SAEs, and the Dose 3 treatment arm experienced the highest number and percent of patients with SAEs: 16 (19.3%). These data are summarized in Table 36:

Table 36: Serious Adverse Events (Study E001-All Randomized Patients)

Serious Adverse Event	Dose 1	Dose 2	Dose 3	Total
	n (%)	n (%)	n (%)	n (%)
Number of patients in treatment group	78	78	83	239
Number of patients for whom an event was reported	11 (14.1)	4 (5.1)	16 (19.3)	31 (13.0)
Total number of events	12	8	18	38

Source: Table E001.12.6.

The following SAEs are reported once: cancer (intra-abdominal desmoplastic tumor), appendicitis, bronchitis, convulsion, dehydration, delayed puberty, epilepsy, enuresis, epiphysiolysis and surgical correction, hematuria, hematemesis, polymyositis, cosmetic surgery, cyst removal, dental avulsion, insertion of transtympanic drain, nasal septum correction, surgery NOS (toe arthralgia), surgery NOS (aortic valve stenosis), surgery NOS, esophageal atresia, tularemia, and accidental overdose (non-therapeutic agent). The following SAEs are reported more than once: abdominal pain (2 patients), fractures (3 patients), appendectomy (2 patients), tonsillectomy/adenoidectomy (5 patients), and convulsions NOS (4 patients). Due to the small number of individual SAEs encountered, no dose-dependent relationship can be gleaned, with the exemption of fractures, all three of which occurred in the Dose 3 treatment arm.

Of interest are the following patients:

- Patient 302-3012, a 15-year-old female who received high-dose (Dose 3) Humatrope and developed 4 years later arthralgia of left 2nd metatarsus-1st phalanx which required 2 corticosteroid infiltrations and surgery.
- Patient 305-3044, a 12-year 9-month-old male who had received low-dose Humatrope (Dose 1) and four years later was hospitalized because of abdominal pain; an abdominal mass was diagnosed and identified as a desmoplastic tumor with small cell and triple differentiation (muscular, epithelial, and neuroendocrine). The tumor was subsequently ablated and the patient was discontinued from the Humatrope therapy. He died four years later.
- Patient 601-6027, a 15 years 7 months male with a history of epilepsy who was diagnosed with slipped capital femoral epiphysis after receiving Humatrope (Dose 3) for more than 5 years. During an epileptic seizure, the patient fell and broke the head of his right femur. A hospital examination detected slipped capital femoral epiphysis. The patient was discontinued from the study.

C.2.3 Serious Adverse Events: Comparison Across Studies for Different Indications

Table 37 provides a summary of SAE incidence across studies and indications. SAEs were reported with similar frequency in patients with NGHDS irrespective of the study: 13.5% in study GDCH vs. 13% across all treatment arms in study E001. The percentage of patients with SAEs was lower for patients with NGHDS when compared to patients with either GHD (approximately 13% vs. 27%) and Turner syndrome (13% vs. 27% in trial GDCT; and 13% vs. 17.8% in trial GDCI for the whole duration of the trial).

Table 37: Serious Adverse Events

	GH Deficiency		Turner Syndrome		Non-Growth Hormone Deficient Short Stature			
	GDAB		GDCT		GDCH		E001	
	N=333		N=136		N=238		N=239	
	Humatrope ^a	Control	Humatrope ^c	Control	Humatrope ^d	Control	Humatrope ^e	
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	
Number of patients in group	333	74	62	184	46	37	31	238
Number (%) of patients with SAE	90 (27.0)	20 (27.0)	9 (12.9)	10 (5.4)	4 (8.7)	5 (13.5)	2 (6.5)	31 (13.0)
Total number of SAEs	137	31	9	11	4	9	2	38

Source: Table 3. H. 21. GH = growth hormone; N = number of patients in safety analysis; n = number of patients; SAE = serious adverse event. For study GDCH the comparison between treatment groups is presented for the first 1.5 years, the period during which the study was placebo controlled. For the total period of Humatrope treatment (mean exposure to Humatrope was approximately 4.0 years), 51 SAEs were reported for 41 (17.8%) patients (for 1 patient an SAE was reported during placebo treatment and during Humatrope treatment).

A qualitative description of the 175 SAEs reported for 90 (27%) patients with GHD contains the following observations:

- The majority of these events were hospitalizations, with surgical procedure being the most common reason for hospitalization.
- There were four cases of CNS tumor recurrence or progression (three craniopharyngiomas and one germinoma).
- One patient was diagnosed with a craniopharyngioma during the study (no information regarding prestudy CNS imaging is available for this patient).
- A papillary carcinoma of the thyroid was reported in a patient who had a history of acute lymphoblastic leukemia.
- One patient with a ventriculo-peritoneal shunt and history of nasopharyngeal lymphoma was hospitalized because of an enlarged thymus (no malignancy at biopsy).
- SAEs associated with neurological disorders included hospitalizations for concussion (1), cerebral vascular accident (1), seizures (seven events in 5 patients), and dysfunction or replacement of ventriculo-peritoneal shunts (six events in 3 patients). One patient was monitored for intracranial hypertension after complaints of headaches and vomiting (no increased intracranial pressure was observed).

- SAEs related to ear disorders were reported for 3 patients (two hospitalization for myringotomy and one surgery for replacement myringotomy tubes).
- One patient, an 18-year-old male was hospitalized for hip repair due to a slipped capital femoral epiphysis.

A qualitative description of the SAEs recorded during studies GDCT and GDCI (both in patients with Turner syndrome) contains the following observations:

- In Study GDCT, the majority of SAEs were hospitalizations, most often for surgical procedures such as ear disorders (including ear surgery not otherwise specified, chronic mastoiditis, removal of a cholesteatoma, combined mastoidectomy/nasoplasty/tympanoplasty, and tympanoplasty). One patient had intracranial hypertension due to shunt malfunction and required two separate surgeries.
- In study GDCI the most frequent SAE was hospitalization for surgical procedure. There were no neoplasms or neurological disorders reported during this study. As in study GDCT, there were numerous events related to ear disorders (including ear surgery NOS, surgery for chronic mastoiditis, mastoidectomy, and eardrum repair).

In summary, this across-trial comparison indicates a higher overall proportion of SAEs in patients with GHD or Turner syndrome when compared to patients with NGHDSS. Disease-specific patterns of SAEs were noted (e.g. SAEs associated with neurological disorders in GHD and SAEs associated with ear disorders in Turner syndrome). Two new malignancies were recorded in patients with GHD (papillary carcinoma of the thyroid as a secondary malignancy and a possibly undiagnosed craniopharyngioma) and none in patients with Turner syndrome. By comparison, two neoplasms (Hodgkin disease and desmoplastic small round cell tumor) were reported in the NGHDSS patient population over a similar period of time, in similar numbers of patients.

C.3. Patient Discontinuations Due to Adverse Events

C.3.1 Patient Discontinuations Due to Adverse Events in study GDCH

One Humatrope patient discontinued the study due to an adverse event (Hodgkin lymphoma). One placebo patient (008/1068) was listed as discontinuation due to an adverse event (bike/motor vehicle accident). The event, however, occurred after the patient, reportedly, completed the study.

C.3.2 Patient Discontinuations Due to Adverse Events in study E001

Three patients discontinued due to adverse events. They were:

- Patient 305-3044, a 12 year-old, male patient who had been on Humatrope treatment (Dose 1) for over 6 years when he was diagnosed with a large intraabdominal desmoplastic tumor.
- Patient 601-6027, a 16 year-old male with known history of epilepsy and psychomotor retardation, treated with Humatrope (Dose 3) for over 5 years, who, during an epileptic

seizure sustained a fracture of the right femoral head; at the same time a diagnosis of slipped epiphysial femoral head was made.

- Patient 406-4052, a 13 year-old female who, after over 8-years of Humatrope treatment (Dose 1) was noted to have decreased glucose tolerance as determined by elevated HbA1c concentration and an abnormal oral glucose tolerance test (plasma glucose concentration = 11.1 mmol/L, 2 hours after a glucose load). Throughout the entire trial, reported fasting blood glucose was between 3.66 mmol/L and 4.61 mmol/L. Follow up information revealed a normal HbA1c test (5.3%). The patient was not diagnosed with diabetes mellitus. The family medical history was negative for diabetes mellitus and impaired glucose intolerance.

C.3.3 Patient Discontinuations Due to Adverse Events - Comparison Across Studies for Different Indications

Table 38 provides a summary of the number and percent of patients who discontinued study participation due to adverse events (comparison across studies and indications). Overall, there were few discontinuations due to adverse events in patients treated with Humatrope. They were between 2.7 % (study GDCH) and 1.3% (study E001) in NGHDSS patients, between 2.7% (study GDCT) and 1.7% (study GDCI) in Turner syndrome patients, and 2.1% in GHD patients.

Table 38: Patient Discontinuations Due to Adverse Events

	GH Deficiency GDAB N=333		Turner Syndrome		Non-Growth Hormone Deficient Short Stature			
	GDCT N=136		GDCI N=236		GDCH N=65		E001 N=239	
	Humatrope ^a n (%)	Humatrope ^b n (%)	Control n (%)	Humatrope ^c n (%)	Control n (%)	Humatrope ^d n (%)	Control n (%)	Humatrope ^e n (%)
Number of patients in group	333	74	62	184	46	37	31	239
Number (%) of patients discontinued due to AE	7 (2.1)	2 (2.7)	0 (0.0)	1 (0.5)	0 (0.0)	1 (2.7)	1 (3.2)	3 (1.3)

Source: Table 3. H. 22. For study GDCI the comparison between Humatrope-treated patients and control patients, data are presented for the first 1.5 years, the period during which the study was placebo controlled. During the total period of Humatrope treatment (mean exposure for Humatrope was approximately 4.0 years. Four (1.7%) patients discontinued due to an AE.

Table 39 lists the individual patients who discontinued Humatrope treatment due to adverse events in individual trials. Patients' ages at the time of discontinuation and the duration of Humatrope treatment are also presented. Newly diagnosed malignancies are highlighted (grayed out).

Table 39: Patient Discontinuation Due to Adverse Events - Individual Patient Listing

Trial	Treatment	Reason for Discontinuation	Age (y)	Treatment Duration (y)
GDAB (GHD)	Humatrope	Accidental injury	12	5.7
	Humatrope	Anxiety regarding injections	8	1.0
	Humatrope	Craniopharyngioma	14	2.8
	Humatrope	Personality disorder (pre-existing)	17	1.1

	Humatrope	Preexisting germinoma	10	0.4
	Humatrope	Recurrent craniopharyngioma	6	0.7
	Humatrope	Recurrent craniopharyngioma	19	1.9
Study GDCT (Turner**)	Humatrope	SGOT increased	14	1.6
	Humatrope	Intracranial hypertension (VP shunt malfunction)	7	1.4
Study GDCI (Turner**)	Humatrope	Bone disorder (scoliosis)	16	1.7
	Humatrope	Gastrointestinal disorder	9	0.2
	Humatrope	Migraine	14	2.7
	Humatrope	Vascular disorder (aortic aneurism)	15	5.0
Study GDCH (NGHDSS)	Humatrope	Hodgkin disease	11	0.4
	Placebo*	Motor vehicle accident	16	2.3
Study E001 (NGHDSS)	Humatrope	Desmoplastic small round cell tumor	12.8	6.4
	Humatrope	Decreased glucose tolerance	13.9	8.4
	Humatrope	Accidental injury/slipped capital femoral epiphysis	16.2	5.3

*Occurred after the patient completed the study.

**Turner = Turner syndrome.

Abbreviations: GHD = growth hormone deficiency. NGHDSS = non-growth hormone deficiency short stature

Source: AS.6.1., AS.6.2, AS.6.3, and AS.6.4.

C.4. Treatment-Emergent Adverse Events

C.4.1 Treatment-Emergent Adverse Events in Trial GDCH

Similar proportions of patients in each treatment group developed a treatment-emergent adverse event (TEAE) in trial GDCH (97.3% in the Humatrope group and 96.8% in the placebo group). The body systems for which TEAEs were most frequently reported were the respiratory system (84% of patients) and the digestive system (66% of patients).

Table 40 presents individual TEAEs which occurred with higher frequency in the Humatrope group (selected are only TEAEs which occurred in at least 2 patients in the Humatrope group). For most adverse events, the difference in incidence between the Humatrope and placebo group was minimal. Adverse events with frequency in the Humatrope group ≥ 2 over placebo are: back pain (2.7X), tooth disorder (2.6X), otitis media (2.5X), cardiovascular disorder (2X), migraine (2X), gastrointestinal disorder (4.2X), surgical procedure (4.2X), arthralgia (3.3X), fungal dermatitis (3.3X), dysmenorrhea (2.5X), eye disorder (2.5X), hyperlipidemia (2.5X), abnormal liver function tests (2.5X), nausea and vomiting (2.5X), and benign skin neoplasm (2.5X).

Table 40: Treatment-Emergent Adverse Events in Trial GDCH*

Adverse Event	Humatrope (N=37) n (%)	Placebo (N=31) n (%)	Ratio**
Flu syndrome	20 (54.1)	11 (35.5)	1.5X
Pain	17 (45.9)	12 (38.7)	1.2X
Infection	18 (48.6)	9 (29.0)	1.7X
Abdominal pain	13 (35.1)	10 (32.3)	1.1X
Injection site pain	12 (32.4)	7 (22.6)	1.4X
Ear pain	10 (27.0)	5 (16.1)	1.7X
Lab test abnormal	9 (24.3)	5 (16.1)	1.5X
Acne	9 (24.3)	4 (12.9)	1.9X
Back Pain	10 (27.0)	3 (9.7)	2.7X

Bone disorder	9 (24.3)	4 (12.9)	1.9X
Lymphadenopathy	9 (24.3)	4 (12.9)	1.9X
Myalgia	9 (24.3)	4 (12.9)	1.9X
Albuminuria	6 (16.2)	4 (12.9)	1.2X
Allergic reaction	5 (13.5)	4 (12.9)	1X
Nausea	5 (13.5)	4 (12.9)	1X
Neck pain	6 (16.2)	3 (9.7)	1.7X
Tooth disorder	7 (18.9)	2 (6.5)	2.9X
Otitis media	6 (16.2)	2 (6.5)	2.5X
Cardiovascular disorder	5 (13.5)	2 (6.5)	2X
Migraine	5 (13.5)	2 (6.5)	2X
Arthrosis	4 (10.8)	2 (6.5)	1.7X
Gastrointestinal disorder	5 (13.5)	1 (3.2)	4.2X
Surgical procedure	5 (13.5)	1 (3.2)	4.2X
Anorexia	3 (8.1)	2 (6.5)	1.2X
Arthralgia	4 (10.8)	1 (3.2)	3.3X
Asthenia	3 (8.1)	2 (6.5)	1.2X
Bilirubinemia	3 (8.1)	2 (6.5)	1.2X
Bronchitis	3 (8.1)	2 (6.5)	1.2X
Fungal dermatitis	4 (10.8)	1 (3.2)	3.3X
Pustular rash	3 (8.1)	2 (6.5)	1.2X
Dysmenorrhea	3 (8.1)	1 (3.2)	2.5X
Ear disorder	4 (10.8)	0	-
Eye disorder	3 (8.1)	1 (3.2)	2.5X
Hyperlipemia	3 (8.1)	1 (3.2)	2.5X
Abn. liver function tests	3 (8.1)	1 (3.2)	2.5X
Nausea and vomiting	3 (8.1)	1 (3.2)	2.5X
Skin benign neoplasm	3 (8.1)	1 (3.2)	2.5X
Urine abnormality	4 (10.8)	0	-
Amblyopia	2 (5.4)	1 (3.2)	1.7X
Constipation	2 (5.4)	1 (3.2)	1.7X
Gynecomastia	2 (5.4)	1 (3.2)	1.7X
Thinking abnormal	2 (5.4)	1 (3.2)	1.7X
Anxiety	2 (5.4)	0	-
Breast pain	2 (5.4)	0	-
Conjunctivitis	2 (5.4)	0	-
Convulsion	2 (5.4)	0	-
Depression	2 (5.4)	0	-
Nail disorder	2 (5.4)	0	-

*Included are only adverse events which occurred more frequently in the Humatrope treatment group in ≥ 2 patients.

**Ratio = Humatrope AE incidence/Placebo AE incidence.

Source: Table GDCH.12.4.

Several TEAEs related to the musculoskeletal system occurred more frequently in the Humatrope treatment group (back pain, bone disorder, myalgia, neck pain, arthrosis, arthralgia). In addition, most of the actual terms covered under the umbrella term of "pain" are musculoskeletal complaints. Some of these distinct AEs occurred in the same patients but some did not. This Humatrope to placebo imbalance occurred in the context of a frequency of accidental injuries which was slightly higher in the placebo treatment group (51.4% Humatrope vs. 61.3% placebo).

Another Humatrope-to-placebo imbalance is recorded for events captured by the “cardiovascular disorder” term which included the following actual terms: mitral valve prolapse, possible mitral valve prolapse, heart murmur, systolic click, mild PR and cardiovascular disorder. The applicant reports the “cardiovascular disorder” to occur in 5 (13.3%) of Humatrope patients and in 2 (6.5%) of placebo-treated patients (this reviewer identified 3 additional patients in the Humatrope group in the dataset). The actual term for the two placebo patients is heart murmur. All four mitral valve prolapse-related actual terms (including a possible and a rule out MVP) are in the Humatrope treatment group. Heart murmurs in general and mitral valve prolapse are not known to be AEs related to GH treatment. Both are relatively common in pediatric patients.

Several other Humatrope-to-placebo imbalances in TEAE incidence were analyzed at the level of individual patient by this reviewer. The following observations were made:

- all of the “laboratory tests abnormal” AEs are related to abnormalities of the carbohydrate metabolism and/or to thyroid function (they are reviewed in detail in the laboratory results section of the review)
- “surgical procedures” AEs represent routine pediatric surgeries
- “abnormal liver function test” AEs were associated with a diagnosis of Gilbert syndrome (a benign condition) in 3 Humatrope patients

C.4.2 Treatment-Emergent Adverse Events in Trial E001

Table 41 summarizes the most frequent treatment-emergent adverse events for All Randomized Patients. Included are only those TEAEs which occurred with a frequency $\geq 5\%$ in any treatment arm. The majority of these events represent common childhood illnesses. Similar incidence of patients with TEAEs is noted in all three treatment groups. No TEAE displays a dose-dependent increase in incidence. There were no statistically significant differences between treatment arms. TEAEs which occurred more frequently in the Humatrope group in trial GDCH had a lower overall incidence recorded in trial E001 and, therefore, no dose-dependent trend could be analyzed or identified. It should be noted that the 239 patients exposed to Humatrope in trial E001 reported overall fewer adverse events (644) than the 37 patients who received Humatrope during trial GDCH (1482 AEs reported).

Table 41: Treatment- Emergent Adverse Events (All Randomized Patients)*

Event	Dose 1 N=78 n (%)	Dose 2 N=78 n (%)	Dose 3 N=83 n (%)	Total N=239 n (%)
Patients with ≥ 1 TEAE	47 (60.3)	57 (73.1)	58 (69.9)	162 (67.8)
Infection	16 (20.5)	12 (15.4)	15 (18.1)	43 (18.0)
Pharyngitis	14 (17.9)	8 (10.3)	12 (14.5)	34 (14.2)
Flu syndrome	8 (10.3)	9 (11.5)	8 (9.6)	25 (10.5)
Rhinitis	6 (7.7)	10 (12.8)	6 (7.2)	22 (9.2)
Bronchitis	11 (14.1)	7 (9.0)	2 (2.4)	20 (8.4)
Accidental Injury	4 (5.1)	2 (2.6)	8 (9.6)	14 (5.9)
Gastroenteritis	5 (6.4)	4 (5.1)	5 (6.0)	14 (5.9)
Surgical procedure	4 (5.1)	3 (3.8)	7 (8.4)	14 (5.9)
Otitis media	4 (5.1)	4 (5.1)	4 (4.8)	12 (5.0)

Abdominal pain	4 (5.1)	4 (5.1)	0	8 (3.3)
Fever	4 (5.1)	3 (3.8)	1 (1.2)	8 (3.3)
Pain	0	4 (5.1)	3 (3.6)	7 (2.9)
Diarrhea	1 (1.3)	5 (6.4)	0	6 (2.5)
Anemia	1 (1.3)	4 (5.1)	0	5 (2.1)

Source: Table E001.12. 4.

*Data are presented as number and (%) of patients with event. Included are TEAEs which occurred with a frequency $\geq 5\%$ in any treatment arm.

C.4.3 Treatment-Emergent Adverse Events - Comparison Across Studies for Different Indications

A comparison of TEAEs between the GHD, Turner syndrome, and NGHDSS trials is difficult because of different background rates of disease specific adverse events and because of methodological differences in data collection among trials. TEAEs were reported in a majority of patients receiving Humatrope. Their frequency ranged from 67.8% in patients with NGHDSS (trial E001) to 100% in patients with Turner syndrome (trial GDCT). Placebo-receiving patients had TEAEs in the 93-97% range. The most frequent TEAEs represented common childhood illnesses. The five most frequently reported events reported in the GHD trial were rhinitis (57.4%), pharyngitis (45.3%), fever (38.4%), headache (38.1%), and infection (33.3%). In both Turner syndrome studies otitis media was reported more frequently for patients receiving Humatrope than for patients in the control group (43% vs. 26% in study GDCT, and 29% vs. 13% in study GDCI).

The following TEAEs were reported at a higher frequency in the NGHDSS patient population of study GDCH than in the GHD or Turner syndrome patient populations: accidental injury, pain, injection site pain, myalgia, migraine, and arthralgia. Several TEAEs were reported in the NGHDSS patient population of study GDCH but not in the GHD and Turner syndrome patient populations; they were albuminuria, arthrosis, and urine abnormality. Further inferences are limited by the methodological limitations of this analysis (different coding dictionaries, different methods of ascertainment of adverse events, absence of similar control groups, etc.).

C.5. Clinically Significant Treatment-Emergent Adverse Events

C.5.1 Clinically Significant Treatment-Emergent Adverse Events in Trial GDCH

The applicant provides additional information about the incidence of specific TEAE that have been associated with growth hormone treatment. Some of these events were prospectively identified in the protocol and some were identified posthoc. They are presented in Table 42. Highlighted are the AE with higher incidence in the Humatrope group. They include scoliosis (reportedly mild in general), otitis media, hyperlipidemia, gynecomastia, hip pain and hypertension. Overall, the Humatrope group had a slightly higher incidence of AEs (40.5% vs. 32.3% in the placebo group).

Table 42: Clinically Significant Treatment-Emergent Adverse Events Safety Population-Study GDCH

Adverse Event	Humatrope N=37 n (%)	Placebo N=31 n (%)
Patients with TEAEs	15 (40.5)	10 (32.3)
Scoliosis	7 (18.9)	4 (12.9)
Otitis Media	6 (16.2)	2 (6.5)
Hyperlipidemia	3 (8.1)	1 (3.2)
Gynecomastia	2 (5.4)	1 (3.2)
Hypothyroidism	0	2 (6.5)
Aching joints	0	1 (3.2)
Hip pain	1 (2.7)	0
Hypertension	1 (2.7)	0

Source: Table GDCH.12.7.

The same information is also presented for the Final height population which, although smaller in total number of patients, includes the longest exposure per patient (Table 43). Highlighted are the AE with higher incidence in the Humatrope group. They include otitis media, scoliosis, gynecomastia, and hip pain.

Table 43: Clinically Significant Treatment-Emergent Adverse Events Final Height Population-Study GDCH

Adverse Event	Humatrope N=22 n (%)	Placebo N=11 n (%)
Patients with TEAEs	11 (50.0)	5 (45.5)
Otitis Media	6 (27.3)	1 (9.1)
Scoliosis	5 (22.7)	2 (18.2)
Gynecomastia	2 (9.1)	0
Hyperlipidemia	1 (4.5)	1 (9.1)
Hip pain	1 (4.5)	0
Hypothyroidism	0	1 (9.1)

Source: Table GDCH.12.8.

C.5.2 Clinically Significant Treatment-Emergent Adverse Events in Trial E001

As in trial GDCH, the applicant provides additional information about the frequency of several TEAEs that have the potential to develop or worsen during growth hormone treatment (Table 44). Several TEAEs occurred more frequently in the higher dose arms (Dose 2 and Dose 3) but the number of patients was too small to draw any firm conclusions. They were arthralgia, hyperlipidemia, myalgia, hypothyroidism, and joint disorder.

Table 44: Clinically Significant Treatment- Emergent Adverse Events (All Randomized Patients)*

Event	Dose 1 N=78 n (%)	Dose 2 N=78 n (%)	Dose 3 N=83 n (%)	Total N=239 n (%)
Patients with ≥ 1 TEAE	8 (10.3)	14 (17.9)	14 (16.9)	36 (15.1)
Otitis media	6 (7.7)	5 (6.4)	5 (6.0)	16 (6.7)
Arthralgia	0	3 (3.8)	3 (3.6)	6 (2.5)
Hyperlipidemia	1 (1.3)	2 (2.6)	3 (3.6)	6 (2.5)
Myalgia	0	2 (2.6)	1 (1.2)	3 (1.3)
Hypothyroidism	0	1 (1.3)	1 (1.2)	2 (0.8)
Joint disorder	0	1 (1.3)	1 (1.2)	2 (0.8)
Glucose tolerance decreased	1 (1.3)	0	0	1 (0.4)
Hyperglycemia	0	0	1 (1.2)	1 (0.4)
Scoliosis	0	1 (1.3)	0	1 (0.4)

Source: Table E001.12. 7.

*Data are presented as number and (%) of patients with event.

C.5.3 Clinically Significant Treatment-Emergent Adverse Events - Comparison Across Studies for Different Indications

Clinically significant TEAEs that have been associated with GH treatment, were analyzed and compared between patient populations treated with Humatrope (GHD, Turner syndrome, and NGHDSS). These events include edema, benign intracranial hypertension, prepubertal gynecomastia, scoliosis, slipped capital femoral epiphysis, neoplasm, hypertension, abnormal carbohydrate metabolism (including insulin resistance, glucose intolerance, hyperglycemia, diabetes mellitus), hypothyroidism, and otitis media.

Edema

The applicant does not report any events of edema in any of the NGHDSS trials. In the GHD patient population, events relating to edema included face edema (8 events), edema (5 events), and peripheral edema (3 events). In the Turner syndrome patient population, events included peripheral edema (16 events), edema (6 events), face edema (4), generalized edema (1), and lung edema (1).

Benign Intracranial Hypertension

There were no reports of intracranial hypertension in the NGHDSS patient population. In the GHD patient population, 1 patient developed intracranial hypertension due to ventriculo-peritoneal shunt malfunction. In addition, 1 patient was hospitalized for intracranial pressure monitoring during an evaluation of headaches and vomiting (no increase in intracranial pressure was detected). In the Turner syndrome patient population, there was one event of intracranial hypertension, due to a ventriculo-peritoneal shunt malfunction.

Prepubertal and Pubertal Gynecomastia

There were no reports of prepubertal gynecomastia in the NGHDSS and GHD patient populations (patients in study GDCH were mostly pubertal at the beginning of Humatrope

therapy). Pubertal gynecomastia was reported in two Tanner stage II males with GHD, and in two Humatrope-treated patients in the NGHDSS patient population (Tanner stage III Tanner stage V, respectively).

Scoliosis

In the NGHDSS patient population, scoliosis was reported for 19% of patients in Study GDCH (7 patients or 19% in Humatrope arm and 4 patients or 12.9% in the placebo arm) and for 1 patient (0.4%) in Study E001. In Study GDCH, scoliosis had been identified in the protocol as an event to be monitored prospectively (all events of scoliosis were, reportedly, mild). In the GHD patient population, scoliosis was reported for 5 of 333 (2%) patients (reportedly of mild severity). In the Turner syndrome patient population, there was one report of scoliosis, which resulted in patient discontinuation from the study.

Slipped Capital Femoral Epiphysis

One case of slipped capital femoral epiphysis occurred in each of the GHD and NGHDSS patient populations.

Neoplasm

As neoplasms were considered SAEs, they are discussed in the serious adverse event section. No neoplasm were reported in the Turner syndrome patient population.

Hypertension

Elevated blood pressure was reported for 1 patient with NGHDSS in study GDCH. The event, recorded as mild, began 1 week after initiation of Humatrope treatment and resolved after approximately 5.5 months. No treatment for the hypertension was reported. One event of hypertension was reported in the GHD patient population. There were 15 reports of hypertension in patients with Turner syndrome (two events were considered serious and required hospital evaluation).

Abnormal Carbohydrate Metabolism

In the NGHDSS patient population, there was one report of decreased glucose tolerance which resulted in study discontinuation. In addition, one patient had increased insulin secretion during a glucose tolerance test (however, this was not reported as a TEAE). Carbohydrate metabolism changes in studies GDCH and E001 are detailed in a different section of this review. In the GHD patient population, there were no reports of impaired glucose tolerance or diabetes mellitus. In the Turner syndrome patient population, there was one report of type 1 diabetes mellitus. Hyperglycemia was reported in 3 patients (one in each of the three patient populations).

Hypothyroidism

Hypothyroidism was reported in 2 (0.7%) patients with NGHDSS (study E001). Hypothyroidism was reported in 23% of patients with GHD and in 16% of patients with Turner syndrome.

Otitis Media

In the NGHDSS patient population, otitis media was reported for 16% of the Humatrope-treated patients in Study GDCH, compared with 7% of the placebo-treated patients. In Study E001, 7% of patients were reported to have otitis media or related events. There were no distinct dose-related differences in the frequency of otitis media in Study E001. Otitis media was reported in 29% of patients with GHD and in more than 40% of patients with Turner syndrome receiving Humatrope treatment. In both Turner syndrome studies, there was a higher frequency of otitis media and other ear disorders in the Humatrope-treated patients compared to control patients.

C.6. Clinical Laboratory Data

A direct and detailed comparison between studies was hampered by the fact that different studies used different laboratory methodologies, with different reference ranges, and, in some cases, measured different analytes (for example, glycosylated hemoglobin versus HbA1c). The applicant places special emphasis on laboratory data related to carbohydrate metabolism, thyroid function, and insulin-like growth factor-I (IGF-I).

In Study GDCH, additional clinical laboratory measures, such as clinical chemistry, lipids, hematology, urinalysis, gonadotropins, sex steroids, anti-GH binding capacity, and anti-*Escherichia coli* popyptide antibodies (anti-ECP antibodies), were measured. Analysis of anti-ECP antibodies was discontinued subsequently [amendment GDCH(e)], since data from other GH-treated populations and data from other Lilly studies had demonstrated no clinically significant development of anti-ECP antibodies.

In Study E001, laboratory measures included clinical chemistry, fasting glucose, glycosylated hemoglobin, hematology, urinalysis, and thyroid function tests. Because these measurements were performed in 39 local laboratories, which employed diverse methodologies, the applicant presented only the laboratory data related to carbohydrate metabolism.

C.6.1. Carbohydrate Metabolism

C.6.1.1 Carbohydrate Metabolism Data in study GDCH

Assessment of carbohydrate metabolism variables (fasting glucose, fasting insulin, and glycosylated hemoglobin/hemoglobin A1c) was done at the beginning of the trial and every 6-months thereafter. Glycosylated hemoglobin was assayed for the first decade of the study (1988 to 1998) followed by hemoglobin A1c (HbA1c) after 1998. Because of varying reference

ranges across the duration of the study, this analyte is reported as “adjusted HbA1c” relative to the appropriate reference range (in this form, normal values fall between 0 and 1.0).

Table 45 presents baseline values and changes from baseline to endpoint in the Safety Population for fasting glucose (mmol/L), fasting insulin (pmol/L), insulin/glucose ratio, the Quantitative Insulin Sensitivity Check Index (QUICKI), and HbA1c. Mean baseline values for carbohydrate metabolism analytes were both normal and similar for both treatment groups. There were no statistically significant differences between treatment groups for change from baseline to endpoint. There was a 11.7% increase in mean fasting insulin at the end of treatment for the Humatrope group. In contrast, the placebo group experienced a 2.2% reduction in mean fasting insulin. Consequently, insulin/glucose ratio increased minimally in the Humatrope group. QUICKI diminished insignificantly in both treatment groups.

Table 45: Carbohydrate Metabolism Changes from Baseline to Endpoint-Safety Population

Lab Test	Treatment Group	N	Baseline Mean (SD)	Change Mean (SD)
Fasting glucose (mmol/L)	Humatrope	36	4.907(0.346)	0.065(0.494)
	Placebo	29	4.748(0.357)	0.234(0.452)
Fasting insulin (pmol/L)	Humatrope	33	84.774(64.800)	9.945(63.909)
	Placebo	28	90.969(48.461)	-2.027(60.878)
Insulin/glucose ratio	Humatrope	33	2.391(1.798)	0.250(1.752)
	Placebo	28	2.652(1.319)	-0.135(1.723)
Adjusted hemoglobin A1c	Humatrope	35	0.374(0.300)	-0.056(0.409)
	Placebo	29	0.296(0.279)	-0.042(0.393)
QUICKI*	Humatrope	33	0.346(0.035)	-0.011(0.038)
	Placebo	28	0.338(0.028)	-0.002(0.035)

Source: Table GDCH.12.13.

*QUICKI = $1/(\log(\text{fasting plasma insulin (uU/ml)}) + \log(\text{fasting glucose(mg/dl)}))$.

P-value tests between-group difference for change from baseline to endpoint.

n=Total number of patients in each treatment group having the variable in both baseline and postbaseline visits.

Table 46 presents the incidence of values outside the reference range for carbohydrate metabolism analytes at any time in the study. The number and proportion of patients with high carbohydrate analytes were similar between the two treatment groups and there were no statistically significant differences between treatment groups.

One patient in the Humatrope group had an abnormal and high fasting glucose level at Visit 14 with accompanying normal serum insulin and HbA1c values. Similar number of patients had abnormal and high serum insulin and HbA1c levels.

Table 46: Incidence of High or Low Carbohydrate Analytes after Baseline-Safety Population

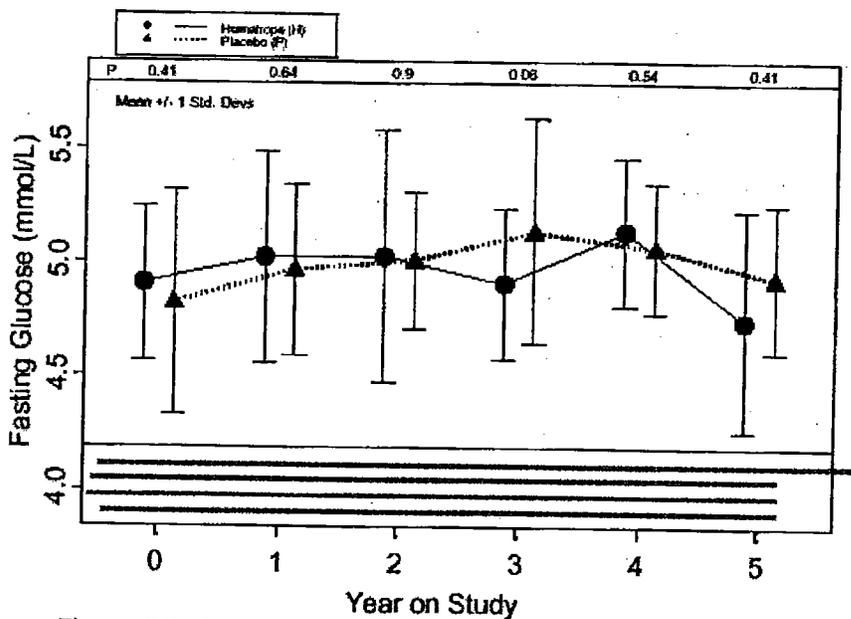
Lab test	Humatrope (N=36)			Placebo (N=30)		
	Normal n (%)	Low n (%)	High n (%)	Normal n (%)	Low n (%)	High n (%)
Fasting glucose	33 (91.7)	2 (5.6)	1 (2.8)	28 (96.6)	1 (3.4)	0
Fasting insulin	20 (58.8)	11 (32.4)	4 (11.8)	17 (60.7)	7 (25.0)	4 (14.3)
Adjusted HbA1c	22 (61.1)	13 (36.1)	2 (5.6)	16 (55.2)	13 (44.8)	2 (6.9)

Source: Table GDCH.12.14. N=Total number of patients in the treatment group within the requested time interval. The time interval includes visit 2 (Month 1) through the visit prior to visit 99 (i.e. penultimate visit). A total of 66 patients had values in this interval.

Scatterplots of fasting plasma glucose levels, fasting insulin levels and HbA1c show similar global patterns of distribution for both treatment arms.

Carbohydrate metabolism was also evaluated by analyzing between-group differences in mean values at each year on study. Such an analysis for fasting serum glucose is presented in Figure 18. There were no statistically significant between-group differences for this variable.

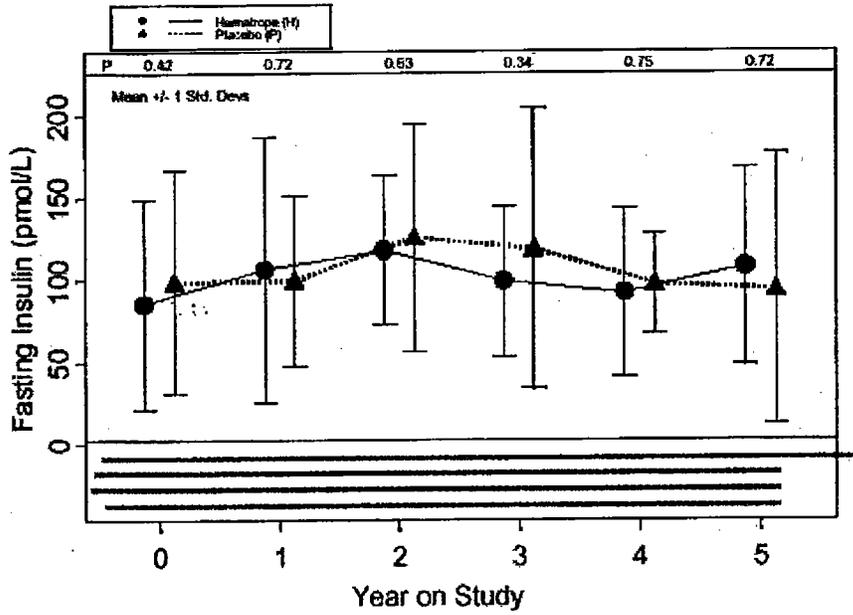
Figure 18: Mean Fasting Serum Glucose by Year on Study (Safety population)



Source: Figure GDCH.12.4.

Similarly, there were no statistically significant between-group differences for mean fasting insulin at each year on study (Figure 19).

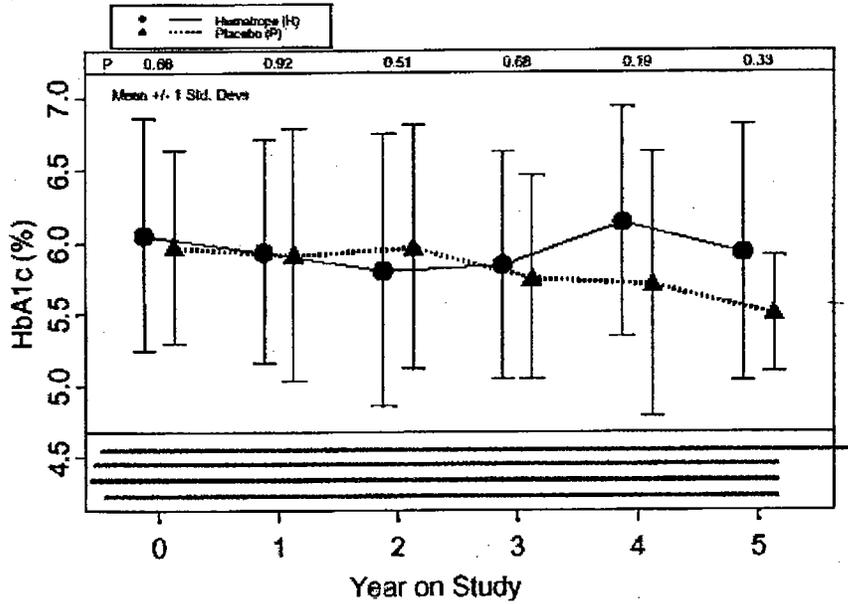
Figure 19 : Mean Fasting Serum Insulin by Year on Study (Safety Population)



Source: Table GDCH.12.5.

In addition, the absence of between-group differences for mean HbA1c is noted (Figure 20).

Figure 20 : Fasting HbA1C by Year on Study (Safety Population)



Source: Figure GDCH.12.6

C.6.1.2 Carbohydrate Metabolism Data in Study E001

Carbohydrate metabolism was assessed by measuring fasting glucose and glycosylated hemoglobin at each visit during the “core phase” and “extension phases” of study E001 (fasting serum insulin concentrations are not presented). Table 47 presents baseline values and changes from baseline to the two-year endpoint for all the randomized patients for fasting glucose (mmol/L), and glycosylated hemoglobin. There were no statistically significant differences between the mean fasting glucose and the mean glycosylated hemoglobin measurements at baseline and at the end of the two-year study. The mean change in fasting glucose showed a discrete dose-dependent trend. This was not mirrored by the glycosylated hemoglobin changes.

Table 47: Carbohydrate Metabolism Changes from Baseline to Two-Year Endpoint - All Randomized Patients

Lab Test	Treatment Group	N	Baseline Mean (SD)	Change Mean (SD)
Fasting glucose (mmol/L)	Dose 1	59	4.545(0.725)	0.004(0.830)
	Dose 2	61	4.457(0.825)	0.157(0.947)
	Dose 3	58	4.510(0.698)	0.204(0.809)
Glycosylated hemoglobin (%)	Dose 1	62	5.314(1.076)	-0.217(1.247)
	Dose 2	64	5.420(0.926)	-0.029(1.024)
	Dose 3	67	5.396(1.027)	-0.049(0.924)

Source: Table E001. 12. 8. N = Total number of patients in each treatment group having the variable in both baseline and postbaseline visits.

Table 48 summarizes the incidence of high (>7.0 mmol/L) or low (<2.0 mmol/L) fasting blood glucose values after baseline for All Randomized Patients. No statistically significant differences among groups in the incidence of high fasting blood glucose values were reported. Nine patients had fasting blood glucose concentrations above the upper limit of the reference range (7 mmol/L) on a single occasion after baseline. All had subsequent measurements below the defined upper limit. In all cases, reportedly, the glycosylated hemoglobin was normal. There was a discrete dose-dependent upward trend for the incidence of patients with high glucose levels.

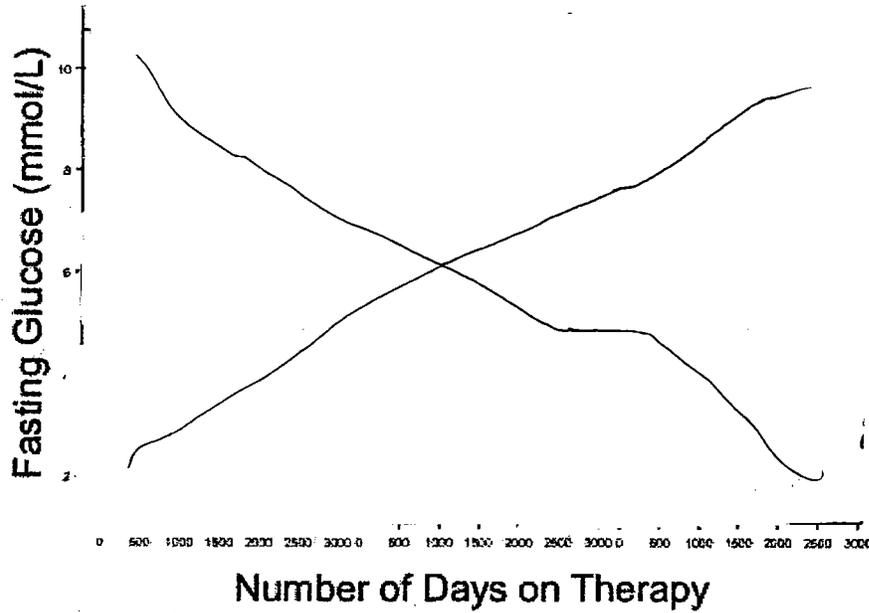
Table 48: Incidence of High or Low Fasting Blood Glucose After Baseline (All Randomized Patients)

Variable	Dose 1 (N=75)		Dose 2 (N=73)		Dose 3 (N=80)	
	No	n (%)	No	n (%)	No	n (%)
Low glucose	72	1 (1.4)	76	0	77	2 (2.6)
High glucose	72	2 (2.8)	76	3 (3.9)	77	4 (5.2)
All normal	72	69 (95.8)	76	73 (96.1)	77	71 (92.2)

Source: Table E001. 12. 9. N= number of patients in the treatment group. No=number of patients with measures fasting plasma glucose in each treatment group. n(%) = number and % of patient within the specified range (high, low, or normal)

Figure 21 presents the overall pattern of fasting glucose values for all three treatment groups throughout the study. This pattern was, generally, similar among treatment groups.

Figure 21: Fasting Glucose by Number of Days on Treatment

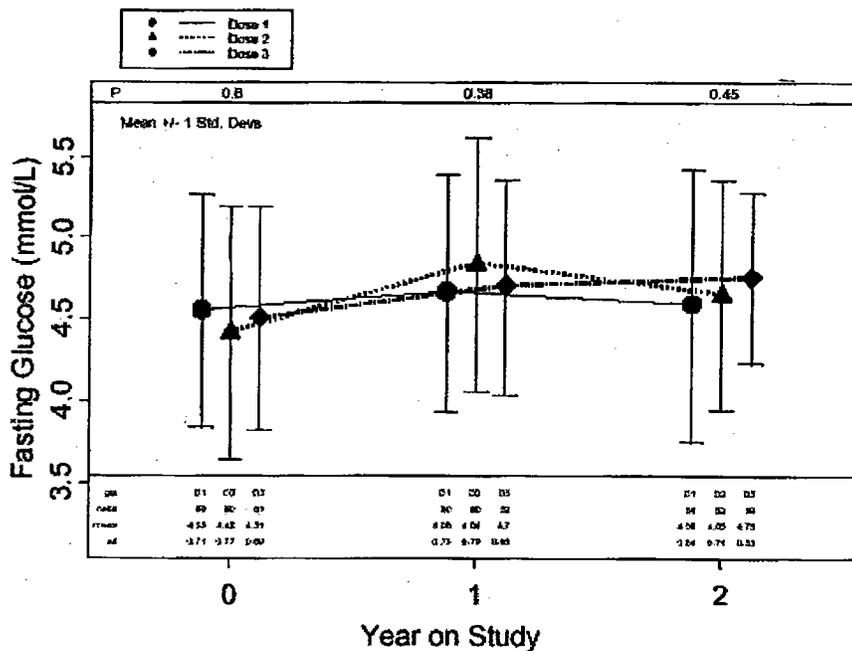


Source: Figure E001. 12. 1.

Figure 22 illustrates the average fasting glucose concentrations by year on study for the first two years of study (“core response phase”). The average fasting glucose concentrations remained normal at these time intervals and there were no statistically significant differences among dose groups.

Figure 22: Fasting Glucose at Baseline, One-year, and Two-year for all Randomized Patients

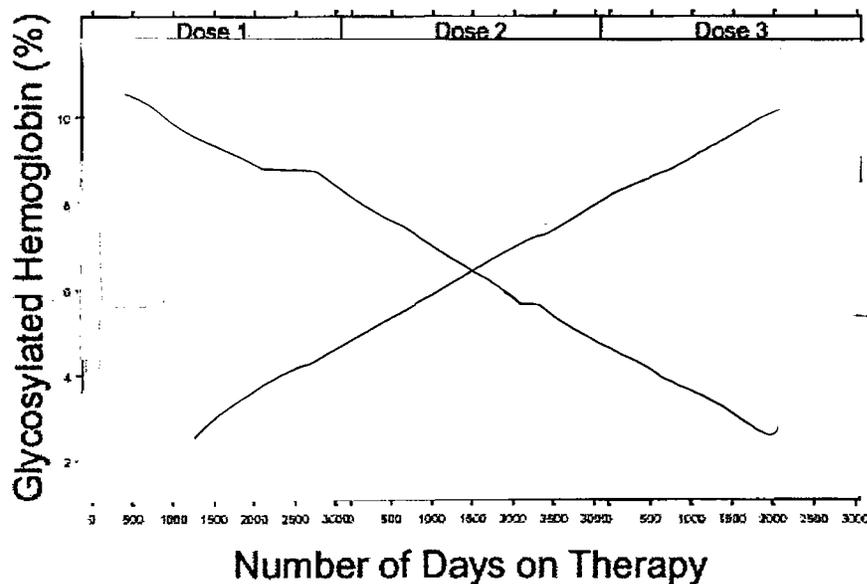
Source: Figure E001. 12. 3.



Glycosylated hemoglobin was measured locally at baseline and at subsequent visits during the "core phase" of the trial. Different methodologies were utilized (either glycosylated hemoglobin or HbA1c was analyzed). If the glycosylated hemoglobin was elevated, an oral glucose tolerance test (OGTT) was to be performed. Patients were to be discontinued from the clinical trial if OGTT was abnormal (plasma glucose concentration > 11 mmol/L, 2 hours after a glucose load).

In addition, during the extension phase, some investigators performed OGTTs to obtain baseline (control) values as part of their routine care. Consequently, these OGTTs were performed when glycosylated hemoglobin values were normal. One patient (406-4052, Dose 1) was noted to have an elevated HbA1c (6.1%, reference range 2.0-6.0%) at one visit; a subsequent OGTT indicated decreased glucose tolerance and the patient was discontinued from the trial. Interestingly, this patient's weight at birth was -2.63 standard deviation (SD) for gestational age.

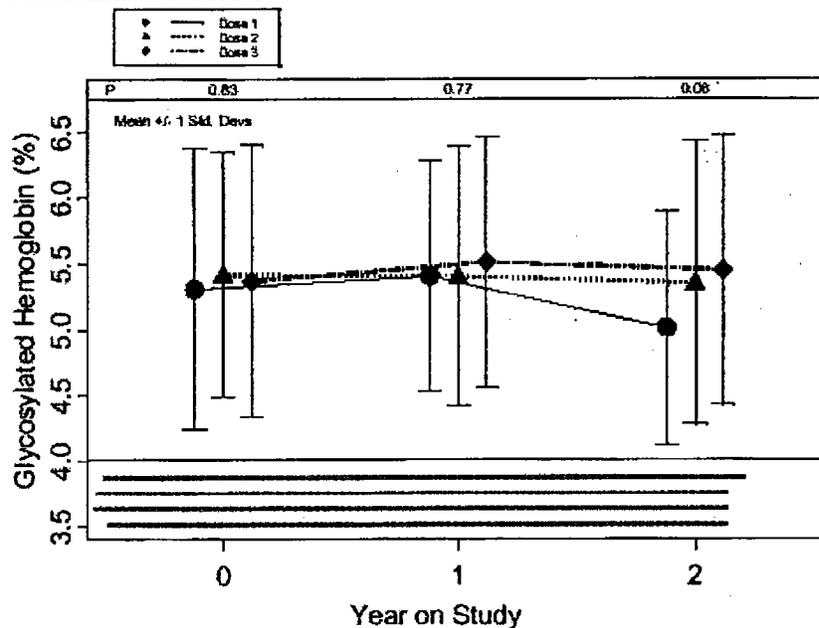
Figure 23 presents a scatterplot of glycosylated hemoglobin values for all three treatment groups throughout the study. This pattern was, generally, similar among treatment groups. However, in the upper range of the distributions there are a number of values in each treatment arm that are elevated (the range of the local lab was not available, though). The applicant plotted the pattern of glycosylated hemoglobin during the study for each patient and concluded that, with exemption of patient 304-3038, "glycosylated hemoglobin levels were relatively stable for all patients". This patient had increased glycosylated hemoglobin during the second year of therapy with fasting blood glucose within normal range; no OGTT was performed. No additional information is available. **Figure 23: Glycosylated Hemoglobin by Number of Days on Treatment**



Source: Figure E001. 12. 2.

Figure 24 illustrates the average glycosylated hemoglobin concentrations for the “core-response” phase of the trial. They did not increase significantly in the first 2 years of the study. There were no statistically significant differences among dose groups for glycosylated hemoglobin during the study. Although the HbA1c in low-dose regimen (Dose 1), was visually lower than the higher dose regimens (Dose 1, and Dose 2), the general trend for the latter was horizontal.

Figure 24: Glycosylated Hemoglobin at Baseline, One-year, and Two-year for all Randomized Patients



Source: Figure E001. 12. 4.

C.6.1.3 Carbohydrate Metabolism Data - Comparison Across Studies for Different Indications

A comparison of carbohydrate metabolism data collected during trials for GHD, Turner syndrome, and NGHDSS allows for the following observations:

- 1) Baseline mean fasting blood glucose values were similar among the three patient populations and changed minimally with Humatrope treatment.
- 2) Mean glycosylated hemoglobin or HgA1c (available only for Turner syndrome and NGHDSS patients) did not change significantly from baseline to endpoint.

Mean fasting insulin concentrations were available for Turner syndrome patients in only one study (GDCH) and for NGHDSS patients in study GDCH. In patients with Turner syndrome, mean fasting insulin concentrations approximately doubled between baseline and endpoint but remained within the normal laboratory reference range. In patients with NGHDSS there was a 11.7% increase in mean fasting insulin at the end of treatment for the Humatrope group, while

the placebo group experienced a 2.2 reduction in mean fasting insulin). These comparative findings are presented in table 49.

Table 49: Fasting insulin changes from baseline to endpoint*

Fasting insulin (pmol/L)	Study GDCH (Turner syndrome) N=230		Study GDCH (NGHDSS) N=68	
	Humatrope ^a N=80	Humatrope ^b N=117	Humatrope ^c N=33	Placebo N=28
Baseline	37.3±49.3	29.9±59.8	84.8±64.8	91.0±48.5
Change to endpoint	36.4±121.1	39.5±96.9	10.0±63.9	-2.0±60.9

Source: Table 3. H. 24.

*Included are only patients with Turner syndrome and NGHDSS for which these data were available.

^aDose = 0. 27 mg/ kg/ wk.

^bDose = 0. 36 mg/ kg/ wk. This column includes placebo- treated patients who were transitioned to Humatrope treatment after 1. 5 years.

^cDose = 0. 222 mg/ kg/ wk.

C.6. 2. Thyroid Function

C.6. 2.1 Thyroid Function in Trial GDCH

Thyroid function assessments were performed at baseline and every 6 months thereafter until the end of the study. The data are presented as mean changes from baseline and as incidence of values outside the reference range. Table 50 provides mean baseline values and changes from baseline to endpoint for thyroid function tests for the following: total thyroxine (T4), free thyroxine (free T4), triiodothyronine (T3), and thyroid stimulating hormone (TSH). Mean baseline values were similar for both treatment groups. There were minimal on-study changes and no statistically significant differences between treatment groups.

Table 50: Thyroid Function Changes from Baseline to Endpoint-Safety Population

Lab Test	Treatment Group	N	Baseline Mean (SD)	Change Mean (SD)
T ₄ -RIA (nmol/L)	Humatrope	36	103.747(19.774)	-4.505(21.985)
	Placebo	29	103.226(13.952)	-6.036(13.870)
Free T ₄ (pmol/L)	Humatrope	36	17.053(2.892)	-0.858(3.653)
	Placebo	29	16.864(2.694)	-0.754(4.967)
Total T ₃ (nmol/L)	Humatrope	36	2.586(0.339)	-0.451(0.411)
	Placebo	29	2.743(0.368)	-0.556 (0.366)
TSH (mU/L)	Humatrope	36	2.330(1.308)	-0.384(1.037)
	Placebo	29	2.187(0.989)	-0.069(1.241)

Source: Table GDCH.12.7.

n=Total number of patients in each treatment group having the variable in both baseline and postbaseline visits.

Table 51 presents the incidence of abnormal (low or high) values for thyroid analytes at any postbaseline timepoint in the study for both treatment groups.

Table 51: Incidence of High or Low Thyroid function Tests after Baseline-Safety Population

	Humatrope	Placebo	Total	Humatrope	Placebo	Total
T ₄ -RIA	22 (61.1)	11 (30.6)	3 (8.3)	22 (75.9)	6 (20.7)	1 (3.4)
Free T ₄	32 (88.9)	4 (11.1)	0	28 (96.6)	0	1 (3.4)
Total T ₃	30 (83.3)	2 (5.6)	4 (11.1)	25 (86.2)	0	4 (13.8)
TSH	28 (77.8)	3 (8.3)	6 (16.7)	23 (79.3)	2 (6.9)	4 (13.8)

Source: Table GDCH.12.16. N=Total number of patients with the lab test within the requested time interval. The time interval includes visit 2 (Month 0) through the visit prior to visit 99 (i.e. penultimate visit). A total of 66 patients had values in this interval.

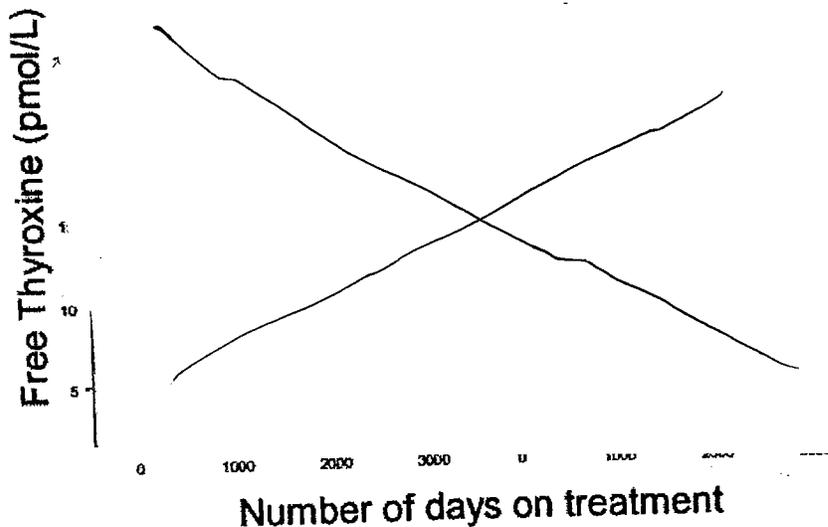
A number of patients in each group had out-of-reference range values for thyroid analytes. The great majority of these values were, reportedly, only slightly above or below the reference range. The majority of patients had only a single out-of-range thyroid parameter at one or two visits across the duration of the study, accompanied by normal values for the remaining analytes at the given visit. There were no statistically significant differences between treatment groups in incidence of out-of-reference values.

A single patient developed hypothyroidism while on study (patient 1108 in the placebo group). Four patients in the Humatrope group (and none in the placebo group) had a low postbaseline free T₄ value. Three of them had minimally depressed free T₄ values on a single occasion, in the presence of normal TSH values. The fourth patient (008/1059) had a very low free T₄ at one visit, which was subsequently determined to be due to laboratory error and was normal upon repeat analysis.

Six patients were reported to have hypothyroidism as a preexisting condition in the Safety Population at baseline (three in each treatment group). Five of these patients were receiving thyroid hormone replacement from Visit 1 (randomization). All patients appeared to have been controlled with replacement thyroxine therapy during the study.

A scatterplot of free T₄ serum levels shows similar global patterns of distribution in the normal and abnormal range for patients in both treatment groups throughout the study. This is illustrated in Figure 25:

Figure 25: Free Thyroxine by Number of Days on Treatment



Note: Dotted lines correspond to reference range.
 The one extreme low value was determined to be due to a laboratory error.
 Source: Figure GDCH. 12. 7.

C.6. 2.2 Thyroid Function in Trial E001

In this study, laboratory measurements were performed in 39 local laboratories, which employed different methodologies, thus limiting the robustness of this analysis. Two patients reported hypothyroidism: they were patient 401-4005 (Dose 3 treatment group) and patient 401-4006 (Dose 2 treatment group). Both were diagnosed with hypothyroidism at Visit 3 (Month 3 of Humatrope treatment) and began replacement therapy.

C.6. 2.3 Thyroid Function - Comparison Across Studies for Different Indications

Mean baseline values and changes from baseline to endpoint for thyroid function tests are presented in Table 52. Criteria for data collection were different in different studies. Overall, baseline and change-to-endpoint values for thyroid function tests appeared similar among the three patient populations. Hypothyroidism was reported as a TEAE in 23% of patients with GHD. In patients with Turner syndrome, hypothyroidism was reported as a TEAE for 15% of patients (if data across studies are combined). In patients with NGHDS, hypothyroidism was diagnosed in two Humatrope-receiving patients study E001 (< 1%) and in one placebo patient in study GDCH.

Table 52: Thyroid Function Changes from Baseline to Endpoint

	GH Deficiency		Turner Syndrome			Non-Growth Hormone Deficient Short Stature		
	GDAB	GDCT	GDCI		GDCH	E001		
	N=333	N=136	N=230	N=68	N=239			
	Humatrope ^a	Humatrope ^b	Control	Humatrope ^c	Humatrope ^d	Humatrope ^e	Control	Humatrope ^f
Total number of patients in treatment group	333	74	62	93	137	37	31	239
Total T4 (nmol/L)								
n	333	74	60	92	134	36	29	ND
Baseline	115.8	107.4 ± 18.1	109.5 ± 24.9	119.5 ± 25.1	115.8 ± 22.3	103.8 ± 19.8	103.2 ± 14.0	
Change to endpoint	-10.3	19.5 ± 30.8	22.2 ± 34.1	-2.5 ± 24.3	0.7 ± 24.3	-4.5 ± 22.0	-6.0 ± 13.9	
Free T4								
n	333	ND	ND	ND	ND	36	29	ND
Baseline	2.5 ±					17.1 ± 2.9 ^h	16.9 ± 2.7 ^h	
Change to endpoint	-0.2 ±					-0.9 ± 3.7 ^h	0.8 ± 5.0 ^h	
TSH (mIU/L)								
n	333	74	60	90	134	36	29	ND
Baseline	2.0	3.3 ± 1.3	3.5 ± 3.1	3.1 ± 1.9	3.2 ± 2.4	2.3 ± 1.3	2.2 ± 1.0	
Change to endpoint	-0.7	-0.5 ± 1.9	1.1 ± 13.8	0.1 ± 4.4	4.5 ± 39.5	-0.4 ± 1.0	-0.1 ± 1.2	

Note: The Control group for Study GDCT was a randomized, untreated control, whereas for Study GDCI and Study GDCH it was a randomized, placebo control. Values represent mean ± standard deviation (SD), except in Study GDAB, where values represent the median. Study GDCI was placebo controlled for the first 1.5 years; however, placebo control data for laboratory values were not summarized separately in the clinical study report and, thus, placebo control data for Study GDCI are not presented in this table. For each of the studies, endpoint refers to the last visit on treatment. Abbreviations: GH = growth hormone; N = number of patients in safety analysis; n = number of patients with baseline or endpoint value; ND = not determined; T4 = thyroxine; TSH = thyroid-stimulating hormone.

Source: Table 3. H. 25.

C.6.3 Insulin-Like Growth Factor-I

C.6.3.1 Insulin-Like Growth Factor-I in Study CDGH

Table 53 provides mean baseline values and changes from baseline to endpoint for insulin-like growth factor-I (IGF-I) for the Safety Population. At baseline, the mean serum IGF-I concentration was low for age and gender in both treatment groups (below the 10th percentile of IGF-I values for the age- and gender-matched general population). The Humatrope group had a significantly greater increase in mean serum IGF-I from baseline to endpoint (p=0.007); this difference was not statistically significant when expressed as the change in IGF-I standard deviation score (p=0.273). At the end of treatment the IGF-I values remained below the mean value for the general population at endpoint (mean IGF-I SDS <-1.0).

Table 53: Insulin-Like Growth Factor-I Changes from Baseline to Endpoint-All Males Safety Population

Parameter	Treatment Group	N	Baseline Mean (SD)	Endpoint Mean (SD)
IGF-I (ng/ml)	Humatrope	33	189.568(74.111)	186.553(123.479)
	Placebo	27	225.579(100.295)	102.791(105.205)
IGF-I SDS	Humatrope	33	-1.933(1.111)	0.710(2.251)
	Placebo	27	-1.391(1.557)	0.170(1.281)

Source: Table GDCH.12.24.
n=Total number of patients in each treatment group having the variable in both baseline and postbaseline visits.
The endpoint is the last visit prior to visit 99.

The incidence of low or high IGF-I SDS (defined as less than or greater than 3 SD from the mean for age and gender at any time in the study) is presented in Table 54. The majority of patients in both treatment groups had serum IGF-I values within 3.0 SDS of the mean throughout the study. There was no statistically significant difference between treatment groups in incidence of high IGF-I values. Twice as many patients in the Humatrope group had serum IGF-I concentrations that exceeded 3 (SD) above the mean for age and gender at some postbaseline time point, when compared to the placebo group. Most of these patients, had high IGF-I SDS at only a single visit. Only four patients (three in the Humatrope group and one in the placebo group) had high IGF-I concentrations at 2 or 3 visits. All patients, reportedly, had normal values at conclusion of their study participation.

Table 54: Incidence of High or Low Insulin-Like Growth Factor-I SDS after Baseline-Safety Population

Lab Test	Humatrope (N=36)			Placebo (N=30)		
	Normal (n=2)	Low (n=22)	High (n=12)	Normal (n=22)	Low (n=12)	High (n=6)
IGF-I SDS	21 (60.0)	7 (20.0)	7 (20.0)	18 (64.3)	7 (25.0)	3 (10.7)

Source: Table GDCH.12.25. N=Total number of patients with the lab test within the requested time interval. The time interval includes visit 2 (Month 1) through the visit prior to visit 99 (i.e. penultimate visit). A total of 66 patients had values in this interval.

C.6.3.3 Insulin-Like Growth Factor-I in Study E001

IGF-I level changes recorded during this trial were not presented.

C.6.3.4 Insulin-Like Growth Factor-I - Comparison Across Studies for Different Indications

IGF-I values were available only for two studies: study GDCI (Turner syndrome) and study GDCH (NGHDSS). Table 55 summarizes the mean baseline values and the changes from baseline-to-endpoint for serum IGF-I concentrations in these two studies. In patients with Turner syndrome, the change in mean IGF-I concentration from baseline to endpoint was greater for the 0.36 mg/kg/wk dosage group than for the 0.27 mg/kg/wk dosage group. In the study GDCH, the Humatrope group had a higher baseline mean serum IGF-I, when compared to the Turner syndrome patients from study GDCI, but the change to endpoint was similar between the two patients populations for similar dose regimen (0.22 mg/kg/wk in NGHDSS patients and 0.27 mg/kg/wk in Turner syndrome patients)

Table 55: Insulin- Like Growth Factor- I Changes from Baseline to Endpoint

	Turner Syndrome		Non-Growth Hormone Deficient Short Stature		p-value ^d
	GDCH N=230		GDCH N=68		
	Humatrope ^a	Humatrope ^b	Humatrope ^c	Control	
Total number of patients in treatment group	93	137	37	31	
IGF-I (ng/mL)					
N	81	124	33	27	
Baseline	136 ± 76	142 ± 89	190 ± 74	226 ± 100	
Change to endpoint	188 ± 165	241 ± 239	187 ± 123	103 ± 105	0.007
IGF-I SDS ^e					
N	NA	NA	33	27	
Baseline	NA	NA	-1.9 ± 1.1	-1.4 ± 1.6	
Change to endpoint	NA	NA	0.7 ± 2.3	0.2 ± 1.3	0.273

Note: Values represent mean ± standard deviation (SD). Study GDCH was placebo controlled for the first 1.5 years; however, placebo control data for laboratory values were not summarized separately in clinical study report and, thus, placebo control data are not presented in this table for Study GDCH. For both studies, endpoint refers to the last visit on treatment. Abbreviations: IGF-I = insulin-like growth factor-I; IGF-I SDS = insulin-like growth factor-I standard deviation score; N = number of patients in safety analysis; n = number of patients with baseline or endpoint value; NA = not applicable.

Source: Table 3. H. 26.

C.6.4. Other Laboratory Parameters – study GDCH

Several additional laboratory parameters were presented for study GDCH alone. They include clinical chemistry, serum lipids, hematology, urinalysis, gonadotropins, sex steroids, anti-growth hormone antibodies, and anti-*Echerichia coli* polypeptide antibodies.

C.6.4.1 Clinical Chemistry

Clinical chemistry assessments were performed at baseline and every 6 months thereafter until the end of the study. The data are presented as mean changes from baseline and as incidence of abnormal values. Table 56 includes the description of baseline and change-to endpoint for the measured analytes. In general, both treatment groups had similar baseline values and on-treatment changes. The only analyte which displayed a statistically significant between-group difference was BUN; mean blood urea nitrogen fell by 0.33 mmol/L in the Humatrope group and rose by 0.28 mmol/L in the placebo group (likely due to the anabolic effect of growth hormone). There were no significant differences between groups at baseline or in changes from baseline to endpoint for any of the other chemistry analytes.

Table 56: Electrolyte Changes from Baseline to Endpoint-Safety Population

Lab Test	Treatment Group	N	Baseline Mean (SD)	Change Mean (SD)
Sodium (mmol/L)	Humatrope	36	138.583(1.730)	0.778(2.356)
	Placebo	29	139.483(1.993)	-0.345(2.676)
Potassium (mmol/L)	Humatrope	35	4.160(0.252)	-0.011(0.342)
	Placebo	29	4.266(0.335)	-0.152(0.445)
Chloride (mmol/L)	Humatrope	36	104.778(2.269)	0.806(2.926)
	Placebo	29	105.034(2.884)	-0.069(3.484)
CO2 (mmol/L)	Humatrope	34	24.382(2.045)	0.235(0.235)
	Placebo	28	25.179(2.389)	-0.607(2.846)
BUN (mmol/L)	Humatrope	36	4.792(1.211)	-0.328(1.124)
	Placebo	29	4.320(0.949)	0.283(1.337)
Creatinine (umol/L)	Humatrope	36	62.132(12.044)	7.342(17.585)
	Placebo	29	62.488(12.927)	10.972(15.060)
ALT (U/L)	Humatrope	36	15.500(5.422)	-2.083(4.959)
	Placebo	29	14.069(4.174)	-0.483(6.156)
AST (U/L)	Humatrope	35	25.057(5.641)	-4.829(5.096)
	Placebo	29	24.655(5.440)	-3.586(6.115)
GGT (U/L)	Humatrope	34	16.471(6.779)	0.706(16.310)
	Placebo	29	16.828(5.305)	-0.448(4.128)
T. Bilirubin (umol/L)	Humatrope	36	9.284(5.232)	1.640(6.322)
	Placebo	29	8.035(4.948)	1.882(5.235)
T. Protein (g/L)	Humatrope	36	71.944(5.054)	-2.111(4.083)
	Placebo	29	72.000(4.383)	-1.655(4.624)
Albumin (g/L)	Humatrope	36	45.972(3.056)	-2.333(3.489)
	Placebo	29	46.483(2.668)	-2.138(4.129)
Alk. Phosph. (U/L)	Humatrope	36	253.861(66.826)	-76.944(85.670)
	Placebo	29	276.241(83.873)	-96.862(98.661)
Calcium (mmol/L)	Humatrope	36	2.375(0.099)	-0.086(0.123)
	Placebo	29	2.419(0.102)	-0.103(0.084)
Phosphorus (mmol/L)	Humatrope	36	1.600(0.201)	-0.156(0.214)
	Placebo	29	1.566(0.166)	-0.118(0.209)
Uric Acid (umol/L)	Humatrope	36	216.297(52.273)	81.774(70.927)
	Placebo	29	220.471(39.405)	56.813(48.022)
CPK (U/L)	Humatrope	36	125.806(67.153)	-12.944(75.383)
	Placebo	29	126.379(48.708)	49.586(122.309)

Source: Tables GDCH.12.10. and GDCH.12.11. N = Total number of patients in each treatment group having the variable in both baseline and postbaseline visits.

The incidence of abnormal (low or high) chemistry analytes in the safety population for each of the two treatment groups is presented in Table 57. There were no statistically significant differences between the treatment groups for the incidence of high or low values for any of the chemistry analytes. Hypo- and hypercalcemia, elevated CPK, and elevated ALT were slightly higher in the Humatrope group. The number of patients with values outside the normal range is too small to draw any other conclusions.

Table 57: Incidence of High or Low Chemistry Analytes after Baseline-Safety Population

Analyte	Humatrope (N=35)			Placebo (N=30)		
	Normal (n/N)	Low (n/N)	High (n/N)	Normal (n/N)	Low (n/N)	High (n/N)
Alk. Phosph:	20 (55.6)	3 (8.3)	13 (36.1)	17 (58.6)	3 (10.3)	10 (34.5)
ALT/SGPT	33 (91.7)	1 (2.8)	2 (5.6)	29 (100)	0	0
AST/SGOT	33 (91.7)	0	3 (8.3)	26 (89.7)	1 (3.4)	2 (6.9)
GGT	33 (94.3)	0	2 (5.7)	29 (100)	0	0
CPK	27 (75.0)	0	9 (25.0)	25 (86.2)	0	4 (13.8)
Calcium	28 (77.8)	5 (13.9)	3 (8.3)	27 (93.1)	1 (3.4)	1 (3.4)
Phosphorus	26 (72.2)	1 (2.8)	9 (25.0)	22 (75.9)	0	7 (24.1)
BUN	36 (100)	0	0	28 (96.6)	1 (3.4)	0

Source: Table GDCH.12.12.

N=Total number of patients in the treatment group within the requested time interval. The time interval includes visit 2 (Month 1) through the visit prior to visit 99 (i.e. penultimate visit). A total of 66 patients had values in this interval.

C.6.4.2 Lipids:

Lipid change assessments were performed at baseline and every 6 months thereafter until the end of the study. The data are presented as mean changes from baseline and as incidence of abnormal values. Table 58 presents baseline values and changes from baseline to endpoint for cholesterol (mmol/L), high density lipoprotein (HDL) cholesterol (mmol/L), low density lipoprotein (LDL) cholesterol (mmol/L), very low density lipoprotein (VLDL) cholesterol (mmol/L), and triglycerides (mmol/L) for the Safety Population. There were no significant differences between groups for baseline values or changes from baseline to endpoint for any of these analytes.

Table 58: Lipid Changes from Baseline to Endpoint-Safety Population

Analyte	Treatment Group	N	Baseline	Change
			Mean (SD)	Mean (SD)
Cholesterol (mmol/L)	Humatrope	36	4.610(0.836)	-0.733(0.689)
	Placebo	29	4.512(0.670)	-0.574(0.494)
HDL-C (mmol/L)	Humatrope	35	1.432(0.347)	-0.237(0.340)
	Placebo	28	1.422(0.295)	-0.208(0.223)
LDL-C (mmol/L)	Humatrope	36	2.714(0.854)	-0.440(0.785)
	Placebo	28	2.739(0.555)	-0.415(0.481)
VLDL-C (mmol/L)	Humatrope	35	0.399(0.267)	0.015(0.235)
	Placebo	29	0.347(0.139)	0.090(0.498)
Triglycerides (mmol/L)	Humatrope	36	0.872(0.574)	0.034(0.504)
	Placebo	29	0.759(0.304)	0.195(1.088)

Source: Table GDCH.12.15.

n=Total number of patients in each treatment group having the variable in both baseline and postbaseline visits.

The incidence of abnormal (low or high) values for lipid analytes at any postbaseline time point in the study for both treatment groups is presented in table 59. Although there were no statistically significant differences between the treatment groups, twice as many patients in the Humatrope group had abnormal and high triglyceride levels (incidence: 41.7% vs. 20.7%) and VLDL-C levels (incidence: 13.9% vs. 6.9%). A mild increase in incidence of patients with high serum cholesterol was present in the Humatrope treatment group (16.7% vs. 10.3%). All other high cholesterol measurements were lower in the Humatrope group when compared to placebo.

Table 59: Incidence of High or Low Lipid Analytes after Baseline-Safety Population

Lipid Analyte	Humatrope (N=30)			Placebo (N=30)		
	Normal n(%)	Low n(%)	High n(%)	Normal n(%)	Low n(%)	High n(%)
Cholesterol	18 (50.0)	12 (33.3)	6 (16.7)	18 (62.1)	8 (27.6)	3 (10.3)
HDL-C	34 (94.4)	0	2 (5.6)	26 (89.7)	0	3 (10.3)
LDL-C	22 (61.1)	8 (22.2)	6 (16.7)	16 (55.2)	7 (24.1)	6 (20.7)
VLDL-C	21 (58.3)	10 (27.8)	5 (13.9)	21 (72.4)	6 (20.7)	2 (6.9)
Triglycerides	16 (44.4)	9 (25.0)	15 (41.7)	17 (58.6)	6 (20.7)	6 (20.7)

Source: Table GDCH.12.16. N=Total number of patients with the lab test within the requested time interval. The time interval includes visit 2 (Month 1) through the visit prior to visit 99 (i.e. penultimate visit). A total of 66 patients had values in this interval.

C.6.4.3 Hematology

Complete white blood and differential white cell count assessments were performed at baseline and every 6 months thereafter until the end of the study. The data are presented as mean changes from baseline and as incidence of abnormal values. Table 60 provides baseline values and changes from baseline to endpoint for hematological tests for the Safety Population. There were no statistically significant between-group differences for baseline values or change from baseline to endpoint for any hematology measure.

Table 60: Hematology Changes from Baseline to Endpoint-Safety Population

Lipid Analyte	Treatment Group	N	Baseline Mean (SD)	Change Mean (SD)
Hemoglobin (nmol/L-Fe)	Humatrope	36	8.345(0.552)	0.416(0.600)
	Placebo	29	8.428(0.528)	0.205(0.747)
Hematocrit	Humatrope	36	0.395(0.026)	0.020(0.027)
	Placebo	29	0.401(0.023)	0.005(0.032)
RBCs (T/L)	Humatrope	36	4.733(0.336)	0.081(0.306)
	Placebo	29	4.693(0.263)	-0.036(0.352)
WBC (G/L)	Humatrope	36	6.022(1.673)	-0.283(1.360)
	Placebo	29	6.343(2.130)	-0.892(2.477)
Myelocytes	Humatrope	33	0.000	0.000
	Placebo	28	0.000	0.000
Bands (G/L)	Humatrope	23	0.016(0.062)	-0.016(0.062)
	Placebo	22	0.008(0.030)	0.009(0.090)
Polys (G/L)	Humatrope	36	3.113(1.519)	-0.063(1.384)
	Placebo	29	3.269(1.983)	-0.718(2.276)
Lymphocytes	Humatrope	36	2.224(0.519)	-0.247(0.581)

(G/L)	Placebo	29	2.305(0.557)	-0.120(0.643)
Monocytes (G/L)	Humatrope	36	0.450(0.181)	0.011(0.175)
	Placebo	29	0.496(0.274)	-0.039(0.298)
Eosinophils (G/L)	Humatrope	36	0.173(0.156)	0.031(0.186)
	Placebo	29	0.222(0.248)	-0.012(0.228)
Basophils (G/L)	Humatrope	36	0.047(0.040)	0.002(0.048)
	Placebo	29	0.045(0.051)	-0.009(0.038)
Platelet count (G/L)	Humatrope	35	289.743(51.607)	-46.229(54.466)
	Placebo	29	317.828(61.762)	-51.724(56.544)
ESR (mm/h)	Humatrope	34	11.176(8.600)	0.529(7.798)
	Placebo	27	11.074(9.306)	-0.593(9.065)

Source: Table GDCH.1219.

n=Total number of patients in each treatment group having the variable in both baseline and postbaseline visits.

Table 61 presents the incidence of abnormal (low or high) values for hemoglobin and leukocyte count at any postbaseline time point in the study for both treatment groups. There were no statistically significant between-group differences in the incidence of high or low values for any hematology measure.

Table 61: Incidence of High or Low Hematology Parameters after Baseline-Safety Population

Parameter	Humatrope (N=36)			Placebo (N=29)		
	Normal (%)	High (%)	Low (%)	Normal (%)	High (%)	Low (%)
Hemoglobin	27 (75.0)	6 (16.7)	3 (8.3)	21 (72.4)	8 (27.6)	0
Leukocyte count	18 (50.0)	18 (50.0)	0	17 (58.6)	12 (41.4)	0

Source: Table GDCH.12.20. N=Total number of patients with the lab test within the requested time interval. The time interval includes visit 2 (Month 1) through the visit prior to visit 99 (i.e. penultimate visit). A total of 66 patients had values in this interval.

C.6.4.4 Urinalysis

Table 62 provides baseline values and changes from baseline to endpoint for urinalysis parameters for the Safety Population. Mean baseline values for urine specific gravity and pH were similar for both treatment groups. There was a statistically significant difference in change in urine pH from baseline to endpoint ($p=0.20$). The clinical significance of this finding, if any, is unclear.

Table 62: Urinalysis Changes from Baseline to Endpoint-Safety Population

Parameter	Treatment Group	N	Baseline Mean (SD)	Endpoint Mean (SD)
Urine specific gravity	Humatrope	36	1.020(0.007)	0.001(0.007)
	Placebo	29	1.020(0.006)	-0.000(0.007)
Urine pH	Humatrope	36	5.542(0.740)	0.347(1.020)
	Placebo	29	5.879(0.970)	-0.224(0.872)

Source: Table GDCH.12.21.

n=Total number of patients in each treatment group having the variable in both baseline and postbaseline visits.

C.6.4.5 Gonadotropins and Sex Steroids

Table 63 provides gonadotropin and sex steroid concentrations at baseline and changes from baseline to endpoint for males in the Safety Population. There were no statistically significant

between-group differences for baseline values or change from baseline to endpoint in luteinizing hormone (LH), follicle stimulating hormone (FSH), testosterone, or dehydroepiandrosterone (DHAS).

Table 63: Gonadotropin and Sex Steroid Changes from Baseline to Endpoint-All Males Safety Population

Parameter	Treatment Group	N	Baseline Mean (SD)	Change Mean (SD)
LH (mIU/ml)	Humatrope	26	4.157(1.844)	6.338(5.200)
	Placebo	22	4.777(3.400)	4.021(3.776)
FSH (mIU/ml)	Humatrope	26	3.855(3.004)	5.010(5.782)
	Placebo	22	4.300(4.339)	3.573(3.702)
Testosterone (ng/ml)	Humatrope	26	44.662(50.743)	445.984(268.751)
	Placebo	21	62.932(104.466)	407.245(267.535)
Dehydroepiandrosterone (mcg/dl)	Humatrope	27	83.254(62.306)	120,372(126.784)
	Placebo	22	92.493(58.772)	98.728(73.845)

Source: Table GDCH.12.22.

n=Total number of patients in each treatment group having the variable in both baseline and postbaseline visits.

Table 64 provides gonadotropin and sex steroid concentrations at baseline and changes from baseline to endpoint for females in the Safety Population. There were no statistically significant between-group differences for baseline values or change from baseline to endpoint in luteinizing hormone (LH), follicle stimulating hormone (FSH), testosterone, or dehydroepiandrosterone (DHAS). There were no statistically significant differences between treatment groups for baseline FSH, estradiol, or DHAS, or for changes in concentrations of these hormones across the study. The mean baseline to endpoint increase in LH was significantly greater for females in the placebo group than for those in the Humatrope group (p=0.11). (This difference may be attributable to menstrual cycle differences and was not considered clinically relevant).

Table 64: Gonadotropin and Sex Steroid Changes from Baseline to Endpoint-All Females Safety Population

Parameter	Treatment Group	N	Baseline Mean (SD)	Change Mean (SD)
LH (mIU/ml)	Humatrope	8	3.330(3.009)	3.101(4.387)
	Placebo	7	3.413(2.430)	10.252(4.971)
FSH (mIU/ml)	Humatrope	8	3.969(3.095)	2.304(4.111)
	Placebo	7	5.090(2.968)	7.163(5.168)
Estradiol (pg/ml)	Humatrope	8	11.905(12.410)	32.710(46.235)
	Placebo	7	21.455(21.148)	43.234(35.006)
Dehydroepiandrosterone (mcg/dl)	Humatrope	8	60.696(32.209)	27.113(43.306)
	Placebo	7	46.355(36.903)	60.369(37.814)

Source: Table GDCH.12.23.

n=Total number of patients in each treatment group having the variable in both baseline and postbaseline visits.

C.6.4.6 Anti-Growth Hormone Binding Capacity

All patients underwent screening for anti-GH antibodies at each visit. Those patients found to be positive on screening subsequently had serum assayed for anti-GH binding capacity. Twelve patients were tested for anti-GH binding capacity; no patient demonstrated a positive result.

C.6.4.7 Anti-Escherichia coli Polypeptide Antibodies

Patients in this study underwent testing for anti-Escherichia coli polypeptide (ECP) antibodies at Visit 1 (baseline), Visit 4, and at each visit thereafter until this test was discontinued in 1995. Of the 181 samples analyzed, none was positive for antibodies to ECP based upon the definition criteria criteria (greater than 200% relative to control and an increase by a factor of 2.0 or greater from baseline).

Growth hormone (GH) and Escherichia coli polypeptide (ECP) antibodies in Trial E001

Although an initially planned safety analysis, the antibody data were not analyzed for this study report since "it has been determined from clinical studies that GH antibodies have minimal clinical relevance".

C.7 Vital Signs

Vital signs were not recorded during study GDCH. They were part of the safety evaluation in trial E001. The vital signs trial data are presented in Table 65 as baseline and changes to two-year endpoint for three vital signs variables (pulse, systolic blood pressure, and diastolic blood pressure). There were no statistically significant differences among dose groups in mean change between baseline and endpoint.

Table 65: Blood Pressure and Heart Rate Changes from Baseline to Two-Year Endpoint (All Randomized Patients)

Parameter	Treatment Group	N	Baseline Mean (SD)	Change Mean (SD)
Pulse (bpm)	Dose 1	72	85.597(12.670)	-7.306(15.392)
	Dose 2	76	85.632(14.990)	-6.882(16.414)
	Dose 3	77	83.961(13.574)	-5.052(15.169)
Systolic blood pressure (mmHg)	Dose 1	74	97.284(10.948)	6.865(14.632)
	Dose 2	78	100.500(12.396)	2.282(12.560)
	Dose 3	80	100.413(10.178)	2.138(13.610)
Diastolic blood pressure (mmHg)	Dose 1	74	59.851(10.408)	-1.351(12.365)
	Dose 2	78	60.615(9.884)	1.474(10.674)
	Dose 3	80	62.463(9.680)	-1.713(11.907)

Source: Table E001. 12. 11. N= Total number of patients in each treatment group having the variable in both baseline and postbaseline visits.

C.8 Additional Safety Studies

The applicant provides safety data from three additional studies of Humatrope use in pediatric patients with NGHDSS. The cumulative safety information includes 71 patients. The studies are:

- (1) study GDCG; this one year-long study includes 34 patients and approximately 32 patient-years of exposure to Humatrope;

(2) study GDCP; it includes 10 patients and approximately 10 patient-years of exposure to Humatrope;

(3) study GDFC; it includes 23 patients and approximately 55 patient-years of exposure to Humatrope.

No deaths and no discontinuations due to AEs were reported in any of these studies. Three SAEs were reported in Study GDCG, which were considered by the investigators unrelated to Humatrope treatment. At least one AE was reported for 41 of the 71 (58%) patients. The clinical studies GDCG, Study GDCP, and GDFC are summarized in Appendix B.

D. Adequacy of Safety Testing

The safety information presented in this NDA is adequate to allow a regulatory action. The extent of patient exposure to Humatrope for patients with NGHDS (1212 patient-years) is similar to the Humatrope exposure accumulated for other indications (1232 patient-years for patients with growth hormone deficiency and 1219 patient-years for patients with Turner syndrome). The total number of patients is also similar among the three indications (a little over 300). It should be noted, however, that, while the safety dataset presented in this NDA is comparable in size to the safety databases for other pediatric Humatrope indications, the target population for this new indication is appreciably larger.

The safety data accumulated during trial GDCH was extensive in scope. It covered, in addition to standard adverse events, a broad range of analytes in areas of concern for GH use (e.g. carbohydrate and lipid metabolism, thyroid function) and beyond (standard analytes). Although the safety database of this trial is limited in number of patients (68 overall, 37 Humatrope) the duration of exposure is significant (3.5 years mean exposure, with range between 0 and 9.1 years; for the Final Height Population the mean duration of exposure was even longer, 4.62 years). The strengths of the safety evaluation in trial GDCH are: (1) the presence of a placebo control group which allows to estimate background rates for adverse events, (2) extensive ascertainment of laboratory data, and (3) long duration of the trial. The limitations are: (1) a small number of patients enrolled and (2) exposure limited to the peripubertal and pubertal periods (while anticipated use may be longer).

The safety data accumulated in trial E001 is somewhat smaller in scope (for instance, the only analytes presented are those related to carbohydrate metabolism), but larger in total number of patients studied (239 patients). The mean duration of exposure is also considerable (4.5 years across all groups, ranging between 0 and 11.75 years). For the final height population the mean duration of exposure across treatment groups is even longer (6.5 years). The main strengths of trial E001 are: (1) the longer patient exposure and (2) the larger number of patients enrolled. The limitations are: (1) absence of a control group, (2) limited amount of laboratory data, and (3) different ascertainment of adverse events. To this end, it is noted that the 239 patients exposed to Humatrope in trial E001 reported a total of 766 adverse events, while the 37 patients who received Humatrope during trial GDCH reported 1748 adverse events.

E. Summarize Critical Safety Findings and Limitations of Data

The safety profile of Humatrope use in patients with NGHDS is similar to the Humatrope safety profile in other patient populations such as GHD or Turner syndrome. This statement is based on a relatively small patient population studied (about 337 patients between studies GDCH and E001) but on comparative exposure with other approved indications.

Although there were no deaths during the clinical trials, two patients were diagnosed with malignancies (one patient in study E001 had an abdominal desmoplastic small round cell tumor diagnosed six years in the clinical trial, discontinued the trial and died four years later; desmoplastic small round cell tumor has not been seen in association with GH therapy). One patient in trial GDCH was diagnosed with stage 3B Hodgkin disease approximately 4-5 months in the trial but had a evidence of subclinical disease at enrollment.

Most SAEs recorded during the NGHDS clinical trials were due to conditions commonly occurring in pediatric patients, such as accidental trauma. In clinical trial GDCH, SAEs occurred twice more often in the Humatrope treatment group than placebo but were mostly accidental injuries. Trial E001 showed a slightly higher overall incidence of SAEs in the higher, "Dose 3", dose regimen (19.3%) compared to the lower, "Dose 1," regimen (14.1%). No distinct, dose-dependent pattern of SAEs emerged, though. Clinical trial E001 recorded two SAEs which represent conditions previously known to be associated with GH use (arthralgia and slipped capital femoral epiphysis).

There were few patient discontinuations related to adverse events. One patient discontinued trial GDCH due to the development of Hodgkin lymphoma and three patients discontinued trial E001 due to desmoplastic abdominal tumor, slipped capital femoral epiphysis, and glucose intolerance/elevated HbA1c, respectively.

There were no distinct patterns of treatment-emergent adverse events (TEAEs) associated with Humatrope use in patients with NGHDS. Study GDCH identified several TEAEs that occurred with higher frequency over placebo but the small number of affected patients limits the ability to draw firm conclusions. The list of TEAE that occurred ≥ 2 times more frequently in the Humatrope group over placebo includes the following: back pain, tooth disorder, otitis media, cardiovascular disorder, migraine, gastrointestinal disorder, surgical procedure, arthralgia, fungal dermatitis, dysmenorrhea, eye disorder, hyperlipidemia, abnormal liver function tests, nausea and vomiting, skin benign neoplasm. TEAEs related to the musculoskeletal system (back pain, bone disorder, myalgia, neck pain, arthrosis, arthralgia) occurred more frequently in the Humatrope treatment group despite a similar frequency of accidental injuries in the two treatment groups. Another Humatrope-to-placebo imbalance is recorded for events under the "cardiovascular disorder" term; in this group, four patients with the AE of mitral valve prolapse or possible MVP were in the Humatrope group and none in the placebo arm. A comparison of the TEAE incidence between trials GDCH and E001 was not informative since background rates of AEs reported in trial E001 were lower. GH use has not been associated with mitral valve prolapse, which, in addition, is a common clinical finding.

In trial GDCH, among TEAEs known to be associated with GH therapy in general, scoliosis, otitis media, hyperlipidemia, gynecomastia, hip pain, and hypertension occurred more frequently in the Humatrope arm than placebo. However, the number of patients experiencing these TEAEs was very small (for instance hip pain and hypertension occurred in one patient each). In trial E001, arthralgia, hyperlipidemia, joint disorder, hypothyroidism suggested a dose-dependent trend but the number of patients with any of these symptoms in any treatment arm were very small (≤ 3). The following TEAEs were not identified in the NGHDSS trials despite being described previously in association with GH therapy in general: edema, carpal tunnel syndrome, benign intracranial hypertension.

Evaluation of carbohydrate metabolism in patients with NGHDSS treated with Humatrope during trial GDCH showed findings consistent with the observed effects of GH therapy in previous trials for other pediatric indications (i.e. an increase in mean serum fasting insulin levels in the presence of normal mean fasting serum glucose levels and mean HbA1c levels). In trial E001, there was no distinct, dose-related pattern of abnormalities related to carbohydrate metabolism for the two variables assessed (fasting serum glucose and HbA1c). Data on serum insulin concentration was not available for this trial. In this trial, one patient discontinued due to glucose intolerance/elevated HbA1c. One additional patient had elevated HbA1c measurements during the second year of treatment (no additional data are available).

No clinically relevant differences in clinical laboratory measures between Humatrope-treated patients and placebo-treated patients were observed in Study GDCH for thyroid analytes, lipids, standard hematology assessments, urinalysis, gonadotropins, sex steroids (testosterone, or dehydroepiandrosterone), and IGF-I serum concentrations. With the exception of thyroid analytes, these analytes were not presented for trial E001.

The following safety observations can be made when adverse event rates during the NGHDSS clinical trials are compared to adverse event rates recorded during the clinical trials for GHD and Turner syndrome:

- There were no meaningful differences in number of deaths recorded during and after the trials.
- Two de novo malignancies were recorded in patients with NGHDSS (desmoplastic abdominal tumor and Hodgkin lymphoma); a secondary tumor (papillary carcinoma of the thyroid) and a possibly undiagnosed craniopharyngioma were recorded in GHD patients during similar exposure to Humatrope; no de novo malignancies were diagnosed in the Turner patients trials.
- Overall, SAEs occurred somewhat less frequently in patients with NGHDSS when compared to patients with GHD (13% vs. 27%) or patients with Turner syndrome (13% vs. 17.8%).
- The rates of patient withdrawals were low and similar among all trials (generally less than 2.7%).
- Among adverse events known to be associated with GH treatment, scoliosis was identified more commonly in the NGHDSS patients in one study (study GDCH); in this study scoliosis was a protocol specified measure of safety.
- The changes in carbohydrate metabolism-related analytes for patients with NGHDSS were similar to those observed in Turner syndrome patients (normal mean serum glucose levels, elevated mean serum insulin concentrations), albeit less pronounced.

- Hypothyroidism occurred less frequently in patients with NGHDSS.
- Changes in mean serum IGF-I concentrations were similar in patients with NGHDSS and patients with Turner syndrome.

In general, there are no major differences between the applicant's interpretation of the safety data and this reviewer's analysis.

VIII. Dosing, Regimen, and Administration Issues

Clinical trial GDCH establishes an effective dose regimen of Humatrope in patients with NGHDSS. This dose regimen is 0.22 mg/kg/week of Humatrope given three times a week (TIW) in equally divided doses. This dose regimen has been demonstrated to be superior to placebo in enhancing final height and was not associated with unexpected safety signals.

Clinical trial E001 provides evidence that a weekly dose of 0.37 mg/kg given in equally divided daily injections is more effective than a similar regimen of 0.24 mg/kg/week. The 0.37 mg/kg/week regimen is superior both as short-term treatment (as judged by superior height velocity over a 2-year period), and as long-term treatment (as judged by greater final height than baseline predicted adult height and greater height gain on treatment among a subgroup of patients with final height).

The daily Humatrope regimen in trial E001 (0.24 mg/kg/week) resulted in a larger magnitude of treatment effect than a TIW regimen of almost identical dose in trial GDCH (0.22 mg/kg/week). Although the two regimens were not compared side by side in the same trial and the two trials differed in duration (trial E001 was longer) superiority of daily regimens over TIW regimens is well established.

The dosage and the regimen established in this application for patients with NGHDSS is within the range of GH dose regimens approved for other pediatric indications and is consistent with GH regimens currently used in clinical practice (Tanaka et al., 2002). The approved range of GH doses varies between 0.16 mg/kg/week (GH deficiency) and 0.48 mg/kg/week (SGA patients). For patients with GH deficiency entering puberty, a regimen as high as 0.7 mg/kg/week is currently labeled.

The dose-related Humatrope effect on efficacy was not clearly associated with a dose-dependent pattern of adverse events. The strength of this statement is limited by the relatively small database (300 patients) and by the lower level of ascertainment of adverse events and analytes in trial E001.

IX. Use in Special Populations

A. Gender Effects Analyses

Four decades of GH therapy have not provided any evidence of gender specific response to growth hormone therapy. Very recently (Cohen et al, 2002), identified effects of gender on GH

response in patients with GHD (males demonstrate a linear dose-response curve, whereas girls showed a bell-shaped curve). It is not known whether these findings will be replicated and whether the same observation will apply to NGHDSS.

GH usage in patients with NGHDSS appears to be gender-biased (boys are more likely to be treated than girls). Indeed, both trials GDCH and E001 show a 2:1 to 3:1 male to female predominance. Since the number of patients in the Final Height population is small in both studies submitted, gender-specific efficacy analyses were not informative. Gender-specific evaluation of the time of onset of puberty during the Humatrope treatment did not reveal an abnormal tempo of progression during puberty.

B. Age, Race, or Ethnicity Effects on Safety or Efficacy

The two clinical studies GDCH and E001 enrolled mostly prepubertal and pubertal patients. The fact that school-age children and adolescents are better represented in the data base is consistent with the fact that most patients with NGHDSS are evaluated and diagnosed in later childhood.

The vast majority of patients in study GDCH were Caucasians (79.7%). Minorities (such as African Americans, Hispanics, and "other") totaled approximately 20%. This seems to roughly represent the US ethnic/racial distribution. Appropriately, in the presence of such small numbers of patients, no ethnic/racial efficacy or safety analyses were done.

Study E001, was done in Europe and, thus, included overwhelmingly Caucasian patients.

C. Pediatric Program

Humatrope use in NGHDSS patients is a pediatric indication. To this end the patients included in this NDA efficacy and safety datasets are exclusively children.

D. Special Populations

Some GH drug products are approved for use in pediatric patients with renal failure and inadequate linear growth. The Humatrope label states that no studies have been performed with Humatrope in patients with renal or hepatic insufficiency. Although Humatrope is degraded in both liver and kidneys, conditions affecting these two organs are not likely to result in any drug toxicity.

X. Overall Conclusions, Recommendations, and Labeling

A. Conclusions Regarding Safety and Efficacy/Risk Benefit Analysis

The benefit provided by Humatrope treatment in children with NGHDSS is an improvement in linear growth. The consequence of improved linear growth during sustained Humatrope treatment is higher final (adult) height. On average, Humatrope treatment increases final height by 3.7 cm over placebo (about 0.5 SD) if started at the beginning of puberty as a TIW regimen of

0.22 mg/kg. A higher dose regimen (0.37 mg/kg/week) given daily and started before puberty adds on average about 3 more cm (or a little less than 0.5 SD) to a 0.24 mg/kg/wk daily regimen. These two observations combined suggest an overall mean height benefit > 6 cm over placebo for the 0.37 mg/kg/week regimen. This degree of efficacy is consistent with a benefit of 7.2 cm in final height over the baseline predicted adult height recorded for the 0.37 mg/kg/wk daily Humatrope regimen. Despite a mean benefit on final height, the benefit to individual patients is variable, with some patients responding no better than placebo and others having significant improvement in final height.

Assessment of the safety risks of Humatrope treatment in children with NGHDSS needs to take into consideration (1) the safety findings recorded during the Humatrope clinical trials (which included approximately 300 patients and 1200 patient-years) and (2) the general knowledge and experience accumulated with GH treatment in pediatric patients during the last four decades (over 100,000 patients and several hundreds of thousands of patient-years). NGHDSS patients represent a significant segment of the pediatric exposure because of the off-label use of GH in this patient population (Hilken et al., 2001; Guyda H J., 1999).

Based on the safety information gleaned from the NGHDSS clinical trials, there are three potential safety issues that may be associated with Humatrope treatment when compared to placebo: (1) effects on carbohydrate metabolism (development of glucose intolerance and/or diabetes), (2) articular and musculoskeletal events (arthritis, arthrosis, scoliosis, etc.), and (3) malignancy. Other adverse events associated with use of GH in other pediatric indications (pseudotumor cerebri, sodium retention, edema,) were not observed during the NGHDSS clinical trials.

The Humatrope effect on carbohydrate metabolism recorded in the clinical trials has been of limited clinical consequence: no patients developed type 2 diabetes, one patient developed glucose intolerance, and one had abnormally high HbA1c (lack of data does not allow firm conclusions on this patient). Overall, the Humatrope effects on glucose metabolism are consistent with the known metabolic effects of GH and are similar to those observed in registration clinical trials conducted for another approved Humatrope indication (Turner syndrome). They are manageable with good surveillance (periodic fasting serum glucose/HbA1c measurements and glucose tolerance testing in selected patients).

The association of articular and musculoskeletal symptoms with GH therapy has also been previously characterized in both children and adults. With the exception of a patient who discontinued the trial due to slipped femoral head epiphysis, and another patient who required surgery for foot arthralgia (both observed in an uncontrolled trial) most articular and musculoskeletal adverse events have been of no clinical consequence. To this end, all cases of scoliosis have been mild. In general, musculoskeletal signs and symptoms are easy to diagnose, seem easy to manage and only rarely require surgical interventions.

The theoretical risk of malignancy(ies) is central to risk/benefit analyses in any patient population anticipated to be treated with GH. However, after 40 years of GH use in over 200,000 patients covering > 500,000 patient-years, the general consensus is that GH per se does not increase the risk of malignancy in either adult or pediatric patients (Consensus Statement of

the Growth hormone Research Society, 2001; Update of Guidelines for the Use of Growth Hormone in Children, 2003, in print). Postmarketing studies have not reported any increase in incidence of pediatric malignancies in patients treated with GH without prior risk factors (Wilton P, 1999. Maneatis T, et al., 2000, Wilton P, 2003). An increased risk of leukemia appears to be associated with GH therapy and it is limited to children with underlying conditions that already predisposes them to develop malignancies (e.g. neurofibromatosis type 1, Down syndrome, Bloom syndrome, and Fanconi anemia). None of the patients in the NGHDSS clinical trials developed leukemia. The two malignancies noted on Humatrope treatment during the NGHDSS clinical trials were Hodgkin lymphoma (in one patient who had evidence of subclinical disease not recognized at enrollment) and small round cell desmoplastic tumor (which occurred in one patient in an uncontrolled trial and which has never been described in association with GH). A recent memorandum

It is the opinion of this reviewer that, based on the current understanding of the Humatrope (and GH) efficacy and safety profile, a favorable risk/benefit balance can be achieved in patients with NGHDSS. Thus, this reviewer agrees with the recommendation for approval of Humatrope use in patients with NGHDSS formulated at the June 10th, 2003 Endocrinologic and Metabolic Drugs Advisory Committee. This reviewer's recommendation to approve Humatrope for the treatment of short stature in patients with NGHDSS is based on the following:

- Humatrope has been proven efficacious in increasing final height in patients with NGHDSS.
- Pharmacological GH treatment in patients with NGHDSS is consistent in with previously approved GH indications. In fact, all previously approved pediatric GH indications other than growth hormone deficiency are for pharmacological GH treatment of short stature (chronic renal insufficiency in 1993, Turner syndrome in 1996, Prader-Willi syndrome in 2000, and SGA children without catch up growth in 2001).
- The mean magnitude of effect on final height in NGHDSS patients is similar to that seen in patients with Turner syndrome and short stature for comparable Humatrope doses.
- There were no new safety signals associated with the use of Humatrope in patients with NGHDSS during the registration clinical trials and the safety profile in this patient population is similar to the safety profile of other approved indications.
- The safety profile of GH has been well characterized for pediatric patients over the last 4 decades.
- There is already significant off label exposure to GH for patients with NGHDSS as evidenced by the two postmarketing surveillance studies (about 9,000 patients) without any clear safety signals specific to this patient population.
- In order to limit inappropriate Humatrope distribution, the applicant proposed a voluntary risk management plan which includes, among others, restrictive labeling for the indication, limited marketing, a controlled distribution process.
- The applicant has already initiated a postmarketing surveillance study (GeNeSIS study). Inclusion in this study will be offered to any Humatrope treated patient at over 400 sites (140 in the US) in 30 countries. Two substudies of GeNeSIS are of particular importance: a growth prediction substudy (whose purpose is to identify clinical and biochemical

characteristics that correlate with clinical responses to GH therapy) and a neoplasia substudy (which will characterize the natural history of neoplastic disease in children treated for growth disorders).

- On June 10, 2003 the Endocrinologic and Metabolic Drugs Advisory Committee has recommended approval of Humatrope treatment in NGHDSS.

B. Recommendations

In order to promote safe use of Humatrope in this patient population, the following recommendation follow:

- The name of the proposed indication should change to _____ This term better reflects the currently accepted medical terminology used to designate patients with non-growth hormone deficient short stature. In addition, ("idiopathic short stature") excludes more explicitly other conditions with normal growth hormone secretion such as "syndromic short stature" (an extremely heterogeneous group of conditions that may have efficacy and safety characteristics considerably different from those observed in NGHDSS patients) and small for gestational age children with short stature (an approved orphan indication).
- The indication should stipulate that, in addition to pre-treatment short stature, patients with NGHDSS should also have a slow pre-treatment height velocity (HV). This will ensure that patients who are treated with Humatrope are not only short (as defined by the height SDS < -2.25 criterion) but also grow at a subnormal rate and, thus, are likely to reach adult heights below the normal range without GH treatment⁵.
- The label should contain language / _____
/ _____
/ _____
- The label should contain language that discourages use of Humatrope below age 7⁷. Patient exposure below this age was limited in the clinical trials. In addition, the applicant has not demonstrated that longer therapy per se results in higher final height in patients with NGHDSS.
- Humatrope treatment should not be continued unnecessarily in patients who fail to respond to treatment⁸. Currently there are no baseline clinical or biochemical patient characteristics that can predict clinical response to GH and, as stated above, long-term efficacy did not correlate with length of treatment in the NGHDSS clinical trials. To this end, language in the label should specify that Humatrope treatment should be discontinued in absence of clinical response / _____
/ _____

⁵ Recommendation consistent with the June 10th Advisory Committee recommendation.

⁶ Recommendation consistent with the June 10th Advisory Committee recommendation.

⁷ Recommendation consistent with the June 10th Advisory Committee recommendation.

⁸ Recommendation consistent with the June 10th Advisory Committee recommendation.

This reviewer recommends the following Phase 4 commitments/studies:

- The applicant should make any effort to capture the final height data on the 21 patients (11 Humatrope, 10 placebo) who were still growing at the height velocity >1.5 cm/y at the end of study GDCH and therefore could not be included in the final analysis.
- During the postmarketing phase, the applicant should conduct studies that will: (1) demonstrate that the post approval safety profile of Humatrope is not different from the safety profile observed during the drug development program (this is particularly important since Humatrope use in NGHDSS is anticipated to be substantial and it may unmask serious adverse events previously not recognized and therefore, not labeled); (2) identify predictors of efficacy in this patient population (to date small clinical trials have failed to find such predictors but this may change with a large postmarketing exposure). The postmarketing study GeNeSIS appears to be an appropriate vehicle for these goals. Further details on this study, as well as periodic safety reports of the safety findings of this study (with emphasis on incidence of malignancies and known GH-associated adverse events) should be presented to the agency for evaluation and further regulatory decisions.
- The applicant should implement an active surveillance program for bone tumors (osteosarcoma, osteochondroma) ~~if~~

The applicant has implemented a similar program for a recently approved recombinant PTH (Forteo) in the treatment of adult osteoporosis. A similar program can serve the same purpose in patients with NGHDSS treated with Humatrope.

C. Labeling

The agreed upon labeling is reproduced below.

Effect of Humatrope treatment in pediatric patients with idiopathic short stature

Two randomized, multicenter trials, 1 placebo-controlled and 1 dose-response, were conducted in pediatric patients with idiopathic short stature, also called non-growth hormone deficient short stature. The diagnosis of idiopathic short stature was made after excluding other known causes of short stature, as well as growth hormone deficiency. Limited safety and efficacy data are available below age 7 years. ~~if~~

The placebo-controlled study enrolled 71 pediatric patients (55 males, 16 females) 9 to 15 years old (mean age 12.38 ± 1.51 years), with short stature, 68 of whom received study drug. Patients were predominately Tanner I (45.1%) and Tanner II (46.5%) at baseline.

In this double-blind trial, patients received subcutaneous injections of either Humatrope 0.222 mg/kg/wk or placebo. Study drug was given in divided doses 3 times per week until height velocity decreased to ≤ 1.5 cm/year ("final height"). Thirty-three subjects (22 Humatrope, 11 placebo) had final height measurements after a mean treatment duration of 4.4 years (range 0.11-9.08 years).

The Humatrope group achieved a mean final height ~~if~~

(Table 4). Height gain across the duration of the study and final height SDS minus baseline predicted height SDS were also significantly greater in Humatrope-treated patients than in placebo-treated patients (Table 4 and 5). In addition, the number of patients who achieved a final height above the 5th percentile of the general population for age and sex was significantly greater in the Humatrope group as was the number of patients who gained at least 1 SDS unit in height across the duration of the study (50% vs. 0%, $p < 0.05$).

Table 4
Baseline Height Characteristics and Effect of Humatrope on Final Height^a

	Humatrope (n=22) Mean (SD)	Placebo (n=11) Mean (SD)	Treatment Effect Mean (95% CI)	p-value
Baseline height SDS	-2.7 (0.6)	-2.75 (0.6)		0.77
BPH SDS	-2.1 (0.7)	-2.3 (0.8)		0.53
Final height SDS ^b	-1.8	-2.3	0.51 (0.10, 0.92)	0.017
FH SDS - baseline height SDS	0.9 (0.7)	0.4 (0.2)	0.51 (0.04, 0.97)	0.034
FH SDS - BPH SDS	0.3 (0.6)	-0.1 (0.6)	0.46 (0.02, 0.89)	0.043

^a For final height population.

^b Between-group comparisons performed using analysis of covariance with baseline predicted height SDS as the covariant. Data are expressed as least squares mean.

Abbreviations: FH = final height. SDS = standard deviation score. BPH = baseline predicted height.

CI = Confidence interval.

The dose-response study included 239 pediatric patients (158 males, 81 females), 5 to 15 years old, (mean age 9.76 ± 2.28 years). Mean baseline characteristics included: a height SDS of $-3.21 (\pm 0.70)$, a predicted adult height SDS of $-2.63 (\pm 1.08)$, and a height velocity SDS of $-1.09 (\pm 1.15)$. All but 3 patients were Tanner I. Patients were randomized to one of three Humatrope treatment groups: 0.24 mg/kg/wk; 0.24 mg/kg/wk for 1 year, followed by 0.37 mg/kg/wk; and 0.37 mg/kg/wk.

The primary hypothesis of this study was that treatment with Humatrope would increase height velocity during the first 2 years of therapy in a dose-dependent manner. Additionally, after completing the initial 2 year dose-response phase of the study, 50 patients were followed to final height.

Patients receiving 0.37 mg/kg/wk had a significantly greater increase in mean height velocity after 2 years of treatment than patients receiving 0.24 mg/kg/wk (4.04 vs. 3.27 cm/year, $p = 0.003$).

While no patient had height above the 5th percentile in any dose group at baseline, 82% of the patients receiving 0.37 mg/kg/wk and 47% of the patients receiving 0.24 mg/kg/wk achieved a final height above the 5th percentile of the general population height standards ($p = \text{NS}$).

Table 5

Final Height Minus Baseline Predicted Height: Idiopathic Short Stature Trials

	Placebo-controlled Trial 3x per week dosing		Dose Response Trial 6x per week dosing		
	Placebo (n=10)	Humatrope 0.22 mg/kg (n=22)	Humatrope 0.24 mg/kg (n=13)	Humatrope 0.24/0.37 mg/kg (n=13)	Humatrope 0.37 mg/kg (n=13)
FH - Baseline PH Mean cm (95% CI)	-0.7 (-3.6, 2.3)	+2.2 (0.4, 3.9)	+5.4 (2.8, 7.9)	+6.7 (4.9, 9.2)	+7.2 (4.6, 9.8)
Mean inches (95% CI)	-0.3 (-1.4, 0.9)	+0.8 (0.2, 1.5)	+2.1 (1.1, 3.1)	+2.6 (1.6, 3.6)	+2.8 (1.8, 3.9)

Abbreviations: PH= predicted height; FH=final height. CI = Confidence interval.

INDICATIONS AND USAGE

Humatrope is indicated for the long-term treatment of idiopathic short stature, also called non-growth hormone deficient short stature, defined by height SDS ≤ -2.25 , and associated with growth rates unlikely to permit attainment of adult height in the normal range, in pediatric patients whose epiphyses are not closed and for whom diagnostic evaluation excludes other causes associated with short stature that should be observed or treated by other means.

ADVERSE REACTIONS

Patients with Idiopathic Short Stature

In the placebo-controlled study, the adverse events associated with Humatrope therapy were similar to those observed in other pediatric populations treated with Humatrope (Table 7). Mean serum glucose levels did not change during the Humatrope treatment. Mean fasting serum insulin levels increased 10% in the Humatrope treatment group at the end of treatment baseline values but remained within the normal reference range. For the same duration of treatment the mean fasting serum insulin levels decreased by 2% in the placebo group. The incidence of above-range values for glucose, insulin, and HbA_{1c} were similar in the growth hormone and placebo-treated groups. No patient developed diabetes mellitus. Consistent with the known mechanism of growth hormone action, Humatrope-treated patients had greater mean increases.

However, there was no significant difference between the Humatrope and placebo treatment groups for the proportion of patients who had at least one serum IGF-I concentration more than 2.0 SD above the age- and gender-appropriate mean (Humatrope: 9 of 35 patients [26%]; placebo: 7 of 28 patients [25%]).

Table 7
Nonserious Clinically Significant Treatment-Emergent Adverse Events by
Treatment Group in Idiopathic Short Stature

Adverse Event	Treatment Group	
	Humatrope	Placebo
Total Number of Patients	37	31
Scoliosis	7 (18.9%)	4 (12.9%)
Otitis media	6 (16.2%)	2 (6.5%)
Hyperlipidemia	3 (8.1%)	1 (3.2%)
Gynecomastia	2 (5.4%)	1 (3.2%)
Hypothyroidism	0	2 (6.5%)
Aching joints	0	1 (3.2%)
Hip pain	1 (2.7%)	0
Arthralgia	4 (10.8%)	1 (3.2%)
Arthrosis	4 (10.8%)	2 (6.5%)
Myalgia	9 (24.3%)	4 (12.9%)
Hypertension	1 (2.7%)	0

The adverse events observed in the dose-response study (239 patients treated for 2 years) did not indicate a pattern suggestive of a growth hormone dose effect. Among Humatrope dose groups, mean fasting blood glucose, mean glycosylated hemoglobin, and the incidence of elevated fasting blood glucose concentrations were similar. One patient developed abnormalities of carbohydrate metabolism (glucose intolerance and high serum HbA1c) on treatment.

XI. Appendix

A. Additional Safety Data

A.1 Study GDCG

The results of this study were submitted to the agency as a Final Study Report on July 27, 1992, (IND 28,574). The applicant includes this study as supportive safety data to the current NDA. The results of the study have been published in 1990 by Dempsher et al. in *Pediatric Research*, Vol.28, No. 4. The title of the article is "Whole body nitrogen kinetics and their relationship to growth in short children treated with recombinant human growth hormone." The following review uses both the published information and the final report safety results.

Study GDCH is a single-center, phase II/III open-label investigation of the effects of several days of Humatrope exposure on whole body nitrogen kinetics followed by one year of Humatrope treatment. It includes 34 short, prepubertal, growth-hormone sufficient children and three growth hormone deficient subjects. The major enrollment criteria for the GH-sufficient patients were: Tanner stage I, height > 2SD below the mean for their age, bone age delay > 2 years, slow growth rates when compared to normal age specific-growth rates. Growth hormone sufficiency was defined as a peak plasma GH > 7 ng/mL in at least one GH stimulation test (insulin and/or clonidine). The main baseline characteristics (and the clinical response after one year of treatment) for the study population are presented in the following table.

Baseline clinical characteristics of patient population*

Variable	Before GH treatment (mean ± SD)	After Treatment (mean ± (SD)
n	37	32
CA (y)	8.7±2.6	9.7±2.6
BA (y)	6.3±2.3	7.5±2.5
Weight (kg)	20.2±5.7	24.6±7.1
Ht (cm)	113.4±13.5	122.3±13.6
Ht (Z score)	-3.0± 0.7	-2.4±0.7
Ht velocity (cm/yr)	4.7±1.2	8.3±1.6
Ht velocity (Z score for CA)	-1.4±1.4	3.1±2.7
Ht velocity (Z score for BA)	-1.8±1.1	2.3±2.0

*Data combines GH-sufficient and GH-deficient patients. CA = chronological age. BA = bone age. Ht = height.

Two patients dropped out (one discontinued before the 3-month visit and one at 9 months of therapy). There were no deaths reported during the study and none of the patient discontinuations were due to an adverse event. There were three patients who were hospitalized (accidental injury/broken bone in left forearm, acute asthma exacerbation, and surgical dilatation of the right nostril). The publication reports no adverse events "during the prolonged growth hormone treatment". There were no "significant changes in post-absorbitive blood glucose, cholesterol, or triglyceride values measured by routine clinical chemistry assays." In addition, "there was no significant rise in antibody titers to *Escherichia coli* proteins or to growth hormone as measured by the standardized assays at the Eli Lilly Company."

Thirty four (89.5%) of study subjects experienced at least one treatment emergent adverse event (TEAE). The following TEAEs occurred with a frequency >5% (the data are presented in descending order of frequency): pharyngitis (55.3%), fever (39.5%), rhinitis (39.5%), vomiting (36.8%), otitis media (34.2%), accidental injury (28.9%), flu syndrome (28.9%), headache (28.9%), cough (26.3%), iron deficiency anemia (26.3%), abdominal pain (15.8%), asthma (15.8%), infection (15.8%), injection site pain (15.8%), diarrhea (13.2%), sinusitis (13.2%), bronchitis (10.5%), otitis externa (10.5%), rash (10.5%), surgical procedure (10.5%), dyspepsia (7.9%), eye disorder (7.9%), nausea (7.9%), pain (7.9%), pneumonia (7.9%), tooth disorder (7.9%), allergic reaction (5.3%), conjunctivitis (5.3%), ear pain (5.3%), and myalgia (5.3%). Most, if not all, of the TEAEs reflect commonly occurring signs and symptoms in children. The lack of a control group does not allow any further analyses to be done or any other conclusions to be drawn. The overall safety information collected in this study is consistent with the safety information collected in studies GDCH and E001.

The efficacy data on auxological variables generated by this study is consistent with observations made in other studies of GH treatment in short patients with apparently normal growth hormone secretion: a significant percentage of patients will augment their height velocity when treated with exogenous growth hormone. In this study mean height velocity almost doubled at the end of 12 months of therapy (8.3 cm) over baseline mean height velocity (4.7 cm). Interestingly, three children failed to increase by more than 2 cm/y above their pretreatment height velocity values (and were discontinued from the study). Six children during the second six months of treatment failed to reach this mark despite doing so in the first six months of the study (the authors of the study do not comment on compliance). The dose of 75 µg/kg/day given three times weekly (0.225/mg/kg/week) is almost the same as the dose and regimen used in the pivotal study GDCH (0.22 mg/kg/week given three times a week).

The nitrogen kinetics data obtained in the study indicate an increase in protein turnover, protein synthesis, protein breakdown and net protein accretion (despite the increase in protein breakdown). The nitrogen excretion decreased by a mean of 30% after GH single day treatment (the individual responses varied from 5.7% to 50.5%; the three GH-deficient patients diminished their nitrogen excretion by 31.5%, 31.8%, and 50.5% respectively). The short-term changes in acute nitrogen kinetics in response to growth hormone did not correlate with the changes in growth rate at the end of one year of GH treatment.

A. 2. Study GDCP

The results of this study were submitted to the agency as a Final Study Report on December 9, 1994 (IND 28,574). The applicant includes this study as supportive safety data to the current NDA. The results of the study have been published in 1992 by Rosebaum et al. in the *Journal of Clinical Endocrinology and Metabolism*, Vol.75, No. 1. The title of the article is "Effects of systemic growth hormone administration on regional adipose tissue in children with non-GH-deficient short stature." The following review uses both the published information and the final report safety results.

This was a one center, phase II, open-label study whose objective was to measure the *in vitro* response of adipose tissues collected from gluteal and abdominal subcutaneous sites to growth hormone, insulin and various catecholaminergic agents. Ten patients (6 males and 4 females) had subcutaneous adipose tissue biopsies before and after 3 months of Humatrope therapy at a weekly dose of 0.3 mg/kg given in three injections. The main inclusion criteria were (1) peak plasma growth hormone secretion > 10 ng/L, following one provocative test, (2) Tanner I sexual maturity staging, (3) growth velocity < 5cm/year and height below the 5th percentile for age and sex, bone age delayed at least 2 years relative to chronological age.

Safety measures included a physical examination at each visit, "routine laboratory analyses of blood and urine," collection of adverse event reports, evaluation of growth hormone and *Escherichia coli* (ECP) antibodies. Five (50%) of the ten patients enrolled experienced at least one TEAE. A total of 33 TEAEs were reported. Most TEAEs were reported once. Four TEAEs were reported twice; they were accidental injury, arthralgia, fever, and rhinitis. The TEAEs reported once were bronchitis, convulsion, diarrhea, drug level decreased, flu, gastrointestinal disorder, headache, hemorrhage, infection, myopathy, nausea and vomiting, pain, pharyngitis, sinusitis, and vertigo. The small number of patients and the absence of a control group limit the ability to draw any conclusions from this report. Most adverse events are suggestive of common childhood signs/symptoms and illnesses. Arthritis and myopathy are less typical. Two patients reported arthralgias. None of the TEAEs were severe. No deaths or SAEs are reported. None of the patients developed measurable anti human GH or ECP antibodies.

From an efficacy perspective, the study showed that growth hormone therapy was associated with a significant reduction in abdominal adipocyte size and a significant increase in responsiveness of gluteal subcutaneous adipose tissue to the lipogenic actions of insulin.

A.3. Study (Protocol) GDFC (GENESIS)

Study GDFC is a phase IV multicenter (14 centers), open-label, observational study. The formal title of the study is "The Genetics and Neuroendocrinology of Short Stature International Study (GeNeSIS)." The overall objective of the GeNeSIS study is to evaluate the clinical management of pediatric patients receiving Humatrope treatment for improvement of linear growth. It includes an evaluation of the long-term efficacy and safety of Humatrope treatment in a diversity of patients, such as those with growth hormone deficiency, short stature homeobox-containing gene (SHOX) deficiency syndromes, and chronic renal failure. The planned duration of GeNeSIS is at least 5 years.

An interim safety analysis of NGHDSS pediatric patients enrolled in this study is presented as supportive information in the current NDA. It reports safety data on 23 patients (14 males and 9 females) with NGHDSS collected between March 1999 and December 2001. Patients entered the study (1) if they had received Humatrope treatment prior to epiphyseal closure at any time before or after enrollment in GeNeSIS, (2) if they had completed more than one visit while on Humatrope treatment, (3) if specified safety information (including pre-existing morbidity, data on Humatrope dosing, and adverse event status) has been provided, and (4) if they met the criteria for NGHDSS. The NGHDSS criteria were: growth impairment either idiopathic, or not

attributable to growth hormone deficiency (GHD) or any other defect of the growth hormone (GH) axis, any short stature homeobox-containing gene (SHOX) deficiency syndrome, intrauterine growth retardation (IUGR) of known cause, or a defined clinical condition or syndrome (meningomyelocele), but was attributable to at least one of the following: IUGR of unknown cause, familial short stature, or constitutional delay of growth and adolescence. The Humatrope regimen and duration of treatment are left at the discretion of the individual investigators. Safety data collected during the study include the whole range of adverse events (deaths, SAEs, discontinuations due to SAEs, and TEAEs). The study is ongoing.

Twenty-three patients met the selection criteria for the interim analysis. On average, patients were 10.4 years of age (range 3.69 to 15.24). The population included male (61%) and female patients (39.1%). Most patients were Caucasian (83%). Sixty-one percent of the patients were naive to Humatrope treatment, whereas 39% of these patients had received Humatrope therapy previously. The 23 patients included in this analysis received Humatrope for an average of 2.4 ± 3.1 years. Main growth-related baseline characteristics of the enrolled patients are listed in the next table.

Summary of Baseline Clinical Characteristics*

Variable	Humatrope (N=23)
Weight (kg)	23.56 (7.04)
Body Mass Index (kg/m ²)	15.38 (1.50)
Height (cm)	122.50 (16.03)
Height SDS	-2.84 (0.89)
Age (yrs)	10.38 (3.00)
Bone Age (yrs)	8.67 (2.72)
Bone Age/Chronological Age Ratio	0.84 (0.17)
Target Height (cm)	164.62 (7.83)
Target Height SDS	-0.93 (0.70)

Source: Table GDFC.4.1.

*Data are presented as mean and (standard deviation) and are calculated for all 23 patients with the exemption of BA and BA/CA which were calculated from 18 patients.

The safety of Humatrope therapy was evaluated on the basis of reports by site investigators who recorded information about treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and discontinuations due to adverse events (AEs). There were no deaths, SAEs, or discontinuations due to AEs. Two patients (8.7%) experienced TEAEs: allergic reaction in one patient; diarrhea and vomiting in the second patient. All TEAEs were considered mild in severity.

B. References

- American Academy of Pediatrics: *Considerations related to the use of recombinant human growth hormone in children*. Pediatrics 1997, 99: 122-9.
- Brook CDG, 1977. *Growth hormone: panacea or punishment for short stature?* BMJ 315: 692-3.
- Cuttler L et al. *Short stature and growth hormone therapy. A National study of physician recommendations*. JAMA 1996; 276: 531-37.
- Cohen P, Bright GM, Rogol AD, Kappelgaard A-M, Rosenfeld RG, American Norditropin Clinical Trials Group. 2002. *Effects of dose and gender on the growth and growth factor response to GH in GH-deficient children: implications for efficacy and safety*. J Clin Endocrinol Metab 87:90-98.
- Consensus: *Critical evaluation of the safety of recombinant human growth hormone administration statement from the Growth Hormone Research Society, 2001*. J Clin Endocrinol Metab 86:1868-70.
- Finkelstein B S, Imperiale TF, Speroff T, Marrero U, Radcliffe DJ, Cuttler L. 2002. *Effect of growth hormone therapy on height in children with idiopathic short stature. A meta-analysis*. Arch Pediatr Adolesc Med 156:230-240.
- Finkelstein BS et al., 1998. *Insurance coverage, physician recommendations, and access to emerging treatments. Growth hormone therapy for childhood short stature*. JAMA, 279: 663-8.
- Goddard AD, Covello R, Luoh S-M, Clackson T, Attie KM, Gesundheit N, Rundle AC, Wells JA, Carlsson LMS, Growth Hormone Insensitivity Study Group. 1995. *Mutations of the growth hormone receptor in children with idiopathic short stature*. N Engl J Med 333:1093-1098.
- Growth Hormone Research Society, 2000. *Consensus guidelines for the diagnosis and treatment of growth hormone deficiency in childhood and adolescence*. J Clin Endocrinol Metab 85:3990-93.
- Guyda H J. *Four decades of growth hormone therapy for short stature: what have we achieved?* J Clin Endocrinol Metab, 1999; 84: 4307-16.
- Hilken et al. *UK audit of childhood growth hormone prescription, 1998*. Arch Dis Child 2001; 84: 387-9.
- Hintz R L, Attie KM, Baptista J, Roche A, Genentech Collaborative Group. 1999. *Effect of growth hormone treatment on adult height of children with idiopathic short stature*. N Engl J Med 340:502-507.

Kuczmarski RJ, Ogden CL, Grummer-Strawn LM, Flegal KM, Guo SS, Wei R, Mei Z, Curtin LR, Roche AF, Johnson CL. 2000. *CDC growth charts: United States*. US Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Health Statistics 314:1-28.

Lawson Wilkins Pediatric Endocrine Society 1995: *Guidelines for the use of growth hormone in children with short stature*. *J.Peds* 127: 857-67.

Lawson Wilkins Pediatric Endocrine Society 2003: *Update of guidelines for the use of growth hormone in children with short stature*. (in print)

Maneatis T, Baptista J, Connelly K, Blethen S. 2000. *Growth hormone safety update from the National Cooperative Growth Study*. *J Pediatr Endocrinol Metab* 13:1035-1044.

Rappold GA, Fukami M, Niesler B, Schiller S, Zumkeller W, Bettendorf M, Heinrich U, Vlachopapadopoulou E, Reinehr T, Onigata K, Ogata T., 2002. *Deletions of the homeobox gene SHOX (short stature homeobox) are an important cause of growth failure in children with short stature*. *J Clin Endocrinol Metab* 87:1402-1406.

Rosenfeld RG, 2001. *Editorial: a SHOX to the system*. *J Clin Endocrinol Metab* 86:5672-5673.

Tanaka T et al. 2002. *Diagnosis and management of growth hormone deficiency in childhood and adolescence-Part 2: growth hormone treatment in growth hormone deficient children*. *Growth Hormone & IGF Research* 12, 323-41

Wilton P, 1999. *Adverse events during GH treatment: 10 years' experience in KIGS, a pharmacoepidemiological survey*. In: Ranke MB, Wilton P, editors. *Growth hormone therapy in KIGS. 10 years' experience*. Heidelberg: Johann Ambrosius Barth Verlag. p 349-364.

Wilton P, 2003. Presentation at the Endocrine Society's 85th Annual Meeting, June 19-22, Philadelphia

**C. Quick Minutes of the June 10, 2003, Endocrinologic and Metabolic Drugs Advisory
Committee Meeting**

**Endocrinologic and Metabolic Drugs Advisory Committee Meeting
June 10, 2003**

The following is an internal report, which has not been reviewed. A verbatim transcript will be available in approximately two weeks, sent to the Division and posted on the FDA website at <http://www.fda.gov/ohrms/dockets/ac/cder03.html#EndocrinologicMetabolicDrugs>. Slides shown at the meeting will be available at least 3 days after the meeting at the same website.

All external requests for the meeting transcripts should be submitted to the CDER, Freedom of Information office.

The Endocrinologic and Metabolic Drugs Advisory Committee of the Food and Drug Administration, Center for Drug Evaluation and Research met on June 10, 2003, at the Holiday Inn, located at 8120 Wisconsin Avenue, Bethesda, Maryland. Dr. Glenn Braunstein chaired the meeting.

Endocrinologic and Metabolic Drugs Advisory Committee Members Present (voting):

Glenn Braunstein, M.D (Chair), Marie Gelato, M.D., Ph.D., Nancy Worcester, Ph.D. (Consumer Representative), Deborah Grady, M.D., M.P.H., William Tamborlane, M.D., Dean Follman, Ph.D., David Schade, M.D., Nelson Watts, M.D., Paul Woolf, M.D.

Endocrinologic and Metabolic Drugs Advisory Committee Consultants (voting):

Jose Cara, M.D.

Acting Industry Representative (non-voting):

George Goldstein, M.D, F.A.A.P.

Endocrinologic and Metabolic Drugs Advisory Committee Members Absent:

Lynn Levitsky, M.D., Michael McClung, M.D.

FDA Guest Speaker:

Harvey Guyda, B.S.c., M.D.

FDA Participants:

Robert Meyer, M.D., David Orloff, M.D., Dragos Roman, M.D.

Open Public Hearing Speakers:

Patricia Costa

Human Growth Foundation

Glen Head, New York

Nicole Costa

Glen Head, New York

Deno Andrews

**New Heights Medical Clinic
Oak Park, Illinois**

**Sidney Wolfe
Director, Public Citizens Health Research Group**

The Committee discussed sNDA 19640/S-033, Humatrope (somatropin [rDNA origin] for injection), sponsored by Eli Lilly and Company, proposed for the indication of non-growth hormone deficient short stature. Prior to the meeting, the members and the invited consultant had been provided the background material from the FDA and from the sponsor.

The meeting was called to order at 8:40 a.m. by Glenn Braunstein, M.D. (Committee Chair). The Committee members, consultants, and FDA participants introduced themselves. The conflict of interest statement was read into the record by Dornette Spell-LeSane, N.P.C., M.H.A. (Executive Secretary). Opening remarks were made by Dr. David Orloff, M.D., Director, Division of Metabolic and Endocrine Drug Products. Dr. Orloff acknowledged the retiring committee members, Drs: Gelato, Grady and Tamborlane. The agenda proceeded as follows:

Eli Lilly and Company gave the following presentation:

Introduction	Gregory Enas, Ph.D. Director, US Regulatory Affairs Eli Lilly and Company
Rationale for treatment	Raymond Hintz, M.D. Professor of Pediatrics Stanford University Medical Center
Efficacy	Gordon Cutler, M.D. Director, Growth and Recovery Research and Clinical Investigation Eli Lilly and Company
Safety	Charmian Quigley, M.B.B.S. Senior Clinical Research Physician Endocrinology Eli Lilly and Company
Benefit-Risk Assessment and Risk Management Plan	Charmian Quigley, M.B.B.S.
Concluding Statements	Margaret MacGillivray, M.D. Professor of Pediatrics University of Buffalo Pediatric Endocrinologist School of Medicine & Biomedical Sciences Children's Hospital Buffalo

Break

Committee Discussion

Agenda (cont.)

Presentation, FDA Guest Speaker Harvey John Guyda, B.Sc. (Med), M.D., FRCPC
Professor, Department of Pediatrics
McGill University

Committee Discussion

Lunch

Open Public Hearing

Charge to the Committee David Orloff, M.D.
Division Director
Metabolic and Endocrine Drug Products
FDA

Questions to the Committee:

1. Has the efficacy of Humatrope in NGHDSS been sufficiently characterized?

Yes: 10
No: 0

a. Is the dose regimen proposed supported by the results of the studies presented?

Yes: 10
No: 0

b. Please comment on the discussion by the sponsor of the importance of height augmentation in the target population and on the conclusion that the expected effects are clinically meaningful.

Discussion:

Three members agreed; that height augmentation in the target population was important and they agreed with the conclusions by the sponsor that the expected effects are clinically meaningful. However, based on the evidence presented, a majority of the committee members were undecided; further, they agree that no conclusions could be made as to whether the effect was clinically meaningful. Committee members suggested that more information such as quality of life data was needed. One member stated that the decision regarding a clinically meaningful benefit should be left up to the physician and family.

2. Has the safety of Humatrope in NGHDSS been sufficiently characterized?

Yes: 6
No: 3
Undecided: 1

- a. Do the results of the trials and the current knowledge of the safety profile of GH in children support a favorable balance of risk and benefit in NGHDSS?**

Yes: 4
No: 1
Undecided: 5

- b. Please comment on the proposal for long-term follow up of these children as part of the Genetics and Neuroendocrinology of Short Stature International Study (GeNeSIS). What other surveillance of the safety of this intervention, if any, do you recommend?**

Discussion:

Nine committee members recommended that a mandatory registry for long term follow-up of children be added to the GeNeSIS proposal. One member recommended that the registry not be mandatory but agreed that close monitoring was in order. The committee unanimously agrees that yearly updates regarding safety and efficacy should also be reported.

- 3. Are the available data from the studies presented sufficient to guide the safe and effective use of Humatrope in patients with NGHDSS?**

Yes: 5
No: 5

- a. The sponsor has proposed a restrictive height criterion for treatment eligibility. Is this proposal satisfactorily rationalized?**

Yes: 7
No: 3

- b. Are additional criteria needed, such as pre-treatment height velocity, bone age, chronological age, serum IGF-1 level?**

Discussion:

The consensus of the committee was that a variety of data should be collected. Information should be collected on the front end. However, in addition to height velocity, bone age, chronological age and serum IGF-1 level, they stated that establishing a height criteria would be helpful and perhaps the most critical. Some members cautioned that there were no good predictors and one member strongly recommended that stopping criteria be added to the list of treatment criteria.

- c. **The range of responses observed in the trials (and thus expected in the clinic) is broad. Additionally, a dose-response is evident. Please discuss the following:**

- (i) the need for information on effect of individualization of dose, age at initiation of therapy, and duration of therapy on growth response and on safety

Discussion:

The committee felt that data regarding individualize dosing, age at initiation of therapy and duration of therapy was not adequately provided. Several members felt that there should be an age limitation placed on initiation of therapy. One member recommended less than five years of age, two members recommended at least seven years of age for initiation of therapy. One member agreed that there should be an age limitation but could not make a recommendation based on the information provided. Two committee members agreed that a growth response should be at the upper limits of normal. One committee member recommended a 5-year treatment duration. One committee member stated that constitutional growth delay should not be treated if constitutional growth indicators are normal.

- (ii) the need for information on potentially useful predictors of response, both pre-treatment and on-treatment (e.g., early growth or biomarker effects), again to enhance safe and effective use

Discussion:

The committee unanimously agreed that predictors of responses should be established and that treatment should be discontinued if no response was observed.

4. Please comment on the sponsor's risk management proposals?

Discussion:

The committee restated their concerns with regard to the sponsor's risk management proposal (see question 2. and transcript comments regarding recommendations for GeNeSIS). The committee added their concerns regarding Web-Page advertising by the sponsor and marketing to general practitioners. The committee agreed with the sponsor's plan to restrict prescribing privileges to board certified pediatric endocrinologist. Finally, mandatory long-term follow-up of treated patients was again recommended.

5. Please comment on additional concerns regarding safety and efficacy.

Discussion:

No formal discussion; see previous comments to question 3.

6. Do you recommend that the use of GH in NGHDSS as proposed by the sponsor be approved by FDA?

Yes: 8

No: 2

The meeting was adjourned at approximately 5:05 p.m.

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Dragos Roman
7/17/03 05:13:48 PM
MEDICAL OFFICER

David Orloff
7/23/03 11:17:22 AM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 19-640/S-033

CHEMISTRY REVIEW(S)

EA
1.16.03

CHEMISTS REVIEW		1. ORGANIZATION	2. NDA NUMBER
		DMEDP II, HFD-510	19-640
3. NAME AND ADDRESS OF APPLICANT		4. SUPPLEMENT NUMBER, DATE	
Eli Lilly and Co. Lilly Corporate Center Indianapolis, IN 46285		SE1-033	
5. PROPRIETARY NAME	6. NAME OF THE DRUG	7. AMENDMENTS, REPORT, DATE	
Humatrope	Somatropin (rDNA origin) for injection		
8. SUPPLEMENT PROVIDES FOR			
A new indication: non-growth hormone deficient short stature			
9. PHARMACOLOGICAL CATEGORY	10. HOW DISPENSED	11. RELATED IND, NDA, DMF	
Growth hormone	RX		
12. DOSAGE FORM	13. POTENCY		
Injection	6, 12, 24 mg		
14. CHEMICAL NAME AND STRUCTURE			
See Chemistry Review #1			
15. COMMENTS			
<p>This supplement was submitted and filed as an efficiency supplement for a new indication; non-growth hormone deficient short stature in children. There are no changes to the CMC portion of the approved application. The presentation of the product will be in vials and cartridges and will remain unchanged from that found in the NDA. Each vial contains 5 mg of lyophilized hGH and excipients that will be supplied as a combination package with an accompanying 5 ml vial of diluting solution. Cartridges contain 6, 12 or 24 mg of lyophilized hGH and excipients and will be supplied in a combination package with an approximately 3 ml of diluting solution in a syringe. The manufacture and fill/finishing of this product and the sites of these operations will remain the same as described in the NDA. Further, there are no CMC-related labeling changes to the approved NDA.</p>			
16. CONCLUSION AND RECOMMENDATION			
From a chemistry standpoint, this application can be approved.			
17. NAME	18. REVIEWERS SIGNATURE	19. DATE COMPLETED	
Janice T. Brown	See appended electronic signature	06-Jan-2002	
DISTRIBUTION: ORIGINAL JACKET CSO REVIEWER DIVISION FILE			

AP

1 Page(s) Withheld

X § 552(b)(4) Trade Secret /
Confidential

 § 552(b)(4) Draft Labeling

 § 552(b)(5) Deliberative Process

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Janice Brown
1/14/03 07:23:42 PM
CHEMIST

Stephen Moore
1/16/03 11:51:49 AM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 19-640/S-033

ENVIRONMENTAL ASSESSMENT

Environmental Analysis Requirement

Claim for a Categorical Exclusion from the Requirement to Submit an Environmental Assessment (EA).

Description of the Proposed Action

The approval of a supplement to the NDA for biosynthetic human growth hormone (hGH), formulated as Humatrope[®], has been requested by Eli Lilly and Company. This supplement proposes the use of Humatrope for non-growth hormone deficient short stature in children. Approval of the new indication will not increase use of Humatrope to a significant level as the current use rate is very low. The presentation of the product will be in vials and cartridges and will remain unchanged from that found in the NDA. Each vial contains 5 mg of lyophilized hGH and excipients that will be supplied as a combination package with an accompanying 5 ml vial of diluting solution. Cartridges contain 6, 12 or 24 mg of lyophilized hGH and excipients and will be supplied in a combination package with an approximately 3 ml of diluting solution in a syringe. The manufacture and fill/finishing of this product and the sites of these operations will remain the same as described in the NDA. Facilities currently associated with the production and processing of hGH into Humatrope will continue to comply with all appropriate environmental statutes, regulations, and permits that are in place.

Based on this information and the technical support information listed below, Eli Lilly and Company claims a categorical exclusion under 21 CFR 25.24 (c) (1) from the requirement to prepare an environmental assessment for this action as described under 21 CFR 25.31. This action is one that is ordinarily excluded from the preparation of an environmental assessment.

Technical Support Information**Physical Properties of Biosynthetic Human Growth Hormone:**

Chemical Name: Biosynthetic human growth hormone

Physical Description: White, amorphous powder

Solubility: _____

Isoelectric Point: _____

Molecular Formula: _____

Molecular Weight: 22,125

Safety of Proposed Action

The proposed action would not be expected to have adverse effects on human health or the environment. While approval of Humatrope for non-growth hormone deficient short stature will increase its production and use, the quantity of hGH entering the environment will not increase. In the kidney, growth hormone in mammals is extensively filtered and absorbed into renal cells in the tubules. Within the renal cells, growth hormone is catabolized with at least a portion of the breakdown products being returned to the circulation (Johnson and Maack, 1977). Thus, significant elimination of hGH from humans is unlikely. If the intact compound were eliminated from humans it would be discharged to either a sewage treatment facility or a septic tank where microbial degradation of the protein would occur. Thus, the increased use of Humatrope is not likely to impact human health or the environment.

References (available upon request)

Johnson V, Maack T. 1977. Renal extraction, filtration, absorption and catabolism of growth hormone. *Am J Physiol* 233(3):F185-F196.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 19-640/S-033

STATISTICAL REVIEW(S)



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION CLINICAL STUDIES

NDA/Serial Number: 19-640 / SE1-033

Drug Name: Humatrope (somatropin)
Recombinant human growth hormone

Indication(s): Non-growth hormone deficient short stature

Applicant: Eli Lilly and Company

Date(s): Received 9/28/02; User Fee 7/28/03

Review Status: Standard

Documents reviewed: \\CDSE\SUB1\N19640\033\2002-11-20\CRT\DATASETS and
\\CDSE\SUB1\N19640\033\2002-09-26\CLINSTAT

Biometrics Division: Division of Biometrics 2 (HFD-715)

Statistical Reviewer: Joy Mele, M.S.

Concurring Reviewers: Todd Sahlroot, Ph.D. (Biometrics Team Leader)

Medical Division: Division of Metabolic and Endocrine Drug Products (HFD-510)

Clinical Team: Dragos Roman, M.D. (Medical Reviewer)
David Orloff, M.D. (Medical Division Director)

Project Manager: Monika Johnson (HFD-510)

Keywords: Clinical Studies, NDA review, Dropouts

INTRODUCTION	3
STUDY GDCH	5
Design	5
Efficacy Variables	6
Patient Disposition	7
Baseline Characteristics	9
Statistical Methods	12
Efficacy Results	13
Examination of analysis population	18
Estimate of treatment effect	22
STUDY E001	26
Design	26
Patient Disposition	26
Baseline Characteristics	27
Efficacy Results	29
SUMMARY AND CONCLUSIONS	32
LABELING COMMENTS:	36
SIGNATURES/DISTRIBUTION LIST	38
APPENDICES	39
Appendix 1. Start and stop dates in GHCD	39
Appendix 2. Patient 1601	40
Appendix 3. GDCH Last height on study in cm	41
Appendix 4. E001 Plots of FH versus baseline height, baseline PH and target height	42

Introduction

The applicant has presented the results from two clinical trials, Study B9R-MC-GDCH (henceforth referred to as GDCH) and Study B9R-EW-E001 (henceforth referred to as E001) (Table 1) to demonstrate the efficacy and safety of humatrope treatment in children who are not growth hormone deficient but are considered to be of extreme short stature (NGHDSS).

Height velocity is expected to be impacted by the administration of growth hormone. The largest impact on change in height velocity is generally seen in the first year of drug therapy in growth hormone deficient children; this is also seen to be the case in these studies of children with NGHDSS. The issue for this NDA is not whether humatrope impacts growth velocity but whether a significant (both statistically and clinically) improvement in final height is attained. Study GDCH was specifically designed to examine this issue so the primary efficacy variable is final height standard deviation score (SDS). On the other hand, Study E001 was designed to compare the height velocities after 2 years of treatment of three humatrope dose groups (Table 1). Nevertheless, final height data was collected in a long term extension of E001.

Table 1. Clinical Trials

Study (# of centers)	Design	Treatment groups (N)	Primary Efficacy Variable
B9R-MC-GDCH 2 centers USA	Randomized Parallel Blinded NGHDSS	Placebo (33) Humatrope 0.22 mg/kg/wk (38)	Final Height Treat until height velocity < 1.5 cm/yr Mean duration 3.5 yrs
B9R-EW-E001 28 centers Europe	Randomized Parallel Open-label Dose response NGHDSS	Humatrope 0.24 mg/kg/wk Humatrope 0.24 (1 yr) / 0.37 mg/kg/wk Humatrope 0.37 mg/kg/wk	Height Velocity (HV) at 2 years Treat until height velocity < 2.0 cm/yr Mean duration 4.5 yrs

Studies GDCH and E001 differ in several important ways:

- GDCH is a blinded, placebo-controlled study and E001 is an open-label dose response study
- 3 times a week dosing of a 0.22 mg/kg/wk dose was used in GDCH and 6 times a week dosing of a comparable dose (0.24) and a higher dose of 0.37 mg/kg/wk was used in E001
- Entry criteria differed as follows:

	GDCH	E001
Tanner Stage	I and II	I
Age (years)	9-15 females 10-16 males	≥5
Bone Age	≤11 for females ≤13 for males	<10 for females <12 for males
Peak GH response	>7 ng/mL	>~10 ng/mL
Height SDS	≤-2.5	≤-2.0
Height velocity	Measured for 6 months or longer	Measured for 1 year or longer Below 25 th percentile

- Final height was measured when height velocity decreased to 1.5 cm/yr or less in GDCH and to 2 cm/yr or less in E001

- Median duration of treatment for the final height populations was about 4.5 years in GDCH and about 6.5 years in E001.

In both studies, a final height population was defined based on slowing of height velocity. For Study GDCH, 46% (33/71) of the randomized patients comprise the final height population and for Study E001, 21% (50/239) of the randomized patients comprise the final height population. Estimates from these populations may be biased since the final height populations are a subset of the randomized population. Intent-to-treat analyses including all randomized patients and height data measured before attaining final height are generally desirable but may introduce bias as well because of assumptions that must be made regarding growth patterns. Nevertheless, this reviewer presents several sensitivity analyses performed by both the applicant and by the reviewer with the goal of testing the robustness of the final height population results.

In addition to presenting the mean results from several statistical analyses of final height, this reviewer has designed several graphics to depict the individual patient data. Given the small numbers of patients in the final height populations, it is quite straightforward to visualize all the data and see the impact of therapy on individual patients. The intention is to provide information that will aid in the clinical interpretation of the statistical results.

All tables and graphs in this review were produced by this reviewer. Results computed by the reviewer agreed with results presented by the applicant unless otherwise noted.

Note that a more detailed review was afforded Study GDCH than Study E001, the former trial being placebo-controlled and specifically designed to assess final height.

Study GDCH

(conducted 1/88 to 2/01)

Design

Study GDCH is a double-blind, placebo-controlled, randomized trial of children with extreme short stature but without growth hormone deficiency (NGHDSS). The primary objective of the trial was to determine if children treated with growth hormone (Humatrope 0.22 mg/kg, 3 x week) had significant increases in adult height compared to children treated with placebo. Studies have shown an increase in height velocity as a result of growth hormone treatment in this population but effects on final height compared to placebo treatment have not been previously studied.

Patients were recruited at two sites; ~~_____~~ / NICHD at the NIH. There were three primary investigators and several subinvestigators.

The randomization was stratified on predicted height (PH, cm) and gender to form the following 6 strata:

Males	Females
PH<158.5	PH<143.6
158.5≤PH≤166	143.6≤PH≤154
PH>166	PH>154

Patients were evaluated for hormonal status and then followed for 6 months to compute growth velocity. Eligible patients were randomized and seen every 6 months. The first 20 patients were seen monthly for 3 months to obtain lower leg measurements. Patients who discontinued early were asked to continue height measurements every 6 months and return to the NIH when height velocity fell below 1.5 cm/year for a final height measurement.

Entry criteria included the following (for complete list, see Dr. Roman's medical review):

- Males (10-16 years, bone age≤13) and females (9-15 years, bone age≤11) with Tanner Stage 1 or 2
- Peak growth hormone response>7 ng/mL
- Height SDS≤-2.5 or predicted adult height SDS≤-2.5

Data was reviewed annually from 1993 to 2000 by a Data and Safety Monitoring Board (DSMB). On June 5, 2000, the DSMB recommended termination of the trial because it would have taken another 5 years for remaining patients to attain final height and further placebo injections were not justified for that time period. Only 8 patients were on study at the time of study closure. All patients (including discontinued patients) had the option to enter the extension phase and receive open-label Humatrope; no efficacy data was collected during this extension period.

Efficacy Variables

The primary efficacy variable was final height measured as SD scores (standardized for age and gender). Final height was considered attained when the patient's growth dropped to 1.5 cm or less per year or if the investigator determined that growth was near completion based on height velocity and/or bone age.

To obtain the height SDS for a given measurement, the following equation was used:

$$\text{Height SDS} = \left(\frac{(X/M)^L - 1}{L \cdot S} \right)$$

where X is the height measurement in centimeters; L is power in the Box-Cox transformation; M is the median and S is the generalized coefficient of variation. Values for L, M and S come from the appropriate reference population corresponding to the age in months of the child (these values are available at <http://www.cdc.gov/growthcharts>). The LMS data end at age 20 years. For patients older than 20 years, the height SDS was computed using the values at 20 years.

Patient height was measured every 6 months; 10 stadiometer measurements were averaged to determine height.

Secondary variables included the following:

- Standing height (cm)
- Height velocity (cm/year)
- Height velocity SDS
- Psychological assessment
- Achenbach child behavior questionnaire
- Harter self-perception questionnaire
- Injection-experience questionnaire
- Carbohydrate tolerance
- Lipid profile
- Tibial growth velocity by knemometry
- Bone age
- Pubertal development
- Sex steroid levels
- Tanner stage

Data from the psychological assessments were collected by the sites but were not transferred to Lilly and henceforth are not included in the NDA.

Baseline height velocity was computed from growth measured during the 6 months prior to randomization. Height velocity SDS is computed as follows:

$$\frac{\text{Patient's Height Velocity} - \text{Mean Height Velocity of normals of same age and gender}}{\text{Standard Deviation for normals of same age and gender}}$$

Baseline predicted height was a stratifier and a covariate in the analysis model. Predicted height is determined by the Bayley-Pinneau method using baselines for height, age and bone age and the gender of the patient. Predicted height SDS is computed as shown for final height above.

Compliance was computed as the percentage of expected injections recorded as completed.

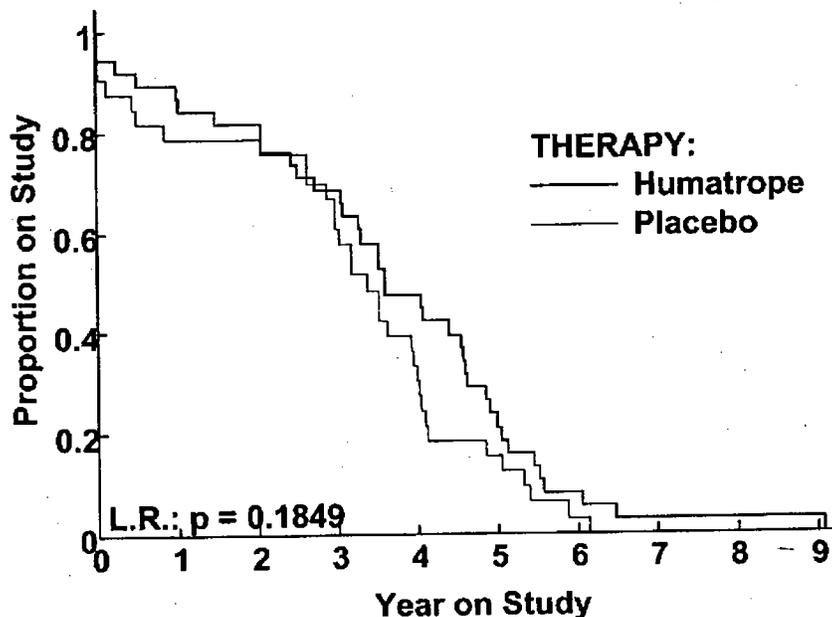
Patients 80-120% compliant were considered compliant.

Patient Disposition

The trial was powered to detect a 0.67 SDS (about 3 cm) treatment difference with 40 patients in each group assuming a 10% dropout rate and alpha of 0.05. The applicant fell short of their goal of 80 patients by 9, randomizing a total of 71 patients (33 placebo and 38 humatrope). A total of 68 patients were enrolled at the NIH and only three at ~~_____~~

Figure 1 shows the proportion of patients on study by study year with no significant difference in time to discontinuation between the groups ($p=0.18$). During the first year of the study, about 10% of the humatrope patients and 20% of the placebo patients discontinued. The median time on study was about 3.5 years for the total population. Appendix 1 shows the time on study for each patient and the date the patient entered the trial; no patterns in recruitment or duration of treatment are seen that would bias the results.

Figure 1. Kaplan Meier curves of time to discontinuation



The dropout rate was very high in both groups with only 27% of placebo-treated patients and 42% of humatrope treated patients completing the study (Table 2). Three patients (2 placebo and 1 humatrope) discontinued from the study without receiving any study drug. Two analysis populations (an efficacy evaluable population and a final height population) were defined in the protocol based on completion of Visit 5 (about Month 6) and availability of height data. The sample sizes for these populations are summarized in Table 2. The efficacy evaluable population best represents the randomized groups, however, 6 months of data is not sufficient to assess growth improvement. To assess final height, the final height population is, by definition,

the appropriate analysis population. The small number of patients in that group (less than half of the total) is problematic because it may not be representative of the randomized groups; this issue is examined further in the efficacy section of this review.

Table 2. Study GDCH Patient Disposition

	Humatrope	Placebo
Randomized	38 (100%)	33 (100%)
Completers	16 (42%)	9 (27%)
Discontinued+Returned for FH	7 (18%)	5 (15%)
Analysis Populations		
Efficacy Evaluable	35 (92%)	29 (88%)
Final Height	22 (58%)	11 (33%)

The time on study for each analysis population is summarized in Table 3. As would be expected, the time on study for the final height population is notably longer than the efficacy evaluable population with 88% of the patients treated for more than three years.

Table 3. Time on study by analysis population

	Efficacy Evaluable N=64	Final Height N=33	Completers N=25
Mean	3.7	4.4	5.0
Median	3.6	4.6	4.9
% < 1 year	6%	6%	0%
% 1-2 years	10%	3%	0%
% > 2-3 years	14%	3%	4%
% > 3 years	70%	88%	96%

The primary reason patients discontinued treatment in both groups was patient request (Table 4). The most common reasons patients gave for discontinuing included "too busy", "hassle" and injections too painful. One patient in each group dropped due to a perceived lack of efficacy and one in each group dropped due to satisfaction with self and height. The median time on study for placebo patients dropping due to patient request was 3 years (5 patients for less than 1 year); for humatrope patients, 2.5 years (2 patients for less than 1 year).

Only two patients (one in each group) dropped due to an adverse event. The nine patients dropping due to investigator (sponsor) request include eight patients still on study when the trial was ended.

Table 4. Study GDCH Reasons for discontinuation

	Humatrope (n=39)	Placebo (n=33)
ADE	1 (3%)	1 (3%)
Pt request	17 (45%)	12 (36%)
Inv request	4 (10.5%)	5 (15%)
Entry crit., not met	0	2 (6%)
Lost-to-Follow-up	0	4 (12%)

Included in the database were three sets of siblings; a set of fraternal twins, a set of biological siblings and a set of adopted siblings. Siblings were randomized to the same treatment as dictated by the protocol. Only one (a humatrope patient) of the six patients is included in the

final height population; this patient's sibling (5 years younger) chose to stop therapy at age 11.7 years. The twins were still on study when the trial was terminated; they were 14.6 years old at the time. The two adopted siblings were lost to follow-up after 2.5 years of therapy.

Baseline Characteristics

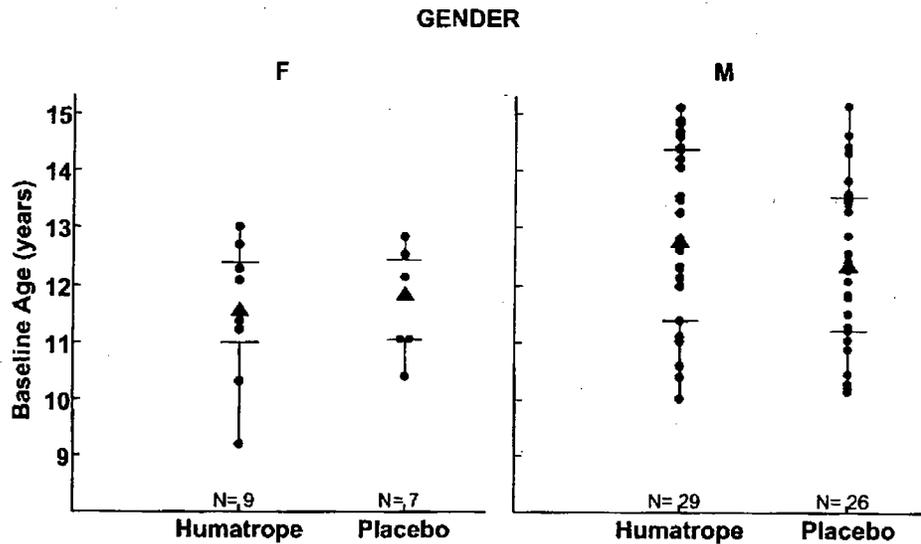
The baseline characteristics for all randomized patients and for the final height population are summarized in Table 5. About 80% of the patients were male; most were Caucasian. Six patients entered with a Tanner stage of 3 though the entry criteria required a Tanner stage of 1 or 2. A non-significant treatment group imbalance in Tanner score is seen for the final height population.

Table 5. Study GDCH Baseline Characteristics

	All Randomized Patients		Final Height Population	
	Humatrope (n=38)	Placebo (n=33)	Humatrope (n=22)	Placebo (n=11)
Age				
Mean (SD)	12.5 (1.6)	12.3 (1.4)	12.5 (1.6)	12.9 (1.1)
Range	9.2 to 15.1	10.1 to 15.1	10 to 15.1	11.5 to 15.1
Bone Age	(n=36)	(n=28)	(n=21)	(n=9)
Mean (SD)	10.45 (1.9)	10.36 (1.7)	10.4 (1.9)	10.7 (1.2)
Range	6 to 13	6 to 13	6 to 13	6 to 12.5
Bone Age/ Age				
Mean (SD)	0.84 (0.12)	0.84 (0.11)	0.84 (0.13)	0.81 (0.07)
Tanner stage				
1	18 (47%)	14 (42%)	9 (41%)	2 (18%)
2	18 (47%)	15 (46%)	12 (55%)	7 (64%)
3	2 (5%)	4 (12%)	1 (5%)	2 (18%)
Gender				
Female	9 (24%)	7 (21%)	4 (18%)	2 (18%)
Male	29 (76%)	26 (79%)	18 (82%)	9 (82%)
Race				
Caucasian	30 (79%)	25 (76%)	18 (82%)	7 (64%)
Hispanic	7 (18%)	4 (12%)	4 (18%)	1 (9%)
Other	1 (3%)	4 (12%)	0	3 (18%)
BMI (kg/m ²)				
Mean (SD)	17.1 (1.7)	17.5 (2.6)	17.0 (1.8)	17.5 (2.2)
Range	13.8 to 20.1	14.5 to 28.5	13.8 to 19.8	15.3 to 21.7

The average age at baseline was about 12 years (range 9 to 15) with bone ages about two years younger. Female patients were generally younger than male patients (Figure 2 on the following page).

Figure 2. Age (years) at baseline by gender (boxplots with observations)



No significant treatment imbalances for characteristics related to height were seen (Table 6).

Table 6. Study GDCH Baseline Height Characteristics

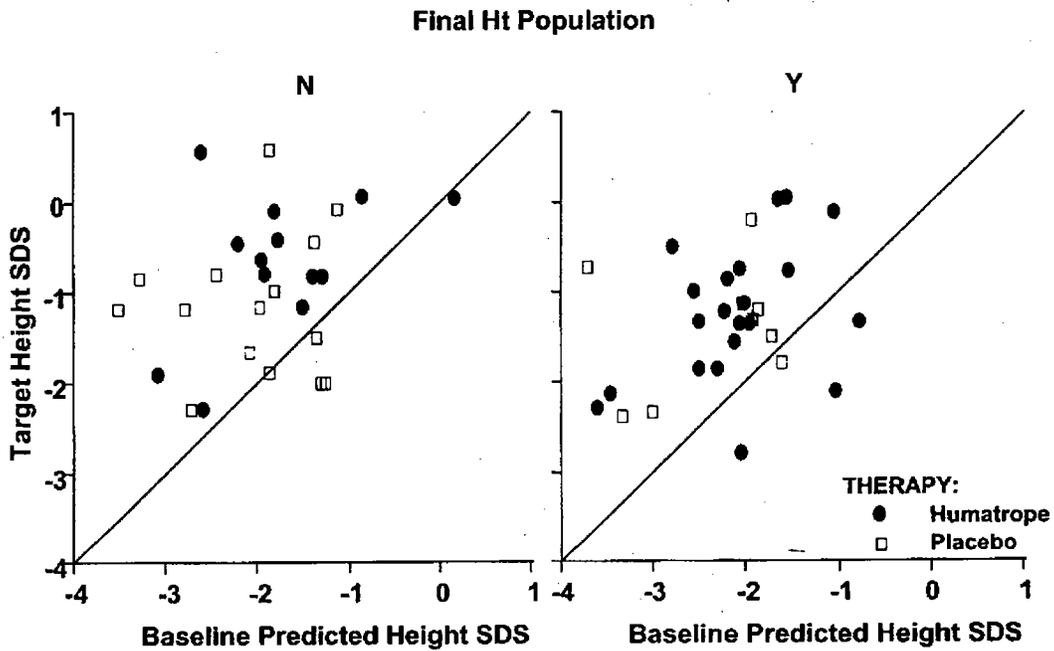
	All Randomized Patients		Final Height Population	
	Humatrope (n=38)	Placebo (n=33)	Humatrope (n=22)	Placebo (n=11)
Height (cm)				
Mean (SD)	132.8 (8.2)	131.0 (7.7)	132.8 (8.0)	134.9 (6.7)
Range	115.4 to 149.1	120.3 to 145.2	119.4 to 149.1	120.3 to 143.3
Height SDS				
Mean (SD)	-2.75 (0.49)	-2.81 (0.49)	-2.69 (0.55)	-2.75 (0.57)
Range	-3.9 to -1.8	-4.0 to -1.85	-3.9 to -1.8	-3.8 to -2.1
Predicted Height (cm)				
Based on baseline ht, bone age, age and gender	(n=35)	(n=28)	(n=22)	(n=10)
Mean (SD)	159.3 (8.3)	156.9 (8.1)	159.0 (7.5)	157.4 (7.8)
Range	140.8 to 177.3	135.6 to 167.9	140.8 to 170.5	143.6 to 166.5
Predicted Height SDS				
Mean (SD)	-1.96 (0.75)	-2.26 (0.83)	-2.08 (0.69)	-2.26 (0.80)
Range	-3.6 to 0.16	-4.2 to -1.14	-3.6 to -0.78	-3.7 to -1.34
Target Height (cm)				
Based on gender and parents' hts	(n=38)	(n=29)	(n=22)	(n=10)
Mean (SD)	165.9 (8.4)	165.1 (8.3)	165.8 (8.2)	164.3 (8.4)
Range	148.3 to 189.4	148.2 to 180.5	149.2 to 189.4	148.2 to 174.9
Height Velocity (cm/yr)				
Mean (SD)	4.81 (1.8)	4.77 (2.1)	5.2 (1.8)	5.6 (2.4)
Range	1.7 to 8.4	1.2 to 9.7	1.9 to 8.4	2.5 to 9.7
Height Velocity SDS				
Mean (SD)	-0.6 (1.1)	-0.8 (1.1)	-0.4 (1.1)	-0.2 (1.1)
Range	-2.5 to 1.9	-3.7 to 1.4	-2.5 to 1.8	-1.7 to 1.4

Baseline height ranged from 115 cm (45 inches) to 149 cm (58 inches) for all randomized patients who were aged 9 to 15 years.

While the mean height SDS at baseline was about -2.75 (considered "abnormal"), the mean height velocity SDS for all groups was close to zero and ranged up to a maximum value of 1.9. So for many patients, height velocity was within a so-called normal range.

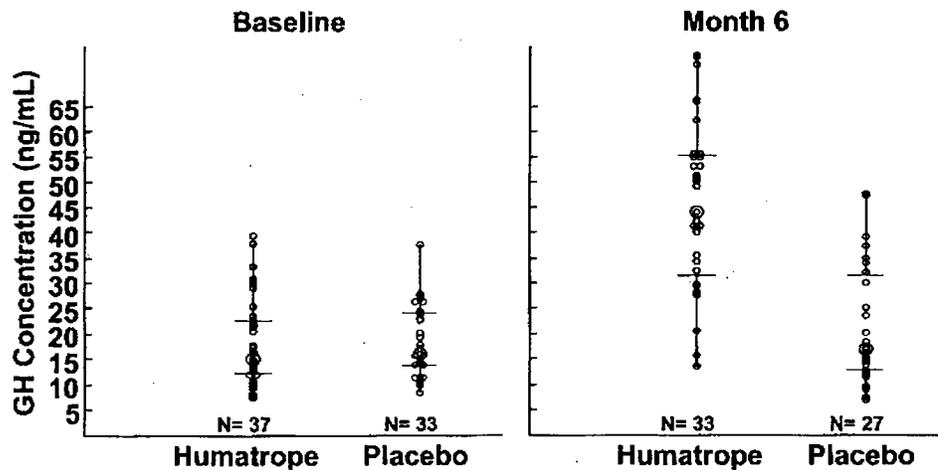
Figure 3 below shows the relationship between baseline predicted height SDS (which is calculated based on baseline height, baseline bone age, baseline age and gender) and target height SDS (which is calculated based on the parents' heights and the patient's gender). Though the two measures are correlated, the target height is clearly greater than the baseline predicted height and therefore a higher hurdle to meet than the predicted height. The treatment group distributions suggest adjustment for these variables at the analysis stage would be prudent.

Figure 3. Target height SDS by baseline predicted height SDS by treatment for patients in and not in the final height population



Growth hormone concentration was measured at baseline and after six months of treatment. To be eligible for the trial, a peak concentration less than 7 ng/mL was needed. Figure 4 shows the comparability of the peak growth hormone concentration at baseline across the treatment groups (the same was seen looking at just the final height population). This reviewer found no relationship between the baseline peak and baseline height SDS. As expected, the peak growth hormone concentration increases after six months of humatrope therapy.

Figure 4. Peak growth hormone concentration at baseline and Month 6 by treatment group



About one-third of the final height population presented with headache, allergies or a cardiovascular disorder (mild murmurs).

No patients were on Ritalin at the start of treatment. Five patients were given Ritalin during the study; two of those patients were included in the FH population. In both cases the Ritalin was given during the final visit(s), after growth spurts had occurred and did not appear to affect growth (weight or height).

Statistical Methods

Three efficacy analysis datasets were named in the protocol:

1. **Efficacy evaluable population:** all randomized patients who stayed on study and had height data up to at least Visit 5 (about Month 6).
2. **Final height population:** all randomized who stayed on study and had height data up to at least Visit 5 (i.e. efficacy evaluable) and had final height data.
3. **Protocol completers:** all randomized patients who completed the study.

All patients were to be followed to final height regardless of whether treatment was discontinued; a total of 12 discontinued patients returned for a final height visit (8 of these patients were included in the final height population). The safety population consisted of all randomized patients who took medication.

The protocol-defined primary efficacy analysis of final height SDS is an analysis of covariance

(ANCOVA) with baseline predicted height SDS as the covariate. The primary analysis population was the final height population. Tests for interaction were planned. Eight other covariates considered were: baseline height SDS, baseline bone age, target height (sex-adjusted mid-parental height), baseline age, baseline BMI, baseline IGF-I SDS and gender. Baseline height SDS was the covariate most strongly correlated with outcome with a correlation coefficient of 0.68.

Secondary analyses (ANCOVA) include the following:

- Analysis of final height (cm) minus baseline predicted height (cm) for the final height population.
- Analysis of the final height SDS for the protocol completers
- Analysis of the last observed height SDS for the efficacy evaluable population
- Analysis of the last observation of height SDS, height velocity, and height velocity SDS for all three analysis populations
- Analysis of lower leg growth in a subset of 20 patients to see if initial lower leg growth is predictive of final height

Analyses of all the other secondary variables were planned by the applicant but no details regarding the statistical tests were provided in the protocol.

Additional exploratory analyses were performed including a likelihood-based repeated measures analysis using all available data for each patient.

Efficacy Results

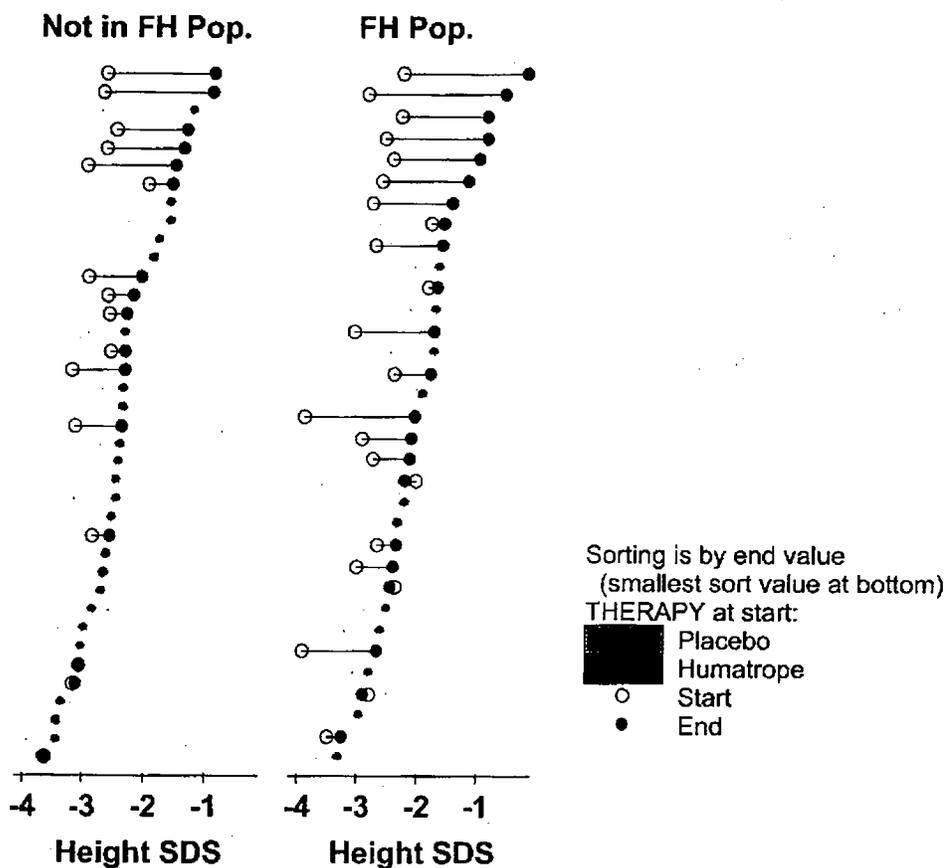
Compliance to the treatment regimen was high with 85% of the final height patients having a compliance of 80% or greater. Mean compliance for this population was 89% with a minimum of 56% and maximum of 99.9%.

Two placebo patients took growth hormone. One patient (008 1201) dropped out of the study after Visit 5 (Month 6), took growth hormone for 4 years and then returned for a final height measurement. This patient was not included in the applicant's efficacy evaluable or final height population though she fit the definitions for those populations; this patient is discussed further in the next section of this review. The second placebo patient (007 1601) took humatrope from May 1990 to Dec 1990 and from May 1992 to November 1992. This patient's height SDS and height velocity data are shown in Appendix 2. There is a growth spurt at the time of the humatrope treatment in 1990; this spurt occurs when the patient is about 15, a time at which a growth spurt might be expected. Note that no change in velocity is seen at the time of the second set of humatrope injections. Inclusion of this data could bias against the drug; however it is impossible to ascertain a measure of the bias. Patient 1601, then, was analyzed as randomized according to the principles of intent-to-treat.

The primary efficacy variable is the final height SDS for all patients reaching a low height velocity of 1.5 cm per year or less (the final height population). The last height on study was used for the analysis.

Both the final height SDS and the baseline height SDS are depicted in Figure 5 for all patients. Note that more black lines at the top of the graph indicate higher height SDS values at endpoint for humatrope patients. The length of the lines indicate the magnitude of change from baseline; visually it appears that larger changes are seen for humatrope compared to placebo.

Figure 5. Height SDS at baseline and endpoint by patient, treatment and analysis population



A statistically significant treatment difference in final height SDS of 0.50 SDS units was observed ($p=.017$, Table 7 on following page). Also analyses of change in height SDS, final height in cm and final height change in cm revealed borderline significant results ($p \leq .04$). A difference in final heights of about 3.2 cm was seen (LSM adjusted for baseline predicted height). So data from the final height population shows statistically significant effects on final height.

Table 7. Results of analyses of height SDS for the final height population

	Humatrope (n=22) Mean (SD)	Placebo (n=11) Mean (SD)	p-value
Height SDS			
Baseline	-2.69 (0.55)	-2.75 (0.57)	0.77
Final	-1.77 (0.78)	-2.34 (0.55)	
LS Mean	-1.81	-2.31	0.017
Change	+0.93 (0.73)	+0.42 (0.23)	0.03
Height (cm)			
Baseline	132.82 (7.95)	134.88 (6.74)	0.47
Final	161.12 (7.42)	157.46 (5.87)	
LS Mean	160.75	157.58	0.034
Change	+28.30 (7.38)	+22.58 (6.90)	0.04

SDS=standard deviation score

LS Mean for height SDS and height in cm from model with predicted height SDS as covariate.
p-values are from ANOVA or ANCOVA (LS mean results)

Due to the large number of dropouts, the applicant performed several additional analyses of height SDS which are summarized in Table 8 below. With the exception of the protocol completers (a small group of 25 patients), all analyses revealed significant treatment effects. Note that the treatment effect of about 0.5 SDS units is seen for most analyses; the main exception is the repeated measures analysis results which yielded a treatment effect of about 0.68.

Table 8. Results of sensitivity analyses of final height SDS performed by the applicant

Analysis Population	Analysis Model	Humatrope LS Mean	Placebo LS Mean	p-value
Efficacy Evaluable	ANCOVA BPH SDS	n=35 -1.89	n=27 -2.40	0.001
Protocol Completers	ANCOVA BPH SDS	n=16 -1.86	n=9 -2.32	0.06
All Patients with BPH	Repeated Measures Analysis	n=35 -1.52	n=27 -2.20	<0.0001
All Randomized Patients	ANCOVA Ht. SDS LOCF BPH SDS imputed where missing	n=38 -1.96	n=33 -2.36	0.011
All Randomized Patients	ANOVA Ht. SDS LOCF	n=38 -1.90	n=33 -2.42	0.003

BPH=Baseline predicted height

One of the problems with the sensitivity analyses is the use of non-final height data for those patients that have not reached final height. The reason this is problematic is that patients may achieve a peak height SDS and not maintain this SDS level as they continue to age. For the final height population, about 2/3 of the patients in each treatment group had a lower height SDS at the end of the trial than at some time earlier in the trial. So though analyses using the data from all randomized patients are generally recommended and desirable, in this setting the results of these analyses may primarily reflect an improvement in height velocity and not an improvement in final height. This may or may not bias the results favorably for the drug since both placebo and drug estimates would be impacted by the inclusion of non-final height data.

The repeated measures analysis performed by the sponsor yielded a treatment effect larger than the effect observed for the primary analysis by almost 0.2 SDS unit (approximately a 2 cm difference). The applicant's likelihood-based repeated measures model to analyze height SDS included the following terms:

- Treatment**
- Interaction of baseline age by treatment**
- Age at visit rounded an integer (observation for age closest to integer was used)**
- Baseline height SDS**
- Baseline predicted height SDS**
- Interaction of gender by age at visit rounded**
- Interaction of treatment by age at visit rounded**

All explanatory variables were modeled as fixed effects; a first-order autoregressive structure was assumed. The primary comparison from this model was a comparison of humatrope and placebo patients at age 18 years. Patients 18 or older at their last measurement were counted as being age 18.

Reduced models excluding one or more the terms in the model above did not produce notably different results. Also a model including a quadratic term produced similar results. The results, then, are not model dependent. However, the applicant's results are driven by the age chosen for obtaining the estimate of effect on final height.

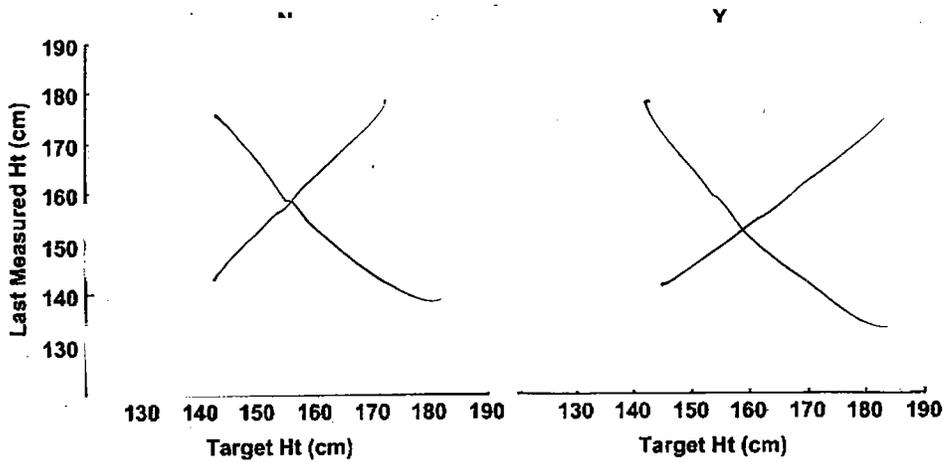
Six humatrope patients who were part of the final height population were under age 18 at their final height and did not contribute age 18 data in the applicant's repeated measures analysis. These six patients were most likely at their final height based on low height velocity and bone age at or above chronological age; therefore it is reasonable to assume that these 6 patients will remain at their observed height at age 18. Performing a repeated measures analysis using the applicant's model and including these 6 patients produces a treatment effect of 0.53; much closer to the primary analysis results of 0.51. This reviewer concludes that the estimate of 0.685 presented by the sponsor overestimates the treatment effect and is not representative of the data collected.

As stated earlier in this review, predicted height is smaller than target height and therefore, seemingly, an easier goal to achieve. The results comparing final height to predicted height and target height bear this out (Table 9, Figures 6 and 7). A statistically significant treatment effect is seen for the difference between final height and predicted height (a 2.9 cm [~1 inch] increase for humatrope over placebo) while no statistically significant difference is seen for the difference between final height and target height.

Table 9. Results for the difference between final height (FH) and predicted height (PH) and target height.

	Humatrope (n=22) Mean (SD)	Placebo (n=11) Mean (SD)	p-value
FH SDS - NCHS PH SDS	+0.32 (0.55)	-0.14 (0.59)	0.04
FH (cm) - NCHS PH (cm)	2.2 (4.0)	-0.67 (4.2)	
FH SDS - Target Ht SDS	-0.66 (0.89)	-1.01 (0.80)	0.28
FH (cm) - Target Ht (cm)	-4.7 (6.4)	-7.1 (5.7)	

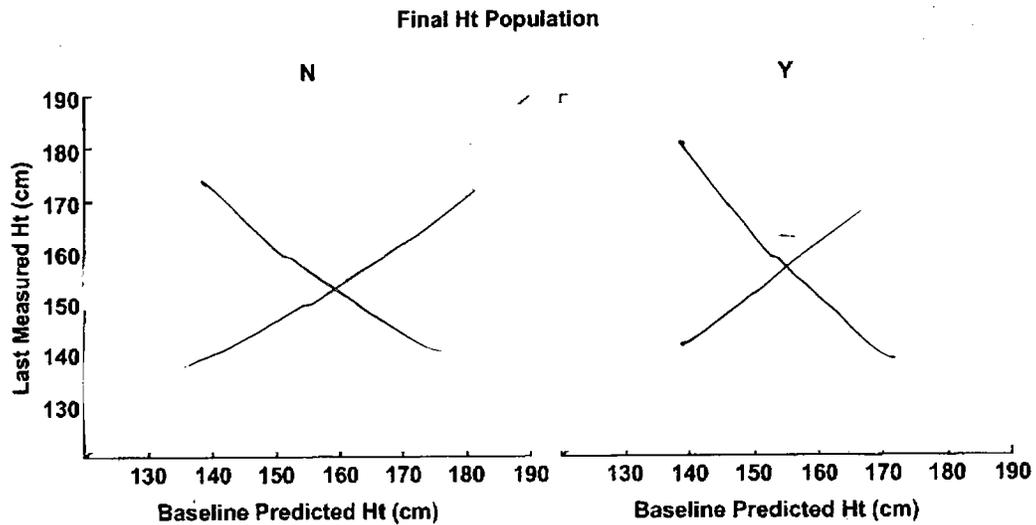
Figure 6. Last measured height (cm) by target height (cm) for the non-FH and FH Populations
Final Ht Population



Figures 6 and 7 both show individual patient data; points above the identity line represent those patients with final heights greater than their target (Figure 6) or predicted (Figure 7) heights. Most patients in both group surpass their predicted heights while only a few humatrope patients reach or surpass their target heights.

The side-by-side graphs illustrate the general difference between patients in the FH population and not in the FH population with a number of non-FH patients falling far below the identity line.

Figure 7. Last measured height (cm) by baseline predicted height (cm) for the non-FH and FH Populations
Final Ht Population



Examination of analysis population

The small number of patients in the final height population (about 40% of the randomized patients) is cause for concern. Methodologies for analysis of data with missing observations are not readily applicable here due to the assumptions one must make in the application of these methods. For example, a last-observation-carried-forward approach to deal with missing data is not appropriate since one can not assume that the height SDS would not change over time, perhaps dramatically depending on the time of dropout. The unpredictability of growth and the diversity of the patient population make it difficult to impute for missing data based on the observed data.

Some patients not included in the final height population may have come close to their final height even though their height velocity had not fallen below 1.5 cm/year. This reviewer then examined the data for patients with growth characteristics similar to the patients in the final height population. As a post hoc look at the data, analyses are not confirmatory but merely serve to test the robustness of the primary analysis of the final height population data.

First, the height velocities of both FH patients and non-FH patients were examined. Table 10 on the following page summarizes the peak and minimum height velocity for patients included and not included in the FH population. The objective here is to see if the non-FH population has similar height velocity characteristics to the FH population. Looking first to the maximum (peak) velocity, the means for the maximum observed velocity are greater for the patients in the final height population suggesting that some patients not included in the final height population may not have had a growth spurt on study though it is interesting to note that the mean ages at the maximum velocity were similar regardless of treatment or gender. (This latter point may suggest that humatrope does not promote early growth spurts; although the largest changes in height velocity occur during the first year of humatrope treatment [Table 10 on the following page].) The two populations clearly differ by minimum height velocity as expected, although the height velocities for the non-final height population fall to about half the peak velocities. This data suggests that some patients in the non-final height population experienced a growth spurt and had significant drops in height velocity while still on study.

Table 10. Height velocity (HV, cm/ year for previous 12 months) for patients not included and included in the FH population by treatment and gender

	Male		Female	
	Humatrope Mean (SD) n	Placebo Mean (SD) n	Humatrope Mean (SD) n	Placebo Mean (SD) n
FH Population	n=17	n=8	n=4	n=2
Pretreatment HV	5.5 (1.7)	6.0 (2.7)	4.3 (2.5)	4.7 (0.1)
First Year HV	8.7 (2.3)	7.5 (2.8)	8.4 (0.7)	5.6 (0.3)
Baseline Age	12.8 (1.7)	13.0 (1.2)	11.1 (0.6)	12.7 (0.2)
Max HV	10.0 (1.7)	9.8 (1.2)	8.4 (0.7)	5.8 (0.1)
Age at Max (years)	13.8 (1.4)	13.8 (0.8)	11.2 (0.7)	13.1 (0.5)
Years on Study at Max	2.0 (1.2)	1.8 (0.9)	1.1 (0.2)	1.5 (0.7)
Minimum HV	1.6 (1.8)	1.2 (0.6)	1.8 (1.4)	0.9 (0.2)
Age at Min	16.4 (1.9)	16.6 (0.8)	14.6 (1.7)	15.2 (0.4)
Not in FH Population	n=9	n=12	n=4	n=4
Pretreatment HV	4.2 (2.0)	4.3 (1.9)	5.0 (0.8)	5.8 (0.5)
First Year HV	6.9 (1.4)	5.7 (2.0)	6.9 (1.1)	6.4 (1.0)
Baseline Age	12.8 (1.7)	12.2 (1.6)	11.8 (1.8)	11.5 (0.6)
Max HV	8.1 (1.9)	7.8 (2.0)	7.2 (1.3)	7.8 (0.9)
Age at Max (years)	13.9 (2.0)	13.7 (1.6)	12.3 (1.1)	12.2 (0.3)
Years on Study at Max	2.1 (1.0)	2.5 (1.0)	1.5 (0.7)	1.8 (0.6)
Minimum HV	5.2 (1.1)	3.8 (1.2)	5.1 (2.6)	3.4 (0.8)
Age at Min	14.1 (2.4)	13.4 (2.5)	12.9 (2.4)	13.9 (0.8)

In a small population of only 71 patients, examination of the individual data is possible and also very helpful when trying to distinguish analysis populations. The two figures below illustrate two characteristics of the final height population: 1) a clear rise and dramatic drop in height velocity while on study (Figure 8), and 2) the leveling off of growth (a consequence of the low height velocity, Figure 9). By contrast, the growth in the non-FH population shows little leveling off of growth (particularly for males) though the height velocity is clearly decreasing for most patients.

Figure 8. Height velocity (cm/year for the previous 12 months) plotted against age by gender for patients not included and included in the FH population

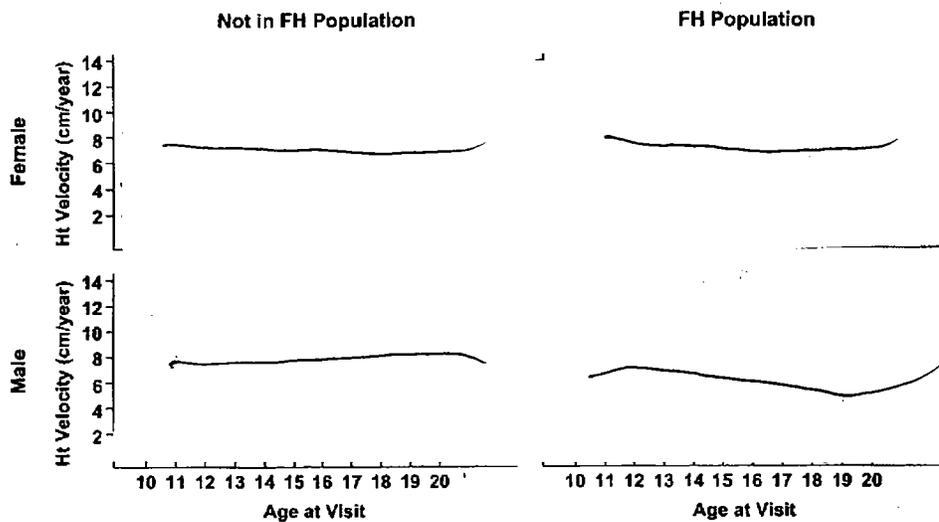
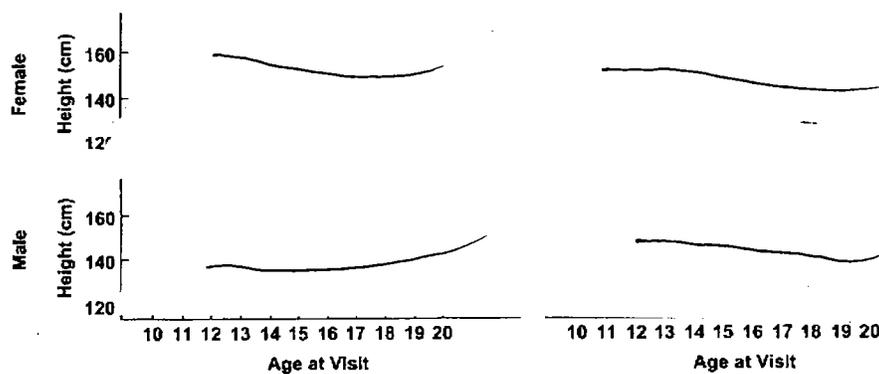


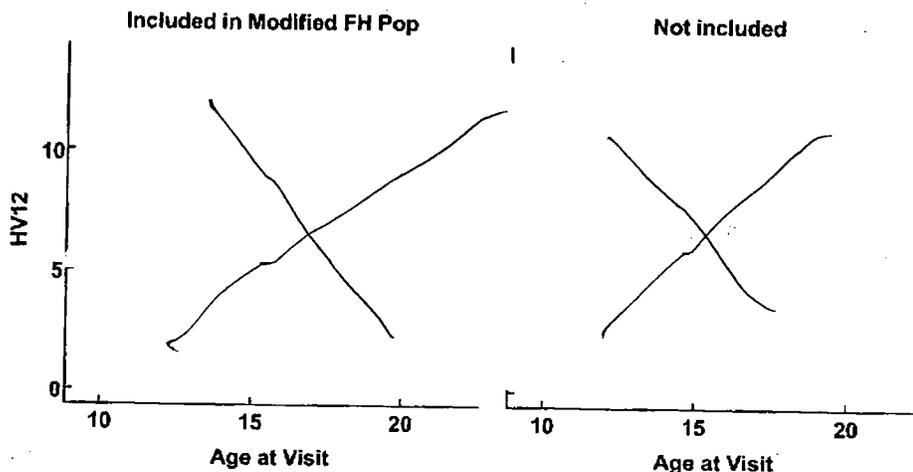
Figure 9. Height (cm) plotted against age by gender for patients not included and included in the FH population



From looking at the above graphs, this reviewer chose two criteria to identify non-FH patients close to their final height (patients needed to have only 1 of these criteria to be included in the

modified final height population) : 1) 17 or older at last height measurement or 2) a 12-month or 6-month height velocity $\frac{1}{2}$ their peak height velocity and a smaller 6-month HV than 12-month HV at their final visit. Using this approach, eighteen additional patients (11 placebo and 7 humatrope) were identified and are depicted in Figure 10 below¹. Note that these additional patients all had final heights after age 15, had experienced a growth spurt and had a large drop in growth velocity. The addition of these 18 patients brings the size of the analysis population to 72% of the randomized patients.

Figure 10. Height velocity (cm/year for the previous 12 months) plotted against age by gender for patients added to the FH population to form a modified-FH population and those not included.



An analysis of height SDS using the modified final height population produced a height SDS of -1.81 for humatrope and -2.24 for placebo; a statistically significant difference of 0.44 ($p=.007$). So the addition of the near final height patients decreased the treatment effect but nevertheless yielded highly significant results. The inclusion of patient 1201 (a placebo patient who discontinued, took growth hormone for four years and returned for a study final height) had an appreciable effect on the treatment effect estimate; without patient 1201, the treatment effect is 0.49 ($p=.002$) and reassigning 1201 to humatrope, the effect is 0.51 (the same effect size seen for the final height population).

Overall this post hoc analysis of a modified final height population yields results consistent with the results for the protocol-defined final height population and speak to the robustness of the primary efficacy results.

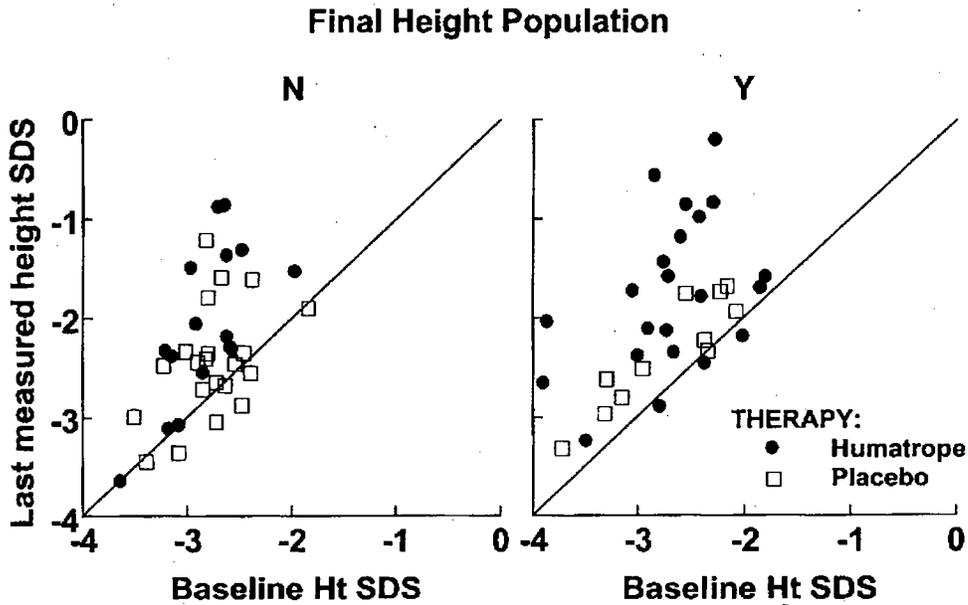
¹ One patient (1201) was included in the modified final height population although this placebo patient had received growth hormone for the 4 years not on study. The inclusion of this patient will bias against humatrope if the therapy was effective for the patient.

Estimate of treatment effect

The data from GDCH shows a statistically significant treatment effect for humatrope over placebo using a several different analysis populations and analyzing several different efficacy variables. The issue now is how to characterize the magnitude of the treatment effect to aid in judging its clinical significance. Though data from all patients will be presented here, the treatment effects will be defined for the protocol defined final height population.

Most patients in both treatment groups had an improvement in final height SDS over baseline height SDS (Figure 11) with a large increase seen for the humatrope patients (+0.93, FH population) compared to the placebo patients (+0.42, FH population, $p=0.03$). About 55% of the humatrope patients and 36% of the placebo patients had a final height SDS greater than -2 (approximately the third percentile). Note that a SDS of -2 is equivalent to 5'3.5" for males and 4'11" for females and is considered a cut-off for short stature.

Figure 11. Last measured height SDS by baseline height SDS



Estimates of the treatment effect show an improvement in final height for humatrope compared to placebo (Table 11) with a SDS difference of 0.51 and a difference of 3.2 cm (1.2 inches). These estimates are least squares means from an analysis of covariance with baseline predicted height SDS as covariate ($r=0.68$ for correlation with FH SDS) or with baseline predicted height in cm as covariate ($r=0.84$ for correlation with FH in cm). Humatrope males show a significant increase in height SDS compared to placebo males while the results for females are non-significant (most likely due to the small sample size of a total of 6 patients).

Analysis of variance of the difference between final height and baseline predicted height and of the difference between final height and target height yielded estimates in favor of humatrope but non-significant results ($p=0.075$ and $p=0.32$, respectively).

Table 11. GDCH Summary of Treatment Effect for the Final Height Population (LS means and SE)

	Humatrope (n=22)	Placebo (n=11)	Trt Effect	95% CI
Final Height SDS				
All	-1.805 (0.11)	-2.31 (0.17)	0.51	0.10, 0.92
Males*	-1.91 (0.12)	-2.385 (0.18)	0.40	0.03, 0.91
Females*	-1.34 (0.25)	-2.0 (0.35)	0.66	-0.23, 1.54
Final Height (cm)				
All	160.7 (0.8)	157.6 (1.2)	3.2	0.3, 6.1
Males	160.5 (1.0)	157.6 (1.4)	2.9	-0.4, 6.3
Females	161.6 (2.5)	157.7 (3.1)	3.9	-2.9, 10.7
FH minus Baseline PH (cm)				
All	2.2 (0.9)	-0.7 (1.3)	2.8	-0.3, 5.9
Males	1.5 (0.9)	-1.2 (1.4)	2.6	-0.8, 6.0
Females	5.3 (1.9)	1.3 (2.8)	4.0	-2.9, 10.9
FH minus Target Height (cm)				
All	-4.7 (1.3)	-7.1 (2.0)	2.4	-2.4, 7.2
Males	-4.6 (1.5)	-8.4 (2.2)	3.8	-1.6, 9.2
Females	-5.2 (3.1)	-1.8 (4.4)	-3.4	-14.4, 7.7

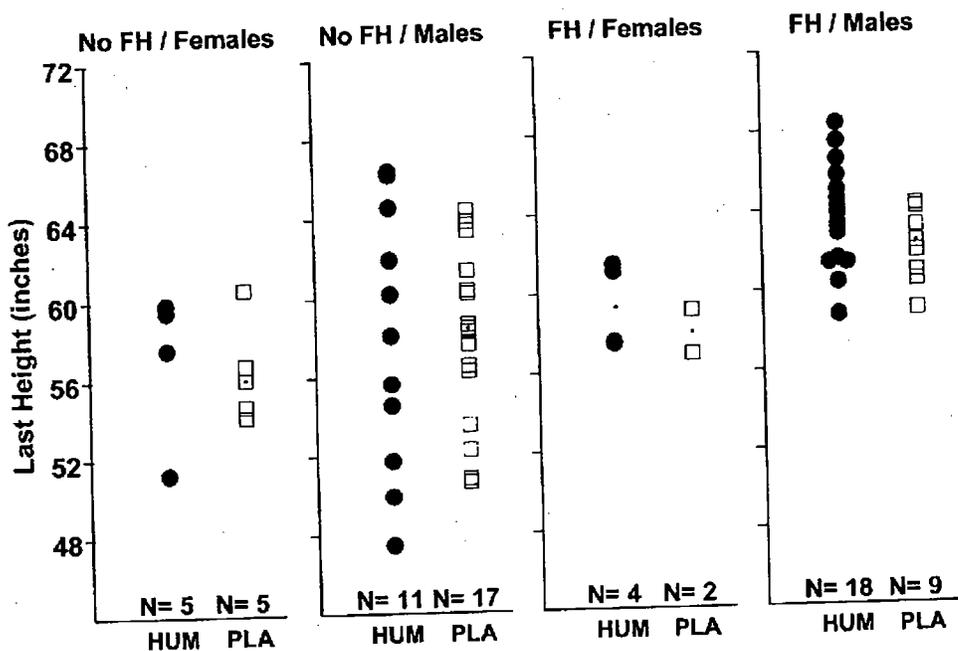
*In the final height population, there are 18 males on humatrope, 9 males on placebo, 4 females on humatrope and 2 females on placebo.

To obtain an estimate of the treatment effect in cm, the applicant converted the overall SDS value for each treatment group to a measurement in cm for each gender. Then, the treatment difference for each gender was computed and these differences were combined weighting on the proportion of each gender. Using this method, the applicant computed a 3.7 cm treatment effect for humatrope compared to placebo. Analyses by this reviewer of final height in cm yields a treatment effect of 3.2 cm; with an effect of 2.9 cm for males and 3.9 cm for females. So the different methodologies yield treatment estimates that differ by 0.5 cm (0.2 inches); most likely, a difference of no clinical consequence.

The distribution of the final heights for all the patients is shown in Figure 12. The data here is depicted in inches for an US audience and is provided in cm in Appendix 3.

The two right graphs depict the data for the final height population broken down by gender. The data for females shows that 2 of the 4 humatrope patients reached heights greater than 5 feet and heights greater than the 2 placebo patients. For the males, almost all patients in both treatment groups reach heights above 5 feet (one patient in each group had a final height of 59 inches) with about half of the humatrope patients reaching heights above 5'3".

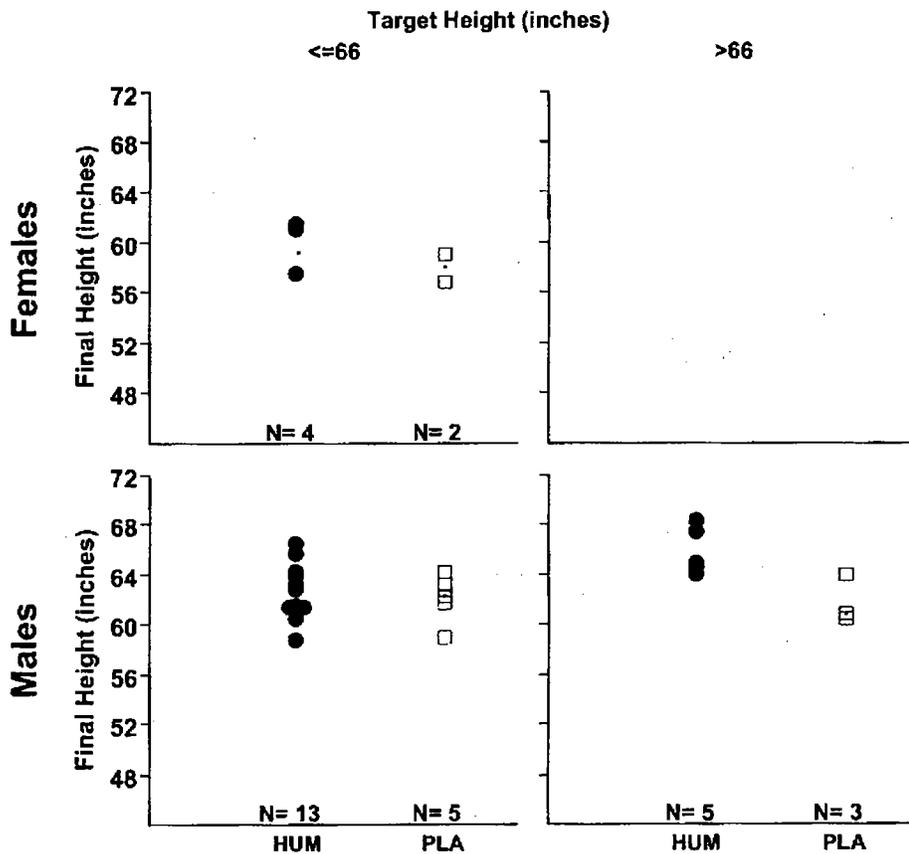
Figure 12. Final height in inches for the final height population and non-FH population by gender and treatment



The lowest point for FH females on humatrope represents two patients with the exact same height. For the placebo FH males, two patients with a height of 62.5 inches are represented by a single point.

Figure 13 shows the relationship of target height and final height with the tallest humatrope patients in the tallest target height group. This relationship though does not obfuscate the impact of humatrope.

Figure 13. Final height in inches for the final height population by target height (inches), gender and treatment



Overall Comments on GDCH

A statistically significant treatment effect on final height is seen for humatrope compared to placebo. An analysis by this reviewer of final height (cm) yields an estimate of treatment effect of 3.2 cm (LSM adjusted for predicted height) with a 95% CI of 0.3 to 6.1 cm (0.1 to 2.4 inches). The applicant reports a treatment effect of 3.7 cm based on an analysis of final height SDS and a conversion to cm.

Study E001

(conducted 3/88 to 1/01)

Design

Study E001 is a Phase 3 trial designed to compare 3 doses of humatrope in NGHDSS children. A total of 239 patients were recruited at 28 centers in 10 countries. The three doses studied were: 0.24 mg/kg/wk, starting dose of 0.24 mg/kg/wk for 1 year followed by 0.37 mg/kg/wk thereafter and 0.37 mg/kg/wk. The objective of E001 was to assess height velocity after two years of therapy (the primary efficacy outcome) and then assess final height in a long-term extension. For this review, the focus is on the final height data.

Entry criteria included the following:

- Males or females 5 years or older
- Tanner stage I
- Bone age less than 10 years for females and less than 12 years for males
- Height SDS of -2.0 or less
- Peak GH greater than ~ 10 ng/mL

Patient Disposition

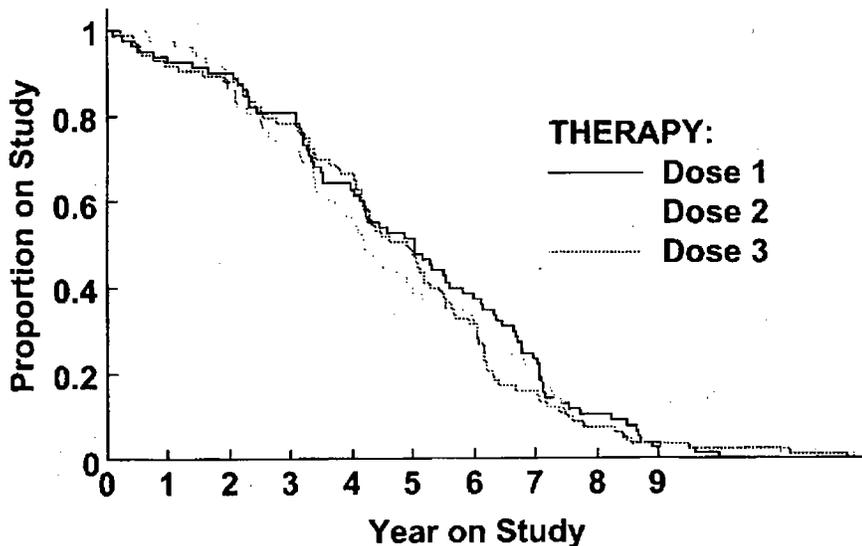
A total of 239 patients were randomized to treatment (Table 12). About 88% completed two years of treatment and provided 2-year height velocity data. Only about 1/5 of the patients were included in a final height population; these patients are the focus of this review. About half of the final height population consisted of patients from a single center where the investigator measured final height on patients who had discontinued treatment.

Table 12 Study E001 Patient Disposition

	HUM 0.24	HUM 0.24/0.37	HUM 0.37
Randomized	78	78	83
Completed 2 years	70 (90%)	67 (86%)	72 (87%)
Completed extension	18 (23%)	11 (14%)	14 (15%)
FH Population	17 (22%)	16 (21%)	17 (20%)
On Trt at FH	8	10	10
Off Trt at FH	9	6	7

The patterns of discontinuation for the three dose groups are similar as seen in Figure 14. The median time on study was 4.5 years for the overall population.

Figure 14. Kaplan Meier Curves of time to discontinuation



Patient request was the primary reason for discontinuation in all treatment groups with the highest percentage seen for the high dose group (Table 13).

Table 13. Reasons for discontinuation

	HUM 0.24 (n=78)	HUM 0.24/0.37 (n=78)	HUM 0.37 (n=83)
ADE	2 (3%)	0	1 (1%)
Pt request	22 (28%)	31 (40%)	38 (46%)
Inv request	10 (13%)	7 (9%)	8 (10%)
Sponsor decision	6 (8%)	7 (9%)	5 (6%)
Entry crit.. not met	7 (9%)	9 (12%)	8 (10%)
Lost-to-Follow-up	3 (5%)	2 (3%)	3 (4%)
Protocol violation	6 (8%)	6 (8%)	2 (2%)
LOE	3 (4%)	4 (5%)	2 (2%)
Other	0	1 (1%)	2 (2%)

Baseline Characteristics

Generally the treatments were comparable regarding baseline characteristics for the overall population and the final height population (Table 14). A significant difference in baseline heights between the low and high dose was seen in the all randomized patients group but not the FH population.

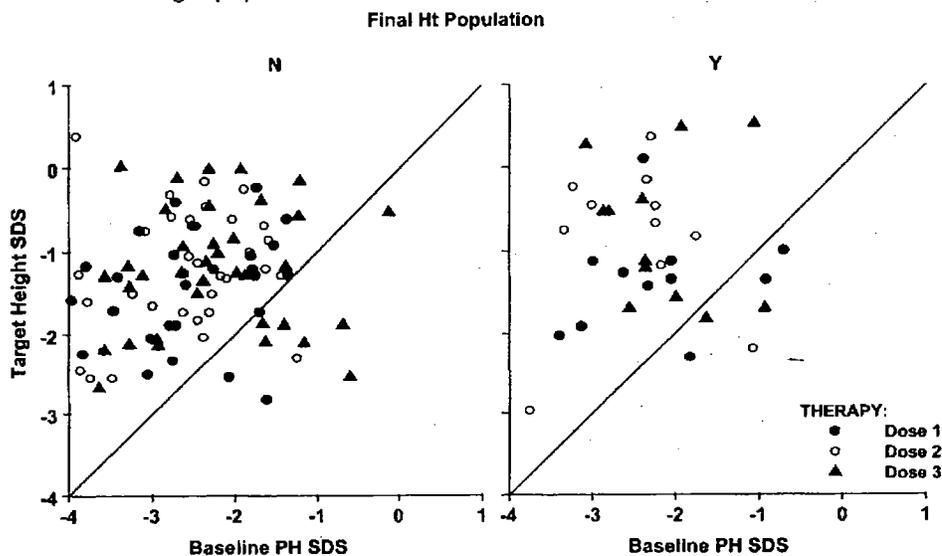
Patients in this study were younger at baseline than those of GDCH with a mean age of 10 years compared to 12 years for GDCH. Nearly all patients presented with Tanner Stage of 1; in GDCH about half presented with Tanner Stage of 1. Baseline height velocities are similar across treatment groups and are also similar to those seen in GDCH.

Table 14. Baseline Characteristics for all randomized patients and for the final height population

	All Randomized Patients			Final Height Population		
	HUM 0.24 (n=78)	HUM 0.24/0.37 (n=78)	HUM 0.37 (n=83)	HUM 0.24 (n=17)	HUM 0.24/0.37 (n=16)	HUM 0.37 (n=17)
Age	9.4 (2.4)	9.9 (2.2)	10 (2.2)	10.4 (2.3)	10.4 (2.1)	10.2 (2.1)
Range	5-15	5-14	5-14	6-15	6-12	5-12
Gender						
%male	63%	64%	71%	65%	56%	65%
Height (cm)	116.8 (13)	119.5 (11)	120.7 (11)	121.7 (11)	122.3 (11)	122.4 (10)
Height SDS	-3.37 (0.8)	-3.21 (0.7)	-3.04 (0.5)	-3.26 (0.8)	-3.08 (0.8)	-2.88 (0.6)
Bone Age (yrs)	7.4 (2.6)	8.1 (2.3)	8.0 (2.1)	8.5 (2.1)	8.5 (2.1)	8.9 (1.9)
Tanner Stage						
1	99%	99%	99%	100%	100%	100%
2	1%	1%	1%			
Height Velocity cm/yr	4.3 (1.1)	4.4 (1.3)	4.3 (1.1)	4.7 (1.4)	5.1 (2.0)	4.4 (1.5)

For most patients, the target height is greater than the baseline predicted height (Figure 15) with target heights generally greater than -2.0 for the final height population.

Figure 15. Target height SDS by baseline predicted height SDS by dose group for patients not in and in the final height population

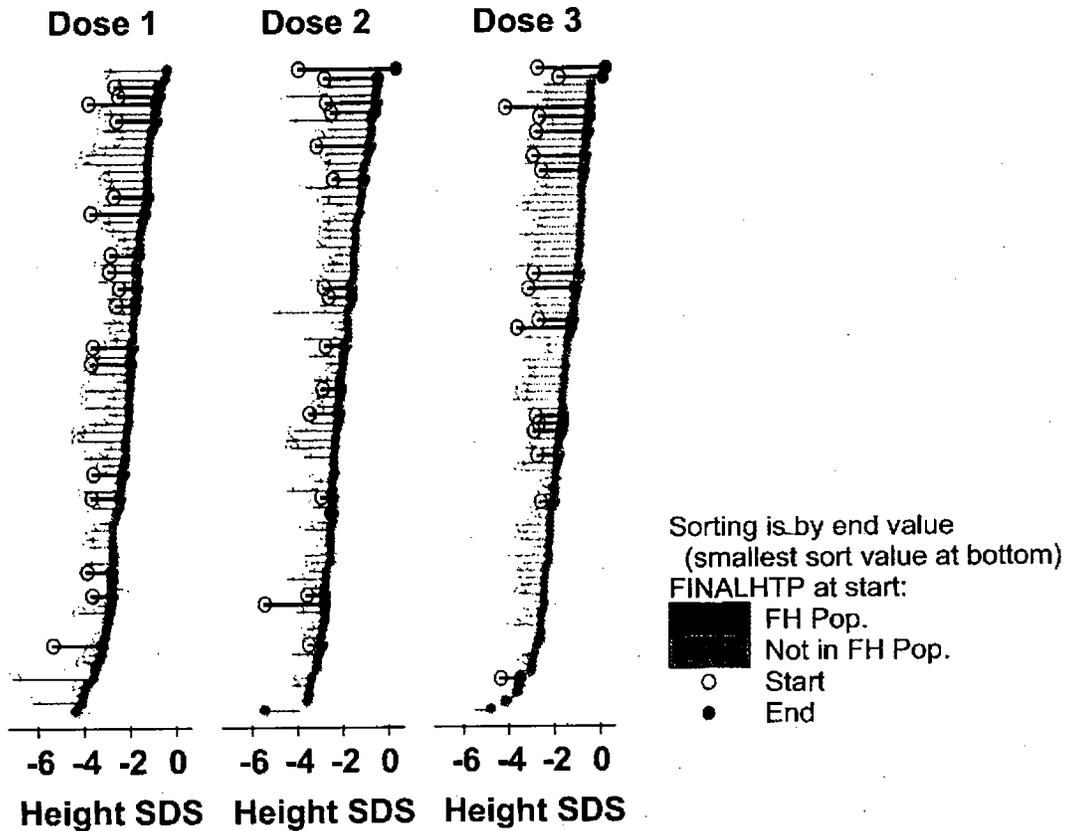


Efficacy Results

The primary efficacy variable was change in height velocity after two years of treatment with the primary comparison being between the low dose group and high dose group. In the low dose group height velocity increased by 3.3 cm/yr and in the high dose group by 4.0 cm/yr; the treatment difference (LSM=0.78), reported by the applicant, was statistically significant ($p=0.003$).

As mentioned, the focus in this review is on the final height data. Height SDS is the efficacy variable. Figure 16 shows for each patient the change in height SDS from baseline to last measured height. The majority of the final height population had a final height greater than -2 at endpoint (70% in the low dose [0.24, Dose 1] and 94% in the high dose [0.37, Dose 3]). About half of the high dose patients in the final height population had an SDS greater than -1 at endpoint.

Figure 16. Height SDS at baseline and endpoint by patient and dose for the final height population (black lines) and for patients not in the final height population (blue or gray in print).



Analyses were performed by this reviewer using the same models used in GDCH: ANCOVA of final height with baseline predicted height as the covariates and ANOVA for analyses of the differences of final height from baseline predicted height and target height. The results of these analyses are summarized in Table 15. P-values for comparisons of the low dose to the high dose show no statistically significant differences between the two groups though a dose-response relationship is evident.

Overall, the estimates from E001 show larger improvements in final height than were seen for humatrope in GDCH; even when comparing the comparable doses. This could be due to the administration of drug more frequently since previous studies have shown a benefit to 6x per week dosing over 3x per week dosing. Other factors, such as age at start of therapy or change in Tanner Stage, may have played a role as well and will be examined in a later version of this review.

Table 15. Study E001 Final height results for the Final Height Population (LS means and SE)

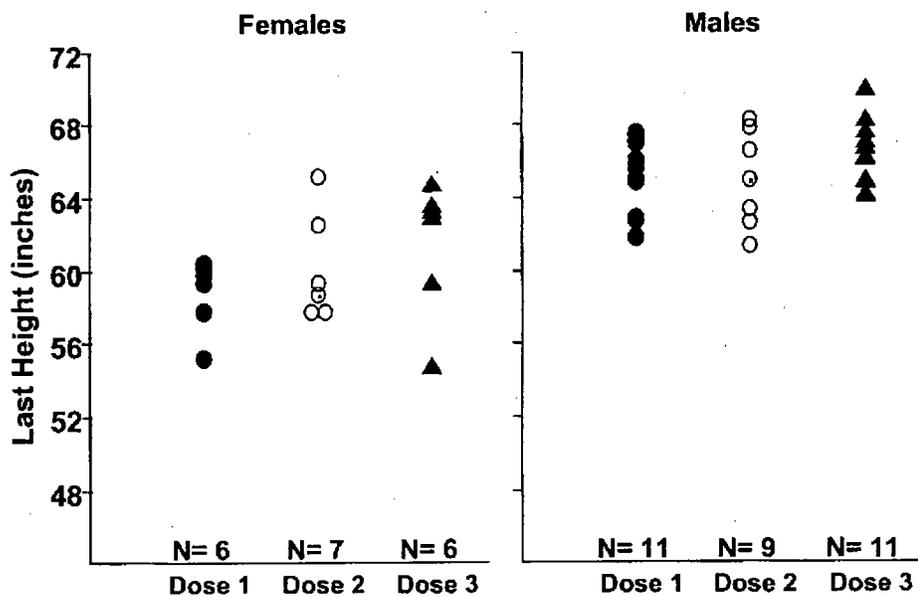
	HUM 0.24 (n=13)	HUM 0.24/0.37 (n=13)	HUM 0.37 (n=13)	p-value 0.24 vs. 0.37
Final Height SDS				
All	-1.65 (0.18)	-1.38 (0.18)	-1.19 (0.18)	0.09
Males	-1.58 (0.20)	-1.71 (0.22)	-1.09 (0.12)	0.10
Females	-1.85 (0.36)	-0.83 (0.29)	-1.40 (0.28)	0.33
Final Height (cm)				
All	162.5 (1.3)	163.6 (1.3)	164.3 (1.3)	0.32
Males	163.5 (1.4)	157.6 (1.4)	166.5 (1.6)	0.14
Females	159.5 (2.7)	165.0 (2.4)	160.9 (2.0)	0.67
FH minus Baseline PH (cm)				
All	5.4 (1.3)	6.7 (1.3)	7.2 (1.3)	0.31
Males	5.8 (1.4)	4.7 (1.5)	8.8 (1.5)	0.15
Females	3.9 (2.5)	9.8 (1.9)	4.7 (1.9)	0.81
FH minus Target Height (cm)	(n=17)	(n=16)	(n=17)	
All	-3.8 (1.8)	-5.3 (1.9)	-1.3 (1.8)	0.34
Males	-2.2 (2.3)	-6.8 (2.5)	-1.2 (2.3)	0.76
Females	-6.7 (3.1)	-3.4 (2.9)	-1.6 (3.1)	0.25

11 patients were missing baseline predicted height data and 1 patient was missing target height data; these patients are excluded from respective analyses.

Graphs of final height versus baseline height, baseline predicted height and target height are provided in Appendix 4. All patients in the final height population have a larger height SDS at endpoint than at baseline. The majority of patients show an improvement in height over their baseline predicted height but not over their target height.

A graph of final heights in inches (Figure 17) shows a slight shift in the distribution upwards with increasing dose. All males on the high dose had a final height greater than 5'4" at endpoint and most females on the high dose were taller than 5'.

Figure 17. Final height in inches for the final height population by gender and dose



Overall comments on Study E001

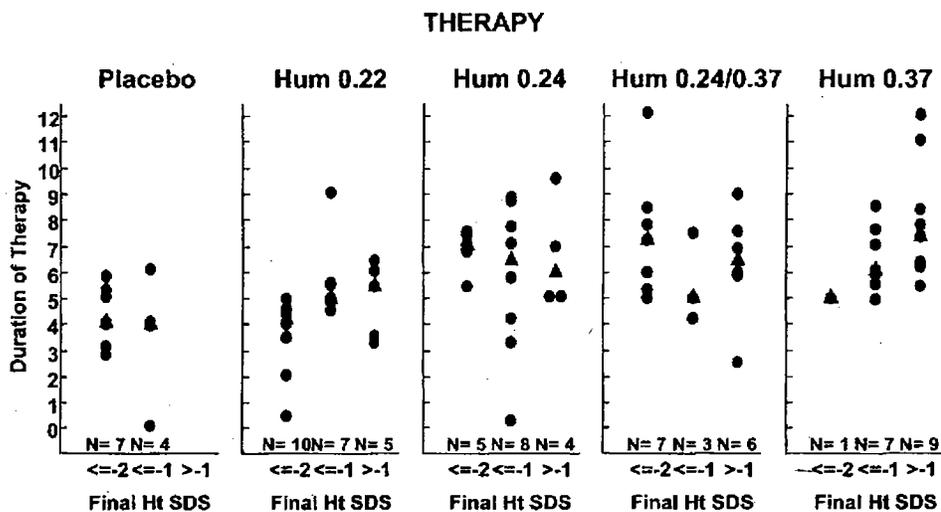
Pairwise comparisons of final height SDS (or other measures of final height) showed no statistically significant differences among the doses though the magnitude of the treatment response for the 0.37mg/kg/wk dose is greater than the effect seen for the 0.24 mg/kg/wk dose. Most patients showed an improvement in height SDS and in final height compared to baseline predicted height.

Summary and Conclusions

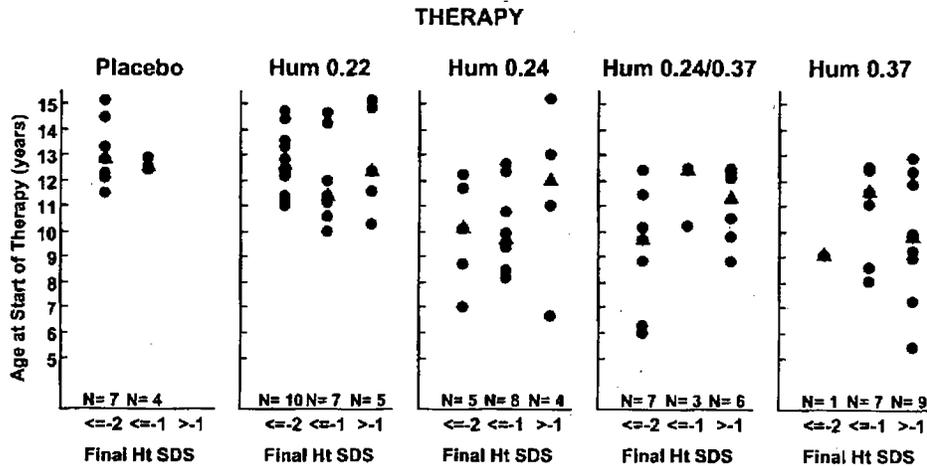
The applicant has presented the results of two randomized clinical trials to assess the benefit of humatrope for children who are not growth hormone deficient but are of short stature. One trial (GDCH) was designed to compare humatrope (0.22 mg/kg/wk with 3x per week dosing) to placebo and the other trial was a dose-response study of three doses of humatrope (0.24 mg/kg/wk, 0.24 mg/kg/wk for one year followed by 0.37 mg/kg/wk and 0.37 mg/kg/wk administered 6x per week). The endpoint of primary interest is final height SDS measured when the patient's height velocity slowed to 1.5 cm/yr or less in GDCH or to 2 cm/yr or less in E001.

A total of 33 patients (46% of the randomized patients) in GDCH and 50 patients (21% of the randomized patients) in E001 were analyzed for final height. To address the issue of dropout bias, additional analyses including patients without final height data were performed by both the applicant and the reviewer. In general, these analyses supported the primary analysis of height SDS for the final height population.

The duration of treatment varied between the two studies and is depicted in the figure below. Duration of therapy is plotted against final height SDS; there appears to be no clear relationship between time on therapy and height SDS achieved. Patients with the most favorable results (height SDS larger than -1) had durations of treatment ranging from about 3 to 12 years.



Likewise, age at initiation of treatment, as shown below, was not related to outcome. Patients with the most favorable results (height SDS larger than -1) initiated treatment at ages 6 to 15 years.



The effect of humatrope is best measured in Study GDCH where the gain in height due to humatrope treatment can be compared to the placebo effect; the emphasis in this review then has been on Study E001 provides additional descriptive data on two different doses of humatrope.

The results for Study GDCH showed a statistically significant treatment effect for humatrope compared to placebo for final height SDS (treatment effect of 0.51, $p=0.017$, Table 15). The applicant converted the SDS difference to cm coming up with an improvement in height of 3.7 cm (see page 22 for a further description of this computation). Analysis of final height in cm adjusting for baseline predicted height yields a treatment effect of 3.2 cm. The difference between these estimates is probably of no clinical significance.

Table 15. Final Height Results for Study GDCH

	Humatrope 0.22	Placebo	Treatment Effect 95% CI	P-value
FH ¹				
SDS	-1.81	-2.31	0.51 (0.10, 0.92)	0.017
cm	160.7	157.6	3.17 (0.26, 6.07)	0.03

¹ Means are least squares means from ANCOVA with baseline predicted height as a covariate.

The applicant reported an estimate of 5 cm gain for humatrope over placebo based on a repeated measures analysis. This analysis was a post-hoc analysis of the efficacy evaluable population. The 5 cm estimate is an overestimate of final height gain because six final height humatrope patients did not contribute age 18 data (see page 16 of this review for more details).

To describe the results of both GDCH and E001, this reviewer summarized the difference between final height and baseline predicted height and between final height and target height (Table 16). Patients reaching final height show an improvement in final height over baseline predicted height with larger differences seen with increasing dose. The benefit of 6 times per

week dosing in E001 over 3 times a week dosing in GDCH is evident. The highest dose of 0.37 mg/kg/week gives the largest response of about 3 inches with the confidence interval indicating that increases over predicted height as large as about 4 inches are possible. Note that the overlap of the confidence intervals across doses illustrates the lack of statistically significant differences observed for the high dose versus the low dose.

Very few patients reach their target height though clearly patients on the highest dose of humatrope get closer than the placebo patients or the low dose patients.

Table 16. LS Means adjusting for baseline PH for the Final Height Population

	GDCH		E001		
	Placebo	Humatrope 0.22	Humatrope 0.24	Humatrope 0.24/0.37	Humatrope 0.37
FH - Baseline PH SDS	-0.18	+0.33	+0.83	+1.10	+1.29
cm (95% CI)	-0.9 (-3.3, 1.5)	+2.3 (0.6, 3.9)	+5.4 (2.9, 8.0)	+6.5 (3.9, 9.1)	+7.3 (4.7, 9.8)
inches (95% CI)	-0.4 (-1.3, 0.6)	+0.9 (0.1, 2.4)	+2.1 (1.1, 3.2)	+2.6 (1.6, 3.6)	+2.9 (1.8, 3.9)
FH - Target Height SDS	-0.96	-0.68	-0.46	-0.64	-0.26
cm (95% CI for cm)	-7.0 (11.3, -2.6)	-4.8 (-7.6, -2.0)	-3.3 (-7.7, 1.0)	-4.8 (-9.2, -0.4)	-1.9 (-6.3, 2.4)

Figures 18 and 19 show the individual data for the variables summarized in Table 16. Overlap across the groups is clearly evident though medians (black filled circles) suggest a dose response relationship of increasing response with increasing dose.

Figure 18. Final height minus baseline predicted height for the final height populations of Studies GDCH and E001

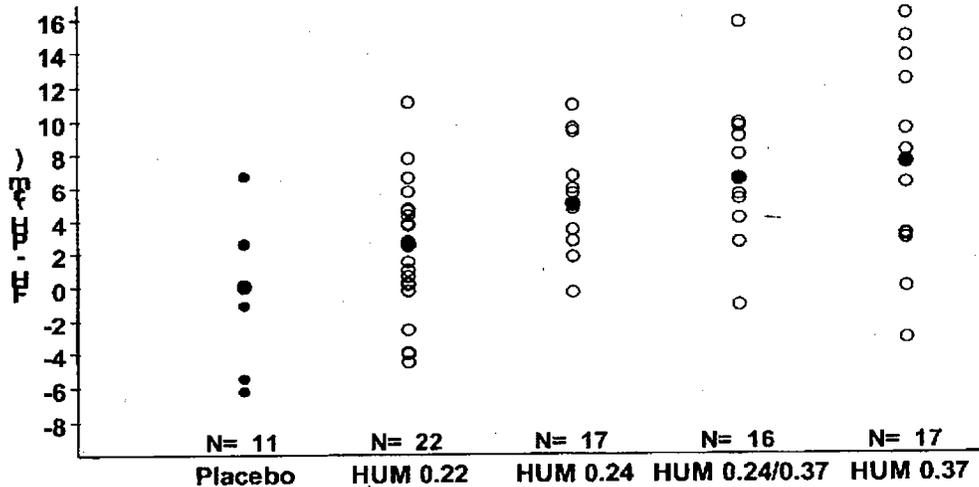
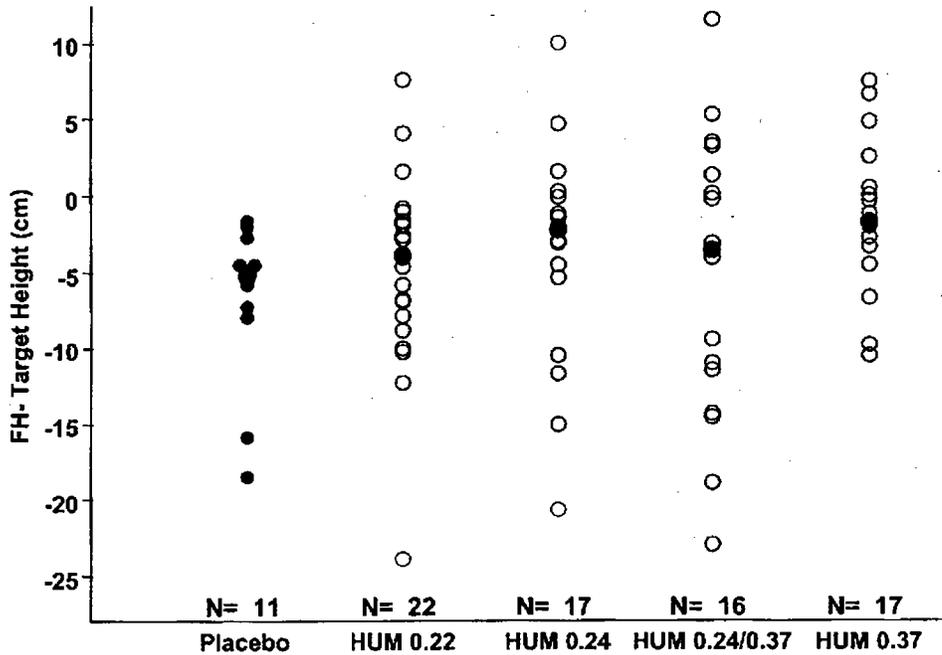


Figure 19. Final height minus target height for the final height populations of Studies GDCH and E001



This reviewer has the following overall comments:

- the administration of humatrope in patients not growth hormone deficient but of small stature results in statistically significant gains in height compared to placebo (GDCH)
- mean gains of about 3-4 cm (1 to 1 ½ inches) in height over placebo were observed
- no statistically significant differences between 0.24 mg/kg/wk and 0.37 mg/kg/wk were seen comparing final height SDS, although, the magnitude of responses suggests a trend of increasing response with increasing dose
- alternate analyses of different patient populations and different efficacy variables supported the results of the analyses of the final height data from the GDCH final height population (about 40% of the randomized patients)
- the small sample sizes preclude making definitive statements about subgroup analyses and about the characteristics of patients most likely to benefit from treatment

This reviewer concludes that Study GDCH showed a statistically significant treatment effect on final height for humatrope compared to placebo.

This reviewer recommends that the benefit of long-term versus short-term treatment be studied further. This recommendation is based on the following:

1. There is insufficient data in the submitted studies to ascertain whether long-term treatment is warranted given that there were several patients with beneficial effects with less than 4 years

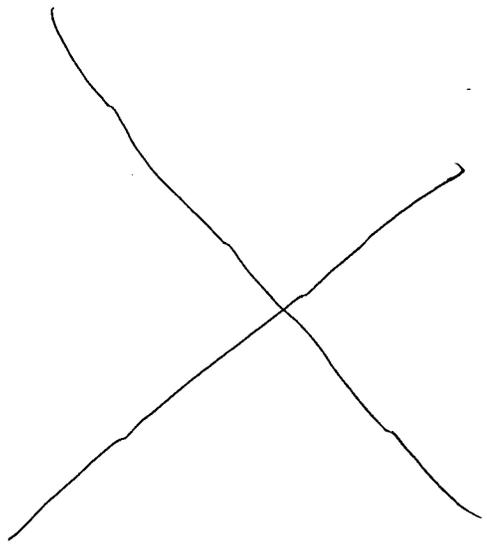
- of therapy.
2. The primary reasons patients discontinued treatment was due to discomfort or due to time constraints (e.g. too busy); compliance may be improved with short-term treatment.
 3. It is unethical to cause injection discomfort long-term without clear evidence of added benefit.
 4. The most significant change in growth is seen during the first two years of treatment (see graphs under Labeling Comments and significant difference between high and low doses in height velocity during first two years of treatment in Study E001).

Labeling Comments:

This reviewer recommends that the following two tables be included in the label. The first table may be substituted for the applicant's Table 4 and the second table should be labeled as Table 5.

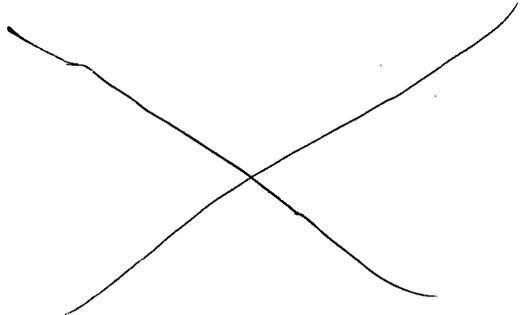
	Humatrope (n=22)	Placebo (n=11)	Treatment Effect Mean (95% CI)	p-value
	Mean (SD)	Mean (SD)		
Baseline height SDS	-2.7 (0.6)	-2.75 (0.6)		0.77
BPH SDS	-2.1	-2.3 (0.8)		0.53
Final height SDS	-1.8 (0.8)			0.017
FH SDS – baseline height SDS	0.9 (0.7)	0.4 (0.2)		
FH SDS - BPH SDS	0.3 (0.6)	-0.1 (0.6)		

	Placebo-controlled Trial 3x per week dosing		Dose Response Trial 6x per week dosing		
	Placebo (n=10)	Humatrope (n=22)	Humatrope (n=13)	Humatrope (n=13)	Humatrope (n=13)
FH – Baseline PH Mean cm (95% CI)	X	X	+5.4		9.8
Mean inches (95% CI)	X	X	+2.1 (1.1, 3.1)	+2.6 (1.6, 3.6)	(1.8, 3.9)



This reviewer was not able to replicate the applicant's curves and found no statistical difference at Year 5 (figure below)

~~_____~~
~~_____~~ The applicant's figure clearly exaggerates the results at Year 5.



~~_____~~

The applicant proposes under Indications that "humatrope is indicated for the long-term treatment

SIGNATURES/DISTRIBUTION LIST

Primary Statistical Reviewer:
Joy Mele, M.S.
Mathematical Statistician

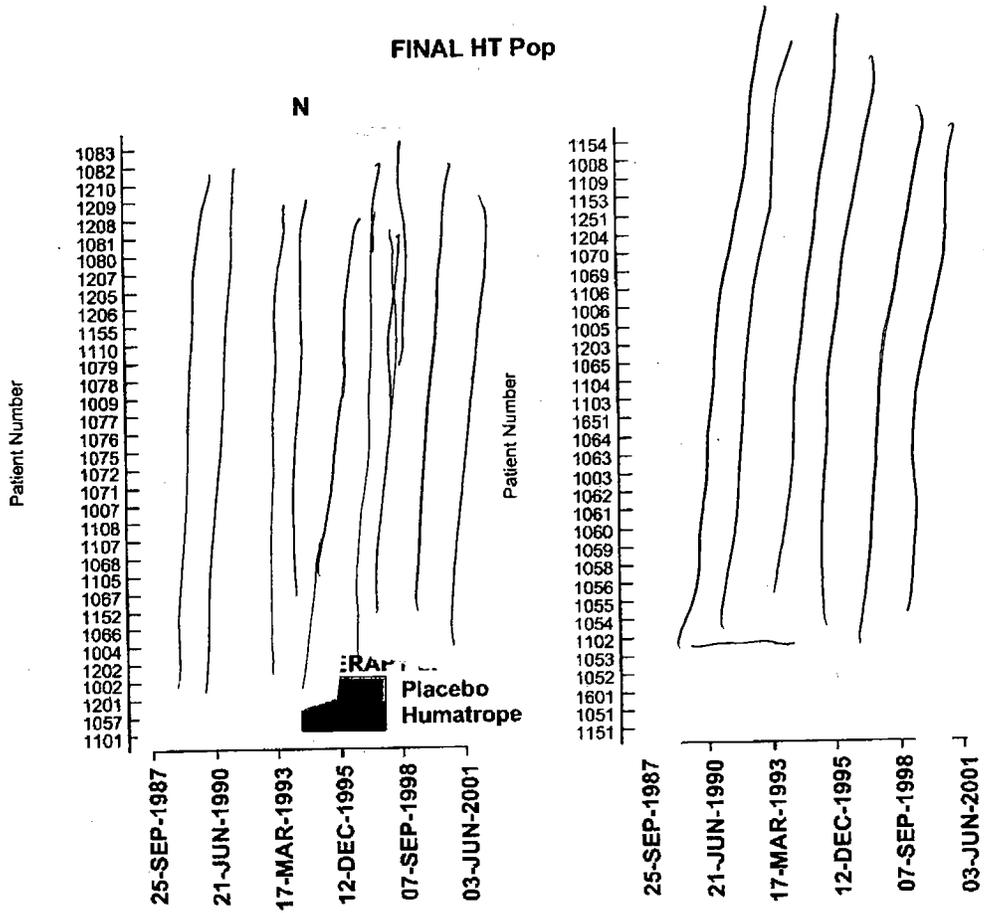
Date: July 1, 2003

Concurring Reviewer(s):
Statistical Team Leader: Todd Sahlroot, Ph.D.

cc:
HFD-510/Project Manager M. Johnson
HFD-510/Medical Officer D. Roman
HFD-510/Medical Team Leader D. Orloff
HFD-715/Primary Statistical Reviewer J. Mele
HFD-715/Statistical Team Leader T. Sahlroot
HFD-715/Biometrics Division Director E. Nevius
HFD-715/Office of Biostatistics C. Anello

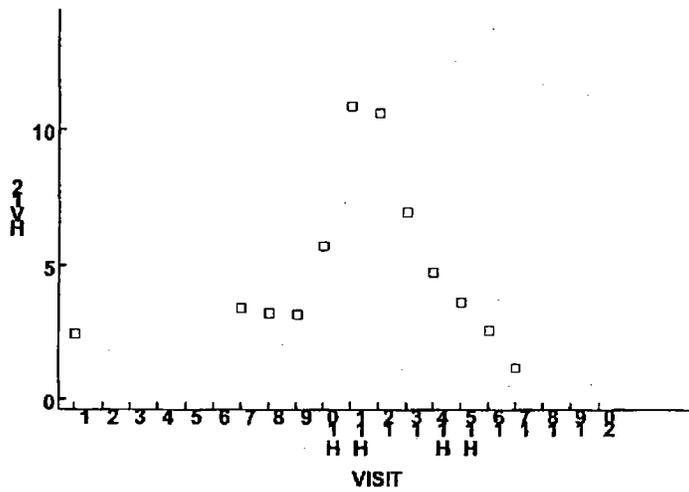
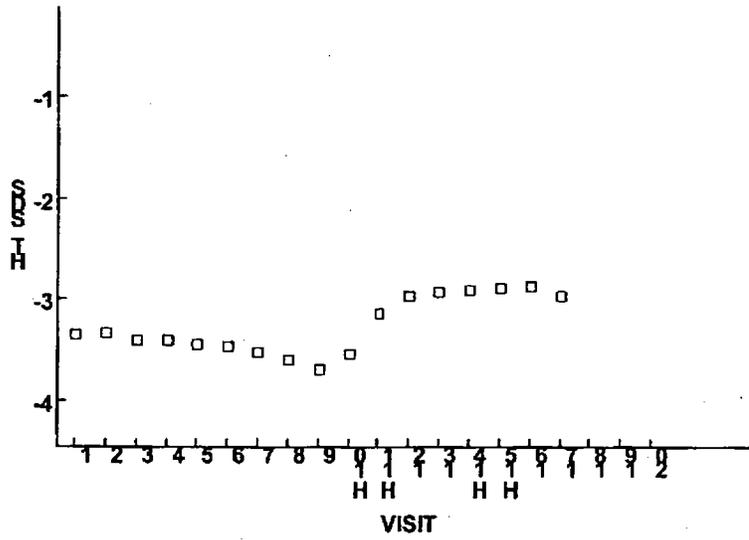
Appendices

Appendix 1. Start and stop dates in GHCD

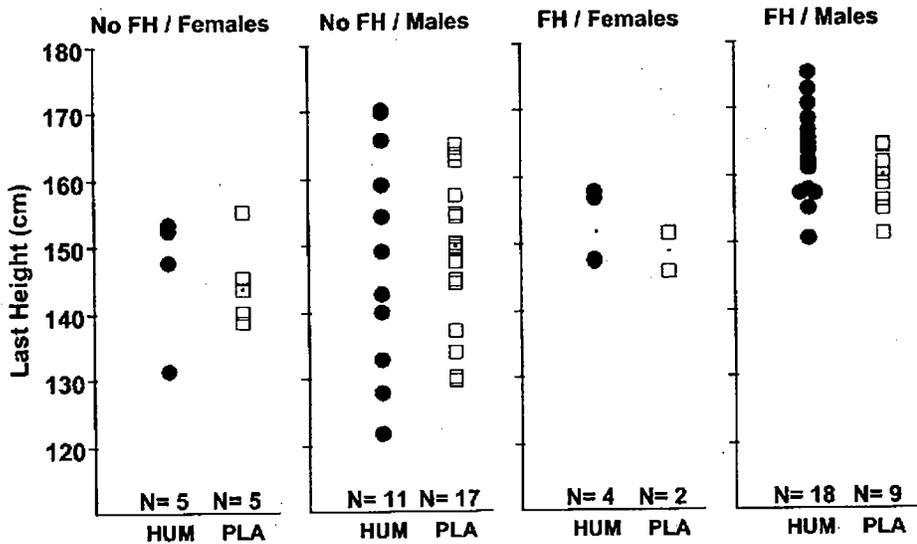


Appendix 2. Patient 1601

Patient started placebo therapy at age 12. Humatrope therapy was mistakenly given from Visits 10 to 11 (age 14.5 to 15) and Visits 14 to 15 (age 16.4 to 16.9).

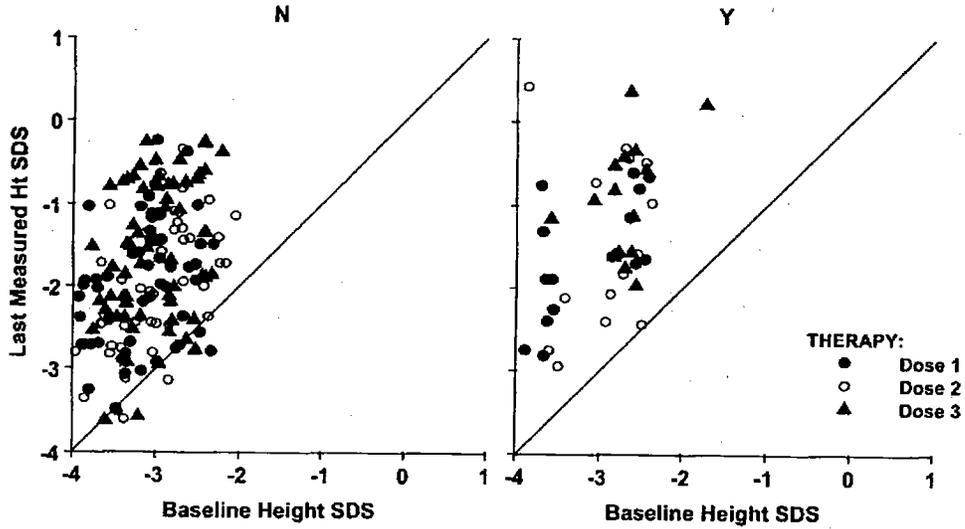


Appendix 3. GDCH Last height on study in cm

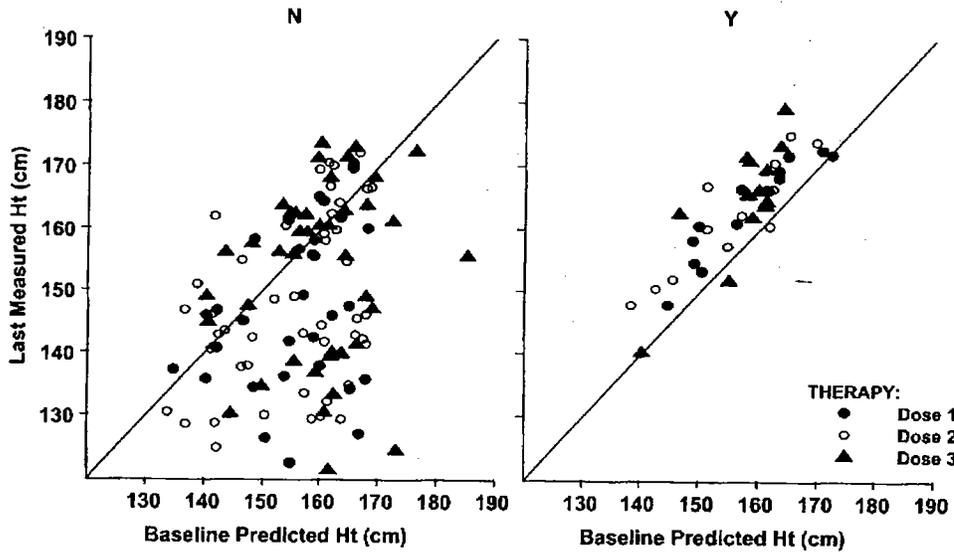


Appendix 4. E001 Plots of FH versus baseline height, baseline PH and target height

Final Height SDS (or last measured height) versus Baseline Height SDS
Final Ht Population



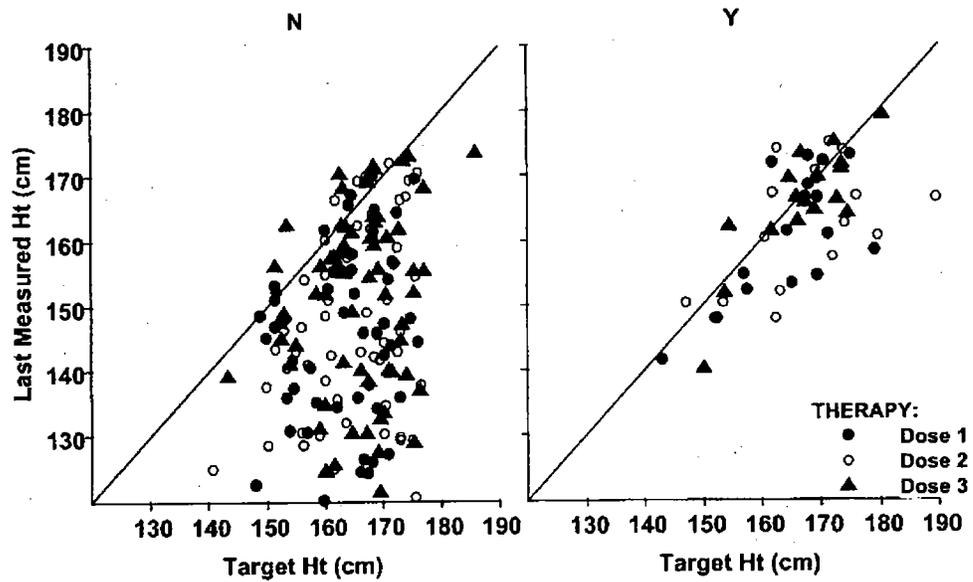
Final Height (or last measured height) versus Baseline Predicted Height
Final Ht Population



Appendix 4 continued

Final Height (or last measured height) versus Target Height

Final Ht Population



**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Joy Mele
7/2/03 10:07:08 AM
BIOMETRICS

Todd Sahlroot
7/2/03 10:10:33 AM
BIOMETRICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 19-640/S-033

ADMINISTRATIVE DOCUMENTS
AND
CORRESPONDENCE

ITEM 13/14: PATENT INFORMATION**NDA 19-640****Re: HUMATROPE NDA SUPPLEMENT FOR TREATMENT OF
SHORT STATURE IN NON-GROWTH HORMONE DEFICIENT
PEDIATRIC PATIENTS****ITEM 13: PATENT INFORMATION**

The undersigned declares that the following patent covers the formulation, composition, and/or method of use of Humatrope, as indicated. This product is currently approved under section 505 of the Federal Food, Drug, and Cosmetic Act and the subject of this supplemental application for which approval is being sought.

Patent Number	Patent Expiry Date	Type of Patent (Drug Substance, Drug Product, or Method of Use)	Patent Owner's Name
5,612,315	March 17, 2014	Formulation	Eli Lilly and Company

ITEM 14: PATENT CERTIFICATION

We certify that there is no patent covering the use of somatropin.

Eli Lilly and Company (Lilly) requests a three year period of exclusivity for the use of somatropin in the treatment of pediatric patients with non-growth hormone deficient short stature.

This NDA contains reports of new clinical investigations (other than bioavailability studies) conducted or sponsored by Lilly that are essential to obtain its approval. Upon approval of this NDA, Lilly is entitled to a three (3) year period of marketing exclusivity for this new indication as provided by Section 505(c)(3)(D)(iii) and 505(j)(4)(D)(iii) of the Federal Food, Drug, and Cosmetic Act, as amended, [21 U.S.C. 355(c)(3)(D)(iii) and 21 U.S.C. 355(j)(4)(D)(iii)].

Clinical trials conducted for this NDA are essential to obtain approval of this NDA and are identified as follows:

B9R-EW-E001 **The Efficacy and Safety of Biosynthetic Authentic Human Growth Hormone in Short Pre-pubertal Children with Normal Growth Hormone Response to Standard Provocation Tests**

B9R-MC-GDCH Humatrope in Non-Growth Hormone Deficient Children with Short Stature

Lilly certifies (in support of its request) that to the best of Lilly's knowledge:

1. the above clinical investigations did not form part of the basis of a finding of substantial evidence of effectiveness for a previously approved new drug application,
2. the above clinical investigations were each sponsored or conducted by Lilly,
3. Lilly, through its employees and others, electronically searched the Scientific literature as of May 10, 2002 via Medicine, and discovered fifty-six published studies of publicly available reports of clinical investigations relevant to the use of somatropin in the treatment of pediatric patients with non-growth hormone deficient short stature. These published reports are attached hereto and identified as:

Azzarito C, Boiardi L, Zini M, et al. Short and long-term effects of growth hormone treatment on lipid, lipoprotein, and apolipoprotein levels in short normal children. 1994. *Horm Metab Res* 26:432-435.

Bernasconi S, Street ME, Volta C, Mazzardo G, and the Italian Multicentre Study Group. Final height in non-growth hormone deficient children treated with growth hormone. 1997. *Clin Endocrinol (Oxf)* 47:261-266.

Bierich JR, Nolte K, Drews K, Brugmann G. Constitutional delay of growth and adolescence: results of short-term and long-term treatment with GH. 1992. *Acta Endocrinol (Copenh)* 127:392-396.

Buchlits JG, Irizarry L, Crotzer BC, Shine BJ, Allen L, MacGillivray MH. Comparison of final heights of growth hormone-treated vs untreated children with idiopathic growth failure. 1998. *J Clin Endocrinol Metab* 83:1075-1079.

Chalew SA, Phillip M, Kowarski AA. Effect of six months of growth hormone therapy, followed by treatment withdrawal in short children with normal quantitative indexes of growth hormone secretion. 1996. *J Pediatr* 129:456-458.

Chanoine JP, Vanderschueren M, Maes M, Thiry G, Craen M, Van-Vliet G. Growth hormone (GH) treatment in short normal children: absence of influence of time of injection and resistance to GH autocrine feedback. 1991. *J Clin Endocrinol Metab* 73:1269-1275.

Colle M, Sagnard L, Ducret JP, Auzeur J. Growth response to growth-hormone administration during the decelerating phase of the pubertal growth spurt in short normal children. 1990. *Horm Res* 34:204-208.

Darendeliler F, Hindmarsh PC, Brook CG. Dose-response curves for treatment with biosynthetic human growth hormone. 1990. *J Endocrinol* 125:311-316.

Daubeney PE, McCaughey ES, Chase C, et al. Cardiac effects of growth hormone in short normal children: results after four years of treatment. 1995. *Arch Dis Child*. 72:337-339.

Downie AB, Mulligan J, McCaughey ES, Stratford RJ, Betts PR, Voss LD. Psychological response to growth hormone treatment in short normal children. 1996. *Arch Dis Child*. 75:32-35.

Genentech Collaborative Study Group. Idiopathic short stature: results of a one-year controlled study of human growth hormone treatment. 1989. *J Pediatr* 115:713-719.

Genentech Collaborative Study Group. Response to growth hormone in children with idiopathic short stature. 1990. *Acta Paediatr Scand Suppl* 366:24-26.

Hernandez M, Nieto JA, Sobradillo B, Pombo M, Ferrandez A, Rejas J. Multicenter clinical trial to evaluate the therapeutic use of recombinant growth hormone from mammalian cells in the treatment of growth hormone neurosecretory dysfunction. 1991. *Horm Res* 35:13-18.

Hershkovitz E, Belotserkovsky O, Limony Y, Leiberman E, Shany S, Phillip M. Increase of serum lipoprotein (a) levels during growth hormone therapy in normal short children. 1998. *Eur J Pediatr* 157:4-7.

Hindmarsh PC, Brook CG. Final height of short normal children treated with growth hormone. 1996. *Lancet* 348:13-16.

Hindmarsh PC, Brook CGD. Effect of growth hormone on short normal children. *Br Med J (Clin Res Ed)* 1987 295:573-577.

Hindmarsh PC, Pringle PJ, Di Silvio L, Brook CG. Effects of 3 years of growth hormone therapy in short normal children. 1990. *Acta Paediatr Scand Suppl* 366:6-12.

Hindmarsh P, Brook CG. Final height is not improved in short normal children treated with growth hormone. Paper presented at: The Endocrine Society Annual Meeting; June 1995; Washington, DC. Abstract OR30-1.

Hintz RL. Growth hormone treatment of idiopathic short stature. 1996. *Horm Res* 46:208-214.

Hintz RL, Attie KM, Johanson A, Baptista J. Near final height in GH-treated short children without classical GH deficiency [abstract]. 1995. *Pediatr Res* 37:91A.

Hintz RL, Attie KM, Johanson A, et al. Use of GH for promotion of growth in ISS children: final height results of the US study [abstract]. 1997.

Hintz RL, Attie KM, Baptista J, et al, for the Genentech Collaborative Group. Effect of growth hormone treatment on adult height of children with idiopathic short stature. 1999. *N Engl J Med* 340:502-507.

Hopwood NJ, Hintz RL, Gertner JM, et al. Growth response of children with non-growth-hormone deficiency and marked short stature during three years of growth hormone therapy. 1993. *J Pediatr* 123:215-222.

Ito RK, Vig KW, Garn SM, et al. The influence of growth hormone (rhGH) therapy on tooth formation in idiopathic short statured children. 1993. *Am J Orthod Dentofacial Orthop* 103:358-364.

Job JC, Toubiane JE, Landier F. Growth of short normal children in puberty treated for 3 years with growth hormone alone or in association with gonadotropin-releasing hormone agonist. 1994. *Horm Res*. 41:177-184.

Lanes R. Effects of two years of growth hormone treatment in short, slowly growing non-growth hormone deficient children. 1995. *J Pediatr Endocrinol Metab*. 8:167-171.

Loche S, Cambiaso P, Setzu S, et al. Final height after growth hormone therapy in non-growth-hormone-deficient children with short stature. 1994. *J Pediatr* 125:196-200.

Loche S, Pintor C, Cambiaso P, et al. The effect of short-term growth hormone or low-dose oxandrolone treatment in boys with constitutional growth delay. 1991. *J Endocrinol Invest* 14:747-750.

Lopez-Siguero JP, Martinez-Aedo MJ, Moreno-Molina JA. Final height after growth hormone therapy in children with idiopathic short stature and a subnormal growth rate [abstract]. 1996. *Acta Paediatr Suppl* 417:121.

Lopez-Siguero JP, Garcia-Garcia E, Carralero I, Martinez-Aedo MJ. Adult height in children with idiopathic short stature treated with growth hormone. 2000. *J Pediatr Endocrinol Metab*. 13: 1595-1602.

Low LC, Kwan E, Karlberg J. A partial transient effect of short-term growth hormone (GH) treatment in short non-GH deficient prepubertal children. 1995. *J Pediatr Endocrinol Metab* 8:173-179.

Low LC, Lau YL. Serum osteocalcin in normal and short Chinese children. 1992. *J Paediatr Child Health* 28:432-435.

Lin TH, Kirkland RT, Sherman MD, Kirkland JL. Growth hormone testing in short children and their response to growth hormone therapy. 1989. *J Pediatr* 115:57-63.

McCaughy ES, Mulligan J, Voss LD, Betts PR. Randomised trial of growth hormone in short normal girls. 1998. *Lancet* 351:940-944.

McCaughy ES, Mulligan J, Voss LD, Betts PR. Growth and metabolic consequences of growth hormone treatment in prepubertal short normal children. 1994. *Arch Dis Child* 71:201-206.

Pasquino AM, Pucarelli I, Roggini MSM. Adult height in short normal girls treated with gonadotropin-releasing hormone analogs and growth hormone. 2000. *J Clin Endocrinol Metab*. 85:619-622.

Rekers-Mombarg LT, Kamp GA, Massa GG, Wit JM. Influence of growth hormone treatment on pubertal timing and pubertal growth in children with idiopathic short stature. 1999. Dutch Growth Hormone Working Group. *J Pediatr Endocrinol Metab*. 12(5 Suppl 2): 611-622.

Rochiccioli P, Dechaux E, Tauber MT, Pienkowski C, Tiberge M. Growth hormone treatment in patients with neurosecretory dysfunction. *Horm Res*. 1990. 33(suppl 4):97-101.

Schmitt K, Blumel P, Waldhor T, Lassi M, Tulzer G, Frisch H. Short- and long-term (final height) data in children with normal variant short stature treated with growth hormone. 1997. *Eur J Pediatr* 156:680-683.

Schwartz ID, Hu CS, Shulman DI, Root AW, Bercu BB. Linear growth response to exogenous growth hormone in children with short stature. 1990. *AJDC* 144:1092-1097.

Soliman AT, Abdal Khadir MM. Growth parameters and predictors of growth in short children with and without growth hormone (GH) deficiency treated with human GH: a randomized controlled study. 1996. *J Trop Pediatr*. 42:281-286.

Spagnoli A, Branca F, Spadoni GL, et al. Urinary pyridinium collagen cross-links predict growth performance in children with idiopathic short stature and with growth hormone (GH) deficiency treated with GH: skeletal metabolism during GH treatment. 1996. *J Clin Endocrinol Metab* 81:3589-3593.

Spagnoli A, Spadoni GL, Boscherini B. Preliminary validation of a prediction model for the short term growth response to growth hormone therapy in children with idiopathic short stature. 1996. *Acta Paediatr Suppl* 417:66-68.

Spagnoli A, Spadoni GL, Cianfarani S, Pasquino AM, Troiani S, Boscherini B. Prediction of the outcome of growth hormone therapy in children with idiopathic short stature: a multivariate discriminant analysis. 1995. *J Pediatr* 126:905-909.

Volta C, Bernasconi S, Tondi P, et al. Combined treatment with growth hormone and luteinizing hormone releasing hormone-analogue (LHRHa) of pubertal children with familial short stature. 1993. *J Endocrinol Invest* 16:763-767.

Volta C, Ghizzoni L, Muto G, Spaggiari R, Virdis R, Bernasconi S. Effectiveness of growth-promoting therapies: comparison among growth hormone, clonidine, and levodopa. 1991 *AJDC*. 145:168-171.

Walker JM, Bond SA, Voss LD, Betts PR, Wootton SA, Jackson AA. Treatment of short normal children with growth hormone: a cautionary tale? 1990. *Lancet* 336:1331-1334.

Wit JM, Rekers-Mombarg LT. Final height gain by GH therapy in children with idiopathic short stature is dose dependent. *J Clin Endocrinol Metab*. 2002; 87(2):604-611.

Wit JM, Fokker MH, de Muinck Keizer-Schrama SM, Oostdijk W, Gons MH, (Dutch Growth Hormone Working Group). Effects of two years of methionyl growth hormone therapy in two dosage regimens in prepubertal children with short stature, subnormal growth rate, and normal growth hormone response to secretagogues. 1989. *J Pediatr*. 115:720-725.

Wit JM, Rietveld DHF, Drop S, et al. A controlled trial of methionyl growth hormone therapy in prepubertal children with short stature, subnormal growth rate and normal growth hormone response to secretagogues. 1989. *Acta Paediatr Scand*. 78:426-435.

Zadik Z, Mira U, Landau H. Final height after growth hormone therapy in peripubertal boys with a subnormal integrated concentration of growth hormone. 1992. *Horm Res*. 37:150-155.

Zadik Z, Chalew S, Zung A, et al. Effect of long-term growth hormone therapy on bone age and pubertal maturation in boys with and without classic growth hormone deficiency. 1994. *J Pediatr* 125:189-195.

Zadik Z, Zung A. Final height after growth hormone therapy in short children: correlation with siblings' height. 1997. *Horm Res* 48:274-277.

Zadik Z, Segal N, Limony Y. Final height prediction models for pubertal boys. 1996. *Acta Paediatr Suppl* 417:53-56.

Zadik Z, Lieberman E, Altman Y, Chen M, Limoni Y, Landau H. Effect of timing of growth hormone administration on plasma growth-hormone-binding activity, insulin-like growth factor-I and growth in children with a subnormal spontaneous secretion of growth hormone. 1993. *Horm Res*. 39:188-191.

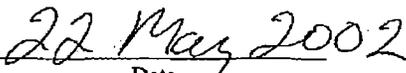
Zadik Z, Vaisman N, Lotan D, et al. Effect of growth hormone therapy on IGF-I, bone GLA-protein and bone mineral content in short children with and without chronic renal failure. 1992. *Horm Res.* 38:145-149.

4. the aforementioned articles, as published, are, in the opinion of Lilly, insufficient to support the approval of this application and therefore, in Lilly's opinion, there is not sufficient published or publicly available reports of clinical investigations, other than those conducted by or sponsored by Lilly, that would support the approval of this application.

The undersigned on behalf of Lilly certifies that to the best of his knowledge the information presented herein are true and accurate.



Gregory G. Enas, PhD
Director, US Regulatory Affairs



Date

EXCLUSIVITY SUMMARY for NDA # 19-640 SUPPL # 033
Trade Name Humatrope Generic Name Somatropin rDNA origin
for injection
Applicant Name Eli Lilly and Co. HFD- 510
Approval Date July 25, 2003

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

a) Is it an original NDA? YES/___/ NO /X_/

b) Is it an effectiveness supplement? YES /X/ NO /___/

If yes, what type(SE1, SE2, etc.)? SE1

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

YES /X_/ NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES /___/ NO /_X/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /X_/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES /___/ NO /X_/

If yes, NDA # _____ Drug Name

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/- NO /X_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES / X / NO / ___ /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #	<u>20-280</u>	<u>Genotropin</u>
NDA #	<u>21-148</u>	<u>Norditropin</u>
NDA #	<u>20-604</u>	<u>Serotim</u>
NDA #	<u>19-764</u>	<u>Saizen</u>
NDA #	<u>20-522</u>	<u>Nutropin</u>

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES / ___ / N/A / X /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /_X/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as

bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

- (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /_X_/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

- (b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /_X_/ NO /___/

- (1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /_X_/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /_X_/

If yes, explain:

(c) If the answers to (b) (1) and (b) (2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study Humatrope in Non-Growth Hormone Deficient Children with Short Stature (Study B9R-MC-GDCH)

Investigation #2, Study The Efficacy and Safety of Biosynthetic Authentic Human Growth Hormone in Short Prepubertal Children with Normal Growth Hormone Response to Standard Provocation Test (Study B9R-EW-E001)

Investigation #3, Study #

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /_X_/

Investigation #2 YES /___/ NO /_X_/

Investigation #3 YES /___/ NO /_ /

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study #
NDA # _____ Study #
NDA # _____ Study #

- (b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /_X/
Investigation #2 YES /___/ NO /_X_
Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study #
NDA # _____ Study #
NDA # _____ Study #

- (c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation # 1, Study # Study B9R-MC-GDCH
Investigation # 2, Study # Study B9R-EW-E001
Investigation # , Study #

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency,

or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

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

Investigation #1 !
!
IND # 28,574 YES / X / ! NO / ___ / Explain:

Investigation #2 !
!
IND # 28, 574 YES / X / ! NO / ___ / Explain:

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

Investigation #1 !
! YES / ___ / Explain _____ ! NO / ___ / Explain _____

Investigation #2 !
! YES / ___ / Explain _____ ! NO / ___ / Explain _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /_X_/

If yes, explain: _____

Monika Johnson /S/
Signature of Preparer

Date: July 25, 2003

Title: Project Manager

David G. Orloff, MD (see electronic signature/date)

Signature of Office or Division Director

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

David Orloff
7/31/03 05:38:14 PM

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA/BLA #: 19-640 Supplement Type (e.g. SE5): SE1 Supplement Number: 033

Stamp Date: September 26, 2003 Action Date: July 25, 2003

HFD -510 Trade and generic names/dosage form: Humatrope (somatropin [rDNA origin] for injection)

Applicant: Eli Lilly Therapeutic Class:

Indication(s) previously approved:

Pediatric

- indicated for the long-term treatment of patients who have growth failure due to an inadequate secretion of normal endogenous growth hormone.
- indicated for the treatment of short stature associated with Turner syndrome in patients whose epiphyses are not closed.

Adult

Humatrope is indicated for replacement of endogenous growth hormone in adults with growth hormone deficiency who meet either of the following two criteria:

- **Adult Onset:** Patients who have growth hormone deficiency either alone, or with multiple hormone deficiencies (hypopituitarism), as a result of pituitary disease, hypothalamic disease, surgery, radiation therapy, or trauma;
- Or
- **Childhood Onset:** Patients who were growth hormone-deficient during childhood who have growth hormone deficiency confirmed as an adult before replacement therapy with Humatrope is started.

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): One

Indication #1: Idiopathic Short Stature

Is there a full waiver for this indication (check one)?

- Yes: Please proceed to Section A.
- No: Please check all that apply: Partial Waiver Deferred Completed
- NOTE: More than one may apply
- Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____	kg _____	mo. _____	yr. _____	Tanner Stage _____
Max _____	kg _____	mo. _____	yr. _____	Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____	kg _____	mo. _____	yr. _____	Tanner Stage _____
Max _____	kg _____	mo. _____	yr. _____	Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____	kg <u>8.4</u>	mo. _____	yr. <u>5</u>	Tanner Stage <u>1</u>
Max _____	kg <u>48.6</u>	mo. _____	yr. <u>15</u>	Tanner Stage <u>3</u>

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

NDA ##-###

Page 3

This page was completed by:

{See appended electronic signature page}

Monika Johnson, PharmD
Regulatory Project Manager

cc: NDA

HFD-950/ Terrie Crescenzi
HFD-960/ Grace Carmouze
(revised 9-24-02)

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337**

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Is there a full waiver for this indication (check one)?

- Yes: Please proceed to Section A.
- No: Please check all that apply: ___ Partial Waiver ___ Deferred ___ Completed
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

cc: NDA
HFD-960/ Terrie Crescenzi
(revised 1-18-02)

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337**

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Monika Johnson
7/24/03 06:06:50 PM

CERTIFICATION

NDA Application No.: 19-640

Drug Name: Humatrope®

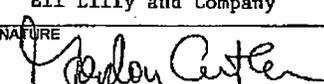
Pursuant to the provisions of 21 U.S.C. 335a(k)(1), Eli Lilly and Company, through Jeffrey T. Fayerman, Ph.D., hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section (a) or (b) [21 U.S.C. 335a(a) or (b)] of the Generic Drug Enforcement Act of 1992, in connection with the above referenced application.

ELI LILLY AND COMPANY

By: Jeffrey T. Fayerman
Jeffrey T. Fayerman, Ph.D.

Title: Sr. Regulatory Research Scientist
U.S. Regulatory Affairs

Date: May 17, 2002

DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service Food and Drug Administration	Form Approved: OMB No. 0910-0398 Expiration Date: 3/31/02						
CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS							
TO BE COMPLETED BY APPLICANT							
With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).							
Please mark the applicable checkbox.							
<input checked="" type="checkbox"/> (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).							
Clinical Investigators	<table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 50%;">See attached tables</td> <td style="width: 50%;"></td> </tr> <tr> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> </tr> </table>	See attached tables					
See attached tables							
<input type="checkbox"/> (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).							
<input type="checkbox"/> (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.							
NAME Gordon B. Cutler, M.D.	TITLE Medical Advisor						
FIRM/ORGANIZATION Eli Lilly and Company							
SIGNATURE 	DATE 12 JUNE 2002						
Paperwork Reduction Act Statement							
An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:							
Department of Health and Human Services Food and Drug Administration 5600 Fishers Lane, Room 14C-03 Rockville, MD 20857							

FORM FDA 3454 (3/99)

Circle 4 for Electronic Download Service. USDA # (10) 413-2132 EF

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		OFFICE OF DRUG SAFETY DIVISION OF DRUG RISK EVALUATION (DDRE)	
TO: Monika Johnson DMEDP, HFD-510		FROM: Allen Brinker, MD, MS, HFD-430	ODS PID# D030026
DATE OF CONSULT: Jan 13, 2002		REQUESTOR: Monika Johnson	
DATE COMPLETED: Jan 15, 2002			
DRUG (Gen): somatropin		NDA # 19-640	SPONSOR: Eli Lilly & Co
DRUG NAME (Trade): "Humatrope"		INDICATION: Humatrope for non-growth hormone deficient short stature (NGHDSS)	
ISSUE / EVENT: Review of a proposed risk management plan for Humatrope			
SUMMARY OF CONTENT: A protocol (dated Sept 9, 2002) from Eli Lilly & Co and entitled "Risk Management program for Humatrope: treatment of patients with non-growth hormone deficient short stature" was reviewed. This risk management program (RMP) is "designed to limit use of Humatrope for NGHDSS to the appropriate patient population through restrictive labeling, limited distribution and marketing, educational programs for physicians, and educational materials for physicians to provide for patients and their parents." The primary tool for evaluation of appropriate use will be through surveillance of patients voluntarily entered into the "GeNeSIS" database of Humatrope recipients. [Humatrope is currently available only through selected outlets. Thus, there will be no changes in this network described as a "limited distribution" system.]			
COMMENTS: <i>As no formal adverse event is identified as a risk to be managed, this program was reviewed from the standpoint of general safe use. This submission does not contain any of the aforementioned educational materials. These materials should be made available to ODS DSRCs for review. The voluntary nature of the GeNeSIS user registry makes it a poor tool for assessment of compliance with labeling as clinicians can simply elect not to enter inappropriate patients into it. The RMP does include a stated commitment (under 3.3.2, page 7) to refrain from direct-to-consumer communication / advertisements.</i>			
RECOMMENDATION: The RMP under review is reasonable from the standpoint of general safe use as per DDRE. Given the potential for off-label use of somatropin in children outside the labeled criteria for treatment, we strongly support a pre-approval commitment for no direct-to-consumer advertising for Humatrope. The sponsor should provide a further description of the protocol for analysis of the GeNeSIS dataset, including a method to estimate participation in order to estimate its generalizability to the population of Humatrope users.			
J. BEITZ SIGNATURE / DATE:		A. BRINKER SIGNATURE / DATE:	

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Allen Brinker
2/14/03 01:20:44 PM
MEDICAL OFFICER

Julie Beitz
2/21/03 08:07:23 AM
DIRECTOR

Risk Management Program

for

Humatrope

**Treatment of Patients with
Non-Growth Hormone Deficient Short Stature**

Approved by Lilly: 9 September 2002

Confidential Information

**Exempt from Public Disclosure under
Exemption 4 of the Freedom of
Information Act**

This document contains trade secrets, or commercial or financial information, privileged or confidential, delivered in confidence and reliance that such information will not be made available to the public without express written consent of Eli Lilly and Company. The intended use of this document is for registration purposes only. The audience for this document should be restricted to Regulatory Agencies reviewing Lilly products or to internal uses within Eli Lilly and Company.

15 Page(s) Withheld

X § 552(b)(4) Trade Secret / Confidential

 § 552(b)(4) Draft Labeling

 § 552(b)(5) Deliberative Process

4 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

X _____ § 552(b)(5) Deliberative Process

17 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

X § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 19-640

8.31.01

Eli Lilly & Co.
Attention: Gregory Enas, Ph.D.
Director, U.S. Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Enas:

Please refer to the meeting between representatives of your firm and FDA on July 31, 2001. The purpose of the meeting was to discuss the acceptability of the planned supplemental NDA submission for Non Growth Hormone Deficient Short Stature (NGHDSS).

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at 301-827-6423.

Sincerely yours,

{See appended electronic signature page}

Crystal King, P.D., M.G.A.
Regulatory Project Manager
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

Meeting Record

NDA 19-640 Humatrope (somatropin [rDNA origin] for injection)
Meeting Date: July 31, 2001
Time: 2:00 pm
Location: Parklawn Conference Room "C"
Indication: Non Growth Hormone Deficiency Short Stature (NGHDSS)
Sponsor: Eli Lilly & Company
Type of Meeting: pre-sNDA
Sponsor Contact: Jeffrey Fayerman @ 317-276-4691
Regulatory Project Manager: Crystal King @ 301-827-6423
FDA Participants: David Orloff, M.D., Division Director
Saul Malozowski, M.D., Medical Team Leader
Robert Perlstein, M.D., Medical Reviewer
Todd Sahlroot, Ph.D., Biometrics Team Leader
Joy Mele, M.S., Biometrics Reviewer
Cynthia Liu, M.S., Biometrics Reviewer
Enid Galliers, Chief, Project Management Staff
Crystal King, P.D., M.G.A., Regulatory Project Manager
Sponsor Participants: Charmian Quigley, M.D., Clinical Research Physician
Gordon Cutler, M.D., Medical Advisor
John Chipman, M.D., Medical Advisor
Jeff Fayerman, Ph.D., Senior Regulatory Research Scientist
Paul Gesellchen, Ph.D., Advisor, United States Regulatory Affairs
Brenda Crowe, Ph.D., Senior Statistician
Keiko Ebihara, Coordinator, Regulatory (Endocrine), Lilly Research Laboratories, Japan

Meeting Objective: To discuss the acceptability of the planned submission for review, dosing frequency, dose range, and structure of the supplemental NDA submission for Non Growth Hormone Deficient Short Stature (NGHDSS).

Background: Lilly submitted a pre-meeting package on June 25, 2001, and corrections to several items on July 20, 2001.

Following introductions, FDA presented responses to the questions presented by Lilly in overhead format. Additional significant points are summarized in *italics*.

AGENDA ITEM 1: Does the Agency believe that Lilly's planned submission will be acceptable for review?

Agency response:

- It appears to be acceptable. You should make every effort to provide as much raw safety and efficacy data as possible with regard to the supportive peer-reviewed literature contained in the sNDA submission.

Lilly presented a summary slide (Slide 1) of the literature studies. Lilly anticipates being able to access the E001 study data and will investigate the accessibility of raw data for other studies.

Slide 1

Other Lilly Studies

Study	Reference	N	Freq (inj/w)	Dose (mg/kg/w)	Dur'n	Ht Vel	Fin Ht	Safety
E001	Rekers-	4	6	0.22	5.6 y	Yes	Yes	Yes
	Mombarg et al. 1998	4		0.22 → 0.33 0.33				
	Witt et al. submitted	10 8 12	6	0.22 0.22 → 0.33 0.33	~6 y	No	Yes	Yes
GDBQ	Takano et al. 1990	39	7	0.21	1 y	Yes	No	Yes
GDCC	Dempsher et al. 1990	34	3	0.23	1 y	Yes	No	Yes
GDCP	Rosenbaum et al. 1992	10	3	0.3	1 y	No	No	Yes

- The overall Table of Contents for the submission should be comprehensive, well organized, easy to read, and user-friendly. It should not be just a list, but should be an expanded outline. Each section of the submission should have a separate, stand-alone Table of Contents for that section so that it is self-contained. An acceptable Table of Contents is required for filing.

Lilly will proffer a proposed Table of Contents for the Division's comments prior to the sNDA submission. Anticipated sNDA submission will be sometime in the calendar year 2002.

AGENDA ITEM 2: Lilly believes that the current dose frequency standard, which is daily dosing, should be available. Does the Agency agree with the proposal for a label that recommends the options of dosing from 3 to 7 times per week?

Agency response:

- This is a review issue. The inclusion of raw data regarding the submitted peer-reviewed literature (see Question 1) may help to support this dosing proposal for the label.

During the E001 study, GH was administered more frequently (e.g., six times per week). Forty-two patients were followed to final height; height velocity data was obtained in 12 of these patients.

Lilly will present outcome data (from the E001 study and other supportive studies, as well as from the pivotal study) providing a rationale for utilizing different frequencies of GH dosing (e.g., six to seven times versus three times per week) in the NGHDSS patient population.

In that the administration of GH three times per week is not the current standard of care, it is not the Division's intention to unreasonably restrict physicians to a three times weekly dosing regimen in NGHDSS patients.

AGENDA ITEM 3: Lilly believes that a dose similar to the current standard of care for other non-growth hormone deficient indications, such as Turner syndrome, should be available. Does the Agency agree with the proposal for a label that recommends divided doses up to 0.37 / ng/kg/wk. _____ .?

Agency response:

- See response to Question 2.

During the E001 study, GH 0.33 mg/kg/week was administered to 28 out of 42 patients. All 28 of these patients were followed to final height; height velocity data was obtained in eight of these patients.

Lilly will present outcome data (from the E001 study and other supportives studies, as well as from the pivotal study), providing a rationale for treating NGHDSS patients with different amounts of GH. The label will need to indicate the relative outcome benefits for the different dosing schedules.

AGENDA ITEM 4: Does the Agency agree with the proposed structure for the sNDA (one clinical study report plus supporting information from peer-reviewed literature, no ISS or ISE)?

Agency response:

- We agree that the comprehensive Application Summary will suffice and that an ISE and ISS need not be submitted. The Application Summary should also have a comprehensive Table of Contents, and each subsection should have a separate Table of Contents. Efficacy and safety issues should be discussed separately.

In that approval of this new indication for GH treatment would result in a substantial increase in the use of GH, a comprehensive GH safety review should be part of the application. More specifically, in this regard, the Agency and Lilly agreed that the safety of GH in the small NGHDSS database should be compared with the safety of GH in the very large safety database for other pediatric populations with short stature previously treated with GH (e.g., children with GHD).

- We refer you to the Guidances for Industry regarding electronic submissions.

AGENDA ITEM 5: Additional Agency Comments:

Clinical:

- If possible, subgroup analyses should be performed for children born small for gestational age (SGA) and non-SGA children.

Lilly indicated that only approximately 10% of the patients in the pivotal study were SGA children. FDA agreed that a descriptive table could be utilized to present data from the small SGA subgroup and that formal statistical analysis would not be necessary.

- If approved, the proposed indication will require substantial editorial changes.

FDA indicated that the proposed indication is very broad. The Division recommended that Lilly proposed appropriate guidelines for usage in the NGHDSS patient population (e.g., height SDS less than -2.5 and/or negative work-up for common causes of short stature and other inclusion/exclusion criteria from the pivotal study) in order to guide appropriate patient selection and avoid over-prescribing of GH to the vast number of "short" children in the United States. FDA emphasized that any boundaries/guidelines for usage proposed by Lilly should be clearly and comprehensively justified in the sNDA submission.

Statistical:

- Please furnish minutes for all DSMB meetings during trial GDCH. Include complete documentation of any interim analyses planned or performed.

The minutes should be submitted to the sNDA, not the IND.

- Please discuss the format of the SAS data sets with our statistical reviewer before submitting this information to the FDA electronic document room.

Lilly agreed.

- In addition to the pre-planned analyses, you should perform an analysis of all randomized patients who took drug and had at least one height measurement on study (e.g., an ITT analysis).

Lilly plans to analyze the linear growth (height velocity SDS, height SDS, etc.) of the 64 patients (of the 71 patients originally randomized) who completed six months on study (the "evaluable population"). The Division was satisfied with this proposal.

- Please provide the study report and protocol for B9R-MC-GDCH as a paper copy.

Lilly agreed.

Administrative:

- The proposed indication will need to be presented to the Endocrine and Metabolism Advisory Committee.

Regardless of the fact that Lilly has completed the randomized, placebo controlled pivotal study recommended by the Endocrine and Metabolism Advisory Committee in 1987, the decision as to whether or not to approve this new indication for GH treatment must be entirely based on the adequacy of the data supporting the safe and effective use of GH in the NGHDSS patient population.

In that (1) there are relatively few patients with final height data, (2) delineating and justifying guidelines for appropriate GH usage in the NGHDSS population will be difficult, and (3) approval could be construed by some as an endorsement by FDA to treat all short children without GHD, the Agency believes that the decision will be controversial—making it imperative that the decision making process be aired publically at a meeting of the Advisory Committee. In addition, the Division believes that the Advisory Committee would be an excellent forum for Lilly to clarify its restricted GH distribution procedures (to well informed pediatric endocrinologists only) and to elaborate on its position that the number of children exposed to GH therapy would not increase substantially if this new indication were to be approved.

Please note that FDA minutes are the official documentation of the meeting.

Prepared by:

See appended electronic signature page.

Crystal King, P.D., M.G.A., Regulatory Project Manager

Concurrence:

See appended electronic signature page.

David Orloff, M.D., Division Director, Meeting Facilitator

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Crystal King
8/13/01 10:35:33 AM

Mary Parks
8/13/01 12:13:24 PM
acting for Dr. Orloff



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

SNDA 19-640/S-033

Eli Lilly and Company
Attention: Jeffrey Fayerman, Ph.D.
Senior Regulatory Research Scientist
Lilly Corporate Center
Indianapolis, IN 46285

J. Cor
4.27.03

Dear Dr. Fayerman:

Please refer to the meeting between representatives of your firm and FDA on April 1, 2003. The purpose of the meeting was to discuss your limited distribution plan for Humatrope (somatropin [rDNA origin] for injection) and preparations for the June 10, 2003, Endocrinological and Metabolic Drugs Advisory Committee.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 827-6429.

Sincerely,

{See appended electronic signature page}

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

Enclosure

Lilly-FDA TELECONFERENCE – Meeting Minutes

NDA 19-640/S-033

**Humatrope® (somatropin [rDNA origin] for injection)
for Treatment of Non-GHD Short Stature**

3:10-4:00 PM

April 1, 2003

FDA Attendees:

David Orloff, MD	Director, Division of Metabolic and Endocrine Drug Products (DMEDP)(HFD-510)
Joy Mele, M.S.	Statistics Reviewer, Division of Biometrics II (HFD-715), Office of Biostatistics, Office of Pharmacoepidemiology & Statistical Science (OPSS)
Dragos Roman, MD	Medical Officer, DMEDP
Todd Sahlroot, PhD	Statistics Team Leader, DB II (HFD-715)
Dornette Spell-LeSane	Executive Secretary, Endocrinological & Metabolic Drugs Advisory Committee (EMDAC) (HFD-021)
Enid Galliers	Chief, Project Management Staff, DMEDP

Lilly Attendees:

Tracy Beck, PhD	Sr. Scientific Communications Associate
Brenda Crowe, PhD	Sr. Statistician
Gordon Cutler, MD	Lilly Clinical Research Fellow
Grégory Enas, PhD	Director, US Regulatory Affairs
Tony Ezell	Leader, US Endocrinology Business Unit
Jeffrey Fayerman, PhD	Sr. Regulatory Research Scientist
Carol Feeney	Manager, Project Management, Product Teams
Coleman Gerstner	Marketing Associate
Hunter Heath, MD	Medical Director, US Endocrinology
Becky Palmer	Clinical Project Management Associate
Robert Petersen	Leader, hGH Product Team
Charmian Quigley, MBBS	Sr. Clinical Research Physician
Mary Sanger	Sr. Clinical Development Associate

Agenda:

1. Humatrope distribution plan – discussion of distribution plan Lilly had provided and FDA response to Lilly questions.
2. Advisory Committee plans – discussion and FDA response to Advisory Committee presentation plan Lilly had provided.

Executive Summary

1. FDA and Lilly agreed that, although the Humatrope distribution process should be mentioned at the June 10, 2003 Advisory Committee meeting, the proprietary details of the distribution process do not need to be discussed. FDA agreed that it would support Lilly in not disclosing distribution process details at the Advisory Committee meeting should questions be asked.
2. FDA will not make a formal presentation at the Advisory Committee meeting and will rely on Lilly to convey not only safety, efficacy, and risk management, but also to address the defined patient population, clinical significance, and objections that some in the community have to the treatment of children with non-GHD short stature.
3. Due diligence requires that FDA ensure that questions are raised at the Advisory Committee about the appropriateness of GH for non-GHD short stature treatment. Lilly should be prepared to preemptively address these questions.

Lilly Questions For FDA:

1. After review of the Humatrope Distribution Process, provided herewith, does FDA require any additional details about Humatrope distribution, reimbursement, or plans for process enhancement?

FDA Response: No.

2. For reasons cited in prior communications, does FDA agree that Lilly should not be compelled to discuss or disclose details of the Humatrope distribution process at the 10 June 2003 Advisory Committee meeting or in the briefing document for that meeting?

FDA response: FDA agrees. However, Lilly should mention the distribution process without going into proprietary details.

3. If the Agency response to Question #2 is “Yes”, will FDA support Lilly in not disclosing or discussing details about the Humatrope distribution process should questions be raised at the 10 June 2003 Advisory Committee meeting?

FDA response: Yes.

4. If the response to Question #2 is “No”, please provide: 1) the FDA perspective as to why discussion and disclosure of detailed information is necessary for the Advisory Committee to conduct its deliberations, and 2) guidance to Lilly regarding the level of detail that should be disclosed, both in the briefing document and at the Advisory Committee meeting.

FDA response: This question is moot.

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Enid Galliers
4/28/03 09:59:33 AM

June 19, 2003, GC submission

Page 1

Briefing Document

**Endocrinologic and Metabolic Drugs
Advisory Committee
June 10, 2003**

**Humatrope®
(somatropin [rDNA origin] for injection)
for Non-Growth Hormone Deficient Short Stature**

Volume 1

Lilly Research Laboratories
Eli Lilly and Company
Lilly Corporate Center
Indianapolis, Indiana 46285

AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION

**June 10, 2003, Meeting of Endocrinologic
and Metabolic Drugs Advisory Committee**

**Briefing documents, transcripts and slides
see: <http://www.fda.gov/ohrms/dockets/ac/acmenu.htm>**

July 14, 2003

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Control Room
12229 Wilkins Avenue
Rockville, MD 20852

AMENDMENT TO SUPPLEMENTAL NDA

Re: NDA 19-640, S-033 Humatrope® (somatropin [rDNA origin] for injection)

Reference is made to the September 26, 2002 submission of a supplemental New Drug Application (sNDA) for Humatrope (NDA 19-640, S-033) for non-growth hormone deficient short stature. Reference is also made to the April 2, 2003 amendment to the above referenced sNDA and to a July 8, 2003 e-mail communication from Dr. Monika Johnson (FDA) to Dr. Jeffrey Fayerman (Lilly) in which FDA provided comments on the label proposed in the April 2, 2003 sNDA amendment.

Lilly is amending the above referenced sNDA to reflect the FDA comments from the July 8, 2003 e-mail communication that are being accepted as well as those for which modifications are being proposed.

Four labeling documents are included. Two of these four documents are in Microsoft Word. The remaining two documents are PDF versions of the Microsoft Word documents.

The Microsoft Word document entitled "proposed.doc" contains the amended proposed label. In this document, Lilly has inserted all FDA comments made in the July 8, 2003 e-mail communication and then, through underlining (addition of text) and strikethrough (deletion of text), has either accepted or modified the FDA comments. Shaded text boxes, inserted near the point of each FDA comment, are provided to explain the Lilly position for all of the FDA comments.

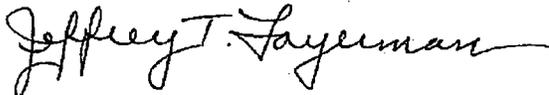
The Microsoft Word document entitled "proposed_clean.doc" contains the amended proposed label without highlighting or text boxes.

This amendment consists of one CD-ROM. The electronic medium has been checked and verified to be free of known viruses. The virus checking software was Norton AntiVirus Corporate Edition version 7.51.847 using Virus Definitions 5062r created on June 26, 2003.

Please call me at (317) 276-4691 if you require any additional information or if there are any questions. Alternatively, you may contact Gregory G. Enas, PhD, Director, U.S. Regulatory Affairs, at (317)276-4038.

Sincerely,

ELI LILLY AND COMPANY



Jeffrey T. Fayerman, PhD
Senior Regulatory Research Scientist
U.S. Regulatory Affairs

Enclosures

cc: Monika Johnson, PharmD (copy of Microsoft Word documents via e-mail)

June 17, 2003

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Control Room
12229 Wilkins Avenue
Rockville, MD 20852

AMENDMENT TO SUPPLEMENTAL NDA

Re: NDA 19-640, S-033 Humatrope® (somatropin [rDNA origin] for injection)

Reference is made to the September 26, 2002 submission of a supplemental New Drug Application (sNDA) for Humatrope (NDA 19-640, S-033) for non-growth hormone deficient short stature. Reference is also made to the Endocrinologic and Metabolic Drugs Advisory Committee meeting held on June 10, 2003.

Immediately following the June 10, 2003 Advisory Committee meeting, a discussion took place between Dr. David Orloff (FDA) and Drs. Gregory Enas and Paul Gesellchen (Lilly). In this discussion, FDA requested that Lilly prepare a document summarizing the recommendations made at the Advisory Committee meeting as well as the response from Lilly to those recommendations.

We are herewith providing the requested document, entitled "Lilly Response to the Recommendations by the FDA Endocrinologic and Metabolic Drugs Advisory Committee", as an amendment to the above-mentioned sNDA (enclosure).

This amendment consists of one CD-ROM. The electronic medium has been checked and verified to be free of known viruses. The virus checking software was Norton Antivirus Corporate Edition version 7.51.847 using Virus Definitions 50611q created on June 11, 2003 and Scan Engine 4.1.0.6.

Please call me at (317) 276-4691 if you require any additional information or if there are any questions. Alternatively, you may contact Gregory G. Enas, PhD, Director, U.S. Regulatory Affairs, at (317) 276-4038.

Sincerely,

ELI LILLY AND COMPANY

Handwritten signature of Jeffrey T. Fayerman in cursive script.

Jeffrey T. Fayerman, PhD
Senior Regulatory Research Scientist
U.S. Regulatory Affairs

enclosure

April 2, 2003

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Control Room
12229 Wilkins Avenue
Rockville, MD 20852

AMENDMENT TO SUPPLEMENTAL NDA

Re: NDA 19-640, S-033 Humatrope® (somatropin [rDNA origin] for injection)

Reference is made to the September 26, 2002 submission of a supplemental New Drug Application (sNDA) for Humatrope (NDA 19-640, S-033) for non-growth hormone deficient short stature.

Lilly is amending the above referenced sNDA to reflect the following:

1. Minor changes to proposed label language.
2. Report of additional safety information that became available after the sNDA submission date of September 26, 2002.

The attached Note-to-Reviewer explains, in detail, the proposed label changes that have been made as well as the reasons for those changes.

This amendment consists of one CD-ROM. The electronic medium has been checked and verified to be free of known viruses. The virus checking software was Norton Antivirus Corporate Edition version 7.51.847 using Virus Definitions 50326b created on March 26, 2003 and Scan Engine 4.1.0.6.

Please call me at (317) 276-4691 if you require any additional information or if there are any questions. Alternatively, you may contact Gregory G. Enas, PhD, Director, U.S. Regulatory Affairs, at (317) 276-4038.

Sincerely,

ELI LILLY AND COMPANY

A handwritten signature in cursive script that reads "Jeffrey T. Fayerman".

Jeffrey T. Fayerman, PhD
Senior Regulatory Research Scientist
U.S. Regulatory Affairs

Enclosures

2 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

X _____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process



Lilly Research Laboratories
A Division of Eli Lilly and Company
Lilly Corporate Center
Indianapolis, Indiana 46285 U.S.A.

Phone 317 276 2000

March 25, 2003

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Control Room
12229 Wilkins Avenue Fishers Lane
Rockville, MD 20852

NDA Amendment

Re: NDA 19-640 (S-033); Humatrope®; somatropin (rDNA origin) for injection

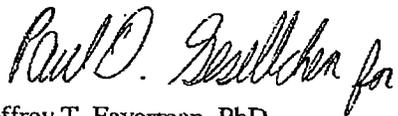
Reference is made to a March 5, 2003 letter from Dr. Jeffrey Fayerman (Lilly) to Dr. Monika Johnson (FDA) in which Lilly requested a teleconference with FDA to address questions regarding the Humatrope distribution and reimbursement process. In that letter, Lilly indicated that it would send a pre-teleconference briefing document to the Agency, which would outline the Humatrope distribution process. Finally, reference is made to telephone conversations and e-mail exchanges (March 21, 24, and 25, 2003) between Dr. Paul Gesellchen (Lilly) and Ms. Galliers in which details of the document submission and a proposed teleconference meeting between Lilly and the FDA were discussed. The teleconference is tentatively scheduled for April 1, 2003 from 3:00 to 4:00 p.m. One of the stated goals of this meeting is to discuss the Humatrope Distribution Process document.

Enclosed is the aforementioned Humatrope Distribution Process document both in hard copy format and on one CD-ROM. A total of six (6) desk copies of this document are being submitted to Ms. Galliers under separate cover. Please note that the information contained within this document supercedes the information contained within Section 3.2 (Limited Distribution) of the Humatrope Risk Management Program that was submitted as part of sNDA 19-640 (S-033) submitted on September 26, 2002.

This Amendment consists of one CD-ROM along with one copy on paper. The electronic medium has been checked and verified to be free of known viruses. The virus checking software was Norton Antivirus Corporate Edition version 7.51.847 using Virus Definitions 50319b created on March 19, 2003 and Scan Engine 4.1.0.6.

Please call me at (317) 276-4691 if you require any additional information or if there are any questions. Alternatively, you may contact Gregory Enas, PhD, Director, U.S. Regulatory Affairs, at (317) 276-4038.

Sincerely,



Jeffrey T. Fayerman, PhD
Senior Regulatory Research Scientist
U.S. Regulatory Affairs
Lilly Research Laboratories
Eli Lilly and Company

cc: Ms. Enid Galliers (six desk copies)



717101



01961 N

www.lilly.com

ORIGINAL

19640
SE 1.033 MR

Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company
Lilly Corporate Center
Indianapolis, Indiana 46285 U.S.A.

Phone 317 276 2000

NDA 19-640

RECEIVED

MAR 06 2003

FOR/ODER

SE1033(MK)
NDA SUPPL AMENDMENT

March 5, 2003

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine
Drug Products, HFD-510
Attn: Dr. Monika Johnson, Room 14B-45
5600 Fishers Lane
Rockville, MD 20857

Meeting Request

Re: [Humatrope®; somatropin (rDNA origin) for injection]

In accordance with 21 CFR §314.103(c), and with reference to a February 14, 2003 e-mail inquiry from Dr. Jeffrey Fayerman (Lilly) to Dr. Monika Johnson (FDA) and two February 26, 2003 e-mail responses from Dr. David Orloff (FDA) to Dr. Gregory Enas (Lilly), we are hereby requesting a meeting with FDA to discuss distribution and reimbursement of Humatrope in the United States.

In the February 14 e-mail, Dr. Fayerman requested that Lilly not be compelled to disclose and discuss proprietary details of Humatrope distribution at the upcoming June 10, 2003 Advisory Committee meeting or in the briefing document for that meeting. Also, in the February 14 e-mail, Lilly expressed a willingness to provide FDA with as much detail as it might like to have about Humatrope distribution in lieu of having that disclosure and discussion take place in the public Advisory Committee setting. In the first February 26 e-mail from Dr. Orloff to Dr. Enas, FDA indicated that it would not be necessary for Lilly to discuss details about Humatrope distribution and reimbursement at the Advisory Committee meeting but that FDA was interested in understanding the processes. In the second February 26 e-mail from Dr. Orloff to Dr. Enas, FDA expressed the acceptability of Lilly providing FDA with information about Humatrope distribution and reimbursement and indicated that this would then be followed by questions from FDA. Lilly is requesting the teleconference as a means of responding to FDA's questions about written information Lilly plans to provide to FDA.

Lilly expects to send a written pre-teleconference Humatrope distribution/reimbursement plan of approximately 15 pages to FDA by March 17, 2003. This plan will include a discussion of the history of Humatrope distribution and reimbursement, ongoing enhancements to the Humatrope distribution process, and Lilly intervention processes in the event of evidence of inappropriate use.

Lilly proposes that the teleconference be scheduled for one hour and that it take place between April 1 and 11, 2003 at a date and time convenient for FDA. This date range will allow sufficient time to make any resulting adjustments, if needed, to our Advisory Committee briefing document which is due to the Advisory Committee Executive Secretary on May 9, 2003.

The purpose of the proposed teleconference:

1. Allow Lilly to answer questions that FDA has about Humatrope distribution and reimbursement.
2. Enable FDA to provide clarity on how to make mention of Humatrope distribution and reimbursement at the June 10 Advisory Committee meeting, and in the Advisory Committee briefing document, without disclosure or discussion of details.

Anticipated Lilly attendees would be:

Gordon Cutler, MD, Lilly Clinical Research Fellow
Gregory Enas, PhD, Director, United States Regulatory Affairs
Antoine Ezell, Leader, U.S. Endocrinology Business Unit
Jeffrey Fayerman, PhD, Senior Regulatory Research Scientist
Coleman Gerstner, Marketing Associate, U.S. Endocrinology Business Unit
Robert Petersen, Product Team Leader
Charmian Quigley, MBBS, Senior Clinical Research Physician

We would suggest that the FDA attendees include:

Monika Johnson, PharmD, Regulatory Review Officer
David Orloff, MD, Division Director
Robert Perlstein, MD, Medical Officer
Dragos Roman, MD, Medical Officer
Dornette Spell-LeSane, NP-C, MHA, Executive Secretary, Endocrinologic and Metabolic Drugs Advisory Committee

Humatrope® (somatropin [rDNA origin] for injection)
Food and Drug Administration – March 5, 2003
Page 3

We look forward to hearing back from FDA about this meeting request as soon as possible. Please call me at (317) 276-4691 if you require any additional information or if there are any questions. Alternatively, you may contact Gregory Enas, PhD, Director, U.S. Regulatory Affairs, at (317) 276-4038.

Sincerely,



Jeffrey T. Fayerman, PhD
Senior Regulatory Research Scientist
U.S. Regulatory Affairs
Lilly Research Laboratories
Eli Lilly and Company

cc: Dr. David Orloff

www.lilly.com



Lilly Research Laboratories
A Division of Eli Lilly and Company
Lilly Corporate Center
Indianapolis, Indiana 46285 U.S.A.

Phone 317 276 2000

February 17, 2003

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
12229 Wilkins Avenue
Rockville, MD 20852

AMENDMENT TO SUPPLEMENTAL NDA

Re: NDA 19-640, S-033 Humatrope® (somatropin [rDNA origin] for injection)

Reference is made to the September 26, 2002 submission of a supplemental New Drug Application (sNDA) for Humatrope (NDA 19-640, S-033) for non-growth hormone deficient short stature.

Reference is also made to an e-mail transmission from Dr. Monika Johnson to Dr. Jeffrey Fayerman dated January 31, 2003. In this e-mail, Dr. Johnson requested further information and clarification about Studies GDCH and E001 (Attachment).

We are herewith providing our response to this request as an amendment to the above-mentioned sNDA (Enclosure).

This amendment consists of one CD-ROM. The electronic medium has been checked and verified to be free of known viruses. The virus checking software was Norton Antivirus Corporate Edition version 7.51.847 using Virus Definitions 50115s created on January 15, 2003 and Scan Engine 4.1.0.6.

Answers That Matter.

Please call me at (317) 276-4691 if you require any additional information or if there are any questions. Alternatively, you may contact Gregory G. Enas, PhD, Director, U.S. Regulatory Affairs, at (317) 276-4038.

Sincerely,

ELI LILLY AND COMPANY



Jeffrey T. Fayerman, PhD
Senior Regulatory Research Scientist
U.S. Regulatory Affairs

Enclosures

ATTACHMENT

January 31, 2003 FDA Request:

A. On Study GDCH:

1. Provide a list of individual baseline values for peak serum GH responses to provocative testing and the type of provocative test performed for each patient in the final height population.
2. Present the baseline mean IGF-I serum levels (ng/ml and SDS) for each treatment group (Humatrope and placebo) in the final height population.
3. Present a table in a format identical to Table GDCH.12.25 that includes high and low IGF-I values on-treatment using a cutoff of 2 SD instead of 3 SD.
4. Present baseline height velocity SDS values for the randomized, evaluable, and final height population in each treatment arm (Humatrope and placebo) and for all study patients (Humatrope and placebo combined).
5. Present the baseline characteristics for patients with final height efficacy data and patients without final height efficacy data
6. Clarify why patients 1063 and 1069 were included in the final height population in absence of Visit 99.

B. On Study E001:

1. Present baseline height velocity SDS values for the randomized, and final height population in each treatment arm (Dose 1, Dose 2, Dose 3) and for all study patients combined.

January 6, 2003

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
12229 Wilkins Avenue
Rockville, MD 20852

AMENDMENT TO SUPPLEMENTAL NDA

Re: NDA 19-640, S-033 Humatrope® (somatropin [rDNA origin] for injection)

Reference is made to the September 26, 2002 submission of a supplemental New Drug Application (sNDA) for Humatrope (NDA 19-640, S-033) for non-growth hormone deficient short stature.

Reference is also made to December 27, 2002 and January 2, 2003 e-mail transmissions from Dr. Monika Johnson to Dr. Jeffrey Fayerman.

In the December 27, 2002 e-mail, Dr. Johnson inquired about whether an underline/strike-out version of the proposed label had been submitted. In a January 2, 2003 follow-up voice mail from Dr. Fayerman to Dr. Johnson, Dr. Fayerman indicated that, although a highlighted/strike-through version of the proposed label had already been submitted in pdf format, Lilly could also provide this same version of the proposed label in Word format. In the January 2, 2002 e-mail, Dr. Johnson requested the Word-formatted version of the proposed label.

We are herewith providing our response to the December 27, 2002 question as an amendment to the above-mentioned sNDA (Attachment).

This amendment consists of one CD-ROM. The electronic medium has been checked and verified to be free of known viruses. The virus checking software was Norton Antivirus Corporate Edition version 7.51.847 using Virus Definitions 41231e created on December 31, 2002 and Scan Engine 4.1.0.6. Also included are paper copies of pages containing original signatures (cover letter and FDA form 356h).

Please call me at (317) 276-4691 if you require any additional information or if there are any questions. Alternatively, you may contact Gregory G. Enas, PhD, Director, U.S. Regulatory Affairs, at (317) 276-4038.

Sincerely,

ELI LILLY AND COMPANY

Handwritten signature of Jeffrey T. Fayerman in cursive script.

Jeffrey T. Fayerman, PhD
Senior Regulatory Research Scientist
U.S. Regulatory Affairs

Enclosures

FDA Question:

December 27, 2002: Did we receive an underline, strike-out version of your proposed label? If not, please forward this to CDR for the electronic document room as soon as you can. We prefer this format in order to most accurately determine what information will be changing in the label. Please use the version that shows us an identifier and revision date.

Lilly Response:

December 27, 2002: Lilly provided a highlighted/strike-through version of the proposed label in the September 26, 2002 submission. This version, in pdf format, appears in the Application Summary of the electronic submission on pages 17-35. Please note that Lilly uses highlighting to indicate proposed additions to the current label and highlighted strike-through to indicate proposed deletions from the current label. The version identifier, indicated in the proposed label is A1.0 NL 1641 AMP. The revision date, also indicated in the proposed label, is July 17, 2002.

FDA Comment:

January 2, 2003: We would like to have the Word version of the marked up labeling.

Lilly Response:

January 6, 2003: Lilly is providing (on the enclosed CD-ROM) the requested version of the proposed label in Word format.

November 20, 2002

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
12229 Wilkins Avenue
Rockville, MD 20852

AMENDMENT TO SUPPLEMENTAL NDA

Re: NDA 19-640, S-033 Humatrope® (somatropin [rDNA origin] for injection)

Reference is made to the September 26, 2002 submission of a supplemental New Drug Application (sNDA) for Humatrope (NDA 19-640, S-033) for non-growth hormone deficient short stature.

Reference is also made to a November 15, 2002 e-mail transmission from Dr. Monika Johnson to Dr. Jeffrey Fayerman. In this e-mail, Dr. Johnson inquired about the Humatrope database that was submitted with the sNDA.

We are herewith providing our response to the November 15, 2002 question as an amendment to the above-mentioned sNDA.

This amendment to the sNDA consists of one CD-ROM. The electronic medium has been checked and verified to be free of known viruses. The virus checking-software was Norton Antivirus Corporate Edition version 7.51.847 using Virus Definitions 41113d created on November 13, 2002 and Scan Engine 4.1.0.6. Also included are paper copies of pages containing original signatures (cover letter and FDA form 356h).

Please call me at (317) 276-4691 if you require any additional information or if there are any questions. Alternatively, you may contact Dr. Gregory G. Enas, Ph.D., Director, U.S. Regulatory Affairs, at (317) 276-4038.

Sincerely,

ELI LILLY AND COMPANY



Jeffrey T. Fayerman, Ph.D.
Senior Regulatory Research Scientist
U.S. Regulatory Affairs

Enclosures

Desk copy: Dr. Monika Johnson

FDA Question: One item has been identified as a problem. It relates to the raw data in the SAS files in the Humatrope database. The files are not usable since the treatment assignment cannot be made (specifically, the therapy column contains an unintelligible series of letters specific for each patient).

Lilly Response: Lilly apologizes for any inconvenience caused by the files that are not usable. Lilly is providing (on the enclosed CD-ROM) the Humatrope database that we intended to provide with the original sNDA submission.

www.lilly.com

Lilly

Eli Lilly and Company
Lilly Corporate Center
Indianapolis, Indiana 46285
U.S.A.

Phone 317 276 2000

September 26, 2002

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
12229 Wilkins Avenue
Rockville, MD 20852

**SUPPLEMENTAL NDA SUBMISSION
NEW INDICATION**

**Re: NDA 19-640 [Humatrope[®]; somatropin (rDNA origin) for injection]
New Indication: Non-growth hormone deficient short stature**

This letter accompanies a submission by Eli Lilly and Company (Lilly) of a supplemental New Drug Application (sNDA) for Humatrope (somatropin [rDNA origin] for injection) for a new indication, non-growth hormone deficient short stature (NGHDSS). This submission is being made in accordance with 21 CFR §314.70(b)(3)(i) and is formatted in accordance with 21 CFR §314.50.

The applicable User Fee (\$156,600) has been submitted under User Fee number 7. A completed Form FDA 3397, User Fee Cover Sheet, is included in this supplement.

The submission consists of one CD-ROM. The size of the electronic medium is approximately 200 MB. The electronic medium has been checked and verified to be free of known viruses. The virus checking software was Norton Antivirus Corporate Edition version 7.51.847 using Virus Definitions 40918h created on September 18, 2002 and Scan Engine 4.1.0.6. Also included is one paper copy of Item 1 (in a single volume) containing original signatures.

Answers That Matter.

Please call me at (317) 276-4691 if you require any additional information or if there are any questions. Alternatively, you may contact Dr. Gregory G. Enas, PhD, Director, U.S. Regulatory Affairs, at (317) 276-4038.

Sincerely,

ELI LILLY AND COMPANY



Jeffrey T. Fayerman, PhD
Senior Regulatory Research Scientist
U.S. Regulatory Affairs

cc: Dr. Monika Johnson, HFD-510 (paper copy of submission in nine volumes)

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		Form Approved: OMB No. 0910-0297 Expiration Date: 04-30-01
USER FEE COVER SHEET		
<i>See Instructions on Reverse Before Completing This Form</i>		
1. APPLICANT'S NAME AND ADDRESS Eli Lilly and Company Lilly Corporate Center Indianapolis, IN 46285 c/o Gregory G. Enas, Ph.D. Director U.S. Regulatory Affairs		3. PRODUCT NAME User Fee Humatrope, somatropin (rDNA origin) for injection for non-growth hormone deficient short stature
2. TELEPHONE NUMBER (Include Area Code) (317) 276-4038		4. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM. IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW: <input checked="" type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION. <input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO _____ (APPLICATION NO. CONTAINING THE DATA).
5. USER FEE I.D. NUMBER Supplement		6. LICENSE NUMBER / NDA NUMBER NDA 19-640
7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.		
<input type="checkbox"/> A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory) <input type="checkbox"/> THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act. (See item 7, reverse side before checking box.) <input type="checkbox"/> THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY (Self Explanatory) <input type="checkbox"/> A 605(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE (See item 7, reverse side before checking box.) <input type="checkbox"/> THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.) FOR BIOLOGICAL PRODUCTS ONLY <input type="checkbox"/> WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION <input type="checkbox"/> AN APPLICATION FOR A BIOLOGICAL PRODUCT FOR FURTHER MANUFACTURING USE ONLY <input type="checkbox"/> BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/92 <input type="checkbox"/> A CRUDE ALLERGENIC EXTRACT PRODUCT <input type="checkbox"/> AN "IN VITRO" DIAGNOSTIC BIOLOGICAL PRODUCT LICENSED UNDER SECTION 351 OF THE PHS ACT		
8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? <input type="checkbox"/> YES <input type="checkbox"/> NO (See reverse side if answered YES)		
A completed form must be signed and accompany each new drug or biologc product application and each new Supplement. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment.		
Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to: DHHS, Reports Clearance Officer, Paperwork Reduction Project (0910-0297) Hubert H. Humphrey Building, Room 531-H 200 Independence Avenue, S.W. Washington, DC 20201 An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.		
Please DO NOT RETURN this form to this address.		
SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE <i>Michael D. Chapman</i> <i>for Gregory G. Enas, Ph.D.</i>	TITLE Gregory G. Enas, Ph.D. Director U.S. Regulatory Affairs	DATE September 18, 2002

FORM FDA 3397 (5/98)

Created by Electronic Document Services/USDHHS: (30) 443-2454 EF



NDA 19-640/S-033

PRIOR APPROVAL SUPPLEMENT

Eli Lilly and Company
Attention: Jeffery Fayerman, PhD
Senior Regulatory Research Scientist, US Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46285

10/3/02

Dear Dr. Fayerman:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Humatrope (somatropin [rDNA origin] for injection)

NDA Number: 19-640

Supplement Number: S-033

Review Priority Classification: Standard (S)

Date of Supplement: September 26, 2002

Date of Receipt: September 26, 2002

This supplement proposes to add a new indication, non-growth hormone deficient short stature.

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on November 25, 2002 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be July 26, 2003.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 FR 66632). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within approximately 120 days of receipt of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the

provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will make a determination whether to grant or deny a request for a waiver of pediatric studies during the review of the application. In no case, however, will the determination be made later than the date action is taken on the application. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will review your pediatric drug development plan and notify you of its adequacy. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

Please cite the application number listed above at the top of the first page of any communications concerning this application. All communications concerning this supplemental application should be addressed as follows:

U.S. Postal/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products, HFD-510
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call me at (301) 827-6370.

Sincerely,

{See appended electronic signature page}

Monika Johnson, PharmD
Regulatory Project Manager
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

**Appears This Way
On Original**

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Monika Johnson
10/3/02 03:40:05 PM

Johnson, Monika

From: Johnson, Monika
Sent: Monday, July 28, 2003 10:00 AM
To: Meyer, Robert J; Roman, Dragos; Ripper, Leah W; Sahlroot, Jon T; Mele, Joy D; Spell Lesane, Dornette D; Tran, Debi Nhu; Mercier, Jennifer L; Mungo, Indya; Brinker, Allen D; Moore, Stephen K; Brown, Janice; Beitz, Julie G
Subject: FW: NDA 19-640/S-033 Humatrope (somatropin [rDNA origin] for injection)

forwarding. Please forgive the delay.

-----Original Message-----

From: Johnson, Monika
Sent: Friday, July 25, 2003 6:29 PM
To: Orloff, David G
Subject: FW: NDA 19-640/S-033 Humatrope (somatropin [rDNA origin] for injection)

-----Original Message-----

From: Johnson, Monika
Sent: Friday, July 25, 2003 4:54 PM
To: CDER-APPROVALS
Subject: NDA 19-640/S-033 Humatrope (somatropin [rDNA origin] for injection)

Date of approval: July 25, 2003
NDA/S#: 19-640/Supplement -033
Name of drug: Humatrope (somatropin [rDNA origin] for injection)
Name of sponsor: Eli Lilly and Company
Indication(s): **previously approved:**

Pediatric

- indicated for the long-term treatment of patients who have growth failure due to an inadequate secretion of normal endogenous growth hormone.
- indicated for the treatment of short stature associated with Turner syndrome in patients whose epiphyses are not closed.

Adult

Humatrope is indicated for replacement of endogenous growth hormone in adults with growth hormone deficiency who meet either of the following two criteria:

- **Adult Onset:** Patients who have growth hormone deficiency either alone, or with multiple hormone deficiencies (hypopituitarism), as a result of pituitary disease, hypothalamic disease, surgery, radiation therapy, or trauma;
- Or
- **Childhood Onset:** Patients who were growth hormone-deficient during childhood who have growth hormone deficiency confirmed as an adult before replacement therapy with Humatrope is started.

newest indication: / _____ /

Dosage form/route of administration: / _____ /

This is a prescription drug product

Project manager: Monika Johnson, PharmD

Monika Johnson, PharmD
LT USPHS
Regulatory Review Officer
Division of Metabolic and Endocrine Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
Tel: 301-827-9087

Johnson, Monika

From: Mercier, Jennifer L
Sent: Friday, July 25, 2003 3:45 PM
To: Mungo, Indya
Cc: Johnson, Monika; Orloff, David G
Subject: FW: Humatrope

Attached you will find the Press Release, Information Alert for HHS and the Q&As for the approval of Humatrope.

Monika, Please let Indya know when the approval happens so she can do the press release.

Have a great Weekend!

Thanks,

Jen

-----Original Message-----

From: Mercier, Jennifer L
Sent: Friday, July 25, 2003 3:16 PM
To: Orloff, David G
Subject: Humatrope



HumatropeQAs HumatropeforI humatrope.doc
-25-03DGO1.dopressrelease7-2

July 25, 2003

PRESS RELEASE

The FDA today approved a new indication for Humatrope (Somatropin, rDNA origin, for injection), a brand of growth hormone, for the long-term treatment of children with idiopathic (of unknown origin) short stature, also called non-growth hormone deficient short stature.

"Short stature" has been defined by the American Association of Clinical Endocrinologists and the Growth Hormone Research Society as height more than 2 standard deviations (SD) below the mean for age and sex. This corresponds to the shortest 2.3 percent of children. This new indication restricts therapy to children who are even shorter, specifically more than 2.25 SD below the mean for age and sex, or the shortest 1.2% of children. For example, for 10-year old boys and girls, this would correspond to heights of less than 4 feet 1 inch. This would further correspond to heights of less than 5' 3" and 4' 11" in adult men and women, respectively.

Today's approval was based on 2 randomized, multicenter trials, conducted in approximately 300 children with idiopathic short stature. The diagnosis of idiopathic short stature was made after excluding other causes of short stature, including growth hormone deficiency.

The pivotal trial was a randomized, double-blind study in 71 children aged 9-15 years. Patients received subcutaneous injections of either Humatrope or placebo three times weekly until adult height was reached. Thirty-three patients contributed final height measurements after a mean treatment duration of 4.4 years. Mean final height of the Humatrope patients exceeded that of the placebo patients by approximately 1.5 inches.

In a second study, patients received one of three increasing doses of Humatrope, in divided doses 6 times weekly. The average duration of treatment to final height was 6.5 years. Final height exceeded that predicted at the time of enrollment in the majority of patients, and by up to nearly 4 inches in some. In the high-dose group, mean final height exceeded mean height predicted at baseline by nearly 3 inches.

The safety profile of Humatrope in children with idiopathic short stature did not differ from that in children with other conditions in which growth hormone is indicated.

Various growth hormone products are currently indicated in children for short stature associated with growth hormone deficiency, chronic renal insufficiency,

Turner syndrome, Prader-Willi syndrome, and in children born small for gestational age.

Humatrope's new indication for idiopathic short stature is the first indication for growth hormone in children that specifies a height restriction (see above).

On June 10, 2003, the application for this new indication was presented to FDA's Endocrine and Metabolic Advisory Committee for public discussion and consideration. The advisory committee voted 8-2 in favor of approval.

The manufacturer has advised FDA that it will not engage in direct-to-consumer advertising of Humatrope and will limit the marketing of this product for this new use to pediatric endocrinologists in order to better ensure the proper use of this product in the indicated pediatric population. In addition, the manufacturer intends to tightly control the distribution of Humatrope.

Humatrope is manufactured and distributed by Eli Lilly Co. of Indianapolis, Ind.

July 25, 2003

NDA 19-640/S-033 Humatrope (somatropin rDNA origin for injection) Questions for 'talk-paper'.

1. Why is Humatrope being approved to treat idiopathic (of unknown cause) short stature?

Data from 2 randomized, multicenter trials, conducted in approximately 300 children with idiopathic short stature, showing that growth hormone therapy safely augments height in these children support this new indication. The diagnosis of idiopathic short stature was made after excluding other causes of short stature, including growth hormone deficiency. Candidates for this therapy are the shortest 1.2% of children. For example, for 10-year old boys and girls, this would correspond to heights of less than 4 feet 1 inch.

The pivotal trial was a randomized, double-blind study in 71 children aged 9-15 years. Patients received subcutaneous injections of either Humatrope or placebo three times weekly until adult height was reached. 33 patients contributed final height measurements after a mean treatment duration of 4.4 years. The average final height of the Humatrope patients exceeded that of the placebo patients by approximately 1.5 inches.

In a second study, patients received one of three increasing doses of Humatrope, in divided doses 6 times weekly. The average duration of treatment to final height was 6.5 years. Final height exceeded that predicted at the time of enrollment in the majority of patients, and by up to nearly 4 inches in some patients. In the high-dose group, which will be the highest recommended dose for this condition, mean final height exceeded mean height predicted at baseline by nearly 3 inches.

The safety profile of Humatrope in children with idiopathic short stature did not differ from that in children with other conditions in which growth hormone is indicated.

2. Is this a change in FDA policy? No.

On the recommendation of an advisory committee convened in 1987, FDA concluded that the efficacy and safety of growth hormone in children with idiopathic short stature should be studied in a trial that was randomized, double-blinded, placebo-controlled, and in which patients were followed on therapy to final adult height. The pivotal study supporting this approval is such a study. The results of the study as well as an important supportive study are discussed above.

The average height gain with the use of Humatrope in idiopathic short stature is similar to that achieved with growth hormone treatment in children with Turner syndrome, another group of short children (destined to be short adults) for whom growth hormone is approved. The FDA Endocrine and Metabolic Drugs advisory committee felt that Humatrope was effective in children with idiopathic short stature in augmenting final height. As with many interventions, response is greater in some than in others. The safety of growth hormone is well established, and it is no different in this population than in other pediatric populations in which it is indicated. The FDA and its advisors concur

July 25, 2003

that the balance of risk and benefit for this use is favorable, and that decisions regarding the use of Humatrope in idiopathic short stature (as for other uses) should be made by the patient, his or her family, and in consultation with a physician based on an assessment of risks and benefits for the individual patient. The studies submitted in this application have permitted FDA and the sponsor to write labeling for this use of Humatrope that conveys expected benefits and risks and will guide safe and effective use.

(Add last paragraph of press release here.)

DATE: July 25, 2003

INFORMATION ADVISORY

SUBJECT/LEAD COMPONENT:

Humatrope (somatropin, rDNA origin, for injection), Eli Lilly Co./FDA

WHY THIS INFORMATION IS IMPORTANT FOR THE SECRETARY:

Significant press and public interest are expected after the approval of the application today, July 25, 2003 because Humatrope's new indication for idiopathic short stature targets very small children with no known reason for their short stature. It is the first indication for growth hormone in children that specifies a height restriction.

SUMMARY OF ISSUE, BACKGROUND, AND DEPARTMENT RESPONSE/ACTIONS:

- ◆ On June 10, 2003, the application for this new indication was presented to FDA's Endocrine and Metabolic Advisory Committee for public discussion and consideration. The advisory committee voted 8-2 in favor of approval.
- ◆ This new indication restricts therapy to children who are very short, specifically more than 2.25 standard deviations below the mean for age and sex, in cases where there is no known condition causing the short stature. This encompasses the shortest 1.2% of children. For example, for 10-year old boys and girls, this would correspond to heights of less than 4 feet 1 inch. This would further correspond to heights of less than 5' 3" and 4' 11" in adult men and women, respectively.
- ◆ The manufacturer has advised FDA that it will not engage in direct-to-consumer advertising of Humatrope and will limit marketing for this product for this new use to pediatric endocrinologists in order to better ensure the proper use of this product in the indicated pediatric population.
- ◆ The safety profile of Humatrope in children with idiopathic short stature did not differ from that in children with other conditions in which growth hormone is indicated. Various growth hormone products are currently indicated in children for short stature associated with growth hormone deficiency, chronic renal insufficiency, Turner syndrome, Prader-Willi syndrome, and in children born small for gestational age.

CONTACT: Jennifer Mercier, FDA, (301) 594-5472



Food and Drug Administration
Division of Metabolic and Endocrine
Drug Products, HFD-510
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: June 25, 2003

To: JEFFERY T. FAYERMAN	From: MONIKA JOHNSON
Company: ELI LILLY & CO.	Division of Metabolic and Endocrine Drug Products
Fax number: 317 276 1652	Fax number: (301) 443-9282
Phone number:	Phone number: 301 - 827 - 9087

Subject: NDA 19-640/s-033 HUMATRONE ACTION LETTER

Total no. of pages including cover: 21

Comments: ~~BE~~ DR. FAYERMAN, SEND ME E-MAIL CONFIRMATION THAT YOU HAVE RECEIVED THIS. THANKS - MONIKA.

Document to be mailed: YES NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 827-6430. Thank you.

If no, explain:

- If an electronic NDA, does it follow the Guidance? YES
If an electronic NDA, all certifications must be in paper and require a signature.
Which parts of the application were submitted in electronic format?
Cover letter, 356 H form (copy), Labeling, Case report tabulations, Case report forms, statistical info, clinical study report
- If in Common Technical Document format, does it follow the guidance? N/A
- Is it an electronic CTD? N/A
- Patent information included with authorized signature? YES
- Exclusivity requested? NO
Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.
- Correctly worded Debarment Certification included with authorized signature? YES
NOTE: Debarment Certification must have correct wording, e.g.: "I, the undersigned, hereby certify that _____ Co. did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with the studies listed in Appendix ____." Applicant may not use wording such as "To the best of my knowledge"
- Financial Disclosure information included with authorized signature? YES
- Has the applicant submitted pediatric data and/or deferral request and/or waiver request for all ages and indications? N/A
- If no, explain.
- Field Copy Certification (that it is a true copy of the CMC technical section)? N/A

Refer to 21 CFR 314.101(d) for Filing Requirements

- PDUFA and Action Goal dates correct in COMIS? YES
- Drug name/Applicant name correct in COMIS? YES
- List referenced IND numbers:
- End-of-Phase 2 Meeting? NO
- Pre-NDA Meeting(s)? Date(s) July 31, 2001

Project Management

- Package insert consulted to DDMAC? YES

- Trade name (plus PI and all labels and labeling) consulted to ODS/Div. of Medication Errors and Technical Support? N/A
- Risk Management Plan consulted to ODS/Div. of Surveillance, Research and Communication Support? YES
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted? N/A

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/ Div. of Surveillance, Research and Communication Support? N/A
- Has DOTCDP been notified of the OTC switch application? N/A

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? YES NO

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES
If no, did applicant submit a complete environmental assessment? NO
If EA submitted, consulted to Nancy Sager (HFD-357)? N/A
- Establishment Evaluation Request (EER) submitted to DMPQ? NO
- If parenteral product, consulted to Microbiology Team (HFD-805)? NO

505(b)(2) application does not apply

ATTACHMENT

MEMO OF FILING MEETING

DATE: October 30, 2002

BACKGROUND:

Humatrope is approved for the long-term treatment/replacement of growth hormone failure in adults and children due to lack of endogenous growth hormone. Humatrope is also indicated for the treatment of short stature associated with Turner syndrome in patients whose epiphyses are not closed. A pre sNDA meeting was held on July 31, 2001 to discuss dose range and dosing frequency (dosing proposal for the label) as well as the structure for the electronic submission. The sponsor was advised by the Agency to propose appropriate guidelines for usage in the non-growth hormone deficient short stature patient population in order to foster appropriate patient selection and avoid over-prescribing of growth hormone to the vast number of "short" kids that exist.

ATTENDEES: Hae Young Ahn, Dragos Roman, Kati Johnson, Todd Sahlroot, Joy Mele

ASSIGNED REVIEWERS:

<u>Discipline</u>	<u>Reviewer</u>
Medical:	Dragos Roman, MD
Secondary Medical:	David Orloff, MD
Statistical:	Joy Mele, PhD
Pharmacology:	
Statistical Pharmacology:	
Chemist:	Janice Brown, MS
Environmental Assessment (if needed):	Janice Brown, MS
Biopharmaceutical:	
Microbiology, sterility:	
Microbiology, clinical (for antimicrobial products only):	
DSI:	
Project Manager:	Monika Johnson, PharmD
Other Consults:	ODS/Risk Management

Per reviewers, all parts are in English or English translation? YES
If no, explain:

CLINICAL FILE X REFUSE TO FILE

- Clinical site inspection needed: NO
- Advisory Committee Meeting needed? YES, June 10, 2003
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?

N/A

STATISTICAL FILE X REFUSE TO FILE

CHEMISTRY FILE X REFUSE TO FILE

- Establishment(s) ready for inspection? N/A

REGULATORY CONCLUSIONS/DEFICIENCIES:

 X The application, on its face, appears to be well organized and indexed. The application appears to be suitable for filing.

 The application is unsuitable for filing. Explain why:

ACTION ITEMS:

Items to be included in the 74-day filing issues letter:

N/A

Monika Johnson, PharmD
Regulatory Project Manager, HFD-510