CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number 019640/S018 and S019

Trade Name HUMATROPE

Generic Name Somatropin (rDNA origin)

Sponsor Eli Lilly and Company

Approval Date : March 11, 1997

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-640/S-018
NDA 19-640/S-019

MAR 11 1997

Eli Lilly and Company
Attention: Timothy R. Franson, M.D.
Executive Director, North American Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Franson:

We acknowledge your supplemental new drug applications dated July 29, received July 31, 1996 (supplement 018) and November 11, received November 12, 1996 (supplement 019) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Humatrope [somatropin (rDNA origin) for injection], 5 mg/vial.

We acknowledge receipt of your submissions to supplement 018 dated July 19 and 29, August 1 and 9, October 25, November 25, February 27, and March 10, 1997. The User Fee goal date for the application (supplement 018) is August 2, 1997.

These supplemental applications provide for:

1. S-018: A new indication for Turners Syndrome.

2. S-019: Labeling changes to reflect agreements reached during September and October 1996 between Eli Lilly and the Division of Metabolic and Endocrine Drug Products including:

a. Throughout the label, when referring to adults with growth hormone deficiency, somatropin is replaced by somatotropin.

b. Under the ***"effects of Humatrope treatment in adults with somatotropin deficiency"*** section in the CLINICAL PHARMACOLOGY section, the results from the 18 month, open-label, quality of life data were deleted from both Table 2 "Changes in Nottingham Health Profile Scores in Adult Onset Somatropin Deficient Patients" and from the accompanying text. In addition, footnote "a" from Table 2 was added and footnote "b" from Table 2 was revised.

c. Under the INDICATIONS AND USAGE section, the criteria for Humatrope treatment for adults with somatropin deficiency have been reordered for clarity.

We have completed the review of these supplemental applications, including the submitted draft labeling, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the draft labeling dated February 27, 1997. Accordingly, these supplemental applications are approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the draft labeling submitted on February 27, 1997.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FINAL PRINTED LABELING" for approved supplemental NDAs 19-640/S-018, 19-640/S-019. Approval of this submission by FDA is not required before the labeling is used.

We remind you of your Phase 4 commitment specified in your submission dated February 27, 1997. This commitment is, along with any completion dates agreed upon, listed below. Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. Should an IND not be required to meet your Phase 4 commitment, please submit protocol, data, and final reports to this NDA as correspondences. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments must be clearly designated "Phase 4 Commitments."

As discussed in your submission of March 10, 1997, please submit a labeling supplement which rewrites the section of the label that describes the adverse event incidence (>5%) in growth hormone deficient adult clinical trial patients and amends this section to give placebo comparative data. Also, attention should be given to expanding the adverse reaction labeling in respect to the Turner studies. The adverse reaction data from the Canadian controlled study should be tabulated and compared to the findings in the control group.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications, HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Should a letter communicating important information about this drug product (i.e., a "Dear Doctor" letter) be issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to these NDAs and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20852-9787

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact Michael F. Johnston, R.Ph., Consumer Safety Officer, at (301) 443-3490.

Sincerely yours,

Solomon Sobel

Solomon Sobel, M.D.
Director
Division of Metabolic and Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation and Research

July 25, 1996

Re: HUMATROPE NDA SUPPLEMENT FOR TURNER'S SYNDROME

ITEM 13: PATENT INFORMATION

The undersigned certifies that there are no patents claiming the drug or formulation or composition of such drug which is the subject of the present New Drug Application.

ITEM 14: PATENT CERTIFICATION

We certify that there is no patent covering the use of somatropin .

Eli Lilly and Company (Lilly) requests a three year period of data exclusivity for the use of somatropin in the treatment of Turner's Syndrome.

This NDA contains reports of new clinical investigations (other than bioavailability studies) conducted or sponsored by Lilly that are essential to obtain its approval. Upon approval of this NDA, Lilly is entitled to a three (3) year period of data exclusivity for this new indication as provided by Section 505(c)(3)(D)(iii) and 505(j)(4)(D)(iii) of the Federal Food, Drug, and Cosmetic Act, as amended, [21 U.S.C. 355(c)(3)(D)(iii) and 21 U.S.C. 355(j)(4)(D)(iii)].

Two clinical trials conducted for this NDA are essential to obtain approval of this NDA and are identified as follows:

B9R-MC-GDCI	Humatrope® and Low-Dose Estrogen in Turner's Syndrome
B9R-CA-GDCT	Humatrope®: Treatment to Final Height in Turner's Syndrome

Supporting data includes the report to the CPMP.

Lilly certifies (in support of its request and following the suggestion in Dr. Paul D. Parkman's letter of October 31, 1986 regarding "developments in

Restoration Act of 1984") that to the best of Lilly's knowledge:

1. the above clinical investigations did not form part of the basis of a finding of substantial evidence of effectiveness for a previously approved new drug application,

2. the above clinical investigations were each sponsored or conducted by Lilly,

3. Lilly, through its employees and others, electronically searched the Scientific literature (as of July 23, 1996) via Medicine, Ringdoc, and World Patents Index and discovered twenty-eight published studies of publicly available report of clinical investigations relevant to the use of somatropin for Turner's Syndrome. These published reports are attached hereto and identified as:

Attanasio A, James D, Reinhardt R, Reders-Mombarg L. 1995. Final height and long-term outcome after growth hormone therapy in Turner syndrome: results of a German multicentre trial. Horm Res 43:147-149.

Cohen A, Kauli R, Pertzelan A, Lavagetto A, Roitman Y, Romano C, Laron Z. 1995. Final height of girls with Turner's syndrome: correlation with karyotype and parental height. Acta Paediatr 84:550-554.

Holl RW, Kunze D, Etzrodt H, Teller W, Heinze E. 1994. Turner syndrome: final height, glucose tolerance, bone density and psychosocial status in 25 adult patients. Eur J Pediatr 153:11-16.

Huisman J, Slijper FME, Sinnema G, Akkerhuis GW, Brugman-Boezeman A, Feenstra J, den Hartog L, Heuvel F, The Dutch Working Group: Psychologists and Growth Hormone). 1993. Psychosocial effects of two years of human growth hormone treatment in Turner syndrome. Horm Res 39(Suppl 2):56-59.

Hultcrantz M, Sylven L. 1995. Hearing problems in women with Turner syndrome. Albertsson-Wikland K, Ranke MB, editors.249-57. Turner syndrome in a life-span perspective. New York:Elsevier Science, B.V.Anonymous

Lenko HL, Soderholm A. Perheentupa J. 1988. Turner syndrome: effect of hormone therapies on height velocity and adult height. Acta Paediatr Scand 77:699-704.

Massa G, Otten BJ, de Muinck Keizer-Schrama SMPF, Delemarre-van de Waal HA, Jansen M, Vulsma T, Oostdijk W, Waelkens JJ, Wit JM, Dutch Growth Hormone Working Group. 1995. Treatment with two growth

hormone regimens in girls with Turner syndrome: final height results. Horm Res 43:144-6.

Mauras N, Rogol AD, Veldhuis JD. 1989. Specific, time-dependent actions of low-dose ethinyl estradiol administration on the episodic release of growth hormone, follicle-stimulating hormone, and luteinizing hormone in prepubertal girls with Turner's syndrome. J Clin Endocrinol Metab 69(5):1053

Naeraa RW, Brixen K, Hansen RM, Hasling C, Mosekilde L, Andresen J-H, Charles P, Nielsen J. 1991. Skeletal size and bone mineral content in Turner's syndrome: relation to karyotype, estrogen treatment, physical fitness, and bone turnover. Calcif Tissue Int 49:77-83.

Nilsson KO, Albertsson-Wikland K, Alm J, Aronson S, Gustafsson J, Hagenas L, Hager A, Ivarsson SA, Karlberg J, Kristrom B, Marcus C, Moell C, Ritzen M, Tuvemo T, Wattsgard C, Westgren U, Westphal O, Aman J. 1995. Growth promoting treatment in girls with Turner syndrome: final height results according to three different Turner syndrome growth standards Albertsson-Wikland K. ,Ranke MB, editors. Turner Syndrome in a Life-Span Perspective. New York: Elsevier Science B.V.

Park E, Bailey JD, Cowell CA. 1983. Growth and maturation of patients with Turner's syndrome. Pediatr Res 17:1-7.

Raiti S, Moore WV, Van Vliet G, Kaplan SL, The National Hormone and Pituitary Program. 1986. Growth-stimulating effects of human growth hormone therapy in patients with Turner syndrome. J Pediatr 109 (6):944-949.

Ranke MB, Pfluger H, Rosendahl W, Stubbe P, Enders H, Bierich JR, Majewski F. 1983. Turner syndrome: Spontaneous growth in 150 cases and review of the literature. Eur J Pediatr 141:81-88.

Ranke MB, Stubbe P, Majewski F, Bierich JR. 1988. Spontaneous growth in Turner's syndrome. Acta Paediatr Scand [Suppl] 343:22-30.

Ranke MB. 1994. Growth in Turner's syndrome. Acta Pediatr 83:343-344.

Rochiccioli P, Battin J, Bertrand AM, Bost M, Cabrol S, le Bouc Y, Chaussain JL, Chatelain P, Colle M, Czernichow P, David M, Job JC, Lecornu M, Leheup B, Pierson M, Limal JM, Mariani R, Ponte C, Rappaport R, Tauber M. 1995. Final height in Turner syndrome patients treated with growth hormone. Horm Res 44:172-176.

Rosenfeld RG, Frane J, Attie KM, Brasel J, Burstein S, Cara JF, Chernausek S, Gotlin RW, Kuntze J, Lippe BM, Mahoney PC, Moore WV, Saenger P, Johanson AJ. 1992. Six-year results of a randomized, prospective trial of

human growth hormone and oxandrolone in Turner syndrome. J Pediatr 121(1):49-55.

Ross JL, Meyerson Long L, Loriaux DL, Cutler GBJ. 1985. Growth hormone secretory dynamics in Turner syndrome. J Pediatr 106:202-206.

Soyka LF, Ziskind A, Crawford JD. 1964. Treatment of short stature in children and adolescents with human pituitary growth hormone (Raben). N Engl J Med 271:754

Stepan JJ, Musilova J, Pacovsky V. 1989. Bone demineralization, biochemical indices of bone remodeling, and estrogen replacement therapy in adults with Turner's syndrome. J Bone and Min Res 4(2):193-8.

Sybert VP. 1984. Adult height in Turner syndrome with and without androgen therapy. J Pediatr 104(3):365-9.

Takano K, Shizume K, Hibi I, Ogawa M, Okada Y, Suwa S, Tanaka T, Hizuka N, Committee for the Treatment of Turner Syndrome. 1995. Long-term effects of growth hormone treatment on height in Turner syndrome: results of a 6-year multicentre study in Japan. Horm Res 43:141-143.

Tzagouris M. 1969. Response to long-term administration of human growth hormone in Turner's syndrome. JAMA 210:2373

Van den Broeck J, Massa GG, Attanasio A, Matranga A, Chaussain J-L, Price DA, Aarskog D, Wit J-M, The European Study Group. 1995. Final height after long-term growth hormone treatment in Turner syndrome. J Pediatr 127(5):729-735.

Werther GA, Dietsch S. 1995. Multicentre trial of synthetic growth hormone and low-dose oestrogen in Turner syndome: analysis of final height. Albertsson-Wikland K., Ranke MB, editors. Turner Syndrome in a Life-Span Perspective. New York: Elsevier Science B.V.

Wright JC, Brasel JA, Aceto TJ. 1965. Studies with human growth hormones in Turner's syndome. Amer J Med 38:499-516.

Zachmann M, Sobradillo B, Frank M, Frisch H, Prader A. 1978. Bayley-Pinneau, Roche-Wainer-Thissen, and Tanner height predictions in normal children and in patients with pathologic conditions. J Pediatr 93(5):749-55.

4. the aforementioned articles, as published, are, in the opinion of Lilly, insufficient to support the approval of this application and therefore, in Lilly's opinion, there is not sufficient published or publicly available reports of clinical investigations, other than those conducted by or sponsored by Lilly, that would support the approval of this application.

The undersigned on behalf of Lilly certifies that to the best of his knowledge the information presented herein are true and accurate.

Robert A. Conrad

EXCLUSIVITY SUMMARY for NDA # 19-640 SUPPL # 018

Trade Name Humatrope Generic Name [somatropin (rDNA origin) for injection]
Applicant Name Eli Lilly and Co.. HFD- 510

Approval Date _____

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES /___/ NO /_X_/

   b) Is it an effectiveness supplement? YES /_X_/ NO /___/

   If yes, what type? (SE1, SE2, etc.) SE1

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

   YES / X / NO /___/

   If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

   _____

   If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

   _____

   d) Did the applicant request exclusivity? YES /___/ NO /_X_/

   If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

   _____

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 7.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?

YES /_X_/ NO /___/

If yes, NDA # 20-656 Drug Name Nutropin

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 7.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /___/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 7 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #_____ _____

NDA #_____ _____

NDA # _____ _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 7.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

   For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

   (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 7:**

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain: _____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # _____

Investigation #2, Study # _____

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study #_____
NDA # _____ Study #_____
NDA # _____ Study #_____

b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study #_____
NDA # _____ Study #_____
NDA # _____ Study #_____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #1_, Study # _____

Investigation #2_, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # _____ YES /__/ NO /__/ Explain: _____

Investigation #2

IND # _____ YES /__/ NO /__/ Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /__/ Explain _____ NO /__/ Explain _____

Investigation #2

YES /__/ Explain _____ NO /__/ Explain _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /__/ NO /__/

If yes, explain: _____

_____

_____

_____

Michael F. Johnston
Signature

12/18/96
Date

Title: Project Manager / Consumer Safety Officer

Solomon Sobel M.D.
Signature of Division Director

3/3/97
Date

cc: Original NDA Division File HFD-85 Mary Ann Holovac

NDA 19-640/SE1-018

This Is Not a New Molecular Entity therefore Pediatric Page Not Applicable to this NDA/Supplement

CERTIFICATION

NDA Application No.: 19-640

Drug Name: Humatrope ®, [somatropin, biosynthetic human growth hormone]

Pursuant to the provisions of 21 U.S.C. 335a(k)(1), Eli Lilly and Company, through Timothy R. Franson, M.D., hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section (a) or (b) [21 U.S.C. 335a(a) or (b)] of the Generic Drug Enforcement Act of 1992, in connection with the above referenced application.

ELI LILLY AND COMPANY

By: _____
for Timothy R. Franson, M.D.

Title: Executive Director
North American Regulatory Affairs

Date: 07/29/96

Summary of Medical Officer Review of NDAs 19-640 and 20-565

Growth hormone treatment to improve final height in girls with Turner's syndrome

Saul Malozowski, Medical Officer
November 27, 1996

INDEX

INTRODUCTION

This review assesses the effects of GH treatment in girls with Turner's syndrome (TS) based upon information provided by Genentech and Lilly. Turner syndrome patients have chronic growth retardation and achieve final heights that are significantly shorter than normal girls. In the past, attempts to reverse short stature were made using different pharmacological interventions, but the final outcomes have not been satisfactory. The availability of recombinant GH provided a new agent that has been shown effective in increasing growth velocities in diverse patient populations. In the studies that will be reviewed in this document Turner patients received GH for several years and many of the subjects reached final adult heights. One of the studies was controlled for its entire duration, and an appropriate long term comparison between concurrent treatment groups could thereby be assessed. In addition, three other studies will be discussed in which patients received GH alone or in combination with steroids or placebo for at least one year. Subsequently, patients on the GH-placebo arms were re-randomized into other arms of the studies. Many of these subjects also reached adult height and this review will center on this population. In two of these, assessment of final heights was performed by comparison to historical controls while in one final heights were compared to available standards. When using historical controls GH treated patients were matched by age with girls from the HC database. Final height for the GH treated patients was defined prospectively as the point at which a bone age was reached such that additional growth would be negligible although data were presented using only chronological age. Additional criteria used to ascertain final height was that the growth velocities exhibited in the previous months must be very low. It should be underscored that these criteria would tend to underestimate result of final adult heights. The difference between near adult height and actual adult height is unknown. The main objective of this review is to estimate the risk-benefit relationship of this intervention and to describe the inherent difficulties in precisely stating this relationship.

BACKGROUND: DESCRIPTION OF TURNER'S SYNDROME

Turner's syndrome is characterized by the absence or structural abnormality of one sex chromosome in a female (total or partial monosomy X) and it is associated with four cardinal features: 1) female phenotype, 2) short stature, 3) gonadal dysgenesis, and 4) a variety of somatic abnormalities.

Adult short stature is one of the most common phenotypic features of the syndrome. Studies of large numbers of girls with TS confirmed by karyotypic analysis confirmed that short stature is present in virtually 100% of 45,X patients. Rather than having a single sex chromosome, many patients with TS have an abnormality of one X chromosome or a mosaicism in which at least one cell line has an abnormal X chromosome. Short stature is found in over 95% of these cases being in approximately 30% of cases the only physical finding at the time of diagnosis.

INCIDENCE, PREVALENCE

Although more than 99% of 45,X concepti are aborted spontaneously before birth, Turner syndrome remains one of the most common chromosomal anomalies among female live births. The currently calculated incidence of TS is approximately 1/2500. The prevalence of TS in the adult population is difficult to ascertain, but it is estimated that there are about 50,000 affected women in the United States, with 800 new cases per year.

ETIOLOGY OF SHORT STATURE

Short final height in Turner syndrome is due to the summation of different identifiable factors and probably also to others that have not been yet clearly characterized. First TS girls have intrauterine growth retardation with mean birth length at 1.2 standard deviations (SD) (2.8 cm) below the mean for normal girls. It has been proposed that malformations of the lymphatic system that usually result in edema and altered vascularization could be responsible for early intrauterine mortality as well as to the growth retardation in the surviving fetuses. Second, between the bone ages of 3 and 11 years, there is a gradual decline in growth rate, reaching a mean growth rate by age 9 that is greater than 2 SD below the mean for normal 9-year-old girls. Third, the absence of gonadal steroids is responsible for the lack of a normal pubertal growth spurt and for a delay in epiphyseal closure. Bone age is delayed 1–2 years throughout most of childhood, but is more significantly delayed after age 12 due to the lack of pubertal development. Thus, between the chronologic ages of 14 and 20, T girls could continue to grow longer relative to normal girls, especially if estrogen replacement is not given, but despite this potential for further growth their final height is significantly reduced.

It has been proposed that the skeletal dysplasia found in the syndrome (possibly related to congenital lymphedema) may be the underlying cause of short stature. Certainly, a large number of other skeletal abnormalities are found in Turner girls, such as thinning of the parietal bones, pectus excavatum, "drumstick" appearance of the distal phalanges, short fourth metacarpal and metatarsal, pes cavus, midface hypoplasia, and irregular tibial metaphyses. In addition, congenital dislocation of the hips is found more frequently (about 15%), as is scoliosis (about 10%). Although the bones are reduced in size, there is a proportionate reduction in length and width, resulting in a normal appearance. There is evidence that long bone growth may be more impaired than vertebral growth, resulting in short-leggedness. In addition to the bones, other tissues and organs are correspondingly small, suggesting a generalized growth retardation affecting all parts of the body including the above listed skeletal structures. Other confounding features such as lack of adequate ossification, a tendency to develop osteopenia, as well as cardiac and renal malformations, and an increased incidence of otitis media could also play a role in their small final stature. The higher prevalence of autoimmune disorders, specifically thyroiditis and diabetes can add to this statural deficit.

Lyon et al. combined data from four European studies (366 girls) to construct growth curves for TS. The resulting chart provides normative data for height for age 2 through adulthood, and permits projections of adult height for an untreated T subject. Based upon this growth chart, Lyon calculated a correlation coefficient of 0.95 for first measured height SD score (age 3–12) and adult height SD score (age 19–24). A steady decline in growth rate from age 3 on and the relative lack of a pubertal growth spurt as compared with the standards for normal girls is observed in girls with TS.

The pathogenesis of growth failure in TS is not well defined at present. The multiple endocrine abnormalities present in TS may contribute to the abnormal growth pattern, although it is unlikely that the ultimate short stature is primarily an endocrine disorder. Gonadal dysgenesis, which manifests during early childhood in most T girls, results in low estrogen production and either absent or arrested pubertal development. The sex steroid-induced pubertal growth spurt, which is associated with increased GH and insulin-like growth factor-I (IGF-I) secretion, is lacking in T girls. However, skeletal

maturation is delayed by this relative estrogen deficiency, resulting in a prolonged growth phase beginning at age 12 (bone age 10) with low growth rates.

Although subtle disorders of GH secretion may contribute to growth failure in some T girls, growth failure typically precedes the reduction of GH and IGF-I levels that occurs in late childhood and adolescence. Hypothyroidism affects as many as 20% of T girls by mid-adolescence and failure to identify this condition might further compromise growth in this subset of patients.
In summary, the endocrine abnormalities in TS, though significant in the adolescent age group, fail to account for the overall growth failure in the syndrome that begins in utero. A combination of genetic deficiencies, lymphedema, and skeletal malformations probably accounts for the short stature associated with TS. Although subtle alterations of GH secretion may be present GH hyposecretion does not account for the short stature of TS that are uniformly short regardless of their GH status.

SUMMARY OF MAJOR STUDIES

GDCT study (Lilly)

This is a randomized, parallel, open-label study that is still ongoing in Canada.
The effects of GH where compared to a concurrent non-treated group. The primary endpoint was to assess the efficacy of GH in promoting an increase in final height in patients with TS. Safety was also assessed in this study.

One hundred fifty four patients were enrolled and of those 76 received GH while 78 did not. All patients met the required entry criteria. Patients were stratified by age into three different groups before randomization into two groups to assure balance. At age 13 years patients in both groups received ethinyl estradiol (2.5 µg/day). One year after the dose of estradiol was increased to 5 µg/day. At age 15 years, this dose was increased to 20 µg/day and medroxyprogesterone (10 mg/day) was added for the last ten days of a 24 day cycle. These drugs were not administered between days 24 and 30.

Baseline characteristics were no different between groups, except for the midparental height that was 2 cm higher in the control group. The baseline age was 11.6±1.2 years.

At the time of this submission 36.5% (27) in the GH group and 31.7% (19) in the control group reached final height as defined in the original protocol. When data on final stature is corrected for midparental height, stature strata, and geographical location GH treated patients were 4.9±1.3 cm taller than controls ($p<0.001$). The final height in the GH treated group was 146±6 cm and in the control 142.1±4.8 cm (Δ 5.4 cm, $p<0.001$). A similar trend was observed using more stringent final height criteria that showed GH treated patients with final heights of 146.3 ± 6.0 cm and controls of 141.2 ± 6.0 cm ($p<0.01$; Δ 6.4 cm). When final statures are expressed as SDS the GH treated group increased by 1.3 SD while the observational group improved by 0.3 SD ($p<0.001$).

Patients were treated on average 4.7±0.9 years. Thus, approximately 1.2 cm/year was the gain observed in the GH treated group and approximately 50% of the total gain was achieved during the first year of therapy.

Several issues should be taken into consideration when analyzing these data. First the mean age at entrance was quite advanced (11.6±1.2 years). It is known from treatment of patients with GH deficiency that younger patients tend to exhibit greater growth acceleration and increased final heights than older subjects. Moreover, induction of pubertal development with estrogen may negatively affect final height. From the information provided more than half of the patients were on estrogen after or during the second years after protocol initiation. While GH alone may induce extensive growth, estrogens lead to epiphyseal closure and growth cessation. Finally what the protocol defines as final height (BA≥ 14 years, growth velocity < 2 cm/year) is not a definitive final height. Patients could continue to grow after this BA is reached and could further increase their final heights. This potential for growth, however, also applies to the control group. In summary, this study shows a significant gain in final height of approximately 5.4 cm.

This study also allows for a meaningful assessment of safety because it has a concomitant control group throughout its duration. This will be discussed after reviewing the efficacy of all other studies.

GDCI study (Lilly)

This is double blind, randomized, placebo controlled study of treatment with GH and low dose estrogen in 232 TS patients. Patients were stratified after enrollment into four groups by age (5-7, 8-9, 10-11, and ≥12 years) and then randomized into five treatment groups. Two groups received GH at a dose of 0.27 mg/kg/week. One of those groups received a low dose of ethinyl estradiol (25-50 ng/kg/day) and the other placebo. Two groups received GH at a dose of 0.36 mg/kg/week. One group received estrogen (25-50 ng/kg/day) and the other placebo. The fifth group received placebo injections and placebo estrogen.

After 18 months, however, the placebo group was switched into the high GH-high estrogen group. This was due to the poor responsiveness of this group when compared to the other five groups.

At baseline there were no statistical differences between all evaluable parameters. The mean age at entry was between 9.43-9.90 years.

Fourteen percent (31) subjects have reached adult height. Patients that were initially in the placebo group were switched into the high GH group. Similarly all patients either on high or low GH dose are pooled into two groups. Twenty subjects that achieved final height received the high GH dose and 11 the lower GH dose. Approximately half of the patients in each group was on the low estrogen dose from age 8 years. Seven of these group of 31 subjects are considered, for this analysis, as protocol completers although they did not met all the criteria.

The mean final height for all 31 patients was 148.7±6.5 cm (148.5 cm and 149.2 cm for high and low GH groups, respectively). The SDS height at baseline was -3.0 SD and -2.3 at the end of the study. The mean age of the 31 completers at baseline was 11.14 years and 16.69 at the end of the study. Patients were 5.3±1.1 years on treatment.

At the end of the treatment protocol the sponsor estimates that 58% of treated patients had SDS approaching the normal range >-2.5 SDS.

When compared to the GH treated TS in the GDCT study, the final height achieved for GDCI girls treated with GH was 2.7 cm greater. When these results are, however, compared with the mean final height for American TS they show an increase of 4.9-5.6 cm for the low and the high GH groups, respectively. Hence, the magnitude of this difference does not differ with the observed in the previous study (GDCT), although at the onset of therapy the patients were approximately one year younger in GDCI. Final comments will be stated at the end of the review.

Study 83-002/85-023 (Genentech)

Study 85-023 is a continuation of 83-002 and patients were switched when they had completed at least 12 month of therapy. In study 83-002, four groups of girls received either GH (all subjects on GH were on a weekly dose of 0.375 mg/kg) alone (n=17), or in combination with oxandrolone, 0.125 mg/kg/day (n=17). A third group received oxandrolone alone (n=19) and the forth group was an observational group that did not receive any treatment (n=18). The mean age was 9 years old for all groups. The mean range of drug exposure was 1.4-1.6 years. Patients in the observational group were then transferred to the next study (83-023) in which the initial 17 subjects on GH alone remained on the same therapy while all other patients (49) received GH+oxandrolone. The oxandrolone dose was reduced to half due to excessive virilization. Conjugated estrogen (0.3 mg/day) was initiated at age $\geq$14 years (mean age 15 years). Six month later the estrogen dose was doubled; progesterone was added at year one.

Final heights were compared to a set of American TS historical controls. Subjects for this database were obtained from the same centers where the patients were treated with GH. Controls were measured after age 18 and estrogen therapy had to be initiated at an appropriate age. TS patients that received androgen were excluded from this HC database.

For this analysis, adult height is considered as the stature attained after age 13.5 years. The initial definition in the protocol called for a BA showing fused epiphyses and no change in height for 12 months. Ninety four percent of all enrolled subjects (63) reached the target age of 13.5 years. The baseline age for these groups was between 9.2$\pm$2.1 and 9.9$\pm$2.3 years. No statistical differences were observed in any variable at baseline. Treatment duration ranged between 3.8-7.6 years.

The final heights were 150.4 cm and 151.5 cm for the GH and combination group, respectively. The HC final height was 144.2 cm. The Δ for both groups was 6.2 cm and 7.3 cm, respectively. When compared to the historical controls (using as covariates age and height at baseline, as well as mid-parental height and karyotype) the GH group had a 7.4 cm increase ($p<0.0001$) in final height. In the combination group the increase was 10.1 cm ($p<0.001$).

Between 63-65% in both groups reached final heights above -2.5 SD for normal females. Historically, only 18% of TS patients reached these heights.

The combination GH+oxandrolone attained a mean final height of 2.7 cm more than the GH treated group ($p<0.037$).

All treated group show increments in final heights when compared with HC. The difference between the HC and the treated girls was $\geq$ 5.7 cm.

Study 85-044 (Genentech)

This study started as a controlled study in which 9 subjects were used as observational controls for one year while 36 received GH 0.375 mg/kg/week. Seventy two additional patients were enrolled on daily GH with the same cumulative dose. The control group was switched into the daily GH group after one year of therapy. The treatment's duration range was between 5.6-6.1 years.

All subjects continuing in the study received estrogen depending on their baseline age. Subjects younger than 11 were randomized to receive estrogen either at age 12 or 15. Subjects older than 11 received estrogen one year after GH was started. Doses of estrogen were similar to those used in the previous study.

One hundred and nine patients (94%) were evaluated for adult height. Some adjustments were made for patients entering spontaneous puberty and for several minor protocol violations. Final height of historical controls for all treatment modalities was 144.1 cm.

For the younger group (n=26) receiving early estrogen the final height was 147±6.1 cm and for the late estrogen (29) 150.4±6.0 cm. Using similar statistical analysis as in the previous study the Δ was 5.9 and 8.3 cm respectively ($p<0.0001$), when compared to historical controls. In patients that started GH late and received estrogen one year after therapy initiation the final height was 148.5±5.5 cm with a Δ of 4.7 cm.

In excess of 50% of subjects at age 13.5 years treated for more than one year had stature >2.5 SDS for the normal American female population.

These data suggest that late estrogen therapy may be beneficial for attaining increments in height for these subjects (>2.4 cm).

The results of this study suggest that GH induces growth acceleration and when compared to HC results in increments in final heights. However, the lack of concomitant controls makes the interpretation of this data very difficult.

SAFETY

GDCT and GDCI

Lilly reported the death of one subject (control group) in the studies and two from spontaneous reports. All these fatal events were related to underlying vascular malformations. The patient in the control group that died as a result of a rupture of an aortic coarctation previously had thrombocytopenic purpura.

Two episodes of cardiac surgery in GH treated girls were considered serious, unexpected and possibly related to the medication. Two episodes of hypertension were also reported. In addition, for the following events there were reported in no more than one patient receiving GH: osteotomy for bunionectomy, hypochromic microcytic anemia, dyspnea, psoriasis, gastroenteritis with SGOT increase, and scoliosis.

Two percent of the study participants discontinued due to an adverse event. GH treated patients discontinued due to SGOT increases, intracranial hypertension (shunt was present but malfunctioned), migraine, and gastrointestinal disorder. In the placebo group one episode of vascular disorder (and death) and one of bone disorder (already switched to GH) lead to discontinuation.

Between groups, patients receiving GH were more prone to require surgery (45% vs 27%), have otitis media (43% vs 26%), ear disorders (17% vs 5%), and accidental overdoses (10% vs 0%). All these were statistically significant ($p \leq 0.05$).Other expected disorders such as scoliosis, edema, hypothyroidism, increased nevi, hyperglycemia and lymphedema did not differ between groups. Most of them were however reported in excess of 5%, except for hyperglycemia which was reported in only one subject.

No dose dependent side effects were apparent in these studies.

During the placebo controlled phase of GDCI, otitis media, ear disorders, increased cough and GI complains were more common in the GH treated subjects. Conversely, rash and local reaction due to placebo injections were more common in the control group. Hypothyroidism was present in both groups in excess of 5%.

LABORATORY

Increased serum alkaline phosphatase and creatinine kinase levels were more common in GH treated subjects. The proportion of cholesterol levels increase was greater in the control group. No differences between baseline and most recent visit were seen between controls or GH treated patients.

There was no evidence of increased rates of hypothyroidism between GH treated and controls or between different GH doses.

In the GDCT study abnormal glucose tolerance tests (one value above designated cut off limits) totaled 4.1% in the GH treated and 4.1% in the controls. Postprandial insulin was elevated (>400 pMol/L) in the GH treated group (17.6% vs 6.3%). No subjects had an elevation of HbA1c above 6.8%.

In the GDCI study a similar trend was observed. Although one third of the patients had intermittent elevations of insulin, neither study showed a significant alteration in glucose metabolism.

Genentech Studies

No deaths were reported in these studies. Between the two studies, six patients discontinued due to adverse events for the following reasons; elbow pain (n=1), foot cellulitis and knee pain (n=1), abnormal glucose tolerance test (n=1, off therapy six month later resolved), and "acromegaloid changes (n=1, later dismissed by her physician when additional data was examined), cerebrovascular accident (1, also on ERT+P), and allergy to the excipient (1).

One patient developed hypoplastic anemia (she was on several other medications). Five patients developed joint pain, and two Bell's palsy.

The remaining of the safety profile of this NDA mimics the data previously depicted. Virilization, however, occurred in patients receiving oxandrolone.

SUMMARY

The data reviewed above indicate that:

1) When using concomitant controls the height increase is 3.9 cm with mean final heights of 146 cm. Corrections for several cofactors show an increase of 5.4 cm. This represents and increment of 3.8% over controls after 4.7 years of treatment. Approximately 50% of this increment was seen in the first year.

2) All other studies lack concomitant controls and all show final heights of at least 1 cm larger than the final height of the controlled study. The range in benefit is from 5.0 cm for the late GH (85-044) to 10.1 cm for the early GH+OX+late estrogen. In all four studies, final heights were provided for 246 TS girls.

3) The percentage increase in final height for all studies after an nearly mean drug exposure of 6 years ranges between 3.48-7.1%. Approximately 50% of this gain was observed in the first year of GH administration.

4) Data from the studies using historical controls suggest that younger patients tend to have better outcomes than older patients. Additionally it appears that late introduction of estrogen therapy may result in further benefit.

5) Many of the data presented as final heights may underestimate real final heights because most of the subjects did not have epiphyseal closure.

6) Historical controls were above 18 years. If estrogen therapy was not properly administered to these patients, they may have grown more. Thus, some of the historical controls final heights may have been underestimated because cessation of growth did not occur. This would overestimate the described benefits induced by GH.

7) Overall the total population that reached (near) adult height is 251 patients. Different modalities for drug administration were used as well as three different dose of GH. In addition, estrogen and androgen therapy were given at different dose and regimens and initiated at different ages. Lack of concomitant controls increases the difficulty to properly assess different variables and drug effects.

8) The small patient population and the lack of concomitant controls significantly limits the assessment of this treatment's safety profile in girls with TS. Some of the currently known side effects associated with GH therapy such as intracranial hypertension, and pancreatitis that seem to occur early on during treatment were unrecognized until recently. However, this data set provides the best available information on GH safety in TS.

9) TS patients are prone to develop thyroid disease. The role of GH in inducing immune disorders, if any, is difficult to evaluate given the small size of the controlled study and the lack of concomitant controls in the others. Similarly scoliosis and cardiovascular diseases are more common in these subjects. It is unclear whether GH may affect these disorders and the limited size of these studies does not provide sufficient information to properly assess these issues.

10) Patients receiving GH showed an significant increase in otic infections, and ear disorders. The reasons for these findings remain unknown.

11) The adverse events described suggest that patients with TS receiving GH are prone to develop insulin resistance, although they do not appear to impair glucose metabolism. The insulin resistance, however, appears to decrease with time. The

potential long term effects of GH hyperinsulinism in TS girls known to be predisposed to develop diabetes is unknown.

FINAL DISCUSSION

Ample information is available in the literature that indicates that the use of historical controls (HC) is problematic for establishing long term treatment effects. HC provide an adequate instrument to observe trends, but clear shortcomings emerge to assess both safety and efficacy. The interpretation of HC data has typically overestimated treatment effects demonstrated with the use of concomitant controls.

In evaluating treatments of girls with Turner's syndrome (TS) confounding factors are prominent when an HC approach is used. The issue of secular trends is one of the most important. Although the sponsors have provided information that indicates that changes in final height have not changed in the US in the last 30 years, it is apparent that our knowledge and ability to recognize TS has dramatically improved during this period. Hence, general practitioners, neonatologists, pediatricians and other health care professionals are able to identify girls with TS in early stages. As a result, close follow-up and recognition of complications that tended to remain undiscovered have helped in the management of girls with TS and presumably improved outcomes. This has resulted in early assessment of complications that are nowadays commonly identified. Among other chronic conditions such as otitis media and urinary infections, that if unrecognized or improperly treated could affect grow, are currently aggressively explored. In addition, the development of sensitive TSH assays in the last ten years has resulted in more aggressive identification of thyroid disorders also responsible for hypothyroidism, another condition that leads to failure to thrive. Similarly, awareness of other autoimmune disorders has increased in the last decade. Some of these conditions although rare such as diabetes and Crohn's disease can also negatively affect linear growth. Cardiac and vascular abnormalities are also forcefully investigated and treated. Some of those (i.e., bicuspid aorta) were not known during the time when HC data were accumulated.

Parts of the improvements seen in any study are the result of being enrolled, followed regularly by a group of dedicated health care professionals, evaluated with tests that

closely monitor dysfunctions of many organ systems that may by themselves negatively impact on final stature, as well as the family commitment to improve the subject underlying condition. All these factors are excluded when comparison are made with HC. HC observations of TS girls usually selected accordingly to age of diagnosis, BA, or a few other hard variables to be explored.

The HC data presented in this NDA do not include a means of establishing who was selected to be included and who was not. Independently of a deliberate effort to include or exclude certain patients, it becomes apparent that initially only the more severe cases are those that are easily diagnosed and these would lead to tilt the data into lower final heights. In the recent past height has become more of a concern to patients, parents, and physicians than before recombinant GH became available. Patient that may have not been presented for evaluation in the past are doing so now. TS patients that were not evaluated because their height was not of concern are not part of the HC database. Adult TS subjects that presented for primary amenorrhea are probably not included in this database. This small subgroup may have not been concerned by height or height was normal. In addition, the type of medical care provided then probably differed from that given to the actively treated, as well as the assessment and monitoring of medications, complications and compliance related or not to those drugs.

Controlled clinical studies are designed to assess efficacy. Most of the time adverse events are unpredictable and depending on the size of the study we may identify or not drug induced complications. In addition, although close supervision is provided during controlled clinical trials, under-reporting of complications during treatment is well recognized. The assessments of safety on the basis of patient/parent reporting of adverse reactions is all the more problematic with an HC approach. During the time of observation used to generate the HC database health care providers could have failed to detect various conditions due to lack of equipment, tests, and knowledge that are now available.

It is therefore questionable whether the final heights obtained from concomitantly uncontrolled studies are sufficient to serve as a basis for approval and to labeling to

reflect both the efficacy of a drug and its safety. It is clear that the lack of concurrent comparison group impinges on our ability to assess safety, however all the data presented suggest that there is no significant increase in undesirable side effects related to GH administration. In addition, improvements on final height are difficult to attribute solely to the treatment or treatments offered. Even though the trend appears to be positive, the magnitude of the treatment effect cannot precisely be determined.

The twenty seven T girls treated with GH that reached adult high in the GDCT achieved a mean final height of 146 cm while the concomitant controls reached mean final heights of 142.1 cm (Δ 3.9 cm). The improvement when compared to the most recent American T heights indicates a gain of 2.4 cm. When the final heights are corrected by several variables the increment in final height of the GH treated when compared to the control group is 5.4 cm. Results in all uncontrolled studies using similar statistical approach suggest that GH treatment may result in increments in final heights of at least 5 cm. Some groups reached mean final heights 7.4, 8.3, and up to 10.1 cm above HC. Although most patients were treated in excess of 4 years, Approximately 50% of the gain was seen in the first year of treatment. Safety information collected in these studies suggest that girls with TS on GH are prone to develop ear infections at a greater rate than controls. No clear explanation for this finding is available. No other significant adverse reactions associated with therapy GH have been described. Although the time of drug exposure is sizeable, the number of subjects treated in a controlled manner is small to adequately assess other drug induced adverse reactions. Thus, the risk to benefit of GH treatment in TS girls cannot be adequately addressed.

NDA 19-640 (S18)
Lilly STUDIES

INDEX

GDCT

This report represents an interim analysis of an ongoing open-label, parallel, randomized study in patients with Turner syndrome. The study is being conducted in Canada, and all investigators are experienced pediatric endocrinologists. At the admission visit, patients were evaluated as to meeting the entry criteria for the study. Eligible patients were stratified according to chronological age and entry height prior to being randomly assigned into one of two groups: 1) Humatrope-treated (also referred to as Humatrope group, or hGH05), 2) Untreated (non-hGH treatment control). Humatrope (0.05 mg/kg/dose) is administered subcutaneously six times per week on Monday, Tuesday, Wednesday, Thursday, Friday, and Saturday. Estrogen (ethinyl estradiol) replacement therapy is given to patients in both groups who are over 13 years of age and who have been at least 12 months in the study. After one year of treatment with ethinyl estradiol, Provera (medroxyprogesterone acetate) is given on a daily basis on Days 15 through 24 of each calendar month to patients 15 years of chronological age or older. The dosages of ethinyl estradiol and medroxyprogesterone acetate are based on chronological age.

The intent of this study is to treat the patients to final height. Efficacy of hGH treatment is determined by a comparison of final heights between the Humatrope-treated and non-hGH-treated (Untreated) control. Although the protocol defines final height in terms of an annualized growth rate of less than 2.0 cm/year, based on at least six months of growth data, and a bone age $\geq$14 years, for purposes of this interim analysis, patients who had achieved near-final height as determined by individual investigators also have been analyzed.

In addition, secondary variables of efficacy with respect to effect of hGH treatment on height are also evaluated based on comparisons between the study population and historical data. Standard deviation scores (SDS) for height were calculated based on the growth curve for both normal females (National Center for Health Statistics [NCHS] Growth Charts, 1976), and females with Turner syndrome according to the Turner reference standard (Lyon et al. 1985), and a comparison of the two groups is made based on height SDS at last visit. In addition, a comparison is made of the mean height (cm) attained at last visit by the Humatrope treatment group versus the Untreated group, adjusted for bone age.

The risks and benefits associated with either Humatrope therapy or non-treatment of patients with Turner syndrome are determined from safety summaries of deaths, serious adverse events, treatment-emergent signs and symptoms, and laboratory results.

Objectives

Primary Objective
The primary objective of this study is to determine the efficacy of Humatrope in promoting an increase in final height in patients with Turner syndrome.

Secondary Objective
The secondary objective of this study is to determine the antigenicity and other variables of clinical safety of Humatrope in these patients.

Investigational Plan

Summary of Study Design
In this randomized, parallel, open-label study in patients with Turner syndrome, eligible patients were randomly assigned to one of two treatment groups: Humatrope (0.05 mg/kg/dose) or a non-hGH treatment (Untreated) control.

Discussion of Design and Control
Randomization was chosen to ensure that there would be no bias in the assignment of patients to treatment and control groups.

Investigator Information
This multicenter study involves 14 sites, 13 of which enrolled patients. Thirty-five experienced pediatric endocrinologists are participating as primary or secondary investigators.

Study Population

Entry Criteria

Inclusion Criteria
The inclusion criteria as specified by the protocol were as follows:

- Patients were females with Turner syndrome, and were treated as outpatients.
- Patients who had presence of Y component in their chromosome analysis provided dysgenetic gonadal tissue (or gonad) had been previously removed.
- Patients had chronological age $\geq$7 years.
- Patients were prepubertal, Tanner Stage I-B (breast).

- Patients had growth velocity less than 6 cm/year and height of less than or equal to the tenth percentile as compared to chronologically age-matched normal female controls.
- Patients had at least a six-month (preferably 12 months) accurate growth measurement available for calculation of prestudy growth velocity. Pretreatment growth measurements were obtained during a time when the patient was not receiving a potential growth-promoting agent (e.g., hGH, androgen, estrogen).
- Patients judged to be thyroxine deficient must have had replacement therapy resulting in normal thyroid function test results over the six-month period prior to enrollment.
- Parents or legal guardians of patients signed an informed consent document. Assent was obtained from all patients competent to understand the protocol. Local Institutional Review Board (IRB) requirements applied (see Federal Register, 8 March 1983, Vol. 48, No. 46, pp. 9818-9820). Applicable National Growth Hormone Advisory Committee guidelines were followed.

Exclusion Criteria

The exclusion criteria were as follows:

- Patients who had received any form of human growth hormone.
- Patients who had been exposed to long term (>2 months) exogenous estrogens while in utero. Also, patients who had been treated with estrogens or adrenal androgens within the preceding 6 months or who had received a cumulative course of therapy totaling greater than 12 months.
- Patients who had presence of Y component in their chromosome analysis and dysgenetic gonadal tissue (or gonad) that had not been removed.
- Patients who had chronological age $\geq$13 years.
- Patients who had clinically significant cardiac, pulmonary, gastrointestinal, hepatic, or renal disease considered sufficient to influence growth and development. Also, those who have or have had any malignancy.
- Patients who received any form of radiation to the central nervous system or >1000 rads of radiation to the spinal axis.
- Patients who had significant hematuria or proteinuria in pretherapy evaluation.
- Patients who had diabetes mellitus.
- Patients who had demonstrated growth hormone deficiency according to National Growth Hormone Advisory Committee Criteria.

- Patients who had any active chronic infection (e.g., tuberculosis).
- Patients who had untreated hypothyroidism.
- Patients who were taking amphetamines or any other drugs (e.g., methylphenidate (Ritalin), pemoline (Cylert)) believed to interfere with growth hormone secretion or actions.
- Patients who were poor medical, psychological, or psychiatric risks for whom, in the opinion of the investigator, therapy with an investigational drug was unwise.
- Patients whose parents were substance abusers, or those who came from homes in which appropriate emotional development was limited.
- Patients who could not be seen on the schedule required by the protocol.

Violation of Entry Criteria

Patients who did not meet entry criteria were not included in the study. Development of any of the exclusion criteria during the course of the study is possible grounds for the patient's early discontinuation from the study. If and when this occurs, the sponsor is notified immediately of any violation of these criteria, and a decision is made whether to continue the patient in the study.

Disease Diagnostic Criteria

All patients were females with Turner syndrome, who were diagnosed according to National Growth Hormone Advisory Committee (Canada) criteria.

Sample Size

The study design determined that in order to obtain analyzable data, 100 patients, 50 per treatment group, would be required, enrolled in multiple centers. Assuming a 20% dropout rate and a Type I error rate of 0.05, this number of patients assured at least an 80% chance of detecting a 2.0 cm/year. difference in growth rate between the treatment groups at the end of one year of treatment. At closure of enrollment in this study, there were in fact 154 patients, 76 in the Humatrope group and 78 in the Untreated group. Of these, there are baseline data available for 140 patients, 75 in the Humatrope group and 65 in the Untreated group.

Patient Assignment

The investigator contacted a representative of the National Growth Hormone Advisory Committee (Canada) for a review of the Entry Criteria prior to Visit 1. If the patient met all entry criteria, the National Growth Hormone Advisory Committee representative contacted Eli Lilly and Company, at which time eligible patients were assigned an identification code number. Patients were identified as belonging to one of three stature strata (Lower, Middle, and Upper) according to their chronological age and height at a

prestudy visit. These stature strata represent groups of patients with similar height for their age, based on historical data for Turner syndrome compiled by Lyon et al. and were designed so that each stratum could be expected to contain approximately one-third of enrolled patients. In order to exclude patients whose height fell within the reference range for normal females, the upper limit of the Upper stratum was set at the smoothed 10th percentile of stature for normal females according to the National Center for Health Statistics (NCHS Growth Charts, 1976). Each patient was randomized, within stratum, to one of the two treatment groups (treated with Humatrope or Untreated). This method of randomization both ensured homogeneity between treatment groups and allowed for adjustment for stature stratum in the assessment of efficacy.

Dosage and Administration

Materials and Supplies

Injectable Study Drug Materials

Humatrope (somatropin) is provided lyophilized in vials, each containing 5.0 mg of the compound. Diluent is also provided.

Oral Study Drug Materials

Ethinyl estradiol (5.0 μg tablets or 20 μg tablets; Estinyl®, Schering) and medroxyprogesterone acetate (10 mg tablets; Provera®, Upjohn) were prescribed by the investigator or patient's physician with supplies being obtained locally.

Dosage Selection and Administration Procedures

Patients were randomly assigned to one of two treatment groups:

1) Humatrope-treated (also referred to as Humatrope group or hGH05): Humatrope 0.05 mg/kg/dose with subsequent addition of ethinyl estradiol and medroxyprogesterone acetate,

2) Untreated (non-hGH treatment control): No Humatrope therapy, with subsequent ethinyl estradiol and medroxyprogesterone acetate.

Here and throughout the report, the Untreated group refers to the group not receiving Humatrope, although as described in detail below, these patients may have received ethinyl estradiol and medroxyprogesterone acetate. Humatrope is injected at the prescribed dose subcutaneously six times per week on Monday, Tuesday, Wednesday, Thursday, Friday, and Saturday for at least 18 months. A patient's weekly dosage does not exceed 15 mg of study drug. The contents of a reconstituted vial are not used if more than 14 days has elapsed since its dilution. Between administrations, the vials (diluted or undiluted) are stored at 2°C to 8°C and protected from light. Subsequently, this study was extended for blocks of additional 12-month periods following the initial 18 months.

With respect to the estradiol and progesterone treatment in this study:

- No oral study drug material (estradiol or medroxyprogesterone) is administered to patients less than 13 years old.
- Patients who have received a minimum of 12 months treatment with Humatrope and are at least 13 years old receive 2.5 μg of ethinyl estradiol daily (half of a 5 μg tablet), in addition to Humatrope therapy.
- Patients at least 14 years old but not yet 15 years old receive 5.0 μg of ethinyl estradiol daily, in addition to Humatrope therapy.
- After one year of treatment with a 5 μg dose of ethinyl estradiol, the dose is increased to 20 μg of ethinyl estradiol per day from the first day of the month for 24 days. For the last 10 days of ethinyl estradiol therapy, (Days 15-24), 10 mg of medroxyprogesterone is given orally. On Day 24 both the ethinyl estradiol and medroxyprogesterone are stopped. On the first day of the following month, ethinyl estradiol is restarted and the cycle repeated as above.

In the original protocol GDCT(c), patients ≥15 years of age received 10 mg medroxypropesterone acetate for the first 5 days of each calendar month. The estradiol dosage regimen was as described above, however, the estradiol was continued throughout the month. The protocol amendment GDCT altered the regimen such that patients ≥15 years of age receive 10 mg of medroxyprogesterone on Days 15-24 of the month. In addition, the estradiol regimen was changed so that estradiol was suspended on Day 24 of the calendar month and restarted on Day 1 of the following month.

Blinding

Not applicable.

Concomitant Therapy

Concomitant therapy with levothyroxine is required for hypothyroid patients. Patients may take prescribed medications (according to the inclusion and exclusion criteria) which they must provide.

Efficacy and Safety Evaluation

The schedule of safety and efficacy measurements is presented in Table 1, the Master Schedule of Procedures. Patients are assessed at three-month intervals for at least 18 months and for three-month intervals thereafter until final height is reached.

Table 1 **Master Schedule of Procedures**

PROCEDURE	Visit Number / Study Month	1 / 0	2 / 3	3 / 6	4 / 9	5 / 12	6 / 15	7 / 18	8 / 21	≥9 / every 3 months
Medical History		X								
Interim History			X	X	X	X	X	X	X	X
Physical Examination:		X	X	X	X	X	X	X	X	X
Height		X	X	X	X	X	X	X	X	X
Weight		X	X	X	X	X	X	X	X	X
Draw blood for[1]:										
Blood Chemistry (incl. glucose)		X	X	X	X	X		X		X[1]
Hematologic Tests		X	X	X	X	X		X		X[1]
Thyroid Function		X	X	X	X	X		X		X[1]
Hemoglobin A_{1C}		X		X		X		X		X[1]
2 Hr. Post Prandial Glucose with Insulin[2]			X	X	X	X		X		X[1]
Growth Hormone Antibody		X	X	X	X	X		X		X[1]
E. Coli Polypeptide Antibody		X	X	X	X	X		X		X[1]
Urinalysis		X	X	X	X	X		X		X[1]
X-ray for Bone Age[3]		X				X				X
Summary[4]										

[1] Obtained at 6-month intervals after first 12 months.
[2] Obtained when clinically indicated on the basis of fasting blood glucose and hemoglobin A_{1C}.
[3] Obtained at 12-month intervals.
[4] Completed at the time study drug is discontinued.

Efficacy Measures

Height measurements (without shoes) are made with a stadiometer, at the same time of day for each visit throughout the study. Each recorded measurement is the average of three separate measurements made by qualified, experienced members of the clinical staff.

Efficacy Criteria

Definitions

Standard Deviation Score - Standard Deviation Score (SDS) for a given variable is derived by subtracting the age-matched population mean value for that variable from the patient's value. The value obtained is then divided by the age-matched population standard deviation.

Height SDS [NCHS]: Height SDS [NCHS] is a standard deviation score using as a reference standard the height of normal females at various chronological ages (NCHS Growth Charts, 1976).

Height SDS [Lyon]: Height SDS [Lyon] is a standard deviation score using as a reference standard the height of females with Turner syndrome at various chronological ages (Lyon et al. 1985).

Final Height - Final height generally refers to the height attained at completion of linear growth. In this study the criteria used to define achievement of final height were bone age $\geq$14 years and growth velocity <2.0 cm/year. For the purposes of this interim analysis, patients whose bone age and growth velocity approached these criteria and were considered by individual investigators to have attained a height approximating final height, were analyzed. Thus in this study, the term final height, as it appears in tables and statistical analyses refers to patients who met final height criteria and, in addition, those who came close to this in the opinion of the investigator. Final height therefore refers more accurately to near final height.

Midparental Height: A gender adjusted average height of parents [(father's height minus 13 cm) plus mother's height]/2 (Tanner et al. 1975).

Growth Velocity - The rate of growth in cm/year as calculated from the difference between two height measurements divided by the time elapsed between those measurements. For this analysis, annualized growth velocities were calculated on the basis of the difference in height between the measurements obtained at each annual visit, and at the visit preceding this (approximately three to six months, depending upon time in study).

Growth Velocity SDS [Ranke] - Growth Velocity SDS [Ranke] is a standard deviation score using as a reference standard growth velocity data for Turner syndrome at various chronological ages (Ranke et al. 1988).

Bone Age - Bone Age represents an estimate of skeletal maturation determined by comparison of a radiograph of the patient's left hand with known standards for skeletal maturation [in this study, the Atlas of Skeletal Maturation by Greulich & Pyle (Greulich and Pyle, 1959)].

Stature Strata - Patients were identified as belonging to one of three Stature Strata (Lower, Middle, and Upper) according to their chronological age and height at a prestudy visit. These stature strata represent groups of patients with similar height for their age, based on historical data for Turner syndrome compiled by Lyon et al. and were designed so that each stratum could be expected to contain approximately one-third of enrolled patients.

Efficacy Variables

The original protocol defined short-term efficacy in terms of growth rate in centimeters per year (cm/year) calculated from the change in height between visits, divided by the actual time between measurements during treatment versus pretreatment growth rate. Long-term efficacy was to be determined by comparison of final height between the two treatment groups.

Pretreatment growth rate was defined as the rate of growth between a height measurement taken approximately 12 months prior to Visit 1 and the height measurement taken at Visit 1. If an untreated pretreatment height measurement was not available 12 months prior to Visit 1, then a measurement taken as remote to Visit 1 as possible (≥6 months) was used in this computation. The growth rate was extrapolated to cm/year, realizing that the shorter intervals between measurement points result in less reliable calculation of growth rate.

Because the intent of this study is to treat until achievement of final height, for purposes of this interim analysis, three main efficacy variables were evaluated.

- Primary Variable

  Final (or near final) Height: the actual height measurement at the last available visit for those patients identified by the investigator as protocol completers. The criteria defined by the protocol were a growth rate of less than 2 cm/year and a bone age of ≥14 years. In addition to those who fulfilled these criteria, patients who, in the estimation of individual investigators came close to meeting these criteria, were also evaluated.

- Secondary Variables

  Height (cm) at Last Visit Adjusted for Bone Age: Height at last visit at which one age X-ray was performed for all patients in the intent-to-treat population, adjusted for bone age. This visit differed from the actual Last Visit for some patients, since not all patients had a bone age X-ray performed at the Last Visit.

  Height SDS at Last Visit: height expressed in terms of height standard deviation scores using as a reference standard the NCHS normal female standard. Height SDS at Last Visit for all patients in the intent-to-treat (ITT) population is the variable on which a statistical comparison between the treatment groups is made.

- Other Variables

  Other variables for protocol completers are Final Height adjusted for midparental height, Height SDS [NCHS], Height SDS [Lyon], and Height SDS [NCHS] adjusted for midparental height.

  Other variables analyzed for the ITT population at Last Visit by years in study include Height SDS [NCHS]; Height SDS [NCHS] Change from Baseline; Height SDS [Lyon]; Growth Velocity SDS [Ranke]; Bone Age; Bone Age Change from Baseline; and Bone Age/Chronological Age Ratio. A statistical comparison between treatment groups at Last Visit is made for each of the above variables.

Safety Measures

All adverse events experienced by patients during the course of this study were reported on clinical report forms at each visit. Each event was followed throughout the study or

until it resolved. Alarming or significant adverse events were reported directly by telephone to the sponsor.

A physical examination including musculoskeletal exam was performed at each visit (i.e., every three months). A listing of laboratory assessments is presented in Table 2.

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Table 2 Clinical Safety Laboratory Tests[1]

BLOOD CHEMISTRY PANEL	URINALYSIS
Total Bilirubin	Appearance
Alkaline Phosphatase	Specific Gravity
GGT	pH
SGOT (AST)	Protein (Qualitative)
SGPT (ALT)	Glucose (Qualitative)
Urea Nitrogen	Ketones (Qualitative)
Creatinine	Bilirubin
Uric Acid	Urobilinogen
Inorganic Phosphate	Blood
Calcium	Nitrite
Total Protein	Leukocyte Esterase
Albumin	Microscopic:
Cholesterol	WBC per hpf
Creatine Kinase	RBC per hpf
	Casts per lpf
ELECTROLYTE PANEL	THYROID PANEL
Sodium	T4 by Radioimmunoassay
Potassium	T3 % Uptake
Bicarbonate	Free Thyroxine Index (FTI)
Chloride	TSH by Radioimmunoassay
HEMATOLOGY PANEL	ANTIBODY ASSAYS
Hemoglobin	Growth Hormone Antibody
Hematocrit	ECP Antibody
Erythrocyte Count (RBC)	
MCV	
MCH	GLUCOSE TOLERANCE PANEL
MCHC	Hemoglobin A_{1C}
White Blood Cell Count (WBC)	Glucose (Fasting and 2-hr postprandial)[2]
Segmented Neutrophils	Insulin (Fasting and 2-hr postprandial)[2]
Lymphocytes	
Monocytes	
Eosinophils	
Basophils	
Platelet Count	
Reticulocyte Count	

Abbreviations: GGT = gamma glutamyl transpeptidase; SGOT (AST) = serum glutamic oxaloacetic transaminase (aspartate aminotransferase); SGPT (ALT) = serum glutamic pyruvic transaminase (alanine aminotransferase); TSH = thyroid stimulating hormone; ECP = *Escherichia coli* polypeptide; MCV = mean corpuscular volume; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; hpf = high power field; lpf = low power field.

1 Obtained when clinically indicated on the basis of fasting blood glucose HbA_{1C}.

Routine laboratory analyses of blood and urine were performed at each visit during the first year of the study and then every six months thereafter. Serum samples were assayed for growth hormone antibodies and ECP (*Escherichia coli* polypeptide) antibodies. The assay for ECP was discontinued following data that demonstrated negligible occurrences of ECP antibody in these patients. Signs of clinically significant antibody response (e.g., hematuria, skin rash, elevation of liver function tests, etc.) were carefully sought and immediately reported. The laboratory analyses of blood and urine, along with the growth hormone and ECP antibody assays, were performed every six months (from Visit 5 onwards), if therapy was continued until achievement of final height. At Visit 1 and at each six-month visit during the study hemoglobin A_{1C} was determined. A two-hour postprandial blood sample was drawn to measure glucose and insulin levels when clinically indicated on the basis of fasting blood glucose level >6.4 mmol/L or HbA_{1C} >0.068.

Appropriateness and Consistency of Measurements

Laboratory safety assessments used in this study are standard (routine blood and urine analyses). The growth hormone antibody and ECP antibody assays are included to assess patients' immune response to injected study material.

Height was to be measured with a stadiometer at the same time of day for each visit throughout the study. Each recorded height is the average of three separate measurements made by qualified, experienced members of the clinical staff.

Patient Disposition Criteria

Terminations

Study medication could be discontinued for any of the following reasons:

- Request of the patient, parent, or guardian to stop the study drug.
- Decision of the investigator to stop the study drug.
- Decision of the sponsor to stop the study or a patient's participation in the study.
- Achievement of final height, as defined by an annualized growth rate of less than 2.0 cm/year, based on at least six months of growth data, and a bone age ≥14 years.
- Occurrence of a serious adverse event that warranted discontinuing study medication.

In the event that the study drug was discontinued for any reason, the patient was scheduled for a final visit, if at all possible. At this visit, the unused study drug was retrieved. The number of days the drug was taken was recorded on the clinical report form, along with any adverse experiences, and the Summary clinical report form was also completed. Even if the patient was unable to schedule this visit, the current clinical

report form and the Summary clinical report form were to be completed and all unused study drug was to be retrieved.

Qualifications for Analysis

The intent-to-treat (ITT) population is defined as those patients who were randomized and had height data at Visit 3 (180 days) or beyond. Analysis of efficacy is performed on data from the intent-to-treat population. The safety population is defined as those patients who were randomized, and either received any study medication or had post-baseline safety data.

Study Extensions

The intent of this study is to treat the patients to final height. Following an initial treatment period of 18 months, extension of therapy was made in blocks of 12 months duration, at the sole discretion of the sponsor.

Compliance

Compliance was assessed by evaluation of drug record cards. These cards were completed at home by the patients or parents and were periodically reviewed by the investigator. The number of injections taken was reported at each follow-up visit on the clinical report forms.

Quality Assurance

Each investigator and on-site study coordinator was initially familiarized with the study procedure through a study start-up meeting. The sponsor also furnished each with a study instructional manual and a booklet summarizing information, principles and United States regulatory requirements that Eli Lilly and Company believes to be helpful to investigators conducting the study *(Principles and Regulations of Clinical Investigation)*. Health Protection Branch (HPB) guidelines were also consulted.

Each study site has been visited by the Lilly Clinical Research Coordinator (CRC) periodically before and during the study to review the status of the study. After patients were enrolled, each investigator was visited by Lilly personnel to review the completed clinical report forms.

Protocol Amendments

The amended version is B9R-CA-GDCT(d) effective 7 December 1992. This amendment allowed the following changes:

1. For patients who had received ethinyl estradiol at a dose of 5 μg/day for one year the dose of ethinyl estradiol was increased to 20 μg/day given on the first 24 days of each month. In addition, on Days 15-24, medroxyprogesterone acetate, 10 mg/day, was added to the treatment regimen. Both drugs were stopped on Day 24 with ethinyl estradiol treatment resuming on the first day of the following month followed by treatment cycle as described above.
2. The frequency of laboratory assessments was changed from three to six months after the patient had been in study for one year.
3. Final height was defined as an annualized growth rate of <2.0 cm/year based on at least six months growth data and a bone age of ≥14 years. These criteria were used to define protocol completion.

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Data Analysis Methods

This report represents an interim analysis of an ongoing, randomized, open-label study. Data analyzed in this report include all clinical report forms received by the Lilly data management center as of 8 February 1996. The SAS® software (version 6.09) (SAS Institute Inc., 1990) was used to perform all analyses. Except where otherwise noted, a p-value of 0.050 was considered statistically significant.

The 13 investigative sites were pooled into three geographical regions as follows:

104, 111, 113, 116British Columbia, Alberta, Manitoba

106, 107, 110, 114Ontario

102, 105, 108, 112, 115Quebec, Nova Scotia

This pooling was performed due to sample size concerns for the primary efficacy variable. Geographically pooled sites were consistently used in all efficacy and safety analyses which adjusted for site.

The safety population is defined as those patients who were randomized, and either received any study medication or had post-baseline safety data. The ITT population is defined as those patients who were randomized and had height data at Visit 3 (180 days) or beyond. Protocol completers were identified by the investigator as those patients who achieved Final Height.

Patient Disposition

Patient accountability and primary reasons for discontinuation were summarized for all patients and by treatment groups. Reasons for discontinuation were summarized for the safety population only.

Patient Characteristics

Patient demographic and baseline characteristics measured at entry were summarized for both the ITT population and patients who completed the protocol. The summaries include descriptive statistics (sample size, mean, standard deviation, median, minimum, and maximum) for the continuous variables, and frequencies and percentages for the categorical variables. Baseline comparability assessments between the treatment groups were performed only for the ITT population and not considered for the protocol completers due to small sample sizes in each treatment group. The baseline comparability for continuous variables was performed using a two-way analysis of variance (ANOVA) (Neter et al. 1990) with effects for treatment and geographically pooled investigative site.

For the categorical variables, baseline comparability was assessed using a Cochran-Mantel-Haenszel statistic (Mantel and Haenszel, 1959) stratifying by geographically pooled site. For origin and karyotype, the test was based on comparing the most

predominant category (Caucasian and 45,X, respectively) relative to all other categories combined.

Efficacy

Efficacy variables, were summarized at yearly visits and at last visit with descriptive statistics (sample size, mean, standard deviation, median, minimum, and maximum). Mathematical definitions of some variables used in efficacy analyses are defined below.

Chronological Age at Each Visit was defined as [visit date - birth date]/365.25.

Height SDS (standard deviation scores) were calculated compared to reference data for normal females [NCHS], and Turner syndrome females [Lyon]. The SDS was defined as:

> [patient's height - mean height for the reference data at the patient's age]/standard deviation for the reference data at the patient's age.

The NCHS reference data contain mean height and standard deviation for intervals of chronological age (generally six-month intervals). The SDS for each patient was calculated using data from the applicable age interval. The Lyon reference data contain mean height and smoothed standard deviation for each year of chronological age. The SDS for each patient was calculated for her exact chronological age using interpolation. The last available age for the Lyon data was 20 years, so Height SDS [Lyon] was undefined for patients in this study who were older than 20 years.

Growth Velocity SDS (standard deviation scores) were calculated compared to reference data for Turner syndrome females [Ranke]. The SDS was defined as:

> [patient's growth velocity - mean growth velocity for the reference data at the patient's age]/ standard deviation for the reference data at the patient's age.

The Ranke reference data contain mean growth velocity and standard deviation for each year of chronological age. The SDS for each patient was calculated for her exact chronological age using interpolation. The last available age for the Ranke data was 18 years, and the Ranke data had no standard deviation for ages 2, 3, 17, and 18. Growth Velocity SDS [Ranke] was therefore undefined for patients in this study who were older than 16 years.

Treatment Comparisons

Treatment groups were compared statistically for primary and secondary efficacy variables, and at last visit only for other efficacy variables. Since this was an interim analysis, the significance level was set at p=0.005 to maintain the type 1 error rate for the final analysis at p=0.048 (O'Brien and Fleming, 1979). All tests for primary and secondary efficacy variables were evaluated using the p=0.005 significance level. Statistical tests of other efficacy variables were provided for descriptive purposes only.

Between-group comparisons for all efficacy variables (except Height at Last Visit Adjusted for Bone Age) were performed using an ANOVA model incorporating the effects for treatment, geographically pooled investigative site, and baseline stature strata.

Some analyses of other efficacy variables (Final Height and Final Height SDS [NCHS] for protocol completers) called for adjustment for midparental height with analysis of covariance (ANCOVA) (Neter et al. 1990). In addition, a near-significant difference in midparental height was observed between the treatment groups; so, to confirm results, treatment group comparisons for all primary and secondary efficacy variables were performed using an ANCOVA incorporating effects for treatment, geographically pooled investigative site, stature strata, and midparental height.

Analyses for the secondary efficacy variable, Height at Last Visit Adjusted for Bone Age, were performed using an ANCOVA model which incorporated the effects for treatment, geographically pooled investigative site, stature strata, midparental height, and bone age.

Tests of Interactions

Tests of interaction between treatment and geographically pooled sites were performed for the primary and secondary efficacy variables using an ANOVA model which incorporated the effects for treatment, geographically pooled investigative site, stature strata, and the treatment-by-site interaction.

Tests of interaction between treatment and baseline stature strata were performed using an ANOVA model incorporating the effects for treatment, geographically pooled investigative site, stature strata, and the treatment-by-strata interaction.

Compliance

Compliance is presented for Humatrope-treated patients in the safety population. Patient compliance is defined as the total number of injections recorded divided by the total number of expected injections, based on the number of years the patient was in the study. In addition, total study compliance is presented as the percent of Humatrope-treated patients who were 80%-120% compliant. The summary for patient compliance includes descriptive statistics (sample size, mean, standard deviation, median, minimum, and maximum). No statistical testing was performed.

Exposure

Years in study is presented both for patients in the safety population and for patients who completed the study. Years in study is defined as the number of years from the first visit to the last visit recorded. The summary includes descriptive statistics (sample size, mean, standard deviation, median, minimum, and maximum) for years in study overall and by treatment group. No statistical testing was performed.

Treatment-Emergent Events

The frequency and percentage of treatment-emergent events were summarized overall and by treatment group. A treatment-emergent event is defined as any event which: (a) had an onset date on or after start of treatment, or (b) worsened in severity on or after the start of treatment. For events with ≥5% incidence overall, the proportion of patients with treatment-emergent events was tested for homogeneity between the two treatment groups using Fisher's exact test (Armitage and Berry, 1987).

Treatment-emergent events of special interest were identified for analysis in this report because of concern that development or worsening of some events previously associated with growth hormone therapy may also occur in this study. These events included bone disorder, edemas, hyperglycemia, hypertension, hypothyroidism, increased nevi, and lymphedema. The frequency and percentage of treatment-emergent events of special interest were summarized overall and by treatment group.

Laboratory Data

For continuous laboratory variables, descriptive statistics (sample size, mean, standard deviation, median, minimum, and maximum) are presented by treatment group for baseline, last visit, and change from baseline at last visit results. For categorical laboratory variables, frequencies and percentages of result values are presented at baseline and last visit. A two-way ANOVA with effects for treatment group and geographically pooled investigative site was performed to assess treatment group differences for fasting glucose, fasting insulin, and hemoglobin A_{1C}. For selected lab tests, the frequency and percentage of patients in each treatment group who had laboratory results that were outside the designated clinically significant cut points are presented.

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Patient Disposition

Disposition

Table 3 and Case Report Tabulation GDCT.C.2 summarize patient accountability. At closure of enrollment in this study, there were 154 patients randomized, 76 to the Humatrope group and 78 to the Untreated group. Of these, there are baseline data available for 140 patients, 75 in the Humatrope group and 65 in the Untreated group. Forty-six (33%) of the 140 randomized patients with data have completed the study having achieved Final Height according to the investigator. Twenty-five patients (18%) were discontinued from the study for a variety of reasons and 69 (49%) are currently still enrolled.

The safety population is defined as those patients who were randomized, and either received any study medication or had post-baseline safety data. The intent-to-treat population consists of patients who were randomized and have efficacy data at Visit 3 (180 days after randomization) or beyond. The safety population comprises 136 patients (97%) and the intent-to-treat population comprises 134 patients (96%). Of the four patients not included in the safety analysis, two decided not to continue shortly after being randomized and had no post-baseline data, and two violated the entry criteria. Six of the patients randomized with data were excluded from the intent-to-treat analysis; four were those excluded from the safety population, one decided to leave the study, and one violated the entry criteria.

A total of 14 of 154 patients were randomized but not included in any data analyses. Twelve patients withdrew without completing Visit 1, and two patients completed Visit 1, but their data have not been received by the sponsor. Thirteen of these 14 patients had been randomized to the Untreated group.

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Table 3 **Summary of Patient Accountability**

Patient Disposition	Overall	hGH05	Untreated
All Randomized	154	76	78
Discontinued without Data	14	1	13
Randomized with Data	140	75	65
Safety Population	136 (97.1%)	74 (98.7%)	62 (95.4%)
ITT Population	134 (95.7%)	74 (98.7%)	60 (92.3%)
Discontinued	25 (17.9%)	8 (10.7%)	17 (26.2%)
Ongoing	69 (49.3%)	40 (53.3%)	29 (44.6%)

Note: Frequencies presented as number (percent). Percentages relative to number of randomized patients with data.

The reasons for patient discontinuation for patients in the safety population are outlined in Table 4. Of the 21 patients in the safety population who discontinued the study, 13 (62%) were discontinued due to patient decision. Of these 13 patients, one patient was satisfied with therapy results; another patient in conjunction with her physician reported satisfaction with therapy results; two patients moved; six patients discontinued due to personal conflict; and three patients discontinued solely due to their personal decision. Two patients were discontinued because of protocol violations, two were lost to follow-up, and one was discontinued because the entry criteria were violated. Two patients, both of whom received Humatrope, discontinued the study due to an adverse event and one patient in the Untreated group died.

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Table 4 **Summary of Reasons Patients Discontinued - Safety Population**

Reason Discontinued	Overall	hGH05	Untreated
Total Patients Discontinued From Safety Population	21	7	14
Patient Decision	13 (61.9%)	5 (71.4%)	8 (57.1%)
Physician Decision	0	0	0
Sponsor Decision	0	0	0
Protocol Violation	2 (9.5%)	0	2 (14.3%)
Lack Of Efficacy	0	0	0
Lost To Follow-up	2 (9.5%)	0	2 (14.3%)
Adverse Event	2 (9.5%)	2 (28.6%)	0
Entry Criteria Exclusion	1 (4.8%)	0	1 (7.1%)
Death	1 (4.8%)	0	1 (7.1%)

Note: Frequencies presented as number (percent). Percentages relative to number of patients discontinued from study.

Significant Protocol Violations

For purposes of this report, protocol violations are defined as events which were considered deviations from the protocol occurring at any time during the study. In most instances, patients were allowed to continue in the study but in two instances the deviations were considered serious enough to merit discontinuation.

A protocol violator of significance is defined as:

1. A patient who discontinued due to protocol violations.
2. A patient who did not take study drug for a consecutive period of at least 180 days.
3. A patient who took concomitant drugs methylphenidate (Ritalin) or pemoline (Cylert).

Patients Who Discontinued Due to Protocol Violations

Two patients from the safety population were discontinued due to protocol violations, both 15 year-old Patient 112-2301 and 14 year-old Patient 116-2703 discontinued due to noncompliance with estradiol treatment.

Patients Who Did Not Take Drug for a Consecutive Period of 180 Days

No patients met this criterion.

Patients Who Took Concomitant Drugs Methylphenidate (Ritalin) or Pemoline (Cylert)

Two patients, aged 10 and 14 years old, both received methylphenidate (Ritalin) therapy. These drugs, prescribed after patient enrollment, were considered essential to the patient's well-being. Because the effect of these drugs upon growth is controversial and data are inconclusive, the patients were allowed to stay in the study.

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Efficacy Results

Data Sets Analyzed

Of the 140 patients randomized with data, 134 were included in the intent-to-treat population. These patients had efficacy data at Visit 3 or beyond (180 days of treatment). The statistical evaluation was based on height data collected on all patients who participated (or are currently participating) in the study until the time of their discontinuation. Table 5 lists the number of patients with efficacy data by visit. The majority of patients, 78/134 (58%), completed four years or more, and 13 patients completed six years.

Table 5 Number of Patients With Efficacy Data at Yearly Visits

	Visit Number (Years in Study)						
Treatment Group	1 (0)	5 (1)	9 (2)	13 (3)	17 (4)	21 (5)	25 (6)
Total Number of Patients	134	131	116	101	78	41	13
hGH05	74	72	65	58	44	26	9
Untreated	60	59	51	43	34	15	4

Patient Characteristics

A summary of patient demographics at Baseline by treatment group for the intent-to-treat population is presented in Table 6 for origin and stature strata. Age, Weight, Height, Height SDS [NCHS], Height SDS [Lyon], Midparental Height, Pretreatment Growth Velocity, Pretreatment Growth Velocity SDS [Ranke], and Bone Age are presented in Table 7

Table 6 **Patient Characteristics at Entry: Origin and Stature Strata - ITT Population**

Characteristic	Overall	hGH05	Untreated	P-value[1]
ITT Population	134	74	60	
Origin				
Total Patients	134	74	60	
Caucasian	113 (84.3%)	65 (87.8%)	48 (80.0%)	0.287[2]
Black	0	0	0	
Hispanic	2 (1.5%)	2 (2.7%)	0	
Native American	2 (1.5%)	1 (1.4%)	1 (1.7%)	
Asian	13 (9.7%)	6 (8.1%)	7 (11.7%)	
Other	4 (3.0%)	0	4 (6.7%)	
Stature Strata				
Total Patients	134	74	60	
Lower	34 (25.4%)	18 (24.3%)	16 (26.7%)	0.490
Middle	51 (38.1%)	26 (35.1%)	25 (41.7%)	
Upper	49 (36.6%)	30 (40.5%)	19 (31.7%)	

*Statistically significant ($p \leq 0.050$).

[1] P-value tests proportions of patients for homogeneity between the treatment groups.

[2] P-value for origin is based on testing Caucasian relative to all other origins combined.

Note: Frequencies presented as number (percent). Percentages relative to number of patients in the ITT population.

At entry there were no significant differences between the Humatrope and Untreated groups for any of the demographic variables except for Midparental Height, where midparental height was on average 2 cm greater in the Humatrope group (p=0.041; Table 7).

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Table 7 **Patient Characteristics at Entry: Age, Weight, and Height Variables - ITT Population (Part 1 of 3)**

Characteristic	N	Mean	SD	Median	Minimum	Maximum	P-value[1]
Age (years)							
All Patients	134	10.44	1.78	10.63			
hGH05	74	10.39	1.80	10.69			0.709
Untreated	60	10.51	1.76	10.61			
Weight (kg)							
All Patients	134	26.74	7.99	25.50			
hGH05	74	26.87	7.81	25.90			0.859
Untreated	60	26.58	8.28	24.60			
Height (cm)							
All Patients	134	119.77	8.43	120.57			
hGH05	74	119.92	8.51	120.93			0.726
Untreated	60	119.60	8.39	119.98			
Height SDS [NCHS][2]							
All Patients	134	-3.27	0.84	-3.20			
hGH05	74	-3.23	0.83	-3.26			0.450
Untreated	60	-3.30	0.85	-3.18			

*Statistically significant ($p \leq 0.050$).

[1] P-value is for comparison of means between the treatment groups.

[2] Normal female reference standard.

[3] Turner syndrome reference standard [Lyon].

[4] Turner syndrome reference standard [Ranke].

Table 7 Patient Characteristics at Entry: Age, Weight, and Height Variables - ITT Population (Part 2 of 3)

Characteristic	N	Mean	SD	Median	Minimum	Maximum	P-value[1]
Height SDS [Lyon][3]							
All Patients	134	-0.15	0.87	-0.11			
hGH05	74	-0.09	0.89	0 01			0.258
Untreated	60	-0.23	0.85	-0.15			
Midparental Height (cm)							
All Patients	129	160.48	6.15	159.80			
hGH05	71	161.38	6.21	161.70			0.041*
Untreated	58	159.37	5.96	158.80			
Pretreatment Growth Velocity (cm/year)							
All Patients	134	4.17	1.06	4.08			
hGH05	74	4.24	1.11	4.20			0.360
Untreated	60	4.08	0.99	3.95			

*Statistically significant ($p \leq 0.050$).

[1] P-value is for comparison of means between the treatment groups.

[2] Normal female reference standard.

[3] Turner syndrome reference standard [Lyon].

[4] Turner syndrome reference standard [Ranke].

Table 7 **Patient Characteristics at Entry: Age, Weight, and Height Variables - ITT Population (Part 3 of 3)**

Characteristic	N	Mean	SD	Median	Minimum	Maximum	P-value
Pretreatment Growth Velocity SDS [Ranke][4]							
All Patients	134	0.32	0.72	0.26			
hGH05	74	0.35	0.75	0.30			0.486
Untreated	60	0.27	0.68	0.14			
Bone Age (years)							
All Patients	131	8.70	1.46	8.83			
hGH05	73	8.80	1.43	8.83			0.272
Untreated	58	8.58	1.50	8.83			

*Statistically significant ($p \leq 0.050$).

[1] P-value is for comparison of means between the treatment groups.

[2] Normal female reference standard.

[3] Turner syndrome reference standard [Lyon].

[4] Turner syndrome reference standard [Ranke].

For those patients who completed the study (reached Final Height), the demographic characteristics for origin and stature strata are presented in Table 8 and for age, weight, height, Height SDS [NCHS], Height SDS [Lyon], Midparental Height, Pretreatment Growth Velocity, Pretreatment Growth Velocity SDS [Ranke], and Bone Age in Table 9.

The Humatrope and Untreated groups appeared to be different in terms of the distribution of patients across stature strata with the Humatrope group having a greater percentage of patients than the Untreated group in the lower stratum and a lower percentage in the upper stratum. For other demographic variables, protocol completers in both treatment groups differed slightly on a few variables but the small sample sizes make comparisons less meaningful than for the ITT population.

Table 8 **Patient Characteristics at Entry: Origin and Stature Strata-Protocol Completers**

Characteristic	Overall	hGH05	Untreated
Protocol Completers	46	27	19
Origin			
Total Patients	46	27	19
Caucasian	38 (82.6%)	22 (81.5%)	16 (84.2%)
Black	0	0	0
Hispanic	1 (2.2%)	1 (3.7%)	0
Native American	0	0	0
Asian	6 (13.0%)	4 (14.8%)	2 (10.5%)
Other	1 (2.2%)	0	1 (5.3%)
Stature Strata			
Total Patients	46	27	19
Lower	12 (26.1%)	9 (33.3%)	3 (15.8%)
Middle	17 (37.0%)	10 (37.0%)	7 (36.8%)
Upper	17 (37.0%)	8 (29.6%)	9 (47.4%)

Note: Frequencies presented as number (percent). Percentages relative to number of patients who completed protocol.

Table 9 **Patient Characteristics at Entry: Age, Weight, and Height Variables - Protocol Completers (Part 1 of 3)**

Characteristic	N	Mean	SD	Median	Minimum	Maximum
Age (years)						
All Patients	46	11.66	1.17	11.72		
hGH05	27	11.66	1.06	11.67		
Untreated	19	11.65	1.34	11.87		
Weight (kg)						
All Patients	46	30.20	8.24	28.80		
hGH05	27	28.87	6.28	28.20		
Untreated	19	32.08	10.32	30.50		
Height (cm)						
All Patients	46	124.84	6.65	125.05		
hGH05	27	123.82	6.91	123.77		
Untreated	19	126.27	6.16	125.60		
Height SDS [NCHS][1]						
All Patients	46	-3.37	0.86	-3.34		
hGH05	27	-3.52	0.80	-3.56		
Untreated	19	-3.15	0.92	-2.90		

[1] Normal female reference standard.
[2] Turner syndrome reference standard [Lyon].
[3] Turner syndrome reference standard [Ranke].

Table 9 **Patient Characteristics at Entry: Age, Weight, and Height Variables - Protocol Completers (Part 2 of 3)**

Characteristic	N	Mean	SD	Median	Minimum	Maximum
Height SDS [Lyon][2]						
All Patients	46	-0.09	0.86	-0.03		
hGH05	27	-0.27	0.92	-0.35		
Untreated	19	0.17	0.70	0.31		
Midparental Height (cm)						
All Patients	45	159.88	6.62	158.60		
hGH05	27	160.62	7.00	159.60		
Untreated	18	158.76	6.03	158.60		
Pretreatment Growth Velocity (cm/year)						
All Patients	46	3.96	0.88	3.87		
hGH05	27	3.88	0.63	3.85		
Untreated	19	4.08	1.15	3.93		

[1] Normal female reference standard.
[2] Turner syndrome reference standard [Lyon].
[3] Turner syndrome reference standard [Ranke].

Table 9 Patient Characteristics at Entry: Age, Weight, and Height Variables - Protocol Completers (Part 3 of 3)

Characteristic	N	Mean	SD	Median	Minimum	Maximum
Pretreatment Growth Velocity SDS [Ranke][3]						
All Patients	46	0.26	0.59	0.19		
hGH05	27	0.19	0.42	0.13		
Untreated	19	0.36	0.77	0.21		
Bone Age (years)						
All Patients	46	9.73	1.09	10.00		
hGH05	27	9.76	1.14	10.00		
Untreated	19	9.68	1.04	10.00		

[1] Normal female reference standard.
[2] Turner syndrome reference standard [Lyon].
[3] Turner syndrome reference standard [Ranke].

Table 10 shows the frequency of karyotypes by treatment group for the ITT Population. Both groups were closely matched with respect to the frequency of karyotypes. Of the 134 patients comprising the ITT Population, 59.7% of these patients had the 45,X karyotype. The next most frequent karyotypes were the 46,XXqi karyotype at 6% and the 45,X/46,XXqi at 5.2%. The Other category, representing rare karyotypes otherwise unspecified on the clinical report form, comprised more than 20% of all patients.

Table 10 Patient Characteristics at Entry: Karyotype - ITT Population

Karyotype	Overall	hGH05	Untreated	P-value
Total Patients	134	74	60	
45,X	80 (59.7%)	44 (59.5%)	36 (60.0%)	0.875[1]
45,X/46,XXqi	7 (5.2%)	2 (2.7%)	5 (8.3%)	
45,X/46,XXr	2 (1.5%)	2 (2.7%)	0	
45,X/46,XX	5 (3.7%)	2 (2.7%)	3 (5.0%)	
46,XXqi	8 (6.0%)	6 (8.1%)	2 (3.3%)	
45,X/47,XXX	2 (1.5%)	2 (2.7%)	0	
46,XXp$^-$	1 (0.7%)	0	1 (1.7%)	
45,X/46,XXp$^-$	1 (0.7%)	1 (1.4%)	0	
45,X/46,XX/47,XXX	0	0	0	
Other	28 (20.9%)	15 (20.3%)	13 (21.7%)	

*Statistically significant ($p \leq 0.050$).

[1] P-value is based on testing 45,X karyotype relative to all other karyotypes combined.

Note: Frequencies presented as number (percent). Percentages relative to number of patients in the ITT population.

Shown in Table 11, the distribution of karyotypes for protocol completers departed slightly from that of the ITT population. As with the ITT population, 45,X was the most common karyotype found in 58.7% of the patients, with a slightly higher percentage in the Humatrope group in comparison to the Untreated group. The next most frequent karyotype categories were 45,X/46,XX (8.7%) and 46,XXqi (6.5%). The Other category accounted for 21.7% of patients.

Table 11 **Patient Characteristics at Entry: Karyotype - Protocol Completers**

Karyotype	Overall	hGH05	Untreated
Total Patients	46	27	19
45,X	27 (58.7%)	17 (63.0%)	10 (52.6%)
45,X/46,XXqi	1 (2.2%)	0	1 (5.3%)
45,X/46,XXr	1 (2.2%)	1 (3.7%)	0
45,X/46,XX	4 (8.7%)	2 (7.4%)	2 (10.5%)
46,XXqi	3 (6.5%)	2 (7.4%)	1 (5.3%)
45,X/47,XXX	0	0	0
46,XXp$^-$	0	0	0
45,X/46,XXp$^-$	0	0	0
45,X/46,XX/47,XXX	0	0	0
Other	10 (21.7%)	5 (18.5%)	5 (26.3%)

Note: Frequencies presented as number (percent). Percentages relative to number of patients who completed protocol.

Results of Efficacy Analysis

Primary Efficacy Variable - Final Height for Protocol Completers

Of the 134 patients included in the ITT population, a total of 46 patients were considered to have completed the protocol having fulfilled, or almost fulfilled, the study criteria for attainment of Final Height. A total of 27/74 (36.5%) patients in the Humatrope group and 19/60 (31.7%) patients in the Untreated group were analyzed as having completed the protocol.

Final Height - Protocol Completers

Final Height is the primary efficacy variable in the study; all other variables described in are also supportive efficacy variables. In this study, Final Height is defined as the actual height (cm) at the last available visit for patients who were identified by the investigator as having completed the study. Criteria for achievement of Final Height were bone age $\geq$14 years and growth velocity <2 cm/year. Fourteen of the patients in this group did not meet these criteria quantitatively; however, they were felt by the investigator to have achieved close to their final height. Therefore, the group was analyzed as a whole. These 14 patients all had bone ages $\geq$13.5 years and all but one had growth velocities of <3 cm/year.

The Final Height data are presented in Table 12. Patients treated with Humatrope were taller than untreated patients by an average of 3.87 cm, and this difference is statistically significant (p=0.001).

Table 12 **Efficacy Variables: Final Height, Final Height SDS [NCHS], and Final Height SDS [Lyon] - Protocol Completers**

Parameter	N	Mean	SD	Median	Minimum	Maximum	P-value[1]
Final Height (cm)							
hGH05	27	145.96	6.17	146.57			0.001†
Untreated	19	142.09	4.79	142.20			
Final Height SDS [NCHS][2]							
hGH05	27	-2.54	0.98	-2.43			0.001*
Untreated	19	-3.11	0.88	-3.06			
Final Height SDS [Lyon][3]							
hGH05	27	1.05	0.99	1.09			0.001*
Untreated	19	0.49	0.82	0.51			

† Statistically significant ($p \leq 0.005$) for primary/secondary efficacy variables.

*Statistically significant ($p \leq 0.050$) for other efficacy variables.

[1] P-value is for comparison of treatment group means.

[2] Normal female reference standard.

[3] Turner syndrome reference standard [Lyon].

Final Height SDS [NCHS] - Protocol Completers

Final Height SDS [NCHS] is the SDS for height using normal females as a reference standard. These data are presented in Table 12. It can be seen from the negative mean values that patients in both the Humatrope and Untreated groups did not attain the height of normal females. Their mean height remains 2.5 to 3.1 SDS below that of normal females. However, the mean Height SDS of the Humatrope group increased from -3.52 at baseline to -2.54 at Final Height. In contrast, the mean Height SDS of the Untreated group remained essentially unchanged. The Humatrope-treated patients exhibited a mean Height SDS which was significantly greater than that of the Untreated group (p=0.001). The Final Height SDS in the Humatrope group is 0.57 SDS greater than that of the Untreated group.

Final Height SDS [Lyon] - Protocol Completers

Final Height SDS [Lyon] is the SDS for height using patients with Turner syndrome as the reference standard. These data are presented in Table 12. Both the Humatrope group and Untreated group had a mean height greater than the mean height of the age matched Turner syndrome patients from the Lyon reference population. In addition, the Humatrope group had a statistically significant greater mean height SDS than the Untreated group (p=0.001); (1.05 SDS versus 0.49 SDS).

Final Height and Final Height SDS [NCHS] Adjusted for Midparental Height - Protocol Completers

Because of baseline differences in midparental height between the Humatrope and Untreated groups (161 cm versus 159 cm), Final Height and Final Height SDS were adjusted for midparental height. These data are presented in Table 13. This adjustment was planned a priori since there is known to be a correlation between parental heights and the adult heights of their offspring. An analysis of covariance (ANCOVA) was conducted with an adjustment for midparental height. When the mean Final Height was adjusted for this variable (in addition to adjustments for stature strata and geographically pooled sites), patients receiving Humatrope achieved a mean adjusted height which was 5.43 cm greater than that of untreated patients. The difference in least squares (adjusted) means was statistically significant (p=0.001). Similar results were found for Final Height SDS [NCHS] when adjusted for midparental height. The Humatrope group achieved greater adjusted mean Height SDS [NCHS] than the Untreated group. Although both groups remained short relative to the normal population, the adjusted mean height SDS for the Humatrope group was 0.77 SDS greater than that of the Untreated group. This difference was statistically significant (p=0.004).

Table 13 **Efficacy Variables: Final Height Adjusted for Midparental Height and Final Height SDS [NCHS] Adjusted for Midparental Height - Protocol Completers**

Parameter	N	Least Squares Mean[1]	SE	P-value[2]
Adjusted Final Height				
hGH05	27	145.89	0.74	0.001†
Untreated	19	140.46	1.02	
Adjusted Final Height SDS [NCHS][3]				
hGH05	27	-2.56	0.14	0.004*
Untreated	19	-3.33	0.20	

†Statistically significant ($p \leq 0.005$) for primary/secondary efficacy variables.

*Statistically significant ($p \leq 0.050$) for other efficacy variables.

[1] Least squares means for Final Height and Final Height SDS [NCHS] are adjusted for midparental height based on an ANCOVA.

[2] P-value is for comparison of treatment group means adjusted for midparental height.

[3] Normal female reference standard.

Secondary Efficacy Variables - Height SDS [NCHS] and Height Adjusted for Bone Age at Last Visit for the ITT Population

Because only 32.9% of patients completed the study prior to the cutoff date for this interim analysis, an examination of Height at Last Visit was made for all patients who were randomized to treatment, provided they remained in the study up to Visit 3,

scheduled at 180 days. An analysis of these data provides a broader overview of the effectiveness of Humatrope in a larger sample of patients.

Height SDS [NCHS] at Last Visit and Height at Last Visit Adjusted for Bone Age at the last visit at which a bone age X-ray was obtained, were evaluated for patients in the intent-to-treat population.

Height SDS [NCHS] at Last Visit - ITT Population

Height SDS [NCHS] data for Baseline and Last Visit for the intent-to-treat population are presented in Table 14. Both treatment groups were equivalent at Baseline and had mean height 3 SDS below the mean height of the normal female reference standard. Height SDS [NCHS] at Last Visit was greater in the Humatrope group relative to the Untreated group, and this difference reached statistical significance (p=0.001). The difference between groups remained statistically significant when the means were adjusted for midparental height (p=0.001). The Humatrope group exhibited an average Last Visit height SDS of 1.32 SDS greater than that of the Untreated group.

Table 14 Efficacy Variable: Height SDS [NCHS][1] at Last Visit - ITT Population

	N	Mean	SD	Median	Minimum	Maximum	P-value[2]	Adjusted P-value[3]
Baseline								
hGH05	74	-3.23	0.83	-3.26				
Untreated	60	-3.30	0.85	-3.18				
Last Visit								
hGH05	74	-2.37	0.96	-2.26			0.001†	0.001†
Untreated	60	-3.69	1.24	-3.55				

† Statistically significant ($p \leq 0.005$) for primary/secondary efficacy variables.

[1] Normal female reference standard.

[2] P-value is for comparison of treatment group means.

[3] P-value is for comparison of treatment group means adjusted for midparental height.

Height at Last Visit Adjusted for Bone Age - ITT Population

Overall, at Last Visit the mean height of patients who received Humatrope was 8.73 cm greater than that of patients in the Untreated group. Because of the potential for growth hormone to induce an increase in skeletal maturation, the effect of Humatrope on height gain was assessed after adjusting for bone age. An ANCOVA was conducted with an adjustment for bone age (in addition to midparental height, stature strata, and geographically pooled sites). When the Last Visit Height for the Humatrope and Untreated groups was adjusted for bone age (and midparental height, stature strata, and

site), the difference in least squares (adjusted) means was 6.02 cm (p = 0.001). These results are depicted in Table 15.

Table 15 **Efficacy Variable: Height at Last Visit[1] Adjusted for Bone Age - ITT Population**

	N	Mean	SD	Median	Minimum	Maximum
Last Visit Height (cm)						
hGH05	71	141.69	9.75	142.83		
Untreated	55	132.96	10.30	133.33		

	N	Least Squares Mean[2]	SE	P-value[3]
Adjusted Last Visit Height (cm)				
hGH05	71	140.12	0.59	0.001†
Untreated	55	134.10	0.68	

† Statistically significant ($p \leq 0.005$) for primary/secondary efficacy variables.

[1] Last visit at which bone age X-ray performed.

[2] Least squares means are adjusted for bone age and midparental height based on an ANCOVA.

[3] P-value is for comparison of treatment group means adjusted for bone age and midparental height.

Efficacy Results and Years of Treatment

Height SDS [NCHS] by Years in Study

Height SDS [NCHS] is presented by treatment group and years in study in Table 16. Two trends emerge from this table. First, relative to the normal female standard, patients treated with Humatrope show a gradual yearly positive change in height SDS. Secondly, as expected for patients in this age range, the Untreated group showed the opposite trend, a continued departure from the NCHS standard with years of treatment. These results suggest a gradual gain in height relative to the normal female standard over a period of years of treatment with Humatrope

Table 16 **Efficacy Variable: Height SDS [NCHS][1] by Years in Study - ITT Population**

Years in Study	N	Mean	SD	Median	Minimum	Maximum	P-value[2]
Baseline							
hGH05	74	-3.23	0.83	-3.26			
Untreated	60	-3.30	0.85	-3.18			
Year 1							
hGH05	72	-2.95	1.20	-2.86			
Untreated	59	-3.62	1.11	-3.41			
Year 2							
hGH05	65	-2.77	1.25	-2.61			
Untreated	51	-3.79	1.17	-3.60			
Year 3							
hGH05	58	-2.69	1.08	-2.55			
Untreated	43	-3.78	1.13	-3.59			
Year 4							
hGH05	44	-2.62	1.11	-2.41			
Untreated	34	-3.64	1.20	-3.62			
Year 5							
hGH05	26	-2.41	1.06	-2.38			
Untreated	15	-3.84	1.08	-4.14			
Year 6							
hGH05	9	-2.14	0.99	-1.65			
Untreated	4	-4.01	0.74	-3.74			
Last Visit							
hGH05	74	-2.37	0.96	-2.26			0.001†
Untreated	60	-3.69	1.24	-3.55			

† Statistically significant ($p \leq 0.005$) for primary/secondary efficacy variables.

[1] Normal female reference standard.

[2] P-value is for comparison of treatment group means at Last Visit.

Height SDS [NCHS] Change from Baseline by Years in Study - ITT Population

Yearly Height SDS [NCHS] expressed in terms of change from Baseline for both treatment groups for each year in the study is presented in Table 17. These results are consistent, revealing a progressively increasing positive change in Height SDS from Baseline in the Humatrope group. At Last Visit there was essentially no change in

Height SDS from Baseline in the Untreated group. In contrast, the Humatrope group showed 0.86 SDS gain from Baseline, a difference that was statistically significant compared with the Untreated group (p=0.001).

Table 17 Efficacy Variable: Height SDS [NCHS][1] Change from Baseline by Years in Study - ITT Population

Years from Baseline	N	Mean	SD	Median	Minimum	Maximum	P-value[2]
+1							
hGH05	72	0.30	0.68	0.32			
Untreated	59	-0.36	0.62	-0.43			
+2							
hGH05	65	0.53	0.97	0.92			
Untreated	51	-0.59	1.06	-0.35			
+3							
hGH05	58	0.65	0.86	0.67			
Untreated	43	-0.64	0.98	-0.46			
+4							
hGH05	44	0.77	0.99	0.49			
Untreated	34	-0.49	1.02	-0.69			
+5							
hGH05	26	0.75	0.47	0.80			
Untreated	15	-0.90	0.80	-0.90			
+6							
hGH05	9	1.07	0.44	0.92			
Untreated	4	-0.92	0.26	-0.90			
Last Visit							
hGH05	74	0.86	0.79	0.77			0.001*
Untreated	60	-0.38	1.02	-0.27			

* Statistically significant ($p \leq 0.050$).
[1] Normal female reference standard.
[2] P-value is for comparison of treatment group means at Last Visit.

Height SDS [Lyon] by Years in Study - ITT Population

Height SDS [Lyon] by years of treatment for the Humatrope and Untreated groups is shown in Table 18. There is a progressive increase in Height SDS in the Humatrope group relative to the Turner syndrome standard with years of treatment. Mean Height SDS for the Untreated group hovered around zero indicating that the Untreated group had

a fairly similar pattern of growth to that of untreated patients with Turner syndrome in the study of Lyon et al. Relative to the Turner syndrome reference standard, Height SDS for the Humatrope group exceeded those of the Untreated group, and this difference became more pronounced with years of treatment. Height SDS [Lyon] was statistically significantly greater in the Humatrope group in comparison to the Untreated group at Last Visit (p=0.001).

Table 18 Efficacy Variable: Height SDS [Lyon][1] by Years in Study - ITT Population

Years in Study	N	Mean	SD	Median	Minimum	Maximum	P-value[2]
Baseline							
hGH05	74	-0.09	0.89	0.01			
Untreated	60	-0.23	0.85	-0.15			
Year 1							
hGH05	72	0.61	0.92	0.59			
Untreated	59	-0.16	0.88	-0.12			
Year 2							
hGH05	65	1.03	0.94	1.01			
Untreated	51	0.04	0.94	0.01			
Year 3							
hGH05	58	1.28	0.95	1.24			
Untreated	43	0.20	0.95	0.26			
Year 4							
hGH05	44	1.36	1.05	1.40			
Untreated	34	0.17	0.96	0.23			
Year 5							
hGH05	26	1.59	1.18	1.59			
Untreated	15	0.09	0.91	0.15			
Year 6							
hGH05	9	2.06	0.83	2.08			
Untreated	4	-0.25	0.51	-0.18			
Last Visit							
hGH05	74	1.41	0.94	1.43			0.001*
Untreated	60	0.01	0.97	0.12			

* Statistically significant ($p \leq 0.050$).

[1] Turner syndrome reference standard [Lyon].

[2] P-value is for comparison of treatment group means at Last Visit.

Growth Velocity SDS [Ranke] by Years in Study - ITT Population

Growth Velocity SDS [Ranke] by years in study for the ITT Population is shown in Table 19 for the Humatrope and Untreated groups. Growth velocity is the rate of growth in cm/year as calculated from the difference between two height measurements. Because the growth velocities in this analysis were calculated on the basis of measurements obtained at less than 12 month intervals during treatment, the variability of these results is increased. This will tend to bias the analysis against detection of differences between groups. At baseline, both groups were growing at a similar rate, and this growth rate was slightly faster than the mean growth rate for the Turner syndrome reference population [Ranke]. The Humatrope group demonstrated an improvement in growth rate, growing almost three SDS faster than the mean growth rate for untreated patients with Turner syndrome in the study of Ranke et al. after one year of treatment. Growth rate was maintained at >2 SDS compared with the Ranke standard after the second year of treatment. In general, rate of growth was higher in the earlier years of treatment in comparison to later years of treatment. The mean growth velocity of the Untreated group remained fairly constant for several years, and then also declined. At Last Visit, there is no statistically significant difference between the groups.

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Table 19 **Efficacy Variable: Growth Velocity SDS [Ranke][1] by Years in Study - ITT Population**

Years in Study	N	Mean	SD	Median	Minimum	Maximum	P-value[2]
Baseline							
hGH05	74	0.35	0.75	0.30			
Untreated	60	0.27	0.68	0.14			
Year 1							
hGH05	72	2.83	1.97	2.49			
Untreated	59	0.26	1.86	0.20			
Year 2							
hGH05	65	2.04	2.10	2.17			
Untreated	49	0.45	1.75	0.28			
Year 3							
hGH05	54	1.25	1.67	1.10			
Untreated	39	0.53	1.61	0.22			
Year 4							
hGH05	34	1.23	2.35	0.86			
Untreated	26	-0.31	2.53	-0.52			
Year 5							
hGH05	20	0.68	1.46	0.61			
Untreated	8	-0.21	2.17	-0.59			
Year 6							
hGH05	9	-0.70	1.89	-1.24			
Untreated	1	0.21	-	0.21			
Last Visit							
hGH05	54	0.43	2.45	0.18			0.587
Untreated	42	0.20	2.20	0.01			

* Statistically significant ($p \leq 0.050$).

[1] Turner syndrome reference standard [Ranke].

[2] P-value is for comparison of treatment group means at Last Visit.

Bone Age

Bone age is an index of skeletal maturation. As bone age advances, the amount of remaining growth potential declines, and at a bone age of 15 years approximately 99% of adult stature has been attained in normal females; thus, administration of somatropin is not considered useful at an advanced bone age.

Bone Age by Years in Study - ITT Population

Bone Age by treatment group and years in study is presented in Table 20. At Baseline and each subsequent year, little difference was observed between the two treatment groups, although at Last Visit mean differences between the groups approached statistical significance (p=0.077), with the Humatrope group showing a higher mean value. However, since Final Height Adjusted for Bone Age failed to reduce the significant difference in final height between the Humatrope group and the Untreated group, this slightly greater bone age of the Humatrope-treated patients is not clinically relevant.

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Table 20 **Efficacy Variable: Bone Age by Years in Study - ITT Population**

Years in Study	N	Mean	SD	Median	Minimum	Maximum	P-value[1]
Baseline							
hGH05	73	8.80	1.43	8.83			
Untreated	58	8.58	1.50	8.83			
Year 1							
hGH05	69	9.79	1.37	10.00			
Untreated	51	9.60	1.44	9.00			
Year 2							
hGH05	64	10.77	1.53	11.00			
Untreated	43	10.74	1.61	11.00			
Year 3							
hGH05	52	12.13	1.47	12.00			
Untreated	39	11.87	1.88	12.00			
Year 4							
hGH05	43	12.85	1.54	13.00			
Untreated	32	12.91	1.71	13.50			
Year 5							
hGH05	24	13.23	1.40	13.50			
Untreated	15	13.60	1.57	14.00			
Year 6							
hGH05	9	13.47	1.00	14.00			
Untreated	2	13.00	0.00	13.00			
Last Visit[2]							
hGH05	71	12.83	2.06	13.50			0.077
Untreated	55	12.20	2.44	13.00			

* Statistically significant ($p \leq 0.050$).

[1] P-value is for comparison of treatment group means at Last Visit.

[2] Last visit at which bone age X-ray performed.

Bone Age Change from Baseline by Years in Study - ITT Population

Bone Age Change from Baseline by years in study is presented in Table 21. These data correspond to those found for Bone Age itself. These data reveal that for both treatment groups bone age advanced by a mean of approximately one year with each year in the study. Change from Baseline results were similar for the two treatment groups at each

year of treatment, with the difference between group means approaching statistical significance at Last Visit (p=0.060).

Table 21 **Efficacy Variable: Bone Age Change from Baseline by Years in Study - ITT Population**

Years from Baseline	N	Mean	SD	Median	Minimum	Maximum	P-value[1]
+1							
hGH05	68	1.02	0.71	1.00			
Untreated	50	1.01	0.59	1.00			
+2							
hGH05	63	1.99	1.05	2.00			
Untreated	42	2.07	1.00	2.04			
+3							
hGH05	51	3.14	0.91	3.17			
Untreated	38	3.02	1.17	3.17			
+4							
hGH05	43	4.14	1.08	4.17			
Untreated	32	4.01	1.15	4.17			
+5							
hGH05	24	4.81	0.95	5.00			
Untreated	15	4.84	1.13	5.00			
+6							
hGH05	9	5.51	1.05	5.17			
Untreated	2	4.67	0.71	4.67			
Last Visit[2]							
hGH05	70	4.14	1.67	4.21			0.060
Untreated	54	3.60	1.77	3.67			

* Statistically significant ($p \leq 0.050$).

[1] P-value is for comparison of treatment group means at Last Visit.

[2] Last visit at which bone age X-ray performed.

Bone Age/Chronological Age Ratio by Years in Study - ITT Population

Bone Age/Chronological Age Ratio by years in study is presented in Table 22. Bone Age/Chronological Age Ratios rise slightly in both treatment groups during the course of the study. At Last Visit, patients receiving Humatrope had a slightly greater mean Bone

Age/Chronological Age Ratio than the Untreated group, and this difference was statistically significant (p=0.006), but is not felt to be clinically meaningful.

Table 22 **Efficacy Variable: Bone Age/Chronological Age Ratio by Years in Study - ITT Population**

Years in Study	N	Mean	SD	Median	Minimum	Maximum	P-value[1]
Baseline							
hGH05	73	0.86	0.10	0.85			
Untreated	58	0.82	0.11	0.82			
Year 1							
hGH05	69	0.87	0.09	0.86			
Untreated	51	0.85	0.09	0.84			
Year 2							
hGH05	64	0.87	0.08	0.87			
Untreated	43	0.86	0.10	0.85			
Year 3							
hGH05	52	0.89	0.07	0.88			
Untreated	39	0.87	0.08	0.87			
Year 4							
hGH05	43	0.90	0.05	0.89			
Untreated	32	0.88	0.08	0.87			
Year 5							
hGH05	24	0.89	0.06	0.90			
Untreated	15	0.88	0.09	0.87			
Year 6							
hGH05	9	0.90	0.03	0.91			
Untreated	2	0.85	0.05	0.85			
Last Visit[2]							
hGH05	71	0.90	0.08	0.90			0.006*
Untreated	55	0.87	0.08	0.86			

* Statistically significant ($p \leq 0.050$).

[1] P-value is for comparison of treatment group means at Last Visit.

[2] Last visit at which bone age X-ray performed.

Treatment Interactions

There was no indication of an interaction for two of the variables, but the interaction between treatment and pooled site showed a statistical trend for Height SDS [NCHS] at Last Visit (p=0.063). The sites forming the region consisting of British Columbia, Alberta, and Manitoba had a greater average Height SDS at Last Visit for the Humatrope group than the other two geographical regions, by approximately 0.75 SDS. Exploratory analysis comparing pooled sites at Baseline found no explanation for this result.

The interaction between treatment and strata showed a statistical trend for Height SDS [NCHS] at Last Visit (p=0.063). The difference in mean Last Visit Height SDS between the Humatrope and Untreated groups was greater for the patients in the lower stratum than the middle or upper stature strata by over 0.8 SDS. There was no similar trend for the other primary and secondary variables. This trend indicates that patients with the lowest stature for their age who receive Humatrope have the largest gain in height SDS [NCHS] compared to the Untreated group.

Summary of Efficacy

Protocol Completers (Patients Achieving Final Height)

Primary Efficacy Variable

1. Of the patients who were considered by investigators to have reached Final Height, those who received Humatrope demonstrated significantly greater mean actual height than that of the Untreated group by approximately 4 cm.

Other Efficacy Variables

1. Although the Final Height of patients treated with Humatrope remained below that of age-matched normal females (-2.54 SDS [NCHS]), it was significantly greater than that of the Untreated group (-3.11 SDS [NCHS]).
2. Both Humatrope-treated and Untreated patients in this study achieved mean final height greater than the mean of the Turner syndrome reference population described in the study of Lyon et al. (+1.05 SDS and +0.49 SDS, respectively). The difference between the Humatrope and Untreated groups was statistically significant.
3. At Last Visit, the differences between treatment groups for height SDS [NCHS] was greater in the lower stature stratum than the other strata.

ITT Population

Secondary Efficacy Variables

1. The Humatrope group demonstrated a greater mean Height SDS [NCHS] than the Untreated group at Last Visit. Patients with Turner syndrome receiving Humatrope showed a Last Visit mean Height SDS of -2.37 cm whereas Untreated patients exhibit a significantly lower mean height SDS of -3.69 cm, at Last Visit. There was evidence that patients in the lowest stature stratum showed greater difference in Height SDS [NCHS] between the Humatrope and the Untreated groups, however, the number of patients in each stratum was small.

2. Patients treated with Humatrope achieved a mean Height Adjusted for Bone Age, midparental height, stature strata, and geographically pooled site of approximately 140 cm at Last Visit compared with a mean Adjusted Height of 134 cm in the Untreated group. This was a statistically significant difference.

Other Efficacy Variables

1. When Height SDS [NCHS] and Height SDS [Lyon] were evaluated by years of treatment, patients receiving Humatrope showed improvement in Height SDS compared with both reference standards, whereas the Untreated patients did not.

2. Growth rate was high in Humatrope-treated patients over the first two years of the study and then declined. In the Untreated group Growth Rate remained low, which is consistent with that seen for untreated patients with Turner syndrome in historical studies (Ranke et al.).

3. There was no clinically significant difference between treatment groups for Bone Age variables.

Results of Compliance Analysis

In this study, patient compliance with the administration of study medication was assessed in terms of average compliance and overall compliance for patients receiving Humatrope. Compliance data are presented in Table 23. Average compliance is defined as the number of injections taken divided by the number of expected injections. Overall compliance is defined as the number of Humatrope-treated patients who were 80 -120% compliant divided by the total number of Humatrope-treated patients. Compliance is evaluated for injectable treatment only (number of injections taken), and not the amount of prescribed volume administered. Of the 74 patients in the safety analysis, 99% of the patients took 98% of their prescribed injections.

Table 23 **Study Compliance for hGH05 Treatment Group - Safety Population**

Patient Study Compliance[1]						
N	Mean	SD	Median	Minimum	Maximum	Total Study Compliance (%)[2]
74	97.91	5.41	99.63			98.6%

[1] Total number of injections taken divided by total number of expected injections.
[2] Percent of patients who were 80-120% compliant.

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Safety Results

Exposure to Study Drugs

Tables 24-25 summarize exposure to study drug as years in study. These tables present descriptive statistics (i.e., sample size, mean, standard deviation, median, minimum, and maximum) overall and by treatment group, for the safety population and protocol completers, respectively. Exposure is defined as the number of years that a patient was in the study and is calculated by using dates of visits attended including lapsed time between visits, up to 180 consecutive days.

Table 24 Years in Study - Safety Population

Treatment Group	N	Mean	SD	Median	Minimum	Maximum
Overall	136	3.93	1.59	4.07		
hGH05	74	4.10	1.54	4.26		
Untreated	62	3.74	1.64	4.02		

Table 25 Years in Study - Protocol Completers

Treatment Group	N	Mean	SD	Median	Minimum	Maximum
Overall	46	4.64	0.84	4.51		
hGH05	27	4.65	0.86	4.75		
Untreated	19	4.62	0.82	4.30		

For the safety population, the mean years in study was approximately 4 years, which was similar to the mean years in study for each of the treatment groups (i.e., 4.1 years for the Humatrope group versus 3.7 years for the Untreated group).

Years in study results were comparable for the safety population and protocol completers. For protocol completers, the mean duration of study exposure was 4.6 years. The intent-to-treat population, approximately 58% of the patients in GDCT were in the study for ≥4 years. Thirteen patients completed at least six years.

Adverse Events

Serious Adverse Events

Deaths

One (<1%) of the 136 patients in the safety population died (Patient 116-2001). This patient, whose death was due to a ruptured aortic aneurysm, was in the Untreated group and therefore did not receive Humatrope.

Unexpected and Possibly Related Serious Adverse Events

As of the 8 February 1996 data cutoff date, 5 (7%) of the 74 patients in the safety population who received Humatrope experienced a serious adverse event which was unexpected and possibly related to study drug. One (2%) of the 62 patients in the Untreated group (who received ethinyl estradiol only) also had an adverse event which was unexpected and possibly related to study drug. Table 26 provides a listing of these adverse events by patient. It should be noted that the hypochromic microcytic anemia observed in Patient 104-2500 was judged by the investigator to be possibly related to treatment with ethinyl estradiol.

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Table 26 **Patients with Serious Adverse Events Classified as Unexpected and Possibly Related to Study Medication**

Patient	Treatment Group	Age	Event Classification Term	Event Description	Days in Study
104-2500	hGH05	13	Hypochromic Microcytic Anemia	Hypochromic Microcytic Anemia	1579
105-2408	hGH05	10	Dyspnea	Shortness of Breath	302
106-2303	hGH05	13	Psoriasis	Pustular Rash	1139
114-2712	hGH05	14	SGOT Increase	SGOT Elevation	586
		12	Gastroinestinal Disorder	Stomach Flu	614
116-2001	Untreated	13	Thrombocytopenic Purpura	Idiopathic Thrombocytopenic Purpura	392
		13	Vascular Disorder	Ruptured Aortic Aneurysm	438
116-2210	hGH05	7	Surgical Procedure	Valve Replacement	515

All Serious Adverse Events

Table 27 providew listings of all patients with serious adverse events reported as of the 8 February 1996 data cutoff date, regardless of relationship to study medication. The listing in Table 27 includes all adverse events which were recorded on the serious adverse event report, whether or not each individual adverse event was considered serious.

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Table 27 **Patients with Serious Adverse Events**

Patient	Treatment Group	Age	Event Classification Term	Event Description
102-2005	hGH05	10	Surgical Procedure	Gonadectomy
102-2700	hGH05	14	Iron Deficiency Anemia	Anemia
104-2500	hGH05	13	Hypochromic Anemia	Hypochromic Microcytic Anemia
			Somnolence	Lethargy
			Vomiting	Vomiting
			Pallor	Pale
		14	Surgical Procedure	Colonoscopy
			Hypochromic Anemia	Hypochromic Anemia
			Microcytic Anemia	Microcytic Anemia
105-2408	hGH05	10	Asthma	Shortness of Breath
			Psoriasis	Pustular Rash
106-2303	hGH05	10	Psoriasis	Acute Psoriasis
		13	Psoriasis	Pustular Psoriasis
			Pustular Rash	Pustular Rash
106-2307	hGH05	12	Surgical Procedure	Dental Cleaning
			Epistaxis	Nose Bleed
			Hemorrhage	Mouth Bleed
106-2716	hGH05	15	Cellulitis	Cellulitis Right Foot
			Pain	Foot Pain
			Vesiculobullous Rash	Blister on Foot
107-2107	Untreated	10	Surgical Procedure	Surgical Procedure
107-2804	hGH05	12	Abdominal Pain	Pain-Left Hypochondrium
			Surgical Procedure	Surgical Procedure
108-2112	hGH05	9	Pyelonephritis	Pyelonephritis
			Urinary Tract Infection	Urinary Tract Infection
108-2121	hGH05	8	Meningitis	Viral Meningitis
			Headache	Headache
			Vomiting	Vomiting

Table 27 **Patients with Serious Adverse Events (Cont'd)**

Patient	Treatment Group	Age	Event Classification Term	Event Description
110-2508	hGH05	10	Dehydration	Dehydration
			Flu Syndrome	Flu Syndrome
		15	Surgical Procedure	Mastoid Operation
		15	Surgical Procedure	Ear Surgery
111-2202	hGH05	10	Dehydration	Dehydration
			Flu Syndrome	Flu Syndrome
		11	Accidental Injury	Broken Left Wrist
112-2106	hGH05	8	Otitis Media	Otitis Media
		14	Surgical Procedure	Mastoidectomy
			Surgical Procedure	Tympanoplasty
			Surgical Procedure	Nasoplasty Procedure
112-2301	Untreated	14	Surgical Procedure	Appendectomy
			Abdominal Syndrome Acute	Appendicitis
			Vomiting	Vomiting
112-2721	Untreated	13	Surgical Procedure	Appendectomy
			Abdominal Pain	Abdominal Pain
			Dyspepsia	Upset Stomach
			Abdominal Syndrome Acute	Appendicitis
			Pain	Post-Operative Pain
112-2801	hGH05	12	Surgical Procedure	Tympanoplasty of Left Ear
			Deafness	Hearing Loss
			Ear Disorder	Ear Disorder-Perforation
113-2105	hGH05	8	Surgical Procedure	Removal of Cholesteatoma
		10	Surgical Procedure	Strabimus Repair
			Somnolence	Postanesthetic Somnolence
		10	Surgical Procedure	Ear Surgery
			Ear Disorder	Ear Disorder
		12	Surgical Procedure	Ear Surgery
			Ear Disorder	Cholesteatoma
113-2506	hGH05	12	Surgical Procedure	Z Plasty Procedure for Neck Web
			Somnolence	Postanesthetic Somnolence
		14	Accidental Injury	Fractured Arm
113-2806	Untreated	15	Surgical Procedure	Reconstructive Surgery for Webbing of Neck

Table 27 **Patients with Serious Adverse Events (Cont'd)**

Patient	Treatment Group	Age	Event Classification Term	Event Description
114-2712	hGH05	14	SGOT Increase	SGOT Elevation
		14	Gastrointestinal Disorder	Stomach Flu
115-2814	Untreated	15	Edema	Swollen Left Leg
			Thrombophlebitis	Transitory Thrombophlebitis
116-2001	Untreated	13	Thrombocytopenic Purpura	Thrombocytopenic Purpura Idiopathic
			Headache	Headache
			Rhinitis	Cold Symptoms
			Petechia	Petechiae
			Ecchymosis	Bruising
			Gum Hemorrhage	Bleeding Gums
			Pharyngitis	Sore Throat
		13	Vascular Disorder	Ruptured Aortic Aneurysm
			Chest Pain	Chest Pain
			Heart Arrest	Cardiac Arrest
			Abdominal Pain	Abdominal Pain
			Tachycardia	Tachycardia
			Convulsion	Seizure
			Vomiting	Vomiting
			Ear Pain	Ear Pain
116-2123	hGH05	7	Surgical Procedure	Coarctation Repair
116-2210	hGH05	7	Surgical Procedure	VP Shunt Revision
			Headache	Headache Worsening
			Dizziness	Dizziness
		7	Surgical Procedure	Shunt Valve Replaced
			Headache	Headache Worsening
			Vomiting	Vomiting
			Pain	Leg Pain
			Intracranial Hypertension	Pseudotumor Cerebri
			Somnolence	Drowsiness
116-2501	hGH05	11	Gastroenteritis	Gestroenteritis

Table 27 Patients with Serious Adverse Events (Cont'd)

Patient	Treatment Group	Age	Event Classification Term	Event Description
116-2703	Untreated	13	Surgical Procedure	Keloid Removal
116-2820	Untreated	13	Pneumonia	Pneumonia
			Nausea and Vomiting	Nausea and Vomiting
			Anorexia	Loss of Appetite
			Pharyngitis	Sore Throat
			Asthenia	Fatigue
			Dysmenorrhea	Cramps Menstrual
			Headache	Headache

Serious adverse events were reported in 20 (27%) of the 74 patients in the safety population who were randomized to the Humatrope group, and in 8 (13%) of the 62 patients randomized to the Untreated group.

Table 28 provides a listing, in order of decreasing overall frequency, of adverse events (both serious and nonserious) which accompanied each serious adverse event report. Table 28 includes only those patients who received Humatrope. Thirty-one reports of serious adverse events occurred among 20 patients who received at least one dose of Humatrope. Among these 31 reports of serious adverse events, 64 adverse events were reported overall (both serious and accompanying nonserious events). The most frequent adverse event by far was surgical procedure, for which 22 events were reported among 11 patients. Somnolence, ear disorder, headache, vomiting, accidental injury, hypochromic anemia, pain, and psoriasis were reported between two and four times each.

Table 28 **Frequency of Adverse Events Listed on Serious Adverse Event Reports: hGH05**

Event Classification Term	hGH05
Total Number of Patients	20
Total Number of SAE Reports	31
Total Number of Events	64
Surgical Procedure	22
Somnolence	4
Ear Disorder	3
Headache	3
Vomiting	3
Accidental Injury	2
Hypochromic Anemia	2
Pain	2
Psoriasis	2
Abdominal Pain	1
Asthma	1
Cellulitis	1
Deafness	1
Dehydration	1
Dizziness	1
Epistaxis	1
Flu Syndrome	1
Gastroenteritis	1
Gastrointestinal Disorder	1
Hemorrhage	1
Intracranial Hypertension	1
Iron Deficiency Anemia	1
Meningitis	1
Microcytic Anemia	1
Otitis Media	1
Pallor	1
Pustular Rash	1
Pyelonephritis	1
Urinary Tract Infection	1
Vesiculobullous Rash	1

Note: This table lists both serious and nonserious adverse events listed on the serious adverse event reports.

Discontinuations Due to Adverse Events

As of the 8 February 1996 data cutoff date, 2 (3%) of the 74 patients in the Humatrope group and 1 (2%) of the 62 patients in the Untreated group prematurely discontinued from the study due to an adverse event. Table 29 provides a listing of these individual patients, their treatment group, and the event leading to discontinuation. Events leading to discontinuation for the two Humatrope-treated patients were an increase in SGOT and intracranial hypertension, events that were considered unexpected and possibly related to study medication. Patient 116-2210 underwent shunt revision and ventriculoperitoneal shunt valve replacement surgery for intracranial hypertension presumably related to shunt malfunction.

Table 29 Patients Discontinued Due to Adverse Events

Patient	Treatment Group	Age	Origin	Visit	Days in Study	Event Classification Term
114-2712	hGH05	14	Native American	8	586	SGOT Increased
116-2001[1]	Untreated	13	Caucasian	20	438	Vascular Disorder
116-2210	hGH05	7	Caucasian	7	515	Intracranial Hypertension

[1] This patient was discontinued due to death following ruptured aortic aneurysm.

Treatment-Emergent Events

Treatment-emergent events reported in ≥5% of patients overall are listed in order of decreasing total frequency by treatment group in Table 30.

Table 30 **Frequency of Common Treatment-Emergent Events by Treatment Group - Safety Population**

Event Classification Term	Overall	Treatment Group	
		hGH05	Untreated
Total Number of Patients	136	74	62
Any Adverse Event	132 (97.1%)	74 (100.0%)	58 (93.5%)
Rhinitis	105 (77.2%)	59 (79.7%)	46 (74.2%)
Pharyngitis	85 (62.5%)	46 (62.2%)	39 (62.9%)
Headache	69 (50.7%)	41 (55.4%)	28 (45.2%)
Infection	69 (50.7%)	38 (51.4%)	31 (50.0%)
Flu Syndrome	63 (46.3%)	37 (50.0%)	26 (41.9%)
Fever	57 (41.9%)	33 (44.6%)	24 (38.7%)
Surgical Procedure*	50 (36.8%)	33 (44.6%)	17 (27.4%)
Cough Increased	49 (36.0%)	30 (40.5%)	19 (30.6%)
Otitis Media*	48 (35.3%)	32 (43.2%)	16 (25.8%)
Vomiting	47 (34.6%)	27 (36.5%)	20 (32.3%)
Abdominal Pain	38 (27.9%)	19 (25.7%)	19 (30.6%)
Ear Pain	34 (25.0%)	22 (29.7%)	12 (19.4%)
Pain	30 (22.1%)	20 (27.0%)	10 (16.1%)
Accidental Injury	28 (20.6%)	18 (24.3%)	10 (16.1%)
Rash	26 (19.1%)	14 (18.9%)	12 (19.4%)
Diarrhea	24 (17.6%)	12 (16.2%)	12 (19.4%)
Tooth Disorder	24 (17.6%)	13 (17.6%)	11 (17.7%)
Otitis Externa	18 (13.2%)	11 (14.9%)	7 (11.3%)
Ear Disorder*	16 (11.8%)	13 (17.6%)	3 (4.8%)
Sinusitis	16 (11.8%)	12 (16.2%)	4 (6.5%)
Dysmenorrhea	15 (11.0%)	8 (10.8%)	7 (11.3%)
Hypothyroidism	15 (11.0%)	10 (13.5%)	5 (8.1%)
Nausea	14 (10.3%)	8 (10.8%)	6 (9.7%)
Bone Disorder	13 (9.6%)	6 (8.1%)	7 (11.3%)
Gastrointestinal Disorder	13 (9.6%)	6 (8.1%)	7 (11.3%)
Bronchitis	12 (8.8%)	8 (10.8%)	4 (6.5%)
Eczema	12 (8.8%)	7 (9.5%)	5 (8.1%)
Back Pain	11 (8.1%)	6 (8.1%)	5 (8.1%)
Epistaxis	11 (8.1%)	6 (8.1%)	5 (8.1%)
Pustular Rash	11 (8.1%)	7 (9.5%)	4 (6.5%)
Skin Benign Neoplasm	11 (8.1%)	7 (9.5%)	4 (6.5%)
Allergic Reaction	10 (7.4%)	7 (9.5%)	3 (4.8%)
Urinary Tract Infection	10 (7.4%)	6 (8.1%)	4 (6.5%)

*Statistically significant ($p \leq 0.050$).

Note: P-value tests proportions of patients for homogeneity between the treatment groups.

Note: This table includes events that occurred in ≥5% of the patients in the safety population.

Table 30 **Frequency of Common Treatment-Emergent Events by Treatment Group - Safety Population (Cont'd)**

Event Classification Term	Overall	Treatment Group	
		hGH05	Untreated
Dizziness	9 (6.6%)	6 (8.1%)	3 (4.8%)
Accidental Overdose*	8 (5.9%)	8 (10.8%)	0
Conjunctivitis	8 (5.9%)	5 (6.8%)	3 (4.8%)
Dyspepsia	8 (5.9%)	5 (6.8%)	3 (4.8%)
Asthenia	7 (5.1%)	3 (4.1%)	4 (6.5%)
Dry Skin	7 (5.1%)	4 (5.4%)	3 (4.8%)
Nausea and Vomiting	7 (5.1%)	2 (2.7%)	5 (8.1%)
Skin Hypertrophy	7 (5.1%)	5 (6.8%)	2 (3.2%)

*Statistically significant ($p \leq 0.050$).

Note: P-value tests proportions of patients for homogeneity between the treatment groups.

Note: This table includes events that occurred in ≥5% of the patients in the safety population.

All patients in the Humatrope group, and almost all patients in the Untreated group, reported at least one treatment-emergent event, a finding not unexpected in a pediatric population. Differences between treatment groups of ≥5% were observed for several events. Surgical procedure, otitis media, ear disorder, and accidental overdose were experienced by a higher percentage of patients in the Humatrope group than in the Untreated group. The difference between the Humatrope group and the Untreated group was statistically significant ($p \leq 0.050$) for these four events. Rhinitis, headache, flu syndrome, fever, increased cough, ear pain, pain, accidental injury, sinusitis, and hypothyroidism were also reported by a higher percentage of patients in the Humatrope group than in the Untreated group, although none of these differences was statistically significant. In contrast, nausea and vomiting was observed in a slightly higher percentage of patients in the Untreated group than in the Humatrope group.

Treatment-emergent events of special interest were identified for this study because of concern that development or worsening of some adverse events is potentially causally related to treatment with Humatrope. These events are presented for the complete safety population and for Humatrope-treated versus Untreated patients in Table 31.

Table 31 **Treatment-Emergent Events of Special Interest by Treatment Group - Safety Population**

Adverse Event	Overall	Treatment Group	
		hGH05	Untreated
Total Number of Patients	136	74	62
Bone Disorder	13 (9.6%)	6 (8.1%)	7 (11.3%)
Edemas			
Conjunctival Edema	1 (0.7%)	0	1 (1.6%)
Edema	3 (2.2%)	2 (2.7%)	1 (1.6%)
Face Edema	1 (0.7%)	1 (1.4%)	0
Peripheral Edema	6 (4.4%)	5 (6.8%)	1 (1.6%)
Hyperglycemia	0	0	0
Hypothyroidism	15 (11.0%)	10 (13.5%)	5 (8.1%)
Increased Nevi [1]	10 (7.4%)	8 (10.8%)	2 (3.2%)
Lymphedema	0	0	0

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

A higher percentage of patients in the Humatrope group than in the Untreated group reported peripheral edema. A higher percentage of patients in the Humatrope group than in the Untreated group also were reported to have hypothyroidism and increased nevi. With respect to the development of hypothyroidism in patients enrolled in this study, it should be noted that patients with Turner syndrome have a well-recognized increase in frequency of thyroid abnormalities, as high as 20-30% in some series. Furthermore, the etiology of the hypothyroidism in the patients in this study was not investigated, as no further studies such as thyroid antibodies, were performed. A slightly higher percentage of patients in the Untreated group than in the Humatrope group were reported to have a bone disorder. No occurrences of hyperglycemia or lymphedema were reported in either treatment group.

Clinical Laboratory Evaluation

Blood and urine samples were obtained at Baseline, at three-month intervals during the first year of the study, and at six-month intervals thereafter for the assessment of blood chemistry, hematology, and urinalysis variables, thyroid function, glucose homeostasis, and antibodies to growth hormone and to *Escherichia Coli* polypeptide. Hemoglobin A_{1C} was measured at six-month intervals throughout the study.

In order to determine whether Humatrope-treated patients were more likely to develop abnormalities of certain key laboratory parameters than Untreated patients, numerical cut points beyond which values were considered likely to be clinically significant were assigned.

Blood Chemistry

Summary statistics for selected blood chemistry variables at Baseline, Last Visit, and for change from Baseline to Last Visit, are presented in Table 32. Mean and median values for representative liver function tests (GGT, AST/SGOT, and ALT/SGPT), other biochemical variables (calcium, phosphorus, and urea nitrogen), and total cholesterol were normal at Baseline and Last Visit in both the Humatrope group and the Untreated group. Mean values for creatinine were slightly lower at Baseline in both treatment groups (58.3 mmol/L and 58.5 mmol/L for the Humatrope group and Untreated group, respectively), than at Last Visit (67.8 mmol/L and 66.0 mmol/L, respectively). However, on both occasions these values were normal for childhood reference ranges. Mean alkaline phosphatase activity was normal at Baseline and Last Visit for both groups. Mean creatine kinase activity was slightly higher in Humatrope-treated patients, perhaps reflecting enhanced tissue growth stimulated by Humatrope.

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Table 32 **Blood Chemistry Test Results - Safety Population**

Analyte	Statistic	hGH05			Untreated		
		Baseline	Last Visit	Change	Baseline	Last Visit	Change
Alkaline Phosphatase (U/L)	n	73	74	73	61	62	61
	Mean	206.2	165.9	-41.2	225.1	166.1	-58.8
	SD	48.1	63.9	64.1	68.0	62.0	77.3
	Median	207.0	160.0	-46.0	223.0	160.0	-48.0
	Minimum	134.0	62.0	-179.0	95.0	38.0	-339.0
	Maximum	359.0	347.0	100.0	435.0	367.0	92.0
Calcium (mmol/L)	n	73	74	73	61	62	61
	Mean	2.29	2.27	-0.03	2.30	2.29	-0.00
	SD	0.15	0.10	0.16	0.11	0.09	0.12
	Median	2.32	2.27	-0.05	2.30	2.30	0.00
	Minimum	1.67	2.02	-0.28	2.02	2.02	-0.28
	Maximum	2.57	2.50	0.55	2.50	2.47	0.27

Table 32 Blood Chemistry Test Results - Safety Population (Cont'd)

Analyte	Statistic	hGH05			Untreated		
		Baseline	Last Visit	Change	Baseline	Last Visit	Change
Total Cholesterol (mmol/L)	n	73	74	73	61	62	61
	Mean	4.50	5.08	0.59	4.68	5.24	0.55
	SD	0.81	1.13	0.88	0.74	0.94	0.90
	Median	4.42	4.97	0.36	4.60	5.07	0.51
	Minimum	2.79	3.10	-1.08	3.23	3.34	-1.30
	Maximum	6.39	8.04	2.74	7.01	7.32	2.46
Creatine Kinase (U/L)	n	72	74	72	61	62	61
	Mean	113.3	129.1	16.5	122.8	113.5	-9.0
	SD	41.9	136.4	124.9	50.2	70.8	69.4
	Median	108.5	97.5	-3.0	109.0	92.5	-19.0
	Minimum	46.0	46.0	-134.0	45	22.0	-142.0
	Maximum	240.0	1142.0	966.0	250.0	464.0	391.0
Inorganic Phosphorus (mmol/L)	n	73	74	73	61	62	61
	Mean	1.48	1.52	0.04	1.50	1.44	-0.06
	SD	0.16	0.22	0.23	0.16	0.16	0.18
	Median	1.49	1.52	0.03	1.49	1.42	-0.07
	Minimum	0.97	0.81	-0.45	1.13	1.03	-0.52
	Maximum	1.78	2.10	0.55	1.81	1.84	0.39

Table 32 Blood Chemistry Test Results - Safety Population (Cont'd)

Analyte	Statistic	hGH05			Untreated		
		Baseline	Last Visit	Change	Baseline	Last Visit	Change
GGT	n	73	74	73	61	62	61
(U/L)	Mean	15.2	13.4	-1.6	19.4	17.0	-2.4
	SD	12.8	9.6	9.4	29.6	16.7	30.3
	Median	12.0	11.0	-1.0	12.0	13.0	0.0
	Minimum	6.0	4.0	-50.0	5.0	4.0	-180.0
	Maximum	99.0	53.0	27.0	207.0	127.0	115.0
SGOT (AST)	n	73	74	73	61	62	61
(U/L)	Mean	30.3	21.6	-8.7	31.1	24.9	-6.2
	SD	17.8	7.0	17.3	11.5	10.4	13.7
	Median	27.0	20.5	-6.0	28.0	23.0	-5.0
	Minimum	15.0	12.0	-143.0	18.0	13.0	-70.0
	Maximum	169.0	52.0	21.0	89.0	65.0	30.0
SGPT (ALT)	n	73	74	73	61	62	61
(U/L)	Mean	21.6	16.3	-5.3	26.3	20.5	-5.8
	SD	19.8	7.5	17.9	22.9	12.1	22.7
	Median	18.0	15.0	-3.0	18.0	15.5	-2.0
	Minimum	9.0	6.0	-137.0	9.0	8.0	-121.0
	Maximum	158.0	42.0	12.0	140.0	58.0	34.0

Table 32 **Blood Chemistry Test Results - Safety Population (Cont'd)**

Analyte	Statistic	hGH05			Untreated		
		Baseline	Last Visit	Change	Baseline	Last Visit	Change
Creatinine	n	73	74	73	61	62	61
(mmol/L)	Mean	58.3	67.8	9.5	58.5	66.0	7.5
	SD	11.5	9.5	12.4	10.6	9.7	9.8
	Median	62.0	71.0	9.0	62.0	62.0	9.0
	Minimum	35.0	44.0	-18.0	27.0	44.0	-18.0
	Maximum	88.0	97.0	36.0	88.0	88.0	35.0
Urea Nitrogen	n	73	74	73	61	62	61
(mmol/L)	Mean	3.98	3.85	-0.14	3.98	3.68	-0.31
	SD	1.14	1.04	1.07	1.17	1.02	1.15
	Median	3.90	3.60	0.00	3.90	3.60	0.00
	Minimum	1.80	1.40	-2.80	2.10	1.80	-3.20
	Maximum	6.40	6.80	2.20	9.60	6.40	2.50

The numbers of patients in the two treatment groups with values that fell above the clinically significant cut points for selected blood chemistry variables are presented in Table 33. A greater proportion of Humatrope-treated than Untreated patients had values above the clinically significant cut points for alkaline phosphatase (28 patients or 37.8% versus 10 patients or 16.1%) and for creatine kinase activity (13 patients or 17.6% versus 3 patients or 4.8%). The tendency for more Humatrope-treated patients to have values above the clinically significant cut point for these variables may reflect growth-related increases of those enzymes. A greater proportion of Untreated patients (44 patients or 71.0%) than Humatrope-treated patients (45 patients or 60.8%) had values above the clinically significant cut points for total cholesterol.

Table 33 **Blood Chemistry: Number of Patients with at Least One Value Above the Clinically Significant Cut Point - Safety Population**

Analyte	hGH05[1]	Untreated[1]	Age Range (Years)	Clinically Significant Upper Cut Point
Alkaline Phosphatase	28 (37.8%)	10 (16.1%)	All Ages	312 (U/L)
Total Cholesterol	45 (60.8%)	44 (71.0%)	All Ages	5 (mmol/L)
Creatine Kinase	13 (17.6%)	3 (4.8%)	All Ages	370 (U/L)
GGT	1 (1.4%)	3 (4.8%)	All Ages	98 (U/L)
SGOT (AST)	6 (8.1%)	5 (8.1%)	All Ages	68 (U/L)
SGPT (ALT)	8 (10.8%)	8 (12.9%)	All Ages	68 (U/L)

[1] Number (percent). Percentages relative to number of patients with test results in respective treatment group.

Electrolytes

Summary statistics for electrolyte concentrations (sodium, potassium, bicarbonate, and chloride) at Baseline, Last Visit, and for change from Baseline to Last Visit, are presented in Table 34. Mean and median electrolyte values at Baseline and Last Visit were normal in both treatment groups, and no meaningful trends in electrolyte concentration were observed during the study.

Table 34 Electrolyte Results - Safety Population

Analyte	Statistic	hGH05			Untreated		
		Baseline	Last Visit	Change	Baseline	Last Visit	Change
Sodium	n	73	74	73	61	62	61
(mmol/L)	Mean	139.0	138.3	-0.7	140.0	138.3	-1.8
	SD	6.4	2.0	6.0	2.2	2.1	2.6
	Median	140.0	138.0	-2.0	140.0	138.0	-2.0
	Minimum	105.0	134.0	-11.0	136.0	134.0	-8.0
	Maximum	149.0	142.0	29.0	147.0	145.0	5.0
Potassium	n	73	74	73	60	62	60
(mmol/L)	Mean	4.17	4.27	0.11	4.17	4.15	-0.02
	SD	0.37	0.27	0.40	0.28	0.25	0.34
	Median	4.10	4.20	0.10	4.20	4.15	0.00
	Minimum	3.10	3.50	-0.80	3.50	3.70	-0.90
	Maximum	5.20	5.00	1.10	4.90	4.70	1.00
Bicarbonate	n	73	74	73	61	62	61
(mmol/L)	Mean	23.00	22.55	-0.47	22.85	22.04	-0.86
	SD	3.28	2.51	4.05	2.53	2.58	3.61
	Median	22.50	22.35	-0.20	22.70	21.95	-0.50
	Minimum	16.20	17.40	-9.30	14.90	15.60	-7.80
	Maximum	31.10	28.80	8.40	28.10	27.70	9.10
Chloride	n	73	74	73	61	62	61
(mmol/L)	Mean	106.2	103.8	-2.5	107.8	104.7	-3.1
	SD	5.2	2.5	5.1	2.9	3.2	3.8
	Median	107.0	104.0	-3.0	108.0	105.0	-3.0
	Minimum	83.0	97.0	-12.0	100.0	98.0	-12.0
	Maximum	114.0	109.0	15.0	114.0	113.0	5.0

Hematology

Summary statistics for selected hematology variables (hemoglobin, hematocrit, RBC, WBC) at Baseline, Last Visit, and for change from Baseline to Last Visit, are presented in Table 35. Mean and median values at Baseline and Last Visit were normal for selected variables in both treatment groups, and no meaningful trends were observed during the study. No patients in either treatment group had values above the clinically significant cut point for these variables.

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Table 35 Hematology Test Results - Safety Population

Analyte	Statistic	hGH05			Untreated		
		Baseline	Last Visit	Change	Baseline	Last Visit	Change
Hemoglobin	n	72	74	72	60	61	59
[mmol/L(Fe)]	Mean	8.54	8.44	-0.09	8.57	8.60	0.02
	SD	0.63	0.65	0.50	0.52	0.49	0.45
	Median	8.55	8.45	-0.06	8.65	8.57	0.02
	Minimum	6.50	6.15	-1.67	7.00	7.64	-1.12
	Maximum	10.20	9.75	1.09	9.63	10.06	1.03
Hematocrit	n	71	74	71	59	61	58
(proportion of whole	Mean	0.40	0.40	-0.01	0.40	0.41	0.00
blood volume)	SD	0.03	0.03	0.03	0.03	0.02	0.03
	Median	0.40	0.39	0.00	0.40	0.40	0.00
	Minimum	0.32	0.34	-0.09	0.34	0.36	-0.05
	Maximum	0.50	0.48	0.08	0.47	0.47	0.06
Erythrocyte Count (RBC)	n	72	74	72	60	61	59
(10^{12}/L)	Mean	4.77	4.60	-0.16	4.75	4.70	-0.05
	SD	0.41	0.39	0.26	0.37	0.32	0.25
	Median	4.80	4.60	-0.20	4.70	4.70	-0.10
	Minimum	3.70	3.90	-0.80	3.90	4.10	-0.60
	Maximum	6.50	6.10	0.40	5.70	5.70	0.40

Note: No patient was found to have a WBC value greater than the clinically significant upper cut point (20 x 10^9/L).

Table 35 Hematology Test Results - Safety Population (Cont'd)

Analyte	Statistic	hGH05			Untreated		
		Baseline	Last Visit	Change	Baseline	Last Visit	Change
White Blood Cell Count (WBC)	n	72	74	72	60	61	59
(10^9/L)	Mean	6.66	5.97	-0.67	6.23	6.29	-0.01
	SD	1.89	1.79	2.15	1.93	1.95	2.19
	Median	6.48	5.64	-0.47	5.96	5.93	-0.01
	Minimum	3.43	3.48	-6.74	1.79	2.20	-5.41
	Maximum	12.16	11.99	5.11	13.07	14.40	10.65

Note: No patient was found to have a WBC value greater than the clinically significant upper cut point (20 x 10^9/L).

Urinalysis

No meaningful differences were observed between the Humatrope group and the Untreated group for any urinalysis parameters.

Thyroid Function

Summary statistics for selected thyroid function tests (total T4 concentration by RIA, TSH activity) at Baseline, Last Visit, and for change from Baseline to Last Visit, are presented in Table 36. Mean and median total T4 concentrations were normal at Baseline and Last Visit in both treatment groups. Mean and median TSH values were normal at Baseline and Last Visit for Humatrope-treated patients, and at Baseline for Untreated patients. The Untreated group had a slightly elevated mean TSH value at Last Visit but a normal median value.

The numbers of patients with at least one value outside the clinically significant cut points for T4 or TSH are presented in Table 37. A high proportion of patients in both treatment groups had T4 values that fell below the assigned lower cut point. This high number in part reflects the fact that the cut point was chosen conservatively (93 nmol/l) in order not to miss patients with potentially significant values. In addition, age-specific cut points were not assigned, and a number of older patients who had values below this cut point may have had normal values for age. Of particular note is the fact that the proportion of Untreated patients with values below the assigned cut point was similar to the proportion of Humatrope-treated patients. Furthermore, while the number of Humatrope-treated patients with T4 values below the defined cut point is high it should be noted that only three Humatrope-treated patients had elevated TSH values (>10 mU/L). This finding indicates that the majority of Humatrope-treated patients with T4 concentrations below the lower clinically significant cut point did not have primary hypothyroidism. It is of note that in fact more patients in the Untreated group than the Humatrope group had elevated TSH (10 versus 3).

Table 36 Thyroid Function Test Results - Safety Population

Analyte	Statistic	hGH05			Untreated		
		Baseline	Last Visit	Change	Baseline	Last Visit	Change
T4	n	74	74	74	60	62	60
(nmol/L)	Mean	107.4	126.9	19.5	109.5	130.0	22.2
	SD	18.1	29.2	30.8	24.9	34.6	34.1
	Median	106.5	124.0	16.0	104.0	126.5	13.0
	Minimum	69.0	79.0	-45.0	72.0	58.0	-51.0
	Maximum	161.0	215.0	93.0	203.0	212.0	135.0
TSH	n	74	74	74	60	62	60
(mU/L)	Mean	3.25	2.80	-0.45	3.47	4.54	1.13
	SD	1.30	1.53	1.92	3.12	12.94	13.79
	Median	3.20	2.50	-0.40	3.15	2.60	-0.00
	Minimum	0.60	0.20	-5.20	0.20	0.10	-24.00
	Maximum	6.70	9.90	6.90	24.50	104.10	102.60

Note: Reference range for T4 from Scicor, Inc. is 93-201 nmol/L. Reference range for TSH from Scicor, Inc. is 0.32-5.00 mU/L.

Table 37 **Thyroid Function Test Results: Number of Patients with at Least One Value Outside the Clinically Significant Cut Points - Safety Population**

Analyte	Lower[1]		Upper[2]		Age Range (Years)	Clinically Significant Lower Cut Point	Clinically Significant Upper Cut Point
	hGH05	Untreated	hGH05	Untreated			
T4	54 (73.0%)	38 (61.3%)	2 (2.7%)	4 (6.5%)	All Ages	93 (nmol/L)	201 (nmol/L)
TSH	--	--	3 (4.1%)	10 (16.1%)	All Ages	---	10 (mU/L)

[1] Indicates number (percent) below the clinically significant lower cut point. Percentages relative to number of patients with test results in respective treatment group.

[2] Indicates number (percent) above the clinically significant upper cut point. Percentages relative to number of patients with test results in respective treatment group.

Glucose Homeostasis

Summary statistics for hemoglobin A_{1C}, and for fasting and two-hour postprandial glucose and insulin concentrations at Baseline, Last Visit, and for changes in these variables from Baseline to Last Visit, are presented in Table 38. Mean and median hemoglobin A_{1C} levels were normal at Baseline and Last Visit in both treatment groups, as were fasting glucose levels. Assessment of two-hour postprandial glucose and fasting and two-hour postprandial insulin levels were performed at post-baseline visits on an as-needed basis as determined by the investigator. Therefore, very little data were available in either treatment group for fasting insulin or two-hour postprandial insulin at Baseline or Last Visit or for changes from Baseline in these variables. Mean and median values for fasting and two-hour postprandial insulin concentrations were normal at last visit in both treatment groups. No statistically significant differences between treatment groups in mean change from baseline to last visit for fasting glucose, fasting insulin, or hemoglobin A_{1C} were observed.

No meaningful differences between treatment groups in the numbers of patients with values above the clinically significant cut points for glucose homeostasis variables were observed during the study.

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Table 38 **Modified Glucose Tolerance Test Results - Safety Population**

Analyte	Statistic	hGH05			Untreated			P-value[1]
		Baseline	Last Visit	Change	Baseline	Last Visit	Change	
Glucose	n	73	74	73	61	62	61	0.790
(fasting)	Mean	4.6	4.5	-0.1	4.5	4.3	-0.2	
(mmol/L)	SD	0.6	0.5	0.7	0.6	0.5	0.6	
	Median	4.7	4.5	-0.1	4.4	4.4	-0.2	
	Minimum	3.3	3.2	-2.8	2.7	3.1	-2.1	
	Maximum	6.6	5.9	1.7	6.5	5.3	1.4	
Glucose	n	-	17	-	1	16	-	
(2-hr postprandial)	Mean	-	4.8	-	3.9	4.8	-	
(mmol/L)	SD	-	0.5	-	-	0.9	-	
	Median	-	4.8	-	3.9	4.7	-	
	Minimum	-	4.1	-	3.9	3.6	-	
	Maximum	-	6.0	-	3.9	7.8	-	
Hemoglobin A_{1C}	n	72	73	71	60	60	58	0.488
(proportion of Total	Mean	0.049	0.047	-0.002	0.048	0.048	0.000	
Hemoglobin)	SD	0.007	0.012	0.013	0.004	0.008	0.007	
	Median	0.047	0.049	0.001	0.048	0.050	0.001	
	Minimum	0.036	0.000	-0.051	0.033	0.001	-0.050	
	Maximum	0.100	0.058	0.010	0.055	0.056	0.009	

* Statistically significant ($p \leq 0.050$).

[1] For fasting Insulin, p-value is for comparison of Last Visit means between the treatment groups. For fasting Glucose and Hemoglobin A_{1C}, p-value is for comparison of Change from Baseline at Last Visit means between the treatment groups.

Note: Reference range from Scicor, Inc. for fasting glucose is 3.9-6.4 mmol/L. Reference range from Guthrie et al. (1973) for 2-hr postprandial glucose is 3.0-7.8 mmol/L. Reference range for hemoglobin A_{1C} from Scicor, Inc. is 0.042-0.112.

Note: Fasting and 2-hr postprandial Insulin and 2-hr postprandial Glucose were analyzed only if clinically indicated.

Table 38 **Modified Glucose Tolerance Test Results - Safety Population (Cont'd)**

Analyte	Statistic	hGH05			Untreated			P-value[1]
		Baseline	Last Visit	Change	Baseline	Last Visit	Change	
Insulin	n	1	18	1	-	14	-	0.132
(fasting)	Mean	93.0	50.3	-57.0	-	31.8	-	
(pmol/L)	SD	-	33.6	-	-	17.1	-	
	Median	93.0	36.0	-57.0	-	29.0	-	
	Minimum	93.0	14.0	-57.0	-	14.0	-	
	Maximum	93.0	144.0	-57.0	-	72.0	-	
Insulin	n	-	16	-	1	13	-	
(2-hr postprandial)	Mean	-	82.4	-	<14.0	75.0	-	
(pmol/L)	SD	-	59.8	-	-	142.7	-	
	Median	-	61.0	-	<14.0	36.0	-	
	Minimum	-	13.0	-	<14.0	7.0	-	
	Maximum	-	201.0	-	<14.0	545.0	-	

* Statistically significant ($p \leq 0.050$).

[1] For fasting Insulin, p-value is for comparison of Last Visit means between the treatment groups. For fasting Glucose and Hemoglobin A_{1C}, p-value is for comparison of Change from Baseline at Last Visit means between the treatment groups.

Note: Reference range from Scicor, Inc. for fasting insulin is 21-251 pmol/L. Reference range from Guthrie et al. (1973) for 2-hr postprandial insulin is 158-550 pmol/L. This reference range for 2-hr postprandial insulin represents 10-90th percentile according to the study of Guthrie et al. (1973).

Note: Fasting and 2-hr postprandial Insulin and 2-hr postprandial Glucose were analyzed only if clinically indicated.

Table 39 **Modified Glucose Tolerance Tests: Number of Patients with at Least One Value Above the Clinically Significant Cut Point - Safety Population**

Analyte	hGH05[1]	Untreated[1]	Clinically Significant Upper Cut Point
Glucose (fasting)	3 (4.1%)	1 (1.6%)	6.4 (mmol/L)
Glucose (2-hr postprandial)	0	0	8.3 (mmol/L)
Hemoglobin A_{1C}	0	0	0.068 (proportion of Total Hemoglobin)
Insulin (fasting)	1 (5.0%)	0	251 (pmol/L)
Insulin (2-hr postprandial)	3 (17.6%)	1 (6.3%)	400 (pmol/L)

[1] Number (percent). Percentages relative to number of patients with test results in respective treatment group.

Note: Fasting and 2-hr postprandial Insulin and 2-hr postprandial Glucose were analyzed only if clinically indicated.

Special Tests: Anti-GH Binding Capacity

A listing of patients with positive anti-GH binding capacity (> 0.02 mg/L) is presented in Table 40. Only two patients had positive anti-GH binding values. These occurred during the first year of the study for Patient 116-2615 and at the end of the second year of the study for Patient 115-2117. None of these values approached 1.00 ng/mL, and neither patient experienced a decrease in growth velocity associated with the presence of anti-GH antibodies.

Table 40 **Positive Anti-GH Binding Capacity (mg/L) by Patient and Visit**

	Visit Number								
Patient	1	2	3	4	5	6	7	8	9
115-2117									0.07
116-2615	0.17	0.04	0.77	0.62	0.03				

Note: A positive value is defined as any value greater than 0.02 mg/L.
Note: No positive values were observed after Visit 9 for any patient.

Discussion of Clinical Laboratory Evaluation

In this study, Humatrope did not appear to have a clinically meaningful effect on blood chemistry, hematology, or urinalysis variables, thyroid function, or glucose homeostasis. A slightly greater proportion of Humatrope-treated patients had elevated alkaline phosphatase and creatine kinase values compared to Untreated patients, likely reflecting increased growth in this group compared to Untreated patients. While the number of Humatrope-treated patients with T4 values below the defined cut point is high it should be noted that only three Humatrope-treated patients had elevated TSH values (>10 mU/L). This finding indicates that the majority of Humatrope-treated patients did not have primary hypothyroidism. In addition, a similar proportion of patients in the Untreated group also had T4 values below the assigned cut point. Relatively low levels of anti-GH binding capacity were observed in two Humatrope-treated patients during the first and second year of the study, respectively, but were not associated with a decrease in growth velocity for these patients.

Overall Summary

Primary Efficacy Variables: Protocol Completers (Patients Achieving Final Height)

1. For patients who met Final Height criteria (and those considered by investigators to have achieved near Final Height), the group that received Humatrope achieved mean Final Height of approximately 146 cm, 4.0 cm greater than the mean Final Height of approximately 142 cm for the Untreated group. This difference was statistically significant.

2. Although the mean Final Height of patients treated with Humatrope remained below that of age-matched normal females (-2.54 SDS [NCHS]), it was significantly greater than that of the Untreated group (-3.11 SDS [NCHS]).

3. Both Humatrope-treated and Untreated patients in this study achieved mean Final Height greater than the mean for the reference Turner syndrome population reported in the study of Lyon et al. (+1.05 SDS and +0.49 SDS, respectively). The Final Height SDS [Lyon] of the Humatrope-treated patients was significantly greater than that of the Untreated patients.

4. The differences between the two treatment groups remained statistically significant when Final Height and Final Height SDS [NCHS] were adjusted for midparental height.

Secondary Efficacy Variables

Height SDS [NCHS] and Height at Last Visit Adjusted for Bone Age were evaluated at the last visit at which a bone age X-ray was obtained for all patients who were randomized and remained in the study for 180 days (intent-to-treat population).

1. Compared with the normal female reference standard [NCHS] there was a significant difference in mean Last Visit height SDS between Humatrope-treated and Untreated patients in this study. Humatrope-treated patients achieved mean height at Last Visit more than 1 SD closer to that of the normal population than Untreated patients (-2.37 SDS versus -3.69 SDS).

2. Even after adjustment for a possible effect of a slightly more advanced bone age in the Humatrope-treated group, the mean height at Last visit remained significantly greater for the Humatrope group (Adjusted Mean Height 140 cm versus 134 cm).

Other Efficacy Variables

1. When Height SDS [NCHS] and Height SDS [Lyon] were evaluated by years of treatment, patients receiving Humatrope showed greater progressive height gains compared to Untreated patients relative to both the normal female and Turner syndrome reference standards. That is, patients receiving Humatrope treatment made a greater progression toward normal height than did Untreated patients and on average exceeded the mean height of the Turner syndrome reference population.

2. The mean growth rate in response to Humatrope was high for the first two years of the study, then declined somewhat, as is commonly seen during growth hormone therapy for a variety of conditions, but remained greater than 1 SD above the reference population mean [Ranke] for the first four years of the study. Notably, the mean growth velocity of the Humatrope-treated patients was greater than that of the Untreated patients throughout this period and at Last Visit. The mean growth velocity of the Untreated group was slightly greater than that of the reference Turner syndrome population [Ranke] in the first three years of the study. Not surprisingly, during the latter years of the study the growth rate of both groups of patients declined, however patient numbers were fairly small at these timepoints.

3. There was a trend for Bone Age to advance slightly more rapidly in the Humatrope group; however, this difference was not significant and is probably not clinically important.

Safety

1. There was one death (patient in Untreated group) in this study. Two (3%) of the 74 patients randomized to the Humatrope group and 1 (2%) of the 62 patients in the Untreated group prematurely discontinued from the study due to an adverse event. All patients in the Humatrope group, and almost all patients in the Untreated group, reported at least one treatment-emergent event, a finding not unexpected in a pediatric population. Surgical procedures, otitis media, ear disorder, and accidental overdose were experienced by a higher percentage of patients in the Humatrope group than in the Untreated group. For these four events, the difference in incidence between the Humatrope group and the Untreated group was statistically significant. Rhinitis, headache, flu syndrome, fever, increased cough, ear pain, pain, accidental injury, sinusitis, and hypothyroidism were also reported by a higher percentage of patients in the Humatrope group than in the Untreated group, although none of these differences was statistically significant. In contrast, nausea and vomiting was observed in a slightly higher percentage of patients in the Untreated group than in the Humatrope group.

A high frequency of otitis media and other ear disorders was noted in the Humatrope-treated patients in this study. It is well recognized that patients with Turner syndrome have a higher rate of otitis media, deafness, and other ear disorders than girls of similar age who do not have Turner syndrome. The relationship between the apparent increase in frequency of ear problems in Humatrope-treated patients in this study is interesting, however its relevance is unclear. One possible explanation is that there is a mild change in the anatomy of the middle ear in response to Humatrope-induced changes in growth of membranous bones of the face and skull; however, no abnormal skull growth has been demonstrated in response to hGH therapy in other studies.

2. In this study, Humatrope did not appear to have a clinically meaningful effect on blood chemistry, hematology, or urinalysis variables, thyroid function, or glucose homeostasis. The slightly greater proportion of Humatrope-treated patients with alkaline phosphatase and creatine kinase concentrations above the assigned cut points may reflect increased growth in this group compared to Untreated patients. Relatively low levels of anti-GH binding capacity were observed in two Humatrope-treated patients during the first and second year of the study, respectively, but were not associated with a decrease in growth velocity for these patients.

Conclusions

In this study of 140 patients treated for an average duration of four years, with a high degree of compliance, the Humatrope-treated protocol completers (n=27) had a significantly greater mean Final Height than Untreated protocol completers (n=19). The mean Final Height of the protocol completers in the Humatrope group is approximately 146 cm. Although this is more than 2.0 SDS below the mean for normal females, it should be noted that this height is more than 1.0 SDS greater than the age-matched mean height of patients with Turner syndrome in the study of Lyon et al. Second, it is likely that for many of these patients true final height has yet to be achieved. It is well established that patients with Turner syndrome have a very prolonged period of slow linear growth during late teenage years, many of these patients completing their growth as late as 19 or 20 years of age. Thus, although the protocol completers in this study were growing slowly (most <2.0 cm/yr), it is likely that they will continue to grow for some time to come and achieve adult height greater than the height referred to in this study as Final Height.

Notably, events commonly associated with growth hormone therapy such as edema, hyperglycemia, hypothyroidism, and joint/bone complaints (coded as bone disorder) were not observed to occur more frequently in Humatrope-treated than in Untreated patients in this study. However, as described in detail above, ear disorders were notably more common in the Humatrope group, as were surgical procedures. Previous studies of jaw growth in Turner syndrome failed to demonstrate significant overgrowth of the jaw in

treated versus untreated patients. Thus the relationship between hGH treatment and ear disorders is unclear.

In conclusion, Humatrope treatment of patients with Turner syndrome enhances final height when compared with untreated controls, and does not pose a significant risk with respect to glucose homeostasis, or thyroid function.

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This represents an interim analysis of an ongoing, double-blind, parallel, randomized, placebo-controlled (first 18-months) dose-response study in patients with Turner syndrome. At the admission visit, patients were evaluated for compliance with meeting the entry criteria for the study. Eligible patients were randomly assigned to one of five treatment groups: (1) Humatrope (0.09 mg/kg/dose) with placebo estrogen, (2) Humatrope (0.09 mg/kg/dose) with low dose estrogen, (3) Humatrope (0.12 mg/kg/dose) with placebo estrogen, (4) Humatrope (0.12 mg/kg/dose) with low dose estrogen, or (5) placebo Humatrope with placebo estrogen. Humatrope or its placebo equivalent was administered subcutaneously three times per week up to and including Visit 25; the dose was halved and given six times per week after Visit 25. Low dose estrogen (ethinyl estradiol) or its placebo equivalent is given orally on a daily basis beginning in patients ≥ 8 years of age and weighing at least 20 kg. The dosage of ethinyl estradiol varies from 0 ng/kg to 200 ng/kg according to the patient's age and weight and whether she receives active or placebo estrogen. Following an initial 18-month treatment period, the treatment group with the lowest mean growth velocity was reassigned to receive one of the other four treatment regimens; none of the treatment groups was unblinded at that time.

The primary efficacy variable in this study is Height SDS [NCHS] (a height standard deviation score based on a normal female reference population, National Center for Health Statistics Growth Charts, 1976). Statistical analyses are performed on data obtained for all patients in the intent-to-treat population. The efficacy of Humatrope is determined by a comparison of the Height SDS at Last Visit for the pooled Humatrope 0.12 mg/kg/dose groups (Humatrope 0.12 mg/kg/dose plus placebo estrogen and Humatrope 0.12 mg/kg/dose plus low dose estrogen) to the pooled Humatrope 0.09 mg/kg/dose groups (Humatrope 0.09 mg/kg/dose plus placebo estrogen and Humatrope 0.09 mg/kg/dose plus low dose estrogen).

Secondary efficacy variables include height at Last Visit for the intent-to-treat population, and Final Height for protocol completers. Final Height is defined in this analysis as the actual height at the last available visit for those patients identified by the investigator as protocol completers. The criteria defined by the protocol for completion were a growth rate of less than 2 cm/year and a bone age of ≥ 15 years. In addition to those patients who fulfilled these criteria, patients who in the estimation of individual investigators came close to meeting these criteria were also evaluated. Thus, in this analysis, the term "Final Height" more accurately represents "near final height."

The risks and benefits associated with either dose of Humatrope therapy or with placebo injections in patients with Turner syndrome are determined from safety summaries of deaths, serious adverse events, treatment-emergent events (also referred to as treatment-emergent signs and symptoms), and laboratory results.

Objectives

Primary Objectives

The primary objectives of this study were to determine the efficacy of Humatrope in promoting linear growth in patients with Turner syndrome and to determine the efficacy of low dose estrogen as adjunctive therapy in promoting linear growth in patients with Turner syndrome.

Secondary Objective

The secondary objective of this study was to determine the antigenicity and other variables of clinical safety of Humatrope in patients with Turner syndrome.

Investigational Plan

Summary of Study Design

In this double-blind, randomized, placebo-controlled, parallel study, eligible patients with Turner syndrome were randomly assigned to one of five treatment groups: (1) Humatrope (0.09 mg/kg/dose) with placebo estrogen [hGH09/PLA]; (2) Humatrope (0.09 mg/kg/dose) with low dose estrogen [hGH09/LDE]; (3) Humatrope (0.12 mg/kg/dose) with placebo estrogen [hGH12/PLA]; (4) Humatrope (0.12 mg/kg/dose) with low dose estrogen [hGH12/LDE]; or (5) placebo Humatrope with placebo estrogen [PLA/Switch].

After completion of the initial 18-month treatment period, patients were allowed to enter an extension phase. During the ongoing extension period, the therapy remained unchanged for four treatment groups which were found, upon blinded analysis, to be more responsive than the fifth group. Patients in the least responsive treatment group were reassigned to one of the remaining four treatment groups [hGH12/PLA].

Each age category (5, 6, and 7 years; 8 and 9 years; 10 and 11 years; 12 years and older) was balanced with respect to treatment groups.

Discussion of Design and Control

Randomization was chosen to ensure that there would be no bias in the assignment of patients to treatment and control groups. Double-blinding was chosen to ensure that the patients' and the physicians' expectations would not influence the assessment of patients' growth. A placebo control was chosen to maintain the double-blind design and to control for possible placebo effects on growth.

None of the treatment groups was unblinded at the time of the reassignment of therapy (at the end of the initial 18-month period). Changing the study drugs for the least responsive treatment group allowed for the determination of dose-response efficacy and monitoring for drug safety.

Investigator Information

This multicenter study involves 50 sites at which experienced pediatric endocrinologists are the principal investigators. The cutoff date of the study was 8 February 1996.

Study Population

Entry Criteria

Inclusion Criteria

The inclusion criteria were as follows:

- Patients with Turner syndrome, (treated as outpatients);
- Patients who had chronological age ≥5 years;
- Patients who were prepubertal, Tanner Stage I-B (breast);
- Patients with growth velocities less than 6 cm/year with heights being less than the tenth percentile, as compared to chronologically age-matched controls;
- Patients who had an accurate growth measurement available six months prior to entry for calculation of prestudy growth velocity; Pretreatment growth measurements were obtained during a time when the patient was not receiving a potential growth-promoting agent (e.g., growth hormone, androgen, estrogen);
- Patients, if judged to be thyroxine deficient, had received levothyroxine replacement therapy resulting in normal thyroid function test results over the 3-month period prior to enrollment;
- Parents or legal guardians of patients signed an informed consent document. Assent was obtained from all patients competent to understand the protocol. Local Institutional Review Board (IRB) requirements applied. Each investigator gave written assurance that the consent document and the IRB procedures were consistent with 21 Code of Federal Regulations (CFR) parts 50 and 56. In addition, Eli Lilly and Company personnel reviewed the signed consent documents and ensured that IRB approval had been obtained.

Exclusion Criteria

The exclusion criteria were as follows:

- Patients who had received any form of human growth hormone within the three months preceding the study, or who had received a cumulative course of growth hormone therapy totaling greater than 12 months;
- Patients who had been exposed to exogenous estrogens while in utero; patients who had been treated with estrogens or androgens within the three months prior to study entry or who had received a cumulative course of estrogen or androgen therapy totaling greater than 12 months;
- Patients who had any Y component in their chromosome analysis;

- Patients who had a bone age >12 years;
- Patients who had clinically significant cardiac, pulmonary, gastrointestinal, hepatic, or renal disease, or had presence or history of any malignancy;
- Patients who had significant hematuria or proteinuria in pretherapy evaluation;
- Patients who had diabetes mellitus;
- Patients who had any active chronic infection (e.g., tuberculosis);
- Patients who were taking amphetamines or any other drugs (e.g., Ritalin® (methylphenidate), Cylert® (pemoline)) considered as potentially interfering with growth hormone secretion or action;
- Patients who were poor medical, psychological, or psychiatric risks for whom, in the opinion of the investigator, therapy with an investigational drug was unwise;
- Patients whose parents were substance abusers, or those who came from homes in which appropriate emotional development might be limited;
- Patients who could not be seen on the schedule required by the protocol.

Disease Diagnostic Criteria

- All patients were females with Turner syndrome who were diagnosed on the basis of karyotype and elevated follicle stimulating hormone (FSH) (for chronological age and Tanner Stage I) where appropriate.
- Estrogen Dosage

Each patient was assigned oral and injectable study drug kit numbers. Kit numbers were determined by a computer randomization program. To balance treatment groups with respect to age, blocks of kit numbers representing the five treatments were divided into four groups, arbitrarily designated for each of the four possible age groups (5, 6, and 7 years; 8 and 9 years; 10 and 11 years; ≥12 years). As patients enrolled in the study, patients were assigned to the next available kit number in the appropriate group of kits for the age category.

The only patients who changed treatment group assignment were those initially assigned to the treatment group found in the first interim analysis to be least responsive (subsequently determined to be the group receiving placebo Humatrope with placebo estrogen, designated the PLA/Switch group). For the extension phase, (after 18 months), all patients in this treatment group were reassigned to the treatment group receiving Humatrope 0.12 mg/kg/dose with placebo ethinyl estradiol (hGH12/PLA) by the Clinical Research Physician. To continue treatment of all groups in a double-blind design, all patients received new study drug kits at the start of the first extension period (Visit 7).

During the extensions patients continue to receive study drug material (kits) in the same manner as in the first 18-month treatment period.

Each vial of injectable study drug contains sufficient material for a single dose for a patient weighing 50 kg. The investigative sites are provided with a table of weight-based injection volumes to maintain blinding but ensure accurate dosing. Because the vials contain either 0 mg, 4.5 mg, or 6.0 mg of Humatrope, the actual dose is 0 mg/kg/dose, 0.09 mg/kg/dose, or 0.12 mg/kg/dose. The prescribed dose was injected subcutaneously three times per week up to and including Visit 25. During the period up to and including Visit 25, any two doses were injected on days separated by at least one nontreatment day. After Visit 25, the dose of Humatrope is halved and injected six times per week. The total weekly dose of Humatrope is approximately 0.27 mg/kg for the hGH09 group and 0.36 mg/kg for the hGH12 group. A patient's weekly dosage does not exceed three vials of study drug. The contents of a reconstituted vial are not used if more than 14 days has elapsed since its dilution. Between administrations, the vials (diluted or undiluted) are stored at 2°C to 8°C and protected from light.

Oral study drug material (ethinyl estradiol or placebo ethinyl estradiol) is administered according to chronological age and body weight. The dose of oral study drug material was assigned according to the patient's chronological age at the admission visit (Visit 1). The dose of oral study drug is not increased as the patient's age increases, although the dosage is adjusted for weight changes at each visit, if necessary. The following exceptions were noted:

- No oral study drug material was administered to patients less than 8 years old, or weighing <20 kg.
- Patients 8 years old or older at Visit 1 but weighing less than 20 kg began oral study drug treatment at Visit 7 (18 months) according to the patient's age at Visit 1 and weight at Visit 7, if >20 kg. Dosage is adjusted for weight changes at each subsequent visit, if necessary.
- Patients less than 8 years old at Visit 1 began oral study drug at Visit 7 (18 months) or Visit 13 (36 months): Therapy began at the visit at which the patient was at least 8 years old and weighed at least 20 kg. The dosage of oral study drug was assigned according to the patient's age at the visit she began oral study drug therapy (Visit 7 or 13 only) and is subsequently adjusted for weight changes, as necessary.

The following dosing requirements for oral study drug apply:

- Patients at least 8 years old but not yet 10 years old receive one tablet per 20 kg of body weight, with no oral study drug administered if the patient weighed less than 20 kg at the admission visit (Visit 1). This dose is equal to approximately 25 - 50 ng of ethinyl estradiol per kg; (0 ng/kg for patients receiving placebo).

- Patients at least 10 years old but not yet 12 years old receive one tablet per 10 kg of body weight. This dose is equal to approximately 67 - 100 ng of ethinyl estradiol per kg (0 ng/kg for patients receiving placebo). No oral study drug is administered if patient weighed less than 20 kg at the admission visit (Visit 1).
- Patients at least 12 years old receive one tablet per 5 kg of body weight. This dose is equal to approximately 160 - 200 ng of ethinyl estradiol per kg (0 ng/kg for patients receiving placebo).

The blinded oral study drug therapy is discontinued when patients are prescribed, by the investigator or their own physician, open-label estrogen to induce breast development or estrogen/progesterone therapy to induce menstrual cycling. This was permitted after 13.5 years of age.

To allow uniform laboratory assessment and observation of injection technique, visits subsequent to the initial visit up to and including Visit 25, were scheduled to occur no sooner than 24 hours after an injection and no sooner than 12 hours after oral study drug administration.

Concomitant Therapy

Patients who are at least 13.5 years old, who have completed the initial 18 months of the study, and who have no breast development can begin feminization with an estrogen preparation as prescribed by their physician. The patients are to provide the prescribed medication.

After the first 18 months of the study, patients who are older than 13.5 years of age and who, during pubertal development or estrogen treatment, have late Tanner Stage III or IV breast development or experience breakthrough bleeding can be prescribed estrogen/progesterone therapy for the purposes of inducing menstrual cycling. These medications are obtained locally by the patients themselves and are not provided as part of the study.

Any other therapy prescribed by the patient's physician or investigator during the course of the study is recorded on the concomitant medication clinical report form page.

Efficacy and Safety Evaluation

The schedule of safety and efficacy measurements is presented in Table of Master Schedule of Procedures. Patients are assessed at three-month intervals for the first six years and for six-month intervals thereafter until final height is reached.

Master Schedule of Procedures

Visit:	1	2	3	4	5	6	7	8	9	(10	11	12	13)[a]
Procedure Study Month	0	3	6	9	12	15	18	21	24	27	30	33	36
Medical History	X												
Interim History		X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination:	X	X	X	X	X	X	X	X	X	X	X	X	X
Height	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X
Draw Blood[b] for:													
Blood Chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X[b]
Hematologic Tests	X	X	X	X	X	X	X	X	X	X	X	X	X[b]
Thyroid Function	X	X	X	X	X	X	X	X	X	X	X	X	X[b]
Hemoglobin A_{1C}	X	X	X	X	X	X	X	X	X		X	X	X[b]
FSH, LH, Estradiol[d]	X		X		X		X						X[c]
Lipids	X		X		X		X		X				X[b]
Fasting Glucose and Insulin	X	X	X		X		X		X		X		X[b]
2-hr Postprandial Glucose with Insulin	X		X		X		X		X		X		X[b]
Somatomedin-C (IGF-I)	X	X	X	X	X	X	X		X				X[b]
Growth Hormone Antibody	X	X	X	X	X	X	X		X				X[b]
E. Coli Polypeptide Antibody	X	X	X	X	X	X	X		X				X[b]
Urinalysis	X	X	X	X	X	X	X	X	X		X		X[b]
X-rays for Bone Age	X		X		X		X		X				X[b]
Summary[c]													

[a] Subsequent visits follow this same yearly schedule pattern (e.g., Visit 14 same as Visit 10, Visit 15 same as Visit 11, Visit 16 same as Visit 17, etc.), up to Visit 25 where visit interval changes to six months.
[b] Performed at yearly intervals or earlier if the patient leaves the study.
[c] Performed when the patient leaves the study.
[d] Data for these hormones are not analyzed in this report.

Efficacy Measures

Height determinations (without shoes, using a stadiometer) were made at Baseline and each subsequent visit thereafter. Each recorded height measurement represents the mean of three separate measurements.

Efficacy Criteria

Definitions

The safety population is defined as all randomized patients who took any study medication. The intent-to-treat population is defined as all randomized patients who have efficacy data at Visit 3 or beyond (scheduled 180 days after randomization). In the PLA/Switch group, patients must also have efficacy data at Visit 9 or beyond (scheduled 180 days after switch to Humatrope treatment at Visit 7). Protocol completers were identified by the investigator as those patients who fulfilled or almost fulfilled the criteria for achievement of Final Height.

Standard Deviation Score - The Standard Deviation Score (SDS) for a given variable for a given patient is derived by subtracting the age-matched population mean value for that variable from the patient's value. The value obtained is then divided by the age-matched population standard deviation.

Height SDS [NCHS]: Height SDS [NCHS] is a standard deviation score using as a reference standard the height of normal females at various chronological ages (NCHS Growth Charts 1976).

Height SDS [Lyon]: Height SDS [Lyon] is a standard deviation score using as a reference standard the height of females with Turner syndrome at various chronological ages (Lyon et al. 1985).

Final Height - Final height generally refers to the height attained at completion of linear growth. In this study the criteria used to define achievement of final height were bone age $\geq$ 15 years and growth velocity <2.0 cm/year. For the purposes of this interim analysis, patients whose bone age and growth velocity approached these criteria and were considered by individual investigators to have completed the protocol were analyzed. Thus in this study, the term Final Height, as it appears in tables and statistical analyses, refers both to patients who met Final Height criteria and to those who came close to this in the opinion of the investigator. The term Final Height as used in this report, refers more accurately to near final height.

Midparental Height: A gender adjusted average height of parents [(father's height minus 13 cm) plus mother's height]/2 (Tanner et al. 1975).

Growth Velocity - The rate of growth in cm/year as calculated from the difference between two height measurements divided by the time elapsed between those measurements.

Growth Velocity SDS [Ranke] - Growth Velocity SDS [Ranke] is a standard deviation score using as a reference standard growth velocity data for Turner syndrome at various chronological ages (Ranke et al. 1988).

Bone Age - Bone Age represents an estimate of skeletal maturation determined by comparison of a radiograph of the patient's left hand with known standards for skeletal

maturation [in this study, the Atlas of Skeletal Maturation by Greulich & Pyle (Greulich and Pyle 1959)].

Baseline Age Strata - Patients were identified as belonging to one of four Baseline age strata (5, 6, and 7 years; 8 and 9 years; 10 and 11 years; ≥12 years) according to their chronological age at a prestudy visit.

Chronological Age - Defined as [Visit Date - Birth Date]/365.25.

Efficacy Variables

The original protocol defined efficacy in terms of the change in growth rate during the study, compared with pretreatment growth rate. Growth rate in centimeters per year (cm/year) is calculated from the actual time between measurements during the study.

Pretreatment growth rate was defined by computing the rate of growth between a height measurement taken 6 - 12 months prior to Visit 1 and the height measurement taken at Visit 1. If a pretreatment height measurement was not available 12 months prior to Visit 1, then a measurement taken as remote to Visit 1 as possible (>6 months) was used in this computation. The growth rate was extrapolated to cm/year, realizing that shorter intervals between measurement points result in less reliable calculation of growth rate.

The change in growth rate as described above was evaluated as one of the efficacy variables. However, for the purposes of this interim analysis, three primary and secondary efficacy variables were evaluated.

All efficacy variables were evaluated by comparing pooled Humatrope dosage groups, for patients receiving 0.12 mg/kg/dose versus 0.09 mg/kg/dose (hGH12 versus hGH09). A secondary analysis, for primary and secondary efficacy variables only, examined the effect of low dose estrogen versus placebo estrogen. For these analyses, the data for both growth hormone dosage groups (hGH12 and hGH09) were pooled.

The following efficacy variables were evaluated:

- Primary Variable

  Height SDS at Last Visit: Height expressed in terms of height standard deviation scores using as a reference standard the NCHS normal female standard. Height SDS at Last Visit for all patients in the intent-to-treat population (defined in Section 3.10.2) is the variable for which a statistical comparison between the treatment groups is made.

- Secondary Variables

  Final (or near final) Height: the actual height measurement at the last available visit for those patients identified by the investigator as protocol completers. The criteria defined by the protocol were a growth rate of less than 2 cm/year and a bone age of ≥15 years. In addition to those who fulfilled these criteria, patients

who in the estimation of individual investigators came close to meeting these criteria and were designated as protocol completers were also evaluated.

Height (cm) at Last Visit Adjusted for Bone Age: for all patients in the intent-to-treat population, Height at the last visit at which a bone age X-ray was performed was adjusted for bone age. For some patients this visit differed from the actual Last Visit, since a bone age X-ray may not have been obtained at that time.

- Other Variables

  Other variables analyzed for the intent-to-treat population by years in study and at Last Visit include Height SDS [NCHS]; Height SDS [NCHS] Change from Baseline; Height SDS [Lyon]; Growth Velocity SDS [Ranke]; Bone Age; Bone Age Change from Baseline; and Bone Age/Chronological Age Ratio. A statistical comparison between treatment groups at Last Visit is made for each of the above variables.

Safety Measures

All adverse or treatment-emergent events experienced by patients during the course of this study were reported on clinical report forms at each visit. Each event was followed throughout the study or until it resolved. Alarming or significant adverse events were reported directly by telephone to the sponsor.

A complete list of laboratory tests is provided in Table

Table **Laboratory Tests**

BLOOD CHEMISTRY PANEL	URINALYSIS PANEL
Total Bilirubin	Appearance
Alkaline Phosphatase	Specific Gravity
GGT	pH
SGOT (AST)	Protein (Qualitative)
SGPT (ALT)	Glucose (Qualitative)
Urea Nitrogen	Ketones (Qualitative)
Creatinine	Bilirubin
Uric Acid	Urobilinogen
Inorganic Phosphate	Blood
Calcium	Nitrite
Total Protein	Leukocyte Esterase
Albumin	Microscopic:
Cholesterol	WBC per hpf
Creatine Kinase	RBC per hpf
	Casts per lpf
ELECTROLYTE PANEL	**THYROID PANEL**
Sodium	T4 by Radioimmunoassay
Potassium	T3 % Uptake
Bicarbonate	Free Thyroxine Index (FTI)
Chloride	TSH by Radioimmunoassay

Table **Laboratory Tests (Cont'd)**

HEMATOLOGY PANEL	GROWTH FACTORS
Hemoglobin	IGF-I (Somatomedin-C)
Hematocrit	
Erythrocyte Count (RBC)	ANTIBODY ASSAYS
MCV	Growth Hormone Antibody
MCH	ECP Antibody
MCHC	
White Blood Cell Count (WBC)	LIPID PANEL
Segmented Neutrophils	Cholesterol
Lymphocytes	Triglycerides
Monocytes	HDL
Eosinophils	LDL
Basophils	VLDL
Platelet Count	
Reticulocyte Count	GLUCOSE TOLERANCE PANEL
	Hemoglobin A_{1C}
SEX HORMONE PANEL	Glucose (Fasting and 2-hr postprandial)
Estradiol	Insulin (Fasting and 2-hr postprandial)
LH	
FSH	

Patient Disposition Criteria

Terminations

Study medication may be discontinued for any of the following reasons:

- Request of patient, parent, or guardian to stop the study drug;
- Decision of investigator to stop the study drug;
- Decision of sponsor to stop the study or a patient's participation in the study, even if final height was not achieved;
- Missing or opened labels from the patient's study drug materials, unless the label was opened for medical emergency;
- Attainment of final height, as defined by an annualized growth rate of less than 2.0 cm/year, based on at least six months of growth data, and bone age $\geq$15 years.

In the event that the study drug was discontinued for any reason, the patient was scheduled for a final visit, if at all possible. At this visit, the unused study drug was retrieved. The number of days the drug was taken were recorded on the clinical report

form, along with any adverse events, and the Summary clinical report form was also completed. Even if the patient was unable to schedule this visit, the current clinical report form and the Summary clinical report form were completed and all unused study drug was retrieved.

Qualifications for Analysis

The protocol designated that data collected from a patient might not be used for efficacy evaluation if any of the following occurred:

- Patient omitted three doses of injectable drug per week for more than one week, two doses per week for more than three weeks, or one dose per week for more than six weeks during a one-year period;
- Patient omitted more than 25% of oral study drug over a four-week period;
- Patient missed more than one office visit;
- Patient had more than one unevaluable visit.

If the interval between visits varied by more than 30 days from the schedule, an individual visit was considered unevaluable for efficacy.

Patients who discontinued the study prematurely were considered evaluable for efficacy if they completed at least 180 days of study drug therapy.

For the purposes of this report, patients had to fulfill one criterion to be included in the efficacy analysis, completion of 180 days of therapy (intent-to-treat population).

Patients were included in the analysis of safety if they were randomized and took any study medication (safety population).

Study Extensions

Extensions of therapy were made at the sole discretion of the sponsor.

Compliance

Compliance was assessed by evaluation of drug record cards. These cards were completed at home by the patients or parents and were periodically reviewed by the investigator or site personnel. The number of vials of injectable study drug used was reported at each follow-up visit on the clinical report forms. In addition, tablets of oral study drug remaining since the previous visit were returned at the next follow-up visit, and the tablets were counted and recorded.

Quality Assurance

Each investigator and on-site study coordinator was initially familiarized with the study procedure through a study start-up meeting. The sponsor also furnished each with a study instructional manual and a booklet summarizing information, principles, and US

regulatory requirements that Eli Lilly and Company believes to be helpful to investigators conducting the study *(Principles and Regulations of Clinical Investigation)*.

Each study site has been visited by the Lilly Clinical Research Coordinator (CRC) periodically before and during the study to review the status of the study. After patients were enrolled, each investigator was visited by Lilly personnel to review the completed clinical report forms.

Protocol Amendments

During the conduct of this protocol there were four protocol amendments [B9R-MC-GDCI(a), B9R-MC-GDCI(b), B9R-MC-GDCI(c), and B9R-MC-GDCI(d)]. The purpose of the first amendment [B9R-MC-GDCI(a), dated 25 August 1987; submitted to IND on 1 September 1987] was to add to the protocol determination of fasting and 2-hour postprandial glucose with simultaneous insulin measurements, FSH, LH, hemoglobin A_{1C}, VLDL, LDL, and HDL cholesterol. In addition, this amendment added to the exclusion criteria that patients with a history of intrauterine exposure to exogenous estrogens were excluded from study. Investigators were sent the first amendment to the protocol to their IRBs prior to enrolling patients into the study. The second amendment [Protocol B9R-MC-GDCI(b), dated 17 February 1989; submitted to IND on 2 March 1989] provided an 18-month extension to the protocol beyond the initial 18-month treatment period. The amendment also outlined procedures used to blindly assign the least responsive of the five treatment groups to one of the other four treatment groups, as patients entered the extension. The amendment was made prior to the first patient reaching the completion of the initial 18-month protocol. The third amendment [Protocol B9R-MC-GDCI(c), dated 6 September 1990; submitted to IND on 24 October, 1990] allowed patients to extend their therapy until achievement of final height. The fourth amendment [Protocol B9R-MC-GDCI(d), dated 10 September 1993; submitted to IND on 13 September 1993] primarily allowed for the acquisition of additional final height data on patients who discontinued the study prior to protocol completion.

Data Analysis Methods

This report represents an interim analysis of an ongoing, randomized, double-blind study. Data analyzed in this report include all clinical report forms received by the Lilly data management center as of 8 February 1996. The SAS® software system (version 6.09) (SAS Institute Inc. 1990) was used to perform all analyses. A p-value of 0.050 was considered statistically significant for all analyses.

The treatment groups into which patients were randomized are defined below:

hGH12/LDE - Humatrope (0.12 mg/kg/dose) with Low Dose Estrogen

hGH12/PLA - Humatrope (0.12 mg/kg/dose) with Placebo Estrogen

hGH09/LDE - Humatrope (0.09 mg/kg/dose) with Low Dose Estrogen

hGH09/PLA - Humatrope (0.09 mg/kg/dose) with Placebo Estrogen

PLA/Switch - placebo Humatrope with placebo estrogen for the first 18 months of the study then switched to hGH12/PLA for the completion of the study. (Patients and investigators were blinded to the details of the treatment both before and after the switch).

For most of the analyses, the treatment groups were pooled by either Humatrope dose, by low dose estrogen versus placebo estrogen treatment, or by receipt of Humatrope versus placebo injections within the first 18 months. The definitions of the pooled groups are as follows:

<u>Pooled by Humatrope Dose</u>

hGH12- hGH12/LDE, hGH12/PLA, PLA/Switch
hGH09- hGH09/LDE, hGH09/PLA

<u>Pooled by Humatrope versus Placebo injections within the first 18 months</u>

All Humatrope combined - hGH12/LDE, hGH12/PLA, hGH09/LDE, hGH09/PLA
Placebo Humatrope - PLA/Switch

<u>Pooled by Low Dose Estrogen versus Placebo Estrogen</u>

Low Dose Estrogen - hGH12/LDE, hGH09/LDE
Placebo Estrogen - hGH12/PLA, hGH09/PLA, PLA/Switch

The safety population is defined as all randomized patients who took any study medication. The intent-to-treat population is defined as all randomized patients who have efficacy data at Visit 3 or beyond (scheduled 180 days after randomization). In the PLA/Switch group, patients must also have efficacy data at Visit 9 or beyond (scheduled 180 days after switch to Humatrope treatment at Visit 7). Protocol completers were identified by the investigator as those patients who fulfilled or almost fulfilled the criteria for achievement of Final Height.

Patient Disposition

Patient accountability and primary reasons for discontinuation were summarized for all patients and by individual treatment group. Reasons for discontinuation were summarized for the safety population only.

Patient Characteristics

Patient demographic and Baseline characteristics measured at entry were summarized for the intent-to-treat population. The summaries include descriptive statistics (sample size, mean, standard deviation, median, minimum, and maximum) for the continuous variables, and frequencies and percentages for the categorical variables. Baseline comparability assessments between the five treatment groups were also performed for the intent-to-treat population. The Baseline comparability for continuous variables was performed using a two-way analysis of variance (ANOVA) (Neter et al. 1990) with effects for treatment and geographically pooled investigative site. For the categorical variables, Baseline comparability was assessed using a Cochran-Mantel-Haenszel statistic (Mantel and Haenszel 1959) stratifying by geographically pooled site. For origin and karyotype, the test was based on comparing the most predominant category (Caucasian and 45,X, respectively) relative to all other categories combined.

Efficacy

Efficacy variables were summarized at yearly visits and at Last Visit for the pooled hGH09 and hGH12 groups with descriptive statistics (sample size, mean, standard deviation, median, minimum, and maximum). In addition, primary and secondary efficacy variables were also summarized for the pooled Low Dose Estrogen and Placebo Estrogen groups.

Mathematical definitions of some variables used in efficacy analyses are given below.

Chronological age at each visit was defined as [visit date - birth date]/365.25.

Height SDS (standard deviation scores) were calculated compared to reference data for normal females [NCHS], and Turner syndrome females [Lyon]. The SDS was calculated as:

> [patient's height - mean height for the reference data at the patient's age]/standard deviation for the reference data at the patient's age.

The NCHS reference data contain mean height and standard deviation for intervals of chronological age (generally six-month intervals). The SDS for each patient was calculated using data from the applicable age interval. The Lyon Turner syndrome reference data contain mean height and smoothed standard deviation for each year of chronological age. The height SDS for each patient was calculated for exact chronological age using interpolation. The last available age for the Lyon data was 20 years, so Height SDS [Lyon] was undefined for patients in this study who were older than 20 years.

Growth Velocity SDS (standard deviation scores) were calculated on the basis of reference data for Turner syndrome females [Ranke]. The growth velocity SDS was defined as:

> [patient's growth velocity - mean growth velocity for the reference data at the patient's age]/ standard deviation for the reference data at the patient's age.

The Ranke reference data contain mean growth velocity and standard deviation for each year of chronological age. The growth velocity SDS for each patient was calculated for exact chronological age using interpolation. The last available age for the Ranke data was 18 years, and the Ranke data had no standard deviation for ages 2, 3, 17, and 18. Growth Velocity SDS [Ranke] was therefore undefined for patients in this study who were older than 16 years.

Treatment Comparisons

The hGH12 and hGH09 groups were compared statistically for primary and secondary efficacy variables, and at Last Visit for other efficacy variables. All tests for primary and secondary efficacy variables were evaluated using the $p \leq 0.050$ significance level. Statistical tests of other efficacy variables are provided for descriptive purposes only. No adjustment to the significance level was made for this interim analysis since the study is scheduled to close December 1996 regardless of the preliminary results.

Between-dose comparisons for all efficacy variables (except height at Last Visit Adjusted for Bone Age) were performed using an ANOVA model incorporating the effects for Humatrope dose, low dose estrogen, geographically pooled investigative site, and Baseline age strata.

Analyses for the secondary efficacy variable, height at Last Visit Adjusted for Bone Age for the intent-to-treat population, were performed using an ANCOVA model which incorporated an additional effect for bone age.

A near-significant difference in Midparental Height was observed among the five treatment groups; so, to confirm results, hGH09 versus hGH12 group comparisons for all primary and secondary efficacy variables were performed using an analysis of covariance (ANCOVA) (Neter et al. 1990) incorporating effects for Humatrope dose, low dose estrogen, geographically pooled investigative site, Baseline age strata, and Midparental Height.

Tests of Interactions

Tests of interaction between Humatrope dose group and geographically pooled site were performed for the primary and secondary efficacy variables using an ANOVA model which incorporated the effects for Humatrope dose, low dose estrogen, geographically pooled investigative sites, Baseline age strata, and the Humatrope dose group-by-site interaction. Interaction testing for height at Last Visit Adjusted for Bone Age was performed using an ANCOVA model with an additional effect for bone age.

The interactions between Humatrope dose groups and Baseline age strata, as well as between Humatrope dose groups and Low Dose Estrogen groups, were analyzed using similar ANOVA (or ANCOVA) models.

Compliance

Compliance is presented for all patients in the safety population, overall, and for the hGH09 and hGH12 groups. Patient compliance is defined as the total number of injections recorded divided by the total number of expected injections, based on the number of years the patient was in the study. In addition, total study compliance is presented as the percent of all safety patients who were 80%-120% compliant. The summary for patient compliance includes descriptive statistics (sample size, mean, standard deviation, median, minimum, and maximum). No statistical testing was performed.

Exposure

Years in study is presented for patients in the safety population and for patients who completed the study. Years in study is defined as the number of years from the first visit to the Last Visit recorded. The summary includes descriptive statistics (sample size, mean, standard deviation, median, minimum, and maximum) for years in study, overall and by Humatrope dose group. No statistical testing was performed.

Treatment-Emergent Events

The frequency and percentage of treatment-emergent events were summarized overall and by pooled hGH09 and hGH12 treatment groups. A treatment-emergent event is defined as any event which: (a) had an onset date on or after start of treatment or (b) worsened in severity on or after the start of treatment.

A comparison of all Humatrope-treated patients versus those receiving Placebo injections was also provided by summarizing the frequency and percentage of treatment-emergent events occurring within the first eighteen months of treatment, the period before the switch of the group with the lowest growth velocity (subsequently determined to be the Placebo injection/Placebo estrogen group) to the hGH12/PLA group occurred. These statistics were provided overall, for all Humatrope-treated patients combined, and for patients receiving Placebo injections.

In order to investigate the effect of estrogen given to patients with Turner syndrome at an early age, on the adverse event profile, the frequency and percentage of treatment-emergent events were summarized for Low Dose Estrogen and for Placebo Estrogen groups.

Treatment-emergent events of special interest were identified for analysis in this report because of concern that development or worsening of some events previously associated with growth hormone therapy may also occur in this study. These events included bone disorder, edemas, hyperglycemia, hypertension, hypothyroidism, increased nevi, and

lymphedema. The frequency and percentage of treatment-emergent events of special interest were summarized overall and for the hGH09 and hGH12 groups.

Laboratory Data

All descriptive statistics for the laboratory data are presented for the pooled hGH09 and hGH12 groups. For continuous laboratory variables, descriptive statistics (sample size, mean, standard deviation, median, minimum, and maximum) are presented for Baseline, Last Visit, and Change from Baseline at Last Visit results. Serum lipid concentrations at yearly visits are also summarized. For categorical laboratory variables, frequencies and percentages of results are presented at Baseline and Last Visit. For fasting glucose, hemoglobin A_{1C}, and IGF-I (Somatomedin-C), descriptive statistics are also presented for the five individual treatment groups, and a two-way ANOVA with effects for pooled Humatrope dose group and geographically pooled investigative site was performed to assess differences between the hGH09 and hGH12 groups. For serum insulin concentrations, descriptive statistics (sample size, minimum, median, maximum, and 5th, 25th, 75th, 95th percentile values) are presented for Baseline, Last Visit, and Change from Baseline at Last Visit results. For selected key laboratory tests, the frequency and percentage of patients in each pooled Humatrope dose group who had laboratory results that fell outside specific cut points designated as clinically significant are presented.

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Patient Disposition

Disposition

Table 3 summarizes patient accountability overall and by treatment group for study GDCI. Two hundred thirty-two patients were initially randomized into five treatment groups. Following an interim analysis performed before the first enrolled patient completed 18 months in the study (9-month data analysis), patients in the group found to be least responsive (subsequently determined to be the PLA/Switch group) were blindly reassigned to the hGH12/placebo ethinyl estradiol group (hGH12/PLA); patients and investigators were unaware of either the initial or the subsequent treatment received by this group.

The safety population is defined as those patients who were randomized and took any study medication. The intent-to-treat population consists of patients who were randomized and had efficacy data at Visit 3 (180 days after randomization) or beyond; or if randomized to the PLA/Switch group, had efficacy data at Visit 9 (180 days after switch) or beyond. Two hundred thirty patients (99%) are included in the safety population and 224 patients (97%) comprise the intent-to-treat population. Two randomized patients (Patients 009-1047 and 018-1522) were excluded from the safety population due to the fact that they had no documentation regarding taking study medication. Eight patients (Patients 004-1018, 006-1032, 009-1047, 017-1128, 018-1522, 021-1179, 053-1455, 061-1534) were excluded from the intent-to-treat population; two were excluded from the safety population and six were excluded due to lack of height data after 180 days of Humatrope treatment.

As of the 8 February 1996 data cutoff date, 31 patients (13%) had completed the study, (i.e., reached Final Height or were considered by the investigator to have almost reached Final Height), while 63 patients (27%) remain active. One hundred thirty-eight patients (59%) were discontinued from the study. Discontinuation rates were slightly higher in the hGH09 Humatrope groups relative to the other three treatment groups.

Table 3 **Summary of Patient Accountability**

Patient Disposition	Overall	hGH12/LDE	hGH12/PLA	hGH09/LDE	hGH09/PLA	PLA/Switch
Randomized	232	43	49	48	46	46
Safety Population	230 (99.1%)	42 (97.7%)	49 (100.0%)	47 (97.9%)	46 (100.0%)	46 (100.0%)
ITT Population	224 (96.6%)	42 (97.7%)	49 (100.0%)	47 (97.9%)	45 (97.8%)	41 (89.1%)
Completed	31 (13.4%)	8 (18.6%)	7 (14.3%)	6 (12.5%)	5 (10.9%)	5 (10.9%)
Discontinued	138 (59.5%)	24 (55.8%)	26 (53.1%)	31 (64.6%)	30 (65.2%)	27 (58.7%)
Ongoing	63 (27.2%)	11 (25.6%)	16 (32.7%)	11 (22.9%)	11 (23.9%)	14 (30.4%)

Note: Frequencies presented as number (percent). Percentages relative to number of randomized patients.

Table 4 summarizes the reasons patients in the safety population were discontinued from the study, overall and by treatment group. Of the 136 patients in the safety population who discontinued the study, 90 (66%) discontinued due to patient decision. Investigators discontinued 16 (12%) patients, most of whom were determined to have diminished growth rates or were noncompliant. Following inspection of the comments made in the final summary report, it appears that approximately 40% of the patient decisions were attributed to satisfaction with attained height, whereas lack of efficacy (about 20%) and complaints with respect to injections or the protocol (about 10% and 3%, respectively) were less common. In contrast, comments made regarding physician decision suggested that physicians were more likely to discontinue patients for reasons associated with poor response (about 30%) than for satisfaction with efficacy of treatment (about 25%).

Twelve patients (9%) were discontinued due to protocol violations with most being noncompliant with respect to either study drug administration or visit schedules. Seven patients (5%) were discontinued for lack of efficacy, five patients (4%) were lost to follow-up, four patients (3%) were discontinued because of adverse events, and two patients (1%) were discontinued by the sponsor.

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Table 4 Summary of Reasons Patients Discontinued - Safety Population

Reason Discontinued	Overall	hGH12/LDE	hGH12/PLA	hGH09/LDE	hGH09/PLA	PLA/Switch
Total Patients Discontinued From Safety Population	136	23	26	30	30	27
Patient Decision	90 (66.2%)	14 (60.9%)	20 (76.9%)	18 (60.0%)	20 (66.7%)	18 (66.7%)
Physician Decision	16 (11.8%)	6 (26.1%)	2 (7.7%)	4 (13.3%)	1 (3.3%)	3 (11.1%)
Sponsor Decision	2 (1.5%)	0	0	0	1 (3.3%)	1 (3.7%)
Protocol Violation	12 (8.8%)	3 (13.0%)	2 (7.7%)	1 (3.3%)	4 (13.3%)	2 (7.4%)
Lack Of Efficacy	7 (5.1%)	0	0	4 (13.3%)	1 (3.3%)	2 (7.4%)
Lost To Follow-up	5 (3.7%)	0	2 (7.7%)	2 (6.7%)	1 (3.3%)	0
Adverse Event	4 (2.9%)	0	0	1 (3.3%)	2 (6.7%)	1 (3.7%)
Entry Criteria Exclusion	0	0	0	0	0	0
Death	0	0	0	0	0	0

Note: Frequencies presented as number (percent). Percentages relative to number of patients discontinued from study.

Significant Protocol Violations

For the purposes of this report, protocol violations are defined as events which were considered deviations from the protocol occurring at any time during the study. In most instances, patients were allowed to continue in the study but in 12 instances the deviations were considered serious enough to merit discontinuation. Patients with less significant protocol violations were allowed to continue in the study after careful review of the violation and its impact on the efficacy and safety analyses.

A protocol violator of significance is defined as:

1. A patient who discontinued due to protocol violations.
2. A patient who did not take study drug for a consecutive period of at least 180 days.
3. A patient who took Ritalin (methylphenidate) or Cylert (pemoline).

Patients Who Discontinued Due to Protocol Violations

A total of 12 patients were discontinued from the study due to protocol violations. At the time of discontinuation, five patients were receiving 0.09 mg/kg/dose Humatrope and six patients were receiving 0.12 mg/kg/dose Humatrope; one patient was receiving placebo injections.

Patients Who Did Not Take Drug for a Consecutive Period of 180 Days

No patients met this criterion.

Patients Who Took Concomitant Drugs Methylphenidate (Ritalin) or Pemoline (Cylert)

A total of seven patients were administered Ritalin or Cylert during the time they were enrolled in the study. Five patients who received Ritalin were in the hGH12 group, one patient who received Cylert was in the hGH09 group, and one patient who received Cylert was in the PLA/Switch group. One patient who received both drugs was in the hGH12 group. All patients are listed in Table 5 Of the three patients whose initial treatment assignment was placebo (PLA/Switch), two were taking Ritalin or Cylert while receiving Humatrope (following the switch to Humatrope after the first 18 months in the study) and one patient received Cylert during the period she was receiving placebo injections and also during the period she received Humatrope. These drugs, prescribed after patient enrollment, were considered essential to the patients' well-being. Because the effect of these drugs upon growth is controversial and data are inconclusive, the patients were allowed to stay in the study.

Table 5 **Patients Who Took Ritalin or Cylert During Study**

Patient	Treatment Group	Age (Years)[1]	Disallowed Medication	Visits[2]	Total Years in Study
003-1381	hGH12/PLA	10.1	Ritalin	13-26	6.6
013-1093	hGH09/LDE	6.3	Cylert	6-10	2.3
014-1100	PLA/Switch	10.3	Cylert	3-27	7.1
018-1139	PLA/Switch	8.4	Ritalin	14	7.3
021-1182	hGH12/LDE	9.5	Ritalin	10,11,14-24	5.9
		10.0	Cylert	12,13	
023-1217	hGH12/PLA	10.3	Ritalin	14-28	7.5
047-1402	PLA/Switch	10.9	Ritalin	18-21	7.0

[1] Age at first visit where Ritalin or Cylert was taken.

[2] Visits at which Ritalin or Cylert was taken.

Note: The generic drug names for Ritalin and Cylert are methylphenidate and pemoline, respectively.

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Efficacy Results

Data Sets Analyzed

Of the 232 patients randomized, 224 were included in the intent-to-treat population. These patients had efficacy data for 180 days of treatments (at Visit 3 or beyond for patients originally randomized to one of the groups receiving Humatrope injections, at Visit 9 or beyond for patients originally randomized to placebo injections). The statistical evaluation was based on height data collected on all patients who participated (or are currently participating) in the study until the time of their discontinuation. Table 6 lists the number of patients with efficacy data by visit. The majority of patients, 122/224 (55%), continued in the study for five years and 45 patients (20%) participated for seven years.

Table 6 Number of Patients With Efficacy Data at Yearly Visits

	Visit Number (Years in Study)							
Treatment Group	1 (0)	5 (1)	9 (2)	13 (3)	17 (4)	21 (5)	25 (6)	27 (7)
Total Number of Patients	224	217	202	181	147	122	81	45
hGH12/LDE	42	42	40	35	27	20	14	9
hGH12/PLA	49	47	42	38	34	31	21	12
hGH09/LDE	47	46	42	33	24	19	11	6
hGH09/PLA	45	41	37	35	27	24	15	4
PLA/Switch	41	41	41	40	35	28	20	14

Patient Characteristics

Table 7 summarizes patient characteristics at study entry, by ethnic origin and age strata for the intent-to-treat population overall and by treatment group. Table 8 summarizes age, weight, height, Height SDS [NCHS], Height SDS [Lyon], Midparental Height, Pretreatment Growth Velocity, Pretreatment Growth Velocity SDS [Ranke], and Bone Age for the intent-to-treat population at study entry for all patients and by treatment group.

Table 7 **Patient Characteristics at Entry: Origin and Age Strata - ITT Population**

Characteristic	Overall	hGH12/LDE	hGH12/PLA	hGH09/LDE	hGH09/PLA	PLA/Switch	P-value[1]
ITT Population	224	42	49	47	45	41	
Origin[2]							
Total Patients	224	42	49	47	45	41	
Caucasian	174 (77.7%)	32 (76.2%)	35 (71.4%)	34 (72.3%)	39 (86.7%)	34 (82.9%)	0.490
Black	8 (3.6%)	2 (4.8%)	2 (4.1%)	1 (2.1%)	1 (2.2%)	2 (4.9%)	
Hispanic	36 (16.1%)	6 (14.3%)	12 (24.5%)	12 (25.5%)	5 (11.1%)	1 (2.4%)	
Native American	1 (0.4%)	1 (2.4%)	0	0	0	0	
Asian	2 (0.9%)	1 (2.4%)	0	0	0	1 (2.4%)	
Other	3 (1.3%)	0	0	0	0	3 (7.3%)	
Age Strata							
Total Patients	224	42	49	47	45	41	
<8 years	74 (33.0%)	14 (33.3%)	15 (30.6%)	18 (38.3%)	14 (31.1%)	13 (31.7%)	0.999
8 to <10 years	45 (20.1%)	8 (19.0%)	11 (22.4%)	8 (17.0%)	9 (20.0%)	9 (22.0%)	
10 to <12 years	53 (23.7%)	11 (26.2%)	11 (22.4%)	10 (21.3%)	11 (24.4%)	10 (24.4%)	
≥12 years	52 (23.2%)	9 (21.4%)	12 (24.5%)	11 (23.4%)	11 (24.4%)	9 (22.0%)	

* Statistically significant ($p \leq 0.050$).

[1] P-value tests proportions of patients for homogeneity across the five treatment groups.

[2] P-value for origin is based on testing Caucasian relative to all other origins combined.

Note: Frequencies presented as number (percent). Percentages relative to number of patients in the intent-to-treat population.

Table 8 **Patient Characteristics at Entry: Age, Weight, and Height Variables - ITT Population (Part 1 of 3)**

Characteristic	N	Mean	SD	Median	Minimum	Maximum	P-value[1]
Age (years)							
Total Patients	224	9.69	2.75	9.75			
hGH12/LDE	42	9.90	2.87	9.88			0.913
hGH12/PLA	49	9.84	2.88	9.61			
hGH09/LDE	47	9.57	2.73	9.42			
hGH09/PLA	45	9.68	2.68	9.85			
PLA/Switch	41	9.43	2.69	9.79			
Weight (kg)							
Total Patients	224	26.96	10.60	25.10			
hGH12/LDE	42	25.27	8.94	22.45			0.643
hGH12/PLA	49	27.28	11.21	24.00			
hGH09/LDE	47	26.52	11.11	23.75			
hGH09/PLA	45	28.55	11.06	27.27			
PLA/Switch	41	27.08	10.55	26.40			
Height (cm)							
Total Patients	224	117.93	12.75	118.01			
hGH12/LDE	42	117.65	12.46	117.50			0.800
hGH12/PLA	49	118.62	12.51	118.53			
hGH09/LDE	47	116.61	12.04	116.37			
hGH09/PLA	45	119.18	13.61	120.90			
PLA/Switch	41	117.55	13.55	120.53			

* Statistically significant ($p \leq 0.050$).

[1] P-value is for comparison of means across the five treatment groups.

[2] Normal female reference standard.

[3] Turner syndrome reference standard [Lyon].

[4] Turner syndrome reference standard [Ranke].

Table 8 **Patient Characteristics at Entry: Age, Weight, and Height Variables - ITT Population (Part 2 of 3)**

Characteristic	N	Mean	SD	Median	Minimum	Maximum	P-value[1]
Height SDS [NCHS][2]							
Total Patients	224	-2.98	0.99	-2.86			
hGH12/LDE	42	-3.14	0.99	-3.02			0.120
hGH12/PLA	49	-2.93	0.91	-2.93			
hGH09/LDE	47	-3.24	1.18	-3.04			
hGH09/PLA	45	-2.74	0.90	-2.63			
PLA/Switch	41	-2.85	0.90	-2.65			
Height SDS [Lyon][3]							
Total Patients	224	0.11	0.90	0.06			
hGH12/LDE	42	-0.08	0.87	-0.02			0.256
hGH12/PLA	49	0.16	0.80	0.15			
hGH09/LDE	47	-0.03	0.94	0.00			
hGH09/PLA	45	0.30	0.99	0.06			
PLA/Switch	41	0.18	0.90	0.13			
Midparental Height (cm)							
Total Patients	214	163.09	5.81	163.68			
hGH12/LDE	41	164.11	5.30	163.80			0.080
hGH12/PLA	47	162.89	5.92	162.10			
hGH09/LDE	43	161.35	6.20	163.15			
hGH09/PLA	44	164.64	6.06	164.69			
PLA/Switch	39	162.41	5.02	163.35			

* Statistically significant ($p \leq 0.050$).

[1] P-value is for comparison of means across the five treatment groups.

[2] Normal female reference standard.

[3] Turner syndrome reference standard [Lyon].

[4] Turner syndrome reference standard [Ranke].

Table 8 Patient Characteristics at Entry: Age, Weight, and Height Variables - ITT Population (Part 3 of 3)

Characteristic	N	Mean	SD	Median	Minimum	Maximum	P-value[1]
Pretreatment Growth Velocity (cm/year)							
Total Patients	224	3.93	1.22	4.08			
hGH12/LDE	42	3.88	1.00	3.96			0.404
hGH12/PLA	49	3.96	1.17	4.01			
hGH09/LDE	47	3.65	1.48	3.95			
hGH09/PLA	45	4.11	1.18	4.20			
PLA/Switch	41	4.08	1.19	4.26			
Pretreatment Growth Velocity SDS [Ranke][4]							
Total Patients	223	0.06	1.01	0.26			
hGH12/LDE	41	0.05	0.71	0.09			0.353
hGH12/PLA	49	0.19	0.99	0.44			
hGH09/LDE	47	-0.20	1.20	-0.01			
hGH09/PLA	45	0.15	1.13	0.32			
PLA/Switch	41	0.10	0.88	0.33			
Bone Age (years)							
Total Patients	224	7.79	2.27	7.83			
hGH12/LDE	42	7.59	2.19	7.83			0.953
hGH12/PLA	49	7.91	2.28	7.83			
hGH09/LDE	47	7.71	2.26	7.83			
hGH09/PLA	45	7.86	2.25	7.83			
PLA/Switch	41	7.86	2.44	7.83			

* Statistically significant ($p \leq 0.050$).

[1] P-value is for comparison of means across the five treatment groups.

[2] Normal female reference standard.

[3] Turner syndrome reference standard [Lyon].

[4] Turner syndrome reference standard [Ranke].

At entry, there were no significant differences among the treatment groups for chronological age, mean weight, height, Height SDS [NCHS], Height SDS [Lyon], Pretreatment Growth Velocity, Pretreatment Growth Velocity SDS [Ranke], or Bone Age. There was a near significant (p=0.080) difference in Midparental Height among the five groups at study entry. Midparental heights were unavailable for 10 of the 224 patients in the intent-to-treat population.

Table 9 summarizes patient characteristics at entry for karyotype for the intent-to-treat population overall and by treatment group. There was no statistically significant difference among treatment groups when comparing patients with the 45,X karyotype to all other karyotypes. One hundred fifty-one (67%) of the 224 patients in the intent-to-treat population had the most frequently reported karyotype, 45,X. Nineteen patients (8%) had the 45,X/46XXqi karyotype. No other karyotype was reported by more than 5% of patients in this group with the exception of the Other category. The Other category, representing rare karyotypes otherwise unspecified on the clinical report form, comprised about 8% of all patients.

Table 9 **Patient Characteristics at Entry: Karyotype - ITT Population**

Karyotype[1]	Overall	hGH12/LDE	hGH12/PLA	hGH09/LDE	hGH09/PLA	PLA/Switch	P-value[2]
Total Patients	224	42	49	47	45	41	0.474
45,X	151 (67.4%)	28 (66.7%)	38 (77.6%)	29 (61.7%)	30 (66.7%)	26 (63.4%)	
45,X/46,XXqi	19 (8.5%)	3 (7.1%)	4 (8.2%)	7 (14.9%)	2 (4.4%)	3 (7.3%)	
45,X/46,XXr	10 (4.5%)	1 (2.4%)	3 (6.1%)	1 (2.1%)	4 (8.9%)	1 (2.4%)	
45,X/46,XX	9 (4.0%)	1 (2.4%)	1 (2.0%)	4 (8.5%)	3 (6.7%)	0	
46,XXqi	9 (4.0%)	1 (2.4%)	1 (2.0%)	1 (2.1%)	1 (2.2%)	5 (12.2%)	
45,X/47,XXX	3 (1.3%)	1 (2.4%)	0	1 (2.1%)	0	1 (2.4%)	
46,XXp$^-$	2 (0.9%)	2 (4.8%)	0	0	0	0	
45,X/46,XXp$^-$	2 (0.9%)	0	0	1 (2.1%)	1 (2.2%)	0	
45,X/46,XX/47,XXX	1 (0.4%)	0	0	1 (2.1%)	0	0	
Other	18 (8.0%)	5 (11.9%)	2 (4.1%)	2 (4.3%)	4 (8.9%)	5 (12.2%)	

* Statistically significant ($p \leq 0.050$).

[1] P-value is based on testing 45,X karyotype relative to all other karyotypes combined.

[2] P-value tests proportions of patients for homogeneity across the five treatment groups.

Note: Frequencies presented as number (percent). Percentages relative to number of patients in the intent-to-treat population.

Results of Efficacy Analyses

Primary Efficacy Variable

A total of 224 patients with Turner syndrome were included in the analysis of Height SDS [NCHS] at Last Visit for the intent-to-treat population.

Height SDS [NCHS] at Last Visit - ITT Population

Height SDS [NCHS] for the hGH12 and hGH09 treatment groups are presented in Table 10 and Case Report Tabulation GDCI.F.3. Height SDS [NCHS] is the SDS for height using normal females as a reference standard. At Baseline, mean Height SDS [NCHS] was similar for the hGH09 and hGH12 groups, mean height being approximately 3 SDS below the mean height of normal females. At Last Visit, mean Height SDS had improved to -2.29 and -2.60 for the hGH12 and hGH09 groups, respectively. There was no statistically significant difference between the treatment groups for Height SDS at Last Visit.

Table 10 Efficacy Variable: Height SDS [NCHS][1] at Last Visit - ITT Population

	N	Mean	SD	Median	Minimum	Maximum	P-value[2]	Adjusted P-value[3]
Baseline								
hGH12	132	-2.97	0.93	-2.85				
hGH09	92	-3.00	1.08	-2.88				
Last Visit								
hGH12	132	-2.29	1.10	-2.16			0.087	0.121
hGH09	92	-2.60	1.12	-2.62				

*Statistically significant ($p \leq 0.050$).

[1] Normal female reference standard.

[2] P-value is for comparison of pooled treatment group means.

[3] P-value is for comparison of pooled treatment group means adjusted for Midparental Height.

Secondary Efficacy Variables

Final Height - Protocol Completers

Of the 224 patients included in the intent-to-treat population, a total of 31 patients were considered to have completed the protocol, having fulfilled or almost fulfilled the study criteria for attainment of Final Height. A total of 20/132 (15.2%) patients in the hGH12 group and 11/92 (12.0%) patients in the hGH09 group were analyzed as having completed the protocol.

Criteria for achievement of Final Height were bone age ≥15 years and a growth velocity <2 cm/year. Seven of the 31 patients in this group did not meet these criteria quantitatively; however, they were felt by the investigator to have achieved close to their final height. Therefore, the group was analyzed as a whole. These seven patients all had bone age ≥13.5 years and growth velocities of <3 cm/year. Final Height results are presented in Table 11. Final Height is defined as the actual height (cm) at the last available visit for patients who were identified by the investigator as having completed the study. There were no statistically significant differences between the hGH12 and hGH09 groups for mean Final Height. The difference was less than 1 cm.

Table 11 Efficacy Variable: Final Height - Protocol Completers

Parameter	N	Mean	SD	Median	Minimum	Maximum	P-value[1]	Adjusted P-value[2]
Final Height (cm)								
hGH12	20	148.50	6.24	149.33			0.984	0.529
hGH09	11	149.18	7.13	147.77				

*Statistically significant ($p \leq 0.050$).

[1] P-value is for comparison of pooled treatment group means.

[2] P-value is for comparison of pooled treatment group means adjusted for Midparental Height.

Height at Last Visit Adjusted for Bone Age - ITT Population

Because of the potential for GH to induce an increase in skeletal maturation, the effect of Humatrope on height was assessed by analysis of height measurements obtained at the last visit at which a bone age X-ray was performed (not necessarily the same visit as the actual Last Visit). An ANCOVA was conducted with an adjustment for bone age (in addition to Midparental Height, low dose estrogen, Baseline age strata, and geographically pooled site). These results are depicted in Table 12. The hGH12 group was taller than the hGH09 group at the actual Last Visit by an average of 3.12 cm. However, when analysis of Height at Last Visit Adjusted for Bone Age was performed, the difference in adjusted means between the hGH12 and hGH09 groups was 1.57 cm. This difference showed a statistical trend ($p = 0.065$), suggesting a possible mild dose effect.

Table 12 **Efficacy Variable: Height at Last Visit[1] Adjusted for Bone Age - ITT Population**

	N	Mean	SD	Median	Minimum	Maximum
Last Visit Height (cm)						
hGH12	132	142.60	11.48	144.60		
hGH09	91	139.48	11.73	141.43		

	N	Least Squares Mean[2]	SE	P-value[3]
Adjusted Last Visit Height				0.065
hGH12	132	141.67	0.56	
hGH09	91	140.10	0.66	

*Statistically significant ($p \leq 0.050$).

[1] Last visit at which bone age X-ray performed.

[2] Least squares means are adjusted for bone age and Midparental Height based on an ANCOVA.

[3] P-value is for comparison of pooled treatment group means adjusted for bone age and Midparental Height.

Other Efficacy Variables

Height SDS [NCHS] by Years in Study - ITT Population

Height SDS [NCHS] by years in study is presented for the pooled treatment groups (hGH12 versus hGH09) in Table 13. The NCHS Height SDS is based on the normal female reference standard. At Baseline, both groups had comparable mean Height SDS, mean height being an average of 3 SDS below the mean height of normal females. Over the first four years of the study, both treatment groups showed an improvement in height relative to the normal female reference standard. At Last Visit, Height SDS [NCHS] had improved to -2.29 and -2.60 for the hGH12 and hGH09 groups, respectively. Although the hGH12 group demonstrated a trend towards greater improvement in Height SDS than the hGH09 group no statistically significant clinical benefit related to dose is apparent at any year or at Last Visit.

Table 13 **Efficacy Variable: Height SDS [NCHS][1] by Years in Study - ITT Population**

Years in Study	N	Mean	SD	Median	Minimum	Maximum	P-value[2]
Baseline							
hGH12	132	-2.97	0.93	-2.85			
hGH09	92	-3.00	1.08	-2.88			
Year 1							
hGH12	127	-2.74	0.97	-2.75			
hGH09	87	-2.60	1.06	-2.63			
Year 2							
hGH12	123	-2.56	1.03	-2.40			
hGH09	79	-2.44	1.04	-2.48			
Year 3							
hGH12	112	-2.47	1.08	-2.34			
hGH09	66	-2.28	1.01	-2.38			
Year 4							
hGH12	96	-2.17	1.00	-2.09			
hGH09	51	-2.22	0.97	-2.14			
Year 5							
hGH12	78	-2.22	1.13	-2.30			
hGH09	43	-2.23	0.92	-2.13			
Year 6							
hGH12	55	-2.30	1.11	-2.21			
hGH09	26	-2.43	0.77	-2.29			
Year 7							
hGH12	35	-2.41	1.11	-2.51			
hGH09	10	-2.96	0.67	-2.86			
Last Visit							
hGH12	132	-2.29	1.10	-2.16			0.087
hGH09	92	-2.60	1.12	-2.62			

*Statistically significant ($p \leq 0.050$).

[1] Normal female reference standard.

[2] P-value is for comparison of pooled treatment group means at Last Visit.

Height SDS [NCHS] Change from Baseline by Years in Study ITT Population

Height SDS [NCHS] Change from Baseline by years in study is presented for the pooled hGH12 and hGH09 treatment groups in Table 14. Although the Change from Baseline scores are slightly higher in the hGH09 group in comparison to the hGH12 group at

Years 1, 2, and 3, they are similar in both groups at Years 4, 5, and 6. These results may be influenced by inclusion of the Placebo/Switch group in the analyses for the hGH12 group. The Placebo injections received by patients in this group during the first 18 months of the study would bias the data for the hGH12 group towards a smaller change in Height SDS in the early years of the study. At Last Visit, the mean change in Height SDS from Baseline is significantly greater in the hGH12 group compared to the hGH09 group by an SDS of 0.28 ($p = 0.012$).

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Table 14 **Efficacy Variable: Height SDS [NCHS][1] Change from Baseline by Years in Study - ITT Population**

Years from Baseline	N	Mean	SD	Median	Minimum	Maximum	P-value[2]
Year 1							
hGH12	127	0.21	0.60	0.20			
hGH09	87	0.38	0.57	0.33			
Year 2							
hGH12	123	0.39	0.86	0.53			
hGH09	79	0.52	0.76	0.55			
Year 3							
hGH12	112	0.45	0.92	0.51			
hGH09	66	0.63	0.84	0.62			
Year 4							
hGH12	96	0.68	0.89	0.63			
hGH09	51	0.61	0.74	0.50			
Year 5							
hGH12	78	0.61	0.89	0.62			
hGH09	43	0.63	0.74	0.56			
Year 6							
hGH12	55	0.42	0.81	0.47			
hGH09	26	0.48	0.69	0.57			
Year 7							
hGH12	35	0.35	0.78	0.30			
hGH09	10	-0.02	0.88	0.05			
Last Visit							
hGH12	132	0.68	0.93	0.61			0.012*
hGH09	92	0.40	0.91	0.43			

*Statistically significant ($p \leq 0.050$).

[1] Normal female reference standard.

[2] P-value is for comparison of pooled treatment group means at Last Visit.

Height SDS [Lyon] by Years in Study - ITT Population

Height SDS [Lyon] by years in study is presented for the pooled hGH12 and hGH09 treatment groups in Table 15. The Lyon Height SDS is based on a Turner syndrome reference standard. At Baseline, the mean Height SDS [Lyon] are close to zero, suggesting that mean height of the study population is consistent with the mean height of this Turner syndrome reference population. As years in study increased, Height SDS [Lyon] showed a gradual improvement in both groups to Year 5 of the study for the hGH09 group, and to Year 7 for the hGH12 group. There was no statistically significant difference between the Humatrope groups for Height SDS [Lyon] at Last Visit. For Years 4, 5, and 6, mean height of patients in both Humatrope dose groups exceeds the Turner syndrome standard by approximately 1.5 SDS, suggesting a treatment-related improvement in height relative to the Turner syndrome reference standard.

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Table 15 **Efficacy Variable: Height SDS [Lyon][1] by Years in Study - ITT Population**

Years in Study	N	Mean	SD	Median	Minimum	Maximum	P-value[2]
Baseline							
hGH12	132	0.09	0.85	0.13			
hGH09	92	0.13	0.97	0.04			
Year 1							
hGH12	127	0.55	0.92	0.59			
hGH09	87	0.75	1.04	0.80			
Year 2							
hGH12	123	0.90	0.96	0.96			
hGH09	79	1.07	1.05	0.97			
Year 3							
hGH12	112	1.18	0.98	1.21			
hGH09	66	1.34	1.03	1.24			
Year 4							
hGH12	96	1.49	1.00	1.45			
hGH09	51	1.53	0.95	1.34			
Year 5							
hGH12	77	1.59	1.04	1.60			
hGH09	43	1.58	0.87	1.53			
Year 6							
hGH12	55	1.64	1.04	1.66			
hGH09	26	1.52	0.83	1.48			
Year 7							
hGH12	35	1.76	1.05	1.73			
hGH09	10	1.31	0.76	1.15			
Last Visit							
hGH12	131	1.46	1.10	1.53			0.291
hGH09	92	1.28	1.10	1.34			

*Statistically significant ($p \leq 0.050$).

[1] Turner syndrome reference standard [Lyon].

[2] P-value is for comparison of pooled treatment group means at Last Visit.

Growth Velocity SDS [Ranke] by Years in Study - ITT Population

Growth Velocity SDS [Ranke] by years in study is shown in Table 16 for each pooled treatment group (hGH12 and hGH09). At Baseline, the Growth Velocity SDS are similar for the two pooled treatment groups. There is a trend for Growth Velocity SDS to be greater in the earlier years of treatment, consistent with growth response patterns seen over time in other GH-treated populations. In the early years of treatment (Years 1 and 2), the mean growth rate of both Humatrope dose groups exceeded the mean of the Turner syndrome reference standard [Ranke] by 1-2 SDS. The hGH12 and hGH09 groups had comparable growth velocity over the first five years of treatment. At Last Visit, no significant difference in growth velocity were found between the hGH12 and hGH09 groups.

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Table 16 **Efficacy Variable: Growth Velocity SDS [Ranke][1] by Years in Study - ITT Population**

Years in Study	N	Mean	SD	Median	Minimum	Maximum	P-value[2]
Baseline							
hGH12	131	0.12	0.87	0.27			
hGH09	92	-0.03	1.18	0.19			
Year 1							
hGH12	123	1.37	2.08	1.27			
hGH09	87	2.04	1.83	2.01			
Year 2							
hGH12	117	2.06	2.03	1.79			
hGH09	75	1.28	2.20	0.96			
Year 3							
hGH12	101	1.26	1.99	1.21			
hGH09	60	1.10	1.79	1.18			
Year 4							
hGH12	82	0.96	1.85	1.07			
hGH09	46	0.70	2.11	0.52			
Year 5							
hGH12	63	1.11	2.59	1.26			
hGH09	39	1.05	1.89	1.22			
Year 6							
hGH12	43	0.47	2.05	0.61			
hGH09	24	0.03	1.82	-0.28			
Year 7							
hGH12	29	0.88	1.77	0.94			
hGH09	9	0.12	0.62	0.27			
Last Visit							
hGH12	85	0.29	2.01	0.38			0.113
hGH09	76	-0.29	2.34	-0.26			

*Statistically significant ($p \leq 0.050$).

[1] Turner syndrome reference standard [Ranke].

[2] P-value is for comparison of pooled treatment group means at Last Visit.

Bone Age

Bone Age represents an index of skeletal maturation. As bone age advances, the amount of remaining growth potential declines, and at a bone age of 15 years approximately 99% of adult stature has been attained in normal females; thus, administration of somatropin is not considered useful at an advanced bone age.

Bone Age by Years in Study - ITT Population

Bone Age by years in study is presented in Table 17. At Baseline, the hGH09 and hGH12 groups had identical average bone ages. The mean bone age for both groups remained similar at each year of treatment and at Last Visit. Mean bone age advanced by approximately one year for each year of Humatrope therapy for the first 4 years of the study, slowing thereafter to advance by approximately 1.5 years over the last 3 years of the study (it should be noted that patient numbers are small in the later study years). Thus, no untoward influence of Humatrope treatment upon skeletal maturation was noted during the treatment period.

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Table 17 **Efficacy Variable: Bone Age by Years in Study - ITT Population**

Years in Study	N	Mean	SD	Median	Minimum	Maximum	P-value[1]
Baseline							
hGH12	132	7.79	2.29	7.83			
hGH09	92	7.79	2.25	7.83			
Year 1							
hGH12	127	8.86	2.23	8.83			
hGH09	86	9.00	2.34	8.83			
Year 2							
hGH12	123	9.90	2.26	10.00			
hGH09	77	10.24	2.38	10.00			
Year 3							
hGH12	107	10.92	2.12	11.00			
hGH09	64	11.15	2.26	11.00			
Year 4							
hGH12	94	11.55	2.14	12.00			
hGH09	51	11.84	2.17	12.00			
Year 5							
hGH12	74	12.35	2.07	12.00			
hGH09	43	12.64	2.10	13.00			
Year 6							
hGH12	48	12.83	1.86	13.00			
hGH09	23	13.20	1.66	13.00			
Year 7							
hGH12	21	13.50	1.64	13.50			
hGH09	4	13.50	2.38	13.50			
Last Visit[2]							
hGH12	132	12.78	2.34	13.50			0.368
hGH09	91	12.59	2.56	13.00			

*Statistically significant ($p \leq 0.050$).

[1] P-value is for comparison of pooled treatment group means at Last Visit.

[2] Last visit at which bone age X-ray performed.

Bone Age Change from Baseline by Years in Study - ITT Population

Bone Age Change from Baseline by years in study for pooled treatment groups is presented in Table 18. Bone Age increased similarly for both groups as years of treatment continued, with no statistical difference between the Humatrope dosage groups at Last Visit.

Table 18 **Efficacy Variable: Bone Age Change from Baseline by Years in Study - ITT Population**

Years from Baseline	N	Mean	SD	Median	Minimum	Maximum	P-value[1]
Year 1							
hGH12	127	1.13	0.65	1.00			
hGH09	86	1.28	0.58	1.00			
Year 2							
hGH12	123	2.17	0.99	2.00			
hGH09	77	2.63	1.07	2.83			
Year 3							
hGH12	107	3.21	1.11	3.17			
hGH09	64	3.67	1.01	3.83			
Year 4							
hGH12	94	4.20	1.22	4.17			
hGH09	51	4.78	0.99	5.00			
Year 5							
hGH12	74	5.24	1.27	5.17			
hGH09	43	5.82	1.10	5.83			
Year 6							
hGH12	48	6.20	1.39	6.17			
hGH09	23	6.72	0.95	6.83			
Year 7							
hGH12	21	7.04	1.47	7.17			
hGH09	4	8.04	0.16	8.08			
Last Visit[2]							
hGH12	132	4.99	2.23	5.17			0.311
hGH09	91	4.80	2.28	5.17			

*Statistically significant ($p \leq 0.050$).

[1] P-value is for comparison of pooled treatment group means at Last Visit.

[2] Last visit at which bone age X-ray performed.

Bone Age/Chronological Age Ratio by Years in Study - ITT Population

Bone Age/Chronological Age by years in study is presented in Table 19. Bone Age/Chronological Age Ratios rose slightly with years of treatment. At Last Visit, there was a small difference in means between the hGH12 and hGH09 groups (0.88 versus 0.92) which showed a statistical trend but was not clinically significant (p=0.066; Table GDCI.6.14). Notably, in neither group does the average Bone Age/Chronological Age Ratio exceed 1.0 at any time during the study.

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Table 19 **Efficacy Variable: Bone Age/Chronological Age Ratio by Years in Study - ITT Population**

Years in Study	N	Mean	SD	Median	Minimum	Maximum	P-value[1]
Baseline							
hGH12	132	0.81	0.13	0.80			
hGH09	92	0.81	0.12	0.83			
Year 1							
hGH12	127	0.84	0.11	0.84			
hGH09	86	0.86	0.11	0.88			
Year 2							
hGH12	123	0.86	0.11	0.86			
hGH09	77	0.90	0.10	0.90			
Year 3							
hGH12	107	0.88	0.10	0.89			
hGH09	64	0.91	0.09	0.90			
Year 4							
hGH12	94	0.88	0.10	0.89			
hGH09	51	0.93	0.09	0.92			
Year 5							
hGH12	74	0.89	0.09	0.90			
hGH09	43	0.94	0.08	0.93			
Year 6							
hGH12	48	0.90	0.08	0.91			
hGH09	23	0.96	0.07	0.96			
Year 7							
hGH12	21	0.89	0.07	0.88			
hGH09	4	0.94	0.06	0.96			
Last Visit[2]							
hGH12	132	0.88	0.10	0.89			0.066
hGH09	91	0.92	0.09	0.92			

*Statistically significant ($p \leq 0.050$).

[1] P-value is for comparison of pooled treatment group means at Last Visit.

[2] Last visit at which bone age X-ray performed.

Primary and Secondary Efficacy Variables - Analysis of the Effects of Low Dose Estrogen at an Early Age

Patients in two of the treatment groups in this study received low dose estrogen at an early age, from eight years of age onward, in those weighing >20 kg. Patients in the other three treatment groups received placebo estrogen, only between 8 years and 13.5 years, and started standard estrogen replacement therapy after 13.5 years of age. Therefore, to evaluate the potential effects of low dose estrogen at a young age and its interaction with GH on height, the following groups were pooled for the purpose of making statistical comparisons: Humatrope alone (Placebo Estrogen group: hGH12/PLA; hGH09/PLA; and PLA/Switch) versus combined Humatrope and estrogen therapy (Low Dose Estrogen group: hGH12/LDE and hGH09/LDE).

Height SDS [NCHS] at Last Visit - ITT Population

Height SDS [NCHS] for the pooled groups from the intent-to-treat population is presented in Table 20. Both at Baseline and at Last Visit, the pooled Low Dose Estrogen group had significantly lower mean height SDS than the Placebo Estrogen. However, change in mean Height SDS between Baseline and Last Visit was similar for both groups; the Low Dose Estrogen group had an increase of 0.52 SDS and the Placebo group had an increase of 0.59 SDS.

Table 20 Efficacy Variable: Height SDS [NCHS][1] at Last Visit hGH/LDE Versus hGH/PLA - ITT Population

	N	Mean	SD	Median	Minimum	Maximum	P-value[2]	Adjusted P-value[3]
Baseline								
hGH/LDE	89	-3.19	1.09	-3.02			0.011[4]	
hGH/PLA	135	-2.84	0.90	-2.70				
Last Visit								
hGH/LDE	89	-2.67	1.10	-2.62			0.010*	0.008*
hGH/PLA	135	-2.25	1.09	-2.04				

*Statistically significant ($p \leq 0.050$).

[1] Normal female reference standard.

[2] P-value is for comparison of pooled treatment group means.

[3] P-value is for comparison of pooled treatment group means adjusted for Midparental Height.

Note: hGH/LDE = hGH with LDE (treatment groups hGH12/LDE and hGH09/LDE).
hGH/PLA = hGH with oral placebo (treatment groups hGH12/PLA, hGH09/PLA, and PLA/Switch).

Final Height - Protocol Completers

Final Height data were available for 31 patients. These are presented for the pooled low dose estrogen versus Placebo Estrogen groups in Table 21. The Placebo Estrogen group achieved a mean Final Height of 150.96 cm, which was 4.91 cm greater than that of the

Low Dose Estrogen group. This difference was statistically significant after adjusting for Midparental Height (p=0.008).

Table 21 Efficacy Variable: Final Height hGH/LDE Versus hGH/PLA - Protocol Completers

Parameter	N	Mean	SD	Median	Minimum	Maximum	P-value[1]	Adjusted P-value[2]
Final Height (cm)								
hGH/LDE	14	146.05	5.55	144.52			0.073	0.008*
hGH/PLA	17	150.96	6.44	150.77				

*Statistically significant ($p \leq 0.050$).

[1] P-value is for comparison of pooled treatment group means.

[2] P-value is for comparison of pooled treatment group means adjusted for Midparental Height.

Note: hGH/LDE = hGH with LDE (treatment groups hGH12/LDE and hGH09/LDE).
hGH/PLA = hGH with oral placebo (treatment groups hGH12/PLA, hGH09/PLA, and PLA/Switch).

Height at Last Visit Adjusted for Bone Age - ITT Population

Height at Last Visit Adjusted for Bone Age for the intent-to-treat population is presented in Table 22. Height at actual Last Visit was 3.02 cm greater in the Placebo Estrogen group than the Low dose Estrogen group. When mean heights at the last visit at which a bone age X-ray was performed were adjusted for bone age (and Midparental Height, Humatrope dose, strata, and site) the difference was 3.91 cm and was statistically significant (p=0.001).

Table 22 **Efficacy Variable: Height at Last Visit[1] Adjusted for Bone Age hGH/LDE Versus hGH/PLA - ITT Population**

	N	Mean	SD	Median	Minimum	Maximum
Last Visit Height						
hGH/LDE	89	139.51	11.10	141.13		
hGH/PLA	134	142.53	11.90	145.15		

	N	Least Squares Mean[2]	SE	P-value[3]
Adjusted Last Visit Height				
hGH/LDE	89	138.93	0.67	0.001*
hGH/PLA	134	142.84	0.55	

*Statistically significant ($p \leq 0.050$).

[1] Last visit at which bone age X-ray performed.

[2] Least squares means are adjusted for bone age and Midparental Height based on an ANCOVA.

[3] P-value is for comparison of pooled treatment group means adjusted for bone age and Midparental Height.

Note: hGH/LDE = hGH with LDE (treatment groups hGH12/LDE and hGH09/LDE).
hGH/PLA = hGH with oral placebo (treatment groups hGH12/PLA, hGH09/PLA, and PLA/Switch).

Adjustment for Baseline Imbalances for Pooled Treatment Groups

A trend toward Baseline imbalance was found for Midparental Height. No statistically significant differences were present for any of the Baseline characteristics evaluated. No significant differences were found comparing the pooled Humatrope groups. A number of differences were found comparing the Placebo Estrogen and Low Dose Estrogen groups. At Baseline, the mean Height SDS [NCHS] of the Low Dose Estrogen group was 0.35 SDS lower than that of the Placebo Estrogen group (p=0.011). At Baseline, the mean Height SDS [Lyon] of the Low Dose Estrogen group was 0.27 SDS lower than that of the Placebo Estrogen group [Lyon] (p=0.031). There was also a trend for the Low Dose Estrogen group to have lower pretreatment growth velocity (p=0.090).

Although Baseline imbalances were detected for these height SDS variables, it was decided not to adjust the analyses for these imbalances since Height SDS are derived variables, based on data from patients not included in this study (NCHS and Lyon reference populations). It might be expected, in the presence of imbalances in Height SDS at Baseline, that there would be baseline imbalances for age or height; however, these were not observed. Tests for the combined effects of these variables on the treatment group comparisons for the primary and secondary efficacy variables were not performed. Adjustments for these and other influences may be necessary in the future.

Treatment Interactions

Interactions between pooled Humatrope dosage groups and each of (a) geographically pooled site, (b) Baseline age strata, and (c) Low Dose Estrogen versus Placebo Estrogen groups were assessed using analysis of variance. There was no indication of an interaction between Humatrope dosage groups and any of (a) - (c) for the primary and secondary efficacy variables.

Summary

Primary Efficacy Variable

1. The hGH12 and hGH09 groups of the intent-to-treat population had similar mean Height SDS [NCHS] at Baseline and Last Visit, improving from approximately -3 SDS at Baseline to -2.3 and -2.6 SDS, respectively at Last Visit. This indicates an increase in height with respect to normal standards in response to Humatrope therapy. There was no statistically significant difference in mean Height SDS [NCHS] at Last Visit between Humatrope dosage groups (hGH12 versus hGH09).

Secondary Efficacy Variables

1. For those patients achieving Final Height (protocol completers, n=31), there was no statistically significant difference in mean actual height achieved by the hGH12 and hGH09 groups.

2. For patients in the intent-to-treat population, the mean height achieved at the last visit at which a bone age X-ray was performed was 1.57 cm greater in the hGH12 group than the hGH09 group when mean heights were adjusted for bone age. This was a trend towards statistical significance (p=0.065) suggesting a possible mild dose effect.

Other Efficacy Variables (Intent-to-Treat Population)

1. Patients receiving Humatrope showed an increase in mean height relative to both the normal female [NCHS] and the Turner syndrome [Lyon] reference standards. The hGH12 and hGH09 groups did not differ significantly from each other for either SDS variable at Last Visit. However, the hGH12 group showed significantly greater mean change from Baseline in Height SDS [NCHS] compared to the hGH09 group [0.68 SDS versus 0.40 SDS] (p=0.012), supporting the suggestion of a mild dose effect of Humatrope in this study.

2. For the first five years of treatment patients receiving Humatrope exhibited a mean growth velocity that exceeded the Turner syndrome reference [Ranke] standard by approximately 1.0 SDS (1-2 SDS in the first three years). The hGH12 and hGH09 groups did not differ significantly from each other with respect to this variable.

3. Bone Age increased similarly for both groups, advancing by approximately one year with each year of treatment, and remained similar at Last Visit. No untoward influence of growth hormone treatment upon skeletal maturation was noted during the treatment period.

Additional Efficacy Analyses

1. For the intent-to-treat population, mean Height SDS [NCHS] was greater both at Baseline and at Last Visit for the Placebo Estrogen group than the Low Dose Estrogen group. However, change in Height SDS from Baseline to Last Visit was similar for both groups. In addition, baseline imbalances were also noted between the groups for Height SDS [Lyon], so outcome differences should be interpreted with caution.

2. For the small number of patients who achieved Final Height (protocol completers), patients treated with a combination of Humatrope and low dose estrogen at early age achieved a mean Final Height which was almost 5 cm below that of patients receiving Humatrope without estrogen at an early age. These results should be interpreted with caution, in light of the small number of patients included in this analysis and the fact that the patients who completed the protocol were the older patients in the study, who received greater estradiol doses per kg bodyweight than those who entered the study at a younger age.

3. For the intent-to-treat population, mean Height (cm) at last visit at which a bone age X-ray was obtained was greater in the Placebo Estrogen group than the Low Dose Estrogen group, when adjusted for bone age and Midparental Height.

Results of Compliance Analyses

Table 23 summarizes patient compliance with the administration of study medication. Compliance was assessed for the study as a whole and by pooled treatment group for the safety population. Average compliance to the injection schedule is defined as the total number of injections reported divided by the total number of expected injections. Total study compliance is defined as the percent of patients in the safety population who were 80-120% compliant.

Table 23 **Study Compliance - Safety Population**

Pooled Treatment Group	Patient Study Compliance (%)[1]						Total Study Compliance (%)[2]
	N	Mean	SD	Median	Minimum	Maximum	
Overall	229	92.95	10.05	96.29			91.3%
hGH12	137	93.08	10.04	96.92			90.5%
hGH09	92	92.76	10.12	95.94			92.4%

[1] Total number of injections taken divided by total number of expected injections.
[2] Percent of patients who were 80-120% compliant.

Since the total number of expected injections was not available for Patient 031-1282, only 229 patients in the safety population have compliance data available. The majority of patients were highly compliant with the injection regimen. The group as a whole, and both of the growth hormone dosage groups received an average of 93% of their prescribed injections. Over 90% of patients overall and in each growth hormone dosage group were 80-120% compliant.

Safety Results

Exposure to Study Drugs

Tables 24 and 25 summarize exposure to study drugs as years in study. These tables present descriptive statistics (i.e., sample size, mean, standard deviation, median, minimum, and maximum) overall and by treatment group, for the safety population and protocol completers, respectively. Exposure is defined as the number of years that a patient was in the study and is calculated by using dates of visits attended including lapsed time between visits, up to 180 consecutive days. One patient (031-1282) is not included in this analysis due to the fact that this patient was lost to follow-up at an unspecified date after Visit 12 (approximately 2.6 years). Therefore, it was not possible to precisely calculate this patient's number of years in the study.

Table 24 Years in Study - Safety Population

Pooled Treatment Group	N	Mean	SD	Median	Minimum	Maximum
Overall	229	4.33	2.18	4.17		
hGH12	137	4.51	2.23	4.27		
hGH09	92	4.05	2.09	3.98		

Table 25 Years in Study - Protocol Completers

Pooled Treatment Group	N	Mean	SD	Median	Minimum	Maximum
Overall	31	4.54	1.66	4.54		
hGH12	20	4.49	1.64	4.37		
hGH09	11	4.63	1.77	5.00		

The mean years in study for each of the pooled Humatrope dose groups, for the safety population as a whole, was approximately four years.

The years in study for protocol completers were comparable to the findings for the safety population. For protocol completers for each treatment group and for the group as a whole, the mean duration of study exposure was approximately 4.5 years. As presented

in Table GDCI.6.1, for the intent-to treat population, approximately 54% of the patients were in the study for ≥ 5 years. Forty-five patients completed at least seven years.

Adverse Events

Serious Adverse Events

A serious event is defined as an event that:

- Results in death;
- Results in initial or prolonged inpatient hospitalization;
- Is life-threatening;
- Results in severe or permanent disability;
- Results in cancer;
- Results in a congenital anomaly;
- Results in a drug overdose;
- Is significant for any other reason.

Deaths

There were no deaths in this study.

Serious Adverse Events Classified as Unexpected and Possibly Related to Study Medication

As of the 8 February 1996 cutoff date, 5 (2%) of the 230 patients in the safety population had experienced a serious adverse event which was unexpected and possibly related to study drug. All of these patients were receiving Humatrope at the time the adverse event was reported. Table 26 provides a listing by patient of these adverse events. These events included two incidences of hypertension (in one patient this had been present for 11 years), two surgical procedures (osteotomy/bunionectomy and repair of aortic aneurysm), and one incidence of bone disorder (scoliosis).

Table 26 **Patients with Serious Adverse Events Classified as Unexpected and Possibly Related to Study Medication**

Patient	Treatment Group	Age	Event Classification Term	Event Description	Days in Study
021-1171	hGH09/PLA	15	Surgical Procedure	Repair of aortic aneurysm	1825
026-1242	hGH12/LDE	15	Hypertension	Hypertension	1800
040-1568	PLA/Switch	8	Hypertension	Hypertension	730
045-1386	hGH12/LDE	14	Surgical Procedure	Osteotomy and Bunionectomy	2299
059-1502	PLA/Switch	16	Bone Disorder	Scoliosis	635

All Serious Adverse Events

Table 27 provides a listing of all patients with serious adverse events reported as of the 8 February 1996 cutoff date, regardless of relationship to study medication. The listing in Table 27 includes all adverse events which were recorded on the serious adverse event report, whether or not each individual adverse event was considered serious.

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Table 27 **Patients with Serious Adverse Events**

Patient	Treatment Group	Age	Event Classification Term	Event Description
003-1011	PLA/Switch	9	Arthralgia	Occasional Joint Pain at Ankles
003-1012	hGH12/PLA	14	Cyst	Cyst Ovary
			Dizziness	Dizziness
			Asthenia	Fatigue
			Menorrhagia	Heavy Menstrual Bleeding
003-1015	PLA/Switch	11	Accidental Injury	Multiple Fractures
			Surgical Procedure	Facial Surgery
		14	Surgical Procedure	Surgery for Webbed Neck
003-1383	PLA/Switch*	6	Surgical Procedure	Removal of Hardware Left and Right Forehead
			Respiratory Disorder	Breathing Difficulty
004-1016	hGH09/PLA	10	Cellulitis	Cellulitis Right Ear
			Otitis Media	Right Otitis Media
			Otitis Externa	Otitis Externa Right Ear
			Fever	Fever
			Ear Pain	Right Ear Pain
		11	Surgical Procedure	Cardiac Catheterization and Balloon Angioplasty
			Aortic Stenosis	Aortic Coarctation (Recurring)
004-1021	hGH09/PLA	15	Surgical Procedure	Valgus Osteotomy Right Knee
014-1099	PLA/Switch	13	Surgical Procedure	Retinal Surgery
			Retinal Detachment	Detached Retina Right Eye
015-1140	PLA/Switch*	11	Surgical Procedure	Repair of Coarctation of Aorta
018-1136	hGH12/PLA	12	Surgical Procedure	Repair of Coarctation of Aorta
018-1139	PLA/Switch	8	Agitation	Panic Reaction to Droperidol
			Surgical Procedure	Tonsillectomy/Adenoidectomy
		11	Accidental Overdose	Overdose of Naldecon
019-1141	PLA/Switch	18	Accidental Overdose	Accidental Overdose
020-1158	hGH09/PLA	14	Surgical Procedure	Surgery for Webbed Neck
021-1171	hGH09/PLA	15	Surgical Procedure	Surgery for Aortic Aneurysm
			Surgical Procedure	Surgery for Kyphosis

*Event occurred while patient was receiving placebo injections.

Table 27 Patients with Serious Adverse Events (Cont'd)

Patient	Treatment Group	Age	Event Classification Term	Event Description
021-1172	hGH12/LDE	11	Surgical Procedure	Cardiac Catheterization
021-1173	hGH09/LDE	13	Accidental Injury	Fracture Lower Leg/Ankle
			Surgical Procedure	Surgical Repair of Fracture
			Fever	Fever
021-1175	hGH09/PLA	10	Liver Function Tests Abnormal	Liver Biopsy
022-1206	hGH09/PLA	10	Abdominal Syndrome Acute	Ruptured Appendix
			Surgical Procedure	Surgery to Remove Appendix
			Cachexia	Poor Nutritional Level
023-1217	hGH12/PLA	9	Surgical Procedure	Repair of Eardrum Perforation
026-1242	hGH12/LDE	15	Congestive Heart Failure	Congestive Heart Failure
			Hypertension	Hypertension
			Edema	Edema
			Asthenia	Exercise Intolerance
			Tachycardia	Tachycardia
			Ventricular Extrasystoles	PVC's
			Kidney Function Abnormal	Decreased Renal Function
			Generalized Edema	Anasarca
			Cardiovascular Disorder	S 3 Gallop
			Lung Edema	Pulmonary Edema
			Pleural Effusion	Right Pleural Effusion
			Pericardial Effusion	Pericardial Effusion
			Hepatomegaly	Hepatomegaly
			Peripheral Edema	Ankle Edema
			Cardiomegaly	Cardiac Enlargement
			Asthma	Wheezing
			Dyspnea	Shortness of Breath
		18	Surgical Procedure	Harrington Rod Placement
026-1243	PLA/Switch	13	Antisocial Reaction	Adolescent Adjustment Reaction
030-1273	hGH12/PLA	16	Accidental Overdose	Accidental Overdose
030-1274	hGH12/PLA	13	Accidental Overdose	Accidental Overdose

*Event occurred while patient was receiving placebo injections.

Table 27 Patients with Serious Adverse Events (Cont'd)

Patient	Treatment Group	Age	Event Classification Term	Event Description
031-1282	hGH09/PLA	8	Dehydration Pharyngitis Pneumonia Gastroenteritis	Not Available
036-1481	PLA/Switch*	8	Surgical Procedure	Dental Work
040-1351	hGH09/LDE	14	Accidental Overdose	Accidental Overdose of Study Drug
040-1352	hGH09/LDE	9	Surgical Procedure	Repair of Mandibular Thrust
040-1353	PLA/Switch	16	Accidental Overdose	Accidental Overdose of Study Drug
040-1566	hGH12/PLA	17	Cellulitis	Cellulitis
040-1568	PLA/Switch	8	Hypertension	Hypertension
041-1362	hGH09/PLA	12 14	Accidental Injury Surgical Procedure Hypertension Aortic Stenosis	Fractured Arm Cardiac Catheterization Not Available Acquired Aortic Stenosis
044-1376	hGH12/PLA	9	Gastroenteritis	Not Available
044-1377	hGH12/LDE	13	Hyperglycemia Diabetes Mellitus	Hyperglycemia Diabetes Mellitus
045-1386	hGH12/LDE	14	Surgical Procedure Arthrosis	Osteotomy and Bunionectomy Bunion
046-1393	PLA/Switch*	9	Surgical Procedure Surgical Procedure Surgical Procedure	Cardiac Catheterization Cardiac Catheterization Valvotomy
049-1422	hGH12/PLA	17	Flu Syndrome Vomiting Nausea Fever	Influenza

*Event occurred while patient was receiving placebo injections.

Table 27 Patients with Serious Adverse Events (Cont'd)

Patient	Treatment Group	Age	Event Classification Term	Event Description
052-1439	hGH12/PLA	10	Surgical Procedure Urinary Tract Infection Hostility	Repair of Rectovaginal Fistula Not Available Aggression
053-1453	hGH12/LDE	14	Gastroenteritis Surgical Procedure Surgical Procedure	Food Poisoning Surgical Removal of Keloid Ear Surgery
053-1576	hGH12/PLA	9	Accidental Injury Surgical Procedure Pain	Fractured Jaw Wired Jaw Jaw Pain
055-1466	hGH12/LDE	13	Surgical Procedure Surgical Procedure	Mastoidectomy Surgical Removal of Cholesteatoma
056-1472	hGH12/LDE	14	Surgical Procedure Lymphadenopathy Fever	Lymphadenectomy Lynphadenopathy Cat Scratch Fever
056-1473	hGH12/PLA	8	Surgical Procedure	Effective Surgery of Webbed Neck
056-1571	hGH12/PLA	11	Surgical Procedure	Tonsillectomy
059-1502	PLA/Switch	16	Bone Disorder	Scoliosis
059-1504	hGH09/LDE	8	Surgical Procedure	Tonsillectomy and Adenoidectomy
060-1516	PLA/Switch	12	Hematuria	Hematuria
061-1532	hGH09/LDE	12	Arthralgia	Pain, Knee
061-1536	hGH09/LDE	7	Surgical Procedure	Surgical Reduction of Fractured Right Arm
062-1550	hGH09/LDE	10	Surgical Procedure	Surgery for Chronic Mastoiditis

*Event occurred while patient was receiving placebo injections.

Serious adverse events were reported for 48 patients of the 230 in the safety population overall [14 patients in the PLA/Switch group (4 of these while receiving placebo injections), 12 patients in the hGH12/PLA group, 7 patients in the hGH12/LDE group, 8 patients in the hGH09/PLA group, and 7 patients in the hGH09/LDE group].

Table 28 provides a listing, in order of decreasing overall frequency, of adverse events (both serious and nonserious) which were listed on the serious adverse event reports. Fifty-two reports of serious adverse events occurred among 44 patients receiving Humatrope at some point during the study. Among the 52 reports of serious adverse events that occurred in patients who were taking Humatrope at the time of the event, 102 adverse events were reported overall (both serious and accompanying nonserious events). The most frequent adverse event was surgical procedure, for which 34 incidences were reported among 26 patients. Accidental overdose, accidental injury (bone fractures), fever, gastroenteritis, cellulitis, hypertension, aortic stenosis, asthenia, and vomiting were reported between two and six times each. Four patients in the PLA/Switch treatment group were receiving placebo injections at the time of their serious adverse event. These patients were Patient 003-1383 (surgical procedure/removal of hardware left and right forehead, and respiratory disorder/breathing difficulty), Patient 015-1140 (surgical procedure/repair of coarctation of aorta), Patient 036-1481 (surgical procedure/dental work), and Patient 046-1393 (surgical procedure/cardiac catheterization, and surgical procedure/valvotomy).

Table 28 **Frequency of Adverse Events Listed on Serious Adverse Event Reports: All hGH**

Event Classification Term	All hGH[1]
Total Number of Patients	44
Total Number of SAE Reports	52
Total Number of Events	102
Surgical Procedure	34
Accidental Overdose	6
Accidental Injury	5
Fever	4
Gastroenteritis	4
Cellulitis	3
Hypertension	3
Aortic Stenosis	2
Asthenia	2
Vomiting	2
Abdominal Syndrome Acute	1
Agitation	1
Antisocial Reaction	1
Arthrosis	1
Asthma	1
Cachexia	1
Cardiomegaly	1
Cardiovascular Disorder	1
Congestive Heart Failure	1
Cyst	1
Dehydration	1
Dizziness	1
Dyspnea	1
Ear Pain	1
Edema	1
Flu Syndrome	1
Generalized Edema	1
Hepatomegaly	1
Hostility	1
Kidney Function Abnormal	1
Liver Function Tests Abnormal	1

[1] All hGH includes all patients who reported serious adverse events while on Humatrope.

Note: This table lists both serious and nonserious adverse events listed on the serious adverse event reports.

Table 28 **Frequency of Adverse Events Listed on Serious Adverse Event Reports: All hGH (Cont'd)**

Event Classification Term	All hGH[1]
Lung Edema	1
Lymphadenopathy	1
Menorrhagia	1
Nausea	1
Otitis Externa	1
Otitis Media	1
Pain	1
Pericardial Effusion	1
Peripheral Edema	1
Pharyngitis	1
Pleural Effusion	1
Pneumonia	1
Retinal Detachment	1
Tachycardia	1
Urinary Tract Infection	1
Ventricular Extrasystoles	1

[1] All hGH includes all patients who reported serious adverse events while on Humatrope.

Note: This table lists both serious and nonserious adverse events listed on the serious adverse event reports.

Discontinuations Due to Adverse Events

As of the 8 February 1996 cutoff date, 4 (2%) of the 230 patients in the safety population prematurely discontinued from the study due to an adverse event. Table 29 provides a listing of these individual patients, their treatment group, and the event leading to discontinuation. Events leading to discontinuation were: migraine, vascular disorder, gastrointestinal disorder, and bone disorder (scoliosis). Two of these patients, Patients 021-1171 (vascular disorder) and 059-1502 (bone disorder) had serious adverse events that were considered unexpected and possibly related to study medication. It could not be determined whether the patient with scoliosis had the condition at the start of the study. No serious adverse events were reported for Patient 012-1328 (migraine). Patient 021-1176 (gastrointestinal disorder/Crohn's disease) had symptoms prior to receiving study medication but was not diagnosed until after receiving Humatrope.

Table 29 Patients Discontinued Due to Adverse Events

Patient	Treatment Group	Age	Origin	Visit	Days in Study	Event Classification Term
012-1328	hGH09/LDE	14	Caucasian	13	1000	Migraine
021-1171	hGH09/PLA	15	Caucasian	18	1825	Vascular Disorder
021-1176	hGH09/PLA	9	Caucasian	3	62	Gastrointestinal Disorder
059-1502	PLA/Switch	16	Caucasian	15	635	Bone Disorder

Treatment-Emergent Events

Treatment-emergent events reported in ≥5% of patients in the safety population overall are listed in order of decreasing total frequency by Humatrope dose group in Table 30. For each dose group in Table 30, results for patients who received low dose estrogen treatment were pooled with the results for patients who did not.

Table 30 **Frequency of Common Treatment-Emergent Events: hGH12 Versus hGH09 - Safety Population**

Event Classification Term	Overall	Pooled hGH Treatment Group	
		hGH12	hGH09
Total Number of Patients	230	137	93
Any Adverse Event	228 (99.1%)	136 (99.3%)	92 (98.9%)
Rhinitis	191 (83.0%)	120 (87.6%)	71 (76.3%)
Pharyngitis	148 (64.3%)	87 (63.5%)	61 (65.6%)
Headache	145 (63.0%)	92 (67.2%)	53 (57.0%)
Flu Syndrome	124 (53.9%)	82 (59.9%)	42 (45.2%)
Fever	116 (50.4%)	73 (53.3%)	43 (46.2%)
Cough Increased	102 (44.3%)	62 (45.3%)	40 (43.0%)
Otitis Media	99 (43.0%)	55 (40.1%)	44 (47.3%)
Infection	93 (40.4%)	57 (41.6%)	36 (38.7%)
Surgical Procedure	89 (38.7%)	58 (42.3%)	31 (33.3%)
Vomiting	78 (33.9%)	45 (32.8%)	33 (35.5%)
Accidental Injury	75 (32.6%)	45 (32.8%)	30 (32.3%)
Sinusitis	74 (32.2%)	42 (30.7%)	32 (34.4%)
Ear Pain	68 (29.6%)	44 (32.1%)	24 (25.8%)
Rash	65 (28.3%)	42 (30.7%)	23 (24.7%)
Pain	59 (25.7%)	34 (24.8%)	25 (26.9%)
Tooth Disorder	55 (23.9%)	35 (25.5%)	20 (21.5%)
Abdominal Pain	52 (22.6%)	31 (22.6%)	21 (22.6%)
Diarrhea	51 (22.2%)	31 (22.6%)	20 (21.5%)
Bronchitis	49 (21.3%)	24 (17.5%)	25 (26.9%)
Ear Disorder	45 (19.6%)	26 (19.0%)	19 (20.4%)
Gastrointestinal Disorder	43 (18.7%)	28 (20.4%)	15 (16.1%)
Hypothyroidism	40 (17.4%)	27 (19.7%)	13 (14.0%)
Otitis Externa	36 (15.7%)	20 (14.6%)	16 (17.2%)
Urinary Tract Infection	34 (14.8%)	21 (15.3%)	13 (14.0%)
Nausea	33 (14.3%)	17 (12.4%)	16 (17.2%)
Allergic Reaction	32 (13.9%)	21 (15.3%)	11 (11.8%)
Conjunctivitis	30 (13.0%)	20 (14.6%)	10 (10.8%)
Back Pain	26 (11.3%)	14 (10.2%)	12 (12.9%)
Dyspepsia	26 (11.3%)	13 (9.5%)	13 (14.0%)
Myalgia	26 (11.3%)	14 (10.2%)	12 (12.9%)
Gastroenteritis	25 (10.9%)	13 (9.5%)	12 (12.9%)
Nausea and Vomiting	21 (9.1%)	12 (8.8%)	9 (9.7%)
Asthenia	19 (8.3%)	13 (9.5%)	6 (6.5%)
Epistaxis	19 (8.3%)	13 (9.5%)	6 (6.5%)
Lymphadenopathy	18 (7.8%)	11 (8.0%)	7 (7.5%)
Bone Disorder	17 (7.4%)	8 (5.8%)	9 (9.7%)
Dizziness	16 (7.0%)	12 (8.8%)	4 (4.3%)

Note: This table includes events that occurred in ≥ 5% of the patients in the safety population.

Table 30 **Frequency of Common Treatment-Emergent Events: hGH12 Versus hGH09 - Safety Population (Cont'd)**

Event Classification Term	Overall	Pooled hGH Treatment Group	
		hGH12	hGH09
Skin Benign Neoplasm	16 (7.0%)	12 (8.8%)	4 (4.3%)
Metrorrhagia	14 (6.1%)	6 (4.4%)	8 (8.6%)
Arthralgia	13 (5.7%)	5 (3.6%)	8 (8.6%)
Hypertension	13 (5.7%)	8 (5.8%)	5 (5.4%)
Pustular Rash	13 (5.7%)	9 (6.6%)	4 (4.3%)
Respiratory Disorder	13 (5.7%)	6 (4.4%)	7 (7.5%)
Eye Disorder	12 (5.2%)	9 (6.6%)	3 (3.2%)
Fungal Dermatitis	12 (5.2%)	6 (4.4%)	6 (6.5%)
Menstrual Disorder	12 (5.2%)	7 (5.1%)	5 (5.4%)
Pneumonia	12 (5.2%)	3 (2.2%)	9 (9.7%)
Stomatitis	12 (5.2%)	8 (5.8%)	4 (4.3%)

Note: This table includes events that occurred in ≥ 5% of the patients in the safety population.

Almost all patients in both Humatrope dose groups reported at least one treatment-emergent event. Differences between treatment groups of ≥5% were observed for several events. Rhinitis, headache, flu syndrome, fever, surgical procedure, ear pain, rash, and hypothyroidism were reported for a higher percentage of patients in the hGH12 dose group than in the hGH09 dose group. In contrast, otitis media, bronchitis, arthralgia, and pneumonia were reported for a higher percentage of patients in the hGH09 dose group than in the hGH12 dose group.

The number and percentage of patients for whom treatment-emergent events were reported (in patients who received concomitant low dose estrogen therapy at a young age versus those who did not) are shown in Table 31 For each group (estrogen versus placebo), events for patients who received the hGH09 dose were pooled with those of patients who received the hGH12 dose. Treatment-emergent events which occurred in ≥5% of patients overall are displayed in order of decreasing total frequency.

Table 31 **Frequency of Common Treatment-Emergent Events: hGH/LDE Versus hGH/PLA - Safety Population**

Event Classification Term	Overall	Pooled Treatment Group	
		hGH/LDE[1]	hGH/PLA[2]
Total Number of Patients	230	89	141
Any Adverse Event	228 (99.1%)	89 (100.0%)	139 (98.6%)
Rhinitis	191 (83.0%)	71 (79.8%)	120 (85.1%)
Pharyngitis	148 (64.3%)	60 (67.4%)	88 (62.4%)
Headache	145 (63.0%)	52 (58.4%)	93 (66.0%)
Flu Syndrome	124 (53.9%)	44 (49.4%)	80 (56.7%)
Fever	116 (50.4%)	49 (55.1%)	67 (47.5%)
Cough Increased	102 (44.3%)	43 (48.3%)	59 (41.8%)
Otitis Media	99 (43.0%)	41 (46.1%)	58 (41.1%)
Infection	93 (40.4%)	36 (40.4%)	57 (40.4%)
Surgical Procedure	89 (38.7%)	28 (31.5%)	61 (43.3%)
Vomiting	78 (33.9%)	34 (38.2%)	44 (31.2%)
Accidental Injury	75 (32.6%)	28 (31.5%)	47 (33.3%)
Sinusitis	74 (32.2%)	29 (32.6%)	45 (31.9%)
Ear Pain	68 (29.6%)	30 (33.7%)	38 (27.0%)
Rash	65 (28.3%)	27 (30.3%)	38 (27.0%)
Pain	59 (25.7%)	24 (27.0%)	35 (24.8%)
Tooth Disorder	55 (23.9%)	17 (19.1%)	38 (27.0%)
Abdominal Pain	52 (22.6%)	22 (24.7%)	30 (21.3%)
Diarrhea	51 (22.2%)	19 (21.3%)	32 (22.7%)
Bronchitis	49 (21.3%)	15 (16.9%)	34 (24.1%)
Ear Disorder	45 (19.6%)	18 (20.2%)	27 (19.1%)
Gastrointestinal Disorder	43 (18.7%)	13 (14.6%)	30 (21.3%)
Hypothyroidism	40 (17.4%)	18 (20.2%)	22 (15.6%)
Otitis Externa	36 (15.7%)	15 (16.9%)	21 (14.9%)
Urinary Tract Infection	34 (14.8%)	13 (14.6%)	21 (14.9%)
Nausea	33 (14.3%)	14 (15.7%)	19 (13.5%)
Allergic Reaction	32 (13.9%)	12 (13.5%)	20 (14.2%)
Conjunctivitis	30 (13.0%)	9 (10.1%)	21 (14.9%)
Back Pain	26 (11.3%)	15 (16.9%)	11 (7.8%)
Dyspepsia	26 (11.3%)	14 (15.7%)	12 (8.5%)
Myalgia	26 (11.3%)	9 (10.1%)	17 (12.1%)
Gastroenteritis	25 (10.9%)	12 (13.5%)	13 (9.2%)
Nausea and Vomiting	21 (9.1%)	11 (12.4%)	10 (7.1%)
Asthenia	19 (8.3%)	5 (5.6%)	14 (9.9%)

[1] hGH/LDE = hGH with LDE (treatment groups hGH12/LDE and hGH 09/LDE).

[2] hGH/PLA = hGH with oral placebo (treatment groups hGH12/PLA, hGH09/PLA, and PLA/Switch).

Note: This table includes events that occurred in ≥ 5% of the patients in the safety population.

Table 31 **Frequency of Common Treatment-Emergent Events: hGH/LDE Versus hGH/PLA - Safety Population (Cont'd)**

Event Classification Term	Overall	Pooled Treatment Group	
		hGH/LDE[1]	hGH/PLA[2]
Epistaxis	19 (8.3%)	9 (10.1%)	10 (7.1%)
Lymphadenopathy	18 (7.8%)	7 (7.9%)	11 (7.8%)
Bone Disorder	17 (7.4%)	7 (7.9%)	10 (7.1%)
Dizziness	16 (7.0%)	8 (9.0%)	8 (5.7%)
Skin Benign Neoplasm	16 (7.0%)	4 (4.5%)	12 (8.5%)
Metrorrhagia	14 (6.1%)	11 (12.4%)	3 (2.1%)
Arthralgia	13 (5.7%)	7 (7.9%)	6 (4.3%)
Hypertension	13 (5.7%)	3 (3.4%)	10 (7.1%)
Pustular Rash	13 (5.7%)	4 (4.5%)	9 (6.4%)
Respiratory Disorder	13 (5.7%)	3 (3.4%)	10 (7.1%)
Eye Disorder	12 (5.2%)	6 (6.7%)	6 (4.3%)
Fungal Dermatitis	12 (5.2%)	3 (3.4%)	9 (6.4%)
Menstrual Disorder	12 (5.2%)	6 (6.7%)	6 (4.3%)
Pneumonia	12 (5.2%)	6 (6.7%)	6 (4.3%)
Stomatitis	12 (5.2%)	6 (6.7%)	6 (4.3%)

[1] hGH/LDE = hGH with LDE (treatment groups hGH12/LDE and hGH 09/LDE).
[2] hGH/PLA = hGH with oral placebo (treatment groups hGH12/PLA, hGH09/PLA, and PLA/Switch).
Note: This table includes events that occurred in ≥ 5% of the patients in the safety population.

All patients who received low dose estrogen at an early age, and almost all patients who did not receive estrogen (i.e. received placebo estrogen), reported at least one treatment-emergent event. Differences between treatment groups of ≥5% were observed for several events. Pharyngitis, fever, increased cough, otitis media, ear pain, back pain, vomiting, dyspepsia, nausea and vomiting, and metrorrhagia were reported by a higher percentage of patients who received estrogen than by patients who received placebo estrogen. In contrast, rhinitis, headache, flu syndrome, surgical procedure, tooth disorder, bronchitis, and gastrointestinal disorder were reported by a higher percentage of patients who received placebo estrogen than by patients who received estrogen. Although gastrointestinal symptoms might be expected to occur with increased frequency in patients taking estrogen, this does not appear to be the case in this study. While the percentage of patients with nausea and vomiting and dyspepsia is greater in the estrogen-treated group, the reverse is true for the more general complaint of gastrointestinal disorder. The one treatment-emergent event that does appear to be substantially different between the groups is metrorrhagia. Probably not surprisingly, this event was reported by 12% of patients receiving low dose estrogen, compared with 2% of patients receiving placebo estrogen.

Table 32 presents an analysis of treatment-emergent events during the first 18 months of this study. During this period, the PLA/Switch treatment group received only placebo trial materials (placebo injections and placebo estrogen). Thus, incidence rates for all patients receiving growth hormone (all doses combined) are compared with those for patients receiving placebo.

Treatment-emergent events which occurred in ≥5% of patients overall within the first 18 months of treatment are displayed in order of decreasing total frequency in Table 32.

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Table 32 **Frequency of Common Treatment-Emergent Events for First Eighteen Months of Treatment: hGH Versus PLA - Safety Population**

Event Classification Term	Overall	Pooled Treatment Group	
		hGH Treated[1]	Placebo Injected
Total Number of Patients	230	184	46
Any Adverse Event	228 (99.1%)	183 (99.5%)	45 (97.8%)
Rhinitis	161 (70.0%)	128 (69.6%)	33 (71.7%)
Headache	104 (45.2%)	81 (44.0%)	223 (50.0%)
Pharyngitis	99 (43.0%)	77 (41.8%)	22 (47.8%)
Flu Syndrome	77 (33.5%)	63 (34.2%)	14 (30.4%)
Fever	73 (31.7%)	59 (32.1%)	14 (30.4%)
Infection	60 (26.1%)	43 (23.4%)	17 (37.0%)
Otitis Media	60 (26.1%)	54 (29.3%)	6 (13.0%)
Cough Increased	59 (25.7%)	51 (27.7%)	8 (17.4%)
Surgical Procedure	50 (21.7%)	35 (19.0%)	15 (32.6%)
Vomiting	44 (19.1%)	36 (19.6%)	8 (17.4%)
Accidental Injury	42 (18.3%)	34 (18.5%)	8 (17.4%)
Ear Pain	38 (16.5%)	31 (16.8%)	7 (15.2%)
Rash	35 (15.2%)	24 (13.0%)	11 (23.9%)
Sinusitis	34 (14.8%)	25 (13.6%)	9 (19.6%)
Diarrhea	32 (13.9%)	24 (13.0%)	8 (17.4%)
Tooth Disorder	28 (12.2%)	22 (12.0%)	6 (13.0%)
Pain	26 (11.3%)	22 (12.0%)	4 (8.7%)
Abdominal Pain	25 (10.9%)	21 (11.4%)	4 (8.7%)
Bronchitis	25 (10.9%)	19 (10.3%)	6 (13.0%)
Ear Disorder	23 (10.0%)	20 (10.9%)	3 (6.5%)
Gastrointestinal Disorder	23 (10.0%)	17 (9.2%)	6 (13.0%)
Dyspepsia	20 (8.7%)	18 (9.8%)	2 (4.3%)
Urinary Tract Infection	20 (8.7%)	15 (8.2%)	5 (10.9%)
Gastroenteritis	19 (8.3%)	17 (9.2%)	2 (4.3%)
Otitis Externa	19 (8.3%)	16 (8.7%)	3 (6.5%)
Allergic Reaction	18 (7.8%)	13 (7.1%)	5 (10.9%)
Hypothyroidism	15 (6.5%)	11 (6.0%)	4 (8.7%)
Conjunctivitis	14 (6.1%)	13 (7.1%)	1 (2.2%)
Myalgia	14 (6.1%)	12 (6.5%)	2 (4.3%)
Nausea and Vomiting	12 (5.2%)	10 (5.4%)	2 (4.3%)

[1] hGH Treated includes all hGH treatment groups.

Note: This table includes events that occurred in ≥ 5% of the patients in the safety population within the first eighteen months of treatment.

Almost all patients in the Humatrope group and the Placebo group reported at least one treatment-emergent event within the first 18 months of treatment. Otitis media, increased cough, dyspepsia, and conjunctivitis were reported by a higher percentage of patients in the Humatrope group than in the Placebo group. In contrast, headache, pharyngitis, infection, surgical procedure, rash, and sinusitis were reported by a higher percentage of patients in the Placebo group than in the Humatrope group.

Treatment-emergent events of special interest were identified for this study because of concern that development or worsening of some adverse events is potentially causally related to treatment with Humatrope. These events are presented for the complete safety population and by pooled Humatrope dose group in Table 33.

Table 33 Treatment-Emergent Events of Special Interest: hGH12 Versus hGH09 - Safety Population

		Pooled hGH Treatment Group	
Adverse Event	Overall	hGH12	hGH09
Total Number of Patients	230	137	93
Bone Disorder	17 (7.4%)	8 (5.8%)	9 (9.7%)
Edemas			
Edema	4 (1.7%)	2 (1.5%)	2 (2.2%)
Face Edema	3 (1.3%)	1 (0.7%)	2 (2.2%)
Generalized Edema	1 (0.4%)	1 (0.7%)	0
Injection Site Edema	1 (0.4%)	1 (0.7%)	0
Labial Edema	1 (0.4%)	1 (0.7%)	0
Lung Edema	1 (0.4%)	1 (0.7%)	0
Peripheral Edema	11 (4.8%)	8 (5.8%)	3 (3.2%)
Hyperglycemia	1 (0.4%)	1 (0.7%)	0
Hypertension	13 (5.7%)	8 (5.8%)	5 (5.4%)
Hypothyroidism	40 (17.4%)	27 (19.7%)	13 (14.0%)
Increased Nevi[1]	14 (6.1%)	10 (7.3%)	4 (4.3%)
Lymphedema	2 (0.9%)	0	2 (2.2%)

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

Apart from hypothyroidism, all treatment-emergent events of special interest occurred in <10% of patients in either group. There was no obvious dose-response relationship between the dose of Humatrope and an increased occurrence of any particular treatment-emergent event of special interest. Hypothyroidism was the most frequently occurring treatment-emergent event of special interest, being reported in 19.7% of patients in the hGH12 group and 14.0% of patients in the hGH09 group. With respect to the development of hypothyroidism in patients enrolled in this study, it should be noted that patients with Turner syndrome have a well-recognized increase in frequency of thyroid

abnormalities, as high as 20-30% in some series. Furthermore, the etiology of the hypothyroidism in the patients in this study was not investigated, as no further studies, such as thyroid antibodies, were performed.

Clinical Laboratory Evaluation

Blood samples were obtained according to the Master Schedule of Procedures. Assessments included variables for blood chemistry, hematology, urinalysis, thyroid function, glucose homeostasis (fasting and 2-hour postprandial glucose and insulin, hemoglobin A_{1C}), sex hormones (FSH, LH, estradiol), lipids (triglycerides, total cholesterol, HDL, LDL, VLDL), IGF-I, and antibodies to hGH and *Escherischi Coli* polypeptide (ECP). Sex hormones are not discussed in this report.

Blood Chemistry

Summary statistics for selected blood chemistry variables at Baseline, Last Visit, and for Change from Baseline to Last Visit are presented for pooled treatment groups in Table 34. Mean and median values for representative liver function tests [GGT, SGOT(AST) and SGPT(ALT)], and other biochemical parameters (calcium, phosphorus, and urea nitrogen) were normal at Baseline and Last Visit in both the hGH12 and hGH09 groups. Mean values for creatinine were slightly lower at Baseline in both pooled treatment groups (57.0 mmol/L and 57.4 mmol/L for the hGH12 group and hGH09 group, respectively) than at Last Visit (68.9 mmol/L and 66.1 mmol/L, respectively). However, on both occasions these values were normal for childhood. Alkaline phosphatase and creatine kinase were normal for both groups at both time points.

Table 34 **Blood Chemistry Test Results - Safety Population**

Analyte	Statistic	Pooled Treatment Group					
		hGH12			hGH09		
		Baseline	Last Visit	Change	Baseline	Last Visit	Change
Alkaline Phosphatase (U/L)	n	135	136	135	90	93	90
	Mean	200.6	175.5	-25.0	199.5	172.0	-27.2
	SD	53.1	59.1	57.8	48.6	68.1	66.8
	Median	194.0	170.0	-22.0	192.0	157.0	-35.0
	Minimum						
	Maximum						
Calcium (mmol/L)	n	134	136	134	90	93	90
	Mean	2.38	2.31	-0.08	2.38	2.31	-0.07
	SD	0.10	0.11	0.12	0.09	0.12	0.12
	Median	2.37	2.30	-0.08	2.39	2.30	-0.07
	Minimum						
	Maximum						
Creatine Kinase (U/L)	n	134	136	134	90	93	90
	Mean	117.3	144.3	26.2	117.6	127.0	10.4
	SD	102.0	148.2	94.6	89.5	71.8	110.1
	Median	96.5	114.0	9.5	98.0	115.0	12.0
	Minimum						
	Maximum						

Table 34 Blood Chemistry Test Results - Safety Population (Cont'd)

		Pooled Treatment Group					
		hGH12			hGH09		
Analyte	Statistic	Baseline	Last Visit	Change	Baseline	Last Visit	Change
Inorganic Phosphorous	n	134	136	134	88	93	88
(mmol/L)	Mean	1.49	1.50	0.01	1.52	1.47	-0.05
	SD	0.15	0.18	0.22	0.15	0.16	0.20
	Median	1.49	1.49	0.00	1.55	1.45	-0.07
	Minimum						
	Maximum						
GGT	n	134	136	134	89	93	89
(U/L)	Mean	18.2	21.3	3.1	17.7	22.8	5.3
	SD	22.0	30.8	24.2	14.2	26.1	19.4
	Median	12.0	13.0	0.0	13.0	14.0	0.0
	Minimum						
	Maximum						
SGOT (AST)	n	134	136	134	90	93	90
(U/L)	Mean	27.5	26.3	-1.1	28.4	27.9	-0.2
	SD	8.8	15.3	13.7	8.0	19.0	18.0
	Median	27.0	23.0	-3.0	26.5	24.0	-3.0
	Minimum						
	Maximum						

Table 34 **Blood Chemistry Test Results - Safety Population (Cont'd)**

		Pooled Treatment Group					
		hGH12			hGH09		
Analyte	Statistic	Baseline	Last Visit	Change	Baseline	Last Visit	Change
SGPT (ALT)	n	134	136	134	90	93	90
(U/L)	Mean	20.0	21.7	1.7	22.3	26.8	4.6
	SD	12.8	19.8	17.1	13.6	32.7	30.4
	Median	17.0	16.0	0.0	18.0	18.0	-1.0
	Minimum						
	Maximum						
Creatinine	n	135	136	135	90	93	90
(mmol/L)	Mean	57.0	68.9	11.9	57.4	66.1	8.8
	SD	12.5	10.0	13.1	11.2	10.1	14.0
	Median	53.0	71.0	9.0	62.0	62.0	9.0
	Minimum						
	Maximum						
Urea Nitrogen	n	135	136	135	90	93	90
(mmol/L)	Mean	4.06	3.95	-0.11	4.23	3.92	-0.32
	SD	1.25	1.18	1.35	1.04	1.20	1.14
	Median	3.90	3.90	0.00	4.30	3.90	-0.40
	Minimum						
	Maximum						

To monitor for potential GH-induced changes in key laboratory studies, numerical cut points were assigned beyond which values were considered to be clinically significant. The number of patients in each pooled treatment group with at least one value above the clinically significant cut point for selected blood chemistry variables is presented in Table 35. The two pooled groups were similar with respect to the proportion of patients with values above the clinically significant cut point for alkaline phosphatase, creatine kinase, GGT, AST/SGOT, and ALT/SGPT. The relatively high frequency of patients with alkaline phosphatase and creatine kinase values above the clinically significant cut points may reflect Humatrope-induced enhancement of growth.

To evaluate any potential effect of Humatrope and low dose estrogen upon hepatic function, all values for GGT, SGOT, and SGPT for all patients with a single value above the clinically significant cut point for any one of the three enzymes, were reviewed. The 151 observations of values above the designated cut points occurred in 30 patients (5 in the hGH09/LDE group; 7 in the hGH09/PLA group; 6 in the hGH12/LDE group; 4 in the hGH12/PLA group; and 8 in the PLA/Switch group). When individual patient data were evaluated, the patients fell into three broad clinical groups: those in whom only one or two enzymes of the three were above the cut point at isolated visits [19 (63%) of the total patients identified with values above the clinically significant cut points]; those in whom all three enzymes were above the cut points at the same visit, or who had one or two enzymes above the cut point intermittently [6 patients (20%)]; and those in whom all three enzymes were above the cutpoint persistently or recurrently [5 patients (17%)]. Of the latter five patients, two were in the hGH09/PLA group, and one each in the hGH12/LDE, hGH12/PLA, and PLA/Switch groups. The visit at which the increased liver enzymes were detected for the patient in the PLA/Switch group occurred while the patient (021-1179) was receiving placebo growth hormone. The highest liver enzyme value recorded was GGT of 350 U/L in Patient 049-1422 (in the hGH12/PLA group). The liver enzymes were entirely normal for this patient at the following visit. The liver enzymes remained persistently increased for Patients 021-1179 (PLA/Switch), 021-1175 (hgh09/PLA), 026-1244 (hGH09/PLA), and 052-1440 (hGH12/LDE). Patient 021-1175, who was receiving 0.09 mg/kg/dose of Humatrope and placebo estrogen, underwent a liver biopsy because of the 9-year persistence of her abnormal liver function tests. For this patient, these abnormalities were a preexisting event.

Table 35 **Blood Chemistry: Number of Patients with at Least One Value Above the Clinically Significant Cut Point - Safety Population**

Analyte	Pooled Treatment Group hGH12[1]	Pooled Treatment Group hGH09[1]	Age Range (Years)	Clinically Significant Upper Cut Point
Alkaline Phosphatase	40 (29.4%)	23 (24.7%)	0-10	312 (U/L)
			10-15	300 (U/L)
			15-20	110 (U/L)
Creatine Kinase	26 (19.1%)	16 (17.2%)	All Ages	338 (U/L)
GGT	9 (6.6%)	5 (5.4%)	All Ages	98 (U/L)
SGOT (AST)	9 (6.6%)	10 (10.8%)	All Ages	68 (U/L)
SGPT (ALT)	14 (10.3%)	11 (11.8%)	All Ages	68 (U/L)

[1] Number (percent). Percentages relative to number of patients with test results in respective treatment group.

Electrolytes

Summary statistics for electrolyte concentrations (sodium, potassium, bicarbonate, and chloride) at Baseline, Last Visit, and for Change from Baseline to Last Visit, are presented for pooled treatment groups in Table 36. Mean and median electrolyte values at Baseline and Last Visit were normal in both pooled treatment groups, and no meaningful trends in electrolyte concentration were observed during the study.

Table 36 **Electrolyte Results - Safety Population**

		Pooled Treatment Group					
		hGH12			hGH09		
Analyte	Statistic	Baseline	Last Visit	Change	Baseline	Last Visit	Change
Sodium	n	135	136	135	90	93	90
(mmol/L)	Mean	139.9	138.8	-1.1	140.0	139.3	-0.7
	SD	2.3	2.3	3.3	2.5	2.8	3.1
	Median	140.0	139.0	-1.0	140.0	139.0	-1.0
	Minimum						
	Maximum						
Potassium	n	135	136	135	88	93	88
(mmol/L)	Mean	4.24	4.18	-0.07	4.30	4.22	-0.08
	SD	0.33	0.30	0.43	0.37	0.32	0.44
	Median	4.20	4.10	-0.10	4.30	4.20	-0.10
	Minimum						
	Maximum						
Bicarbonate	n	136	136	136	90	93	90
(mmol/L)	Mean	23.20	22.39	-0.81	23.97	22.96	-0.97
	SD	2.87	2.74	3.89	2.72	2.67	3.72
	Median	23.00	22.50	-1.40	23.80	22.80	-0.80
	Minimum	16.20	16.20	-11.70	19.00	16.40	-10.10
	Maximum	31.80	31.70	9.20	30.00	29.40	6.70
Chloride	n	135	136	135	90	93	90
(mmol/L)	Mean	105.0	105.0	0.0	105.0	105.2	0.3
	SD	3.4	3.2	4.1	2.7	3.4	4.4
	Median	105.0	105.0	0.0	105.0	106.0	1.0
	Minimum						
	Maximum						

Hematology

Summary statistics for selected hematology variables (hemoglobin, hematocrit, RBC, and WBC) at Baseline, Last Visit, and for Change from Baseline to Last Visit, are presented for pooled treatment groups in Table 37. Mean and median values at Baseline and Last Visit were normal for these selected variables in both treatment groups, and no meaningful trends were observed during the study, although both mean and median values for RBC and WBC decreased from Baseline to Last Visit for both treatment groups. No WBC values above the clinically significant cut point of 20 x 10^9/L were recorded during the study.

Table 37 **Hematology Test Results - Safety Population**

Analyte	Statistic	Pooled Treatment Group					
		hGH12			hGH09		
		Baseline	Last Visit	Change	Baseline	Last Visit	Change
Hemoglobin [mmol/L(Fe)]	n	130	136	130	90	93	90
	Mean	8.52	8.74	0.21	8.52	8.66	0.13
	SD	0.59	0.58	0.53	0.64	0.63	0.57
	Median	8.40	8.76	0.19	8.50	8.63	0.16
	Minimum						
	Maximum						
Hematocrit (proportion of whole blood volume)	n	129	136	129	89	93	89
	Mean	0.40	0.41	0.01	0.41	0.41	0.00
	SD	0.03	0.03	0.03	0.03	0.03	0.03
	Median	0.40	0.41	0.01	0.40	0.41	0.00
	Minimum						
	Maximum						
Erythrocyte Count (RBC) (10^{12}/L)	n	130	136	130	90	93	90
	Mean	4.82	4.75	-0.09	4.82	4.72	-0.11
	SD	0.39	0.34	0.28	0.39	0.36	0.31
	Median	4.80	4.75	-0.10	4.80	4.70	-0.10
	Minimum						
	Maximum						

Note: No patient was found to have a WBC value greater than the clinically significant upper cut point (20 x 10^9/L).

Table 37 Hematology Test Results - Safety Population (Cont'd)

		Pooled Treatment Group					
		hGH12			hGH09		
Analyte	Statistic	Baseline	Last Visit	Change	Baseline	Last Visit	Change
White Blood Cell Count (WBC)	n	130	136	130	90	93	90
(10^9/L)	Mean	6.89	5.74	-1.16	7.40	6.17	-1.22
	SD	2.04	1.42	1.94	2.47	1.89	2.65
	Median	6.37	5.63	-0.91	6.92	5.78	-1.29
	Minimum						
	Maximum						

Note: No patient was found to have a WBC value greater than the clinically significant upper cut point (20 x 10^9/L).

Urinalysis

No meaningful differences were observed between the pooled growth hormone dosage groups for any urinalysis parameter.

Thyroid Function

Summary statistics for selected thyroid function tests [total T4 concentration by radioimmunoassay and thyroid stimulating hormone (TSH) activity] at Baseline, Last Visit, and for Change from Baseline to Last Visit, are presented for pooled treatment groups in Table 38. Mean and median total T4 concentrations were normal at Baseline and Last Visit in both growth hormone dosage groups. Mean and median TSH values were normal at Baseline and Last Visit for the hGH09 group and at Baseline for the hGH12 group. The hGH12 group had a mildly elevated mean TSH value at Last Visit (7.69 mU/L) but a normal median value at Last Visit (2.70 mU/L). The elevated TSH mean value is predominately driven by a single elevated TSH value (391.70 mU/L) at the Last Visit.

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Table 38 **Thyroid Function Test Results - Safety Population**

Analyte	Statistic	Pooled Treatment Group					
		hGH12			hGH09		
		Baseline	Last Visit	Change	Baseline	Last Visit	Change
T4	n	134	136	134	92	93	92
(nmol/L)	Mean	115.8	116.3	0.7	119.5	116.8	-2.5
	SD	22.3	26.2	24.3	25.1	21.4	24.3
	Median	115.0	113.0	1.0	115.0	113.0	-2.0
	Minimum						
	Maximum						
TSH	n	134	136	134	90	93	90
(mU/L)	Mean	3.25	7.69	4.52	3.10	3.17	0.12
	SD	2.36	39.38	39.47	1.87	4.18	4.36
	Median	2.85	2.70	0.00	2.70	2.50	-0.15
	Minimum						
	Maximum						

Note: Age-specific reference ranges for T4 from SciCor, Inc. are: 94-193 nmol/L (1-6 yr), 82-171 nmol/L (6-11 yr), 72-151 nmol/L (11-16 yr), 54-152 nmol/L (16-21 yr), and 58-161 nmol/L (>21 yr). Reference range for TSH from Scicor, Inc. is 0.3-4.5 mU/L.

The numbers of patients with at least one value beyond the clinically significant cut points for T4 or TSH are presented for pooled treatment groups in Table 39. A large number of patients in both the growth hormone dosage groups had T4 values outside the specified cut points. In part, this reflects the fact that the cut points were chosen conservatively to ensure that patients with potentially significant values would not be missed. Forty-one (30.1%) patients in the hGH12 group and 17 (18.3%) patients in the hGH09 group had T4 values below the clinically significant cut point. Review of the individual patient data reveals eight patients with primary hypothyroidism, defined by increased TSH values accompanying their low T4 concentrations. Six of these patients were in the hGH12/LDE group, one was in the hGH12/PLA group, and one was in the hGH09/PLA group. Of the remaining 50 patients with T4 values below the cut point, 10 had low T4 with low or normal TSH, possibly representing secondary or tertiary hypothyroidism. The other 40 patients had values that were only marginally below the assigned cut point and occurred sporadically, without associated TSH increase. These are felt likely to be of no true clinical significance.

Twenty-one patients (17 in the hGH12 group and 4 in the hGH09 group) had TSH values at some time in the study that fell above the clinically significant cut point. Eight of these were the patients described above, with concomitant low T4 values indicative of primary hypothyroidism. The remaining 13 patients had mild, unsustained TSH elevations (TSH 10.1-23.1 mU/L), in the presence of normal T4. These patients likely had mild compensated primary hypothyroidism or may have been receiving slightly inadequate L-thyroxine replacement therapy. As their T4 concentrations were normal, this mild biochemical abnormality would not be expected to have an influence upon growth or response to growth hormone.

Sixty patients (31 in the hGH12 group, and 29 in the hGH09 group) had T4 values above the upper cut points. Review of these data reveals that, in all but nine cases, these elevations were marginal and sporadic. One of the remaining nine patients had a concomitantly low TSH, suggesting the presence of thyrotoxicosis. Three patients with high T4 values subsequently had T4 and TSH values consistent with primary hypothyroidism, and these patients may have been experiencing a hyperthyroxinemic phase of thyroiditis at the time the high T4 values were recorded. The other five patients had high T4 values (>20 nmol/L) without suppression of TSH. Possible explanations for these findings include overtreatment with levothyroxine, or increases in thyroxine-binding globulin related to therapy with estrogen or to other factors. These possibilities have not been addressed in the present study.

Table 39 **Thyroid Function Test Results: Number of Patients with at Least One Value Outside the Clinically Significant Cut Point - Safety Population**

	Pooled Treatment Group						
	Lower[1]		Upper[2]		Age Range	Clinically Significant	Clinically Significant
Analyte	hGH12	hGH09	hGH12	hGH09	(Years)	Lower Cut Point	Upper Cut Point
T4	41 (30.1%)	17 (18.3%)	31 (22.8%)	29 (31.2%)	1-6	94 (nmol/L)	193 (nmol/L)
					6-11	82 (nmol/L)	171 (nmol/L)
					11-16	72 (nmol/L)	151 (nmol/L)
					16-21	54 (nmol/L)	152 (nmol/L)
TSH	---	---	17 (12.5%)	4 (4.3%)	All Ages	---	10 (mU/L)

[1] Indicates number (percent) below the clinically significant lower cut point. Percentages relative to number of patients with test results in respective treatment groups.

[2] Indicates number (percent) above the clinically significant upper cut point. Percentages relative to number of patients with test results in respective treatment groups.

Glucose Homeostasis

Modified glucose tolerance tests (fasting and 2-hour postprandial glucose and insulin concentrations) and hemoglobin A_{1C} were analyzed for both pooled (hGH12 and hGH09) and individual treatment groups. Summary statistics for these variables at Baseline, Last Visit, and for Change from Baseline to Last Visit, are presented for the two pooled growth hormone dosage groups in Table 40. Differences between pooled treatment groups (hGH12 and hGH09) in changes from Baseline to Last Visit in fasting glucose and hemoglobin A_{1C} were also tested for statistical significance. Fasting and 2-hour postprandial glucose concentrations were normal at Baseline and Last Visit for both pooled treatment groups and no meaningful changes from Baseline to Last Visit were observed. There was no significant difference between the Humatrope dosage groups for mean change in fasting blood glucose from Baseline to Last Visit.

Mean and median hemoglobin A_{1C} values were normal at Baseline and Last Visit for both pooled treatment groups and did not change appreciably during the study. There was no significant difference between the two pooled treatment groups with respect to mean Change from Baseline to Last Visit in hemoglobin A_{1C}.

Median and 95th percentile fasting insulin concentrations were normal for both Humatrope dosage groups (hGH12 and hGH09) at Baseline and Last Visit, values at Last Visit being somewhat greater than those at Baseline. Although median 2-hour postprandial insulin concentrations were within the normal range at Baseline and Last Visit for both Humatrope dosage groups, an increase in the median value was noted for both groups at Last Visit. The 95th percentile values for 2-hour postprandial insulin were above the normal range in both groups, even at Baseline. A substantial increase in 95th percentile value was noted in the Change from Baseline results. These increases in postprandial serum insulin concentration during Humatrope therapy were not unexpected and likely reflect the development of mild insulin resistance induced by growth hormone. No appreciable dose-related influence on Last Visit 2-hour postprandial insulin values was observed. Notably, no changes in mean fasting glucose, 2-hour postprandial glucose, or hemoglobin A_{1C} were noted during Humatrope therapy, indicating that although there was a trend towards development of insulin resistance, this did not result in impairment of carbohydrate tolerance. Furthermore, the insulin resistance observed in this study was a preexisting condition in some patients, as evidenced by high Baseline 2-hour postprandial insulin concentrations.

Table 40 Modified Glucose Tolerance Test Results - Safety Population

		Pooled Treatment Group						
		hGH12			hGH09			
Analyte	Statistic	Baseline	Last Visit	Change	Baseline	Last Visit	Change	P-value[1]
Glucose	n	135	136	135	90	93	90	0.388
(fasting)	Mean	4.7	4.5	-0.2	4.6	4.5	-0.1	
(mmol/L)	SD	0.7	0.8	0.9	0.5	0.6	0.7	
	Median	4.7	4.5	-0.1	4.6	4.4	-0.1	
	Minimum							
	Maximum							
Glucose	n	109	134	108	73	89	70	
(2-hr postprandial)	Mean	5.7	5.4	-0.3	5.9	5.5	-0.5	
(mmol/L)	SD	1.3	2.1	2.3	1.5	1.4	2.0	
	Median	5.4	5.2	-0.4	5.7	5.1	-0.4	
	Minimum							
	Maximum							
Hemoglobin A_{1C}	n	129	132	126	90	91	88	0.325
(proportion of total	Mean	0.046	0.045	-0.001	0.045	0.045	0.001	
Hemoglobin)	SD	0.013	0.005	0.013	0.010	0.005	0.011	
	Median	0.044	0.045	0.002	0.044	0.045	0.002	
	Minimum							
	Maximum							

*Statistically significant ($p \leq 0.050$)

[1] P-value is for comparison of pooled treatment group means for Change from Baseline.

Note: Reference range for fasting Glucose from Scicor, Inc. is 3.9-6.4 mmol/L. Reference range for 2-hr postprandial Glucose from Guthrie, et al. (1973) is 3.0-7.8 mmol/L. Reference range for Hemoglobin A_{1C} from Scicor, Inc. is 0.033-0.068 (proportion of Total Hemoglobin).

Table 40 Modified Glucose Tolerance Test Results - Safety Population (Cont'd)

		Pooled Treatment Group					
		hGH12			hGH09		
Analyte	Statistic	Baseline	Last Visit	Change	Baseline	Last Visit	Change
Insulin (fasting) (pmol/L)	n	117	133	114	80	90	79
	Minimum						
	5th Percentile	<14.0	<14.0	-86.0	<14.0	<14.0	-101.0
	25th Percentile	<14.0	29.0	7.0	<14.0	29.0	0.0
	Median	14.0	50.0	32.5	14.0	43.0	22.0
	75th Percentile	36.0	86.0	72.0	50.0	86.0	65.0
	95th Percentile	129.0	187.0	158.0	122.0	172.0	151.0
	Maximum						
Insulin (2-hr postprandial) (pmol/L)	n	116	134	115	77	89	75
	Minimum						
	5th Percentile	<14.0	29.0	-187.0	<14.0	36.0	-351.0
	25th Percentile	57.0	129.0	-7.0	79.0	136.0	-43.0
	Median	100.0	208.0	94.0	144.0	230.0	71.0
	75th Percentile	215.0	366.0	230.0	244.0	395.0	230.0
	95th Percentile	502.0	789.0	552.0	947.0	832.0	538.0
	Maximum						

*Statistically significant ($p \leq 0.050$).

[1] P-value is for comparison of pooled treatment group means for Change from Baseline.

Note: For fasting and 2-hr postprandial Insulin, <14 is set to 0.0 for the calculation of Change from Baseline at Last Visit.

The numbers and percentages of patients with values for glucose, insulin, and hemoglobin A_{1C} above the assigned clinically significant cut points, are shown in Table 41. The two pooled treatment groups were similar with respect to the percentage of patients who had at least one value above the clinically significant cut point for each of the variables analyzed. More than half of the patients in each pooled treatment group (75 patients or 55.6% in the hGH12 group and 55 patients or 60.4% in the hGH09 group) had at least one value above the clinically significant cut point for 2-hour postprandial insulin concentration. To determine whether the elevated 2-hour postprandial insulin concentrations occurred sporadically, or represented a more significant disturbance, all of the 2-hour postprandial insulin values for all patients found to have any single value above the clinically significant cut point were reviewed. For most patients between 5 and 20 measurements of 2-hour postprandial insulin were obtained over the course of the study and it should be noted that in a number of cases the high serum insulin concentrations were present even at Baseline, prior to initiation of growth hormone therapy. When individual patient data were evaluated, the patients fell into the three broad clinical groups: those in whom the insulin concentrations were only mildly above the cut point and who had increased values only once or twice throughout the study period (approximately 45% of the total patients identified with values above the clinically significant cut point); those in whom the insulin concentrations were modestly increased and/or occurred up to four times during the course of the study (approximately 25%); and those in whom the hyperinsulinemia was moderate (>1000 pmol/L) and/or persistent (approximately 30% of the group). Patients in this third group appeared to have a moderate degree of insulin resistance, although it should be noted that even in this group the abnormality was present somewhat erratically in some patients, while quite persistent in others. Sixteen patients in this latter group had significant hyperinsulinemia, with values over 2000 pmol/L in five patients. Surprisingly, in two of these five patients, the high insulin concentrations occurred sporadically and were followed by return to normal values at the next analysis. Another 11 patients had 2-hour postprandial insulin concentrations between 1500 and 2000 pmol/L. Further analysis of this group of patients with significant and/or persistent hyperinsulinemia is in progress to evaluate other aspects of glucose homeostasis.

Table 41 **Modified Glucose Tolerance Test Results: Number of Patients with at Least One Value Above the Clinically Significant Cut Point - Safety Population**

Analyte	Pooled Treatment Group		Clinically Significant Upper Cut Point
	hGH12[1]	hGH09[1]	
Glucose (fasting)	12 (8.8%)	3 (3.2%)	6.4 (mmol/L)
Glucose (2-hr postprandial)	22 (16.3%)	14 (15.2%)	8.3 (mmol/L)
Hemoglobin A_{1C}	10 (7.4%)	9 (9.7%)	0.068 (proportion of total hemoglobin)
Insulin (fasting)	17 (12.5%)	10 (11.0%)	251 (pmol/L)
Insulin (2-hr postprandial)	75 (55.6%)	55 (60.4%)	400 (pmol/L)

[1] Number (percent). Percentages relative to number of patients with test results in respective treatment group.

Summary statistics for modified glucose tolerance tests and for hemoglobin A_{1C} at Baseline and Last Visit, and for Changes from Baseline to Last Visit, are presented for individual treatment groups in Table 42. Mean and median values for fasting and 2-hour postprandial glucose and for hemoglobin A_{1C} were normal at Baseline and Last Visit and did not change appreciably during the study. Median values for fasting and 2-hour postprandial insulin concentration increased from Baseline to Last Visit. As shown in Table 42, there were no marked differences across the five individual treatment groups with respect to numbers of patients who had at least one value above the clinically significant cut point for fasting insulin, fasting and 2-hour postprandial glucose, or hemoglobin A_{1C}.

Table 42 **Modified Glucose Tolerance Test Results by Individual Treatment Group - Safety Population**

Analyte	Visit	Statistic	Treatment Group				
			hGH12/LDE	hGH12/PLA	hGH09/LDE	hGH09/PLA	PLA/ Switch
Glucose (fasting) (mmol/L)	Baseline	n	42	47	46	44	46
		Mean	4.7	4.7	4.6	4.7	4.6
		SD	0.7	0.5	0.6	0.5	0.7
		Median	4.6	4.8	4.6	4.7	4.6
		Minimum					
		Maximum					
	Last Visit	n	42	48	47	46	46
		Mean	4.5	4.5	4.4	4.6	4.5
		SD	1.3	0.5	0.6	0.6	0.5
		Median	4.4	4.5	4.4	4.6	4.6
		Minimum					
		Maximum					
	Change	n	42	47	46	44	46
		Mean	-0.2	-0.3	-0.1	-0.1	-0.2
		SD	1.4	0.5	0.7	0.8	0.8
		Median	-0.2	-0.2	-0.1	-0.2	0.0
		Minimum					
		Maximum					

Note: Reference range for fasting Glucose from Scicor, Inc. is 3.9-6.4 mmol/L.

Table 42 Modified Glucose Tolerance Test Results by Individual Treatment Group - Safety Population (Cont'd)

Analyte	Visit	Statistic	Treatment Group				
			hGH12/LDE	hGH12/PLA	hGH09/LDE	hGH09/PLA	PLA/ Switch
Glucose (2-hr postprandial) (mmol/L)	Baseline	n	37	36	36	37	36
		Mean	5.7	5.7	5.5	6.2	5.5
		SD	1.1	1.3	1.3	1.7	1.4
		Median	5.4	5.5	5.6	6.3	5.4
		Minimum					
		Maximum					
	Last Visit	n	42	48	47	42	44
		Mean	5.5	5.2	5.6	5.3	5.5
		SD	3.2	1.2	1.7	1.0	1.4
		Median	4.9	5.3	4.9	5.3	5.3
		Minimum					
		Maximum					
	Change	n	37	36	36	34	35
		Mean	-0.2	-0.5	-0.2	-0.9	0.0
		SD	3.2	1.6	1.8	2.1	1.8
		Median	-0.6	-0.6	-0.1	-0.7	0.0
		Minimum					
		Maximum					

Note: Reference range for 2-hr postprandial Glucose from Guthrie, et al. (1973) is 3.0-7.8 mmol/L.

Table 42 **Modified Glucose Tolèrance Test Results by Individual Treatment Group - Safety Population (Cont'd)**

Analyte	Visit	Statistic	Treatment Group				
			hGH12/LDE	hGH12/PLA	hGH09/LDE	hGH09/PLA	PLA/ Switch
Hemoglobin A_{1C} (proportion of Total Hemoglobin)	Baseline	n	40	46	47	43	43
		Mean	0.046	0.044	0.046	0.043	0.047
		SD	0.012	0.011	0.012	0.007	0.014
		Median	0.044	0.043	0.044	0.043	0.044
		Minimum					
		Maximum					
	Last Visit	n	42	48	47	44	42
		Mean	0.046	0.044	0.045	0.045	0.045
		SD	0.006	0.004	0.007	0.004	0.004
		Median	0.045	0.045	0.044	0.045	0.045
		Minimum					
		Maximum					
	Change	n	40	46	47	41	40
		Mean	0.000	0.000	-0.001	0.002	-0.003
		SD	0.013	0.012	0.014	0.007	0.015
		Median	0.002	0.002	0.002	0.003	0.001
		Minimum					
		Maximum					

Note: Reference range for Hemoglobin A_{1C} from Scicor, Inc. is 0.033-0.068 (proportion of total hemoglobin).

Table 42 Modified Glucose Tolerance Test Results by Individual Treatment Group - Safety Population (Cont'd)

Analyte	Visit	Statistic	Treatment Group				
			hGH12/LDE	hGH12/PLA	hGH09/LDE	hGH09/PLA	PLA/ Switch
Insulin (fasting) (pmol/L)	Baseline	n	36	39	39	41	42
		Minimum					
		5th Percentile	<14.0	<14.0	<14.0	<14.0	<14.0
		25th Percentile	<14.0	<14.0	<14.0	<14.0	<14.0
		Median	<14.0	14.0	22.0	14.0	14.0
		75th Percentile	32.5	43.0	72.0	50.0	29.0
		95th Percentile	208.0	165.0	158.0	115.0	79.0
		Maximum					
	Last Visit	n	42	47	46	44	44
		Minimum					
		5th Percentile	<14.0	<14.0	<14.0	<14.0	<14.0
		25th Percentile	29.0	29.0	29.0	29.0	36.0
		Median	43.0	57.0	36.0	57.0	57.0
		75th Percentile	65.0	100.0	65.0	104.0	96.5
		95th Percentile	115.0	194.0	136.0	172.0	144.0
		Maximum					
	Change	n	36	38	39	40	40
		Minimum					
		5th Percentile	-151.0	-108.0	-122.0	-68.5	-25.5
		25th Percentile	0.0	14.0	-29.0	14.0	10.5
		Median	29.0	43.0	14.0	29.0	36.0
		75th Percentile	50.5	79.0	36.0	90.0	82.5
		95th Percentile	150.0	244.0	237.0	147.0	118.5
		Maximum					

Note: Reference range for fasting Insulin from Scicor, Inc. is 21-251 pmol/L.

Note: For fasting and 2-hr postprandial Insulin, <14 is set to 0.0 for the calculation of Change from Baseline at Last Visit.

Table 42 Modified Glucose Tolerance Test Results by Individual Treatment Group - Safety Population (Cont'd)

Analyte	Visit	Statistic	Treatment Group				
			hGH12/LDE	hGH12/PLA	hGH09/LDE	hGH09/PLA	PLA/ Switch
Insulin	Baseline	n	35	41	38	39	40
(2-hr postprandial)		Minimum					
(pmol/L)		5th Percentile	<14.0	43.0	<14.0	<14.0	<14.0
		25th Percentile	43.0	72.0	79.0	79.0	57.0
		Median	93.0	93.0	125.5	165.0	111.5
		75th Percentile	129.0	230:0	208.0	337.0	218.5
		95th Percentile	574.0	502.0	1514.0	947.0	452.5
		Maximum					
	Last Visit	n	42	48	46	43	44
		Minimum					
		5th Percentile	36.0	29.0	29.0	86.0	29.0
		25th Percentile	108.0	140.0	136.0	129.0	115.0
		Median	215.0	204.5	201.0	280.0	208.0
		75th Percentile	373.0	355.0	323.0	459.0	358.5
		95th Percentile	689.0	674.0	674.0	832.0	933.0
		Maximum					
	Change	n	35	41	38	37	39
		Minimum					
		5th Percentile	-137.0	-94.0	-517.0	-351.0	-316.0
		25th Percentile	8.0	-7.0	-44.0	-28.0	-29.0
		Median	136.0	101.0	72.0	35.0	93.0
		75th Percentile	215.0	201.0	151.0	265.0	230.0
		95th Percentile	467.0	330.0	531.0	652.0	718.0
		Maximum					

Note: Reference range for 2-hr postprandial Insulin from Guthrie, et al. (1973) is 158-550 pmol/L. This reference range represents 10-90th percentile according to study of Guthrie, et al. (1973).

Note: For fasting and 2-hr postprandial Insulin, <14 is set to 0.0 for the calculation of Change from Baseline at Last Visit.

Table 42 **Modified Glucose Tolerance Test Results: Number of Patients in Individual Treatment Groups with at Least One Value Above the Clinically Significant Cut Point - Safety Population**

Analyte	Treatment Group					Clinically Significant Upper Cut Points
	hGH12/LDE[1]	hGH12/PLA[1]	hGH09/LDE[1]	hGH09/PLA[1]	PLA/Switch[1]	
Glucose (fasting) (mmol/L)	7 (16.7%)	1 (2.1%)	1 (2.1%)	2 (4.3%)	4 (8.7%)	6.4 (mmol/L)
Glucose (2-hr postprandial) (mmol/L)	7 (16.7%)	7 (14.6%)	6 (12.8%)	8 (17.8%)	8 (17.8%)	8.3 (mmol/L)
Hemoglobin A_{1C} (proportion of total Hemoglobin)	4 (9.5%)	3 (6.3%)	6 (12.8%)	3 (6.5%)	3 (6.7%)	0.068 (proportion of total Hemoglobin)
Insulin (fasting) (pmol/L)	3 (7.1%)	10 (20.8%)	4 (8.7%)	6 (13.3%)	4 (8.7%)	251 (pmol/L)
Insulin (2-hr postprandial) (pmol/L)	20 (47.6%)	25 (52.1%)	27 (58.7%)	28 (62.2%)	30 (66.7%)	400 (pmol/L)

[1] Number (percent). Percentages relative to number of patients with test results in respective treatment groups.

Special Tests: IGF-I Concentration

IGF-I (somatomedin-C) concentration was analyzed for both pooled growth hormone dosage (hGH09 and hGH12) and individual treatment groups. The difference between pooled Humatrope treatment groups (hGH09 and hGH12) with respect to mean Change from Baseline to Last Visit in IGF-I concentration was tested for statistical significance.

Summary statistics for IGF-I concentration at Baseline and Last Visit and for Change from Baseline to Last Visit are presented for the two pooled treatment groups in Table 43. Mean and median IGF-I concentrations were normal at Baseline and Last Visit in both pooled treatment groups. Mean and median increases in IGF-I concentration from Baseline to Last Visit were greater for the hGH12 group than the hGH09 group, but this difference was of marginal statistical significance ($p = 0.061$). As shown in Table 44, a greater proportion of patients in the hGH12 group (62 patients or 45.6%) than in the hGH09 group (35 patients or 37.6%) had at least one value for IGF-I concentration above the assigned cut point of 455 ng/ml. This finding, in addition to the greater mean Change from Baseline for IGF-I for the hGH12 group, likely reflects dose-related effects of Humatrope upon IGF-I generation. Inspection of the individual values indicates that those above the clinically significant cut point were sporadic events for individual patients. The relationship between blood sampling time and last injection is unknown.

Table 43 **IGF-I Concentration (ng/mL) - Safety Population**

Visit	Statistic	Pooled Treatment Group hGH12	Pooled Treatment Group hGH09	P-value[1]
Baseline	n	124	81	
	Mean	141.6	136.3	
	SD	89.2	76.0	
	Median	128.0	118.0	
	Minimum			
	Maximum			
Last Visit	n	136	92	
	Mean	374.8	333.0	
	SD	223.8	169.4	
	Median	325.0	296.5	
	Minimum			
	Maximum			
Change	n	124	80	0.061
	Mean	240.9	188.3	
	SD	239.4	165.4	
	Median	191.0	163.0	
	Minimum			
	Maximum			

*Statistically significant ($p \leq 0.050$).

[1] P-value is for comparison of pooled treatment group means for Change from Baseline.

Note: The minimum value of 0.0 reported for the hGH12 treatment group represents a missing data point which was entered as 0.0 due to a data management error. The true minimum value for this treatment group was 45.0.

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Table 44 **IGF-I Concentration: Number of Patients with at Least One Value Above the Clinically Significant Cut Point - Safety Population**

Pooled Treatment Group		Clinically Significant
hGH12[1]	hGH09[1]	Upper Cut Point
62 (45.6%)	35 (37.6%)	455 ng/mL

[1] Number (percent). Percentages relative to number of patients with test results in respective treatment group

Summary statistics for IGF-I concentration at Baseline and Last Visit and for Change from Baseline to Last Visit are presented for the five individual treatment groups in Table 45. As with the two pooled treatment groups, mean and median IGF-I concentrations were normal at Baseline and Last Visit for each of the five individual treatment groups. Each individual treatment group had increases in mean and median IGF-I concentration from Baseline to Last Visit. The numbers of patients in individual treatment groups who had at least one IGF-I value above the clinically significant cut point are presented in Table 46. The hGH12/PLA treatment group demonstrated a higher percentage of patients with values above the clinically significant cut point than the other four groups, all of which had similar percentages.

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Table 45 IGF-I Concentration (ng/mL) by Individual Treatment Group - Safety Population

Visit	Statistic	Treatment Group				
		hGH12/LDE	hGH12/PLA	hGH09/LDE	hGH09/PLA	PLA/Switch
Baseline	n	40	44	40	41	40
	Mean	122.8	146.0	131.2	141.4	155.6
	SD	54.9	95.9	66.8	84.5	106.4
	Median	128.0	128.0	120.5	112.0	124.5
	Minimum					
	Maximum					
Last Visit	n	42	48	47	45	46
	Mean	364.1	371.5	313.1	353.8	388.0
	SD	216.3	223.6	146.3	190.0	234.8
	Median	311.3	322.0	287.0	312.0	335.5
	Minimum					
	Maximum					
Change	n	40	44	40	40	40
	Mean	234.0	245.4	180.0	196.5	242.8
	SD	223.7	239.3	165.4	167.0	259.8
	Median	181.0	199.5	152.5	171.5	176.5
	Minimum					
	Maximum					

Note: The minimum value of 0.0 reported for the hGH12/PLA treatment group represents a missing data point which was entered as 0.0 due to a data management error. The true minimum value for this treatment group was 75.0.

Table 46 **IGF-I Concentration: Number of Patients in Individual Treatment Groups with at Least One Value Above the Clinically Significant Cut Point - Safety Population**

Treatment Group					Clinically Significant
hGH12/LDE[1]	hGH12/PLA[1]	hGH09/LDE[1]	hGH09/PLA[1]	PLA/Switch[1]	Upper Cut Point
15 (35.7%)	27 (56.3%)	16 (34.0%)	19 (41.3%)	20 (43.5%)	455 ng/mL

[1] Number (percent). Percentages relative to number of patients with test results in respective treatment group.

Special Tests: Anti-GH Binding Capacity

A listing of patients with positive anti-GH binding capacity (>0.02 mg/L) is presented in Table 47. Four patients had positive anti-GH binding capacity concentrations. Of these, two patients had relatively low concentrations: Patient 013-1092 (hGH12/LDE) had 0.070 mg/L and 0.160 mg/L values at Visits 4 and 6, respectively; and Patient 019-1143 (hGH09/PLA) had a 0.030 mg/L value at Visit 17. Patient 019-1150 (hGH09/LDE) had an isolated value of 1.999 mg/L at Visit 5 and Patient 014-1476 (hGH09/PLA) had values from 0.100 mg/L to 3.370 mg/L from Visit 2 to Visit 7. None of these patients experienced a decrease in growth velocity associated with the presence of anti-GH antibodies.

Special Tests: Anti-ECP Antibody

Data have been submitted previously (IND 31087 submitted on 31 March 1995) with regard to a reanalysis of ECP antibodies in a highly sensitive chemiluminescent assay for samples collected during the first 18 months. On the previously submitted bridging study report ECP antibody was essentially undetectable. No difference could be found between placebo and Humatrope groups. Further analysis for ECP antibodies was discontinued as per FDA agreement (letter dated 31 May 1995).

Table 47 **Positive Anti-GH Binding Capacity (mg/L) by Patient and Visit**

Patient Number	Visit Number										
	1	2	3	4	5	6	7	8	...	16	17
013-1092				0.070		0.160					
019-1150					1.999						
014-1476		0.120	0.860	0.860	3.370	0.100	0.160				
019-1143											0.030

Note: A positive value is defined as any value greater than 0.02 mg/L.
Note: No positive values were observed at Visits 8-16 or after Visit 17 for any patient.

Lipids

Summary statistics for serum lipid concentrations (triglycerides, total cholesterol, HDL, LDL, VLDL) at Baseline, at the end of each year of the study, and at Last Visit are presented for the two pooled Humatrope dosage groups (hGH09 and hGH12) in Table 48. Summary statistics for changes from Baseline at the end of each year of the study and at Last Visit for these variables are presented in Table 49. Mean and median values for each of these variables were normal for both pooled treatment groups at Baseline, annual visits, and Last Visit. No consistent differences between the two pooled treatment groups were observed in mean or median lipid concentrations or in changes from Baseline at any annual visit or at Last Visit.

The numbers of patients in the two pooled treatment groups with at least one value above the clinically significant cut point for serum lipid concentrations are presented in Table 50. Approximately two-thirds of patients in each pooled treatment group (83 patients or 61.0% in the hGH12 group and 62 patients or 66.7% in the hGH09 group) had values above the clinically significant cut point for total cholesterol (5.0 mmol/L). Because the number of patients found to have cholesterol values above the clinically significant cut point was high, all cholesterol values for those patients with a single value above the cut point were reviewed. When individual patient data were evaluated, the patients fell into three broad clinical groups: those in whom the serum cholesterol concentrations were only mildly above the cut point and who had increased values only once or twice throughout the study period (approximately 40% of the total patients identified with values above the clinically significant cut point); those in whom the cholesterol concentrations were modestly increased and/or occurred up to four times during the course of the study (approximately 20%); and those in whom the cholesterol concentrations were more significantly or persistently increased (approximately 40% of the group). Notably, in this latter group, approximately 72% of the patients in fact had cholesterol concentrations greater than 5.0 mmol/L at Baseline (Visit 1 of the study), before initiation of growth hormone therapy, and no persistent change was noted over the course of the study. These patients may represent a subgroup of patients with Turner syndrome in whom there exists an intrinsic abnormality of lipid metabolism. Further analysis of this group of patients is in progress.

Table 48 **Lipid Test Results - Safety Population**

Analyte/Visit	N	Mean	SD	Median	Minimum	Maximum
Triglycerides (mmol/L)						
Visit 1 (Baseline)						
hGH12	135	0.88	0.48	0.75		
hGH09	90	0.94	0.51	0.83		
Visit 5 (Year 1)						
hGH12	125	1.01	0.53	0.85		
hGH09	82	0.99	0.44	0.94		
Visit 9 (Year 2)						
hGH12	121	0.97	0.53	0.86		
hGH09	78	1.01	0.53	0.90		
Visit 13 (Year 3)						
hGH12	108	0.94	0.49	0.83		
hGH09	63	1.01	0.50	0.90		
Visit 17 (Year 4)						
hGH12	91	1.02	0.51	0.91		
hGH09	51	1.04	0.50	0.84		
Visit 21 (Year 5)						
hGH12	74	1.00	0.53	0.91		
hGH09	43	1.12	0.71	0.88		
Visit 25 (Year 6)						
hGH12	54	1.02	0.49	0.87		
hGH09	26	1.19	0.56	1.09		
Visit 29 (Year 7)						
hGH12	32	1.07	0.75	0.93		
hGH09	10	0.98	0.35	0.96		
Last Visit						
hGH12	134	1.09	0.62	0.99		
hGH09	91	1.16	0.64	0.96		

Note: Reference range for Triglycerides from Scicor, Inc. is 0.50-2.40 mmol/L.

Table 48 **Lipid Test Results - Safety Population (Cont'd)**

Analyte/Visit	N	Mean	SD	Median	Minimum	Maximum
Total Cholesterol (mmol/L)						
Visit 1 (Baseline)						
hGH12	135	4.66	0.76	4.53		
hGH09	90	4.68	0.76	4.63		
Visit 5 (Year 1)						
hGH12	125	4.83	0.90	4.81		
hGH09	83	4.85	0.84	4.78		
Visit 9 (Year 2)						
hGH12	120	4.60	0.78	4.52		
hGH09	78	4.68	0.92	4.50		
Visit 13 (Year 3)						
hGH12	108	4.40	0.77	4.32		
hGH09	63	4.38	0.77	4.32		
Visit 17 (Year 4)						
hGH12	92	4.46	0.74	4.37		
hGH09	51	4.44	0.68	4.37		
Visit 21 (Year 5)						
hGH12	74	4.49	0.79	4.41		
hGH09	43	4.46	0.75	4.50		
Visit 25 (Year 6)						
hGH12	54	4.61	0.65	4.67		
hGH09	26	4.54	0.99	4.41		
Visit 29 (Year 7)						
hGH12	33	4.56	0.63	4.47		
hGH09	10	4.14	0.78	4.06		
Last Visit						
hGH12	136	4.67	0.79	4.61		
hGH09	93	4.76	0.83	4.58		

Note: Reference range for Total Cholesterol from Scicor, Inc. is 3.62-6.75 mmol/L.

Table 48 **Lipid Test Results - Safety Population (Cont'd)**

Analyte/Visit	N	Mean	SD	Median	Minimum	Maximum
HDL (mmol/L)						
Visit 1 (Baseline)						
hGH12	134	1.48	0.35	1.45		
hGH09	89	1.43	0.33	1.42		
Visit 5 (Year 1)						
hGH12	124	1.45	0.38	1.40		
hGH09	82	1.48	0.33	1.50		
Visit 9 (Year 2)						
hGH12	118	1.41	0.35	1.33		
hGH09	78	1.42	0.35	1.40		
Visit 13 (Year 3)						
hGH12	107	1.35	0.31	1.32		
hGH09	63	1.32	0.35	1.29		
Visit 17 (Year 4)						
hGH12	90	1.35	0.31	1.34		
hGH09	51	1.38	0.37	1.29		
Visit 21 (Year 5)						
hGH12	71	1.47	0.32	1.53		
hGH09	43	1.37	0.37	1.34		
Visit 25 (Year 6)						
hGH12	54	1.39	0.27	1.39		
hGH09	26	1.38	0.39	1.36		
Visit 29 (Year 7)						
hGH12	32	1.38	0.37	1.40		
hGH09	10	1.33	0.28	1.28		
Last Visit						
hGH12	134	1.44	0.34	1.39		
hGH09	91	1.46	0.37	1.42		

Note: Reference range for HDL Cholesterol from Scicor, Inc. is 0.36-2.02 mmol/L.

Table 48 **Lipid Test Results - Safety Population (Cont'd)**

Analyte/Visit	N	Mean	SD	Median	Minimum	Maximum
LDL (mmol/L)						
Visit 1 (Baseline)						
hGH12	134	2.79	0.72	2.69		
hGH09	89	2.86	0.75	2.82		
Visit 5 (Year 1)						
hGH12	124	2.92	0.75	2.89		
hGH09	82	2.93	0.73	2.86		
Visit 9 (Year 2)						
hGH12	117	2.75	0.71	2.74		
hGH09	78	2.81	0.69	2.73		
Visit 13 (Year 3)						
hGH12	106	2.61	0.64	2.64		
hGH09	63	2.60	0.61	2.53		
Visit 17 (Year 4)						
hGH12	90	2.59	0.72	2.56		
hGH09	51	2.55	0.62	2.59		
Visit 21 (Year 5)						
hGH12	71	2.57	0.68	2.51		
hGH09	43	2.58	0.59	2.64		
Visit 25 (Year 6)						
hGH12	54	2.75	0.58	2.77		
hGH09	26	2.62	0.77	2.50		
Visit 29 (Year 7)						
hGH12	32	2.73	0.65	2.69		
hGH09	10	2.36	0.63	2.47		
Last Visit						
hGH12	134	2.72	0.65	2.71		
hGH09	91	2.84	0.73	2.74		

Note: Reference range for LDL Cholesterol from Scicor, Inc. is 1.63-5.97 mmol/L.

Table 48 Lipid Test Results - Safety Population (Cont'd)

Analyte/Visit	N	Mean	SD	Median	Minimum	Maximum
VLDL (mmol/L)						
Visit 1 (Baseline)						
hGH12	134	0.40	0.22	0.34		
hGH09	90	0.43	0.23	0.38		
Visit 5 (Year 1)						
hGH12	125	0.46	0.24	0.39		
hGH09	82	0.46	0.20	0.42		
Visit 9 (Year 2)						
hGH12	121	0.44	0.24	0.39		
hGH09	78	0.46	0.24	0.41		
Visit 13 (Year 3)						
hGH12	108	0.43	0.23	0.39		
hGH09	63	0.46	0.23	0.41		
Visit 17 (Year 4)						
hGH12	91	0.47	0.23	0.41		
hGH09	51	0.48	0.23	0.39		
Visit 21 (Year 5)						
hGH12	74	0.46	0.24	0.41		
hGH09	43	0.51	0.32	0.41		
Visit 25 (Year 6)						
hGH12	54	0.47	0.23	0.39		
hGH09	26	0.54	0.25	0.51		
Visit 29 (Year 7)						
hGH12	32	0.49	0.34	0.43		
hGH09	10	0.45	0.16	0.44		
Last Visit						
hGH12	134	0.50	0.29	0.46		
hGH09	91	0.53	0.29	0.44		

Note: Reference range for VLDL Cholesterol from Scicor, Inc. is 0.18-0.88 mmol/L.

Table 49 **Change from Baseline in Lipid Test Results - Safety Population**

Analyte/Visit	N	Mean	SD	Median	Minimum	Maximum
Triglycerides (mmol/L)						
Visit 5 (Year 1)						
hGH12	124	0.13	0.48	0.06		
hGH09	80	0.07	0.49	0.06		
Visit 9 (Year 2)						
hGH12	120	0.09	0.52	0.03		
hGH09	75	0.04	0.64	0.02		
Visit 13 (Year 3)						
hGH12	107	0.07	0.40	0.00		
hGH09	60	0.04	0.58	0.04		
Visit 17 (Year 4)						
hGH12	90	0.15	0.51	0.17		
hGH09	48	0.04	0.49	0.08		
Visit 21 (Year 5)						
hGH12	73	0.15	0.55	0.11		
hGH09	40	0.12	0.51	0.05		
Visit 25 (Year 6)						
hGH12	53	0.19	0.50	0.13		
hGH09	24	0.17	0.47	0.14		
Visit 29 (Year 7)						
hGH12	32	0.28	0.76	0.22		
hGH09	8	0.19	0.29	0.21		
Last Visit						
hGH12	133	0.20	0.56	0.17		
hGH09	88	0.21	0.73	0.16		

Table 49 **Change from Baseline in Lipid Test Results - Safety Population (Cont'd)**

Analyte/Visit	N	Mean	SD	Median	Minimum	Maximum
Total Cholesterol (mmol)/L						
Visit 5 (Year 1)						
hGH12	124	0.15	0.66	0.13		
hGH09	81	0.19	0.72	0.18		
Visit 9 (Year 2)						
hGH12	119	-0.07	0.62	-0.05		
hGH09	75	0.07	0.84	0.02		
Visit 13 (Year 3)						
hGH12	107	-0.25	0.52	-0.28		
hGH09	60	-0.18	0.71	-0.34		
Visit 17 (Year 4)						
hGH12	91	-0.19	0.55	-0.18		
hGH09	48	-0.04	0.66	-0.07		
Visit 21 (Year 5)						
hGH12	73	-0.05	0.65	-0.10		
hGH09	40	0.01	0.75	-0.17		
Visit 25 (Year 6)						
hGH12	53	0.06	0.53	0.05		
hGH09	24	0.17	0.83	0.02		
Visit 29 (Year 7)						
hGH12	33	0.15	0.38	0.15		
hGH09	8	0.07	0.61	0.19		
Last Visit						
hGH12	135	0.00	0.61	-0.05		
hGH09	90	0.09	0.82	-0.04		

Table 49 **Change from Baseline in Lipid Test Results - Safety Population (Cont'd)**

Analyte/Visit	N	Mean	SD	Median	Minimum	Maximum
HDL (mmol/L)						
Visit 5 (Year 1)						
hGH12	122	0.00	0.38	0.00		
hGH09	80	0.07	0.30	0.08		
Visit 9 (Year 2)						
hGH12	116	-0.05	0.31	-0.08		
hGH09	74	0.00	0.28	-0.02		
Visit 13 (Year 3)						
hGH12	105	-0.10	0.29	-0.08		
hGH09	59	-0.07	0.28	-0.08		
Visit 17 (Year 4)						
hGH12	88	-0.09	0.32	-0.10		
hGH09	47	0.02	0.35	-0.03		
Visit 21 (Year 5)						
hGH12	69	-0.02	0.33	0.00		
hGH09	39	0.04	0.33	0.03		
Visit 25 (Year 6)						
hGH12	53	-0.09	0.33	-0.05		
hGH09	23	0.00	0.30	0.05		
Visit 29 (Year 7)						
hGH12	32	-0.11	0.43	-0.05		
hGH09	8	0.13	0.14	0.17		
Last Visit						
hGH12	132	-0.04	0.32	-0.02		
hGH09	87	0.04	0.37	0.05		

Table 49 **Change from Baseline in Lipid Test Results - Safety Population (Cont'd)**

Analyte/Visit	N	Mean	SD	Median	Minimum	Maximum
LDL (mmol/L)						
Visit 5 (Year 1)						
hGH12	122	0.09	0.63	0.05		
hGH09	80	0.09	0.66	0.09		
Visit 9 (Year 2)						
hGH12	115	-0.07	0.56	-0.05		
hGH09	74	0.03	0.69	0.00		
Visit 13 (Year 3)						
hGH12	104	-0.18	0.48	-0.16		
hGH09	59	-0.18	0.54	-0.21		
Visit 17 (Year 4)						
hGH12	88	-0.20	0.60	-0.21		
hGH09	47	-0.14	0.64	-0.08		
Visit 21 (Year 5)						
hGH12	69	-0.11	0.59	-0.16		
hGH09	39	-0.13	0.51	-0.23		
Visit 25 (Year 6)						
hGH12	53	0.05	0.54	0.10		
hGH09	23	0.03	0.67	-0.13		
Visit 29 (Year 7)						
hGH12	32	0.14	0.52	0.13		
hGH09	8	-0.14	0.67	-0.05		
Last Visit						
hGH12	132	-0.07	0.61	-0.10		
hGH09	87	-0.01	0.76	-0.08		

Table 49 **Change from Baseline in Lipid Test Results - Safety Population (Cont'd)**

Analyte/Visit	N	Mean	SD	Median	Minimum	Maximum
VLDL (mmol/L)						
Visit 5 (Year 1)						
hGH12	123	0.06	0.22	0.03		
hGH09	80	0.03	0.23	0.03		
Visit 9 (Year 2)						
hGH12	119	0.04	0.23	0.01		
hGH09	75	0.02	0.29	0.00		
Visit 13 (Year 3)						
hGH12	106	0.03	0.17	0.00		
hGH09	60	0.02	0.27	0.01		
Visit 17 (Year 4)						
hGH12	89	0.06	0.23	0.07		
hGH09	48	0.02	0.22	0.03		
Visit 21 (Year 5)						
hGH12	72	0.07	0.25	0.05		
hGH09	40	0.06	0.23	0.00		
Visit 25 (Year 6)						
hGH12	53	0.09	0.23	0.08		
hGH09	24	0.08	0.22	0.08		
Visit 29 (Year 7)						
hGH12	32	0.13	0.35	0.10		
hGH09	8	0.08	0.13	0.09		
Last Visit						
hGH12	132	0.09	0.26	0.08		
hGH09	88	0.10	0.33	0.08		

Table 50 **Lipid Test Results: Number of Patients with at Least One Value Above the Clinically Significant Cut Point - Safety Population**

Analyte	Pooled Treatment Group hGH12[1]	Pooled Treatment Group hGH09[1]	Clinically Significant Upper Cut Point
Triglycerides	12 (8.8%)	14 (15.1%)	2.4 (mmol/L)
Total Cholesterol	83 (61.0%)	62 (66.7%)	5.00 (mmol/L)
HDL	23 (16.9%)	16 (17.2%)	2.02 (mmol/L)
LDL	3 (2.2%)	3 (3.2%)	5.09 (mmol/L)
VLDL	25 (18.4%)	24 (25.8%)	0.88 (mmol/L)

[1] Number (percent). Percentages relative to number of patients with test results in respective treatment group.

Discussion of Clinical Laboratory Evaluation

In this study, two different doses of Humatrope (0.12 mg/kg/dose and 0.09 mg/kg/dose) had no differential effects on blood chemistry (including electrolytes), hematology, or lipids in patients with Turner syndrome. A large number of patients in both the Humatrope dosage groups had T4 values below the specified cut points with the proportion being greater for the patients receiving the higher dose of Humatrope (30.1% versus 18.3%). Review of the individual patient data revealed eight patients with unequivocal primary hypothyroidism, seven of whom were receiving 0.12 mg/kg/dose of Humatrope. An additional 10 patients had T4 and TSH concentrations that could possibly represent mild central (secondary or tertiary) hypothyroidism. In addition to the patients whose T4 concentrations fell below the lower clinically significant cut points, there were also 60 patients with sporadic T4 values above the upper clinically significant cut points. Possible explanations for these findings include excess levothyroxine treatment, or alterations in levels of thyroxine-binding globulin. Abnormalities of thyroid function are common in patients with Turner syndrome and the frequency of abnormal thyroid function tests in the patients in this study is consistent with the underlying rate of thyroid disease in Turner syndrome. As no further investigations such as antithyroid antibodies were performed as part of this study, the etiology of the thyroid dysfunction in these patients is unknown.

In general, glucose homeostasis did not appear to be affected differentially by the two doses of Humatrope. While median fasting insulin concentrations were normal for both treatment groups at Baseline and Last Visit, values at Last Visit were somewhat greater than those at Baseline. In addition, an increase in median 2-hour postprandial insulin concentration was noted for both groups at Last Visit. Notably, the 95th percentile values for 2-hour postprandial insulin were above the normal range in both groups at Baseline

indicating preexisting insulin resistance in some patients. Increases in these values noted between Baseline and Last Visit were not unexpected and likely reflected the development of insulin resistance induced by growth hormone. Notably, no changes in mean fasting glucose, 2-hour postprandial glucose or hemoglobin A_{1C} were observed during Humatrope therapy, indicating that although there was a trend towards development of insulin resistance, this did not result in impairment of carbohydrate tolerance. When individual patient values were reviewed, a moderate degree of insulin resistance was noted in a small number of patients (2-hour postprandial insulin >1500 pmol/L), however, even in these patients, the abnormality was present somewhat erratically. Further analysis of patients with evidence of insulin resistance is in progress.

A high number of patients were found to have cholesterol values above the clinically significant cut point (5.0 mmol/L), however in more than half of the cases this finding was mild and/or transient. Of those in whom the cholesterol concentrations were more significantly or persistently increased, approximately three-quarters of the patients in fact had cholesterol concentrations greater than 5.0 mmol/L at Visit 1 of the study (Baseline) before initiation of growth hormone therapy, and no persistent change was noted over the course of the study. These patients may represent a subgroup of patients with Turner syndrome in whom there exists an intrinsic abnormality of lipid metabolism. Further analysis of this group of patients is in progress.

There did not appear to be a significant effect of Humatrope upon hepatic function in this study. Although 30 patients had values for liver enzymes above the designated cut points at some time in the study, in the great majority these findings were transient and mild. In five patients all three enzymes were above the cut points persistently or recurrently, however in only three of these patients did the enzymes remain increased throughout the study. Even in these three patients the abnormality was only modest, the highest recorded liver enzyme value being GGT of 241 U/L. One patient had a 9-year history of abnormal liver function tests, so the increased liver enzymes detected during this study reflected a preexisting condition.

With respect to IGF-I concentration, a greater proportion of patients in the pooled hGH12 group than in the pooled hGH09 group had values above the clinically significant cut point, likely reflecting the effect of the higher dose of growth hormone upon IGF-I generation.

Humatrope did not have significant antigenicity in this study. Anti-GH binding antibodies were detected at a binding capacity of >0.02 mg/L in only four patients, none of whom experienced a decrease in growth velocity. Anti-ECP antibodies were essentially undetectable, as previously reported to the FDA.

Overall Summary

Primary Efficacy Variable

At Last Visit for the intent-to-treat population, patients in the hGH12 group had mean Height SDS of -2.29 [NCHS] compared with a mean Height SDS of -2.60 for the hGH09 group. Although the trend favored the hGH12 group, the difference in mean Height SDS did not reach statistical significance. At Last Visit, both groups showed an increase from Baseline to Last Visit in mean Height SDS relative to Baseline mean Height SDS, which was approximately -3.0 in both groups.

Secondary Efficacy Variables

The mean Final Height (cm) attained by protocol completers was similar in both treatment groups (148.50 cm in the hGH12 group, n=20; and 149.18 cm in the hGH09 group, n=11).

For all patients in the intent-to-treat population, the mean Height (cm) at Last Visit achieved by the hGH12 group was 3.12 cm greater than that of the hGH09 group. When mean Height at last visit at which a bone age x-ray was performed was analyzed, after adjustment for bone age, this difference was 1.57 cm. This difference showed a statistical trend, suggesting a possible mild dose effect of Humatrope.

Other Efficacy Variables

For the intent-to-treat population, the mean change in Height SDS [NCHS] from Baseline to Last Visit was significantly greater for the hGH12 group than the hGH09 group, supporting the suggestion of a mild dose effect of Humatrope in this study. After four years of treatment, the mean height for both groups exceeded the mean height of the Turner syndrome reference standard [Lyon] by an average Height SDS of 1.5. Both groups had similar mean Growth Velocity SDS [Ranke] throughout the treatment period, and grew at a rate 1-2 SDS faster than the mean for the reference population in the first three years of the study.

The increase in bone age had over the years of treatment was similar for both Humatrope dose groups, and bone age/chronologic age ratios remained <1.0 throughout the study.

Primary and Secondary Efficacy Variables - Analysis of the Effects of Low Dose Estrogen at an Early Age

The mean Final Height of protocol completers in the Low Dose Estrogen group was significantly less than that of the Placebo Estrogen group. However, these results should be interpreted with caution since patient numbers used in this analysis were fairly small, and the patients completing the protocol were the older patients in the study, who received higher doses of ethinyl estradiol per kg bodyweight at study entry than those entering the study at a younger age. For the intent-to-treat population, at the last visit at

which a bone age x-ray was performed, mean height of the Low Dose Estrogen group was lower than that of the Placebo Estrogen group by 3.91 cm when mean heights were adjusted for bone age and Midparental Height.

Safety Assessment

There were no deaths in this study. Five (2%) of the 230 patients in the safety population experienced a serious adverse event which was unexpected and possibly related to study drug. These events included two incidences of hypertension (in one patient this had been present for 11 years), two surgical procedures (osteotomy/bunionectomy and repair of aortic aneurysm), and one incidence of bone disorder (scoliosis). Four (2%) of the 230 patients in the safety population discontinued due to an adverse event. Reasons for discontinuation were: migraine, vascular disorder, gastrointestinal disorder, and bone disorder (scoliosis). Two of these patients, Patients 021-1171 (vascular disorder) and 059-1502 (bone disorder) had serious adverse events that were considered unexpected or possibly related to study medication.

Almost all patients reported at least one treatment-emergent event, a finding not unexpected in a pediatric population. There was no obvious relationship between the dose of Humatrope tested in this study and the occurrence of treatment-emergent events throughout the duration of the study. Rhinitis, headache, flu syndrome, fever, surgical procedure, ear pain, rash, and hypothyroidism were reported by a higher percentage of patients in the hGH12 dose group than in the hGH09 dose group. In contrast, otitis media, bronchitis, arthralgia, and pneumonia were reported by a higher percentage of patients in the hGH09 dose group than in the hGH12 dose group.

During the first 18 months of treatment, at which time there was a Placebo group that received placebo injections in place of Humatrope, otitis media, increased cough, dyspepsia, and conjunctivitis were reported in a higher percentage of patients in the Humatrope group than in the Placebo group. In contrast, headache, pharyngitis, infection, surgical procedure, rash, and sinusitis were reported for a higher percentage of patients in the Placebo group than in the Humatrope group.

A high frequency of otitis media and other ear disorders was noted in the Humatrope-treated patients in this study. It is well known that patients with Turner syndrome have a higher rate of otitis media, deafness, and other ear disorders than females of similar age who do not have Turner syndrome. The relationship between the apparent increase in frequency of ear problems in Humatrope-treated patients in this study is interesting, however its relevance is unclear. One theoretical explanation is that a mild change in the anatomy of the middle ear could occur in response to Humatrope-induced alterations in growth of membranous bones of the face and skull; however, no abnormal skull growth has been demonstrated in response to GH therapy in other studies.

In this study, the dose of Humatrope (0.09 mg/kg/dose versus 0.12 mg/kg/dose) did not appear to have differential effects on blood chemistry (including electrolytes), hematology, or lipids in patients with Turner syndrome. Summary statistics for selected thyroid function tests (total T4 concentration and TSH activity) did not differ between

treatment groups in a meaningful manner; however, the percentage of patients with values above the clinically significant cut points for these parameters was somewhat greater for the higher Humatrope dosage group.

An increase in 2-hour postprandial insulin concentration was noted between Baseline and Last Visit for patients in both Humatrope dosage groups, likely reflecting the development of mild insulin resistance. Notably, no changes in mean fasting glucose, 2-hour postprandial glucose, or hemoglobin A_{1C} were observed during growth hormone therapy, indicating that although there was a trend towards development of insulin resistance, this did not result in impairment of carbohydrate tolerance. In addition, insulin resistance was present at Baseline in a proportion of patients, evidenced by high postprandial insulin concentrations prior to Humatrope therapy.

With respect to IGF-I (somatomedin-C) concentration, a greater proportion of patients in the pooled hGH12 group than in the pooled hGH09 group had values above the clinically significant cut points, reflecting a dose effect of Humatrope upon IGF-I generation.

Conclusions

In general, there were no statistically significant differences between the hGH12 and hGH09 groups with respect to the primary efficacy variable Height SDS [NCHS] at Last Visit for the intent-to-treat population, and the secondary efficacy variable, Final Height for protocol completers. However, a possible dose effect of Humatrope was suggested by the finding of a significantly greater mean change from Baseline in Height SDS [NCHS] for the hGH12 group compared with the hGH09 group. In addition, a statistical trend favoring the hGH12 group was noted for Height at Last Visit Adjusted for Bone Age. Both treatment groups achieved a mean Height SDS at Last Visit which was greater than that of age-matched reference patients with Turner syndrome, but remained below the reference standard for normal females.

There was no obvious relationship between the doses of Humatrope tested in this study and the occurrence of treatment-emergent events throughout the study. Rhinitis, headache, flu syndrome, fever, surgical procedure, ear pain, rash, and hypothyroidism were reported by a higher percentage of patients in the hGH12 dose group than in the hGH09 dose group. In contrast, otitis media, bronchitis, arthralgia, and pneumonia were reported by a higher percentage of patients in the hGH09 than in the hGH12 dose group. Similarly, the dose of Humatrope (hGH09 versus hGH12) did not appear to have meaningful effects on blood chemistry (including electrolytes), hematology, or lipids in patients with Turner syndrome. However, there was an apparent dose effect with respect to IGF-I concentrations.

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NDA 20-656

GENENTECH STUDIES

INDEX

CONTROLLED CLINICAL TRIALS

Genentech initiated clinical trials of GH in Turner syndrome shortly after recombinant GH was available for clinical use. Both clinical trials are near completion with adult or near-adult height available for the vast majority of patients. Each study began as a short-term study and was later amended to follow patients to adult height. In this process the contol gropus were discontinued and patients were switched into the active drug gropus. Other important factors considered in the design of the studies were the timing of estrogen therapy, which is a requirement for these patients due to ovarian failure and the potential utility of concurrent androgen therapy suggested by previous clinical studies. The first Genentech-sponsored study (83-002/85-023) investigated the androgen factor, while the second study (85-044) investigated the age of initiation of estrogen therapy. Both studies contain an arm in which patients were treated with early initiation of GH with delayed initiation of estrogen are shown in Table 1.

For both studies, 85-044 and 85-023, safety evaluations were made at scheduled visits: physical exams included measurements of height, weight, blood pressure, and bone age; laboratory analyses included serum chemistries, liver function tests, thyroid function tests, hemoglobin A_{1c}, glucose, IGF-I, and insulin levels, as well as measurements of antibodies to GH. Patients were also requested to report intercurrent illnesses and adverse events at each visit.

UNCONTROLLED DATA

The NCGS post-marketing surveillance study includes patients on various GH dosing regimens. Patients were enrolled in the study on a voluntary basis by physicians upon prescription of GH and continued on therapy for a duration determined by the physician. Concomitant medications, such as estrogen or androgen therapy, were given at the discretion of the physician. Follow-up data after discontinuation of GH therapy are available on some patients. Due to the nature of the post marketing study the Turner patients followed in the NCGS were not subject to any inclusion or exclusion criteria. Patients were identified as having Turner syndrome based on text written by the physician on the enrollment form. Karyotype information was provided voluntarily and was not available for all patients. **The relaibility of data obtained in a volunatry basis, without clear defined entry criteria, physician discretion on drug dosages and steroid administration,makes the use of this information extremely limited to adequately assess either efficacy or safety.**

Table 1

Turner Syndrome Clinical Trials

Protocol No.	Etiology	Dates	Treatment	Product Code	Total Weekly Dose (mg/kg)	Treatment Group	n	Mean Baseline Age yr (range)	Maximum Length of Treatment (years)	Mean Exposure to Drug (years)
85-044	Turner syndrome	2/87 to 2/95	Nutropin	G042A	0.375	untreated	9	11 (9–14)	NA	NA
				G072A		TIW	36	12 (8–16)	7.6	4.7
						daily	81[a]	11 (8–15)	7.5	4.6
83-002	Turner syndrome	8/83 to 10/85	Protropin (somatrem)	G015A	0.375	untreated	18	9 (5–12)	NA	NA
						oxandrolone	19	9 (4–12)	1.9	1.4
						combination[b]	17	9 (5–12)	1.9	1.5
						Protropin	17	9 (5–12)	2.0	1.6
85-023[c]	Turner syndrome	5/85 to 11/94	Protropin	G015A	0.375	Protropin	17	9 (5–12)	8.9	6.0
						combination[b]	49	9 (4–12)	9.6	4.9

[a] Includes previously untreated controls.

[b] Combination=Protropin and oxandrolone.

[c] Continuation of 83-002.

NA=Not applicable.

STUDY DESIGNS

STUDY 85-044: A PHASE III, MULTICENTER, OPEN-LABEL, RANDOMIZED STUDY OF THE EFFICACY AND SAFETY OF NUTROPIN IN TWO DOSAGE SCHEDULES IN ALLEVIATING GROWTH RETARDATION ASSOCIATED WITH TURNER SYNDROME

Initiated February 18, 1987, Study 85-044 began as a one-year, open-label, randomized, controlled study designed to assess the safety and growth-promoting effects of Nutropin in girls with Turner syndrome. There were three groups: untreated controls (n=9), patients treated three times a week (TIW) (n=36), and patients treated daily (n=72). The cumulative weekly dose of Nutropin was 0.375 mg/kg/week.

The protocol was amended to allow for treatment beyond one year. After the first year, patients who were initially enrolled in the untreated control group were assigned to receive Nutropin daily during the second and subsequent study years. Patients initially enrolled in the TIW and daily groups continued with their original Nutropin treatment schedule. A total of 117 patients were enrolled in the study. The last patient enrolled on May 19, 1988.

All patients continuing in the study after one year were assigned to one of two estrogen replacement regimens. Patients under age 11 at the beginning of the study were randomized to begin estrogen therapy either in late adolescence (at age 15) or early adolescence (age 12). Patients over age 11 at the beginning of the study began estrogen therapy at Month 12. The protocol was further amended to provide for treatment and follow-up of patients until final adult height is achieved. American untreated historical Turner syndrome subjects were used as controls.

STUDY 83-002/85-023: THE EFFICACY AND SAFETY OF PROTROPIN ALONE AND IN COMBINATION WITH OXANDROLONE IN ALLEVIATING GROWTH RETARDATION ASSOCIATED WITH TURNER SYNDROME

Study 83-002 was an open-label, randomized, controlled study to assess the safety and growth-promoting effects of Protropin in Turner syndrome, with and without the concomitant administration of oxandrolone. From August 1983 to June 1984, patients were enrolled in Protocol 83-002 and randomized into one of four study groups: untreated control, oxandrolone alone, Protropin alone, and the

combination of Protropin and oxandrolone. The dose of Protropin was 0.125 mg/kg TIW (0.375 mg/kg/week).

After all patients had completed at least 12 months in Study 83-002, continuing patients were studied under Protocol 85-023. When the patients began treatment in Study 85-023, they had been studied under Protocol 83-002 for between 12 and 24 months.

The second study period (Protocol 85-023) began April 2, 1985, and consisted of two treatment arms: Protropin alone and the combination of Protropin and oxandrolone. The original untreated control and oxandrolone groups from Study 83-002 switched to combination therapy, while the original Protropin and combination groups continued with the same therapy. There was no interruption of therapy during the transition between studies. The dose of Protropin throughout the study was 0.375 mg/kg/week. With the initiation of Study 85-023, the dose of oxandrolone was decreased from 0.125 to 0.0625 mg/kg/day administered orally.

Amendments to the study provided for a switch from intramuscular (IM) to SC injections, the change from TIW to daily injections in all patients in the Protropin group and one-half of the patients in the combination group (randomly selected), and the initiation of estrogen replacement therapy, which was withheld until patients reached at least age 14. The protocol was further amended to provide for treatment and follow-up of patients until final adult height is achieved. American untreated historical Turner subjects were used as controls for both the Protropin and the combination groups.

TREATMENT GROUPS

The adult heights of the treated patients were analyzed by treatment group (see Table 2) and compared with appropriate historic controls. The number of patients in each group is described in Table 5.

Table 2

Patient Groups in Studies 85-044 and 83-002/85-023

Group	Study	Mean Baseline Age (yr)	Treatment
A	85-044	9.6	Early Nutropin + early estrogen (at age 12)
B	85-044	9.4	Early Nutropin, randomized to early estrogen, but received estrogen after age 14
C	85-044	9.4	Early Nutropin + late estrogen (at age 15)
D	85-044	12.7	Late Nutropin + Month 12 estrogen
E	85-044	14.2	Late Nutropin, only in study one year
F	85-023	9.1	Early Protropin + late estrogen (at age 15)
G	85-023	9.1	Early Protropin + late estrogen (at age 15) + oxandrolone

PATIENT ACCOUNTABILITY

Table 3

Accountability for Patients Treated with GH in Studies 85-044 and 85-023

	Study 85-044		Study 85-023		
	TIW	Daily	Protropin	Combination	Total
Patients completing protocol	23	40	13	33	109
Patients discontinued prior to completing protocol	11	28	4	17	60
Adverse event	0	2	2	2	6
Noncompliance	4	9	1	4	18
Lost to follow-up	1	2	0	0	3
Requested removal	6	15	1	11[a]	33
Patients currently on study	2	13	0	0	15
Total	36	81	17	50	184

[a] Includes one patient who discontinued from Study 83-002.

STUDY 85-044

A total of 117 patients were enrolled in the study between February 1987 and May 1988. Nine patients were randomized and enrolled in the untreated control group, 36 patients were enrolled in the group treated TIW with Nutropin and 72 patients were enrolled and treated daily with Nutropin. At Month 12, the nine patients in the control group were switched to daily Nutropin therapy.

Accordingly, treatment data for patients originally in the control group are included in the daily treatment group, using Month 12 of the study as the baseline for treatment (daily treatment group n=72+9=81).

As of this report, 102 patients have discontinued treatment (see Table 3) and 15 remain active. Sixty-three patients discontinued after meeting the protocol amendment criteria for treatment discontinuation and 39 patients discontinued for the reasons described below. The discontinuation criteria were a growth rate <2.5 cm/yr and a bone age of 14 years (which was interpreted as a bone age >13.5 years).

STUDY 83-002/85-023

Between August 1983 and June 1984, 71 patients were enrolled in Study 83-002. Patients were originally randomized to four treatment groups as follows: control group, 18 patients; oxandrolone group, 19 patients; combination group, 17 patients; Protropin group, 17 patients.

As of this report, all 71 patients have discontinued treatment. Forty-six patients discontinued after having met the protocol amendment criteria for treatment discontinuation and 25 patients discontinued prior to completing the protocol for the reasons described below. The discontinuation criteria were a growth rate <2.5 cm/yr and a bone age of 14 years (which was interpreted as bone age >13.5 years).

BASELINE CHARACTERISTICS

Table 4 shows the enrollment characteristics of the 184 Turner patients treated with GH in the two clinical trials. There were no significant differences between groups within each study with respect to any of the variables in Table 4 except that patients in Study 85-044 were older than those in Study 85-023. In both studies, baseline heights standardized for the Turner norms of Lyon et al. were very close to the mean of zero with an SD close to 1.0, which indicates the lack of biased selection and supports the appropriateness of these standards for American Turner subjects.

Table 4

Baseline Characteristics for Patients Treated with GH
in Studies 85-044 and 83-002/85-023
Mean±SD

	Nutropin TIW n=36	Nutropin Daily n=81	Protropin n=17	Combination n=50
Karyotype				
45,XO	24	48	13	38
non-45,XO	12	33	4	12
Chronological age (yr)	11.5±2.2	10.9±1.9	9.1±2.1	9.7±2.4
Bone age (yr)	9.4±1.6 n=33	9.2±1.5 n=78	7.7±1.9	8.3±2.1 n=49
Height standardized for age (Turner norms)	0.0±0.9	0.0±0.8	–0.2±0.9	–0.2±0.9
Mid-parental target height (cm)	163.9±4.9 n=35	162.5±4.2 n=79	164.5±3.7	162.3±4.0 n=49
Pretreatment growth rate (cm/yr)	3.6±0.9 n=34	4.1±1.0 n=74	4.5±0.8	4.2±0.9

ANALYSIS POPULATIONS

The primary endpoint of the studies is adult height. Adult height was defined in the protocols as evidence of fused epiphyses on bone age X-ray and no change in height for 12 months. However, in order to include as many patients as reasonable, all patients with a height measured after age 13.5 are used in the analysis of adult height, which results in a more conservative analysis. Table 5 summarizes the number of patients enrolled and available for adult height analysis. The majority of patients (172 of 184) from the two trials were available for adult height analysis.

Table 5

Enrollment and Analysis Populations
for Studies 85-044 and 83-002/85-023

Group		Enrolled	Height After Age 13.5	No Height After Age 13.5
	Study 85-044: Nutropin			
	Early GH			
A	Early estrogen	27	26	1
B	Early estrogen assigned, but received late estrogen	3	3	0
C	Late estrogen	30	29	1
	Late GH			
D	Estrogen at Month 12	51	51	0
E	GH received ≤1 year, no estrogen assigned	6	0	6
F	Study 83-002/85-023: Protropin	17	17	0
	Total patients treated with GH but not oxandrolone	134	126	8
G	Study 83-002/85-023: Combination	50	46	4
	Total patients treated with GH with or without oxandrolone	184	172	12
	Patients who did not receive GH			
	83-002 only: controls	2	0	2
	83-002 only: oxandrolone	2	0	2
	Total patients enrolled	188	172	16

RATIONALE FOR SELECTION OF THE CONTROL GROUPS

The use of concurrent, randomized, untreated controls was considered to be important for both clinical studies for the demonstration of short-term response to therapy. Since neither trial was originally designed to extend to final height, the control groups were observed for up to 24 months in Protocol 83-002 and for 12 months in Protocol 85-044. The shift of the major clinical endpoint from improved growth rate (demonstrated in the early phase of both studies) to improved final height was subsequently made in response to a developing consensus among pediatric endocrinologists and to Endocrine and Metabolic Drug Advisory Committee discussions that this endpoint should not be inferred from short-term growth rate data for non-GH-deficient patients. These decisions were reached after initiation of both Genentech clinical trials for Turner syndrome

and after a commitment had been made to the control subjects in both studies to provide GH therapy after the control period. As an alternative to a concurrent long-term control group, a database of untreated American Turner girls was developed by Genentech that has established baseline age- and height-matched historical controls for the comparison of adult height.

STUDY MEDICATION

STUDY 85-044

Nutropin

Patients received SC injections of Nutropin either TIW or daily at a weekly dose of approximately 0.375 mg/kg. The dose was calculated according to each patient's weight at baseline and then adjusted for weight every 6 months.

Estrogen

Estrogen was added to the treatment regimen after a minimum of one year of Nutropin therapy according to the following guidelines:

- If the patient's age at study initiation was 8 to 11 years, she was randomly assigned to begin estrogen treatment at a chronological age of either 12 or 15 years.
- If the patient's age at study initiation was 11 to 14 years, she began treatment with estrogen at the Month 12 visit.
- Estrogen replacement is as follows: Premarin® (conjugated estrogens) at a dose of 0.3 mg daily for 6 months followed by Premarin® at a dose of 0.625 mg daily for 6 months. After one year, the patients are cycled using the following schedule: Premarin® 0.625 mg daily on Days 1–26 of each month, Provera® (medroxyprogesterone acetate) 10 mg daily on Days 17–26, and no medication on the remaining days of the month.

STUDY 83-002/85-023

Protropin

During the first study period (Protocol 83-002), patients in Group 3 (combination) and Group 4 (Protropin only) received Protropin IM at a dose of 0.375 mg/kg/week divided TIW (0.125 mg/kg/dose). The dose was calculated according to each patient's weight at baseline and was adjusted for weight every

6 months. For the second study period (Protocol 85-023), all patients were initially treated IM with Protropin at a dose of 0.375 mg/kg/week divided TIW (0.125 mg/kg/dose).

An amendment to the protocol in 1987 provided for the change in all patients from IM to SC injections. This amendment also provided for a change in the Protropin dosing schedule for some of the patients from TIW to daily injections. This change occurred after 2 years of the second study period had been completed (Protocol 85-023, Month 24 visit). All of the patients in the Protropin group switched to daily injections, while the patients receiving a combination of Protropin and oxandrolone were randomized to either daily or TIW injection schedules of Protropin. The dose of Protropin for the patients receiving daily injections was 0.054 mg/kg/day (approximately 0.375 mg/kg/week). Thus, despite the change in the dosing interval in some patients, a constant total weekly dose was maintained throughout the study for all patients receiving Protropin.

Oxandrolone

Anavar® (oxandrolone, G.D. Searle Company) was supplied in bottles of 100 tablets, 2.5 mg/tablet. The medication was shipped directly to the investigator by G.D. Searle Company.

During the first study period (Protocol 83-002), patients in Groups 2 and 3 (oxandrolone only and combination therapy, respectively) received oxandrolone at a dose of 0.125 mg/kg/day PO. The dose was calculated according to each patient's weight at baseline and was adjusted for weight every 6 months.

During the second study period (Protocol 85-023), patients in the original Groups 1, 2, and 3 were treated with a combination of Protropin and oxandrolone. No patients received only oxandrolone during the second study period. The dose of oxandrolone was decreased from 0.125 mg/kg/day PO to 0.0625 mg/kg/day PO at the start of the second study period due to a high incidence of clitoromegaly during the first study period that was directly attributable to oxandrolone.

Estrogen

Estrogen replacement therapy was provided for in an amendment to the protocol in 1986. Estrogen supplements were prescribed at the discretion of the investigator if the patient had reached age 14 and had completed 3 years of participation in the study. The patient was given Premarin® (conjugated estrogens), 0.3 mg PO daily during the first 6 months, and then 0.625 mg daily for the next 6 months. After one year, the patients were cycled with Premarin® and a progestin according to the preference of the individual investigator.

STUDY PROCEDURES

For both studies, 85-044 and 83-002/85-023 evaluations were made at scheduled visits; physical exams included measurements of height, weight, blood pressure, and bond age; laboratory analyses included serum chemistries, liver function tests, thyroid function tests, hemoglobin A_{1c}, glucose, IGF-I, and insulin levels, as well as measurements of antibodies to GH. Patients were also requested to report intercurrent illnesses and adverse events.

Procedures for Study 85-044 including baseline assessments are outlined in Table 6.

Table 6

Study 85-044 Flowchart

Evaluations	Baseline	Treatment Period (Annual)				Follow-Up	
		Month 3	Month 6	Month 9	Month 12	Every 6 mo	Every 12 mo
Medical history	x						
Physical examination[a]	x	x	x	x	x	x	
Height and weight measurements[a]	x	x	x	x	x	x	
Blood pressure[a]	x	x	x	x	x	x	
Tanner stage[a]	x	x	x	x	x		
Interval medical history[a]		x	x	x	x	x	
Adverse events/Illnesses[a]	x	x	x	x	x	x	
Bone age X-ray[b]	x		x		x		x
CBC, differential, platelet count[c]	x	x	x	x	x		
Hemoglobin A_{1c}[d]					x		
Serum chemistry panel[e]	x	x	x	x	x		
Routine urinalysis[c]	x	x	x	x	x		
Fasting glucose[d]	x		x	x	x		
2-hr postprandial glucose[b,f]			x		x		
Fasting insulin[b,f]			x		x		
2-hr postprandial insulin[b,f]			x		x		
TSH and free T_4[e]	x	x	x		x		
Antibody to GH test[b]	x	x	x	x	x		x
IGF-I[b]	x	x	x	x	x		
Study meds dispensed[a]	x	x	x	x	x		
Dose adjustments for weight[a]			x		x		

[a] Every 6 months after 1990 amendment.
[b] Every 12 months after 1990 amendment.
[c] Every 12 months after 1988 amendment.
[d] Added by 1988 amendment (every 3 months).
[e] Every 6 months after 1988 amendment.
[f] Added by 1988 amendment (every 6 months).

Procedures for Study 85-023 including baseline assessments are outlined in Table 7.

Table 7

Study 85-023 Flowchart

		Treatment Period (Annual)				Follow-Up	
Evaluations	Baseline	Month 3	Month 6	Month 9	Month 12	Every 6 mo	Every 12 mo
Medical history	x						
Physical examination	x	x	x	x	x	x	
Height and weight measurements	x	x	x	x	x	x	
Blood pressure	x	x	x	x	x	x	
Tanner stage	x	x	x	x	x		
Interval medical history		x	x	x	x	x	
Adverse events/Illnesses	x	x	x	x	x	x	
Bone age X-ray[a]	x		x		x		x
CBC, differential, platelet count[a]	x	x	x	x	x		
Hemoglobin A_{1c}[a,b]					x		
Serum chemistry panel[a]	x	x	x	x	x		
Routine urinalysis[a]	x	x	x	x	x		
Fasting glucose	x		x	x	x		
2-hr postprandial glucose[a,c]			x		x		
Fasting insulin[a,c]			x		x		
2-hr postprandial insulin[a,c]			x		x		
TSH and T_4[d]	x	x	x		x		
Antibody to hGH test[d]	x	x	x	x	x		x
IGF-I[a]	x	x	x	x	x		
Study meds dispensed	x	x	x	x	x		
Dose adjustments for weight			x		x		

[a] Every 12 months after 1990 amendment.

[b] Every 3 months after 1988 amendment.

[c] Added to protocol by 1988 amendment.

[d] Every 6 months after 1990 amendment.

Comparisons of adult height are made with American untreated historical controls. There are five treatment arms in the two studies (see Table 13): Protropin alone (Group F), the combination of Protropin and oxandrolone (Group G), early Nutropin and early estrogen (Group A), early Nutropin and late estrogen (Group C), and late Nutropin and Month 12 estrogen (Group D). In addition, three patients randomized to early estrogen who did not receive estrogen until after age 14 constitute Group B. Six patients who were over age 11 at baseline did not continue in the study beyond Year 1 (Group E) and are not included in the analysis of adult height. (The Protropin and combination patients in Study 85-023 are also characterized as having early GH therapy since 56/67 [84%] of these patients began therapy before age 12.) The historical controls were chosen to match the treated patients with respect to childhood age (and consequently the corresponding height) and to be of an appropriate age at the initiation of estrogen therapy. In Study 85-023, 25 historical controls were chosen to match the Protropin alone group; in Study 85-044, two historical control groups were chosen to match baseline age: under age 11 for both the early (Group A) and the late (Group C) estrogen therapy patients (n=14) and over age 11 for the late GH (Group D) patients (n=55). The comparisons were made using analysis of covariance, where the covariates are baseline age and height, karyotype, and mid-parental target height.

A comparison for each of the five treatment arms was also made with respect to pretreatment projected adult heights. The pretreatment projected height of a patient is based on norms for height from a pool of untreated Turner syndrome subjects from four Western European studies. The use of these norms for projected adult height was first crossvalidated by Lyon et al. using additional data from England. Subsequently, the use of the Western European norms was validated using American untreated Turner subjects.
Comparisons of adult height (most recent height measured after age 13.5) are also made between randomized treatment regimens within each study using analysis of covariance, where the covariates include baseline age and height, karyotype, and mid-parental target height. In Study 85-023, the groups compared are Protropin alone (Group F) and the combination of Protropin and

oxandrolone (Group G). In Study 85-044, the comparison is between patients who received early estrogen (age 12) (Group A) and late estrogen (age 15) (Group C).

RESULTS

EFFICACY

The primary endpoint in both studies (85-044 and 85-023) is adult height with primary emphasis on those patients who were at least 13.5 years old when last measured. Thus, Table 8 contains baseline characteristics only for those patients who were at least 13.5 years old when last seen.

Table 8 also contains results for the historical control groups. There were no statistically significant differences in baseline characteristics between any treatment arm and its corresponding historical control group. Neither were there any statistically significant differences between randomized comparison groups (Protropin vs. combination or early vs. late estrogen) for any baseline characteristics.

There were differences between groups with respect to the age at initiation of estrogen therapy, but no historical control group had a mean age of estrogen initiation that was less than the corresponding treated group. Thus, the estrogen treatment schedule for each treated group was, if anything, less favorable to adult height than that for the corresponding control group.

Table 8

Mean Baseline Characteristics and Estrogen Treatment for Studies 85-044 and 83-002/85-023[a]

Group	D	A	B	C	F	G		
	Late GH + Month 12 Estrogen n=51	Early GH + Early Estrogen n=26	Early GH + Age >14 Estrogen n=3	Early GH + Late Estrogen n=29	Early Protropin + Late Estrogen n=17	Early Protropin + Oxandrolone + Late Estrogen n=46	American Historical Controls	
							n=25[b]	n=55[c]
Baseline age (yr)	12.7	9.6	9.4	9.4	9.1	9.9	9.2	13.2
Baseline height (cm)	129.4	116.8	115.6	116.4	114.6	117.5	117.1	131.6
Mid-parental target height (cm)	162.9	161.9	164.3	163.6	164.5	162.4	164.2	162.8
Karyotype (% 45,X)	65%	62%	67%	62%	76%	78%	60%	53%
Patients treated with estrogen	98%	85%	100%	66%	76%	70%	88%	93%
Age at estrogen treatment initiation (yr)	13.7	12.3	14.5	15.0	15.2	14.9	15.8	15.0

[a] GH patients with height measurement after age 13.5; historical control patients with height measurement after age 18 and no estrogen before age 14.

[b] Control subjects for all groups except D.

[c] Control subjects for Group D.

ADULT HEIGHT

Table 9 contains efficacy results for the patients with a height measured after age 13.5. Results are discussed for each treatment arm and appropriate comparisons are made between treatment arms and with untreated controls.

Table 9

Mean Efficacy Results for Studies 85-044 and 83-002/85-023[a]

Group	D	A	B	C	F	G		
	Late Nutropin + Month 12 Estrogen n=51	Early Nutropin + Early Estrogen n=26	Early Nutropin + Age >14 Estrogen n=3	Early Nutropin + Late Estrogen n=29	Early Protropin + Late Estrogen n=17	Early Protropin + Oxandrolone + Late Estrogen n=46	American Historical Controls[b] n=25	American Historical Controls[c] n=55
Duration of GH therapy (yr)	3.8	5.6	7.0	6.1	7.6	5.9	NA	NA
Most recent age (yr)	17.6	15.8	16.5	16.3	18.0	17.3	22.1	21.5
Most recent height (cm)	148.5	147.0	152.0	150.4	150.4	151.5	144.2	144.1
Pretreatment projected adult height (cm)	143.8	141.9	141.3	142.0	142.0	141.7	144.2	144.7
Most recent height minus pretreatment projected adult height (cm)	4.7 95% CI: 3.6 to 5.9	5.1 95% CI: 3.7 to 6.5	10.8 95% CI: 9.6 to 11.9	8.4 95% CI: 6.8 to 10.0	8.4 95% CI: 6.3 to 10.6	9.8 95% CI: 8.3 to 11.3	0.0 95% CI: −1.8 to 1.8	−0.5 95% CI: −1.5 to 0.4
Most recent height: treated minus controls by ANCOVA (cm)	5.0 95% CI: 3.7 to 6.3	5.9 95% CI: 3.3 to 8.5	12.3 95% CI: 8.4 to 16.2	8.3 95% CI: 5.3 to 11.3	7.4 95% CI: 4.6 to 10.2	10.1 95% CI: 7.8 to 12.4	NA	NA

[a] GH patients with height measurement after age 13.5; historical control patients with height measurement after age 18 and no estrogen before age 14.
[b] Controls for all groups except D.
[c] Controls for Group D only.
NA=Not applicable.

Patients with Late GH and Estrogen Therapy at Month 12

In Study 85-044, all 51 patients assigned estrogen therapy after one year of GH therapy had a height measured after age 13.5 (Group D). This group was older (mean age of 12.7 years) at baseline than the other groups (Table 9). These patients also received GH for a shorter period of time (only one year) than the other groups before the initiation of estrogen therapy. This group had less improvement in adult height than any other treated group (5.0 cm by ANCOVA vs. American untreated historical controls and 4.7 cm in comparison with pretreatment projected adult height). Although these patients had a less than ideal treatment regimen, a significant mean improvement in adult height was achieved.

Patients with Early GH Therapy Randomized to Early Versus Late Estrogen Therapy

The improvement in adult height for the early estrogen group was 5.1 cm using analysis of covariance vs. American controls and 5.9 cm on the basis of pretreatment projected adult height. The improvement in adult height for the late estrogen group was 8.3 cm using analysis of covariance vs. American controls and 8.4 cm on the basis of pretreatment projected adult height.

Results for the three patients randomized to early estrogen who did not receive estrogen before age 14 and did not have spontaneous puberty are typical of the other groups (C and F) with delayed estrogen.

The patients randomized to late estrogen (Group C, n=29) had a mean adult height 3.3 cm greater than the patients in the early estrogen group (Group A) ($p=0.003$, for height increase over pretreatment projected adult height). Using analysis of covariance with baseline age, height and bone age at age 12, karyotype, and mid-parental target height as covariates, there was a 2.4 cm advantage in adult height for late estrogen therapy ($p=0.0083$).

Thus, significant gains in adult height were achieved in both estrogen groups, but were significantly greater in the patients with delayed estrogen therapy.

Patients Treated with Protropin or Combination Therapy

The improvement in adult height for patients receiving Protropin alone (Group F) was 7.4 cm using analysis of covariance vs. American controls and 8.4 cm on the basis of pretreatment projected adult height. The improvement in adult height for patients

receiving combination therapy (Group G) was 10.1 cm using analysis of covariance vs. American controls and 9.8 cm on the basis of pretreatment projected adult height.

Using analysis of covariance with baseline age and height, karyotype, and mid-parental height as covariates, the mean adult height in the combination group was 2.7 cm greater than in the Protropin alone group (p=0.037).

Thus, substantial improvements in adult height were achieved in both groups when compared to historical controls.

Pooled Results

Figure 2 shows the most recent heights for all 184 patients who received GH in the two studies, including the patients who were less than age 13.5 when last measured and the patients from Study 85-044 who did not enter the estrogen phase of that study (one year or less of GH therapy, Group E). Figure 2 also shows that most of the patients over age 13.5 (149/172=87%, excluding Group E) achieved heights above the 50th percentile for adults with Turner syndrome. In addition, nearly half of the patients (22/49=45%) over age 13.5 from the groups without oxandrolone or estrogen therapy before age 14 had heights exceeding the 90th percentile for Turner syndrome adults. The most recent mean height of these 49 patients was 150.5 cm, which is 2.3 SDs below the mean for normal girls; while their mean baseline projected adult height was 3.7 SDs below the mean for normal girls. Many of these patients have even entered the range for normal girls, which is extremely rare for untreated Turner subjects.

Figure 2: Most Recent Height versus Most Recent Age: All Patients Treated with GH in Studies 85-044 and 83-002/85-023 (n=184)

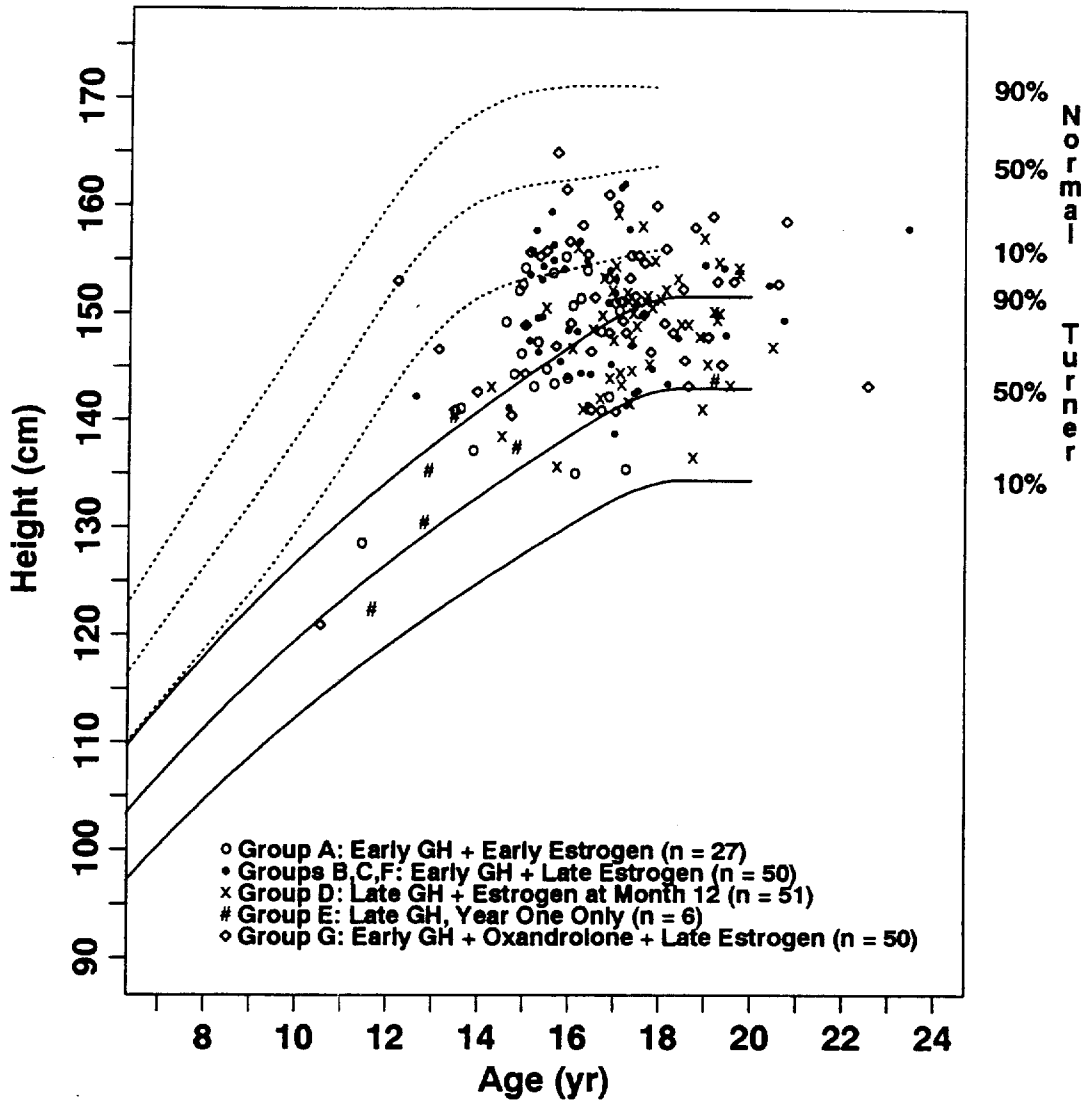

Figure 3 shows the difference between the most recent height and the pretreatment projected adult height for all 184 patients treated with GH with or without concomitant estrogen. The majority of the girls over age 13.5 (161/172=94%, excluding Group E) have heights that exceed their pretreatment projected adult heights. In particular, of the 49 girls from groups without oxandrolone or estrogen therapy before age 14 (17 [Group F] from Study 85-023 and 29 [Group C]+3 [Group B]=32 from Study 85-044) with height measured after age 13.5, only two have not exceeded their pretreatment projected adult height.

Figure 3: Most Recent Height Minus Pretreatment Projected Adult Height vs. Most Recent Age: Patients with GH Treatment in Studies 85-044 and 83-002/85-023 (n=184)

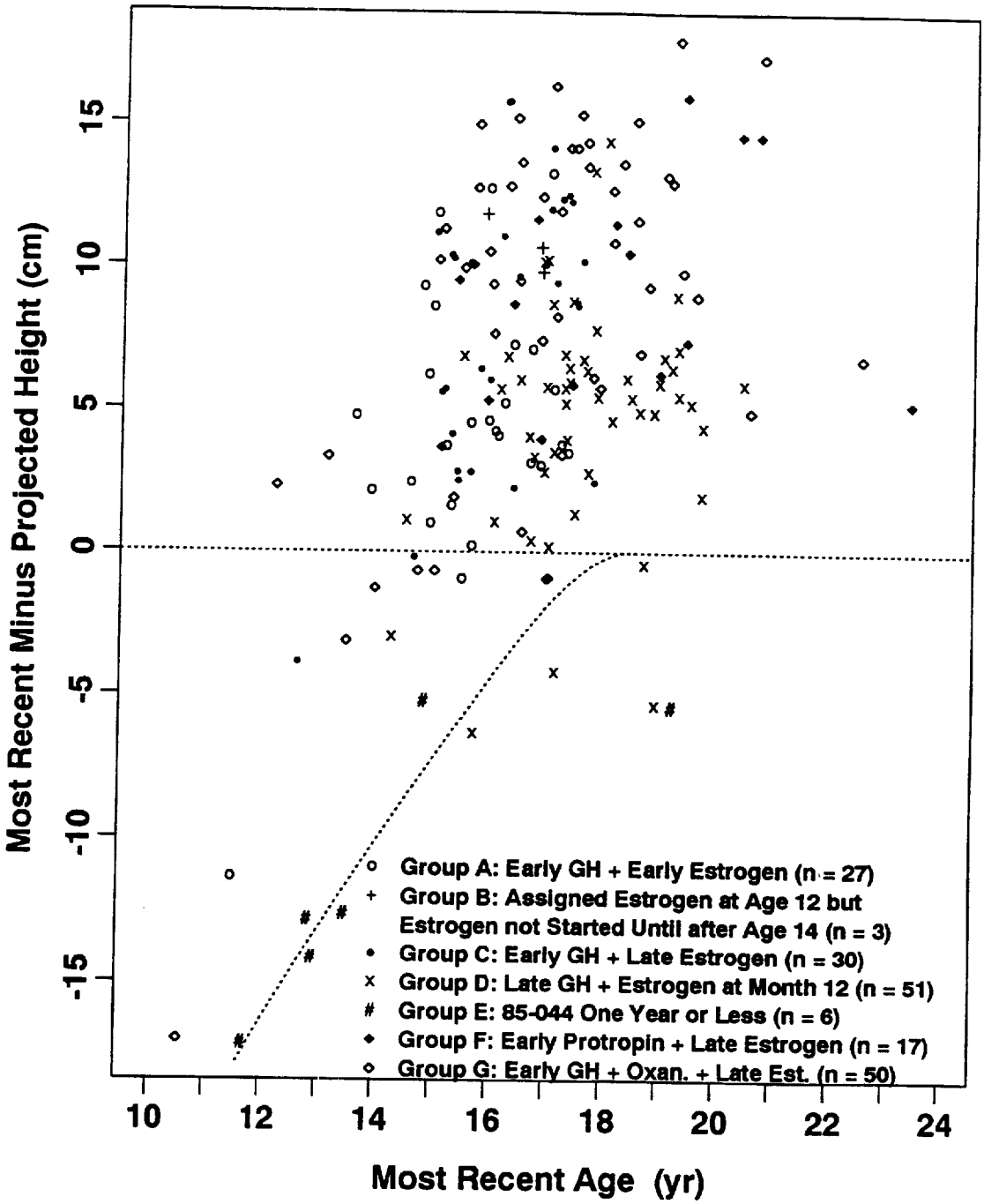

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Figure 4 shows the individual mean differences between the most recent heights and the pretreatment projected adult heights for each of the treatment groups (n=172, age at least 13.5 years [excluding Group E]) and for the group of American untreated historical controls (n=55 and 25, age at least 18 years). Figure 4 also shows that the control patients achieve a mean adult height close to their mean childhood projected adult height. The older patients with only one year of GH before initiating estrogen (Group D, n=51) and the patients with early estrogen (Group A, n=26) had a mean increase over their pretreatment projection of about 5 cm. The patients with late estrogen (Groups B, C, and F; n=3+29+17=49) had a mean increase in height over pretreatment projection of 8.6 cm (3.4 inches). Forty-four patients of these 49 patients (90%) had height increases over 5 cm (approximately 2 inches) and all but two of these patients had a height increase of at least 2 cm. The median increase for these 49 patients was 9.6 cm. The patients with combination therapy had a mean increase of 9.8 cm (3.9 inches). Most of the patients treated with GH or GH + oxandrolone who were at least age 13.5 (58/95=61%) attained heights within 2.5 SDs of the mean for normal adult women. This is uncommon in untreated Turner syndrome subjects, whose mean adult height is 3.5 SDs below the mean for normal adult women.

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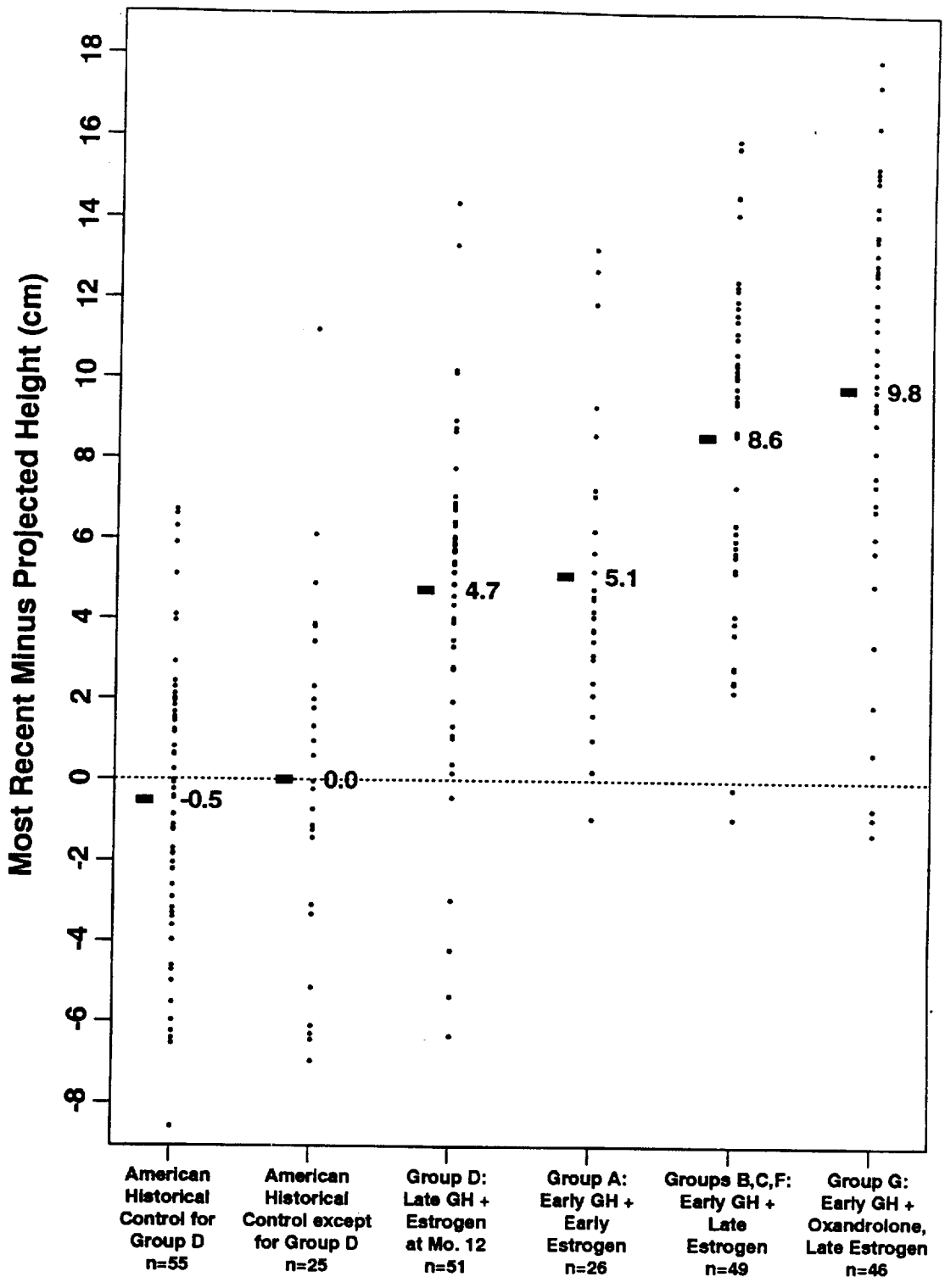

Figure 4: **Most Recent Height Minus Pretreatment Projected Adult Height: American Untreated Historical Controls (≥18 years old, n=55 and 25) and Patients with GH Treatment in Studies 85-044 and 85-023 (>13.5 years old, n=172); '–' Indicates Mean**

SAFETY

Duration Of Exposure To Recombinant GH

The overall duration of exposure to GH in the Turner syndrome studies discussed in this NDA is listed in Table 10. The number of patients, the mean duration of therapy, and the minimum and maximum lengths of therapy are noted for each study arm. A total of 184 Turner syndrome patients exposed to GH in the two pivotal clinical studies are discussed in this submission, with close to 1000 patient-years of exposure to GH.

Table 10

Extent of Exposure to GH (yr)
in Studies 85-044 and 83-002/85-023

Treatment Group	n	Mean	Minimum	Maximum
85-044				
TIW	36	4.7	0.5	7.6
Daily[a]	81	4.6	0.0	7.5
83-002/85-023				
Protropin	17	7.5	4.3	10.5
Combination[b]	50	5.3	1.0	10.8

[a] Includes patients previously in the control group.
[b] Includes patients previously in the control and oxandrolone only groups.

ADVERSE EVENTS

A number of conditions are known to be common in untreated Turner syndrome patients, such as glucose intolerance in 40% of patients, Hashimoto's thyroiditis 34%, edema 21%, scoliosis 12%, and hypertension 7% (2). Other commonly described clinical findings in Turner syndrome include decreased bone mineral content 90%, otitis media 76%, cardiovascular anomalies 55%, renal and renovascular anomalies 37%, multiple pigmented nevi 25%, severe nail dysplasia 12%, and gastrointestinal disorders 3%. Both conductive and sensorineural hearing loss are also common in Turner syndrome.

Safety data should be evaluated in light of these conditions because no concomitant controls were available during the extend of this project to perform appropriate comparisons.

Table 11 (in Adverse Events by Body System, below) contains an integrated summary of adverse events for the two controlled Turner studies (Studies 85-044

and 83-002/85-023). Subjects in the two control groups were pooled as were the groups treated with GH alone in the two studies. Adverse events reported during the two long-term clinical trials are described below.

Serious Adverse Events

One patient in the daily treatment group on Study 85-044 was diagnosed as having had a cerebrovascular accident when symptoms of progressive right-sided weakness and slurred speech were reported after 44 months of Nutropin treatment. She was also receiving Premarin® 0.625 mg and Provera® 10 mg in a cyclical regimen. Work-up revealed a unilateral ischemic stroke in the left lenticulostriate area. Nutropin, Premarin®, and Provera® were discontinued; the incident was considered to be not related to Nutropin therapy, but possibly related to Turner syndrome or estrogen therapy. The patient is progressing with physical and occupational therapy.

Another patient in the daily treatment group on Study 85-044 developed hypoplastic anemia (erythroid hypoplasia) while on Nutropin and Premarin® therapy. At that time, she was concurrently taking Tegretol®, Depakene®, Diuril®, and Inderal® for pre-existing seizure disorder and hypertension. Throughout her hospitalization, all medication other than Nutropin and Premarin® was discontinued as the investigator felt that the erythroid hypoplasia was related to her anticonvulsive therapy. After her discharge, she was started again on Diuril® without any adverse effect. She experienced some mild myoclonic seizures for which Lorazepam® was initiated. Her hemoglobin and hematocrit were stable over the next several clinic visits.

In Study 85-023, one patient on Protropin and Premarin® was diagnosed with a cerebrovascular accident with left-sided weakness. This was considered by the investigator to be due to bacterial endocarditis (*Staphylococcus aureas*) associated with pre-existing aortic stenosis and possibly with eczema. Protropin® therapy was stopped for one month and restarted, as the event was considered unrelated to Protropin® therapy. Virtually all symptoms have since resolved.

Deaths

There were no deaths reported in Study 85-044 or Study 83-002/85-023.

Adverse Events Leading to Treatment Discontinuation

In Study 85-044, one patient discontinued therapy due to an injection site reaction. Another patient discontinued due to a cerebrovascular accident, as described above.

In Study 85-023, six patients discontinued during the study due to adverse events or illnesses. Two untreated patients discontinued during the control period due to onset of Graves disease and an abnormal glucose tolerance test, respectively.

One patient in the Protropin group discontinued due to elbow pain associated with overgrowth of the right ulnar head, which an orthopedist felt might be increased by Protropin therapy. This pain was reported at Months 57, 60, 66, and 72 of the second study period and was considered mild and not related to therapy by the investigator. A second patient in the Protropin group discontinued due to right foot cellulitis and right knee pain; it was also felt that the patient had achieved a satisfactory height of 151 cm at that time.

Another patient was discontinued for "acromegalic" features. Enlargement of her hands and feet and coarsening of facial features was reported after 30 months of combination treatment, at which time therapy was discontinued. Further evaluation showed that while this patient appeared to have some coarsening of facial features, they were similar to those of her mother and thus not clearly distinguishable as due to acromegaly.

In the combination group, one patient discontinued due to a "diabetic" glucose tolerance test. Significant pre-existing medical problems for this patient included hypercholesterolemia treated with cholestyramine, hypertension treated with Tenormin® and Diuril®, and joint stiffness and soreness treated with Trilisate®. Review of her medical history showed that the patient had an increase in weight 2 1/2 years prior to this event, and continued to be moderately overweight. Her family history is positive for non-insulin dependent diabetes mellitus in the maternal grandmother. At Month 72, 60 months after beginning combination therapy, she had a glucose tolerance test which met the criteria for diabetes, having a 2-hour postprandial glucose level of 237 mg/dL and a 1-hour level of 193 mg/dL. Protropin®, oxandrolone, and Trilisate® were discontinued. A subsequent glucose tolerance test performed 6 months after discontinuing the medications was normal.

Abnormalities Associated with Turner Syndrome and Adverse Events Associated with GH Therapy

The following sections are organized by specific abnormalities associated with Turner syndrome followed by adverse events associated with GH therapy. The remaining events are described by COSTART body system terminology.

Glucose Metabolism

No cases of hyperglycemia were reported as adverse events during Study 85-044. Reactive hypoglycemia considered to be probably related to therapy was reported as an adverse event in one patient at Month 27, and not related at Months 54, 60, and 66.

In Study 85-023, one patient in the combination group discontinued due to a "diabetic" glucose tolerance test. A subsequent glucose tolerance test performed 6 months after discontinuing the medications was normal. Another patient had abnormal glucose tolerance reported during the study and, after discontinuing therapy, had a follow-up glucose tolerance test performed that was normal. One patient was reported with low blood sugar while on combination therapy that was considered to be remotely related to therapy.

No cases of sustained diabetes mellitus were reported in either clinical trial.

Lipid Metabolism

In Study 85-023, increased triglycerides were reported in one patient and hypercholesterolemia in another.

Bone Metabolism

In Study 85-044, scoliosis or kyphosis was reported in four patients, all of these cases were considered to be unrelated to therapy. One additional patient had surgical correction of tibial torsion. In Study 85-023, scoliosis was reported in one patient treated with combination therapy and in another combination therapy patient on a post-study follow-up visit.

Cardiovascular Anomalies

Cardiovascular anomalies were reported as described above under Serious Adverse Events. In addition, one investigator in Study 85-023 performed serial M-mode and two dimensional echocardiographic studies in 12 patients treated in the study. No

quantifiable changes in left ventricular mass or aortic root diameter were seen over 11 years of follow-up.

In Study 85-044, two patients were reported with hypertension as an adverse event during the study; both patients completed the study. In Study 85-023, one patient who had a coarctation of the aorta surgically repaired at Month 27 was also treated for hypertension. Three additional patients were reported with hypertension as an adverse event during the study.

Postural hypotension, syncope, or dizziness was reported in six patients in Study 85-023, none of which were reported as related to therapy.

Thyroid Function

In Study 85-044, 16 patients were reported with hypothyroidism, thyroiditis, or goiter during the study, with six of these cases reported at baseline. A total of 15 patients received thyroid replacement therapy at some time during the study, including six patients treated before GH therapy had begun. Of the remaining nine patients, five had laboratory abnormalities at baseline (i.e., elevated TSH and/or low T_4 levels).

In Study 85-023, 15 patients were reported with hypothyroidism, thyroiditis, or with elevated TSH during the study, with two of these cases reported prior to GH therapy. A total of 17 subjects received thyroid replacement therapy during the study, including 7 subjects prior to receiving GH. The incidence of patients on thyroid replacement therapy (13% in Study 85-044, 24% in Study 85-023) is within the range expected for untreated Turner girls.

Edema

Peripheral edema was reported in five patients during Study 85-044 and in 11 patients in 85-023, including two patients prior to receiving GH therapy. Increased edema was considered to be possibly or probably related to therapy in some patients.

Otitis and Hearing Loss

Otitis media, an especially common affliction in Turner syndrome, was reported in 47% of the treated patients in Study 85-044 and over 50% in Study 85-023. In addition, several patients were reported with ear ache, ear drainage, otitis externa, and

myringotomy procedures. The incidence of otitis media was not greater than the expected incidence in Turner syndrome.

Hearing loss was reported in five patients during Study 85-023 and one patient during Study 85-023, again, within the expected incidence.

Pigmented Nevi

Three patients in Study 85-044 were reported with pigmented nevi.

Alopecia

One patient in Study 85-023 was reported with alopecia while on GH. Alopecia areata was also reported in one patient in Study 85-023 during therapy with oxandrolone alone.

Liver Function

In Study 85-023, three patients on combination therapy reported elevated liver function test values. In one instance the elevation was considered possibly related to GH therapy. Liver function tests repeated 2 months later were normal.

Slipped Capital Femoral Epiphysis

One patient in Study 85-023 developed SCFE after 21 months of GH therapy, which was not interrupted.

Leukemia

No cases of leukemia were reported in either of the controlled studies with Turner syndrome patients.

Carpal Tunnel Syndrome

No cases of carpal tunnel syndrome were reported in either of the controlled studies with Turner syndrome patients.

Intracranial Hypertension

No cases of IH were reported in either of the controlled studies with Turner syndrome clinical patients.

Pancreatitis

No cases of pancreatitis were reported in either of the controlled studies with Turner syndrome patients.

Acromegaly

One patient in Study 85-023 was discontinued for "acromegalic" features as described above in Adverse Events Leading to Treatment Discontinuation. Additionally, the hand-wrist X-rays for patients treated in Study 83-002/85-023 were analyzed by two independent authorities for possible acromegalic changes. One examiner measured cartilage and soft tissue thickness and the sesamoid index in X-rays with skeletal age >14 years and found no abnormalities in the measurements to suggest acromegalic changes had taken place. The other evaluator measured the length and width of the second metacarpal on films taken after 3 and 6 years of Protropin therapy and found no evidence of abnormally increased dimensions. Other signs of acromegaloid hand growth, such as tufting and hand size, were absent according to both reviewers. Thus, the dose of GH used in the Turner syndrome studies (0.375 mg/kg/wk) was not associated with acromegalic changes, as assessed by analysis of bone measurements of the hand.

Allergy/Immunology

One patient in Study 85-023 developed anaphylactoid purpura at Month 24 of GH treatment with fever, abdominal pain, rash, and a swollen knee. This occurred immediately following a 2-week course of erythromycin that had been prescribed to treat an infected ingrown toenail. Another patient in the combination group developed migratory arthralgia after receiving first erythromycin and then Ceclor® for a respiratory infection. An allergy/immunology consultant diagnosed an allergic reaction (serum sickness) to erythromycin but not to GH by skin test.

No allergic reactions to GH were reported, although one patient in Study 85-044 was found to be allergic to excipient. Several cases of nonspecific allergy, such as urticaria, were reported in all studies.

Adverse Events by Body System

Adverse events and intercurrent illnesses are summarized by treatment group in Table 11. The table contains an integrated summary of adverse events for the two

controlled Turner studies (Studies 85-044 and 83-002/85-023). Patients in the control groups and the groups treated with GH alone in the two studies were pooled.

Aside from the events described in the previous sections, the intercurrent illnesses listed are mostly those expected in a group of young children. Most recorded events were those related to normal childhood illnesses, e.g., upper respiratory infection, gastroenteritis, or incidental trauma. Unless noted otherwise, reported adverse events were not considered by the investigator to be related to GH therapy.

Table 11

Integrated Summary of Adverse Events

in Studies 85-044 and 83-002/85-023

Treatment Group:	Control[a]	Oxandrolone	Combination	Growth Hormone[a]
Average Duration:	1.3 yr	1.4 yr	5.3 yr	5.0 yr
n:	27	19	50	134
Body as a Whole	12 (44%)	9 (47%)	47 (94%)	108 (81%)
Cardiovascular	1 (4%)	0	8 (16%)	11 (8%)
Digestive	3 (11%)	3 (16%)	16 (32%)	41 (31%)
Endocrine	2 (7%)	4 (21%)	13 (26%)	20 (15%)
Hemic/Lymphatic	0	2 (11%)	6 (12%)	6 (4%)
Metabolic/Nutrition	0	2 (11%)	13 (26%)	11 (8%)
Musculoskeletal	0	0	13 (26%)	13 (10%)
Nervous	1 (4%)	1 (5%)	7 (14%)	13 (10%)
Respiratory	2 (7%)	9 (47%)	26 (52%)	84 (63%)
Skin/Appendages	2 (7%)	5 (26%)	26 (52%)	39 (29%)
Special Senses	6 (22%)	7 (37%)	34 (68%)	80 (60%)
Urogenital	1 (4%)	7 (37%)	22 (44%)	27 (20%)

[a] Includes patients from Studies 85-044 and 85-023.

Body as a Whole

In Study 85-044, headaches were reported in approximately one-fourth of the treated patients, including two with migraine headaches. In Study 85-023, headaches were reported in 12 patients, including two with migraines. In no cases were additional symptoms reported that were consistent with intracranial hypertension.

One patient in Study 85-044 was reported with right thigh hypertrophy and another had left arm hypertrophy.

Cholesteotomas of the ear were reported for three patients in Study 85-023.

Injection site reactions were reported in two patients in Study 85-044 treated with daily injections, one with bruising and the other with large, painful, subcutaneous bumps at injection sites. The latter patient discontinued therapy after one month; skin testing revealed an allergy to an excipient of the formuation.

Cardiovascular

See the Cardiovascular Anomalies section above for a discussion of cardiovascular anomalies and hypertension.

Digestive

Symptoms consistent with gastroenteritis were reported in a number of children in each of the studies. No cases of pancreatitis were reported in Turner patients in either of the studies.

Endocrine

Galactorrhea was reported in one patient in Study 85-044 as not related to therapy.

Virilism was reported in a number of patients, all of whom received oxandrolone or the combination of oxandrolone and GH. Increased musculature was reported in four patients, voice change in two patients, acne in three patients, oily hair in one patient, hirsutism in 11 patients, and clitoromegaly in 18 patients. No patients treated with GH alone reported virilism. Clitoromegaly was reported to have partially resolved in some individuals on the reduced dose of oxandrolone used during the second study period.

See the Thyroid Function section above regarding autoimmune thyroid disease.

Hematology

One patient in Study 85-044 developed hypoplastic anemia (erythroid hypoplasia) while on GH and Premarin® therapy. At that time, she was concurrently taking Tegretol®, Depakene®, Diuril®, and Inderal® for pre-existing seizure disorder and hypertension.

Throughout her hospitalization, all medication other than GH and Premarin® was discontinued as the investigator felt that the erythroid hypoplasia was related to her anticonvulsive therapy. After her discharge, she was started again on Diuril® without any adverse effect. She experienced some mild myoclonic seizures for which Lorazepam® was initiated. Her hemoglobin and hematocrit were stable over the next several clinic visits.

A patient in Study 85-044 with hemophilia reported at baseline reported anemia and heavy menses during the study. Another patient was reported with microcytic anemia at Month 48 that was considered to be not related to therapy.

Metabolic

Weight gain was reported in three patients in Study 85-023 (in two cases during therapy with oxandrolone alone) and weight loss was reported in one patient.

See the Glucose Metabolism and the Edema sections above for a discussion of hyperglycemia and edema.

Musculo/Skeletal

In Study 85-023, two patients discontinued for reasons associated with joint pain as described above in Adverse Events Leading to Treatment Discontinuation. One patient on combination therapy developed septic arthritis of the hip and was hospitalized for one week for surgical drainage and parenteral antibiotic therapy. Therapy was not interrupted.

Five patients in Study 85-044 were reported with joint pain or discomfort that was considered to be remotely related to therapy in one case and probably related in another. Muscle aches associated with headache, vomiting, and loss of appetite were reported in one patient. Nine patients in Study 85-023 were reported with joint pain or discomfort, including one case post-injury. These cases were felt to be not related or remotely related to therapy.

See the Bone Metabolism section above for a discussion of bone abnormalities.

Nervous

Seizures were reported in patients with known histories of seizure disorder in Study 85-044, one at baseline. One of these patients had a seizure while on GH therapy who was found to have a low Tegretol® level. No new seizure disorders have been reported.

Two patients in Study 85-044 were reported with facial paresis or Bell's palsy during the study that were considered to be not related to GH therapy. IGF-I levels were within the normal range for both patients.

Dizziness was reported in four patients during Study 85-023, and in one patient at baseline. Loss of consciousness was reported in two patients, in one case following a GH injection. This event was not considered to be related to GH therapy by the investigator and the patient continued treatment with no further episodes. Emotional or behavioral problems were reported in five patients.

Papilledema was reported in a patient in Study 85-023 while receiving combination treatment. An evaluation by a neurologist and a CT scan of her head were both normal. A diagnosis of pseudotumor cerebri was considered and the patient was monitored closely by the investigator. Further evaluation by an ophthalmologist revealed the disc-margin changes to be anatomic and not true papilledema. Treatment was not interrupted.

No cases of intracranial hypertension were reported in either of the Turner syndrome clinical trials.

Respiratory

A patient in Study 85-044 with a previous history of asthma reported two episodes of asthma during treatment.

One patient in Study 85-023 in the Protropin group reported a single episode of high-altitude pulmonary edema brought on when the family moved to a high altitude location. This patient had a history of polycythemia (RBC 5.8, hemoglobin 16.2 g/dL, hematocrit 50%) and hypertension (BP 140/90), which were present prior to the initiation of GH treatment.

Upper respiratory events, including bronchitis, cough, pharyngitis, rhinitis, and sinusitis occurred in a majority of patients in both studies. Chest pain was reported in one patient with simultaneous bronchitis and cough.

Skin

One patient in Study 85-044 reported peeling of fingers and toes as probably related to therapy. Three patients were reported with warts and one with a pilomatrixoma. In Study 85-023, one patient was reported with a plantars wart and another patient with perianal condylomata. One patient was reported with rash and itching remotely related to therapy. Other events reported in one patient each include darkening pigmentation around eyes, coarsening skin texture, and striae.

See the Pigmented Nevi and Alopecia sections above for a discussion of nevi and alopecia.

Special Senses

Problems related to vision (decreased visual acuity, left eye visual disturbance) were reported in two patients in Study 85-044, but were considered to be unrelated to GH therapy.

See the Otitis and Hearing Loss section above for a discussion of otitis and hearing loss.

Urogenital

Ten patients in Study 85-044 and six patients in Study 85-023 were reported with urinary tract infections, which are commonly seen in Turner syndrome due to urinary tract anomalies.

PHYSICAL AND LABORATORY EVALUATIONS

Physical examination and laboratory data are available for the two clinical trials in Turner syndrome.

Blood Pressure

Systolic/diastolic blood pressure measurements are summarized in Table 12. Gradual increases in mean systolic and diastolic blood pressure were observed during both clinical studies, consistent with expected age-related changes.

Table 12

Integrated Summary of Blood Pressure (mmHg)
Mean±SD

Treatment Group	n	Baseline	Month 12	Month 60	Month 0–12 Change	Month 0–60 Change
Systolic						
85-044 GH	51	100±11	103±9	111±14	4±11	11±16
85-023 GH	14	99±9	101±9	109±13	2±12	9±14
85-023 Combination	34	101±13	107±11	113±12	6±13	12±14
Diastolic						
85-044 GH	51	65±12	67±9	70±10	2±12	5±14
85-023 GH	14	64±7	66±9	67±11	2±10	2±12
85-023 Combination	34	64±11	69±11	72±10	5±13	8±14

IGF-I

For the first 3 years of Study 85-044 and the first 6 years of Study 85-023, IGF-I was measured by which has since been shown to be highly inaccurate. Data for IGF-I measured by after are available for the remainder of the studies. In Study 85-044, mean IGF-I levels were 599±320 µg/L at Month 36 in the daily group (n=47) and remained in that range thereafter. Mean IGF-I levels were slightly lower (506±218 µg/L at Month 48) in the TIW group (n=22), possibly due to the greater time interval between injections during which the sample may have been drawn. Mean extracted IGF-I levels in Study 85-023 were approximately 500 µg/L. In both studies, mean IGF-I levels were close to the normal female mean for age.

Bone Metabolism

There were no clinically significant changes in mean calcium levels in either study. Inorganic phosphorus levels rose transiently (i.e., at Month 12) in Study 85-044, and remained slightly increased during Study 85-023; these changes are consistent with the known GH effect on phosphorus retention.

There was also a transient increase in mean alkaline phosphatase in Study 85-023, reflective of the expected effect of GH on bone formation. These values gradually returned to baseline levels by Month 60. Mean alkaline phosphatase levels rose in the GH, oxandrolone, and combination groups in Study 85-023, suggesting that both hormonal treatments had an effect on bone formation.

Glucose Metabolism

Fasting and 2-hour postprandial glucose and insulin levels, as well as HbA_{1c} levels are summarized in Table 13. Few baseline data are available for postprandial glucose or fasting and postprandial insulin levels in Study 85-044. Although patients were instructed to report for blood draws in the fasted state, this could not be confirmed in every case.

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Table 13

Integrated Summary of Glucose Metabolism
Mean±SD

	n	Baseline	Month 12	Month 60	Month 0–12 Change	Month 0–60 Change
Fasting Glucose (mg/dL)						
85-044 GH	52	92±14	89±11	86±10	–4±16	–7±16
85-023 GH	14	89±17	87±9	87±9	–2±17	–2±17
85-023 Combination	36	84±10	82±11	84±10	–2±11	–0±12
2 Hr Postprandial Glucose (mg/dL)						
85-044 GH	37	NA	110±25	105±23	NA	NA
85-023 GH	11	118±26	103±23	113±38	–14±24	–5±50
85-023 Combination	20	114±23	124±23	121±33	10±24	6±47
Fasting Insulin (µU/mL)[a]						
85-044 GH	39	NA	5.9	9.0	NA	NA
85-023 GH	14	5.6	5.2	14.2	1.1	7.7
85-023 Combination	19	4.6	6.5	18.3	1.8	15.2
2 Hr Postprandial Insulin (mg/dL)[a]						
85-044 GH	36	NA	27.1	45.0	NA	NA
85-023 GH	10	20.4	25.7	43.1	6.5	19.3
85-023 Combination	18	22.4	42.7	76.4	18.4	46.3
HbA_{1c} (% total Hb)						
85-044 GH	45	4.4±0.8	4.5±0.6	4.9±0.4	0.1±0.8	0.6±0.9
85-023 GH	13	NA	5.6±0.8	4.2±0.5	NA	NA
85-023 Combination	22	NA	5.2±0.5	4.3±0.9	NA	NA

[a] Medians.
NA=Not Available.

Wilson et al. detail the results of oral glucose tolerance testing during the first year of Study 85-023. The study showed that oxandrolone independently caused greater changes in glucose and insulin levels than Protropin.

Mean fasting glucose levels were close to the normal mean for age throughout Study 85-044. Mean levels in treated patients decreased significantly from 92 mg/dL at baseline to 84 mg/dL at Month 36 (n=89, $p<0.0001$). Sporadic values in both treatment

groups were elevated at baseline and during the study. In Study 85-023, individual fasting glucose levels were in the normal range at all times for patients in the Protropin group and were increased at one visit only in two patients in the combination group.

Mean postprandial glucose levels were well within the normal range throughout Study 85-044, although occasional values were above normal that were sustained in a few patients. In Study 85-023, mean 2-hour postprandial glucose levels were increased in the oxandrolone group at one year compared with baseline ($p=0.023$) and decreased in the group treated with Protropin alone ($p=0.020$). Nearly all individual values were in the normal range in the Protropin group throughout the study, whereas several values were greater than normal in the combination group.

A rise in fasting and postprandial insulin levels was seen from Month 12 to Month 24 in Study 85-044 and levels plateaued thereafter on continued Nutropin therapy. Occasional values for fasting and postprandial insulin were above normal and were sustained in a few patients. In Study 85-023, fasting insulin levels were increased in the Protropin and combination groups compared with baseline. All individual values for fasting insulin were within the normal range in the Protropin group throughout the study, whereas some values were elevated in the combination group. Mean 2-hour postprandial insulin levels were increased in the combination group to a greater degree than in the Protropin group. All individual values were <100 mU/L in the Protropin group throughout the study, whereas several values were >100 mU/L in the combination group.

Mean hemoglobin A_{1c} levels remained normal throughout both studies. There were a few, sporadically elevated HbA_{1c} levels at baseline and during the studies. In Study 85-023, there were no patients with a sustained increase in HbA_{1c} in the Protropin group and only one combination group patient had a progressive increase to 7% at Month 60.

In summary, a small increase in mean insulin levels was observed during GH therapy, accompanied by normal glucose and HbA_{1c} levels. The combination of GH plus oxandrolone resulted in greater increases of glucose and insulin values, although HbA_{1c} levels still remained within the normal range. No patient treated with GH in either study developed diabetes mellitus.

These findings are consistent with published data in Turner syndrome, indicating abnormal glucose tolerance in untreated subjects. Detailed metabolic studies of the effects of GH in Turner syndrome also show increased insulin levels but overall euglycemia.

Lipid Metabolism

Mean cholesterol levels were elevated at baseline in both studies. There was a small, statistically significant decline in mean serum cholesterol in the group treated daily in Study 85-023; there was no significant change in mean serum cholesterol in any group during Study 85-023.

Mean triglyceride levels were in the high-normal range at baseline and throughout Study 85-044. There was an initial decrease in serum triglyceride levels (i.e., at Month 12), followed by slightly increased levels. There was a trend toward higher triglyceride levels during Study 85-023 in the Protropin group.

Renal Function

Mean BUN and creatinine levels did not change in a clinically significant manner in either study. A trend toward lower BUN levels with GH treatment is consistent with the known anabolic effects of GH.

Thyroid Function

There were no clinically significant changes in mean free T_4 or mean TSH levels in any treatment group in the two studies.

Five patients had low free T_4 levels during Study 85-044, three of which were associated with elevated TSH levels. Seven additional patients had markedly elevated TSH levels, including two prior to receiving GH therapy. There were several instances of elevated TSH and/or decreased T_4 levels in Study 85-023. No patients in the Protropin group had low T_4 levels during the study, whereas a number of combination patients did. Two patients in the Protropin group had sporadically elevated TSH levels, as did several patients in the combination group. Fourteen patients had elevated TSH levels at baseline. Several of these patients were treated with thyroid replacement therapy. The incidence of laboratory evidence of thyroid disease in both studies is within the expected range for Turner syndrome.

Other Laboratory Parameters

There were no clinically significant changes in liver function tests in the two studies, with a tendency for mean values to decrease while on treatment.

Serum electrolytes were essentially unchanged except for a decrease in mean chloride levels in Study 85-044 and a slight increase in mean sodium levels in Study 85-023. There were no significant alterations in complete blood count and urine analysis with GH therapy. A small increase in mean hematocrit, hemoglobin, and RBC values was seen in the groups receiving oxandrolone, alone or in combination with Protropin in Study 85-023. Decreased platelet counts were also seen in the combination group.

A slight increase in mean uric acid levels were seen in the oxandrolone and combination groups.

Antibodies to GH

Data from Study 85-044 for Nutropin are discussed below. Table 14 shows the incidence and titers for antibodies to GH. The incidence of antibodies to GH was maximal at 12 months (15%) and decreased to 5% at 36 and 48 months. The incidence was similar in the TIW and daily treatment groups. There were no negative effects on growth associated with the presence of antibodies to GH.

Table 14

Incidence and Titers of Antibodies to Growth Hormone in Study 85-044

Month	Antibody Incidence	Antibody Titer Mean±SD (range)	Growth Rate (cm/yr)	
			Seropositive	Seronegative
6	12/112 (11%)	1.9±0.7 (1.1 to 3.0)	8.9±2.2 (n=12)	8.0±2.4 (n=100)
12	17/111 (15%)	1.8±0.7 (1.0 to 3.6)	7.5±2.0 (n=17)	7.5±1.6 (n=94)
24	9/93 (10%)	2.1±0.5 (1.3 to 2.9)	7.5±2.0 (n=9)	6.3±1.5 (n=84)
36	5/80 (6%)	2.0±0.6 (1.3 to 2.8)	6.1±0.9 (n=5)	5.1±1.7 (n=75)
48	4/73 (5%)	1.6±0.6 (1.1 to 2.4)	6.2±0.7 (n=4)	4.1±1.8 (n=69)

Binding capacities were computed for the high affinity site in a biomathematical model with two classes of binding sites. In those instances where the high affinity binding capacity could not be obtained separately from the low affinity binding capacity, a combined binding capacity was obtained. Binding capacities were obtained for all but three patients who were seropositive to antibodies to GH at Month 6. Binding capacities were also obtained for six patients for whom the highest GH antibody titer was at least 2.4. All of the binding capacities were low (i.e., less than 0.7 mg/L) except for one value of 1.8 mg/L. There were no instances of antibodies with binding capacity of 2.0 mg/L or greater at Month 6 or at any other time during the study.

The growth rate for the antibody-positive patients was statistically significantly greater than the growth rate for the antibody-negative patients or there was no statistically significant difference between groups. The six patients with one or more titers ≥ 2.4 each had good growth rates at the time the positive antibody titer was observed.

The absence of growth attenuation for antibody-positive Turner patients treated with Nutropin is consistent with studies of Nutropin in the approved indications for GH deficiency and chronic renal insufficiency.

CONCLUSIONS

The pretreatment heights of the patients in the two Genentech-sponsored studies were consistent with the norms for Turner syndrome. The girls were short compared to normal girls. The girls in the American historical control group were also typical of Turner syndrome. The primary endpoint of the studies was adult height. All treated groups showed a significant improvement in adult height compared to pretreatment projected adult heights and compared to the American historical controls.

The improvement was greatest for patients with early GH therapy and estrogen therapy delayed until after age 14 (the mean improvement in adult height was 8.6 cm and the median was 9.6 cm). As adults, they will have improved their stature on average from an expected 143 cm to over 150 cm, which is close to the normal adult female height range.

In addition, long-term treatment with GH in these clinical trials was found to be safe and well tolerated. No adverse events were observed that would preclude long-term GH therapy in patients with Turner syndrome. None of the laboratory changes noted were of clinical significance. Compared to untreated Turner syndrome patients, no new or unexpected safety signals unique to GH-treated Turner syndrome patients were identified. The incidence of known complications of the underlying syndrome were not altered. Certain rare adverse drug reactions known to be associated with GH administration in children with GH deficiency were also seen in Turner syndrome patients treated with GH.

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrine Drug Products

Date: December 17, 1996

From: Saul Malozowski, M.D., Ph.D.
Medical Officer

Subject: Four Months Safety Update- NDA 19-640 (S18)I

To: The file

The documented received on November 26, 1996 indicates that no new unexpected adverse events have occurred during the period covered by the submission. Thus, GH administration to patients with Turner's syndrome appears to have a similar safety profile to that described in GH deficient patients. No further action is necessary.

STATISTICAL REVIEW AND EVALUATION

NDA#: 19-640/SE1-018

APPLICATION: Lilly Research Laboratories

NAME OF DRUG: Humatrope (Somatropin, biosynthetic human growth hormone)

INDICATION: Treatment of short stature associated with Turner Syndrome

DOCUMENTS REVIEWED: Volumes 1.1, 1.18-1.32 of NDA 19-640/SE1-018, dated July 29, 1996 and submission dated October 11, 1996.

MEDICAL REVIEWER: This review has been discussed with the clinical reviewer, Saul Malozowski, M.D., HFD-510

RELEVANT ISSUES DISCUSSED IN THIS REVIEW

1. Patients randomized to receive Humatrope who achieved final height in Study GDCT statistically outperformed their concurrent untreated counterparts by approximately 2-2.5 inches.

2. The sponsor's speculation that the Study GDCT Humatrope patients "will continue to grow for some time" does not ensure that the exhibited final height treatment effect will increase as the data matures.

3. The Study GDCT and Study GDCI final height data are consistent in that the median Humatrope final heights were 4' 9.7" and 4' 10.6" respectively.

BACKGROUND

Humatrope was approved in 1987 by the FDA for use as replacement therapy for the long-term treatment of children who have growth failure due to an inadequate secretion of normal endogenous growth hormone.

The sponsor's current submission contains an interim analysis from a randomized, concurrent controlled study (Study GDCT), and a preliminary report from an open label dose response study (Study GDCI).

KEYWORDS: estradiol, final height, growth hormone, Turner syndrome

These studies have been submitted to support the expansion of the approved indication to include children with Turner syndrome.

A major conclusion during a meeting on June 4, 1991 between representatives of the FDA and Lilly was that any submission of a new drug application for biosynthetic human growth hormone to be used in patients with Turner syndrome would require clinical data obtained from patients who have been treated to their final height. This was consistent with the recommendations of the Endocrine and Metabolic Drug Advisory Committee on September 28, 1987 that patients be followed until final height is reached and that studies include a control group and be randomized.

In a meeting between representatives of FDA and Lilly on January 12, 1993, the FDA stated that a submission based on improved growth velocity alone was not sufficient and that they would not accept anything short of final height data unless Lilly could provide psychological benefit data.

Consequently, this review will focus on the results of Study GDCT in which final height is the primary efficacy parameter. Descriptive results will be presented for Study GDCI in which final height is a secondary efficacy parameter.

STUDY GDCT

Study GDCT is an ongoing, Canadian, multi-center (13 centers), open-label, parallel, randomized study which is being conducted to determine the efficacy of Humatrope in promoting an increase in final height for patients with Turner syndrome.

A total of 154 patients were enrolled, stratified by stature (low, middle, upper), and randomly assigned to two treatment groups. Seventy-six patients were randomized to receive Humatrope .05 mg/kg subcutaneously 6 times each week (subject to a maximum weekly dosage of 15mg) until final height as defined below was achieved. The remaining 78 patients who were randomized to the concurrent non-treatment control group did not receive Humatrope therapy.

Patients who were at least 13 years old and had been in the study for at least 12 months received ethinyl estradiol and medroxyprogesterone, the dosages of which were based on chronological age.

Fourteen (1 Humatrope, 13 untreated) patients (twelve of whom did not complete the first study visit) did not have baseline data.

The sponsor's safety population consisted of the 136 patients who either received study medication or if in the untreated group, had post-baseline safety data.

The sponsor's intent-to-treat population consisted of the 134 patients who had efficacy data 180 days after randomization. None of the six patients who were excluded from the sponsor's intent-to-treat

population achieved final height which is the primary efficacy parameter for this study.

Final height was defined as the actual height measurement at the last available study visit for patients who had at least 6 months of growth data with an annualized growth rate of less than 2 cm/year and a bone age of at least 14 years.

Twenty-five patients (8 Humatrope, 17 untreated) have discontinued from the study primarily due to patient decision (5 Humatrope, 8 untreated). One untreated patient died due to a ruptured aortic aneurysm and two Humatrope patients have discontinued due to adverse events (an increase in SGOT, intracranial hypertension).

As of the February 8, 1996 data cutoff date, each of the 74 Humatrope and 58 of the 62 untreated safety population patients experienced at least one adverse event. Significant differences (Table 1) were detected in favor of the untreated group over the Humatrope group with regard to surgical procedures, otitis media, ear disorder, and accidental overdose.

Sixty-nine (40 Humatrope, 29 untreated) patents continue to participate in the study whereas 46 patients (27 Humatrope, 19 untreated) were considered by the sponsor to have completed the study having fulfilled or almost fulfilled the above mentioned final height study criteria.

Fourteen (9 Humatrope, 5 untreated) of the above mentioned 46 patients did not meet the final height study criteria. However, they were felt to have "achieved close to their final height" by the study investigators. These fourteen patients all had a bone age of at least 13.5 years and all but one Humatrope patient had a growth velocity less than 3 cm/year.

REVIEWER'S COMMENTS ON STUDY GDCT

The sponsor conducted several final height analyses all of which yielded similar results. One such result is displayed in Table 2.

In examining Table 2, one notes that the Humatrope patients statistically outperformed their untreated counterparts with regard to final height. The estimated difference was 5.4 cm (2.1 inches).

This result was consistent across stature stratums (treatment-by-stature, p=.76) and geographical regions (treatment-by-geographical region, p=.27). The 13 centers were pooled into 3 geographical regions due to sample size concerns.

In more familiar terms (to this reviewer), given that 1 cm=.3937 inches, the mean final heights displayed in Table 2 translate to 4' 9.5" for the Humatrope patients compared to 4' 7.9" for the untreated patients, a difference of approximately 2 inches.

As an aid to assessing the Humatrope treatment effect one should consult Table 3.

Table 3 displays descriptive final height results in one inch intervals for the 46 patients in the sponsor's's final height population. In examining this table one notes that approximately 22% of the Humatrope final height patients achieved an adult height of at least 5'.0".

As mentioned above, fourteen of the patients who were included in the sponsor's final height population did not satisfy the protocol-specified definition of final height.

At the request of this reviewer, the sponsor has conducted additional final height analyses which include only the 32 patients who satisfied the protocol-specified final height criteria.

The sponsor's results (which are similar to those displayed in Table 2) based on these 32 patients are displayed in Table 4. In examining this table, one notes that the Humatrope patients statistically outperformed their untreated counterparts with regard to final height. The estimated difference was 6.3 cm (2.5 inches).

Table 5 displays descriptive final height results in one inch intervals for these 32 patients. In comparing this table to the above mentioned Table 3 (sponsor's final height population), it is apparent that the results are similar. For example, in each case, approximately 22% of the Humatrope final height patients achieved an adult height of at least 5'.0".

The sponsor has indicated that 38 patients (22 Humatrope, 16 untreated) have currently satisfied the protocol-specified final height criteria. Final height analyses based on this 38-patient population yielded results similar to those mentioned above. In this case the treatment effect was 6.1cm (2.4 inches).

In examining Table 2, one notes that final height patients have been in the study for an average of 4.6 years (baseline age: 11.7, most recent age: 16.3).

The sponsor has stated that "it is likely that for many of these patients true final height has yet to be achieved" and that "it is well established that patients with Turner syndrome have a very prolonged period of slow linear growth during late teenage years, many of these patients completing their growth as late as 19 or 20 years of age".

Based on these statements the sponsor has speculated "that although, the protocol completers in this study were growing slowly (most < 2 cm/yr), it is likely that they will continue to grow for some time to come and achieve adult height greater than the height referred to in this study as final height".

The above statement regarding continuing growth pertains of course to Turner patients in both treatment groups. Consequently, given the available data, it is not possible at this time to assume that the existing between-treatment group difference in final height of approximately 2-2.5 inches will increase over time.

Since only 46 (32) patients completed the study prior to the cutoff date for the current interim analysis, the sponsor placed additional emphasis on an examination of height achieved by the last study visit for all patients who remained in the study for at least 180 days. This was done to "provide a broader overview of the effectiveness of Humatrope in a larger sample of patients".

A total of 126 patients (71 Humatrope, 55 untreated) were included in this analysis which adjusted for bone age and midparental height. An estimated difference of 2.4 inches ($p<.001$) was detected in favor of the Humatrope patients over the untreated patients. The magnitude of this effect is similar to the final height treatment effects of 2.1, 2.5, and 2.4 inches which were detected for the above mentioned 46-patient, 32-patient, and 38-patient populations respectively.

STUDY GDCI

Study GDCI is an ongoing, U.S., multi-center (50 centers) study which is being conducted to determine the efficacy of Humatrope in promoting linear growth in patients which Turner syndrome.

A total of 232 patients were enrolled, stratified by age (5-7 years, 8-9 years, 10-11 years, at least 12 years of age), and randomly assigned to the following five treatment groups for an initial 18 month treatment period:

1. Humatrope (.09 mg/kg/dose) with low dose ethinyl estradiol (designated hGH09/LDE).

2. Humatrope (.09 mg/kg/dose) with placebo ethinyl estradiol (designated hGH09/PLA).

3. Humatrope (.12 mg/kg/dose) with low dose ethinyl estradiol (designated hGH12/LDE).

4. Humatrope (.12 mg/kg/dose) with placebo ethinyl estradiol (designated hGH12/PLA).

5. Placebo Humatrope with placebo ethinyl estradiol (designated PLA/Switch).

The prescribed dose of Humatrope was to be injected subcutaneously 3 times per week up to and including visit 25 (72nd study month). The Humatrope dose was then to be halved and injected 6 times per week. Oral study drug material (ethinyl estradiol or placebo ethinyl estradiol) was administered according to chronological age and body weight.

It became apparent to the sponsor that some investigators would remove so-called poorly responding patients (as they defined them) from the study and initiate open-label commercially available growth hormone therapy after the first 18 months of the placebo-controlled trial.

In order to attempt to maintain the integrity of the study, the sponsor blindly reassigned (following the initial 18 month treatment period) the least responsive group with regard to growth velocity (based on an analysis after the first 9 months of therapy) to the hGH12/PLA treatment group.

Patients and investigators were unaware of either the initial or the subsequent treatment received by this and any other treatment group. It was subsequently determined that the reassigned group (designated as PLA/Switch above) had been receiving placebo Humatrope with placebo ethinyl estradiol.

The sponsor has indicated that the study has been unblinded for the purpose of this submission and that the "interpretation of the effect of Humatrope on final height in this study would be subject to the same criticism as historically-controlled trials". Consequently, final height was regarded to be a secondary efficacy parameter.

The sponsor's safety population consisted of the 230 patients who took study medication.

The sponsor's intent-to-treat population consisted of the 224 patients who had efficacy data 180 days after randomization or if randomized to the PLA/Switch treatment group, had efficacy data 180 days after their reassignment.

As of the February 8, 1996 data cutoff date, 31 patients had completed the study (i.e., reached final height or were considered by the investigator to have almost reached final height), while 63 patients remain active. The remaining 138 patients discontinued early. Only 4 of these patients discontinued due to adverse events.

REVIEWER'S COMMENTS OF STUDY GDCI

As mentioned above, final height was a secondary efficacy parameter. However, the remainder of this review will focus on the final height results in order to compare them with those of the above reviewed controlled study GDCT.

Final height was defined as the actual height measurement at the last available visit for patients with an annualized growth rate of less than 2 cm/year and a bone age of at least 15 years. Seven of these patients did not meet these criteria quantitatively. However, they were felt by the investigator to have achieved close to their final height. These seven patients all had a bone age of at least 13.5 years and a growth velocity of less than 3 cm/year.

Table 6 displays descriptive final height results in one inch intervals for the 31 patients in the sponsor's final height population. In examining this table one notes that the mean (median) final height of 4' 10.6" is consistent with the results (Table 3) obtained in the controlled study GDCT.

REVIEWER'S CONCLUDING COMMENTS

Patients randomized to receive Humatrope who achieved final height in Study GDCT statistically outperformed their concurrent untreated counterparts by approximately 2-2.5 inches.

However, it is not possible at this time to assume that the existing between-treatment group final height difference will increase as the data matures.

The final height data in Study GDCI is consistent with that of Study GDCT in that the median Humatrope final heights were 4' 10.6" and 4' 9.7" in Studies GDCI and GDCT, respectively.

Daniel N. Marticello
Mathematical Statistician

Concur: Dr. Nevius 11-21-96

cc:
Archival NDA 19-640/SE1-018
HFD-510
HFD-510/SSobel,AFleming,GTroendle,SMalozowski,EGalliers,MJohnston
HFD-715/Division File,DMarticello,Chron.

This review consists of 7 pages of text and 6 pages of tables.

TABLE 1

STUDY GDCT

ADVERSE EVENTS[+]

EVENT	HUMATROPE	UNTREATED	P-VALUE[++]
Accidental Overdose	8/74 (10.8%)	0/62	.008
Ear Disorder	13/74 (17.6%)	3/62 (4.8%)	.031
Otitis Media	32/74 (43.2%)	16/62 (25.8%)	.047
Surgical Procedure	33/74 (44.6%)	17/62 (27.4%)	.050

+ Adverse events experienced by at least 5% of the patients for which there was a significant ($p<.05$) between-treatment difference.

++ Fisher's Exact Test

TABLE 2

STUDY GDCT

SPONSOR'S FINAL HEIGHT POPULATION+

MEAN FINAL HEIGHT

	HUMATROPE	UNTREATED
N	27	19
Baseline Age (yrs)	11.7	11.7
Most Recent Age (yrs)	16.3	16.3
Baseline Height (cm)	123.8	126.3
Final Height (cm)	146.0	142.1
Difference# (cm)	5.4	
	p<.001*	

\+ 46 patients were included in the sponsor's final height analysis

\# Estimated mean difference in final height based on an analysis of covariance with mid-parental height as a covariate

* p<.001 in favor of Humatrope patients over untreated patients

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STUDY GDCT

SPONSOR'S FINAL HEIGHT POPULATION+

FINAL HEIGHT DISTRIBUTION

FINAL HEIGHT	HUMATROPE		UNTREATED	
	FREQUENCY	CUMULATIVE FREQUENCY	FREQUENCY	CUMULATIVE FREQUENCY
4' 4"	0		1	19 (100.0%)
4' 5"	3	27 (100.0%)	3	18 (94.7%)
4' 6"	1	24 (88.9%)	2	15 (78.9%)
4' 7"	5++	23 (85.2%)	5	13 (68.4%)
4' 8"	3	18 (66.7%)	2	8 (42.1%)
4' 9"	4	15 (55.6%)	4	6 (31.6%)
4' 10"	4	11 (40.7%)	1	2 (10.2%)
4' 11"	1	7 (25.9%)+++	1	1 (5.3%)
5' 0"	5	6 (22.2%)	0	
5' 1"	1	1 (3.7%)	0	
MEAN	4' 9.5"		4' 7.9"	
MEDIAN	4' 9.7"		4' 8.0"	

\+ 46 Patients were included in the sponsor's's final height analyses

++ Example: 5 Humatrope patients had a final height of at least 4' 7" but less than 4' 8"

+++ Example: 25.9% of the Humatrope patients had a final height of at least 4' 11"

TABLE 4

STUDY GDCT

PROTOCOL-SPECIFIED FINAL HEIGHT POPULATION+

MEAN FINAL HEIGHT

	HUMATROPE	UNTREATED
N	18	14
Baseline Age (yrs)	11.7	11.6
Most Recent Age (yrs)	16.5	16.1
Baseline Height (cm)	124.1	126.7
Final Height (cm)	146.7	142.5
Difference# (cm)	6.3	
	p<.001*	

+ 32 patients satisfied the protocol-specified definition of final height

Estimated mean difference in final height based on an analysis of covariance with mid-parental height as a covariate

* p<.001 in favor of Humatrope patients over untreated patients

TABLE 5

STUDY GDCT

PROTOCOL SPECIFIED FINAL HEIGHT POPULATION+

FINAL HEIGHT DISTRIBUTION

FINAL HEIGHT	HUMATROPE		UNTREATED	
	FREQUENCY	CUMULATIVE FREQUENCY	FREQUENCY	CUMULATIVE FREQUENCY
4' 4"	0		1	14 (100.0%)
4' 5"	2	18 (100.0%)	2	13 (92.9%)
4' 6"	1	16 (88.9%)	1	11 (78.6%)
4' 7"	1	15 (8.3%)	3	10 (71.4%)
4' 8"	3	14 (77.7%)	2	7 (50.0%)
4' 9"	3	11 (61.1%)	3	5 (35.7%)
4' 10"	3	8 (44.4%)	1	2 (14.3%)
4' 11"	1	5 (27.8%)	1	1 (7.1%)
5' 0"	3	4 (22.2%)	0	
5' 1"	1	1 (5.6%)	0	
MEAN	4' 9.7"		4' 8.1"	
MEDIAN	4' 9.7"		4' 8.4"	

\+ 32 patients that satisfied the protocol-specified definition of final height

TABLE 6

STUDY GDCI

SPONSOR'S FINAL HEIGHT POPULATION[+]

FINAL HEIGHT DISTRIBUTION

FINAL HEIGHT	FREQUENCY	CUMULATIVE FREQUENCY	
4' 6"	1	31	(100.0%)
4' 7"	7	30	(96.8%)
4' 8"	2	23	(74.2%)
4' 9"	2	21	(67.7%)
4' 10"	5[++]	19	(61.3%)
4' 11"	6	14	(45.2%)
5' 0"	3	8	(25.8%)[+++]
5' 1"	2	5	(16.1%)
5' 2"	2	3	(9.7%)
5' 3"	0	1	(3.2%)
5' 4"	1	1	(3.2%)
	MEAN 4' 10.6"		
	MEDIAN 4' 10.6"		

\+ 31 patients were included in the sponsor's final height analyses

++ Example: 5 patients had a final height of at least 4' 10" but less than 4' 11"

+++ Example: 25.8% of the patients had a final height of at least 5'

Clinical Pharmacology and Biopharmaceutics Review

NDA:	19-640
Somatropin for Injection (5 mg vial)	AUG 2 8 1996
(Humatrope ®)	
Submission Date:	7/29/96
Sponsor:	Eli Lilly, Indianapolis, Indiana
Type of Submission:	Supplemental New Drug Application
Reviewer:	Michael J. Fossler, Pharm. D., Ph. D.

Submission

The submission dated 7/29/96 is a sNDA to support expanding the approved indications for Humatrope to include girls with Turner's syndrome. The recommended dose of somatropin for this proposed new indication is 0.27-0.375 mg/kg divided into equal doses given either on three alternate days or six times a week by subcutaneous injection.

No new pharmacokinetic data were included with the submission. Recently, the CLINICAL PHARMACOLOGY portion of the labeling was extensively revised (see OCPB review dated 7/25/96). The revisions are included in the current draft labeling for the present proposed indication.

Recommendations

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (HFD-870) has reviewed the submission and draft labeling dated 7/29/96 and finds them acceptable, provided the Comment below is addressed by the firm.

Comments (to be sent to firm)

1. Under Special Populations in the CLINICAL PHARMACOLOGY portion of the labeling, the following text should be added:

Turner's Syndrome- No pharmacokinetic data are available for exogenously

administered rhGH. A report[1] examining the pattern of endogenous growth hormone secretion and elimination in Turner's and normal prepubertal girls suggests that the two groups are similar.

8/28/96

Michael J. Fossler, Pharm. D., Ph. D.

Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

FT
~~BD~~ initialed by Hae-Young Ahn, Ph. D., Team Leader 8/28/96

CC: NDA 19-640 (orig., 1 copy), HFD-510(Malozowski, Johnston), HFD-850(Lesko), HFD-870(M. Chen, Fossler, Ahn, Drug File, Chron. File, Reviewer File),HFD-205(FOI), HFD-340 (Vish)
7/24/96

---

[1]Veldhuis JD et al. Decreased Metabolic Clearance of Endogenous Growth Hormone and Specific Alterations in the Pulsatile Mode of Growth Hormone Secretion Occur in Prepubertal Girls with Turner's Syndrome. J. Clin. Endocrin. Metabol. (1991) 73:1073.

A Pharmacology Review of this Submission by Dave Hertig on 7 August 1996 noted no new pharmacology information being submitted. Labeling was reviewed and acceptable.

CHEMIST'S REVIEW	1. ORGANIZATION DMEDP, HFD-510	2. NDA NUMBER FEB 5 1997 19-640
3. NAME AND ADDRESS OF APPLICANT Lilly Research Laboratories Lilly Corporate Center Indianapolis, Indiana 46265		4. SUPPLEMENT NUMBER, DATE S-018 7/29/96 **User Fee Date:** 7/31/97
5. NAME OF THE DRUG Humatrope	6. NONPROPRIETARY NAME Somatropin (rDNA) for Injection	8. AMENDMENTS/REPORT, DATE
7. SUPPLEMENT PROVIDES FOR: expanding the approved indication to include children with Turner Syndrome		
9. PHARMACOLOGICAL CATEGORY Hormone, growth	10 HOW DISPENSED Rx	11. RELATED IND/NDA/DMF
12. DOSAGE FORM Lyophilized Powder for injection	13. POTENCY 5 mg/vial	
14. CHEMICAL NAME AND STRUCTURE. See Chemistry Review #1(191 amino acid polypeptide)		

15. COMMENTS

This efficacy supplement provides for expanding the approved indication to include children with Turner Syndrome, in addition to the currently approved indication for children and adults with growth deficiency. No change in chemistry, manufacturing and controls of both the drug substance and drug product is indicated except that the environmental assessment was updated to accommodate an expected increase in the use of Humatrope by the children with Turner Syndrome(Vol. 46.2). The EA section has been reviewed and found satisfactory (see attached EA review dated 1/14/97 and Finding of No Significant Impact concurred by Dr. Sager, the CDER EA review Team Leader, on 2/1/97). The package insert has been revised to include the children with Turner Syndrome and other related information.

16. CONCLUSION AND RECOMMENDATION

Adequate information has been provided. From chemistry standpoint, the supplement can be approved.

17. NAME	REVIEWER SIGNATURE	DATE COMPLETED
Duu-Gong Wu, Ph.D.	Team Leader II, DNDC II	2/5/97

DISTRIBUTION: ORIGINAL JACKET CSO REVIEWER DIVISION FILE

R/D INITIATED BY: FILE NAME:19640.S18

FEB 2 1997

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

HUMATROPE

(Somatropin)

LYOPHILIZED POWDER FOR INJECTION

NDA 19-640/S-018

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION OF METABOLISM and ENDOCRINE DRUG PRODUCTS (HFD-510)

FINDING OF NO SIGNIFICANT IMPACT
NDA 19-640/S-018
HUMATROPE[somatropin(rDNA origin) for injection]

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. FDA is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process.

The Food and Drug Administration, Center for Drug Evaluation and Research has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

In support of their efficacy supplement to the previously approved New Drug Application for **HUMATROPE[somatropin(rDNA origin) for injection]**, Eli Lilly and Company prepared an environmental assessment update in accordance with 21 CFR 25.31a(attached) which evaluates the potential environmental impacts of the manufacture, use and disposal of the product.

Somatropin (rDNA) for injection is a drug manufactured by recombinant DNA technology which is administered as an injection after reconstitution with diluent in the treatment of children with Turner Syndrome. The drug substance is manufactured by Eli Lilly and Company, Indianapolis, Indiana. The drug product is manufactured and packaged at the same facility. The finished drug product could be used in hospitals, clinics and by patients in their homes.

Somatropin drug substance may enter the environment as emissions from manufacturing sites or from disposal of pharmaceutical wastes. However it is not expected to enter the environment from excretion by patients because it is a protein, which will be completely metabolized. The majority of the somatropin released into either a sewage treatment facility or a septic tank is also expected to be degraded by microorganism.

Disposal of the drug may result from out of specification lots, discarding of unused or expired product, and user disposal of empty or partly used product and packaging. Waste drug substance and drug product will be disposed of at a licensed incineration facility. At U.S. hospitals and clinics, empty or partially empty packages will be disposed according to hospital/clinic procedures. From home use, empty or partially empty containers will typically be disposed of by a community's solid waste management system which may include landfills, incineration and recycling, while minimal quantities of unused drug may be disposed of in the sewer system.

The Center for Drug Evaluation and Research has concluded that the product can be manufactured, used and disposed of without any expected adverse environmental effects. Precautions taken at the sites of manufacture of the bulk product and its final formulation are expected to minimize occupational exposures and environmental release. Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

1/14/97
DATE

PREPARED
Duu-Gong Wu, Ph.D.
Team Leader II
Division of New Drug Chemistry II
Office of New Drug Chemistry, OPS,
at Division of Metabolism and Endocrine
Drug Products
Center for Druq Evaluation and Research

2/1/97
DATE

CONCURRED
Nancy B. Sager
Team Leader, Environmental Assessment Team
Center for Druq Evaluation and Research

Attachment: Environmental Assessment

cc :
NDA 19-640/S-018(HFD-510)
HFD-510/DG Wu/M. Johnston
HFD-~~004~~/FONSI File NDA #19-640
HFD-~~004~~/Docket File
HFD-~~019~~/FOI COPY

Johnston

JAN 14 1997

SENSITIVE

REVIEW

OF

ENVIRONMENTAL ASSESSMENT

FOR

NDA 19-640/S018

Humatrope

[Somatropin(rDNA Origin)for injection]

DIVISION OF METABOLISM AND ENDOCRINE DRUG PRODUCTS
HFD-510

CENTER FOR DRUG EVALUATION AND RESEARCH

DATE COMPLETED: January 14, 1997

ENVIRONMENTAL ASSESSMENT

An updated EA section is submitted in the efficacy supplement S-018 that provides for extending the current indications (children and adults with growth deficiency) to include children with Turner Syndrome. Since expansion of the patient population will increase the use of Humatrope, an Environmental Assessment is required. The applicant includes an EA update submitted previously in the efficacy supplement S-013 dated 4/16/96 for the main body of information(see EA Review completed on 6/7/96 for the supplement S-013) and outlined the changes associated with this supplement in pages 2-4. It was pointed out that very small quantities of Humatrope used in the United States, therefore, the EA update will also follow an abbreviated format.

1. **Date**

   REVIEW: #1
   EA dated: July, 1996
   CSO: Michael Johnston

2. **Name of Applicant/Petitioner:**

   Eli Lilly and Company
   Adequate.

3. **Address:**

   Lilly Corporate Center
   Indianapolis, Indiana 46285
   Adequate.

4. **Description of the proposed action:**

   a. **Requested Approval:**
   Lilly has filed an efficacy supplement(s-018) to their approved NDA 19-640 to expand the indication to use Humatrope in children with **Turner syndrome.**

   Adequate.

   b. **Need for Action:**
   Humatrope is a recombinant human growth hormone produced by recombinant DNA technology using an recombinant *E. coli strain* and was originally approved for treatment of children with growth deficiency. Approval of this supplement will extend the use of Humatrope to children with Turner Syndrome, but would continue to be used in a very small patient population.

   Adequate.

   c. **Production Locations:**

Both the drug substance and drug product are continued to be produced at the same location described in the original NDA. The facility is located at:

Eli Lilly and Company
Lilly Technology Center
1200-1555 Kentucky Avenue
Indianapolis, Indiana 46285.

Adequate.

d. **Expected Locations of Use (Drug Product)**

Drug product will be used throughout the United States in Hospital and health-care facilities. Even with the addition of patients with turner syndrome, **less than a total of of growth hormone per year would be used in the United States five year after approval.**

Adequate.

e. **Disposal Locations:**

Rejected, expired, returned or waste drug product and drug substance will be disposed of by incineration at Clinton Laboratories(Eli Lilly and Company, State Road 63, Clinton IN 47842) according to a Resource Conservation and Recovery Act permit issued by the U.S. EPA under facility identification number IND 072040348 and in another facility at **Indianapolis Resource Recovery Facility(Ogden Martin Systems of Indianapolis, 2320 S. Harding St., Indianapolis, IN 46221).** This facility is operated in compliance with a solid waste permit (FPP No. 4913) issued by the Indiana Department of Environmental Management (IDEM), air permit certificates of operation (Nos. 0123-01, 0123-02, and 0123-3) and an air permit (no. [49]1602) issued by IDEM, and a waste water discharge permit (permit 495301) issued by the City of Indianapolis.

Adequate.

5. **Identification of chemical substances that are the Subject of the proposed action:**

(a) Drug Substance:

INN: Somatropin
Chemical Name (USAN): Somatropin
CAS #: 12629-01-5
Molecular Weight: 22,125 daltons

Physical Description: White to off-white crystals

(b) Drug Product

Humatrope is available and supplied in 5-mg vials, along with 5-mL vials of diluent. Material safety sheet for somatropin is provide in pages 33-39.

A list of materials in the formulation that are in addition to the active ingredient is provided.

Adequate.

6. Introduction of Substances into the environment:

a. **Substances Expected to be Emitted:**

(1). Production host cell
The organism used to produce somatropin is *Escherichia coli* K12, strain RV308 (ATCC31608) containing a non-mobilizable plasmid (pCZR340) which is a derivative of pBR322 and codes for the somatropin molecule as well as tetracycline resistance. The RV308 strain is now in common use in many laboratories around the world. The characteristics of this strain is described in details in pages 6-8. A description of the plasmid (pCZR340), its sequence, and characteristics that code for somatropin has been included in confidential attachments in the previously reviewed EA update dated 4/16/96**(not attached). The production organism will be inactivated prior to discharge into the environment(see below).**

(2). Other substances expected to be emitted also include rejected or returned materials, packageing and labeling components, filters, and typical plant waste.

Adequate.

b. **Controls Excised(Air, Liquid Effluent, Solid)**

A broth inactivation process is used to kill the E. *coli* K12 (RV308/pCZR340) cells after fermentation is complete. The process depends on holding the broth at the appropriate temperature for a long enough period of time to inactivate the cells. Careful determinations of death rates (D-values) in the laboratory allow the temperature and time period to be calculated.

As described in pages 12-13, the contents of the fermenter are inactivated in *situ* by the rapid injection of steam to a temperature of at least 61°C. The temperature is held for 7 minutes during which the temperature of the superstructure (ancillary piping) is raised to at least 107

°C for five seconds. At the end of this period of time the broth is rapidly pumped through an efficient heat exchanger to cool the broth to less than 30 °C before it is pumped into a waiting transport for delivery to the broth processing facility. Firm indicated that this process has been validated. The conditions used are calculated to yield less than a 10^{-6} probability that a single cell in the fermenter would survive processing through the in activator.

Even though somatropin can be manufactured under the GLSP category, Eli Lilly has chosen to maintain a level of containment that is generally consistent with the next higher containment category. This choice was made to help ensure containment of the production organism due to its proprietary value, not due to any perception of increased risk. This level of containment also helps to ensure the purity of the production broth. Finally, experience with large scale processes and equipment are all associated with a tradition of using this higher level of containment established before the GLSP category was available.

Floor drains are closed and sealed to prevent any organisms from being released. Disinfectant and absorbent materials are used to inactivate and remove any small spill of liquid containing the host cell. Absorbent materials are autoclaved and incinerated. Any contaminated uniform are autoclaved. The Good Large-Scale Production (GLSP) category has been adopted by the National Institutes of Health in the United States (Federal Register, 1994). This category provides principles of occupational safety and hygiene for large-scale applications with recombinant organisms of intrinsically low risk and that warrant only minimal containment.

The design, installation, and operation of equipment and presence of containment procedures, preventative maintenance program and monitoring program are described in pages 8-11. In addition, biological as well as thermal validation of the inactivation process has been carried out to insure that the procedure does, in fact, inactivate this specific strain of *E. coli*. Physical containment which minimizes release of the recombinant cells during the fermentation will be accomplished by using a combination of specially designed vessels, detailed operations protocols, and well-trained operators. Firm indicated that the physical and operational containment steps meet or exceed the guideline set out by NIH. The strain has been considered as an GLSP microorganism.

The controls and disposal of waste water, solid wastes, and the control of air emission have been discussed in details in pages 21-22. The waste water discharged from the

manufacturing site will be received by Indianapolis public waste water treatment facility, treated and discharged into the White river. Solid wastes and rejected or returned materials will be disposed of by incineration at Eli Lilly's Clinton Laboratories located at Clinton, IN. All airs at the manufacturing facilities will pass through filters and dust collecter.

Adequate

c. **Compliance with Federal, State and local Requirement**

Lilly indicated that the facilities used to produce, formulate and package Humatrope are in compliance with all appropriate environmental regulation, and permits concerning emission control and waste treatment. Lilly also pointed out that treatment, storage, and disposal of solid liquid, and gaseous wastes from the Indiana plant site are defined by the regulations administered, in certain instances, by the Indiana Department of Environmental Management (IDEM), and in other instances by the Indianapolis Department of Public Works (DPW). A permit associated with liquid waste discharge (DPW Permit Number 283001, expires 12/31/00) was issued by the Indianapolis Department of Public Works. Permits associated with control of emissions to the atmosphere, if required, are administered by the City of Indianapolis.

Adequate.

d. **Effect of Approval on Compliance with Current Emissions Requirements:**

Lilly indicated that the subsequent increase in production at the facility resulting from the inclusion of patients with Turner Syndrome is not expected to affect compliance with current emission requirements or compliance with environmental laws. The amount of materials used in the production process is small and the containment is high, the materials emitted are not expected to have a significant impact on the environment.

Adequate.

e. **Estimated Expected Emitted Concentration/Quantities:**

The Maximum Expected Environmental Concentration (MEEC) is calculated in page 23 indicates that 5 years after approval for use in patients with turner syndrome, the annual use of somatropin will be less than in the United States MEEC=< 0.3 nanogram/L. The level is well below that which requires review of the fate and effects of the materials in the aqueous environment.

Adequate.

7-11. Sections not required. The firm indicated that there is a small amount of somatropin used per year and the patient population is small.

Adequate.

12. **List of preparers, their qualification, and consultants.**

The list of preparers and their positions and qualifications are provided in page 27.

Adequate.

13, **Certification:**

EA is properly certified by Dr. Gregory S. Probst, Executive Director, Toxicology and Drug Disposition(page 28).

Adequate.

14. **References:**

A list of references used in the preparation of the EA is provided in pages 29-32.

Adequate.

Summary: **Information provided in this EA update is sufficient for writing a FONSI.**

Duu-Gong Wu 1/14/97

Duu-Gong Wu, Ph.D.
Team Leader II
Division of New Drug Chemistry II
Office of New Drug Chemistry, OPS,
at Division of Metabolism and
Endocrine Drug Product(HFD-510)

cc:
Org. NDA 19-640/S-018
HFD-510/Division File(NDA 19-640)
HFD-510/D.G. Wu/M. Johnston
R/D Init by:

Filename: **19640.EA2**

NDA 19640/SE1-018
Humatrope: Turners Syndrome
Eli Lilly and Company
Microbiology Review

A Microbiology Review was not Required for this NDA

Food and Drug Administration
Rockville MD 20857

Date AUG - 7 1996

NDA No. 19-640

ELI LILLY AND COMPANY
Lilly Corporate Center
Indianapolis, IN 46285

Attention: Timothy R. Franson, M.D., Executive Director

Dear Sir/Madam:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: HUMATROPE (Somatropin)

NDA Number: 19-640

Supplement Number: S-018

Date of Supplement: JULY 29, 1996

Date of Receipt: JULY 31, 1996

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on SEP 29 1996 in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products
Attention: Document Control Room
5600 Fishers Lane, HFD-510
Rockville, MD 20857

Sincerely yours,

Chief, Project Management Staff
Division of Metabolic and Endocrine Drug Products
Office Drug Evaluation II
Center for Drug Evaluation and Research

Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
(317) 276-2000

March 10, 1997

Dear Dr. Sobel,

Reference is made to a recent phone conversation (March 7, 1997) between Dr. Jennifer Stotka and yourself. This correspondence confirms Lilly's commitment to reexamine the portion of the label that describes the adverse event incidence (≥ 5%) in growth hormone deficient adult clinical trial patients and, if appropriate, to amend this section to more accurately reflect the data. We commit to review the label and provide you our comments by March 21, 1996. We believe that final resolution of the adult replacement labeling issue should not unduly delay the approval for Turner syndrome indication.

Please call Dr. Kim Birch at (317) 277-1443 or me at (317) 276-1249 if you require any additional information or if there are any questions. Thank you for your continued cooperation and assistance.

Sincerely,

ELI LILLY AND COMPANY

Jennifer L. Stotka, M.D.
Director
North American Regulatory Affairs

CC: Saul Malozowski, M.D. (FDA)
Mr. Michael Johnston (FDA)
Timothy Franson, M.D. (Lilly)
John Chipman, M.D. (Lilly)

Lilly

ORIGINAL

Lilly Research Laboratories
A Division of Eli Lilly and Company
Lilly Corporate Center
Indianapolis, Indiana 46285
(317) 276-2000

November 25, 1996

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine
Drug Products, HFD-510
Attn: Document Control Room, 14B-03
5600 Fishers Lane
Rockville, MD 20857-1706

4-Month Safety Update

Re: NDA 19-640 (S018)--Humatrope® [Somatropin, (rDNA origin) for injection)

Reference is made to the submission (July 29, 1996) of a supplemental New Drug Application (sNDA) for Humatrope® [somatropin, (rDNA origin) for injection] to support the expansion of the approved indication to include pediatric patients with Turner syndrome.

Per the requirements of 21 CFR §314.50(d)(5)(vi)(b) we are herewith submitting the requisite 4-month safety update. This safety update provides additional safety information from the data cut-off date for the sNDA (February 8, 1996) through September 30, 1996. The information contained in this update is generated primarily from the two ongoing pivotal safety and efficacy trials that were summarized in the sNDA and from Lilly post-marketing surveillance information ("DEN" database).

Please call Dr. Kim Birch at (317) 277-1443 or me at (317) 276-1249 if you require any additional information or if there are any questions. Thank you for your continued cooperation and assistance.

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO
CSO INITIALS DATE

Sincerely,

ELI LILLY AND COMPANY

Jennifer L. Stotka, MD
Director
North American Regulatory Affairs

enclosure

CENTER FOR DRUG EVALUATION
RECD
NOV 26 1996
HFD-510

Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
(317) 276-2000

October 25, 1996

Solomon Sobel, M.D., Director
Division of Metabolism and
Endocrine Drug Products, HFD-510
Center for Drug Evaluation and Research
Attention: Document Control Room, 14B-03
FOOD AND DRUG ADMINISTRATION
5600 Fishers Lane
Rockville, Maryland 20857

Subject: **NDA 19-640 (S018)**
Humatrope® [somatropin (rDNA origin) for injection]
General Correspondence: Advisory Committee Meeting Preparations

Dear Dr. Sobel:

Reference is made to our pending Supplemental New Drug Application, NDA 19-640 (S018), for Humatrope® [somatropin (rDNA origin) for injection] for the treatment of short stature associated with Turner syndrome. In preparation for the December 10, 1996 Advisory Committee Meeting, Dr. Alexander Fleming of your Division suggested that we draft a list of issues to be discussed in the afternoon interactive session of the Advisory Committee meeting. Additionally, Dr. Fleming suggested that we propose a list of questions to the Advisory Committee members. Eli Lilly and Company and Genentech, Inc. have jointly prepared the following list of issues and questions for your consideration:

<u>Issues to be discussed in the Interactive Session</u>

1. Factors that affect adult height gain
   - age of initiation of growth hormone (GH) therapy
   - GH dose
   - concomitant estrogen therapy

2. The use of historical controls to assess efficacy

3. Range of efficacy - Results of long-term trials from Genentech, Inc., Eli Lilly and Company and the world literature

4. Are there any new safety issues concerning GH therapy for this indication?

Questions to the Advisory Committee

1. Have the sponsors demonstrated efficacy with respect to adult height?

2. Have the sponsors provided adequate information to demonstrate safety in this population?

3. Do the sponsors' data support approval of GH for this indication?

4. Are there any issues that need to be addressed in postmarketing surveillance?

Both sponsors will plan to follow up with your Division within a week or so regarding our proposed list of issues. Thank you in advance for your attention to this submission. If you have any questions in regard to this submission, please contact Dr. Kim Birch at (317) 277-1443 or myself at (317) 276-1249.

Sincerely,

Jennifer L. Stotka, MD
Director
North American Regulatory Affairs

Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
(317) 276-2000

September 24, 1996

Dr. G. Turner
Division of Scientific Investigations-HFD344
Center for Drug Evaluation and Research
7520 Standish Place
Rockville, MD 20855

Re: NDA 19-640 (S018)--Humatrope® [somatropin, (rDNA origin) for injection] for Turner syndrome

Reference is made to a September 13, 1996 phone conversation between Dr. G. Turner (FDA) and Dr. Tim Franson (Eli Lilly and Company) in which Dr. Turner requested one copy of the following information from NDA 19-640 (S018):

1. Full case report forms and all adverse drug reactions (ADRs) for all subjects enrolled by Dr. Silverstein (Investigator #?1) and Dr. Rawlinson (Investigator #40) in clinical study B9R-MC-GDCI
2. Line listings for all subjects enrolled by Dr. Ehrlich (Investigator #106) in clinical study B9R-MC-GDCT

We are herewith providing the requested information. Please note that treatment emergent signs and symptoms (TESS) defined in the FDA guidance document, Guideline for The Format and Content of the Clinical and Statistical Sections of New Drug Applications as "those not seen at baseline or that worsened during treatment" were provided in the original NDA supplement (19-640, S018). Provided here are listings of all adverse drug reactions for each patient enrolled by Dr. Silverstein and Dr. Rawlinson.

Please call Dr. Kim Birch at (317) 277-1443 or me at (317) 277-1324 if you require any additional information or if there are any questions. Thank you for your continued cooperation and assistance.

Sincerely,

ELI LILLY AND COMPANY

for: Timothy R. Franson, MD
Executive Director
North American Regulatory Affairs

Enclosure

CC: Mr. Michael Johnston, RPh. (FDA)—Cover letter only

Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
(317) 276-2000

September 3, 1996

Dr. G. Turner
Division of Scientific Investigations-HFD344
Center for Drug Evaluation and Research
7520 Standish Place
Rockville, MD 20855

Re: NDA 19-640 (S018)--Humatrope® [somatropin, (rDNA origin) for injection] for Turner syndrome

Reference is made to an August 29, 1996 phone conversation between Dr. G. Turner (FDA) and Dr. Kim Birch (Eli Lilly and Company) in which Dr. Turner requested the following information from NDA 19-640 (S018):

1. Volume 1.1
2. Protocols for the two pivotal trials (B9R-CA-GDCT and B9R-MC-GDCI)
3. List of investigators from these two clinical trials
4. Number of patients enrolled by investigator for each of these two trials

We are herewith providing the requested information.

Please call Dr. Kim Birch at (317) 277-1443 or me at (317) 277-1324 if you require any additional information or if there are any questions. Thank you for your continued cooperation and assistance.

Sincerely,

ELI LILLY AND COMPANY

Timothy R. Franson, MD
Executive Director
North American Regulatory Affairs

Enclosure

CC: Mr. Michael Johnston, RPh. (FDA)—Cover letter only

Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
(317) 276-2000

August 9, 1996

Solomon Sobel, M.D., Director
Division of Metabolic and Endocrine
Drug Products, HFD-510
Center for Drug Evaluation and Research
Attn: Document Control Room 14B-03
5600 Fishers Lane
Rockville, MD 20857-1706

Re: Supplemental NDA 19-640--Humatrope® [somatropin, (rDNA origin) for injection] for Turner syndrome
Advisory Committee Meeting Scheduling

Reference is made to the July 29, 1996 submission by Eli Lilly and Company (Lilly) of a supplemental New Drug Application (S-018) for Humatrope® [Somatropin, (rDNA origin) for injection] to support the expansion of the approved indication to include children with Turner syndrome.

We have been informed that November 7 and 8, 1996 have been designated as meeting days for the Advisory Committee. This letter is to inform the Division that these dates are acceptable to Lilly. In addition, Lilly is committed to provide any assistance to the reviewers that would help facilitate their reviews of Lilly's supplemental NDA submission.

We look forward to your reply regarding the definitive date for the Advisory Committee meeting.

Please call Dr. Kim Birch at (317) 277-1443 or me at (317) 277-1324 if you require any additional information or if there are any questions. Thank you for your continued cooperation and assistance.

Sincerely,

ELI LILLY AND COMPANY

Timothy R. Franson, MD
Executive Director
North American Regulatory Affairs

CC: Mr. Mike Johnston (FDA)

Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
(317) 276-2000

August 1, 1996

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine
Drug Products, HFD-510
Attn.: Document Control Room 14B-03
5600 Fishers Lane
Rockville, MD 20857-1706

Re: NDA 19-640—Humatrope® (somatropin, biosynthetic human growth hormone)

Eli Lilly and Company, Indianapolis, Indiana, hereby grants authority to the Food and Drug Administration to refer to the files on its supplemental NDA 19-640 (submitted July 29, 1996) for Humatrope® for Turner syndrome on behalf of Genentech, Inc., South San Francisco, California.

Genentech has submitted an NDA for Nutropin® for Turner syndrome (NDA 20-656). With respect to their submission, this letter provided limited authorization for Genentech to cross-reference and for the Food and Drug Administration to review only that information in Lilly's supplemental NDA 19-640 for Humatrope for Turner syndrome indication necessary for FDA to review the clinical data that support the safety and efficacy of human growth hormone for the treatment of patients with Turner syndrome.

This letter does not authorize nor is it intended to authorize the FDA to release to Genentech or anyone else the Lilly material cross-referenced by Genentech. It also does not authorize nor is it intended to authorize Genentech or anyone else to obtain, view or otherwise receive the material cross-referenced by Genentech.

It is also understood that the material contained in the supplemental NDA 19-640 shall be treated as confidential in accordance with the Federal Food, Drug and Cosmetic Act and other applicable laws and regulations.

Three copies of this letter are submitted for your use in cross-referencing these files. Four additional copies of this letter have been forwarded to Genentech.

Please call Dr. Kim Birch at (317) 277-1443 or me at (317) 277-1324 if you require any additional information or if there are any questions. Thank you for your continued cooperation and assistance.

Sincerely,

ELI LILLY AND COMPANY

Timothy R. Franson, MD
Executive Director
North American Regulatory Affairs

CC: Ms. Enid Galliers, FDA
Genentech, Inc.

Lilly

Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
(317) 276-2000

August 1, 1996

Via Facsimile Transmission
and Federal Express

Marlene E. Haffner, M.D.
Director
Office of Orphan Products Development
Food and Drug Administration
5600 Fisher Lane, Room 15-61
Rockville, MD 20857

Re: Supplemental NDA 19-640 Humatrope® (somatropin [rDNA origin] for injection) Treatment of Growth Failure Associated with Turner Syndrome

Dear Dr. Haffner:

The purpose of this letter is to provide written notice pursuant to Section 527(b)(2) of the Federal Food, Drug and Cosmetic Act that if Humatrope® [somatropin (rDNA origin) for injection] is the first recombinant human growth hormone approved for the treatment of Turner syndrome, Eli Lilly and Company will consent to the approval of Genentech, Inc.'s ("Genentech") Nutropin® [somatropin (rDNA origin) for injection] and Nutropin AQ™ [somatropin (rDNA origin) for injection] for the same rare disease or condition.

Background

Eli Lilly and Company ("Lilly") and Genentech have, independently, submitted to FDA's Office of Orphan Products Development requests for orphan drug designation for the treatment of Turner syndrome with human growth hormone. FDA granted such designation for Humatrope® on May 8, 1989, and for Nutropin® on March 23, 1989. Lilly submitted a Supplemental NDA for Humatrope® for the treatment of Turner syndrome (Supplemental NDA 19-640, submitted July 29, 1996). Genentech submitted an NDA for Nutropin® (NDA 20-656, on September 29, 1995), and for Nutropin AQ™.

Written Consent

Section 526 of the Federal Food, Drug and Cosmetic Act provides that the FDA may designate a drug for the treatment of a rare disease or condition as an orphan drug. Section 527 provides that if such a designated orphan drug is the first to be

approved for marketing, the FDA may not approve the application of another sponsor for the same drug for that rare disease or condition for seven years. Subsection (b) of Section 527 provides two exceptions to the general rule of seven years of market exclusivity. The first exception is not relevant to this letter. The second exception, set forth in Section 527(b)(2), provides that the FDA may approve the application of another sponsor for the same drug for the same rare disease or condition if "such holder (of the approved application) provides the Secretary in writing the consent of such holder for the approval of other applications, issuance of other certifications, or the issuance of other licenses before the expiration of such seven-year period."

Lilly's Written Consent

Pursuant to Section 527(b)(2), Lilly is providing this written consent that if Lilly's Humatrope® for the treatment of Turner syndrome is approved first, Genentech's Nutropin® and Nutropin AQ™ may be approved for the same indication. This written consent applies only to Nutropin® and Nutropin AQ™ for use in the treatment of Turner syndrome, and not to any other NDA, drug product, or indication, and is conditioned on Genentech's provision of consent under section 527(b)(2) to the approval of Lilly's Supplemental NDA 19-640 covering Humatrope® for use in the treatment of Turner syndrome. Lilly intends to confirm this consent at the time Humatrope® is approved for the treatment of Turner syndrome.

Sincerely,

ELI LILLY AND COMPANY

Timothy R. Franson, M.D.
Executive Director, North American Regulatory Affairs

cc: Genentech, Inc.
Division of Metabolic and Endocrine Drug Products

Genentech, Inc.

460 Point San Bruno Boulevard
South San Francisco, CA 94080-4990
(415) 225-1000
FAX: (415) 225-6000

August 1, 1996

Marlene E. Haffner, M.D.
Director
Office of Orphan Products Development
Food and Drug Administration
5600 Fisher Lane, HF-35
Rockville, MD 20857

Subject: NDA 20-656 Nutropin® [somatropin (rDNA origin) for injection]
Treatment of Growth Failure Associated with Turner Syndrome

Dear Dr. Haffner:

The purpose of this letter is to provide written notice pursuant to Section 527 (b)(2) of the Federal Food, Drug and Cosmetic Act that if Nutropin® [somatropin (rDNA origin) for injection] is the first recombinant human growth hormone approved for the treatment of Turner syndrome, Genentech will consent to the approval of Eli Lilly and Company's ("Lilly") Humatrope® [somatropin (rDNA origin) for injection] for the same rare disease or condition.

Background

Genentech, Inc. ("Genentech") and Lilly have, independently, submitted to FDA's Office of Orphan Products Development requests for orphan drug designation for the treatment of Turner syndrome with human growth hormone. FDA granted such designation for Nutropin® on March 23, 1989, and for Humatrope® on May 8, 1989. Genentech submitted an NDA for Nutropin® (referenced above) for the treatment of Turner syndrome on September 29, 1995. Lilly submitted a supplemental NDA for Humatrope® for the treatment of Turner syndrome (NDA 19-640, supplement submitted July 29, 1996).

Written Consent

Section 526 of the Federal Food, Drug and Cosmetic Act provides that the FDA may designate a drug for the treatment of a rare disease or condition as an orphan drug. Section 527 provides that if such a designated orphan drug is the first to be approved for marketing, the FDA may not approve the application of another sponsor for the same drug for that rare disease or condition for seven years. Subsection (b) of Section 527 provides two exceptions to the general rule of seven years of market exclusivity. The first exception is not relevant to this letter. The second exception, set forth in Section 527 (b)(2), provides that the FDA may approve the application of another sponsor for the same drug for the same rare disease or condition if "such holder (of the approved application) provides the Secretary in writing the consent of such holder for the approval of other applications, issuance of other certifications, or the issuance of other licenses before the expiration of such seven-year period."

Genentech's Written Consent

Pursuant to Section 527(b)(2), Genentech is providing this written consent that if Genentech's Nutropin® for the treatment of Turner syndrome is approved first, Lilly's Humatrope® may be approved for the same indication. This written consent applies only to Humatrope® for use in the treatment of Turner syndrome, and not to any other NDA, drug product, or indication, and is conditioned on Lilly's provision of consent under section 527(b)(2) to the approval of Genentech's NDA 20-656 covering Nutropin® for use in the treatment of Turner syndrome. Genentech intends to confirm this consent at the time Nutropin® is approved for the treatment of Turner syndrome.

Sincerely,

Janice Castillo for

M. David MacFarlane, Ph. D.
Vice President
Regulatory Affairs

cc: Eli Lilly and Company
Division of Metabolism and Endocrine Drug Products

2/20656-011 sub jb

NDA SUPPLEMENT ORIGINAL

Lilly

NDA NO. 19-640 REF. NO. 0015

NDA SUPPL FOR SE1

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
(317) 276-2000

JulY 29, 1996

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine
Drug Products, HFD-510
Attn.: Document Control Room 14B-03
5600 Fishers Lane
Rockville, MD 20857-1706

SUPPLEMENT

Re: NDA 19-640--Humatrope® (Somatropin, biosynthetic human growth hormone)

This letter accompanies the submission by Eli Lilly and Company (Lilly) of a supplemental New Drug Application (sNDA) for Humatrope® (Somatropin, biosynthetic human growth hormone) to support the expansion of the approved indication to include children with Turner syndrome. Currently, Humatrope® is approved for use in children with growth hormone deficiency.

This sNDA contains clinical data to support the Turner syndrome indication. An interim analysis from a randomized, concurrent controlled study and a preliminary report from an open label, dose response study, represent the two pivotal studies that comprise the bulk of the clinical efficacy data in this submission. Please note that both of these studies are currently ongoing. A report on final height that was submitted by Lilly to the Committee on Proprietary Medicinal Products in Europe (December, 1994) and the results from a study conducted in Germany by Lilly are provided as supplemental data. Safety information from the two pivotal studies represents over 1500 patient years of experience. Additional summaries of spontaneous adverse event reports from commercial use and European studies are included in the submission.

Eli Lilly and Company has met on several occasions with the FDA personnel to discuss the registration plans for Humatrope® for use in patients with Turner syndrome. These meetings and communications have been summarized in the Regulatory Background Information section of this application. The understandings and agreements reached between Lilly and the FDA have been incorporated into this application.

This application is formatted and organized according to 21 CFR §314.50 and follows the "Guideline for the Format and Content of the Clinical and Statistical Sections of New Drug Applications" and the "Guideline on Formatting, Assembling, and Submitting New Drug and Antibiotic Applications".

The initial User Fee due for this sNDA has been submitted with this submission (Form 3397 is provided). A Pentium Certification and Debarrment Certification have been provided.

Please call Dr. Kim Birch at (317) 277-1443 or me at (317) 277-1324 if you require any additional information or if there are any questions. Thank you for your continued cooperation and assistance.

Sincerely,

ELI LILLY AND COMPANY

for Timothy R. Franson, MD
Executive Director
North American Regulatory Affairs

REVIEWS COMPLETED	
CSO ACTION: ☐ LETTER ☐ N.A.I. ☐ MEMO	
CSO INITIALS	DATE

Enclosure

CC: Ms. Enid Galliers (cover letter only) HFD-510

Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
(317) 276-2000

July 19, 1996

Solomon Sobel, M.D., Director
Division of Metabolism and
Endocrine Drug Products (HFD-510)
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Attention: Document Control Room, 14B-03
5600 Fishers Lane
Rockville, Maryland 20857

GENERAL CORRESPONDENCE

NDA 19-640 - Humatrope® (Somatropin, biosynthetic human growth hormone)

Dear Dr. Sobel:

Reference is made to Genentech's pending New Drug Application, NDA 20-656, for Nutropin [somatropin (rDNA origin) for injection], submitted on September 29, 1995, for treatment of girls with growth failure associated with Turner syndrome. Eli Lilly and Company ("Lilly") will provide an NDA supplement for its growth hormone (GH) product, Humatrope®, for the same indication by the end of this month.

During the last decade, Genentech and Lilly have conducted clinical trials in girls with Turner syndrome to determine whether the use of growth hormone (GH) therapy to increase adult height in this patient population is safe and efficacious. Both Genentech's and Lilly's submissions provide data that such therapy has a favorable risk/benefit ratio and should be approved. Genentech and Lilly have signed an agreement to work collaboratively to seek approval for the use of GH to treat girls with growth failure associated with Turner syndrome. Because various study designs bring forward different data for both efficacy and safety, both Genentech and Lilly have proposed that both submissions be cross-referenced in support of an approval for this indication.

Both companies believe that, taken together, and, given the qualitative consistency of outcomes on adult height and the extensive safety profile available, the data from both submissions will be substantial and will satisfy the criteria established for GH approval for this indication. The following summarizes the available clinical trial data from both companies.

The Genentech-sponsored clinical trials achieved the primary endpoint of the studies: improvement in adult height. The analyses of adult height were made using matched historical control patients (untreated American Turner girls followed primarily by the same investigators). Study 85-044 demonstrated that in patients who started GH before age 11, the effect of delaying estrogen replacement therapy to age 15 compared with starting at age 12 (by randomization) was significant with respect to adult height. The estimated gain in adult height by analysis of covariance vs the matched historical controls was 8.3 cm in the delayed estrogen group (n=29), and 5.9 cm in the early estrogen group (n=26). In patients who started GH therapy after age 11, and estrogen therapy after 12 months of GH therapy, there was an estimated gain of 5.0 cm (n=51). In study 85-023, patients treated similarly to the early GH/delayed estrogen group in study 85-044 had a similar estimated gain of 7.4 cm in adult height (n=17). Patients treated with combination GH + oxandrolone (n=46) had an estimated gain of 10.1 cm. Similar results were obtained using pretreatment projected adult height for each patient. The attached table summarizes efficacy data from both the Genentech-sponsored clinical trials and the Lilly-sponsored clinical trials (described below).

The Lilly-sponsored clinical trials demonstrated significant increase of final height in GH-treated patients as compared to randomized, untreated concurrent controls [Canadian Study (GDCT)]. In this study of 140 patients, 46 have completed the protocol. Final and near final height in the GH-treated patients (0.05 mg/kg/day, 6 days/week) was 146.0 $\pm$ 6.2 (mean $\pm$ SD) (n=27) as compared to the untreated group who attained a near final height of 142.1 $\pm$ 4.8 (n=19). By ANCOVA analysis (including stratification for baseline height relative to age, geographic area, and with adjustment for mid-parental height) the difference was 5.4 cm ($p = 0.001$). The average duration of drug exposure was 4.65 years for protocol completers. All patients were treated with ethinyl estradiol after 13 years of age. In a second, blinded, randomized, dose-response study [U.S. Study (GDCT)] that included oral placebo or low-dose estrogen administered at an early age, 232 patients were enrolled, 31 completed the protocol, 63 remain active and 138 discontinued early, primarily for "patient choice". Estrogen exposure in this study began either after 8 or 13.5 years. In pooled groups, the final height for the high dose (0.36 mg/kg/week) group without regard to estrogen therapy was 148.5 $\pm$ 6.2 cm (n=20) and the final height for the low dose (0.27 mg/kg/week) group without regard to estrogen therapy was 149.2 $\pm$ 7.1 cm (n=11). There was no significance between group dose response difference. However, as compared to the Lyon et al. (1985) Turner reference standard, the height standard deviation score at last visit for the intent-to-treat population increased to 1.46 and 1.28 SD for high dose and low dose groups, respectively.

Safety information from Genentech studies included the two clinical trials, as well as the National Cooperative Growth Study (a phase IV study) and spontaneous adverse event reports for children on commercial GH. The three studies represent over 7000 patient-years of experience in Turner syndrome patients. Serious adverse events were rare, and included two cerebrovascular accidents and 7 deaths, most of which were associated with congenital cardiovascular anomalies. None of these serious events were considered to be drug-related. The incidence of glucose intolerance and hypothyroidism were not affected by GH therapy. Intracranial hypertension and slipped capital femoral epiphysis, known to be associated with GH therapy, were also seen in Turner patients. No cases of leukemia

or pancreatitis were reported. Although fasting and postprandial insulin levels increased with GH therapy, glucose and hemoglobin A1c values remained within normal limits. Growth attenuating antibodies were not reported in any patients, and no other new or unexpected laboratory changes were seen.

Safety information from the two North American Lilly studies represents over 1500 patient years of experience. Additional spontaneous reports from commercial use and European studies are included in the submission. World-wide, there were three deaths, all due to cardiovascular events. One of these deaths came from the untreated group. All were considered unrelated. Otitis media and ear disorder were the only statistically significant events reported as compared to non-treatment patients. Of interest, there were no significant differences between treatment and non-treatment groups (GDCT) for those events historicaly associated with hGH (e.g. headache, edema, skin nevi, bone disorder and hyperglycemia). While fasting and 2 hour post-prandial glucose and HBA_{1c} remained normal through the study, 2 hour post-prandial insulin values varied widely. Approximately 30% of patients (GDCI study) had markedly elevated 2 hour post-prandial insulin values. However, for most of these patients, this was a sporadic and seemingly spontaneous event that could also occur at baseline. One patient developed type I diabetes (IDDM) during the course of the study. This is within the expected prevalence for IDDM. No other new or unexpected laboratory changes were seen.

Taken together, the cumulative efficacy and safety data from the Genentech and Lilly studies provide evidence that GH therapy is safe and well-tolerated in this population and results in significant improvement in adult height. Extensive clinical experience has demonstrated no new or unexpected safety concerns for GH use in Turner syndrome. The various trial designs, when viewed together, provide the information necessary for physicians to determine optimal therapy with respect to improving adult height. Such optimal therapy can provide an adult height of approximately 150 cm.

Both Genentech and Lilly look forward to your suggestions and direction with regard to this indication. Please call Christie Zustak at (415) 225-2038 of Genentech and/or Dr. Kim Birch of Lilly at (317) 277-1443 if you have any questions regarding this submission.

Sincerely,

ELI LILLY AND COMPANY

Timothy R. Franson, M.D.
Executive Director
North American Regulatory Affairs

encl.
cc:Genentech

Summary of Efficacy Results

Study	Study Design	Duration of Randomized Control (mo)	Enrollment N	Mean Baseline Age (yr)	Estrogen Age (yr)	Weekly GH Dose (mg/kg)	Adult Height GH-treated (cm)	Adult Height Gain by ANCOVA (cm)	Control for Adult Height Analysis	p-value
Genentech, Inc.										
Study 85-044	R, OL HC	12	117	A: 9.6 (n=26) C: 9.4 (n=29) D: 12.7 (n=51)	A: 12.3 C: 15.0 D: 13.7 (means)	0.375 (3 or 7x/wk)	A: **147.0** (n=26) C: **150.4** (n=29) D: **148.5** (n=51)	A: 5.9 C: 8.3 D: 5.0	Matched Historical	<0.0001 <0.0001 <0.0001
Study 85-023	R, OL HC	12-21	71	F: 9.1 (n=17) G: 9.9 (n=46)	F: 15.2 G: 14.9 (means)	0.375 (3 or 7x/wk)	F: **150.4** (n=17) G: **151.5** (n=46)	F: 7.4 G: 10.1	Matched Historical	<0.0001 <0.0001
Eli Lilly & Co.										
Canadian Study GDCT	R, OL CC	To adult height	140	10.4 (all patients)	H, I: ^{3} 13	H: 0.300 (6x/wk) I: 0	H: **146.0** (n=27) I: **142.1** (n=19)	5.4	Concurrent Non-treated	0.001
U.S. Study GDCI	R, PC HC	18	232	9.7 (all patients)	J, K: ^{3} 8 or ^{3} 13.5	J: 0.270 (3-6x/wk) K: 0.360 (3-6x/wk)	J: **149.2** (n=11) K: **148.5** (n=20)			
Five European Studies	OL, HC		253	11.6-14.1 (all patients)	14.8 (mean)	L: 0.180 - 0.336 (7x/wk)	L: **150.7** (n=56)			

R = randomized; OL = open-label; HC = historical control; CC = concurrent control; PC = placebo-controlled.

Study Groups (GH = growth hormone; E = estrogen; #'s = age on initiation):

A: GH < 11, E 12. D: GH > 11, E > 12. C: GH < 11, E 15. F: GH < 12, E > 14 G: GH < 12, +oxandrolone, E > 14.

H: GH 0.300, E ^{3} 13. I: No GH, E^{3}13. J: GH 0.270, E ^{3} 8 or 13.5. K. GH 0.36, E ^{3} 8 or 13.5. L. GH 0.180-0.336.

Summary of Efficacy Results

Study	Study Design	Duration of Randomized Control (mo)	Enrollment N	Mean BaselineAge (yr)	Estrogen Age (yr)	Weekly GH Dose (mg/kg)	Adult Height GH-treated (cm)	Adult Height Gain by ANCOVA (cm)	Control for Adult Height Analysis	p-value
Genentech, Inc.										
Study 85-044	R, OL HC	12	117	A: 9.6 (n=26) C: 9.4 (n=29) D: 12.7 (n=51)	A: 12.3 C: 15.0 D: 13.7 (means)	0.375 (3 or 7x/wk)	A: **147.0** (n=26) C: **150.4** (n=29) D: **148.5** (n=51)	A: 5.9 C: 8.3 D: 5.0	Matched Historical	<0.0001 <0.0001 <0.0001
Study 85-023	R, OL HC	12-21	71	F: 9.1 (n=17) G: 9.9 (n=46)	F: 15.2 G: 14.9 (means)	0.375 (3 or 7x/wk)	F: **150.4** (n=17) G: **151.5** (n=46)	F: 7.4 G: 10.1	Matched Historical	<0.0001 <0.0001
Eli Lilly & Co.										
Canadian Study GDCT	R, OL CC	To adult height	140	10.4 (all patients)	H, I: ^{3}13	H: 0.300 (6x/wk) I: 0	H: **146.0** (n=27) I: **142.1** (n=19)	5.4	Concurrent Non-treated	0.001
U.S. Study GDCI	R, PC HC	18	232	9.7 (all patients)	J, K: ^{3}8 or ^{3}13.5	J: 0.270 (3-6x/wk) K: 0.360 (3-6x/wk)	J: **149.2** (n=11) K: **148.5** (n=20)			
Five European Studies	OL, HC		253	11.6-14.1 (all patients)	14.8 (mean)	L: 0.180 - 0.336 (7x/wk)	L: **150.7** (n=56)			

R = randomized; OL = open-label; HC = historical control; CC = concurrent control; PC = placebo-controlled.

Study Groups (GH = growth hormone; E = estrogen; #'s = age on initiation):

A: GH < 11, E 12. D: GH > 11, E > 12. C: GH < 11, E 15. F: GH < 12, E > 14 G: GH < 12, +oxandrolone, E > 14.

H: GH 0.300, E ^{3} 13. I: No GH, E^{3}13. J: GH 0.270, E ^{3} 8 or 13.5. K. GH 0.36, E ^{3} 8 or 13.5. L. GH 0.180-0.336.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

Date November 6, 1996

From Executive Secretary (HFD-21)
Endocrinologic and Metabolic Drugs Advisory Committee

Subject Notice of Scheduled Advisory Committee Meeting

To Committee Management Office (HFA-306)
Through: Director, Division of Metabolic and Endocrine Drug Products, HFD-510 _____
Director, Office of Drug Evaluation II, (HFD-102) _____

We have scheduled an advisory committee meeting as described below and request that a notice be published in the Federal Register as follows:

ENDOCRINOLOGIC AND METABOLIC DRUGS ADVISORY COMMITTEE

Date, time, and place: December 10, 1996, 8 a.m., and December 11, 1996, 8 a.m., Versailles Room I and II, Holiday Inn Bethesda, 8120 Wisconsin Avenue, Bethesda, MD.

Type of meeting and contact person: Open public hearing December 10, 1996, 8 a.m. to 8:30 a.m., unless public participation does not last that long; open committee discussion, 8:30 a.m. to 5 p.m.; open public hearing December 11, 1996, 8 a.m. to 8:30 a.m., unless public participation does not last that long; open committee discussion, 8:30 a.m. to 5 p.m.; Kathleen Reedy or LaNise Giles, Center for Drug Evaluation and Research, HFD-21, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-5455, or FDA Advisory Committee Information Hotline, 1-800-741-8138 (301-443-0572 in the Washington, DC area), Endocrinologic and Metabolic Drugs Advisory Committee, 12536. Please call the Hotline for information concerning any possible changes.

the risks of growth hormone therapy in girls with Turner's syndrome, do you recommend that this drug be approved for marketing? **YES - 6** **NO - 1**

4. If approval is recommended, what studies or other measures are recommended to refine the understanding of this therapy's benefits and risks.

Better understand pathogenesis, source, mechanism of syndrome
Growth hormone action, reaction, long term effect
Optimization of therapy; i.e. age to begin, duration
Criteria for ending treatment
Dose response data
Treatment of poor responders
DSMD and DGCT (current ongoing studies) outcome
Patient Registry

The meeting was adjourned at 5:00 PM.

Kathleen Reedy, Executive Secretary
Endocrinologic and Metabolic Drugs Advisory Committee

General function of the committee: The committee reviews and evaluates data on the safety and effectiveness of marketed and investigational human drugs for use in endocrine and metabolic disorders.

Agenda--Open public hearing. Interested persons may present data, information, or views, orally or in writing, on issues pending before the committee. Those desiring to make formal presentations should notify the contact person before December 4, 1996 and submit a brief statement of the general nature of the evidence or arguments they wish to present, the names and addresses of proposed participants, and an indication of the approximate time required to make their comments.

Open committee discussion. On December 10, 1996 the committee will hear presentations and discuss data submitted regarding New Drug Application (NDA) 20-656, Nutropin®, (somatropin [rDNA origin] for injection, Genentec, Inc.) and Humatrope®, (somatropin [rDNA origin] for injection, Eli Lilly and Companny) for the treatment of Turners' Syndrome. On December 11, 1996 the committee will hear presentations and discuss data submitted regarding NDA 20-720, Rezulin®, (troglidizone, Parke Davis Pharmaceutical Research, a Division of Warner-Lambert) and NDA 20-719, Prelay®, (troglidizone, Sankyo U.S.A.) for the treatment of type II diabetes inadequately controlled with insulin therapy.

Kathleen R. Reedy,
EXECUTIVE SECRETARY