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## EXECUTIVE SUMMARY

### I. Background

Eli Lilly and Company (the applicant) submitted to the Food and Drug Administration (the agency) a supplemental New Drug Application (sNDA) for Humatrope (somatropin) in support of a new pediatric indication: non-growth hormone deficient short stature (NGHDSS).

### II. Brief Description of Clinical Trials and Patient Exposure

The applicant presented clinical efficacy and safety data from several sources. Among these, are two Phase 3 clinical trials conducted in patients with NGHDSS: trial B9R-MC-GDCH (GDCH) and trial B9R-EW-E001 (E001). Trial GDCH is a double-blind, randomized, placebo-controlled, trial in 71 patients; it enrolled patients on the basis of short stature or short predicted adult stature. Trial E001 is a randomized, open-label, dose-response, trial in 239 patients conducted in Europe; it enrolled patients on the basis of short stature and reduced height velocity.

More than 300 patients with NGHDSS have been studied in these two clinical trials for a mean duration of 3.5 years in trial GDCH and 4.5 years in trial E001. In both trials a proportion of patients has been followed to final height and received Humatrope for longer duration (mean of 4.43 years in trial GDCH and 6.47 years in trial E001). The overall exposure for this new indication (approximately 1200 patient years) is similar to the exposure for two approved pediatric Humatrope indications (growth hormone deficiency and Turner syndrome associated with short stature).

### III. 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 have different the 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  $0.51 \pm 0.20$  standard deviation score (SDS) ( $p=0.017$ ) in the primary efficacy analysis of 33 patients who contributed final height data. The primary analysis is supported by an intent-to-treat analysis of height SDS that shows a similar magnitude of treatment effect ( $0.52 \pm 0.15$ ;  $p=0.001$ ). 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 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 ( $7.21 \pm 5.97$  cm or 1.9 height SDS;  $p=0.001$ ), whereas the low-dose Humatrope regimen had a smaller treatment effect of 5.4 cm ( $5.36 \pm 3.20$  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) likely 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) use of GH in this condition was not FDA approved.

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).

#### **IV. 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 during the clinical trial, discontinued the trial and died four years later. One patient in trial GDCH was diagnosed with stage 3B Hodgkin disease approximately 4-5 months on treatment.

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 (see Table 24 in Appendix 1). Evaluation of carbohydrate metabolism in patients with NGHDS 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 NGHDS, GHD and Turner syndrome. No major differences in safety profile were noted across the three patient populations.

## **V. Growth Hormone for Non-growth Hormone Deficient Short Stature – Further Considerations**

While NGHDS 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) NGHDS is not a single medical condition but rather a heterogeneous group of entities linked together by a common clinical sign: short stature. This contrasts with the currently approved GH indications which represent clinical conditions identifiable on the basis of defined clinical and pathological criteria other than short stature.

(2) NGHDS will expand appreciably the number of candidates to GH therapy at a significant financial cost. While previous indications for GH use are orphan indications and the number of candidate patients is limited by the prevalence of the underlying disorders, the NGHDS indication has the potential to expand GH use up to an additional 1-1.7 million candidates who meet the statistical definition of short stature.

3) Ethical concerns over the use of GH in patients with NGHDS have been raised due to the difficulty of differentiating between GH-deficient and GH-sufficient states.

Insofar as NGHDS is a departure from previous approvals of GH use in children, the agency is seeking advice from this Advisory Committee. Specific questions formulated by the agency are attached.

# SUMMARY OF CLINICAL FINDINGS

## 1. INTRODUCTION

Humatrope (somatropin) is recombinant human growth hormone (GH). Humatrope treatment is currently approved for two pediatric indications [growth hormone deficiency (GHD) and Turner syndrome associated with short stature] and for one adult indication (growth hormone deficiency of adult or childhood onset). The approved pediatric Humatrope dose for GHD is 0.18 mg/kg/week to 0.3 mg/kg/week. The approved pediatric Humatrope dose for children with Turner syndrome and short stature is 0.375 mg/kg/week. Humatrope is approved as an injectable form given subcutaneously either three times per week or daily.

Eli Lilly and Company (the applicant) submitted to the Food and Drug Administration (the agency) a supplemental New Drug Application (sNDA) for Humatrope (somatropin) in support of a new pediatric indication. The new proposed indication is “*long-term treatment of non-growth hormone deficient short stature, defined by height SDS<sup>1</sup> ≤ -2.25, in pediatric patients whose epiphyses are not closed and in whom diagnostic evaluation excludes causes of short stature that should be treated by other means.*” The proposed weekly Humatrope dose for patients with NGHDSS is “up to 0.37 mg/kg”, divided equally and given 3 to 7 times per week.

## 2. BRIEF OVERVIEW OF THE CLINICAL PROGRAM

In support of this new indication the applicant presents efficacy and safety data in patients with NGHDSS from the following sources:

- a double-blind, randomized, placebo-controlled, long-term Humatrope clinical trial in 71 patients (study GDCH)
- a randomized, open-label, dose-response, long-term clinical trial of Humatrope in 239 patients (study E001)
- two short-term, open-label Humatrope studies previously presented to the agency (48 patients),
- a post marketing, observational research program supporting Humatrope safety (23 patients)
- a published meta-analysis of 38 GH clinical trials (10 controlled and 28 uncontrolled)

This review will focus on data from clinical trials GDCH and E001 because these two studies are the basis for the efficacy conclusions and the selected dose regimen. In addition, they provide the largest and longest patient exposure to support safety conclusions. Some of the features of these two clinical trials are summarized in Table 1 and described further in the next section.

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<sup>1</sup> Height SDS = height standard deviation score is the calculated number of standard deviations from the mean for age and gender.

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

Study Name	Clinical study characteristics					
	Design	No. and age of patients	Main inclusion criteria	Duration of treatment	Regimen	Criteria for evaluation
GDCH (USA)	Two-center, 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 <u>or</u> predicted height SDS $\leq -2.5$ ( $\leq -2.25$ 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 and height SDS $\leq -2. 0$ 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; y = year; D =dose.

\*Primary efficacy analysis.

### 3. CLINICAL TRIAL DESCRIPTION

#### 3.1 Pivotal Clinical Study GDCH

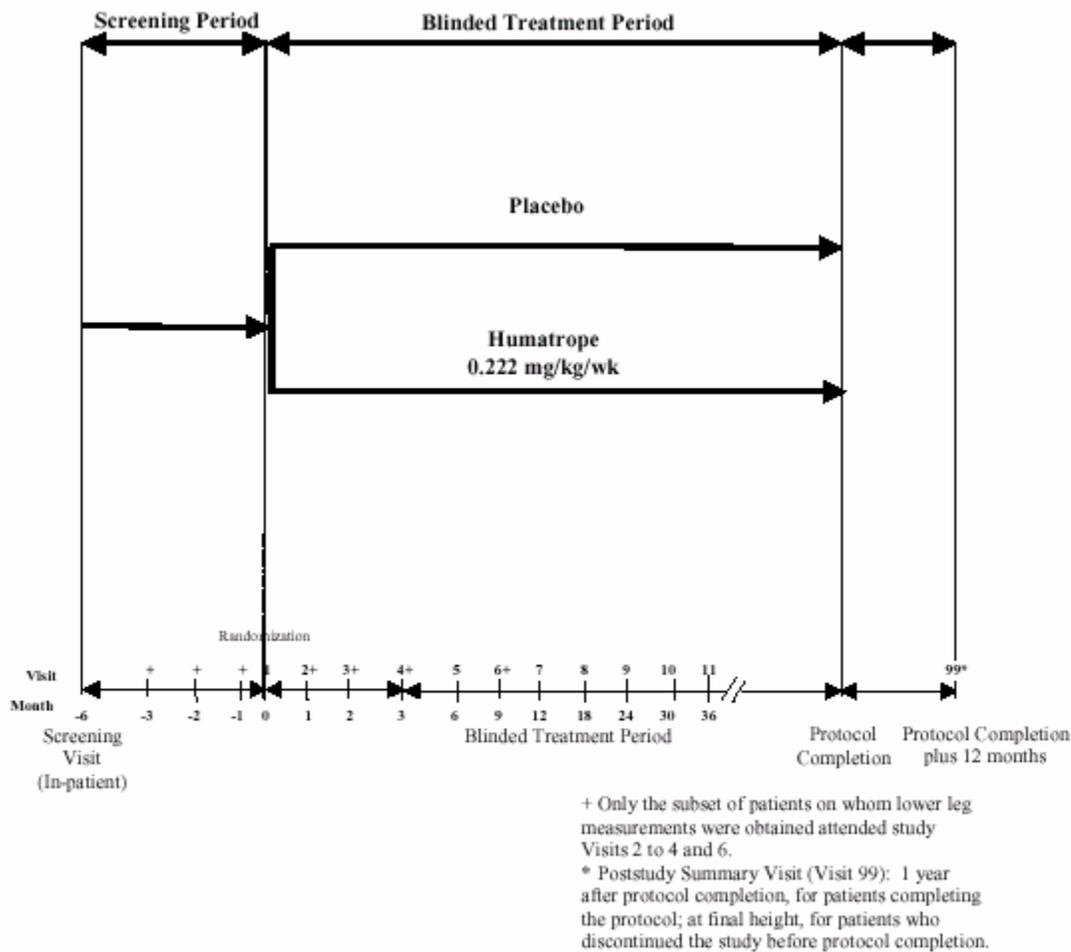
##### 3.1.1 Objective

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)

##### 3.1.2 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 1 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: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 1: Study design of trial B9R-MC-GDCH**



\*Source: Figure GDCH.9.1.

### 3.1.3 Main Inclusion and Exclusion Criteria

The main inclusion criteria are listed in Table 2.

**Table 2: Inclusion Criteria – Trial GDCH**

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

### 3.1.4 Baseline Patient Characteristics

The main growth-related parameters recorded at baseline are presented in Table 3. The mean height SDS was  $-2.78 \pm 0.48$ . The mean predicted adult height SDS at the initiation of treatment was higher ( $-2.09 \pm 0.79$ ). The mean bone age was delayed (bone age/chronological age ratio was  $0.84 \pm 0.12$ ). The target height SDS ( $-1.08 \pm 0.88$ ) 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 3: 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 <sup>2</sup> )	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. BP 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

### 3.1.5 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	Placebo	Total
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	N (%)	N (%)	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%)

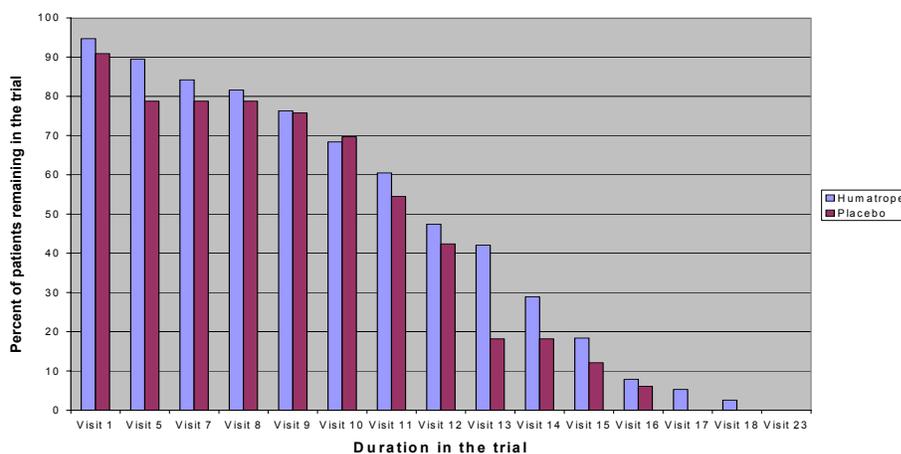
N=number of patients. % is percentage of patients within each group (column).

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

Source: Table GDCH.11.1

Figure 2 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. 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).

Figure 2: Patient Retention in Trial GDCH



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

### 3.2 Supportive Clinical Study E001

#### 3.2.1 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.

### 3.2.2 Study Design

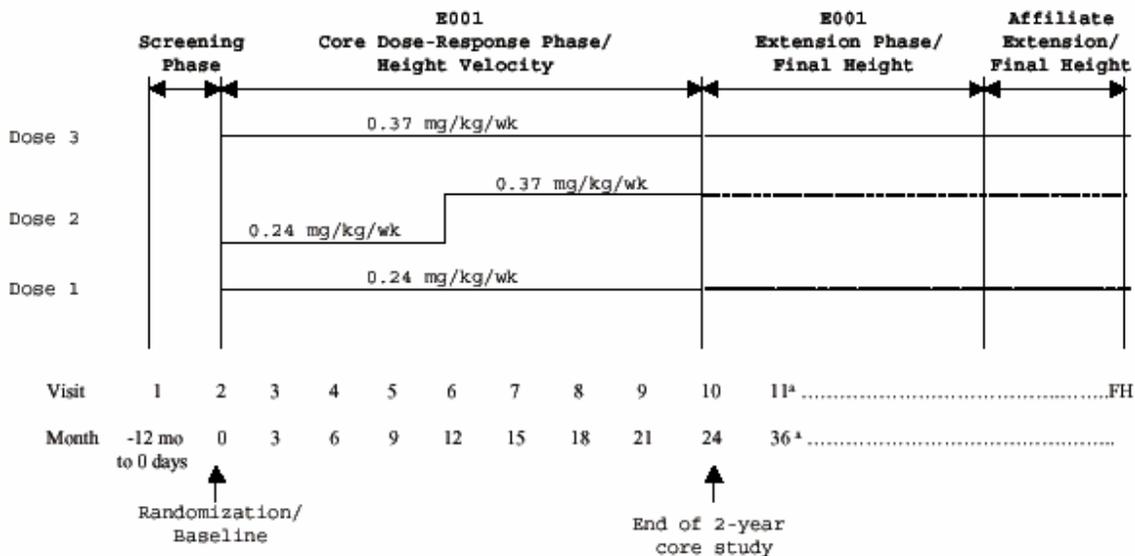
This clinical trial was a multinational, multicenter (28 study centers), randomized, open-label, three-arm, parallel, dose-response study conducted in Europe. The study consisted of a screening phase, during which patients were assessed for study eligibility, followed by a three-arm, randomized, open-label, 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 3 presents the study design for clinical trial E001.

**Figurer 3: Study Design for Trial E001**



Source: FigureE001.9.1. FH = final height.

### 3.2.3 Main Inclusion and Exclusion Criteria

A total of 239 patients with NGHDSS were randomized. The main inclusion criteria are listed in Table 5:

**Table 5: Inclusion Criteria – Study E001**

<b>Height</b>	Height < 2.0 standard deviation (SD) below the mean for age for British standards
<b>Height velocity</b>	below the 25 <sup>th</sup> 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 <sup>th</sup> percentile for bone age.
<b>Chronological age</b>	5 years of age or older
<b>Bone age</b>	less than 10 years in girls and less than 12 years in boys (TW2-RUS method)
<b>Tanner stage</b>	Stage I
<b>Growth hormone diagnostic sufficiency criteria</b>	Peak GH response of greater than 20 mU/L (approximately 10 ng/mL) in <b>one</b> standard stimulation test.
<b>Thyroid function</b>	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.

### 3.2.4 Baseline Patient Characteristics

The main growth-related parameters recorded at baseline are presented in Table 6. The mean height SDS of  $-3.21 \pm 0.70$  was lower than the mean height SDS recorded at baseline in trial GDCH ( $-2.78 \pm 0.48$ ). The mean predicted adult height SDS of  $-2.63 \pm 1.08$  was also lower ( $-2.09 \pm 0.79$  in trial GDCH). The degree of delay in bone age was almost identical (bone age/chronological age ratio was  $0.82 \pm 0.15$  vs.  $0.84 \pm 0.12$  in trial GDCH). Similar to trial GDCH, the target height SDS ( $-1.23 \pm 0.90$ ) 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 6: 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 <sup>2</sup> )	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 “Dose 3” arm, and seven patients overall had unspecified target heights.

### 3.2.5 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.

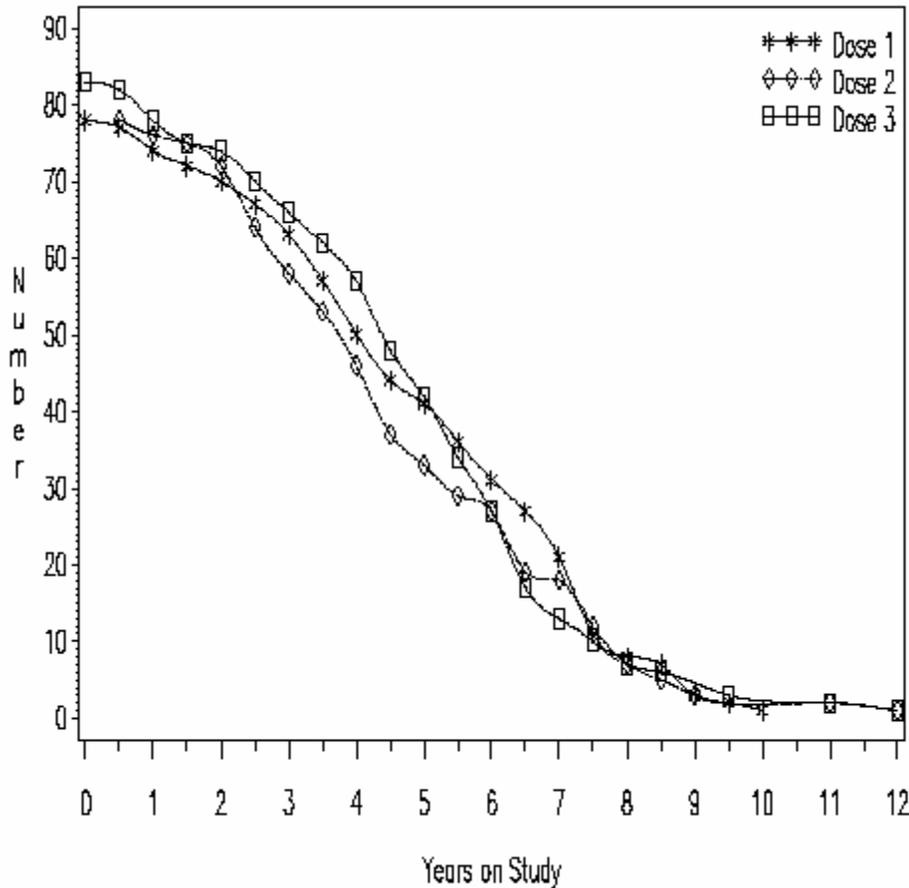
Of the 239 patients in the All Randomized Patient Population, 30 patients discontinued between baseline and end of the 2-year core study. The remaining 209 patients (Dose 1, n = 70; Dose 2, n = 67; Dose 3, n = 72) were included in the Two-Year Height Velocity Population (efficacy dataset for height velocity 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. Of the 50 patients who reached final height, almost half (22 patients) were from one center in the Netherlands.

Figure 4 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. 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. More

patients in the high dose arm discontinued due to patient decision then in the low dose arm (38 patients or 45.8% vs. 22 patients or 28.2 %).

**Figure 4: Patient Retention In Trial E001**



Source: Figure E001.10.2.

#### 4. EFFICACY

This application provides evidence that Humatrope treatment is efficacious in increasing final height in patients with NGHDSS. The evidence of efficacy comes from three sources: (1) a placebo-controlled clinical trial in peripubertal patients (study GDCH), (2) a dose-response supportive study in prepubertal patients (Study E001), and (3) a recently published meta-analysis of 38 clinical trials of GH conducted in patients with NGHDSS.

##### 4.1 Pivotal Study GDCH

Trial GDCH demonstrates that Humatrope is superior to placebo in increasing final height. This clinical trial is unique in that it is the only double-blind, randomized, placebo-controlled trial to final height conducted in patients with NGHDSS. 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  $0.51 \pm 0.20$  standard deviation score (SDS) ( $p=0.017$ ) in the primary efficacy analysis which compared final height between the Humatrope and the placebo treatment arms. This treatment effect is equivalent to **3.7 cm<sup>1</sup>** (1.44 inches).

Additional analyses support the primary analysis. They are:

- an analysis of final height SDS for the 25 patients who completed the protocol; it showed a similar magnitude of treatment effect (height SDS of  $0.46 \pm 0.23$ ) and a trend towards statistical significance ( $p=0.061$ ).
- an intent-to-treat analysis of height SDS on patients with at least 6-months of height measurements on trial; it recorded a similar magnitude of treatment effect (height SDS of  $0.52 \pm 0.15$ ;  $p=0.001$ ).
- a Humatrope to placebo comparison of the height gained from the beginning of the treatment to final height in cm (treatment effect of  $5.71 \text{ cm} \pm 2.67$ ,  $p=0.040$ ).
- a Humatrope to placebo comparison of the height gained from the start of the treatment to final height in SDS (treatment effect of  $0.51 \pm 0.23$ ,  $p=0.034$ ).
- a Humatrope to placebo comparison of the difference between final height SDS and the baseline predicted height SDS (treatment effect of  $0.46 \pm 0.21$ ,  $p=0.043$ ).
- a repeated measures analysis (treatment effect of 5 cm or  $0.69 \pm 0.13$  height SDS)
- a larger proportion of patients in the Humatrope group achieved height threshold values considered important in clinical practice; among the patients followed to final height, 9 (41%) of the Humatrope-treated patients achieved final heights that were greater than the 5th percentile compared to none in the placebo group ( $p=0.015$ ).

The primary efficacy analysis was prespecified in the protocol. The secondary analyses were a mixture of prespecified and non-prespecified analyses. Individual analyses are presented in Appendix 1.

Table 7 highlights efficacy data that describes the magnitude of the Humatrope treatment effect. In addition to data presented in the sNDA it incorporates additional data provided in the applicant's briefing document.

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<sup>1</sup> One centimeter = 0.39 inches.

**Table 7: 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 the patients who remained on trial (see the statistical review for additional efficacy analyses comparing patients with final height and patients without final height data).

This magnitude of therapeutic effect has been achieved without evidence of undue acceleration of bone age and without change in the time of attainment of pubertal stages. 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.

## 4.2 Supportive Study E001

This European, 28-center, open-label, randomized, dose-response clinical trial in 239 patients with NGHDSS provides evidence of efficacy for a higher weekly dose of Humatrope than the one studied in the pivotal trial GDCH. Of the 239 patients enrolled, 50 patients had final height data. Among these, a Humatrope dose regimen of 0.37 mg/kg/week given in six daily injections (high-dose regimen) was superior to a Humatrope dose regimen of 0.24 mg/kg/week administered in the same fashion (low-dose regimen). Final height was a secondary endpoint. Final height analyses are listed below:

(1) Over a mean duration of treatment of 6.47 years, the high-dose Humatrope regimen resulted in a mean final height that exceeded the mean baseline predicted height by an average of **7.2 cm** ( $7.21 \pm 5.97$  cm or 1.9 height SDS;  $p=0.001$ ), whereas the low-dose Humatrope regimen had a smaller treatment effect of **5.4 cm** ( $5.36 \pm 3.20$  or 1.6 SDS;  $p<0.001$ ) for the same endpoint.

(2) On-treatment height SDS gain for patients with final height data was  $1.85 \pm 0.82$  SDS ( $p<0.001$ ) for the high-dose Humatrope regimen and  $1.55 \pm 0.58$  SDS for the low-dose Humatrope regimen ( $p<0.001$ ).

(3) The mean final height measured in the high-dose group was  $1.33 (\pm 5.01)$  cm or 0.1 SDS below the target height. The low-dose treatment group recorded a final height that was  $3.78 (\pm 7.34)$  cm below the target height.

(4) An intent-to-treat analysis of height SDS for the 209 patients with efficacy data at the end of the two-year “core” part of the study showed that patients in the high-dose group had a higher endpoint height SDS than the patients who received low-dose regimen. The treatment effect was  $0.51 \pm 0.18$  SDS ( $p<0.006$ ).

(5) A high-dose and low-dose regimen comparison using a repeated measures analysis of height SDS at age 18 for the patients in the intent-to-treat population shows a treatment effect of  $0.44 \pm 0.17$  ( $p= 0.012$ ).

(6) Analysis of covariance (ANCOVA) of final height SDS for patients with final height using baseline predicted final height SDS as a covariate records a higher mean final height SDS for the high-dose group when compared to low-dose group and a trend toward statistical significance ( $p=0.086$ ).

(7) Almost twice as many patients who received the high-dose Humatrope regimen achieved final heights greater than the 5th percentile when compared to low-dose Humatrope receiving patients.

None of the final height analyses were prespecified in the protocol. Patients with final height data in the high dose group were treated longer (mean = 7 years) than patients in the low dose treatment group (mean = 6.1 years). Compliance was not assessed in trial E001. Individual analyses are presented in Appendix 1.

Table 8 lists efficacy data that describes the dose-effect for the Humatrope treatment. In addition to data presented in the sNDA it incorporates data provided in the applicant’s briefing document.

**Table 8: 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) <sup>#</sup>	0.003

Highlighted areas = protocol specified analyses

\*FH = final height population

\*\* HV = 2-year height velocity population

<sup>#</sup> Dose 3 minus Dose 1 (difference of least square means).

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

In an attempt to integrate some of the efficacy data from trial E001 with those from trial GDCH, Table 9 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). Important 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 9: Efficacy comparisons across trials**

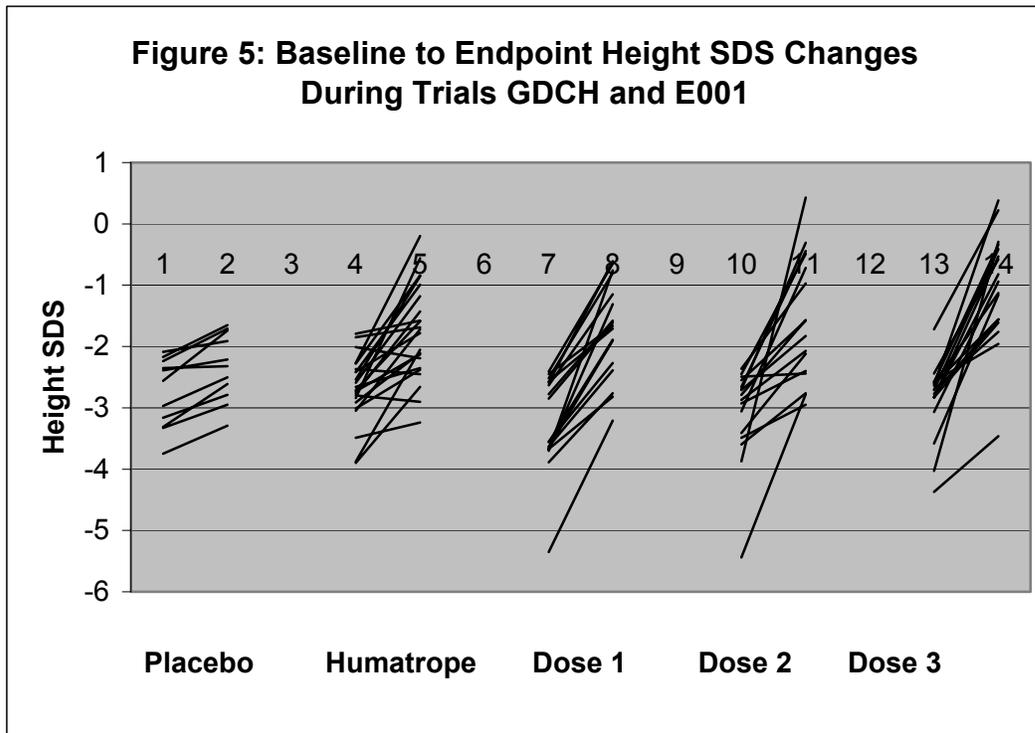
(updated from the applicant’s draft Briefing Document)

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	NA	NA	NA
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.

### 4.2.1 Individual Efficacy Trends

Figure 5 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. “Dose 1” is the low-dose regimen and “Dose 3” is the high-dose regimen.



### 4.3 Supportive Studies from Peer-reviewed Medical Literature

The magnitude of Humatrope treatment effect on final height observed in trials GDCH and E001 is consistent with the results of a recent meta-analysis of 38 clinical trials (10 controlled and 28 uncontrolled) of GH in patients with NGHDSS (Finkelstein B S et al, 2002).. This meta-analysis estimates a benefit on adult height of 4-6 cm (range of 2.3 to 8.7 cm).

The largest single clinical study in children with NGHDSS published to date records a magnitude of treatment effect that is consistent with the treatment effect noted in trials CDGH and E001 (Hintz RL et al., 1999). This trial was conducted in 121 patients and records a mean difference between achieved adult height and predicted adult height at treatment initiation of  $5 \pm 5.1$  cm for boys and  $5.9 \pm 5.2$  cm for girls. It was conducted in a group of patients whose baseline growth characteristics were similar to those of the patients enrolled in studies GDCH and E001 and used a comparable GH dose (0.3 mg/kg/week). The efficacy information recorded in this trial was also included in the above-mentioned meta-analysis.

## 5. SAFETY

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 associated with short stature). This observation is based on a relatively small number of patients with NGHDSS (> 300). Most patients, however, were exposed to Humatrope for long periods of time (mean time on study was 3-4 years depending on the trial, and as long as 9-11 years in a few patients).

Safety analyses come from three main sources: (1) clinical trial GDCH, (2) clinical trial E001, and (3) a comparison of safety data accumulated during the NGHDSS drug development program with the safety data accumulated for the GHD and Turner syndrome drug development programs.

The safety data accumulated during the pivotal trial GDCH was extensive in scope and covered, in addition to adverse events, a broad range of analytes. Some of the analytes evaluated known metabolic effects of GH (e.g. effects on carbohydrate metabolism and thyroid function), while others were standard safety analytes (e.g. hematology, urinalysis). The safety data accumulated in trial E001 was 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).

Ascertainment of adverse events was different between the two trials. 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.

The level of patient exposure in the NGHDSS trials (1212 patient-years) is almost the same as the patient exposure recorded for the two currently approved pediatric indications for Humatrope (GHD and Turner syndrome). However, the target population is appreciably larger.

This review will summarize the safety analyses for the following categories: deaths, serious adverse events (SAEs), trial dropouts, treatment-emergent adverse events (TEAEs), and laboratory results. The data will be presented for trials GDCH and E001 first and comparisons with the data recorded during the GHD and Turner syndrome Humatrope clinical trials will follow. More extensive analyses are presented in Appendix 1.

There were no deaths recorded during any of the NGHDSS clinical trials. Two patients, however, were diagnosed with malignancies. A 12-year-old male enrolled in study E001 had an abdominal desmoplastic small round cell tumor diagnosed during the clinical trial, discontinued the trial and died four years later; the patient received 0.24 mg/kg/wk of Humatrope for approximately 6.4 years prior to study discontinuation. In addition, an 11-year-old patient in trial GDCH has been diagnosed with stage 3B Hodgkin disease after receiving 0.22 mg/kg/week of Humatrope for 19 weeks.

Most serious adverse events (SAEs) recorded during the NGHDSS clinical trials were due to conditions commonly occurring in pediatric patients (e.g. accidental trauma). In trial GDCH, SAEs occurred twice more often in the Humatrope treatment group (7 patients or 13.5%) than in

the placebo group (2 patients or 6.5%), but most SAEs were accidental injuries. The most remarkable SAE in this trial occurred in the Humatrope treatment group. It is the case of malignancy (Hodgkin lymphoma) previously mentioned.

Clinical trial E001 recorded a total of 38 SAEs in 31 patients. There was a higher incidence of SAEs in patients receiving the high-dose regimen (16 patients or 19.3%) compared to the low-dose regimen group (11 patients or 14.1%). However, no single adverse event showed a dose-dependent pattern of incidence and most SAEs represented either interventions for common childhood conditions (tonsillectomies, appendectomies, etc.) or accidental injuries. One remarkable SAE is the previously mentioned malignancy (abdominal desmoplastic small round cell tumor). In addition, there were two SAEs that represent conditions known to be associated with GH treatment. They were arthralgia and slipped capital femoral epiphysis. One patient (high-dose group) developed arthralgia of left 2<sup>nd</sup> metatarsus-1<sup>st</sup> phalanx which required 2 corticosteroid infiltrations and surgery. Another patient (also high-dose group) was diagnosed with slipped capital femoral epiphysis and posttraumatic fracture of the caput femoris immediately following a seizure (this patient also discontinued the study).

There were few patient discontinuations due to adverse events among the patients who received Humatrope. One patient discontinued in trial GDCH due to a diagnosis of Hodgkin lymphoma. Three patients discontinued in trial E001 due to desmoplastic abdominal tumor (low-dose), slipped capital femoral epiphysis (high-dose), and glucose intolerance/elevated HbA1c (low-dose), respectively.

There were no distinct patterns of treatment-emergent adverse events (TEAEs) associated with Humatrope use in patients with NGHDSS. 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. 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.

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. In this trial, one patient discontinued due to glucose intolerance/elevated HbA1c. One additional patient had elevated HbA1c 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.

In addition to safety analyses for the data collected during trials GDCH and E001, the applicant submitted a comparison of the safety profile of Humatrope among patients with GHD, Turner syndrome, and NGHDSS. The results of this analysis, requested by the agency, are more difficult to interpret since the safety information was ascertained and collected in different ways in various trials. In addition, trials had different designs and duration. Other confounding factors are the different background rates of disease-specific adverse events and the variations in Humatrope dose regimens between studies. With these limitations in mind, several observations can be made:

- 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 (demoplastic 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.

## **6. DOSING**

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), as well as long-term treatment (as judged by greater final height than 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). 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. Such a statement is limited by the relatively small database (300 patients). Data on IGF-I serum concentrations was presented only for the 0.22 mg/kg/week regimen in study GDCH and were mostly within 3 SD from the population mean. Whether IGF-I serum concentrations are further elevated with the 0.37 mg/kg/week is not known since this information has not been presented in the sNDA.

## **7. General Comments on NGHDSS as a New Indication**

The FDA approved pediatric indications for GH treatment are:

- growth hormone deficiency
- chronic renal failure with short stature
- Turner syndrome
- Prader-Willi syndrome
- small for gestational age children without catch up growth by age 2 years

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.

The currently approved GH pediatric indications 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. Indeed, 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). In this respect the NGHDSS indication contrasts with prior GH approvals.

Ethical concerns have been raised over the use of GH in patients with NGHDSS by those who hold the view that these are normal, albeit short, children (AAP, 1997; Brook CG, 1997). These concerns include, among others:

- social justice considerations (the cost of the treatment is prohibitive and patients from well-off sectors of society will benefit from the treatment preferentially)
- resource allocation concerns (the shift of financial resources away from other unmet medical needs)
- the relationship between the size of the treatment effect, the cost of treatment and the discomfort associated with daily injection for prolonged periods of time
- the difficulty in accurately differentiating between “normality” and “abnormality” when such definitions are not strictly medical but incorporate sociocultural variables and have statistically defined boundaries
- the difficult task of balancing the potential stigmatization of normal children with the unhappiness, loss of quality of life, and educational/social disadvantages of short children
- avoiding unnecessary GH augmentation therapy

In the face of such a complex decision, anywhere from < 18% up to 64% of pediatric endocrinologists would treat children with NGHDSS and clinical characteristics similar to those of the subjects enrolled in NGHDSS clinical trials. (Cuttler L et al., 1996).

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 is limited to approximately 100,000 patients (GH Research Society Consensus statement, 2001). In contrast, GH treatment for patients with NGHDSS could add between 1 million and 1.7 million children in the US at an estimated cost of \$18-22 billion (Cuttler L. et al., 1996, Finkelstein BS et al., 1998). This cost estimate is based upon a presumed treatment of non-GHD children with heights below the third percentile (approximately 2 SD below the population mean). It contrasts sharply with the estimated annual cost of \$182 million for the US patients with classical GH deficiency. Even if the restrictive criterion proposed by the applicant (height SDS  $\leq$  -2.25) were to be applied, resulting in the exclusion of up to 46% of patients with non-GHD short stature, the potential number of candidates for GH therapy is many multiples of the number of patients currently treated.

## APPENDIX 1

### A. Efficacy Analyses

#### A.1 Trial GDCH

##### A.1.2 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 10. The Humatrope effect of 0.51 SDS corresponds to a mean 3.7 cm difference between groups. The mean age at assessment of final height for the Final Height Population was 18.6 years for Humatrope-treated patients and 19.1 years for placebo-treated patients.

**Table 10: Final Height SDS (Analysis of Covariance-Final Height Population)**

	<b>Humatrope (n=22)</b>	<b>Placebo (n=10) <sup>a</sup></b>	<b>Effect <sup>b</sup></b>	<b>p-value</b>
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.

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

<sup>b</sup> Value represents the difference in the final height SDS between the Humatrope-treated group and the placebo-treated group.

Source: Table GDCH.11.9.

##### A.1.3 Secondary and Other Analyses

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

Table 11 presents 1) the ANCOVA of height SDS at endpoint (last observation carried forward) for the Efficacy Evaluable Population and 2) the ANCOVA of final height SDS for the Protocol Complete Population. Both analyses were prespecified in the protocol. Both use the baseline predicted height SDS as covariate.

**Table 11: Analysis of Covariance of Endpoint Height SDS for the Efficacy Evaluable Population and Final Height for the Protocol Complete Population**

Population	Humatrope	Placebo	Effect <sup>a</sup>	p-value
Efficacy Evaluable				
n	35	27 <sup>b</sup>		
Endpoint height SDS <sup>c</sup>	-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.

<sup>a</sup> Values represent the difference in endpoint or final height SDS between the Humatrope-treated group and the placebo-treated group.

<sup>b</sup> 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.

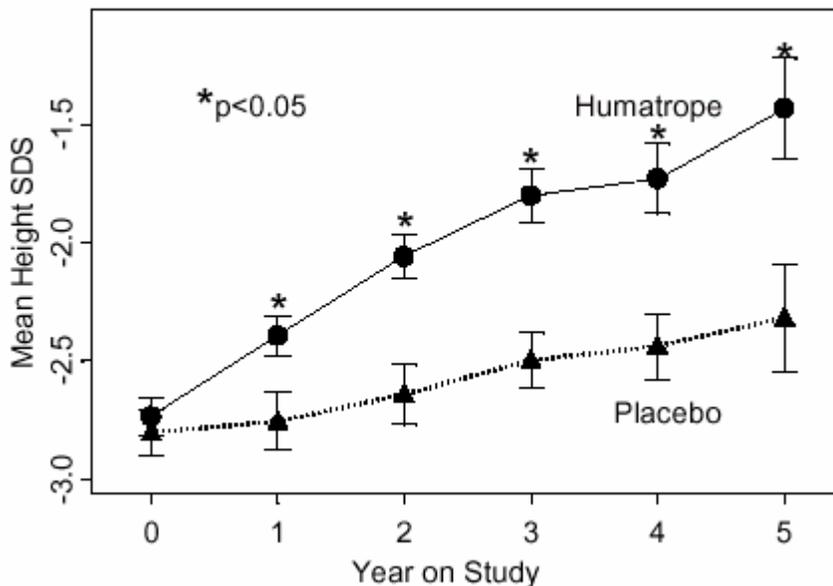
<sup>c</sup> Endpoint height represents the last measured height.

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 6. Although the baseline height SDS was similar between the two treatment groups, 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. Error bars represent 1 SD.

Figure 6: 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 12. Compared with placebo-treated patients, Humatrope-treated patients had a significantly greater difference in final height SDS minus baseline predicted height SDS (prespecified), final height SDS, and gain in height (both SDS and cm).

**Table 12: Final Height Characteristics Final Height Population**

PARAMETER	HUMATROPE (n=22)	PLACEBO (n=11)	EFFECT	P Value
FHSDS - BPHSDS*	0.32 (0.55)	-0.14 (0.59)	0.46	0.043
Final height SDS	-1.77 (0.78)	-2.34 (0.55)	0.57	0.039
Height gain (SDS)**	0.93 (0.73)	0.42 (0.23)	0.51	0.034
Height gain (cm)**	28.30 (7.38)	22.58 (6.90)	5.71	0.040

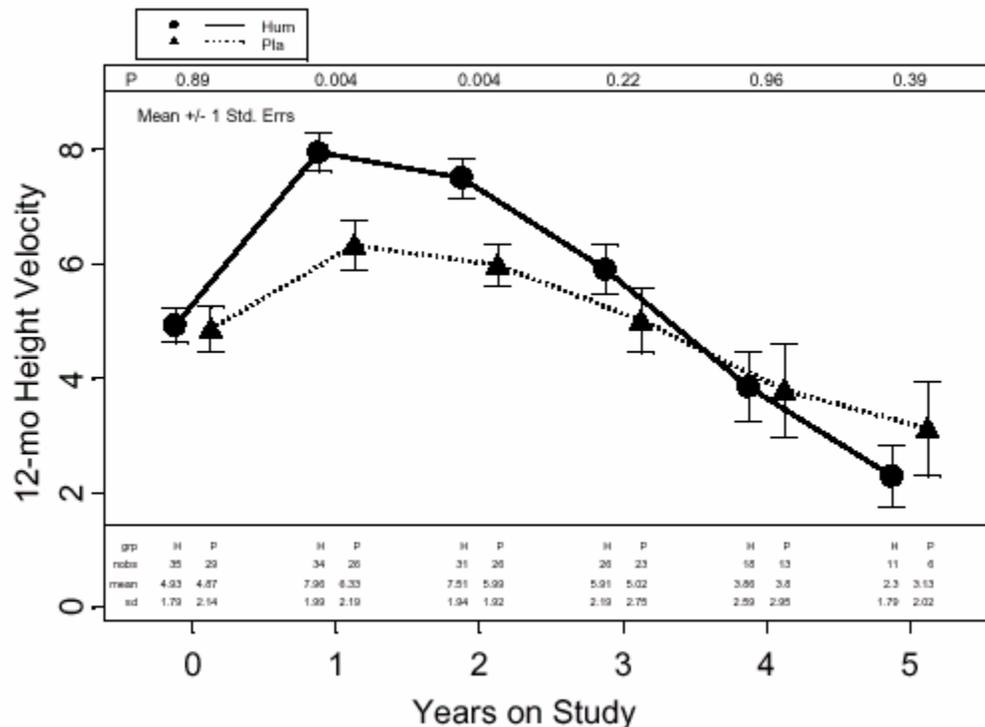
Note: Data are expressed as mean(standard deviation).  
 Abbreviations: n = number of patients; SDS = standard deviation score  
 FHSDS = final height standard deviation score  
 BPHSDS = baseline predicted height standard deviation score  
 \* n=10 for placebo, as one patient did not have a baseline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

Source: Table 3. H. 8.

## Twelve-month Velocity for the Efficacy Evaluable Population

The 12-month height velocity by years on study for the Efficacy Evaluable Population is presented in Figure 7. 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 7: Twelve-month Height Velocity by Year on Study**

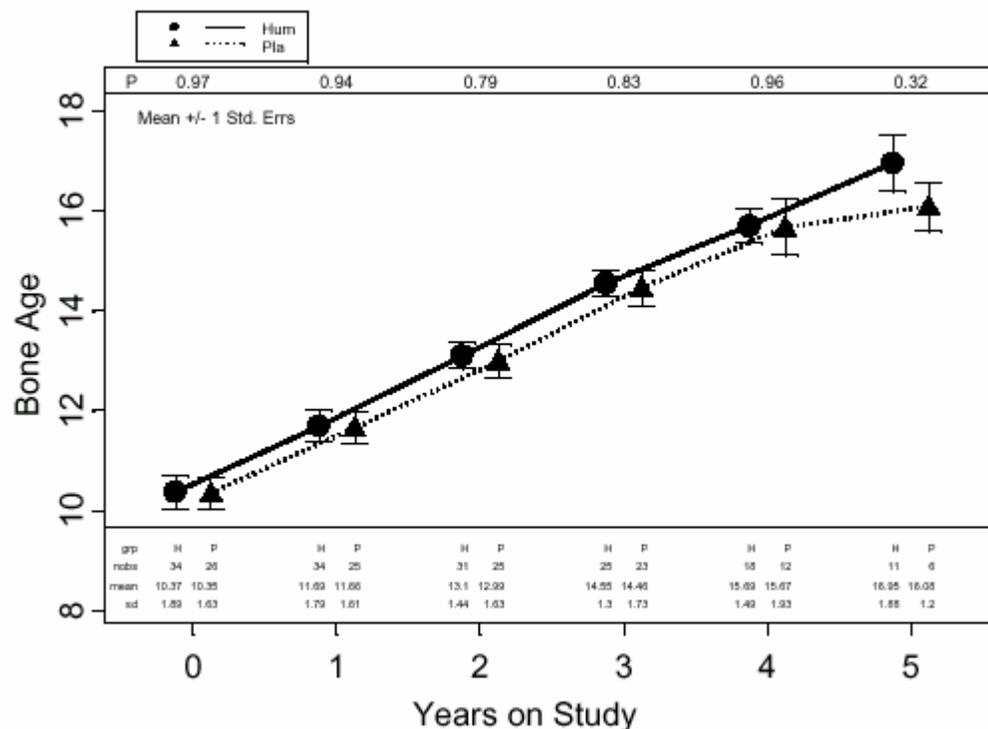


Source: Figure GDCH.11.4.

## Bone Age by Year on Study

The changes in height velocity were not associated with a statistically significant difference in bone age between treatments (Figure 8).

Figure 8: Greulich-Pyle Bone Age (Years) by Year on Study



Source: Figure GDCH.11.5.

## 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 shows a mean treatment effect of Humatrope on height SDS at age 18 years of  $0.69 \pm 0.13$  ( $p < 0.0001$ ), which corresponds to 5.0 cm (Table 13).

Table 13: 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 <sup>a</sup>	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.

<sup>a</sup> 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 5<sup>th</sup> and 10<sup>th</sup> Percentiles for Height

Table 14 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 final height. 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 difference did not reach statistical significance. These analyses were not specified in the protocol.

**Table 14: Patients with Final Height Above 5th or 10th Percentile -Final Height Population**

Number of Patients Above	Humatrope (n=22)	Placebo (n=11)	p-value <sup>a</sup>
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.

<sup>a</sup> Fisher's exact test for between-group differences.

Source: Table 3.H.9.

## A.2 Trial E001

### A.2.1 Primary Analysis

The predefined primary efficacy variable was height velocity. The primary efficacy analysis was the change in height velocity (cm/y) from pretreatment to the two-year endpoint. The primary comparison was between Dose 1 (0.24 mg/kg/wk) and Dose 3 (0.37 mg/kg/wk) treatment arms. Table 15 presents the effect of Humatrope on height velocity from pretreatment two-year endpoint.

**Table 15: 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
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	4.67	0.45
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

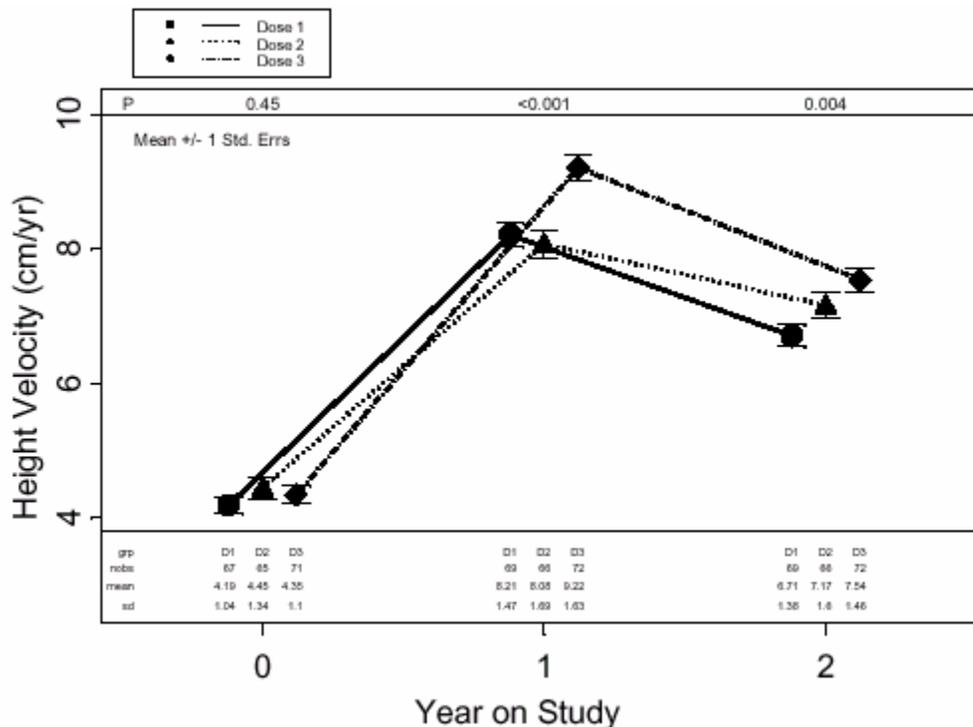
Source: Table E001.11.6. Dose 1 = 0.24 mg/ kg/ wk, Dose 2 = 0.24- 0.37 mg/ kg/ wk, Dose 3 = 0.37 mg/ kg/ wk.

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).

### A.2.2 Other Analyses

With the exception of the primary analysis, none of the other analyses were prespecified. Figure 9 summarizes the height velocity changes on study for all three treatment groups. It includes only patients with height velocity determinations at one year and two years of study.

**Figure 9: Height Velocity by Time on Study in the Two-year Height Velocity Population.**Source: Figure



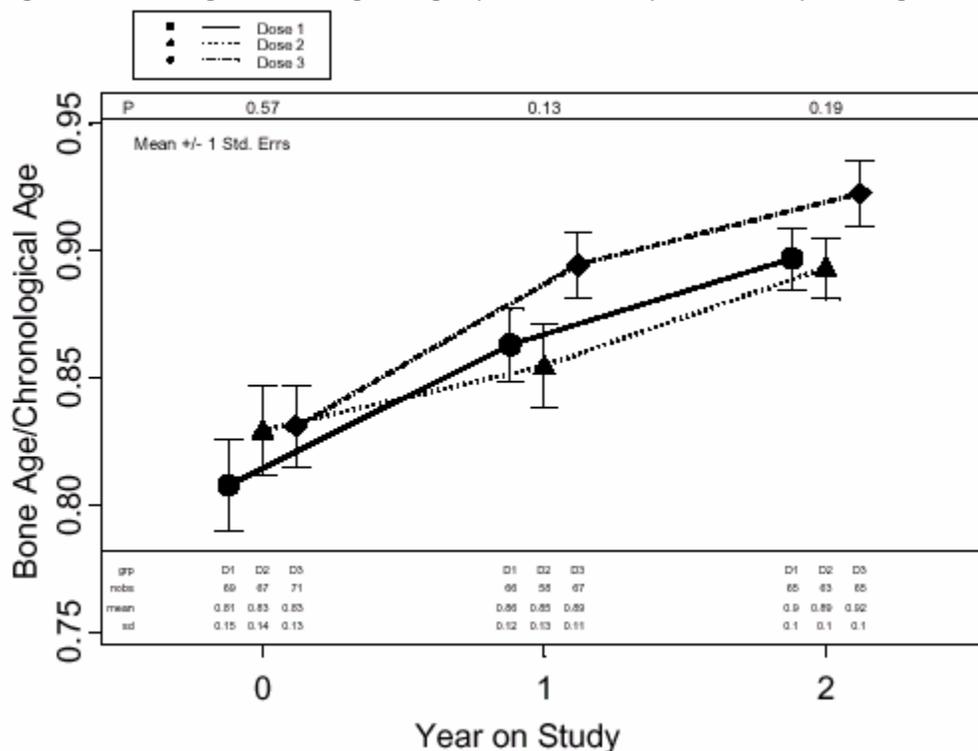
E001.11.1. Dose 1 = 0.24 mg/ kg/ wk, Dose 2 = 0.24- 0.37 mg/ kg/ wk, Dose 3 = 0.37 mg/ kg/ wk.

First-year height velocity was significantly greater in Dose 3 arm when compared to Dose 1 arm ( $p < 0.001$ ) or in Dose 2 arm ( $p < 0.001$ ), and was similar between Dose 1 and Dose 2 arms ( $p = 0.631$ ). Height velocity in the second year in Dose 3 arm was still significantly higher than Dose 1 arm ( $p = 0.001$ ), but no longer significantly greater than Dose 2 arm ( $p = 0.138$ ). In Dose 2 arm, height velocity in the second year was higher than in Dose 1 arm, but this difference was not statistically significant ( $p = 0.076$ ).

### Bone Age to Chronological Age by Time on Study

The ratio of bone age to chronological age by time on study in the Two-Year Height Velocity Population is presented in Figure 10. 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.

Figure 10: Bone Age/ Chronological Age by Time on Study in the Two-year Height Velocity Population



Source: Figure E001.11.2.

### 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 16. 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 [as measured within-treatment group by mean final height minus mean baseline predicted height, ranged from approximately 5.4 cm (Dose 1) to 7.2 cm (Dose 3)]. The treatment effect as measured by mean final height SDS minus baseline height SDS (height SDS gain) ranged from 1.55 SDS (Dose 1) to 1.85 SDS (Dose 3). Patients who received the highest Humatrope dosage (0.37 mg/kg/wk, Dose 3) reached a final height that was not significantly below target height (gender-adjusted midparental height), suggesting that they came closer than the other two regimens in achieving the predicted target height. Dose-response was noted across all above mentioned analyses when Dose 1 and Dose 3 regimens were compared.

**Table 16: Final Height Analyses - Final Height Population**

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

<sup>a</sup> Data are expressed as mean ± standard deviation (SD).

<sup>b</sup> 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 for the Two-Year Height Velocity Population and Repeated Measures Analysis**

Table 17 presents 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. 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 17: 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 <sup>a</sup>	-1.95 ± 0.13	-1.87 ± 0.12	-1.45 ± 0.12	0.51 ± 0.18 <sup>b</sup>	0.006
Repeated measures					
n	39	52	47		
Height SDS at age 18 years <sup>c</sup>	-1.26 ± 0.16	-1.56 ± 0.15	-0.82 ± 0.14	0.44 ± 0.17 <sup>d</sup>	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.

<sup>a</sup> 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.

<sup>b</sup> Value represents the difference in the endpoint height SDS between the Dose 1 group and the Dose 3 group.

<sup>c</sup> 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.

<sup>d</sup> 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

Analysis of covariance (ANCOVA) of final height SDS for the Final Height Population (using baseline predicted final height [BPH] SDS as the covariate) is provided. Although Dose 3 had a higher least squares mean (LSM) final height SDS than Dose 1, this difference did not reach statistical significance (p=0.086).

### Proportion of Patients who Achieved 5<sup>th</sup> and 10<sup>th</sup> Percentiles for Height

Table 18 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 18: Patients With Final Height Above 5th or 10th Percentile (Final Height Population)**

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

Abbreviations: n = number of patients.

<sup>a</sup> Fisher's exact test.

Source: Table E001.11.12.

## **B. Safety analyses**

This review will summarize the safety analyses for the following categories: deaths, serious adverse events (SAEs), trial dropouts, treatment-emergent adverse events (TEAEs), and laboratory results. The data will be presented for trials GDCH and E001 first and comparisons with the data recorded during several GHD and Turner syndrome Humatrope clinical trials (previously presented to the agency) will follow. Although a comparison of Humatrope safety profile across indications is important, several limitations need to be highlighted:

- different dictionaries, be they similar, were used to code adverse events during different studies (e.g. ELECT for studies GDAB and E001, COSTART for studies GDCT, GDCI, and GDCH)
- patients with GHD, Turner syndrome have different incidences of disease-specific associated illnesses, congenital malformations, surgical procedures
- trial designs were different in dose, duration, patient age ranges, presence or absence of a control group

### **B1.Deaths**

#### **B.1.1 Deaths in study GDCH**

There were no patient deaths reported during this study.

#### **B.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).

#### **B.1.3 Deaths: Comparison Across Studies for Different Indications**

Table 19 summarizes the patient deaths recorded during and after clinical studies.

**Table 19: Patient Deaths During and After Study**

Condition	Study	N	Humatrope	Control
GHD	GDAB	333	3 <sup>a</sup>	NA
TS	GDCT	136	0	1 <sup>b</sup>
TS	GDCH	230	0	0
NGHDSS	GDCH	68	0	0
NGHDSS	E001	239	1 <sup>c</sup>	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 patients discontinued from the study: (1) the first patient, 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 Humatrope for approximately 6.4 years died due to 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 association between this tumor and GH treatment.

## B.2. Serious Adverse Events

### B.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 008/1001, 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).

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).

### B.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 percentage of patients with SAEs: 16 (19.3%). These data are summarized in Table 20:

**Table 20: Serious Adverse Events (Study E001-All Randomized Patients)**

Serious Adverse Event	Dose 1 n (%)	Dose 2 n (%)	Dose 3 n (%)	Total 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 2<sup>nd</sup> metatarsus-1<sup>st</sup> 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 isolated 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 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.

### B.2.3 Serious Adverse Events: Comparison across Studies for Different Indications

Table 21 provides a summary of SAE incidence across studies and indications. SAEs were reported with similar frequency in patients with NGHDSS 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 NGHDSS 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 21: Serious Adverse Events**

	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 <sup>a</sup>	Humatrope <sup>b</sup>	Control	Humatrope <sup>c</sup>	Control	Humatrope <sup>d</sup>	Control	Humatrope <sup>e</sup>	
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	
Number of patients in group	333	74	62	184	46	37	31	239	
Number (%) of patients with SAE	90 (27.0)	20 (27.0)	8 (12.9)	10 (5.4)	4 (8.7)	5 (13.5)	2 (6.5)	31 (13.0)	
Total number of SAEs	157	31	9	11	4	5	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 GDCI 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 patients with 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.

### **B.3. Patient Discontinuations Due to Adverse Events**

#### **B.3.1 Patient Discontinuations Due to Adverse Events in study GDCH**

One Humatrope patient discontinued from the study due to an adverse event (AE). It was patient 008/1001 who discontinued the Humatrope treatment when he received a diagnosis of Hodgkin disease. One placebo patient (008/1068) was listed as discontinuation due to an AE (bike/motor

vehicle accident). The event, however, occurred after the patient, reportedly, completed the study.

### B.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 9-month 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-years 2-month 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-years 11-months 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.

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

Table 22 provides a summary of the number and percent of patients who discontinued study participation due to AEs (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 22: Patient Discontinuations Due to Adverse Events**

	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 <sup>a</sup>	Humatrope <sup>b</sup>	Control	Humatrope <sup>c</sup>	Control	Humatrope <sup>d</sup>	Control	Humatrope <sup>e</sup>
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	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 <sup>f</sup> (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 23 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 23: Patient Discontinuation Due to Adverse Events – Individual Patient Listing**

Trial	Treatment	Reason for Discontinuation	Age (y)	Treatment Duration (y)
<b>GDAB (GHD)</b>	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
<b>Study GDCT (Turner**)</b>	Humatrope	SGOT increased	14	1.6
	Humatrope	Intracranial hypertension (VP shunt malfunction)	7	1.4
<b>Study GDCI (Turner**)</b>	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
<b>Study GDCH (NGHDSS)</b>	Humatrope	Hodgkin disease	11	0.4
	Placebo*	Motor vehicle accident	16	2.3
<b>Study E001 (NGHDSS)</b>	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.

## B.4. Treatment-Emergent Adverse Events

### B.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 24 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. AEs with incidence  $\geq 2$  in the Humatrope group 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 24: Treatment-Emergent Adverse Events in Trial GDCH\***

<b>Adverse Event</b>	<b>Humatrope (N=37) n (%)</b>	<b>Placebo (N=31) n (%)</b>	<b>Ratio**</b>
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  $\geq 2$  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 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 in 3 Humatrope patients

#### **B.4.2 Treatment-Emergent Adverse Events in Trial E001**

Table 25 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 25: 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 ≥5% in any treatment arm.

### B.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.).

## B.5. Clinically Significant Treatment-Emergent Adverse Events

### B.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 26. 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). It should be noted that the conclusions of this analysis with respect to osteoarticular findings is not consistent with the observation that musculoskeletal TEAEs occur more frequently in the Humatrope treatment group than in the placebo group.

**Table 26: 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 number of patients, includes the longest exposure per patient (Table 27). Highlighted are the AE with higher incidence in the Humatrope group. They include otitis media, scoliosis, gynecomastia, and hip pain.

**Table 27: 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.

### B.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 28). 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 28: 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.

### B.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 combined 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 18.9% 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.

## **B.6. Clinical Laboratory Data**

A direct and detailed comparison among 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.

## B.6.1. Carbohydrate Metabolism

### B.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 29 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 29: 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 30 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 HgA1c levels.

**Table 30: Incidence of High or Low Carbohydrate Analytes after Baseline-Safety Population**

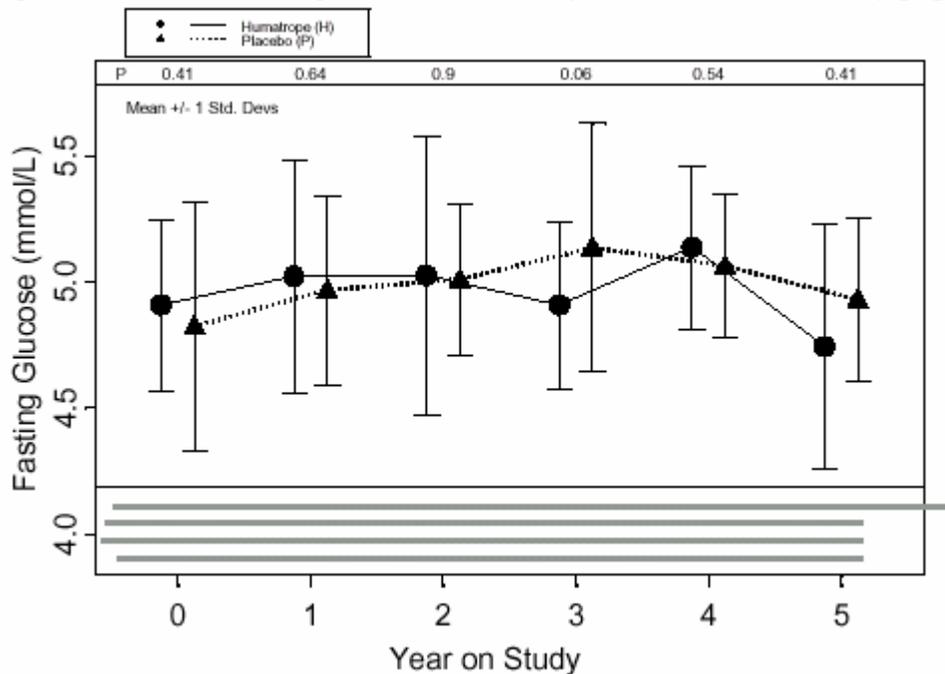
Lab test	Humatrope (N=36)			Placebo (N=30)		
	Normal n (%)	Low n (%)	High n (%)	Normal n (%)	Low n (%)	High n (%)
Fasting glucose	33 (91.7)	2 (5.6)	1 (2.8)	28 (96.6)	1 (3.4)	0
Fasting insulin	20 (58.8)	11 (32.4)	4 (11.8)	17 (60.7)	7 (25.0)	4 (14.3)
Adjusted HbA1c	22 (61.1)	13 (36.1)	2 (5.6)	16 (55.2)	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 11. There were no statistically significant between-group differences for this variable.

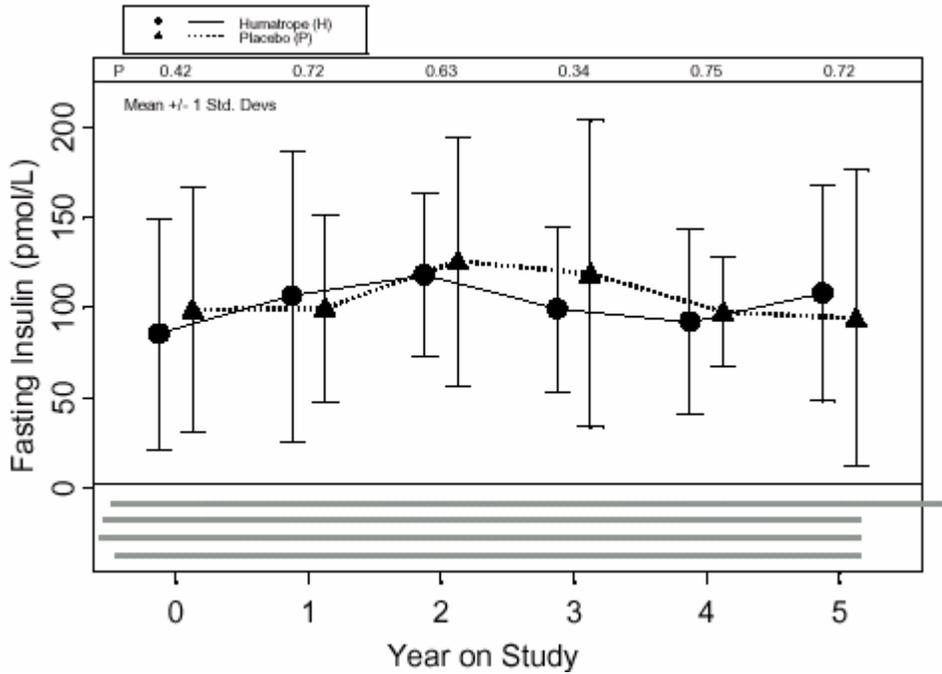
**Figure 11 : Mean Fasting Serum Glucose by Year on Study (Safety population)**



Source: Figure GDCH.12.4.

Similarly, there were no statistically significant between-group differences for mean fasting insulin at each year on study (Figure 12).

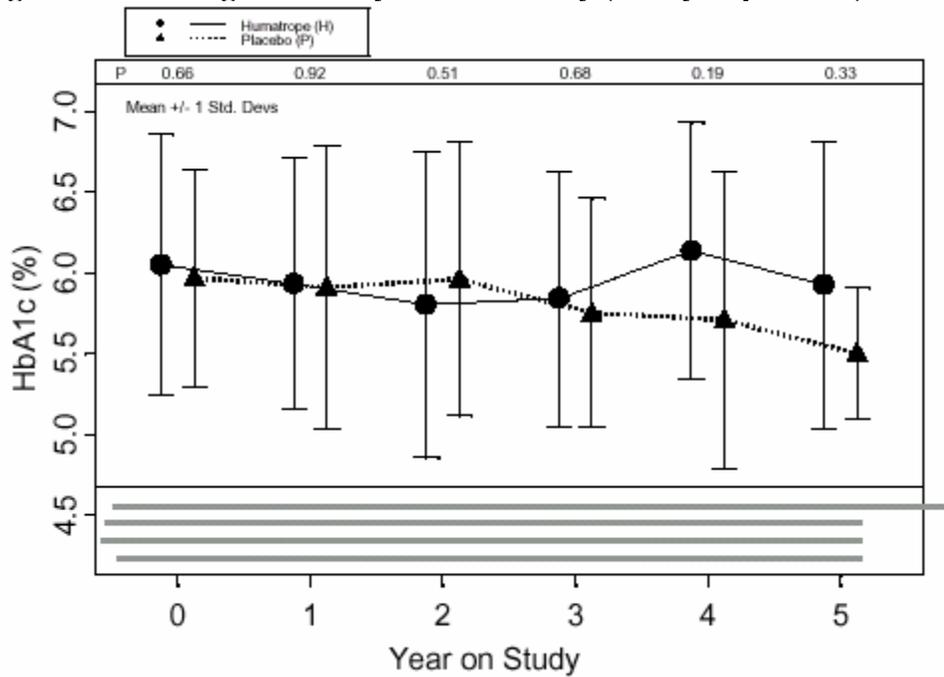
**Figure 12 : Mean Fasting Serum Insulin by Year on Study (Safety Population)**



Source: Table GDCH.12.5.

In addition, the absence of between-group differences for mean HbA1c is noted (Figure 13).

**Figure 13 : Fasting HbA1C by Year on Study (Safety Population)**



Source: Figure GDCH.12.6

### B.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 31 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 31: 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 32 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.

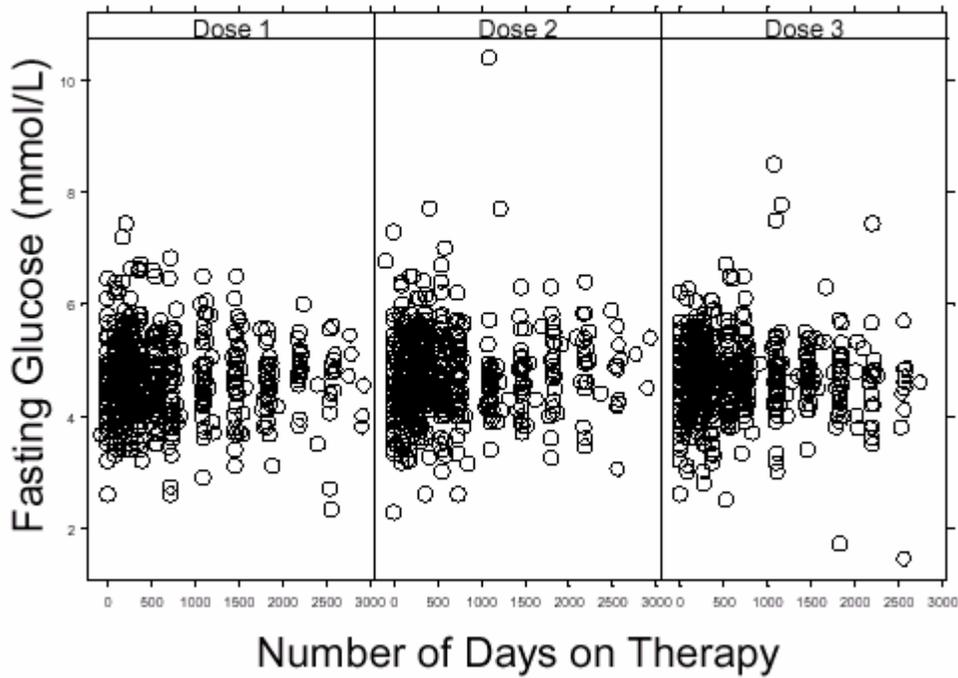
**Table 32: Incidence of High or Low Fasting Blood Glucose After Baseline (All Randomized Patients)**

Variable	Dose 1 (N=75)		Dose 2 (N=78)		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 14 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 14: Fasting Glucose by Number of Days on Treatment**

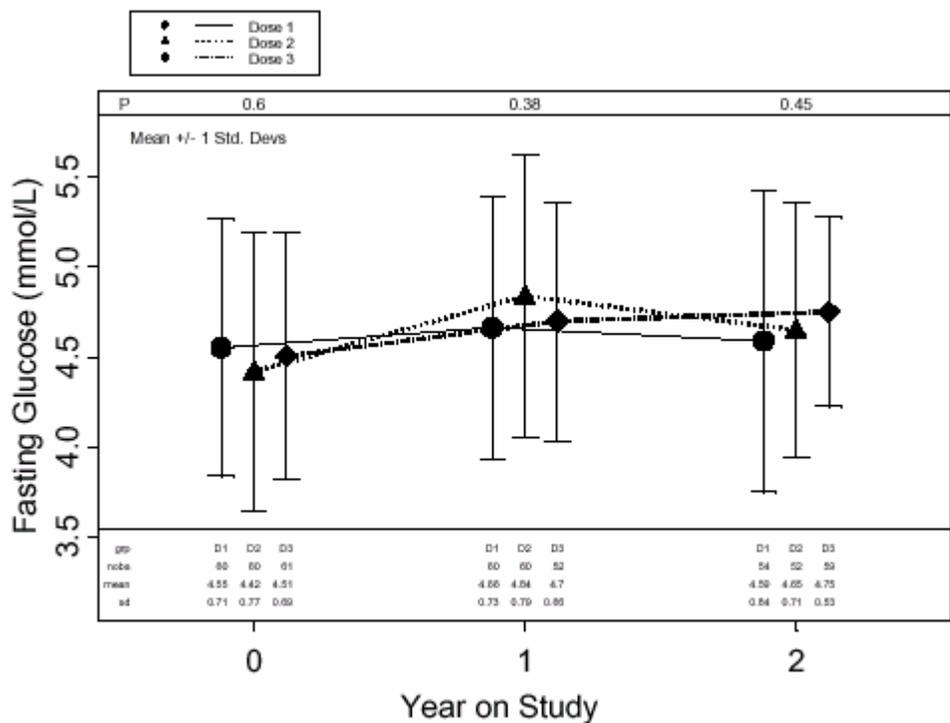


Source: Figure E001. 12. 1.

Figure 15 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 15: Fasting Glucose at Baseline, One-year, and Two-year for all Randomized Patients**

Source: Figure E001. 12. 3.

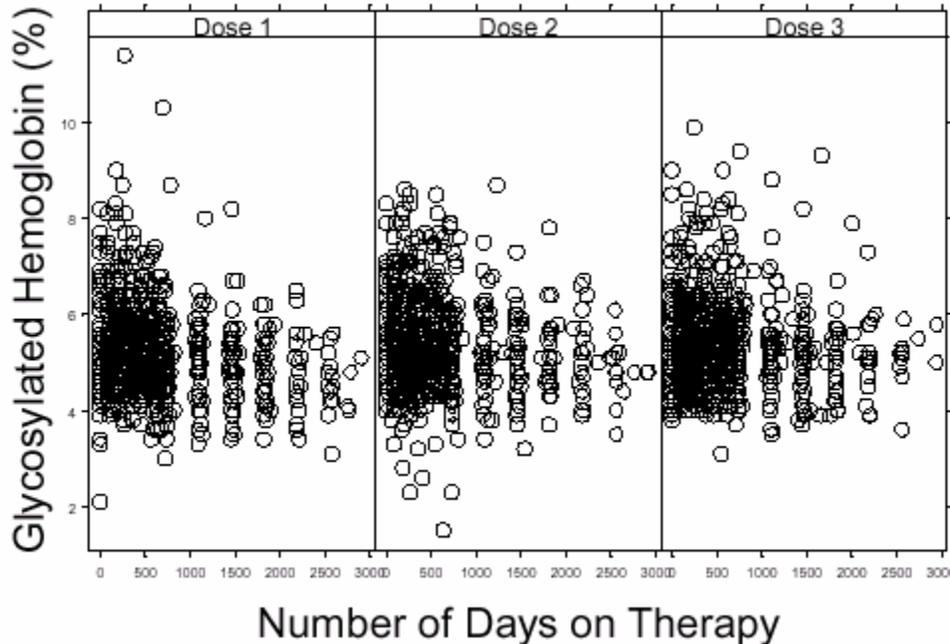


Glycosylated hemoglobin was measured locally at baseline and at subsequent visits during the “core phase” of the trial. Different methodologies were utilized (either glycosylated hemoglobin or HbA1c was analyzed). If the glycosylated hemoglobin was elevated, an oral glucose tolerance test (OGTT) was 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. 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 SD for gestational age.

Figure 16 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 range; no OGTT was performed. No additional information is available.

**Figure 16: Glycosylated Hemoglobin by Number of Days on Treatment**

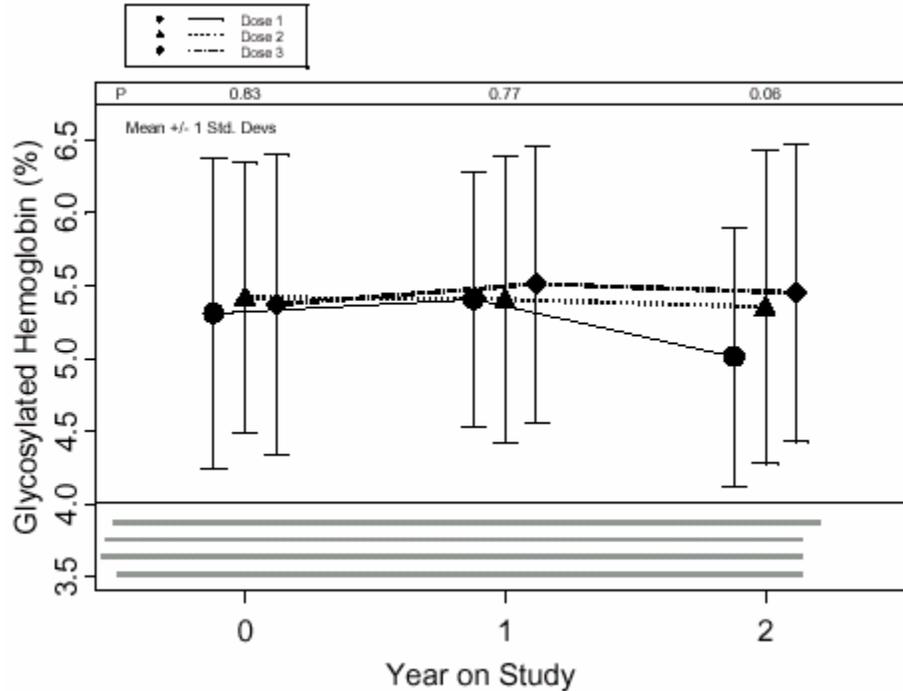


Source: Figure E001. 12. 2.

Figure 17 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 HgA1c 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 17: Glycosylated Hemoglobin at Baseline, One-year, and Two-year for All Randomized Patients**



Source: Figure E001. 12. 4.

### B.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 (GDC1) 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 33.

**Table 33: Fasting insulin changes from baseline to endpoint\***

Fasting insulin (pmol/L)	Study GDCI (Turner syndrome) N=230		Study GDCH (NGHDSS) N=68	
	Humatrope <sup>a</sup> N=80	Humatrope <sup>b</sup> N=117	Humatrope <sup>c</sup> 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.

<sup>a</sup> Dose = 0. 27 mg/ kg/ wk.

<sup>b</sup> Dose = 0. 36 mg/ kg/ wk. This column includes placebo- treated patients who were transitioned to Humatrope treatment after 1. 5 years.

<sup>c</sup> Dose = 0. 222 mg/ kg/ wk.

## B.6. 2. Thyroid Function

### B.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 34 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 34: Thyroid Function Changes from Baseline to Endpoint-Safety Population**

Lab Test	Treatment Group	N	Baseline Mean (SD)	Change Mean (SD)
T <sub>4</sub> -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 <sub>4</sub> (pmol/L)	Humatrope	36	17.053(2.892)	-0.858(3.653)
	Placebo	29	16.864(2.694)	0.754(4.967)
Total T <sub>3</sub> (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 35 presents the incidence of abnormal (low or high) values for thyroid analytes at any postbaseline timepoint in the study for both treatment groups.

**Table 35: Incidence of High or Low Thyroid function Tests after Baseline-Safety Population**

Lab test	Humatrope (N=36)			Placebo (N=30)		
	Normal n (%)	Low n (%)	High n (%)	Normal n (%)	Low n (%)	High n (%)
T <sub>4</sub> -RIA	22 (61.1)	11 (30.6)	3 (8.3)	22 (75.9)	6 (20.7)	1 (3.4)
Free T <sub>4</sub>	32 (88.9)	4 (11.1)	0	28 (96.6)	0	1 (3.4)
Total T <sub>3</sub>	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)
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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.

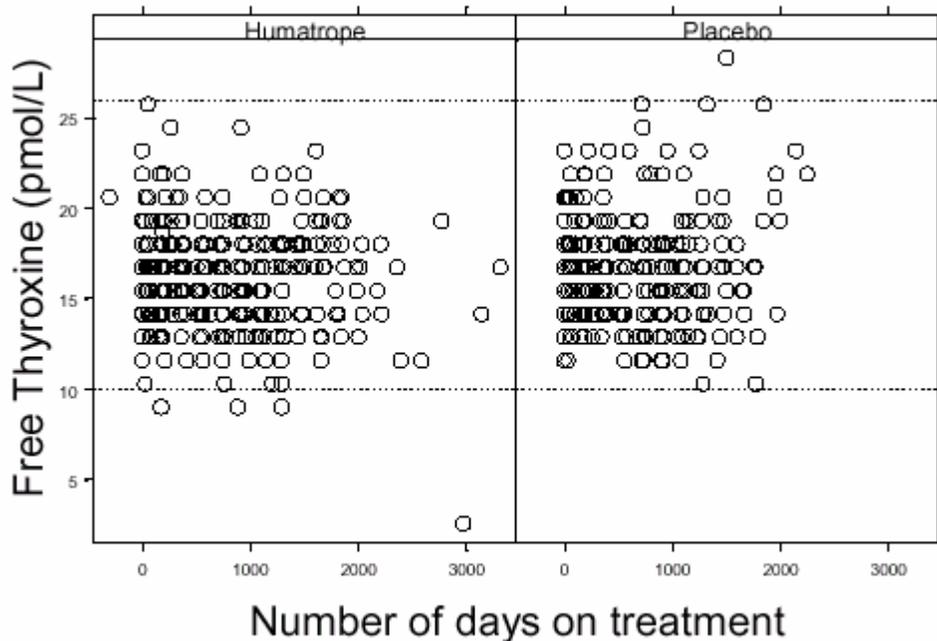
Six patients were reported to have hypothyroidism as a preexisting condition in the Safety Population at baseline (three in each treatment group). Five of these patients were receiving thyroid hormone replacement from Visit 1 (randomization). All patients appeared to have been controlled with replacement 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 18:

**Figure 18: Free Thyroxine by Number of Days on Treatment**

Source: Figure GDCH. 12. 7.

### B.6. 2.2 Thyroid Function in Trial E001



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

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.

### B.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 36. Criteria for data collection was 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 NGHDSS, hypothyroidism was diagnosed in two Humatrope-receiving patients study E001 (< 1%) and in one placebo patient in study GDCH.

**Table 36: Thyroid Function Changes from Baseline to Endpoint**

	GH Deficiency		Turner Syndrome			Non-Growth Hormone Deficient Short Stature		
	GDAB N=333	GDCT N=136	Control	Humatrope <sup>c</sup>	GDCI N=230	GDCH N=68	Control	E001 N=239
	Humatrope <sup>a</sup>	Humatrope <sup>b</sup>			Humatrope <sup>d</sup>	Humatrope <sup>e</sup>		Humatrope <sup>f</sup>
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 <sup>g</sup>					17.1 ± 2.9 <sup>h</sup>	16.9 ± 2.7 <sup>h</sup>	
Change to endpoint	-0.2 <sup>g</sup>					-0.9 ± 3.7 <sup>h</sup>	0.8 ± 5.0 <sup>h</sup>	
TSH (mU/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.

### B.6.3 Insulin-Like Growth Factor-I

#### B.6.3.1 Insulin-Like Growth Factor-I in Study CDGH

Table 37 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 37: Insulin-Like Growth Factor-I Changes from Baseline to Endpoint-All Males Safety Population**

Lab Test	Treatment Group	N	Baseline Mean (SD)	Change 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 38. 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 38: 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 (%)	Low n (%)	High n (%)	Normal n (%)	Low n (%)	High n (%)
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.

### B.6.3.3 Insulin-Like Growth Factor-I in Study E001

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

### B.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 39 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 mean 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 39: Insulin- Like Growth Factor- I Changes from Baseline to Endpoint**

	Turner Syndrome		Non-Growth Hormone Deficient Short Stature		p-value <sup>d</sup>
	GDCI N=230		GDCH N=68		
	Humatrope <sup>a</sup>	Humatrope <sup>b</sup>	Humatrope <sup>c</sup>	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 <sup>e</sup>					
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 GDCI 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 GDCI. 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.

## APPENDIX 2

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