



U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Pharmacoepidemiology and Statistical Science  
Office of Biostatistics

# STATISTICAL REVIEW AND EVALUATION

## CLINICAL STUDIES

**NDA/Serial Number:** 19-640 / SE1-033

**Drug Name:** Humatrope (somatropin)  
Recombinant human growth hormone

**Indication(s):** Non-growth hormone deficient short stature

**Applicant:** Eli Lilly and Company

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## Introduction

The applicant has presented the results from two clinical trials, Study B9R-MC-GDCH (henceforth referred to as GDCH) and Study B9R-EW-E001 (henceforth referred to as E001) (Table 1) to demonstrate the efficacy and safety of humatrope treatment in children who are not growth hormone deficient but are considered to be of extreme short stature (NGHDSS).

Height velocity is expected to be impacted by the administration of growth hormone. The largest impact on change in height velocity is generally seen in the first year of drug therapy in growth hormone deficient children; this is also seen to be the case in these studies of children with NGHDSS. The issue for this NDA is not whether humatrope impacts growth velocity but whether a significant (both statistically and clinically) improvement in final height is attained. Study GDCH was specifically designed to examine this issue so the primary efficacy variable is final height standard deviation score (SDS). On the other hand, Study E001 was designed to compare the height velocities after 2 years of treatment of three humatrope dose groups (Table 1). Nevertheless, final height data was collected in a long term extension of E001.

Table 1. Clinical Trials

Study (# of centers)	Design	Treatment groups (N)	Primary Efficacy Variable
B9R-MC-GDCH 2 centers USA	Randomized Parallel Blinded NGHDSS SDS $\leq$ -2.25 3 x week dosing	Placebo (33) Humatrope 0.22 mg/kg/wk (38)	Final Height Treat until height velocity<1.5 cm/yr Mean duration 3.5 yrs
B9R-EW-E001 28 centers Europe	Randomized Parallel Open-label Dose response NGHDSS SDS $\leq$ -2.0 6 x week dosing	Humatrope 0.24 mg/kg/wk Humatrope 0.24 (1 yr) / 0.37 mg/kg/wk Humatrope 0.37 mg/kg/wk	Height Velocity (HV) at 2 years Treat until height velocity<2.0 cm/yr Mean duration 4.5 yrs

Studies GDCH and E001 differ in several important ways:

- GDCH is a blinded, placebo-controlled study and E001 is an open-label dose response study
- 3 times a week dosing of a 0.22 mg/kg/wk dose was used in GDCH and 6 times a week dosing of a comparable dose (0.24) and a higher dose of 0.37 mg/kg/wk was used in E001
- Entry criteria differed as follows:

	GDCH	E001
Tanner Stage	I and II	I
Age (years)	9-15 females 10-16 males	$\geq$ 5
Peak GH response	>7 ng/mL	>~10 ng/mL
Height SDS	$\leq$ -2.5	$\leq$ -2.0

- Final height was measured when height velocity decreased to 1.5 cm/yr or less in GDCH and to 2 cm/yr or less in E001

- Median duration of treatment for the final height populations was about 4.5 years in GDCH and about 6.5 years in E001.

Due to time constraints imposed by scheduling of an advisory committee meeting, this reviewer was not able to review both studies to the same level of detail so more detail is given to GDCH, the placebo-controlled study, designed to assess final height. Also the literature review presented by the applicant is not reviewed here.

In both studies, a final height population was defined based on slowing of height velocity. For Study GDCH, 46% (33/71) of the randomized patients comprise the final height population and for Study E001, 21% (50/239) of the randomized patients comprise the final height population. Estimates from these populations may be biased since the final height populations are a subset of the randomized population. Intent-to-treat analyses including all randomized patients and height data measured before attaining final height are generally desirable but may introduce bias as well because of assumptions that must be made regarding growth patterns. Nevertheless, this reviewer presents several sensitivity analyses performed by both the applicant and by the reviewer with the goal of testing the robustness of the final height population results.

In addition to presenting the mean results from several statistical analyses of final height, this reviewer has designed several graphics to depict the individual patient data. Given the small numbers of patients in the final height populations, it is quite straightforward to visualize all the data and see the impact of therapy on individual patients. The intention is to provide information that will aid in the clinical interpretation of the statistical results.

All tables and graphs in this review were produced by this reviewer. Results computed by the reviewer agreed with results presented by the applicant unless otherwise noted.

## Study GDCH

(conducted 1/88 to 2/01)

### *Design*

Study GDCH is a double-blind, placebo-controlled, randomized trial of children with extreme short stature but without growth hormone deficiency (NGHDSS). The primary objective of the trial was to determine if children treated with growth hormone (Humatrope 0.22 mg/kg, 3 x week) had significant increases in adult height compared to children treated with placebo. Studies have shown an increase in height velocity as a result of growth hormone treatment in this population but effects on final height compared to placebo treatment have not been previously studied.

Patients were recruited at two sites; Thomas Jefferson University, Philadelphia and NICHD at the NIH. There were three primary investigators and several subinvestigators.

The randomization was stratified on predicted height (PH, cm) and gender to form the following 6 strata:

Males	Females
PH<158.5	PH<143.6
158.5≤PH≤166	143.6≤PH≤154
PH>166	PH>154

Patients were evaluated for hormonal status and then followed for 6 months to compute growth velocity. Eligible patients were randomized and seen every 6 months. The first 20 patients were seen monthly for 3 months to obtain lower leg measurements. Patients who discontinued early were asked to continue height measurements every 6 months and return to the NIH when height velocity fell below 1.5 cm/year for a final height measurement.

Entry criteria included the following (for complete list, see Dr. Roman's medical review):

- Males (10-16 years, bone age≤13) and females (9-15 years, bone age≤11) with Tanner Stage 1 or 2
- Peak growth hormone response>7 ng/mL
- Height SDS≤-2.5 or predicted adult height SDS≤-2.5

Data was reviewed annually from 1993 to 2000 by a Data and Safety Monitoring Board (DSMB). On June 5, 2000, the DSMB recommended termination of the trial because it would have taken another 5 years for remaining patients to attain final height and further placebo injections were not justified for that time period. Only 8 patients were on study at the time of study closure. All patients (including discontinued patients) had the option to enter the extension phase and receive open-label Humatrope; no efficacy data was collected during this extension period.

## ***Efficacy Variables***

The primary efficacy variable was final height measured as SD scores (standardized for age and gender). Final height was considered attained when the patient's growth dropped to 1.5 cm or less per year or if the investigator determined that growth was near completion based on height velocity and/or bone age.

To obtain the height SDS for a given measurement, the following equation was used:

$$\text{Height SDS} = ((X/M)^{L} - 1) / (L*S)$$

where X is the height measurement in centimeters; L is power in the Box-Cox transformation; M is the median and S is the generalized coefficient of variation. Values for L, M and S come from the appropriate reference population corresponding to the age in months of the child (these values are available at <http://www.cdc.gov/growthcharts>). The LMS data end at age 20 years. For patients older than 20 years, the height SDS was computed using the values at 20 years.

Patient height was measured every 6 months; 10 stadiometer measurements were averaged to determine height.

Secondary variables included the following:

- Standing height (cm)
- Height velocity (cm/year)
- Height velocity SDS
- Psychological assessment
- Achenbach child behavior questionnaire
- Harter self-perception questionnaire
- Injection-experience questionnaire
- Carbohydrate tolerance
- Lipid profile
- Tibial growth velocity by knemometry
- Bone age
- Pubertal development
- Sex steroid levels
- Tanner stage

Data from the psychological assessments were collected by the sites but were not transferred to Lilly and henceforth are not included in the NDA.

Baseline height velocity was computed from growth measured during the 6 months prior to randomization. Height velocity SDS is computed as follows:

$$\frac{\text{Patient's Height Velocity} - \text{Mean Height Velocity of normals of same age and gender}}{\text{Standard Deviation for normals of same age and gender}}$$

Baseline predicted height was a stratifier and a covariate in the analysis model. Predicted height is determined by the Bayley-Pinneau method using baselines for height, age and bone age and the gender of the patient. Predicted height SDS is computed as shown for final height above.

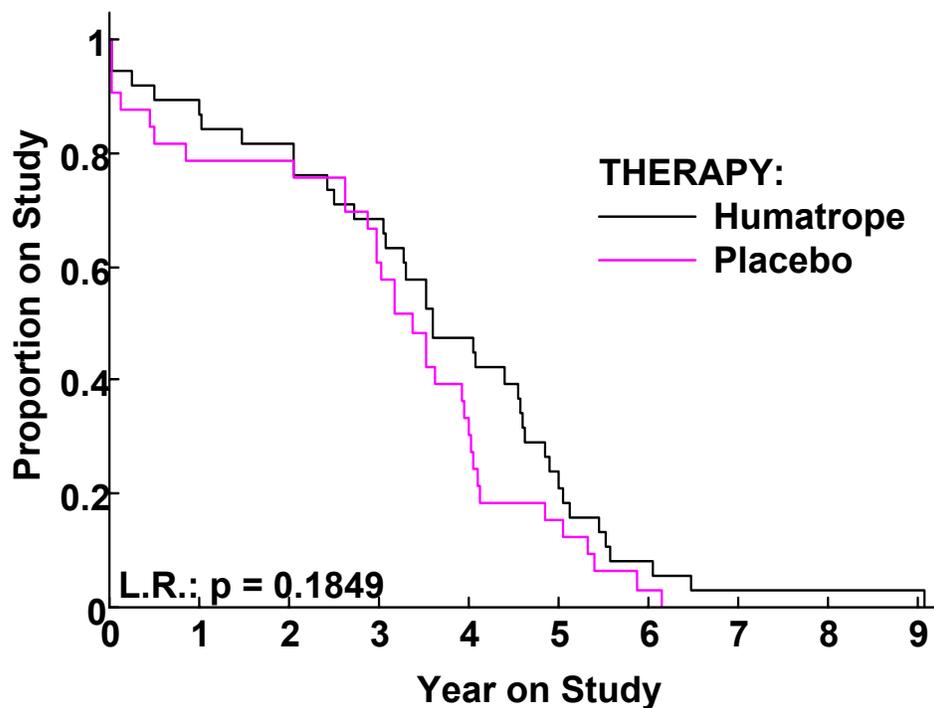
Compliance was computed as the percentage of expected injections recorded as completed. Patients 80-120% compliant were considered compliant.

### **Patient Disposition**

The trial was powered to detect a 0.67 SDS (about 3 cm) treatment difference with 40 patients in each group assuming a 10% dropout rate and alpha of 0.05. The applicant fell short of their goal of 80 patients by 9, randomizing a total of 71 patients (33 placebo and 38 humatrope). A total of 68 patients were enrolled at the NIH and only three at Thomas Jefferson University.

Figure 1 shows the proportion of patients on study by study year with no significant difference in time to discontinuation between the groups ( $p=0.18$ ). During the first year of the study, about 10% of the humatrope patients and 20% of the placebo patients discontinued. The median time on study was about 3.5 years for the total population. Appendix 1 shows the time on study for each patient and the date the patient entered the trial; no patterns in recruitment or duration of treatment are seen that would bias the results.

Figure 1. Kaplan Meier curves of time to discontinuation



The dropout rate was very high in both groups with only 27% of placebo-treated patients and 42% of humatrope treated patients completing the study (Table 2). Three patients (2 placebo and 1 humatrope) discontinued from the study without receiving any study drug. Two analysis populations (an efficacy evaluable population and a final height population) were defined in the protocol based on completion of Visit 5 (about Month 6) and availability of height data. The sample sizes for these populations are summarized in Table 2. The efficacy evaluable population best represents the randomized groups, however, 6 months of data is not sufficient

to assess growth improvement. To assess final height, the final height population is, by definition, the appropriate analysis population. The small number of patients in that group (less than half of the total) is problematic because it may not be representative of the randomized groups; this issue is examined further in the efficacy section of this review.

Table 2. Study GDCH Patient Disposition

	Humatrope	Placebo
Randomized	38 (100%)	33 (100%)
Completers	16 (42%)	9 (27%)
Discontinued+Returned for FH	7 (18%)	5 (15%)
Analysis Populations		
Efficacy Evaluable	35 (92%)	29 (88%)
Final Height	22 (58%)	11 (33%)

The time on study for each analysis population is summarized in Table 3. As would be expected, the time on study for the final height population is notably longer than the efficacy evaluable population with 88% of the patients treated for more than three years.

Table 3. Time on study by analysis population

	Efficacy Evaluable N=64	Final Height N=33	Completers N=25
Mean	3.7	4.4	5.0
Median	3.6	4.6	4.9
%<1 year	6%	6%	0%
% 1-2 years	10%	3%	0%
%>2-3 years	14%	3%	4%
%>3 years	70%	88%	96%

The primary reason patients discontinued treatment in both groups was patient request (Table 4). The most common reasons patients gave for discontinuing included “too busy”, “hassle” and injections too painful. One patient in each group dropped due to a perceived lack of efficacy and one in each group dropped due to satisfaction with self and height. The median time on study for placebo patients dropping due to patient request was 3 years (5 patients for less than 1 year); for humatrope patients, 2.5 years (2 patients for less than 1 year).

Only two patients (one in each group) dropped due to an adverse event. The nine patients dropping due to investigator (sponsor) request include eight patients still on study when the trial was ended.

Table 4. Study GDCH Reasons for discontinuation

	Humatrope (n=39)	Placebo (n=33)
ADE	1 (3%)	1 (3%)
Pt request	17 (45%)	12 (36%)
Inv request	4 (10.5%)	5 (15%)
Entry crit.. not met	0	2 (6%)
Lost-to-Follow-up	0	4 (12%)

Included in the database were three sets of siblings; a set of fraternal twins, a set of biological siblings and a set of adopted siblings. Siblings were randomized to the same treatment as

dictated by the protocol. Only one (a humatrope patient) of the six patients is included in the final height population; this patient's sibling (5 years younger) chose to stop therapy at age 11.7 years. The twins were still on study when the trial was terminated; they were 14.6 years old at the time. The two adopted siblings were lost to follow-up after 2.5 years of therapy.

### **Baseline Characteristics**

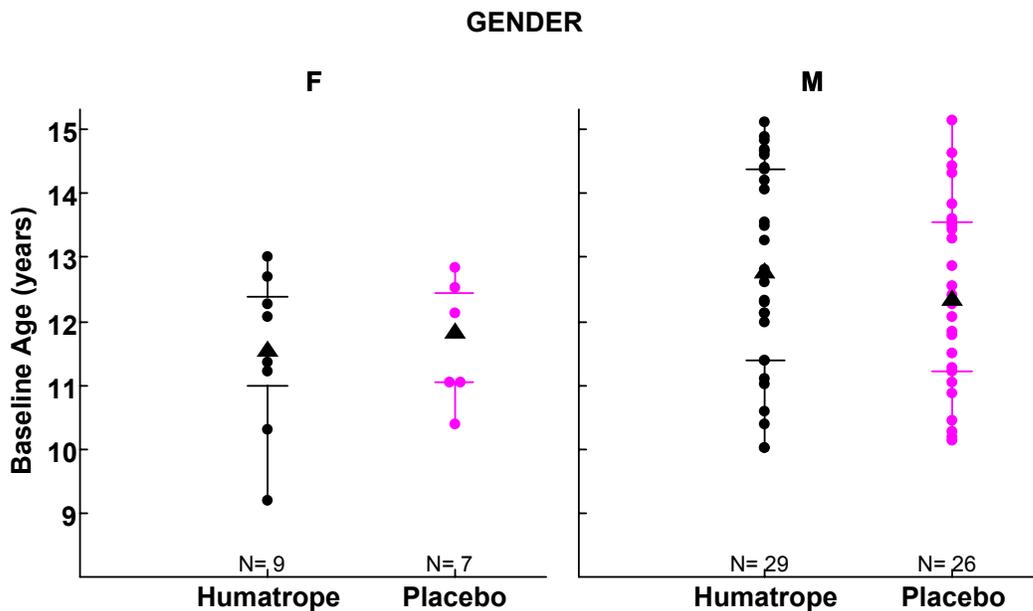
The baseline characteristics for all randomized patients and for the final height population are summarized in Table 5. About 80% of the patients were male; most were Caucasian. Six patients entered with a Tanner stage of 3 though the entry criteria required a Tanner stage of 1 or 2. A non-significant treatment group imbalance in Tanner score is seen for the final height population.

Table 5. Study GDCH Baseline Characteristics

	All Randomized Patients		Final Height Population	
	Humatrope (n=38)	Placebo (n=33)	Humatrope (n=22)	Placebo (n=11)
Age				
Mean (SD)	12.5 (1.6)	12.3 (1.4)	12.5 (1.6)	12.9 (1.1)
Range	9.2 to 15.1	10.1 to 15.1	10 to 15.1	11.5 to 15.1
Bone Age	(n=36)	(n=28)	(n=21)	(n=9)
Mean (SD)	10.45 (1.9)	10.36 (1.7)	10.4 (1.9)	10.7 (1.2)
Range	6 to 13	6 to 13	6 to 13	6 to 12.5
Bone Age/ Age				
Mean (SD)	0.84 (0.12)	0.84 (0.11)	0.84 (0.13)	0.81 (0.07)
Tanner stage				
1	18 (47%)	14 (42%)	9 (41%)	2 (18%)
2	18 (47%)	15 (46%)	12 (55%)	7 (64%)
3	2 (5%)	4 (12%)	1 (5%)	2 (18%)
Gender				
Female	9 (24%)	7 (21%)	4 (18%)	2 (18%)
Male	29 (76%)	26 (79%)	18 (82%)	9 (82%)
Race				
Caucasian	30 (79%)	25 (76%)	18 (82%)	7 (64%)
Hispanic	7 (18%)	4 (12%)	4 (18%)	1 (9%)
Other	1 (3%)	4 (12%)	0	3 (18%)
BMI (kg/m <sup>2</sup> )				
Mean (SD)	17.1 (1.7)	17.5 (2.6)	17.0 (1.8)	17.5 (2.2)
Range	13.8 to 20.1	14.5 to 28.5	13.8 to 19.8	15.3 to 21.7

The average age at baseline was about 12 years (range 9 to 15) with bone ages about two years younger. Female patients were generally younger than male patients (Figure 2 on the following page).

Figure 2. Age (years) at baseline by gender (boxplots with observations)



No significant treatment imbalances for characteristics related to height were seen (Table 6).

Table 6. Study GDCH Baseline Height Characteristics

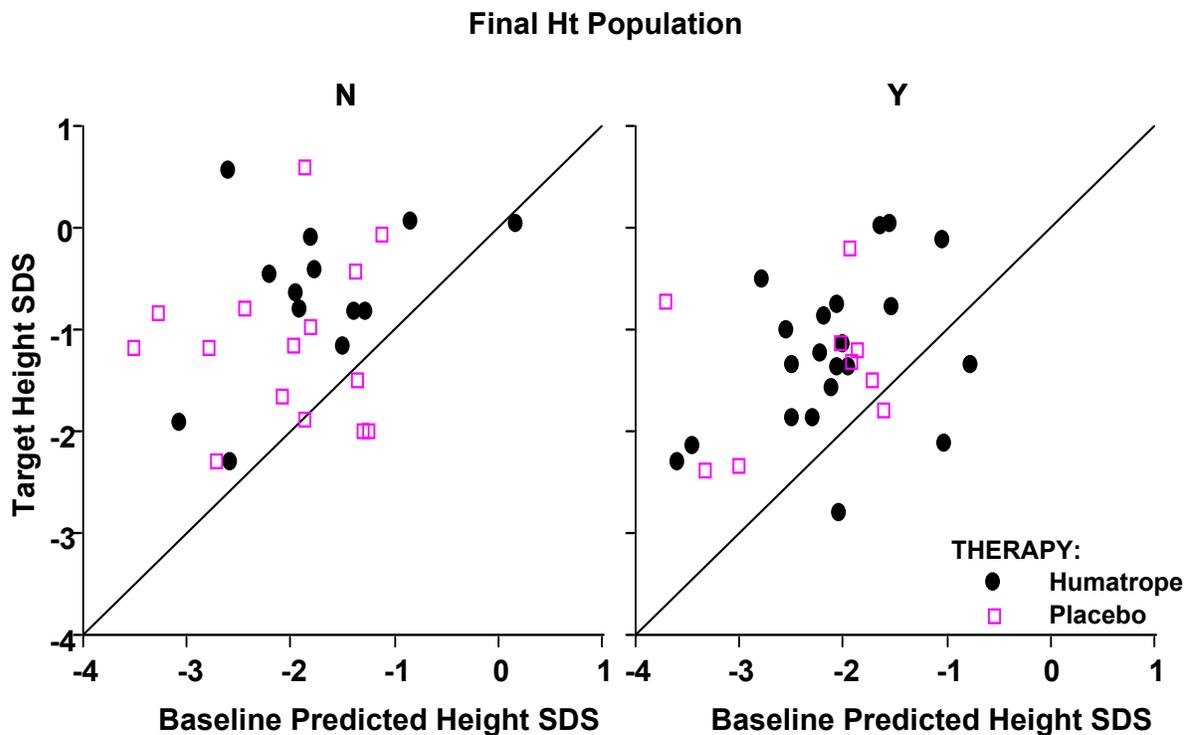
	All Randomized Patients		Final Height Population	
	Humatrope (n=38)	Placebo (n=33)	Humatrope (n=22)	Placebo (n=11)
Height (cm)				
Mean (SD)	132.8 (8.2)	131.0 (7.7)	132.8 (8.0)	134.9 (6.7)
Range	115.4 to 149.1	120.3 to 145.2	119.4 to 149.1	120.3 to 143.3
Height SDS				
Mean (SD)	-2.75 (0.49)	-2.81 (0.49)	-2.69 (0.55)	-2.75 (0.57)
Range	-3.9 to -1.8	-4.0 to -1.85	-3.9 to -1.8	-3.8 to -2.1
Predicted Height (cm)	(n=35)	(n=28)	(n=22)	(n=10)
Based on baseline ht, bone age, age and gender				
Mean (SD)	159.3 (8.3)	156.9 (8.1)	159.0 (7.5)	157.4 (7.8)
Range	140.8 to 177.3	135.6 to 167.9	140.8 to 170.5	143.6 to 166.5
Predicted Height SDS				
Mean (SD)	-1.96 (0.75)	-2.26 (0.83)	-2.08 (0.69)	-2.26 (0.80)
Range	-3.6 to 0.16	-4.2 to -1.14	-3.6 to -0.78	-3.7 to -1.34
Target Height (cm)	(n=38)	(n=29)	(n=22)	(n=10)
Based on gender and parents' hts				
Mean (SD)	165.9 (8.4)	165.1 (8.3)	165.8 (8.2)	164.3 (8.4)
Range	148.3 to 189.4	148.2 to 180.5	149.2 to 189.4	148.2 to 174.9
Height Velocity (cm/yr)				
Mean (SD)	4.81 (1.8)	4.77 (2.1)	5.2 (1.8)	5.6 (2.4)
Range	1.7 to 8.4	1.2 to 9.7	1.9 to 8.4	2.5 to 9.7
Height Velocity SDS				
Mean (SD)	-0.6 (1.1)	-0.8 (1.1)	-0.4 (1.1)	-0.2 (1.1)
Range	-2.5 to 1.9	-3.7 to 1.4	-2.5 to 1.8	-1.7 to 1.4

Baseline height ranged from 115 cm (45 inches) to 149 cm (58 inches) for all randomized patients who were aged 9 to 15 years.

While the mean height SDS at baseline was about -2.75 (considered “abnormal”), the mean height velocity SDS for all groups was close to zero and ranged up to a maximum value of 1.9. So for many patients, height velocity was within a so-called normal range.

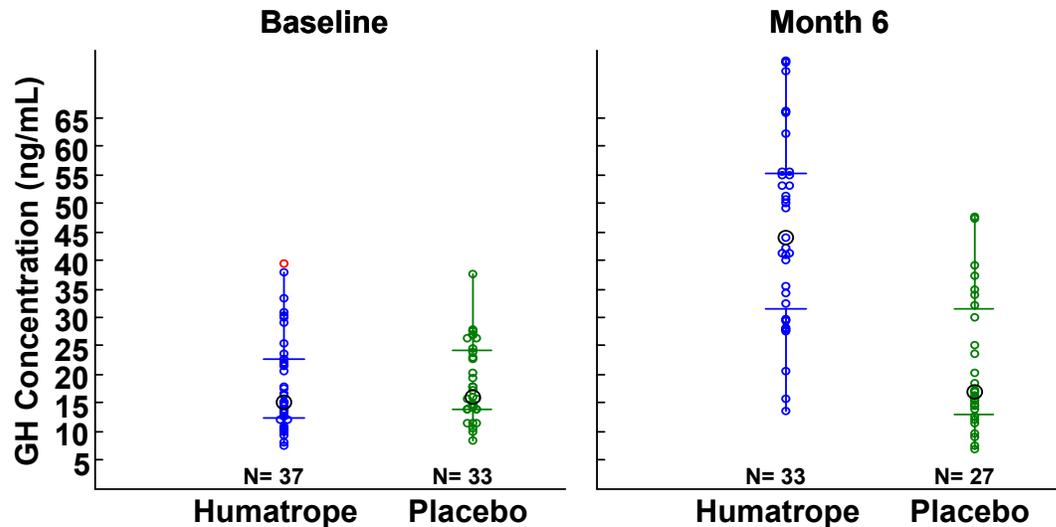
Figure 3 below shows the relationship between baseline predicted height SDS (which is calculated based on baseline height, baseline bone age, baseline age and gender) and target height SDS (which is calculated based on the parents’ heights and the patient’s gender). Though the two measures are correlated, the target height is clearly greater than the baseline predicted height and therefore a higher hurdle to meet than the predicted height. The treatment group distributions suggest adjustment for these variables at the analysis stage would be prudent.

Figure 3. Target height SDS by baseline predicted height SDS by treatment for patients in and not in the final height population



Growth hormone concentration was measured at baseline and after six months of treatment. To be eligible for the trial, a peak concentration less than 7 ng/mL was needed. Figure 4 shows the comparability of the peak growth hormone concentration at baseline across the treatment groups (the same was seen looking at just the final height population). This reviewer found no relationship between the baseline peak and baseline height SDS. As expected, the peak growth hormone concentration increases after six months of humatrope therapy.

Figure 4. Peak growth hormone concentration at baseline and Month 6 by treatment group



About one-third of the final height population presented with headache, allergies or a cardiovascular disorder (mild murmurs).

No patients were on Ritalin at the start of treatment. Five patients were given Ritalin during the study; two of those patients were included in the FH population. In both cases the Ritalin was given during the final visit(s), after growth spurts had occurred and did not appear to affect growth (weight or height).

### **Statistical Methods**

Three efficacy analysis datasets were named in the protocol:

1. **Efficacy evaluable population:** all randomized patients who stayed on study and had height data up to at least Visit 5 (about Month 6).
2. **Final height population:** all randomized who stayed on study and had height data up to at least Visit 5 (i.e. efficacy evaluable) and had final height data.
3. **Protocol completers:** all randomized patients who completed the study.

All patients were to be followed to final height regardless of whether treatment was discontinued; a total of 12 discontinued patients returned for a final height visit (8 of these patients were included in the final height population). The safety population consisted of all randomized patients who took medication.

The protocol-defined primary efficacy analysis of final height SDS is an analysis of covariance (ANCOVA) with baseline predicted height SDS as the covariate. The primary analysis population was the final height population. Tests for interaction were planned. Eight other covariates considered were: baseline height SDS, baseline bone age, target height (sex-adjusted mid-parental height), baseline age, baseline BMI, baseline IGF-I SDS and gender. Baseline height SDS was the covariate most strongly correlated with outcome with a correlation coefficient of 0.68.

Secondary analyses (ANCOVA) include the following:

- Analysis of final height (cm) minus baseline predicted height (cm) for the final height population.
- Analysis of the final height SDS for the protocol completers
- Analysis of the last observed height SDS for the efficacy evaluable population
- Analysis of the last observation of height SDS, height velocity, and height velocity SDS for all three analysis populations
- Analysis of lower leg growth in a subset of 20 patients to see if initial lower leg growth is predicative of final height

Analyses of all the other secondary variables were planned by the applicant but no details regarding the statistical tests were provided in the protocol.

Additional exploratory analyses were performed including a likelihood-based repeated measures analysis using all available data for each patient.

### ***Efficacy Results***

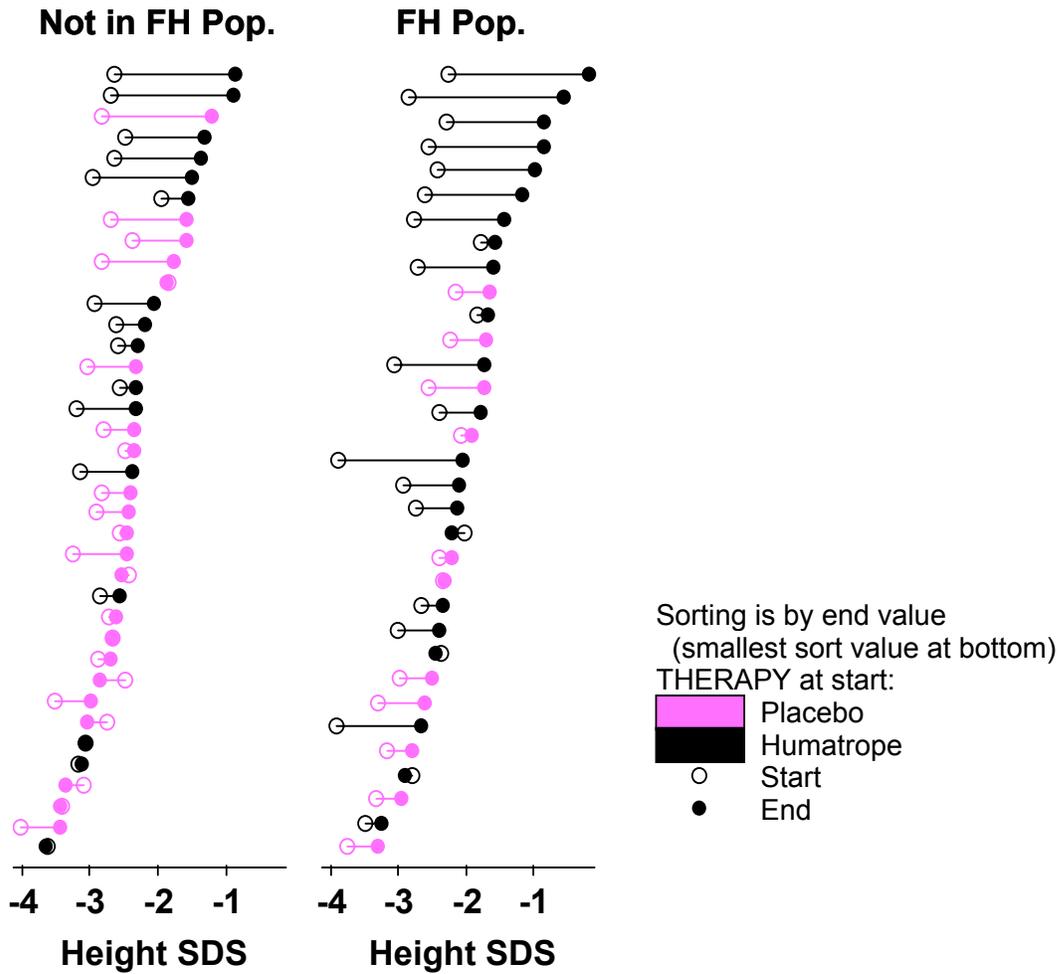
Compliance to the treatment regimen was high with 85% of the final height patients having a compliance of 80% or greater. Mean compliance for this population was 89% with a minimum of 56% and maximum of 99.9%.

Two placebo patients took growth hormone. One patient (008 1201) dropped out of the study after Visit 5 (Month 6), took growth hormone for 4 years and then returned for a final height measurement. This patient was not included in the applicant's efficacy evaluable or final height population though she fit the definitions for those populations; this patient is discussed further in the next section of this review. The second placebo patient (007 1601) took humatrope from May 1990 to Dec 1990 and from May 1992 to November 1992. This patient's height SDS and height velocity data are shown in Appendix 2. There is a growth spurt at the time of the humatrope treatment in 1990; this spurt occurs when the patient is about 15, a time at which a growth spurt might be expected. Note that no change in velocity is seen at the time of the second set of humatrope injections. Inclusion of this data could bias against the drug; however it is impossible to ascertain a measure of the bias. Patient 1601, then, was analyzed as randomized according to the principles of intent-to-treat.

The primary efficacy variable is the final height SDS for all patients reaching a low height velocity of 1.5 cm per year or less (the final height population). The last height on study was used for the analysis.

Both the final height SDS and the baseline height SDS are depicted in Figure 5 for all patients. Note that more black lines at the top of the graph indicate higher height SDS values at endpoint for humatrope patients. The length of the lines indicate the magnitude of change from baseline; visually it appears that larger changes are seen for humatrope compared to placebo.

Figure 5. Height SDS at baseline and endpoint by patient, treatment and analysis population



A statistically significant treatment difference in final height SDS of 0.50 SDS units was observed ( $p=.017$ , Table 7). Also analyses of change in height SDS, final height in cm and final height change in cm revealed borderline significant results ( $p\leq.04$ ). A difference in final heights of about 3.2 cm was seen (LSM adjusted for baseline predicted height). So data from the final height population shows statistically significant effects on final height.

Table 7. Results of analyses of height SDS for the final height population

	Humatrope (n=22) Mean (SD)	Placebo (n=11) Mean (SD)	p-value
Height SDS			
Baseline	-2.69 (0.55)	-2.75 (0.57)	0.77
Final	-1.77 (0.78)	-2.34 (0.55)	
LS Mean	-1.81	-2.31	0.017
Change	+0.93 (0.73)	+0.42	0.03
Height (cm)			
Baseline	132.82 (7.95)	134.88 (6.74)	0.47
Final	161.12 (7.42)	157.46 (5.87)	
LS Mean	160.75	157.58	0.034
Change	+28.30 (7.38)	+22.58 (6.90)	0.04

**SDS=standard deviation score**

LS Mean for height SDS and height in cm from model with predicted height SDS as covariate. p-values are from ANOVA or ANCOVA (LS mean results)

Due to the large number of dropouts, the applicant performed several additional analyses of height SDS which are summarized in Table 8 below. With the exception of the protocol completers (a small group of 25 patients), all analyses revealed significant treatment effects. Note that the treatment effect of about 0.5 SDS units is seen regardless of the analysis performed.

Table 8. Results of sensitivity analyses of final height SDS performed by the applicant

Analysis Population	Analysis Model	Humatrope LS Mean	Placebo LS Mean	p-value
Efficacy Evaluable	ANCOVA BPH SDS	n=35 -1.89	n=27 -2.40	0.001
Protocol Completers	ANCOVA BPH SDS	n=16 -1.86	n=9 -2.32	0.06
All Patients with BPH	Repeated Measures Analysis	n=35 -1.52	n=27 -2.20	<0.0001
All Randomized Patients	ANCOVA Ht. SDS LOCF BPH SDS imputed where missing	n=38 -1.96	n=33 -2.36	0.011
All Randomized Patients	ANOVA Ht. SDS LOCF	n=38 -1.90	n=33 -2.42	0.003

BPH=Baseline predicted height

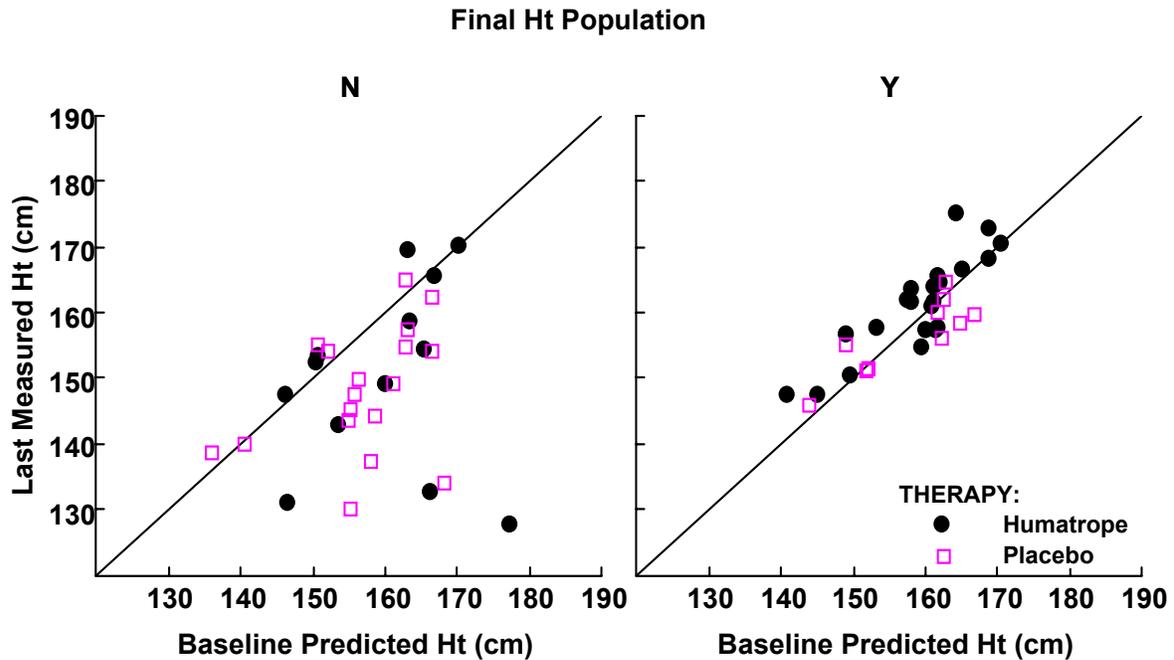
One of the problems with the sensitivity analyses is the use of non-final height data for those patients that have not reached final height. The reason this is problematic is that patients may achieve a peak height SDS and not maintain this SDS level as they continue to age. For the final height population, about 2/3 of the patients in each treatment group had a lower height



reach or surpass their target heights.

The side-by-side graphs illustrate the general difference between patients in the FH population and not in the FH population with a number of non-FH patients falling far below the identity line.

Figure 7. Last measured height (cm) by baseline predicted height (cm) for the non-FH and FH Populations



### ***Examination of analysis population***

The small number of patients in the final height population (about 40% of the randomized patients) is cause for concern. Methodologies for analysis of data with missing observations are not readily applicable here due to the assumptions one must make in the application of these methods. For example, a last-observation-carried-forward approach to deal with missing data is not appropriate since one can not assume that the height SDS would not change over time, perhaps dramatically depending on the time of dropout. The unpredictability of growth and the diversity of the patient population make it difficult to impute for missing data based on the observed data.

Some patients not included in the final height population may have come close to their final height even though their height velocity had not fallen below 1.5 cm/year. This reviewer then examined the data for patients with growth characteristics similar to the patients in the final height population. As a post hoc look at the data, analyses are not confirmatory but merely serve to test the robustness of the primary analysis of the final height population data.

First, the height velocities of both FH patients and non-FH patients were examined. Table 10 summarizes the peak and minimum height velocity for patients included and not included in the FH population. The objective here is to see if the non-FH population has similar height velocity characteristics to the FH population. Looking first to the maximum (peak) velocity, the means for the maximum observed velocity are greater for the patients in the final height population suggesting that some patients not included in the final height population may not have had a growth spurt on study though it is interesting to note that the mean ages at the maximum velocity were similar regardless of treatment or gender. (This latter point is may suggest that humatrope does not promote early growth spurts; although the largest changes in height velocity occur during the first year of humatrope treatment.) The two populations clearly differ by minimum height velocity as expected, although the height velocities for the non-final height population fall to about half the peak velocities. This data suggests that some patients in the non-final height population experienced a growth spurt and had significant drops in height velocity while still on study.

Table 10. Maximum and minimum height velocity (cm/ year for previous 12 months) while on study for all patients and for patients not included and included in the FH population by treatment and gender

	Male		Female	
	Humatrope Mean (SD)	Placebo Mean (SD)	Humatrope Mean (SD)	Placebo Mean (SD)
<b><u>FH Population</u></b>	n=17	n=8	n=4	n=2
Max Ht Velocity (cm/year)	10.0 (1.7)	9.8 (1.2)	8.4 (0.7)	5.8 (0.1)
Age at Max (years)	13.8 (1.4)	13.8 (0.8)	11.2 (0.7)	13.1 (0.5)
Years on Study at Max	2.0 (1.2)	1.8 (0.9)	1.1 (0.2)	1.5 (0.7)
Minimum Ht Velocity	1.6 (1.8)	1.2 (0.6)	1.8 (1.4)	0.9 (0.2)
Age at Min	16.4 (1.9)	16.6 (0.8)	14.6 (1.7)	15.2 (0.4)
<b><u>Not in FH Population</u></b>	n=9	n=12	n=4	n=4
Max Ht Velocity (cm/year)	8.1 (1.9)	7.8 (2.0)	7.2 (1.3)	7.8 (0.9)
Age at Max (years)	13.9 (2.0)	13.7 (1.6)	12.3 (1.1)	12.2 (0.3)
Years on Study at Max	2.1 (1.0)	2.5 (1.0)	1.5 (0.7)	1.8 (0.6)
Minimum Ht Velocity	5.2 (1.1)	3.8 (1.2)	5.1 (2.6)	3.4 (0.8)
Age at Min	14.1 (2.4)	13.4 (2.5)	12.9 (2.4)	13.9 (0.8)

In a small population of only 71 patients, examination of the individual data is possible and also very helpful when trying to distinguish analysis populations. The two figures below illustrate two characteristics of the final height population: 1) a clear rise and dramatic drop in height velocity while on study (Figure 8), and 2) the leveling off of growth (a consequence of the low height velocity, Figure 9). By contrast, the growth in the non-FH population shows little leveling off of growth (particularly for males) though the height velocity is clearly decreasing for most patients.

Figure 8. Height velocity (cm/year for the previous 12 months) plotted against age by gender for patients not included and included in the FH population

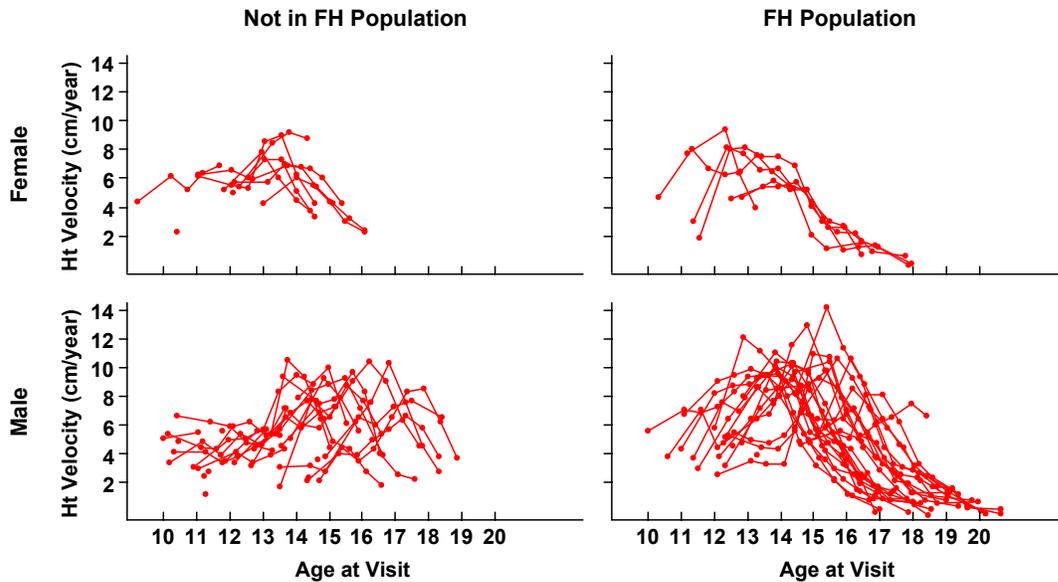
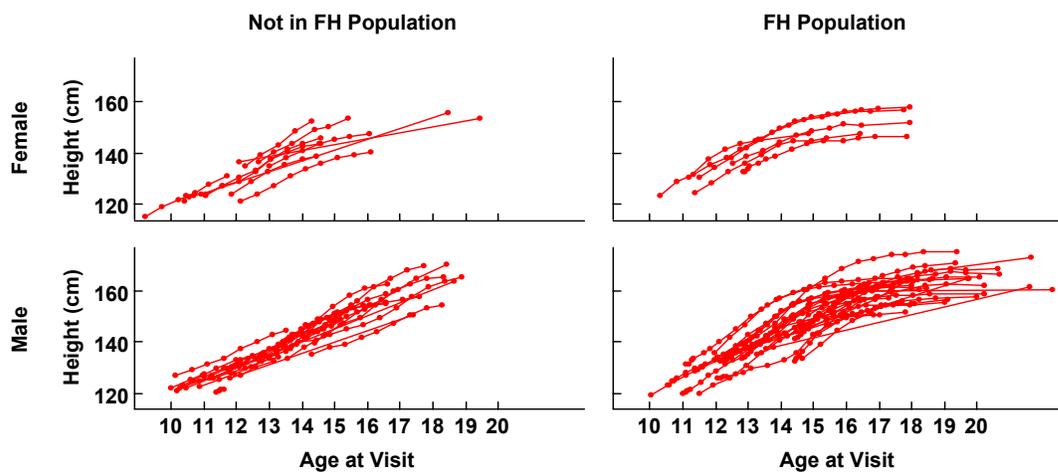


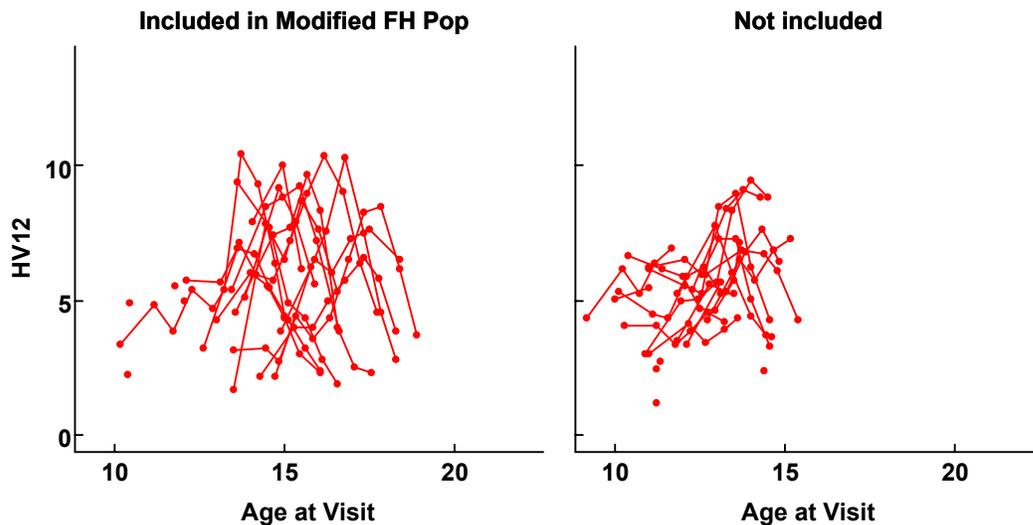
Figure 9. Height (cm) plotted against age by gender for patients not included and included in the FH population



From looking at the above graphs, this reviewer chose two criteria to identify non-FH patients

close to their final height (patients needed to have only 1 of these criteria to be included in the modified final height population) : 1) 17 or older at last height measurement or 2) a 12-month or 6-month height velocity  $\frac{1}{2}$  their peak height velocity and a smaller 6-month HV than 12-month HV at their final visit. Using this approach, eighteen additional patients (11 placebo and 7 humatrope) were identified and are depicted in Figure 10 below<sup>1</sup>. Note that these additional patients all had final heights after age 15, had experienced a growth spurt and had a large drop in growth velocity. The addition of these 18 patients brings the size of the analysis population to 72% of the randomized patients.

Figure 10. Height velocity (cm/year for the previous 12 months) plotted against age by gender for patients added to the FH population to form a modified-FH population and those not included.



An analysis of height SDS using the modified final height population produced a height SDS of  $-1.81$  for humatrope and  $-2.24$  for placebo; a statistically significant difference of  $0.44$  ( $p=.007$ ). So the addition of the near final height patients decreased the treatment effect but nevertheless yielded highly significant results. The inclusion of patient 1201 (a placebo patient who discontinued, took growth hormone for four years and returned for a study final height) had an appreciable effect on the treatment effect estimate; without patient 1201, the treatment effect is  $0.49$  ( $p=.002$ ) and reassigning 1201 to humatrope, the effect is  $0.51$  (the same effect size seen for the final height population).

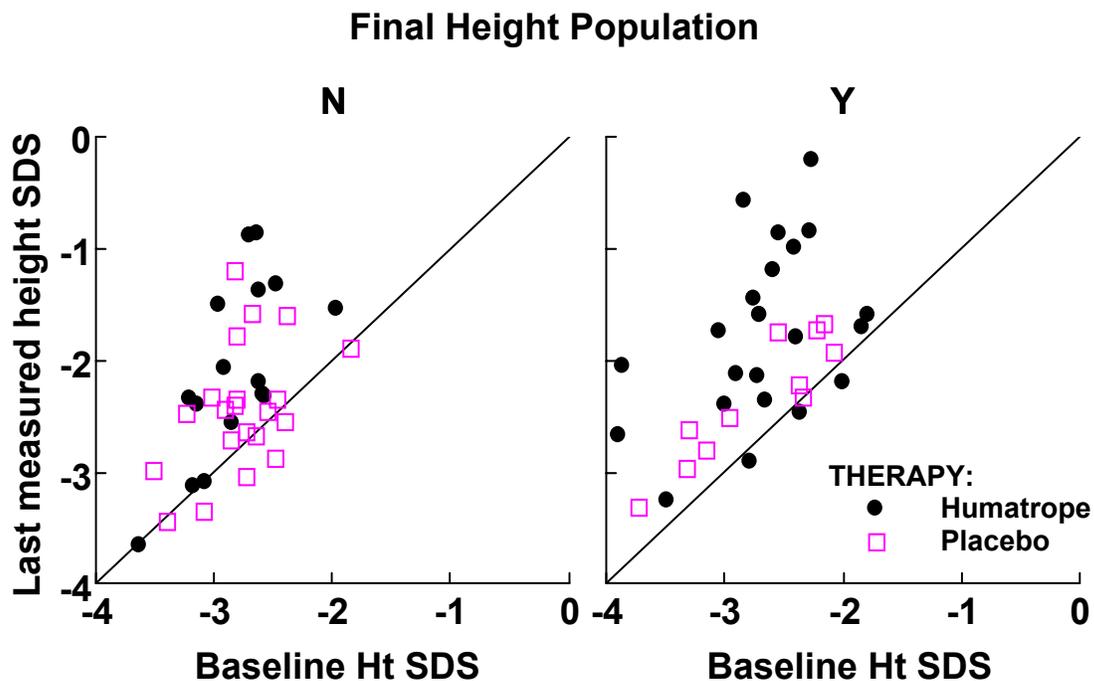
Overall this post hoc analysis of a modified final height population yields results consistent with the results for the protocol-defined final height population and speak to the robustness of the primary efficacy results.

<sup>1</sup> One patient (1201) was included in the modified final height population although this placebo patient had received growth hormone for the 4 years not on study. The inclusion of this patient will bias against humatrope if the therapy was effective for the patient..

### Estimate of treatment effect

The data from GDCH shows a statistically significant treatment effect for humatrope over placebo using a several different analysis populations and analyzing several different efficacy variables. The issue now is how to characterize the magnitude of the treatment effect to aid in judging its clinical significance. Though data from all patients will be presented here, the treatment effects will be defined for the protocol defined final height population. Most patients in both treatment groups had an improvement in final height SDS over baseline height SDS with a large increase seen for the humatrope patients (+0.93, FH population) compared to the placebo patients (+0.42, FH population,  $p=0.03$ ). About 55% of the humatrope patients and 36% of the placebo patients had a final SDS greater than  $-2$ . Note that a SDS of  $-2$  is equivalent to  $5'3.5''$  for males and  $4'11''$  for females and is considered a cut-off for short stature.

Figure 11. Last measured height SDS by baseline height SDS



Estimates of the treatment effect show an improvement in final height for humatrope compared to placebo (Table 11) with a SDS difference of 0.51 and a difference of 3.2 cm (1.2 inches). These estimates are least squares means from an analysis of covariance with baseline predicted height SDS as covariate ( $r=0.68$  for correlation with FH SDS) or with baseline predicted height in cm as covariate ( $r=0.84$  for correlation with FH in cm). Humatrope males show a significant increase in height SDS compared to placebo males while the results for females are non-significant (most likely due to the small sample size of a total of 6 patients).

Analysis of variance of the difference between final height and baseline predicted height and of the difference between final height and target height yielded estimates in favor of humatrope but non-significant results ( $p=0.075$  and  $p=0.32$ , respectively).

Table 11. GDCH Summary of Treatment Effect for the Final Height Population (LS means and SE)

	Humatrope (n=22)	Placebo (n=11)	Trt Effect	95% CI
Final Height SDS				
All	-1.805 (0.11)	-2.31 (0.17)	0.51	0.10, 0.92
Males*	-1.91 (0.12)	-2.385 (0.18)	0.40	0.03, 0.91
Females*	-1.34 (0.25)	-2.0 (0.35)	0.66	-0.23, 1.54
Final Height (cm)				
All	160.7 (0.8)	157.6 (1.2)	3.2	0.3, 6.1
Males	160.5 (1.0)	157.6 (1.4)	2.9	-0.4, 6.3
Females	161.6 (2.5)	157.7 (3.1)	3.9	-2.9, 10.7
FH minus Baseline PH (cm)				
All	2.2 (0.9)	-0.7 (1.3)	2.8	-0.3, 5.9
Males	1.5 (0.9)	-1.2 (1.4)	2.6	-0.8, 6.0
Females	5.3 (1.9)	1.3 (2.8)	4.0	-2.9, 10.9
FH minus Target Height (cm)				
All	-4.7 (1.3)	-7.1 (2.0)	2.4	-2.4, 7.2
Males	-4.6 (1.5)	-8.4 (2.2)	3.8	-1.6, 9.2
Females	-5.2 (3.1)	-1.8 (4.4)	-3.4	-14.4, 7.7

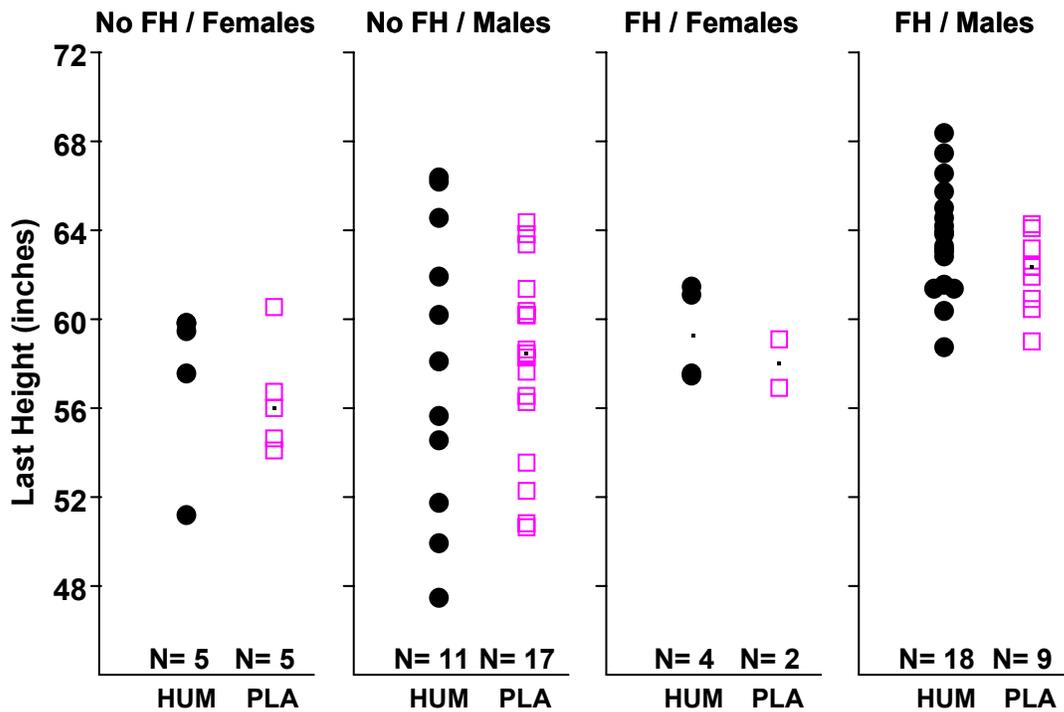
- In the final height population, there are 18 males on humatrope, 9 males on placebo, 4 females on humatrope and 2 females on placebo.

To obtain an estimate of the treatment effect in cm, the applicant converted the overall SDS value for each treatment group to a measurement in cm for each gender. Then, the treatment difference for each gender was computed and these differences were combined weighting on the proportion of each gender. Using this method, the applicant computed a 3.7 cm treatment effect for humatrope compared to placebo. Analyses by this reviewer of final height in cm yields a treatment effect of 3.2 cm; with an effect of 2.9 cm for males and 3.9 cm for females. So the different methodologies yield treatment estimates that differ by 0.5 cm (0.2 inches); most likely, a difference of no clinical consequence.

The distribution of the final heights for all the patients is shown in Figure 12. The data here is depicted in inches for an US audience and is provided in cm in Appendix 3.

The two right graphs depict the data for the final height population broken down by gender. The data for females shows that 2 of the 4 humatrope patients reached heights greater than 5 feet and heights greater than the 2 placebo patients. For the males, almost all patients in both treatment groups reach heights above 5 feet (one patient in each group had a final height of 59 inches) with about half of the humatrope patients reaching heights above 5'3".

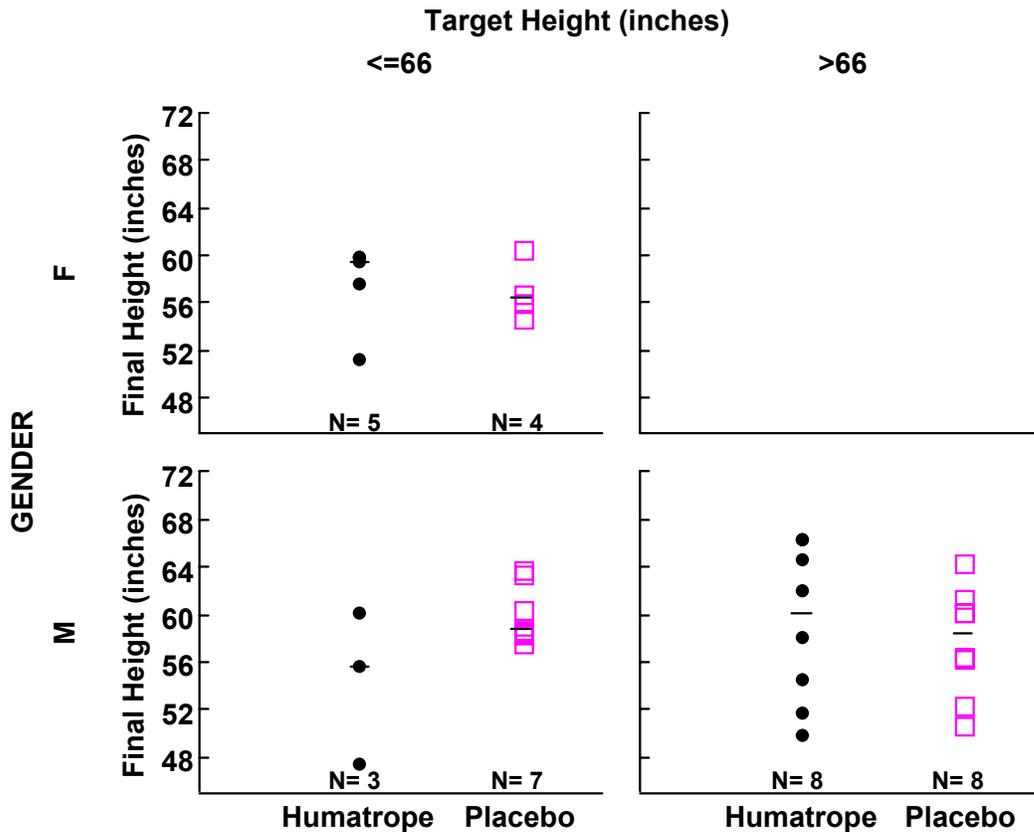
Figure 12. Final height in inches for the final height population and non-FH population by gender and treatment



The lowest point for FH females on humatrope represents two patients with the exact same height. For the placebo FH males, two patients had a height of 62.5 inches are represented by a single point.

Figure 13 shows the relationship of target height and final height with the tallest humatrope patients in the tallest target height group. This relationship though does not obfuscate the impact of humatrope.

Figure 13. Final height in inches for the final height population by target height (inches), gender and treatment



Overall Comments on GDCH

A statistically significant treatment effect on final height is seen for humatrope compared to placebo. An analysis by this reviewer of final height (cm) yields an estimate of treatment effect of 3.2 cm (LSM adjusted for predicted height) with a 95% CI of 0.3 to 6.1 cm (0.1 to 2.4 inches). The applicant reports a treatment effect of 3.7 cm based on an analysis of final height SDS and a conversion to cm.

## Study E001

(conducted 3/88 to 1/01)

### *Design*

Study E001 is a Phase 3 trial designed to compare 3 doses of humatrope in NGHDSS children. A total of 239 patients were recruited at 28 centers in 10 countries. The three doses studied were: 0.24 mg/kg/wk, starting dose of 0.24 mg/kg/wk for 1 year followed by 0.37 mg/kg/wk thereafter and 0.37 mg/kg/wk. The objective of E001 was to assess height velocity after two years of therapy (the primary efficacy outcome) and then assess final height in a long-term extension. For this review, the focus is on the final height data.

Entry criteria included the following:

- Males or females 5 years or older
- Tanner stage I
- Bone age less than 10 years for females and less than 12 years for males
- Height SDS of  $-2.0$  or less
- Peak GH greater than  $\sim 10$  ng/mL

### *Patient Disposition*

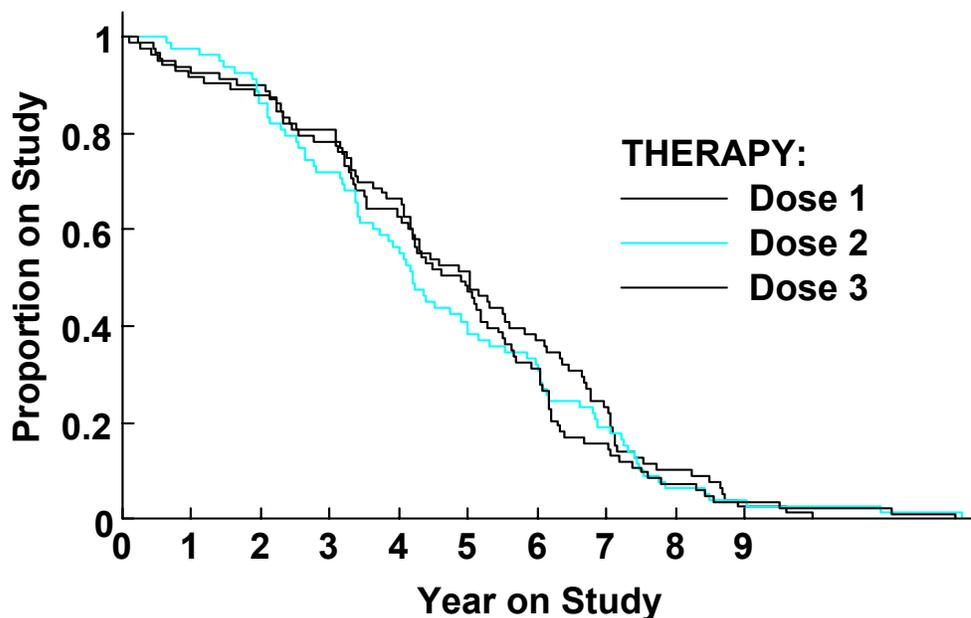
A total of 239 patients were randomized to treatment (Table 12). About 88% completed two years of treatment and provided 2-year height velocity data. Only about 1/5 of the patients were included in a final height population; these patients are the focus of this review. About half of the final height population consisted of patients from a single center where the investigator measured final height on patients who had discontinued treatment.

Table 12 Study E001 Patient Disposition

	HUM 0.24	HUM 0.24/0.37	HUM 0.37
Randomized	78	78	83
Completed 2 years	70 (90%)	67 (86%)	72 (87%)
Completed extension	18 (23%)	11 (14%)	14 (15%)
FH Population	17 (22%)	16 (21%)	17 (20%)
On Trt at FH	8	10	10
Off Trt at FH	9	6	7

The patterns of discontinuation for the three dose groups are similar as seen in Figure 14. The median time on study was 4.5 years for the overall population.

Figure 14. Kaplan Meier Curves of time to discontinuation



Patient request was the primary reason for discontinuation in all treatment groups with the highest percentage seen for the high dose group (Table 13).

Table 13. Reasons for discontinuation

	HUM 0.24 (n=78)	HUM 0.24/0.37 (n=78)	HUM 0.37 (n=83)
ADE	2 (3%)	0	1 (1%)
Pt request	22 (28%)	31 (40%)	38 (46%)
Inv request	10 (13%)	7 (9%)	8 (10%)
Sponsor decision	6 (8%)	7 (9%)	5 (6%)
Entry crit.. not met	7 (9%)	9 (12%)	8 (10%)
Lost-to-Follow-up	3 (5%)	2 (3%)	3 (4%)
Protocol violation	6 (8%)	6 (8%)	2 (2%)
LOE	3 (4%)	4 (5%)	2 (2%)
Other	0	1 (1%)	2 (2%)

### **Baseline Characteristics**

Generally the treatments were comparable regarding baseline characteristics for the overall population and the final height population (Table 14). A significant difference in baseline heights between the low and high dose was seen in the all randomized patients group but not the FH population.

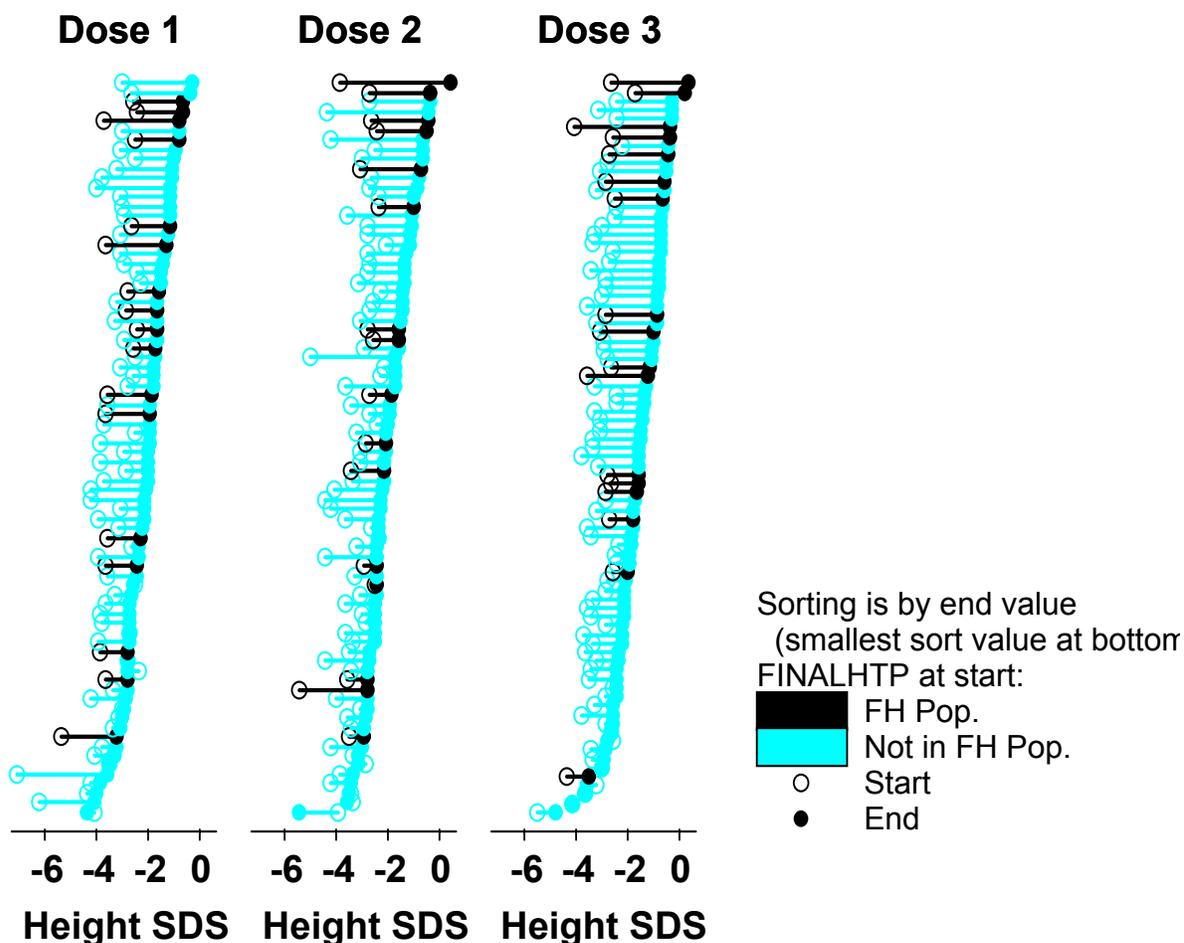


## Efficacy Results

The primary efficacy variable was change in height velocity after two years of treatment with the primary comparison being between the low dose group and high dose group. In the low dose group height velocity increased by 3.3 cm/yr and in the high dose group by 4.0 cm/yr; the treatment difference (LSM=0.78), reported by the applicant, was statistically significant ( $p=0.003$ ).

As mentioned, the focus in this review is on the final height data. Height SDS is the efficacy variable. Figure 16 shows for each patient the change in height SDS from baseline to last measured height. The majority of the final height population had a final height greater than  $-2$  at endpoint (70% in the low dose [0.24, Dose 1] and 94% in the high dose [0.37, Dose 3]). About half of the high dose patients in the final height population had an SDS greater than  $-1$  at endpoint.

Figure 16. Height SDS at baseline and endpoint by patient and dose for the final height population (black lines) and for patients not in the final height population (blue or gray in print).



Analyses were performed by this reviewer using the same models used in GDCH: ANCOVA of final height with baseline predicted height as the covariates and ANOVA for analyses of the differences of final height from baseline predicted height and target height. The results of these analyses are summarized in Table 15. P-values for comparisons of the low dose to the high dose show no statistically significant differences between the two groups though a dose-response relationship is evident.

Overall, the estimates from E001 show larger improvements in final height than were seen for humatrope in GDCH; even when comparing the comparable doses. This could be due to the administration of drug more frequently since studies have shown a benefit to 6x per week dosing over 3x per week dosing. Other factors, such as age at start of therapy or change in Tanner Stage, may have played a role as well and will be examined in a later version of this review.

Table 15. Study E001 Final height results for the Final Height Population (LS means and SE)

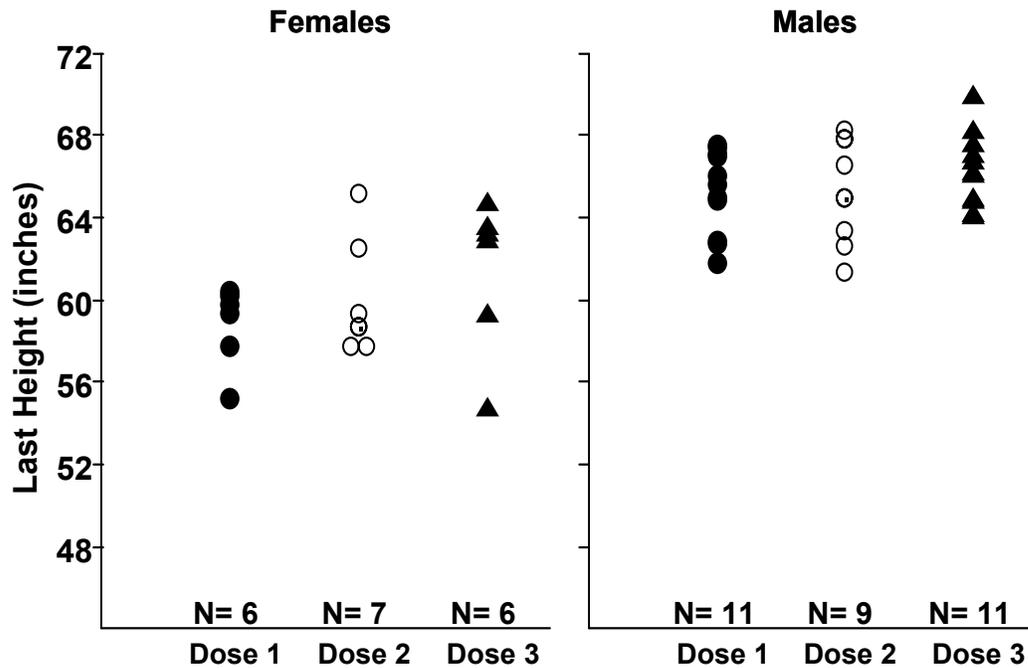
	HUM 0.24 (n=13)	HUM 0.24/0.37 (n=13)	HUM 0.37 (n=13)	p-value 0.24 vs. 0.37
Final Height SDS				
All	-1.65 (0.18)	-1.38 (0.18)	-1.19 (0.18)	0.09
Males	-1.58 (0.20)	-1.71 (0.22)	-1.09 (0.12)	0.10
Females	-1.85 (0.36)	-0.83 (0.29)	-1.40 (0.28)	0.33
Final Height (cm)				
All	162.5 (1.3)	163.6 (1.3)	164.3 (1.3)	0.32
Males	163.5 (1.4)	157.6 (1.4)	166.5 (1.6)	0.14
Females	159.5 (2.7)	165.0 (2.4)	160.9 (2.0)	0.67
FH minus Baseline PH (cm)				
All	5.4 (1.3)	6.7 (1.3)	7.2 (1.3)	0.31
Males	5.8 (1.4)	4.7 (1.5)	8.8 (1.5)	0.15
Females	3.9 (2.5)	9.8 (1.9)	4.7 (1.9)	0.81
FH minus Target Height (cm)				
All	(n=17) -3.8 (1.8)	(n=16) -5.3 (1.9)	(n=17) -1.3 (1.8)	0.34
Males	-2.2 (2.3)	-6.8 (2.5)	-1.2 (2.3)	0.76
Females	-6.7 (3.1)	-3.4 (2.9)	-1.6 (3.1)	0.25

11 patients were missing baseline predicted height data and 1 patient was missing target height data; these patients are excluded from respective analyses.

Graphs of final height versus baseline height, baseline predicted height and target height are provided in Appendix 4. All patients in the final height population have a larger height SDS at endpoint than at baseline. The majority of patients show an improvement in height over their baseline predicted height but not over their target height.

A graph of final heights in inches (Figure 17) shows a slight shift in the distribution upwards with increasing dose. All males on the high dose had a final height greater than 5'4" at endpoint and most females on the high dose were taller than 5'.

Figure 17. Final height in inches for the final height population by gender and dose



Overall comments on Study E001

Pairwise comparisons of final height SDS (or other measures of final height) showed no statistically significant differences among the doses though the magnitude of the treatment response for the 0.37mg/kg/wk dose is greater than the effect seen for the 0.24 mg/kg/wk dose. Most patients showed an improvement in height SDS and in final height compared to baseline predicted height.

## Summary and Conclusions

The applicant has presented the results of two randomized clinical trials to assess the benefit of humatrope for children who are not growth hormone deficient but are of short stature. One trial (GDCH) was designed to compare humatrope (0.22 mg/kg/wk with 3x per week dosing) to placebo and the other trial was a dose-response study of three doses of humatrope (0.24 mg/kg/wk, 0.24 mg/kg/wk for one year followed by 0.37 mg/kg/wk and 0.37 mg/kg/wk administered 6x per week). The endpoint of primary interest is final height SDS measured when the patient's height velocity slowed to 1.5 cm/yr or less in GDCH or to 2 cm/yr or less in E001.

The effect of humatrope is best measured in Study GDCH where the gain in height due to humatrope treatment can be compared to the placebo effect; the emphasis in this review then has been on Study GDCH (note that this review is a draft review prepared for an advisory committee meeting). Study E001 provides additional descriptive data on two different doses of humatrope.

A total of 33 patients (46% of the randomized patients) in GDCH and 50 patients (21% of the randomized patients) in E001 were analyzed for final height. To address the issue of dropout bias, additional analyses including patients without final height data were performed by both the applicant and the reviewer. In general, these analyses supported the primary analysis of height SDS for the final height population.

The results for Study GDCH showed a statistically significant treatment effect for humatrope compared to placebo for final height SDS (treatment effect of 0.51,  $p=0.017$ , Table 15). The applicant converted the SDS difference to cm coming up with an improvement in height of 3.7 cm (see page 22 for a further description of this computation). Analysis of final height in cm adjusting for baseline predicted height yields a treatment effect of 3.2 cm. The difference between these estimates is probably of no clinical significance.

Table 15. Final Height Results for Study GDCH

	Humatrope 0.22	Placebo	Treatment Effect 95% CI	P-value
FH <sup>1</sup>				
SDS	-1.81	-2.31	0.51 (0.10, 0.92)	0.017
cm	160.7	157.6	3.17 (0.26, 6.07)	0.03

<sup>1</sup> Means are least squares means from ANCOVA with baseline predicted height as a covariate.

The applicant reported an estimate of 5 cm gain for humatrope over placebo based on a repeated measures analysis. This analysis was a post-hoc analysis of the efficacy evaluable population using a mixed effects model. The 5 cm estimate may be an overestimate of final height gain because of the use of non-final height data. Humatrope patients show increases in SDS accompanying a large increase in height velocity during the first year of treatment; of patients followed to final height, the majority show a decrease in SDS after a peak at the time of their growth spurt. It is not clear to this reviewer whether the applicant's mixed model fits the trajectory of the data seen by most patients. Other issues that deserve further examination are the choice of covariates and interaction terms in the model. Further detailed review of the mixed effects model by this reviewer is needed and will be discussed in a later version of this review.

To describe the results of both GDCH and E001, this reviewer summarized the difference between final height and baseline predicted height and between final height and target height (Table 16). Patients reaching final height show an improvement in final height over baseline predicted height with larger differences seen with increasing dose. Very few patients reach their target height though clearly patients on the highest dose of humatrope get closer than the placebo patients or the low dose patients.

Table 16. LS Means adjusting for baseline PH for the Final Height Population

	GDCH		E001		
	Placebo	Humatrope 0.22	Humatrope 0.24	Humatrope 0.24/0.37	Humatrope 0.37
FH – Baseline PH					
SDS	-0.18	+0.33	+0.83	+1.10	+1.29
cm	-0.9	+2.3	+5.4	+6.5	+7.3
(95% CI for cm)	(-3.3, 1.5)	(0.6, 3.9)	(2.9, 8.0)	(3.9, 9.1)	(4.7, 9.8)
FH – Target Height					
SDS	-0.96	-0.68	-0.46	-0.64	-0.26
cm	-7.0	-4.8	-3.3	-4.8	-1.9
(95% CI for cm)	(11.3, -2.6)	(-7.6, -2.0)	(-7.7, 1.0)	(-9.2, -0.4)	(-6.3, 2.4)

Figures 18 and 19 show the individual data for the variables summarized in Table 16. Overlap across the groups is clearly evident though medians (black filled circles) suggest a dose response relationship of increasing response with increasing dose.

Figure 18. Final height minus baseline predicted height for the final height populations of Studies GDCH and E001

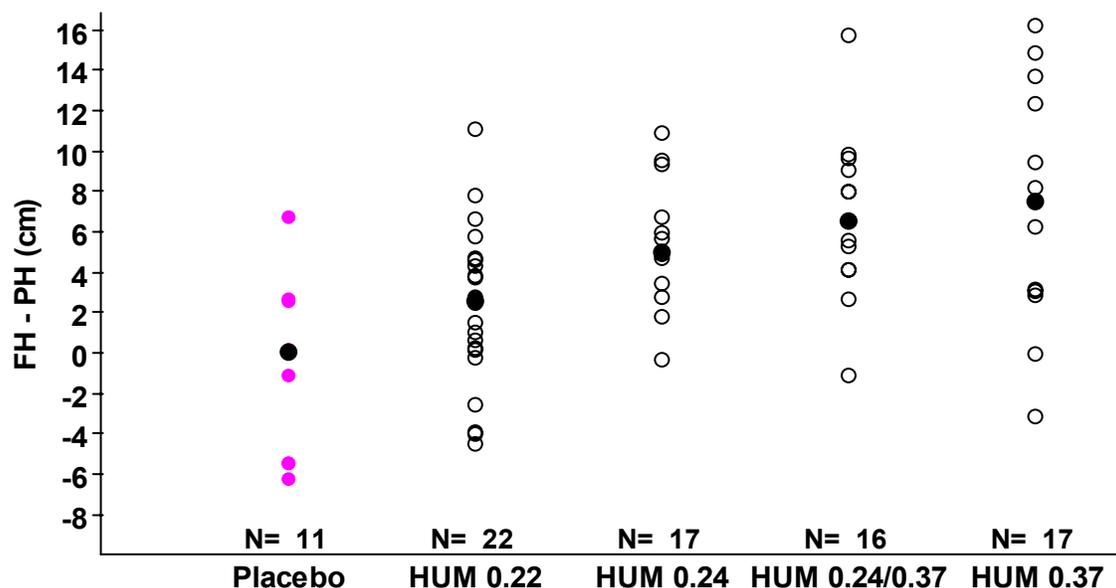
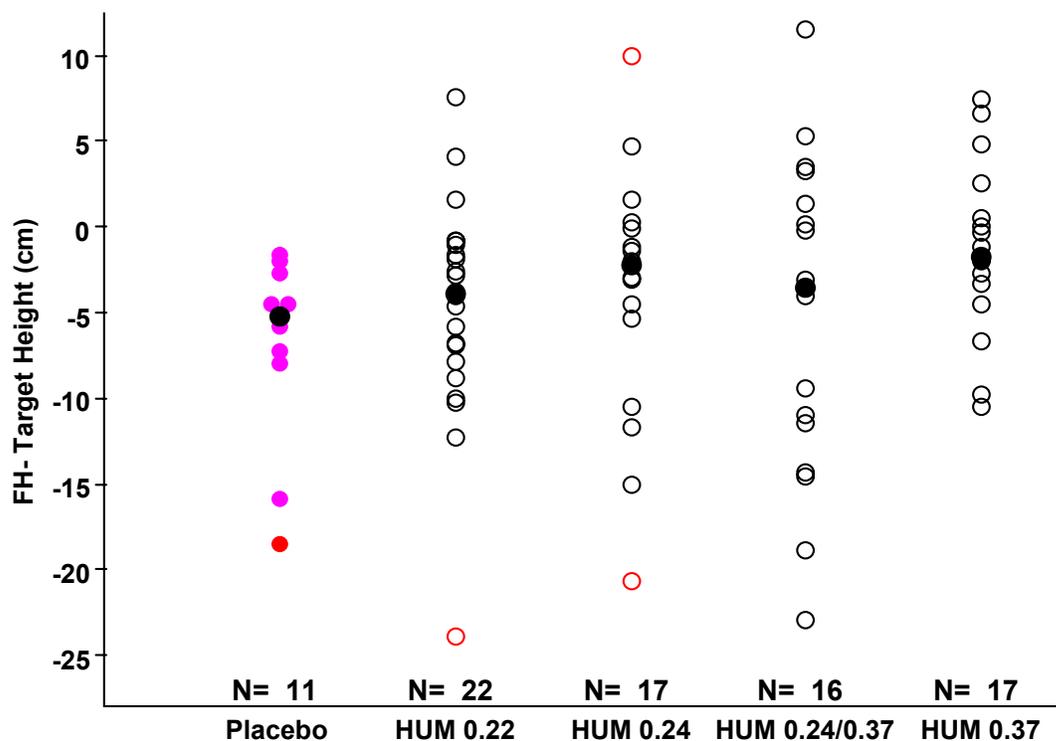


Figure 19. Final height minus target height for the final height populations of Studies GDCH and E001



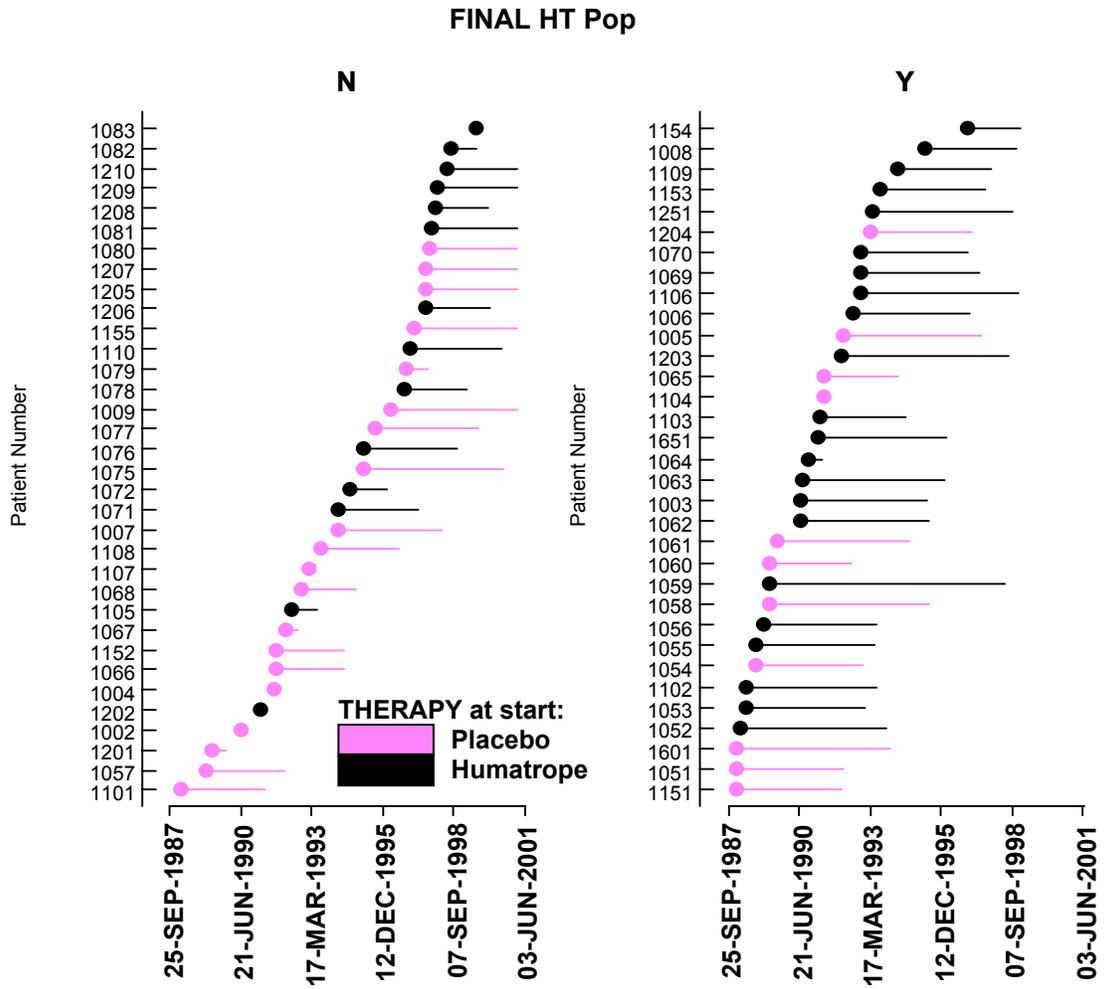
This reviewer has the following overall comments:

- the administration of humatrope in patients not growth hormone deficient but of small stature results in statistically significant gains in height compared to placebo (GDCH)
- mean gains of about 3-4 cm (1 to 1 ½ inches) in height over placebo were observed
  - further review of estimates from the applicant's repeated measures analyses is needed
- no statistically significant differences between 0.24 mg/kg/wk and 0.37 mg/kg/wk were seen comparing final height SDS, although, the magnitude of responses suggests a trend of increasing response with increasing dose
- alternate analyses of different patient populations and different efficacy variables supported the results of the analyses of the final height data from the GDCH final height population (about 40% of the randomized patients)
- the small sample sizes preclude making definitive statements about subgroup analyses and about the characteristics of patients most likely to benefit from treatment

This reviewer concludes that Study GDCH showed a statistically significant treatment effect on final height for humatrope compared to placebo. The clinical significance of this treatment effect deserves full discussion.

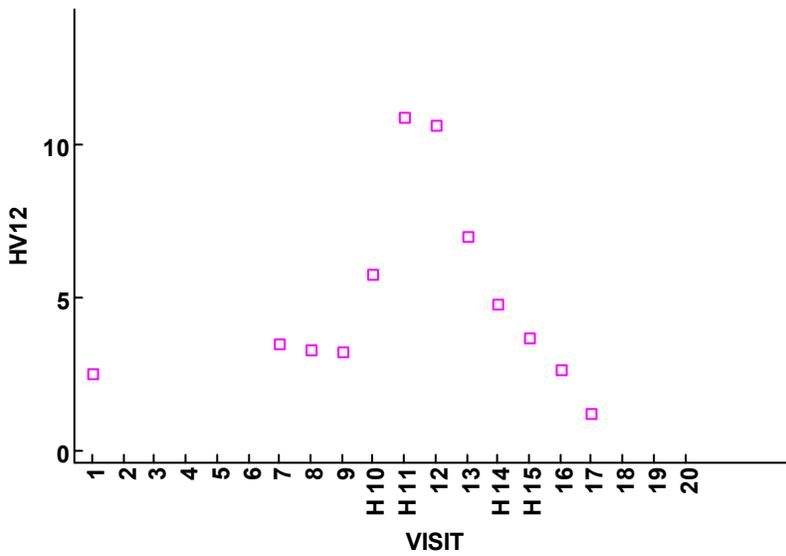
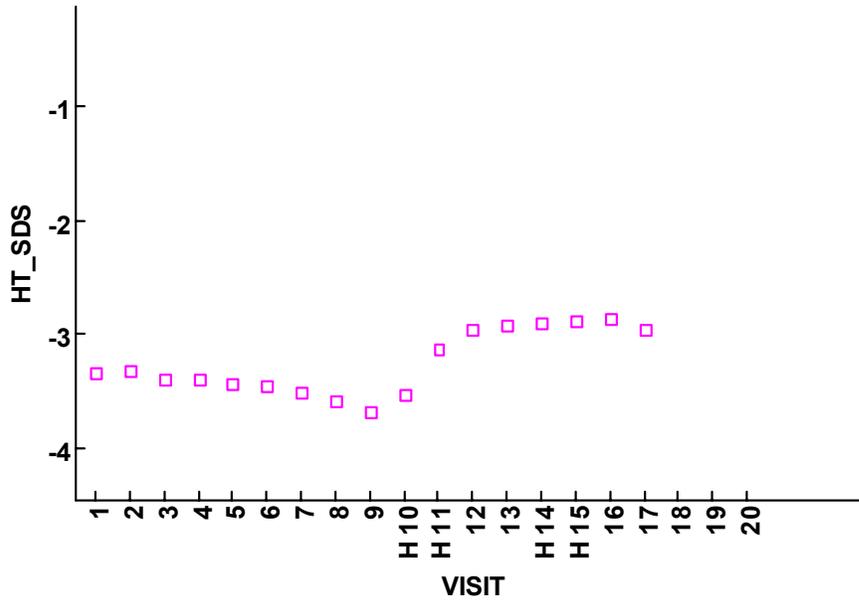
# Appendices

## Appendix 1. Start and stop dates in GHCD

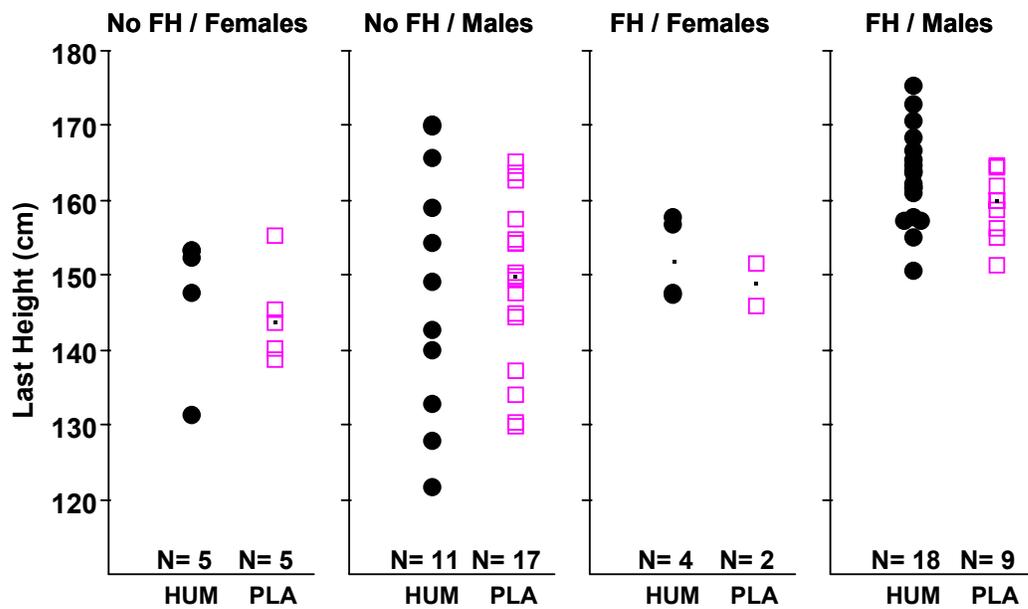


**Appendix 2. Patient 1601**

Patient started placebo therapy at age 12. Humatrope therapy was mistakenly given at Visits 10 to 11 (age 14.5 to 15) and Visits 14 to 15 (age 16.4 to 16.9).

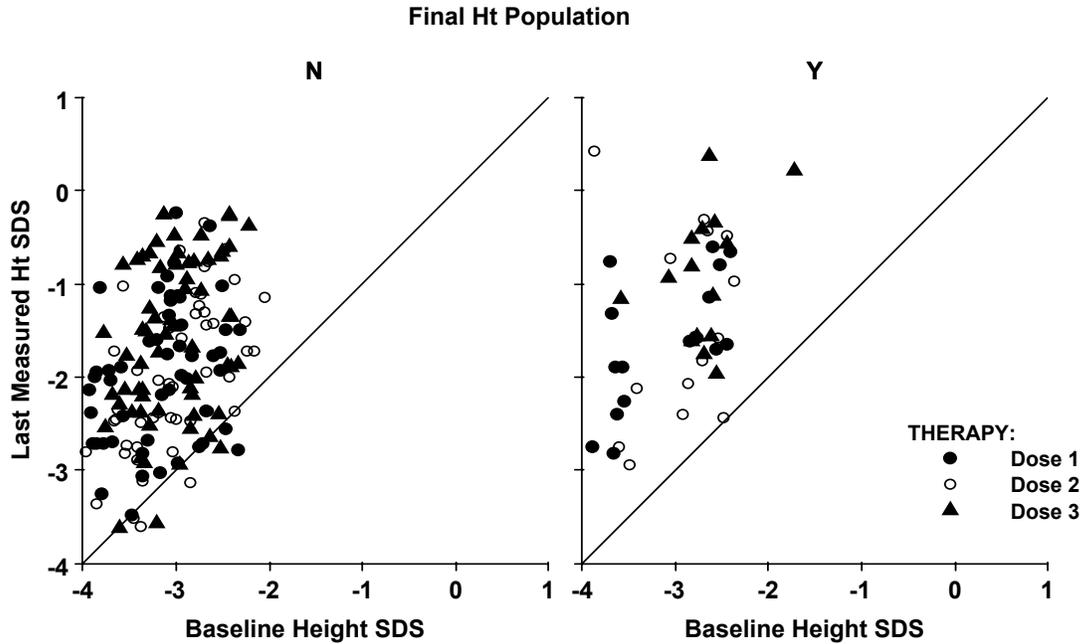


**Appendix 3. GDCH Last height on study in cm**

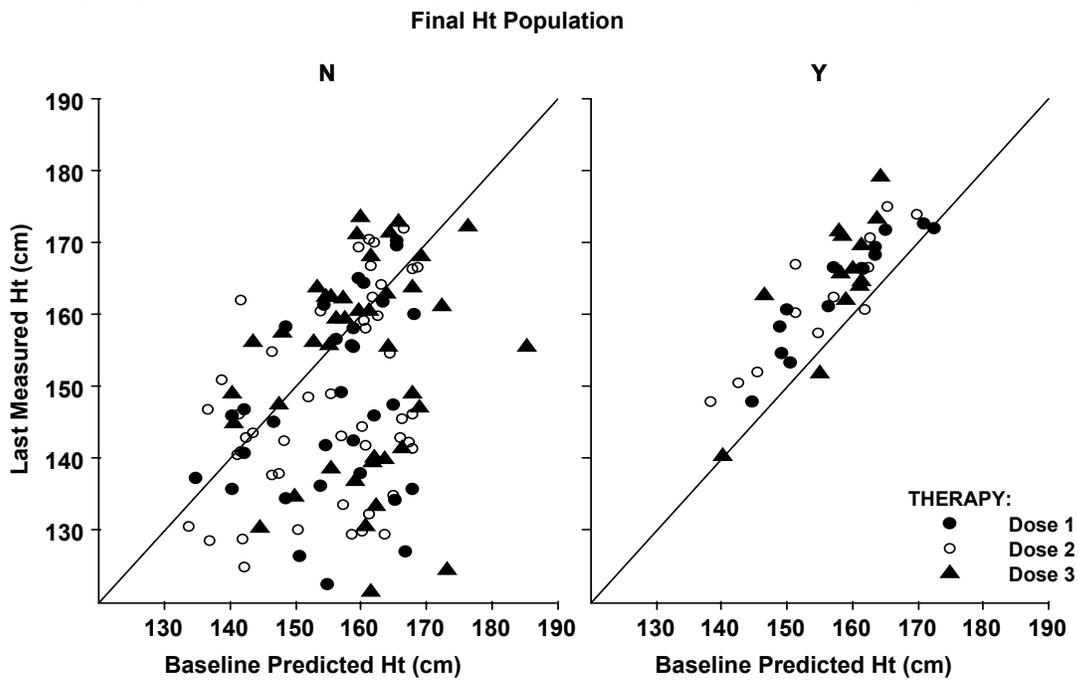


**Appendix 4. E001 Plots of FH versus baseline height, baseline PH and target height**

**Final Height SDS (or last measured height) versus Baseline Height SDS**



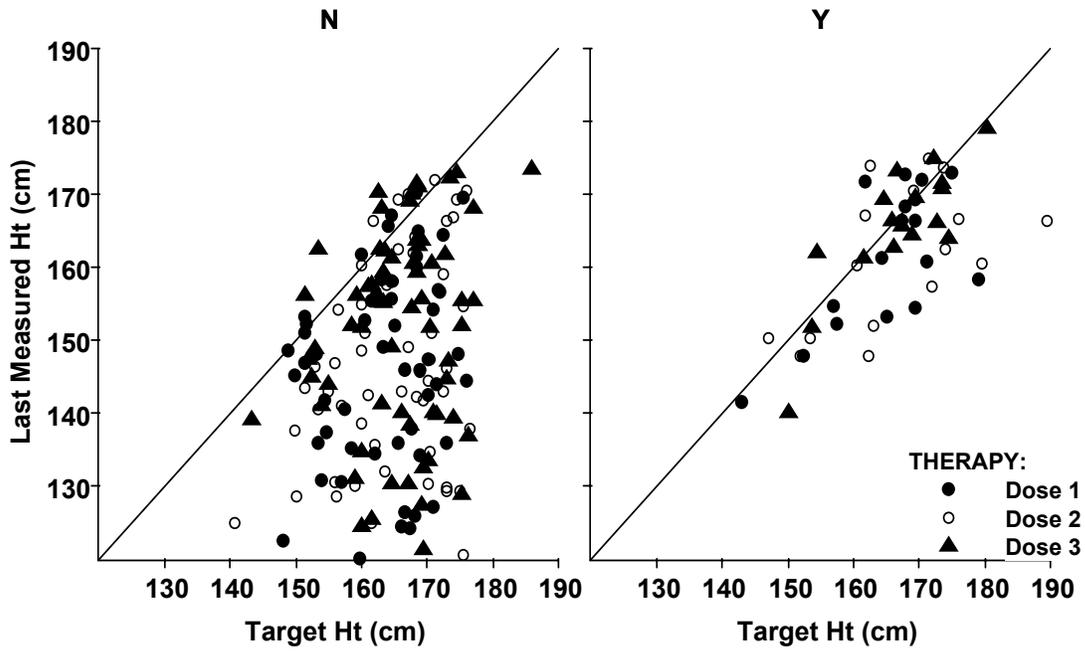
**Final Height (or last measured height) versus Baseline Predicted Height**



*Appendix 4 continued*

**Final Height (or last measured height) versus Target Height**

**Final Ht Population**



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