ENDOCRINOLOGIC AND METABOLIC DRUGS

ADVISORY COMMITTEE MEETING # 65

12/10-11/96

Endocrinologic and Metabolic Drugs Advisory Committee #65

Food and Drug Administration
Center for Drug Evaluation and Research

Bethesda Holiday Inn, 8120 Wisconsin Avenue, Bethesda, MD

December 10, 1996

NDA 20-656; **Nutropin®**, Genentech, Inc.
NDA 19-640/S-018; **Humatrope®**, Eli Lilly and Company

I Agenda
Questions

II Medical Review

III Statistical Review

IV Biopharmaceutics Review

AGENDA

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December 10, 1996

8:00 Call to Order, Introductions, Opening Comments
Henry G. Bone III, MD, Chair
Endocrinologic and Metabolic Drugs Advisory Committee
Meeting Statement: Kathleen Reedy, Executive Secretary
Endocrinologic and Metabolic Drugs Advisory Committee

NDA 20-656; **Nutropin®**, Genentech, Inc.
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8:15 Open Public Hearing

8:45 Introduction:
G. Alexander Fleming, MD, Group Leader
Division of Metabolic and Endocrine Drug Products, FDA
Christie Zustak, MBA, Regulatory Affairs, Genentech, Inc.
Ron Rosenfeld, MD, Chairman, Department of Pediatrics,
Physician in Chief, Doernbacher Children's Hospital,
Oregon Health Sciences University,
Consultant for Genentech and Lilly

9:15 Efficacy: Kenneth Attie, MD, Genentech, Inc.
John Chipman, MD, Eli Lilly and Company
Safety: Sandra Blethen, MD, Genentech, Inc.
Charmian Quigley, MBBS, Assistant Professor of Pediatrics, Section of Pediatric Endocrinology, Indiana University and Consultant for Eli Lilly

10:30 Break

10:45 Benefit/Risks: Margaret MacGillivray, MD, Chief,
Division of Pediatric Endocrinology and Diabetes,
State University of New York at Buffalo Medical School
Consultant for Genentech and Lilly
Conclusion: Barry Bercu, MD, Professor of Pediatrics,
Pharmacology and Therapeutics, University of South Florida, consultant for Eli Lilly

11:15 FDA Presentation of Issues: Saul Malozowski, M.D., Ph.D.,
Division of Metabolic and Endocrine Drug Products
Possible Guest Expert, Department of Pediatric Endocrinology
Middlesex Hospital, London, England

12:15 Lunch

Interactive Discussion of Issues

1:30	Issue #1:	Factors that affect adult height gain
2:00	Issue #2:	Use of historical controls to assess efficacy
2:30	Issue #3:	Estimating efficacy from all available data
3:00	Issue #4:	Estimating risk of growth hormone therapy
3:30	Issue #5:	Refining understanding of growth hormone therapy in the post approval period
4:00	Questions	
5:00	Adjourn	

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Questions

1. On the basis of available data from concurrent and historical controlled trials, what is the mean estimated growth hormone treatment effect over the proposed treatment period?

2. What are the risks of chronic GH therapy in girls with Turner's syndrome?

3. Based on your estimate of the long term benefits compared to the risks of growth hormone therapy in girls with Turner's syndrome, do you recommend that this drug be approved for marketing?

4. If approval is recommended, what studies or other measures are recommended to refine the understanding of this therapy's benefits and risks.

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

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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-placebo 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 (85-023) 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.

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.

STATISTICAL REVIEW AND EVALUATION

OCT 24 1996

NDA#: 20-656

APPLICANT: Genentech, Inc.

NAME OF DRUG: Nutropin [Somatropin (rDNA origin) for injection]

INDICATION: Growth failure associated with Turner syndrome

DOCUMENTS REVIEWED: Volumes 1.1, 1.28-1.44 of NDA 20-656 dated September 29, 1995

MEDICAL REVIEWER: This review has been discussed with the clinical reviewer, Saul Malozowski, M.D., HFD-510

RELEVANT ISSUES DISCUSSED IN THIS REVIEW

1. Analyses conducted by the sponsor as well as by this reviewer detected statistically significant differences in favor of Nutropin and Protropin patients over historical control patients with regard to adult height.

2. It is well accepted that a historical control study is no substitute for a randomized controlled clinical trial. Consequently, the reviewing clinicians should ascertain how representative the sponsor's historical control population which experienced a median adult height of 4' 8.7" is with their perception of the Turner syndrome population at large.

3. The median adult height for the 134 patients who received Nutropin or Protropin monotherapy was 4' 10.7" as 29% of these patients attained a height of at least 5' 0".

KEY WORDS: adult height, bioequivalence, estrogen, growth hormone, historical control, Turner syndrome

SPONSOR'S CLINICAL TRIALS

Genentech has submitted the results of two long-term, multicenter, historical controlled studies of the use of recombinant growth hormone in the treatment of short stature in girls with Turner syndrome.

Study 85-044 used Nutropin [somatropin (rDNA origin) for injection] (product codes G042A and G072A). Study 83-002/85-023 used Protropin (somatrem for injection) (product code G015A).

The bioequivalence of the somatropin formulations has been established and the FDA has agreed that a study using Nutropin in conjunction with a study using Protropin would satisfy the NDA two clinical study requirement.

The primary endpoint in each study is adult height as discussed below.

STUDY 85-044

BACKGROUND

Study 85-044 began as an open-label, multicenter (28 centers), randomized, controlled study which was designed to assess the safety and growth-promoting effects of Nutropin during a one-year period in girls with Turner syndrome.

Patients were randomized from February 1987 to July 1987 to receive either no treatment or subcutaneous (SC) Nutropin .125 mg/kg injections 3 times a week (TIW) for a cumulative weekly dose of .375 mg/kg. The initial Nutropin dose which was based on the patient's baseline weight was weight-adjusted every 6 months.

A total of 48 patients were identified prior to study commencement. The pre-screen patient-data file was sorted by age. Within each group of four successive patients in this sorted file, one patient was randomly selected to receive no treatment and the remaining 3 patients were selected to receive Nutropin TIW injections.

A protocol amendment submitted on August 4, 1987 indicated that all subsequently enrolled patients would receive daily .054 mg/kg Nutropin SC injections for an approximate cumulative weekly dose of .375 mg/kg. There was no interruption of therapy during this protocol amendment transition phase. The protocol amendment also indicated that patients who were randomized to receive no treatment would also receive daily Nutropin .054 mg/kg injections subsequent to completing one-year (i.e, during the second and subsequent study years) of randomized treatment. Patients randomized to receive Nutropin TIW injections would continue to do so.

A second protocol amendment submitted on February 12, 1988 provided for the initiation of estrogen therapy for patients who completed one study year. Patients who were less than 12 years old after completing one study year (less then 11 at baseline) were randomized to begin estrogen therapy either at age 12 or at age 15. Patients who were at least 12 years old at the end of their first study year (at least 11 at baseline) were assigned to begin estrogen therapy at that time.

Patients randomized to receive estrogen at age 12 were referred to as being in the "early estrogen" group whereas patients randomized to receive estrogen at age 15 were referred to as being in the "late estrogen" group.

A provision for long-term treatment and subsequent follow-up was provided for in a protocol amendment which was submitted on April 12, 1990. Under the provisions of this amendment, treatment with Nutropin would continue until a patient's bone age was 14 years and her growth rate was less than 2.5 cm/year. At that point, patients would discontinue Nutropin and be seen at 6-month intervals for height measurements until adult height (minimum of 18 years of age) was attained. Adult height was defined as evidence of fused epiphyses on bone age x-ray and no change in height for 12 months.

As mentioned above, Study 85-044 was originally designed to be a one-year study. The sponsor's primary efficacy objective as originally stated was to assess the effect of Nutropin on short-term improvement in the growth of Turner patients as reflected by annualized growth rates.

At the suggestion of the FDA, the protocol was amended as discussed above to follow patients to adult height. Consequently the sponsor's revised primary objectives for Study 85-044 (which is ongoing) are to assess improvement in adult

height from long-term Nutropin therapy and to evaluate the effect of estrogen administration (early versus late) on adult height.

The sponsor and the FDA have agreed that adult height will be the primary efficacy endpoint for this study. This was the result of discussions between the sponsor and the FDA as well as in consideration of the recommendations of the Endocrine and Metabolic Drug Advisory Committee on September 28, 1987.

Since patients in the original control (untreated) group were reassigned to receive daily Nutropin therapy after the first study year, Genentech created an alternative to a concurrent long-term control group by developing a database of untreated American Turner syndrome patients. Genentech established (from 14 U.S. institutions) a baseline age and height matched historical control group (which includes adult height measurements for 84 patients) comprised of patients who have not received growth hormone, androgens, or early estrogen therapy to act as a control group.

The Study 85-044 patients were compared with the above mentioned historical control patients with regard to adult height by utilizing an analysis of covariance procedure. The covariates were age at the start of Nutropin therapy, mid-parental target height, baseline height, and karyotype.

All available historical controls were selected who had childhood ages within approximately the same range as the Study 85-044 patients. The historical control patients were separated into two groups. The first group consisted of 14 patients who were less than 11 years of age at baseline whereas the second group consisted of 55 patients who were at least 11 years of age at baseline. In each analysis, controls were required to be of appropriate age for the initiation of estrogen therapy. For example, in assessing the effect of Nutropin on adult height in patients receiving late estrogen therapy, controls were selected who did not commence estrogen therapy before age 14. In addition, as mentioned above, control patients had never received androgens or growth hormone therapy. Also, each control patient was required to have a height measurement after the age of 18.

Sponsor's Results

Between February 18, 1987 and May 19, 1988 (enrollment completed), 117 patients (9 untreated, 36 Nutropin TIW, 72 Nutropin daily) were enrolled in Study 85-044.

The sponsor's submitted study report contains all information received and prepared for analysis as of April 1, 1995. At that time, 102 patients had discontinued treatment. Sixty-three of the discontinued patients met the protocol discontinuation criteria. The remaining 39 patients discontinued due to adverse events (2), noncompliance (13), lost to follow-up (3) and requested removal (21).

A total of 109 of the 117 enrolled patients received at least one year of Nutropin therapy in addition to having a height measurement conducted after age 13.5. The sponsor compared the adult heights of 106 (excluded 3 patients randomized to early estrogen who did not receive estrogen until after age 14) of these patients with those of the above mentioned historical control patients.

The sponsor indicated that since the control patients were followed until at least 18 years of age compared to a minimum of 13.5 years of age for the Study 85-044 patients, that the estimate of the effect of Nutropin on adult height obtained from this study is a conservative estimate.

The sponsor partitioned the 117 enrolled patients into 5 groups. A description of each of these groups is given in Table 1.

Adult height population patients (Table 1) in groups A and C were compared with respect to adult height to the above mentioned 14 historical control patients who were less than age 11 at baseline. Patients in group D were compared to the above mentioned 55 historical control patients who were at least 11 years of age at baseline.

The results of the sponsor's adult height analyses are displayed in Tables 2 and 3.

In examining Table 2, one notes that each of the under age at 11 baseline Nutropin treatment groups statistically outperformed their historical control counterparts with regard to adult height. The Group A and C differences were 5.9 cm (2.3 inches) and 8.3 cm (3.3 inches) respectively. The 3 above mentioned patients

(Group B) who were excluded from the sponsor's primary adult height analyses also statistically outperformed their historical control counterparts with a mean difference of 12.3 cm (4.8 inches) with a corresponding 95% confidence interval of (8.4 cm, 16.2 cm).

The patients randomized to Group C (late estrogen) achieved a significantly (p=.008) greater adult height than the patients randomized to Group A (early estrogen).

In examining Table 3, one notes that patients (Group D) who commenced Nutropin therapy when at least 11 years of age and were assigned estrogen therapy after one year of such therapy also statistically outperformed their historical control counterparts with a mean difference in adult height of 5.0 cm (2.0 inches).

Reviewer's Analyses

Additional analyses were conducted by this reviewer in response to the reviewing clinician's concern regarding the relationship (if any) between the increase in height from baseline and the number of years (treatment duration) on Nutropin therapy.

Table 4 displays the results of a regression analysis in which the increase in height from baseline was regressed on the duration of Nutropin therapy. In examining this table, one notes that the correlation coefficients are .60, .59, and .65 for Nutropin groups A, C, and D respectively. In each case, the correlation coefficient is significantly different from zero.

This reviewer also conducted a pooled nonparametric analysis in which the adult heights of the 117 Nutropin enrolled patients were compared to those of the 69 historical control patients. The result of this analysis was supportive of the sponsor's above mentioned analyses in that there was a highly significant (p<.00001) difference in favor of the Nutropin patients over the historical control patients with regard to adult height (Nutropin median adult height = 148.8 cm, historical control median adult height = 144.1 cm).

In more familiar terms (to this reviewer), given that 1 cm = .3937 inches, the above median heights in centimeters translate to 4' 10.6" for the Nutropin patients

compared to 4' 8.7" for the historical control patients, a difference of approximately 2 inches.

It is well accepted that a historical control study is no substitute for a randomized controlled clinical trial. For this reason, the reviewing clinicians should ascertain how representative the sponsor's historical control population (which experienced a mean (and median) adult height of 4' 8.7" is with their perception of the Turner syndrome population at large with regard to the adult height primary efficacy parameter.

As an aid to assessing the Nutropin treatment effect one should consult Table 5.

Table 5 displays descriptive adult height results for the 117 enrolled patients in one inch intervals. In examining this table one notes that approximately 25% of the enrolled patients achieved an adult height of at least 5' 0" and that only 6% of the enrolled patients achieved an adult height of at least 5' 2".

As mentioned above, the sponsor stated that the effect of Nutropin on adult height gleaned from this study is a conservative estimate since control patients who were followed until at least 18 years of age were compared with Nutropin patients who had final height measurements as young as 13.5 years of age.

In examining the adult height data provided by the sponsor, this reviewer noted that only 19 of the enrolled patients had a height measurement conducted at age 18 or later. Eighteen of these patients initiated Nutropin therapy after age 11 and received estrogen after 12 months of such therapy (Group D). The remaining patient was a Group E (see Table 1) patient.

In examining Table 6, one should note that the adult height distribution for these 19 patients is similar to the 117-enrolled patient population adult height distribution (Table 5) as the median adult heights are 4' 10.8" and 4' 10.6" for the 19 and 117 patient populations respectively. Also 26.3% of the age 18 and over population attained an adult height of 5' 0" compared to 24.8% of the enrolled patient population. These comparable adult height results could conceivably lead one to question the conservative estimate Nutropin treatment effect claim made by the sponsor.

STUDIES 83-002/85-023

BACKGROUND

Study 83-002 was a one-year Phase II multi-center (11 centers), open-label, randomized study which was conducted to evaluate the safety and efficacy of Protropin (somatrem for injection) with and without the concomitant administration of oxandrolone in the alleviation of growth retardation associated with Turner's syndrome.

From August 1983, to June 1984, patients were enrolled in Study 83-002 and randomized into one of the following study groups:

Group 1:	Control (no treatment)
Group 2:	oxandrolone (.125 mg/kg/day orally)
Group 3:	Combination (Protropin .125 mg/kg intramuscular (IM) injection TIW, and oxandrolone .125 mg/kg/day)
Group 4:	Protropin (.125 mg/kg IM TIW)

After all patients completed at least 12 months in Study 83-002, continuing patients entered Study 85-023.

Study 85-023 began on April 2, 1985 and consisted of patients who had been in Protocol 83-002 for 12-24 months.

Study 85-023 consisted of only 2 treatment arms as patients in Study 83-002 Groups 1-3 received combination therapy whereas, Study 83-002 Group 4 patients continued to receive Protropin monotherapy.

Due to a high incidence of clitoromegaly during Study 83-002 which was directly attributable to oxandrolone, the oxandrolone dose was decreased from .125 mg/kg/day to .0625 mg/kg/day at the start of Study 85-023.

An amendment to the protocol submitted on May 7, 1986 provided for the initiation of estrogen replacement therapy which was withheld at the discretion of the investigator until the age of 14 so that the study medications could be studied independently of other potential growth-promoting agents.

An amendment to the protocol submitted on March 31, 1987 provided for the switch from IM to SC Protropin injections and a change in the treatment schedule from TIW to daily .05 mg/kg injections for all of the Protropin monotherapy patients and for one-half (randomly selected) of the combination patients.

An amendment to the protocol submitted on April 12, 1990 (mentioned in the above review of Study 85-044) reduced the frequency of visits to 6-month intervals and provided for long-term treatment and follow-up until adult height was attained. Under the provisions of this amendment (as stated earlier), Protropin treatment was continued until the patient's bone age was 14 years and her growth rate was less than 2.5 cm/yr. At that point, patients discontinued Protropin and were seen at 6-month intervals for height measurements until a minimum age of 18 and adult height was attained. Adult height was defined as evidence of fused epiphyses on bone age x-ray and no change in height for 12 months.

Consequently, as mentioned with regard to Study 85-044, the sponsor and the FDA agreed that adult height would be the primary efficacy endpoint for this study.

Study 85-044 used Nutropin [somatropin (rDNA origin) for injection] (Product Code G072A) and an earlier formulation of somatropin (Product Code G042A). Study 83-002/85-023 used Protropin (somatrem for injection) (Product Code G015A). The bioequivalence of all GH formulations used in these studies has been previously established according to the sponsor. Based on this bioequivalence, the sponsor stated that the FDA has agreed that Studies 85-044 and 83-002/85-023 would satisfy the 2 clinical study NDA requirement.

SPONSOR'S RESULTS

A total of 71 patients (18 control, 19 oxandrolone, 17 combination, 17 Protropin) were enrolled and randomized to the original four treatment groups.

The sponsor's submitted study report contains all information received and prepared for analysis as of April 1, 1995. At that time, all 71 patients had either completed the treatment phase of the protocol and were continuing with follow-up or had discontinued from the study. Forty-six patients discontinued after having

met the Study 83-002/85-023 protocol discontinuation criteria. The remaining 25 patients discontinued due to adverse events (6), noncompliance (6), lost to follow-up (1), and requested removal (12).

Sixty-seven of the original 71 patients participated in Study 85-023. Sixty-three of these patients had height measurements after age 13.5 and comprised the sponsor's adult height population which was compared with a historical control population as in Study 85-044. Seventeen of the sixty-three adult height population patients received Protropin monotherapy whereas the remaining 46 patients received Protropin in combination with oxandrolone.

The results of the sponsor's adult height analyses are displayed in Table 7. In examining this table, one notes that the Protropin and combination patients statistically outperformed their historical control counterparts. The Protropin and combination differences were 7.4 cm (2.9 inches) and 10.1 cm (4.0 inches) respectively.

REVIEWER'S ANALYSES

The remainder of this review will focus on the seventeen patients who received Protropin monotherapy as the sponsor is not seeking an indication for Protropin in combination with oxandrolone.

Twenty-four of the twenty-five historical control patients who were compared with the 17 Protropin patients with regard to adult height were also in the Study 85-044 (all 14 patients in the first historical control group, 10 patents in the second historical control group) historical control populations.

In examining the historical control group data supplied by the sponsor it was noted that 7 of the above mentioned 24 patients had baseline data which was not common between Studies 85-044 and 83-002/85-0023. For example, each of these 7 patients had a lower baseline age (mean of 8.2 years) in the Studies 83-002/85-023 historical control group than in the Study 85-044 (mean of 12.8 years) historical control group. Consequently it became apparent that these 7 patients were "observed" during different time intervals in the submitted studies.

In the opinion of this reviewer, the above mentioned 7 patients should not have been observed in two different time intervals for comparative purposes. However, given that the primary efficacy parameter is adult height, the sponsor's use of these 7 patients for comparative purposes should not be viewed as being a fatal flaw.

As for Study 85-044, this reviewer conducted a nonparametric analysis which compared the adult heights between the 17 Protropin patients and the 25 historical control patients. A significant ($p<.01$) result in favor of Protropin (median: 153.1 cm) over the historical control (median: 144.8 cm) was obtained.

Table 8 displays descriptive adult height results for the 17 enrolled Protropin patients. In examining this table, one notes that 59% of these patients achieved an adult height of at least 5'0" compared to only 25% (Table 5) of the Study 85-044 Nutropin patients. This could be due to the longer duration of growth hormone treatment for the Protropin patients than the Nutropin patients (7.6 years vs 4.6 years).

A regression analysis in which the increase in height (cm) from baseline was regressed on the duration of Protropin therapy yielded a correlation coefficient of .71 ($p=.002$) which was consistent with the corresponding Study 85-044 results which are displayed in Table 4. The corresponding regression coefficient (slope) of 2.83 was also consistent with the Study 85-044 results.

REVIEWER'S CONCLUDING COMMENTS

The sponsor has submitted the results of Studies 85-044 and 83-002/85-023 in support of Nutropin in the treatment of girls who have growth failure associated with Turner syndrome.

Significant differences in favor of Nutropin and Protropin with regard to adult height over a historical control population were detected by the sponsor as well as by this reviewer.

The median adult heights were 149.0 cm (4'10.7") and 144.1 cm (4'8.7") for the Nutropin (Protropin) and historical control populations respectively.

The adult height distribution of the 134 patients who received Nutropin or Protropin is displayed in Table 9. The 2 inch differential in median adult height between the Nutropin (Protropin) and the historical control patients should be assessed for its clinical relevance by the reviewing clinicians.

Daniel N. Marticello
Mathematical Statistician

Concur: Dr. Nevius 10/25/91

cc:
Archival NDA 20-656
HFD-510
HFD-510/SSobel,AFleming,GTroendle,SMalozowski,EGalliers,MJohnston
HFD-715/Division File, DMarticello,Chron.

This review consists of 12 pages of text and 9 pages of tables

TABLE 1

STUDY 85-044

ADULT HEIGHT POPULATION

GROUP[+]	ENROLLED	ADULT HEIGHT POPULATION[#]
A	27	26
B	3	3[e]
C	30	29
D	51	51
E	6	0
TOTAL	**117**	**109**

\# Patients who received at least one year of Nutropin therapy in addition to having a height measurement after age 13.5

+:

A Patients initiated Nutropin therapy before age 11 and were randomized to receive estrogen (early) at age 12

B Patients in Group A that did not receive estrogen until after age 14

C Patients initiated Nutropin therapy before age 11 and were randomized to receive estrogen (late) at age 15

D Patients initiated Nutropin therapy after age 11 and received estrogen after 12 months of such therapy

E Patients in Group D that discontinued prior to one year of Nutropin therapy and consequently never received estrogen therapy

e Patients in Group B were not included in the sponsor's adult height analyses which compared the final heights of patients in Groups A, C, and D with those in the historical control groups

TABLE 2

STUDY 85-044

ADULT HEIGHT COMPARISONS[+]

PATIENTS UNDER AGE 11 AT BASELINE

	GROUP A	HISTORICAL CONTROL	GROUP C
N	26	14	29
Baseline Age (yrs)	9.6	9.3	9.4
Most Recent Age (yrs)	15.8	21.9	16.3
Baseline Height (cm)	116.8	117.9	116.4
Most Recent Height (cm)	147.0	144.1	150.4
Difference[#]	5.9(3.3,8.5)		8.3(5.3,11.3)
	p<.0001		**p<.0001**

\+ Analysis of covariance with baseline age (start of Nutropin therapy), baseline height, karyotype, and mid-parental target height as covariates

\# Estimated mean difference in adult height in favor of Nutropin groups A and C over the historical control group. Ninety-five percent confidence intervals for the differences are shown in parenthesis

TABLE 3

STUDY 85-044

ADULT HEIGHT COMPARISONS+

PATIENTS AT LEAST AGE 11 AT BASELINE

	GROUP D	HISTORICAL CONTROL
N	51	55
Baseline Age (yrs)	12.7	13.2
Most Recent Age (yrs)	17.6	21.5
Baseline Height (cm)	129.4	131.6
Most Recent Height (cm)	148.5	144.1
Difference# (cm)	5.0 (3.7,6.3)	
	p<.0001	

\+ See Table 2

\# See Table 2

TABLE 4

STUDY 85-044

INCREASE IN HEIGHT VS TIME ON NUTROPIN

	NUTROPIN GROUP		
	A	C	D
N	26	29	51
Mean Nutropin Therapy Duration (yrs)	5.6	6.1	3.8
Mean Increase in Height from Baseline (cm)	30.25	34.04	19.11
Slope of Regression Line	3.23	2.14	3.40
Correlation Coefficient (height increase vs duration)	.60	.59	.65
Correlation Coefficient P-Value	.001	<.001	<.0001

TABLE 5

STUDY 85-044

NUTROPIN PATIENTS

ADULT HEIGHT DISTRIBUTION

117 ENROLLED PATIENTS

ADULT HEIGHT	FREQUENCY	CUMULATIVE FREQUENCY
<4'5"	3	
4'5"	6	114 (97.4%)
4'6"	2	108 (92.3%)
4'7"	10	106 (90.6%)
4'8"	16	96 (82.1%)
4'9"	11+	80 (68.4%)
4'10"	19	69 (59.0%) Median=4'10.6"
4'11"	21	50 (42.7%)
5'0"	14	29 (24.8%)++
5'1"	8	15 (12.8%)
5'2"	5	7 (6.0%)
5'3"	2	2 (1.7%)

\+ Example: 11 patients had an adult height of at least 4'9" but less than 4'10"

++ Example: 24.8% of the enrolled patients had an adult height of at least 5'0"

TABLE 6

STUDY 85-004

NUTROPIN PATIENTS

ADULT HEIGHT DISTRIBUTION

PATIENTS WITH A HEIGHT MEASUREMENT

AT 18 YEARS OF AGE OR OVER

ADULT HEIGHT	FREQUENCY[+]	CUMULATIVE FREQUENCY[+]	
<4'5"	0		
4'5"	1	19 (100.0%)	
4'6"	0	18 (94.7%)	
4'7"	1	18 (94.7%)	
4'8"	2[#]	17 (89.5%)	
4'9"	2	15 (78.9%)	
4'10"	4	13 (68.4%)	Median=4'10.8"
4'11"	4	9 (47.4%)	
5'0"	4	5 (26.3%)	
5'1"	1	1 (5.3%)	
5'2"	0	0 (0.0%)	
5'3"	0	0 (0.0%)	

+ See Table 5

All 19 Patients were Group D patients except for one Group E patient. The Group E patient had an adult height of 4'8.6"

TABLE 7

STUDIES 83002/85-023

ADULT HEIGHT COMPARISONS[+]

	PROTROPIN	HISTORICAL CONTROL	COMBINATION
N	17	25	46
Baseline Age (yrs)	9.1	9.2	9.9
Most Recent Age (yrs)	18.0	22.1	17.3
Baseline Height (cm)	114.6	117.1	117.5
Most Recent Height (cm)	150.4	144.2	151.5
Difference[#] (cm)	7.4(4.6,10.2)		10.1(7.8,12.4)
	P<.0001		**P<.0001**

+ Analyses of covariance with baseline age, baseline height, karyotype, and mid-parental target height as covariates

Estimated mean difference in adult height in favor of Protropin and the combination patients over the historical control group. Ninety-five percent confidence intervals for the differences are shown in parenthesis

TABLE 8

STUDIES 83002/85-023

PROTROPIN PATIENTS

ADULT HEIGHT DISTRIBUTION

17 ENROLLED PATIENTS

ADULT HEIGHT	FREQUENCY	CUMULATIVE FREQUENCY
4'6"	1	17 (100.0%)
4'7"	0	16 (94.1%)
4'8"	3+	16 (94.1%)
4'9"	0	13 (76.5%)
4'10"	3	13 (76.5%)
4'11"	0	10 (58.8%)
5'0"	8	10 (58.8%)++ Median=5'0.3"
5'1"	1	2 (11.8%)
5'2"	1	1 (5.9%)

\+ Example: 3 patients had an adult height of at least 4'8" but less than 4'9"

++ Example: 58.8% of the enrolled Protropin patients had an adult height of at least 5'0"

TABLE 9

STUDIES
85-044 (NUTROPIN)
83-002/85-023 (PROTROPIN)

ADULT HEIGHT DISTRIBUTION

134 ENROLLED PATIENTS

ADULT HEIGHT	FREQUENCY	CUMULATIVE FREQUENCY
<4'5"	3	
4'5"	6	131 (97.8%)
4'6"	3	125 (93.3%)
4'7"	10	122 (91.0%)
4'8"	19	112 (83.6%)
4'9"	11	93 (69.4%)
4'10"	22+	82 (61.2%) Median=4'10.7"
4'11"	21	60 (44.8%)
5'0"	22	39 (29.1%)++
5'1"	9	17 (12.7%)
5'2"	6	8 (6.0%)
5'3"	2	2 (1.5%)

\+ Example: 22 patients had an adult height of at least 4'10" but less than 4'11"

++ Example: 29% of the enrolled Nutropin and Protropin patients had an adult height of at least 5'0"

Clinical Pharmacology and Biopharmaceutics Review

NDA:	20-656
Somatropin (rDNA origin) for injection (Nutropin®)	JUL 10 1996
Submission Date:	9/29/95
Sponsor:	Genentech, San Francisco, CA
Type of Submission:	New Drug Application (5S)
Reviewer:	Michael J. Fossler, Pharm. D., Ph. D.

Submission

The submission dated 9/29/95 is for Nutropin® (somatropin for injection). The proposed indication is for the treatment of growth failure associated with Turner's syndrome. Somatropin has previously been approved for the long-term treatment of children with growth failure due to a lack of endogenous growth hormone (NDA 19-676) and for treatment of children who have growth failure associated with chronic renal insufficiency (NDA 20-168).

No new data were submitted for this application. OCPB/DPE-II requested that the CLINICAL PHARMACOLOGY section be revised to be consistent with the approved labeling for Nutropin AQ®[1]. Additionally, the firm was asked if any data on the pharmacokinetics of hGH were available in girls with Turner's syndrome. The firm responded with revised labeling and a reference[2] which showed that the t½ of endogenous hGH was slightly increased in Turner girls as compared with normal controls (14 ± 0.93 min in Turner girls vs. 11 ± 0.44 min. in normal girls, $p < 0.029$, Figure 6 in manuscript, attached). Although statistically significant, this difference is unlikely to be of much clinical importance. Examining Figure 6, it is noted that the t½ values obtained for normal girls fall within the range of t½ values obtained for Turner girls. The other hGH parameters show a similar pattern.

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[1]Nutropin AQ is an injectable liquid somatropin product that is bioequivalent to the current lyophilized Nutropin formulation (see biopharm review dated 11/8/95 for NDA 20-522).

[2]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 Cain. End. Meta. (1991) 73:1073)

Recommendations

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (HFD-870) has reviewed the submission dated 9/29/95, as well as the revised labeling, and finds them acceptable. Please send the Labeling Comment below to the firm if/when the indication is approved.

Labeling Comment (send to firm)

1. Under Special populations in the CLINICAL PHARMACOLOGY section, the text under Turner's Syndrome should be modified as follows:

Turner's Syndrome- No pharmacokinetic data are available for exogenously administered rhGH. A report examining the pattern of endogenous growth hormone secretion and elimination rates in Turner's and normal prepubertal girls suggests that the two groups are similar.

7/10/96

Michael J. Fossler, Pharm. D., Ph. D.

Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

FT initialed by Hae-Young Ahn, Ph. D., Team Leader 7/10/96

version: final
CC: NDA 20-656 (orig., 1 copy), HFD-510(Malozowski, Galliers),HFD-850(Lesko) HFD-860(Malinowski), HFD-870(M. Chen, Fossler, Ahn, Drug File, Chron. File, Reviewer File) HFD-880(Fleischer) HFD-205(FOI), HFD-340 (Vish)
rev 4/9/96

Joint Summary
Turner Syndrome Advisory Committee Briefing Document

This briefing document provides information relevant to the FDA Advisory Committee Meeting scheduled for December 10, 1996 to discuss growth hormone treatment of the growth failure associated with Turner syndrome. It contains material derived from two FDA submissions: a New Drug Application (NDA) for Genentech, Inc.'s Nutropin® (somatropin), submitted in September, 1995, and Eli Lilly and Company's NDA supplement for Humatrope® (somatropin), submitted in July, 1996.

For more than a decade, Genentech and Lilly have sponsored 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. Collectively, the two companies conducted four studies which vary with respect to study design and other protocol aspects, but nonetheless are consistent with each other with respect to safety and efficacy. To provide the most comprehensive data package regarding growth hormone use in Turner syndrome, the companies, in consultation with FDA, agreed to cross-reference the two submissions 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 satisfy the criteria established for GH approval for this indication. The following summarizes the key clinical trial data from both companies.

The first two clinical trials (Genentech-sponsored), which are now complete, achieved the primary endpoint of the studies: clinically significant increases in final height. The analyses of final height were made using matched historical control patients, consisting of untreated American girls and women with Turner syndrome, most of whom were followed by the same investigators who participated in the GH studies. All patients who were treated for at least one year and who had a height measurement after age 13.5 years were included in the adult height analyses (94% of enrolled patients).

In the first trial, study 85-023, patients were treated with GH at the relatively young mean age of 9 years, with estrogen replacement therapy given after age 14 years and after at least 3 years on study. One group was treated with GH alone (n=17) and had an increase in adult height of 7.4 cm compared with matched historical controls (n=25), using analysis of covariance. A second method of assessing adult height gain, wherein each patient serves as her own control (using her pretreatment projected adult height), the calculated mean increase was similar at 8.4 cm.

A second group of patients was treated with the combination of GH and the anabolic steroid oxandrolone (n=46); this group had a mean increase in adult height of 10.1 cm

versus matched controls (and similarly, 9.8 cm versus their pretreatment projected adult height). The mean adult heights of the subjects in both groups in this study was over 150 cm (4'11"), compared with their expected mean adult height of 142 cm (4'8"). Over 90% of patients increased their adult height, with more than 80% achieving increases of greater than 5 cm (2").

The second study (85-044), demonstrated that in patients who started GH before age 11 years (mean 9.5 years), the age of initiating estrogen replacement therapy was significant with respect to adult height. These patients were randomized to begin estrogen at either age 12 or age 15. The increase in adult height by analysis of covariance versus the matched historical controls was 8.3 cm in the estrogen at age 15 group (n=29), and 5.9 cm in the estrogen at age 12 group (n=26). The results for the former group are consistent with the results for the GH group in the first study, treated similarly.

In the third group, in study 85-044 patients started GH therapy after age 11 years (mean age 12.7 years), and estrogen therapy after 12 months of GH therapy. By analysis of covariance there was a gain of 5.0 cm for this group (n=51), versus matched historical controls. These patients had a mean duration of GH therapy of less than 4 years, compared with close to 6 years in the groups treated earlier. These results are consistent with a large number of studies in the world literature with similar treatment parameters.

The results obtained for all three treatment groups in study 85-044 were comparable using either matched historical controls or their own pretreatment projected adult height as the method of outcome analysis. The mean adult heights measured for each of the three groups (150.4 cm, 147.0 cm, 148.5 cm) were all substantially greater than their expected mean heights of approximately 143 cm.

Two randomized controlled clinical trials (Lilly-sponsored) also demonstrated significant increases in final height in GH-treated patients. Study GDCT, conducted in Canada, used randomized, untreated concurrent controls to adult height. Mean final height in the GH-treated patients (n=27) was 146.0 cm compared to the untreated group who attained a mean final height of 142.1 cm (n=19). By analysis of covariance, the difference between groups was 5.4 cm. The average duration of GH treatment for these patients was 4.7 years, with estrogen replacement therapy after 1 year in the study in patients at least 13 years of age, in both GH-treated and control groups. An analysis at the most recent visit of 134 patients (74 GH-treated and 60 controls) who had received at least 6 months GH treatment showed a mean GH effect of over 6 cm.

Study GDCI, conducted in the U.S., is a randomized double-blinded dose-response trial that was placebo-controlled for the initial 18 months. In addition to two doses of GH, the study includes oral placebo or low-dose estrogen administered at an early age (after age 8 years). All patients are prescribed standard estrogen replacement from 13.5 years. The mean final height for protocol completers (n=31) was 148.7 cm

consistent with the above studies. In this study, two doses of GH were used, with the higher dose producing significantly greater growth response as of the most recent visit; this dose was similar to that used in the first two (Genentech-sponsored) studies.

Safety information from Genentech studies include data from the two clinical trials, as well as extensive data from the National Cooperative Growth Study (a phase IV study) and spontaneous adverse event reports for children on commercial GH. These three sources represent over 8000 patient-years of experience of GH treatment in Turner syndrome patients. Serious adverse events were rare, and included two cerebrovascular accidents and seven deaths, five of which occurred in patients with congenital cardiovascular anomalies. None 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 both Turner syndrome and GH therapy, were seen infrequently. 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 abnormalities were seen. Thus, no new or unexpected serious adverse events or clinically significant laboratory changes attributable to GH occurred in the Turner syndrome studies.

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. All deaths were considered unrelated to GH. The only patient who died in any of the clinical trials was in the non-GH-treated group of the Canadian study. Otitis media, ear disorder, and surgical procedure were the only events reported significantly more often in GH-treated than the non-GH-treated patients in the Canadian study. Of interest, there were no significant differences between GH-treated and non-GH treated patients in study GDCT for those events historically associated with GH (e.g. headache, edema, skin nevi, bone disorder and hyperglycemia). As with the studies described above, mean fasting and 2-hour post-prandial glucose and HbA_{1c} concentrations remained normal through the study, however 2-hour post-prandial insulin values varied and elevated values were seen sporadically in the U.S. study. 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 serious 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 a mean adult height of over 150 cm, a significant clinical benefit.

Endocrinologic and Metabolic Drugs Advisory Committee Meeting

FDA Center for Drug Evaluation and Research

December 10,1996

Genentech, Inc. and Eli Lilly and Company

NDA 20-656 and Supplemental NDA 19-640

ADVISORY COMMITTEE MEETING: **ITEM A**
NAME OF DRUG: **Growth Hormone—Turner Syndrome**

BACKGROUND

The following background information has been jointly developed by Genentech, Inc. and Eli Lilly and Company.

OVERVIEW OF TURNER SYNDROME

GENERAL CLINICAL FEATURES

Short stature and delayed sexual and skeletal maturation are cardinal features of the syndrome described by Henry Turner in 1938, that bears his name (Turner HH 1938). The condition had earlier been described by Ullrich (Ullrich O 1930) and in Europe is commonly referred to as Ullrich-Turner syndrome. The condition results from partial or complete absence of one sex chromosome in a female (complete or partial monosomy X; karyotype 45,X and variants). More than 99% of 45,X conceptuses are aborted during early pregnancy (Hook EB and Warburton 1983). Nevertheless, Turner syndrome is the most common chromosomal disorder in females, occurring in approximately one in 2500 live female births (Hook EB and Warburton 1983). Based on this incidence figure, it is estimated that there about 50,000 affected women in the United States and approximately 800 new cases born annually.

Short stature is the most characteristic and almost universal feature of Turner syndrome, the adult height of affected women averaging 20 cm less than the population mean for normal adult women (Ranke MB 1994). Although the phenotype of affected individuals varies widely, short stature is present in more than 95% of patients, and may be the only physical finding at the time of diagnosis in up to 30% of cases (Park E et al. 1983). Ranke et al. (Ranke MB et al. 1988) and Holl et al. (Holl RW et al. 1994) contend that affected women often consider short stature to be the feature most disadvantageous in everyday life. In addition to short stature, other common phenotypic findings include: ptosis, unusual or prominent ears, small mandible, high-arched palate, webbing of the neck, low posterior hair-line, "shield chest" (broad chest with wide-spaced nipples), cubitus valgus (increased carrying angle at the elbow), shortened 4th and/or 5th metacarpals or metatarsals, hypoplastic, hyperconvex fingernails (nail dysplasia), an increased number of pigmented nevi, which further increases with age, and a number of other, less common physical findings (Hall JG and Gilchrist 1990; Palmer CG and Reichmann 1976). During childhood there is an increased

rate of occurrence of otitis media, thought to be due to structural abnormalities of the middle ear, and hearing deficit is common in adulthood, due to this as well as sensori-neural haring loss (Hultcrantz M and Sylven 1995; Sculerati N et al. 1990). Affected girls and women have a high incidence of ovarian failure due to the cardinal feature of the syndrome, gonadal dysgenesis (approximately 92%). The most significant health problems in addition to the ovarian failure are due to left sided congenital heart defects and various forms of renal dysgenesis. Hypertension and autoimmune disease of the thyroid and bowel are reported to occur more commonly in Turner syndrome than in the normal population. (Grunerio de Papendieck L et al. 1987). In addition, although IQ is normal, patients with Turner syndrome have an increased occurrence of specific learning difficulties in the area of spatial-temporal relationships (Silbert A et al. 1977).

GROWTH AND THE ETIOLOGY OF SHORT STATURE IN TURNER SYNDROME

Linear growth in Turner syndrome has several distinct characteristics, as documented by a number of detailed studies. The lack of a pubertal growth spurt in most girls is a well-known phenomenon, however the abnormalities of growth in these patients begin well before adolescence. In fact, even intrauterine growth is retarded, with mean birth length of girls with Turner syndrome 2.8 cm less than the mean for normal girls. In addition, there is very poor growth during childhood: after the age of 3 years there is an inexorable decline in growth rate such that by 9 years of age the mean growth rate of patients with Turner syndrome is more than 2 SD below the mean for normal girls (see Figure 1). The greatest loss of height for girls with Turner syndrome occurs during childhood, between the ages of 3 and 14 years. In addition, the lack of gonadal steroids results in absence of the pubertal growth spurt and a further delay in epiphyseal maturation. By the time that growth has been completed, the average young woman with Turner syndrome is about 20 cm (8") shorter than the average for women of the same ethnic or genetic background.

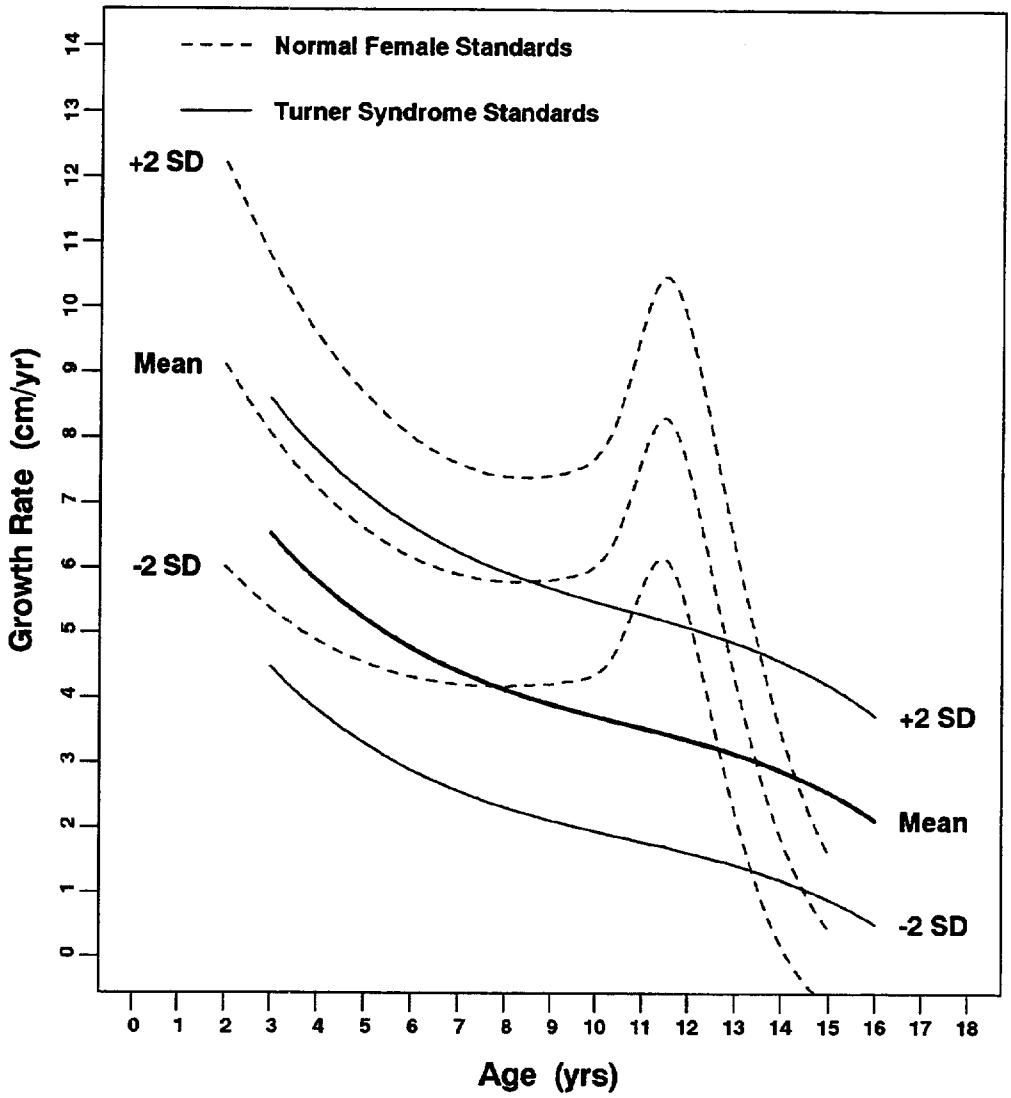

Figure 1: Growth Rate Standards for Turner Syndrome (Ranke MB et al.) and for Normal Females (Tanner JM and Davies 1985)

Detailed information regarding the growth of girls with Turner syndrome derives from a number of studies undertaken in the 1970's and 1980's. Several studies have shown a significant correlation of adult height of women with Turner syndrome with midparental height (the sex-adjusted average of the parental heights). An analysis of 64 patients (Brook CGD et al. 1974) revealed that the short stature of Turner syndrome women resulted from three major factors (after parental height was accounted for): intrauterine growth retardation, reduced growth rate (10%–25% of normal) during childhood, and absence of a pubertal growth spurt.

Similarly, Ranke et al. (1983, 1988) analyzed the spontaneous growth of 150 German girls and women with Turner syndrome. The mean final adult height was approximately 3 SD, or 20 cm, below the mean for adult women of similar ethnic background. This seminal study confirmed the conclusion that the short adult stature was the result of retarded intrauterine growth and marked stunting of postnatal growth, primarily between the ages of 3 and 14 years, during which time girls with Turner syndrome grow 15 cm less than their age-matched peers. The study found no difference in adult height between those with 45,X karyotype and whose those with other karyotypic forms of Turner syndrome.

Ranke noted that there is partial catch-up of height during a prolonged adolescent growth phase, although further adult height potential is lost during this period as well. They concluded that the short stature in Turner syndrome resulted primarily from the combined effects of intrauterine growth retardation and reduced growth between the ages of 3 and 14 years.

In 1985, Lyon et al. (Lyon AJ et al. 1985) created the growth chart specific for Turner syndrome that is in current use in this country. These curves represent the most comprehensive series of growth data currently available for Turner syndrome. They were developed by combining data from four European studies, comprising a total of 446 girls and women with Turner syndrome and added a further 534 data points from follow-up of their own patients, to compile the most comprehensive series of growth data currently available for Turner syndrome. The mean adult height of women in this study was approximately 143 cm. This is approximately 20 cm less than the mean for women of similar ethnic background. By analysis of the longitudinal growth data of their own patients, Lyon et al. calculated a correlation coefficient of 0.95 for the relationship between first measured height percentile (at age 3–12 yrs) and adult height percentile (at age 19–24 yrs). In other words, the childhood height of these patients strongly predicted their adult height. These growth curves, known as the Lyon curves (see Figure 2), provide useful normative data for the height of girls and women with Turner syndrome from the age of 2 years through adulthood, and also enable a reasonable projection of adult height for an untreated patient with Turner syndrome.

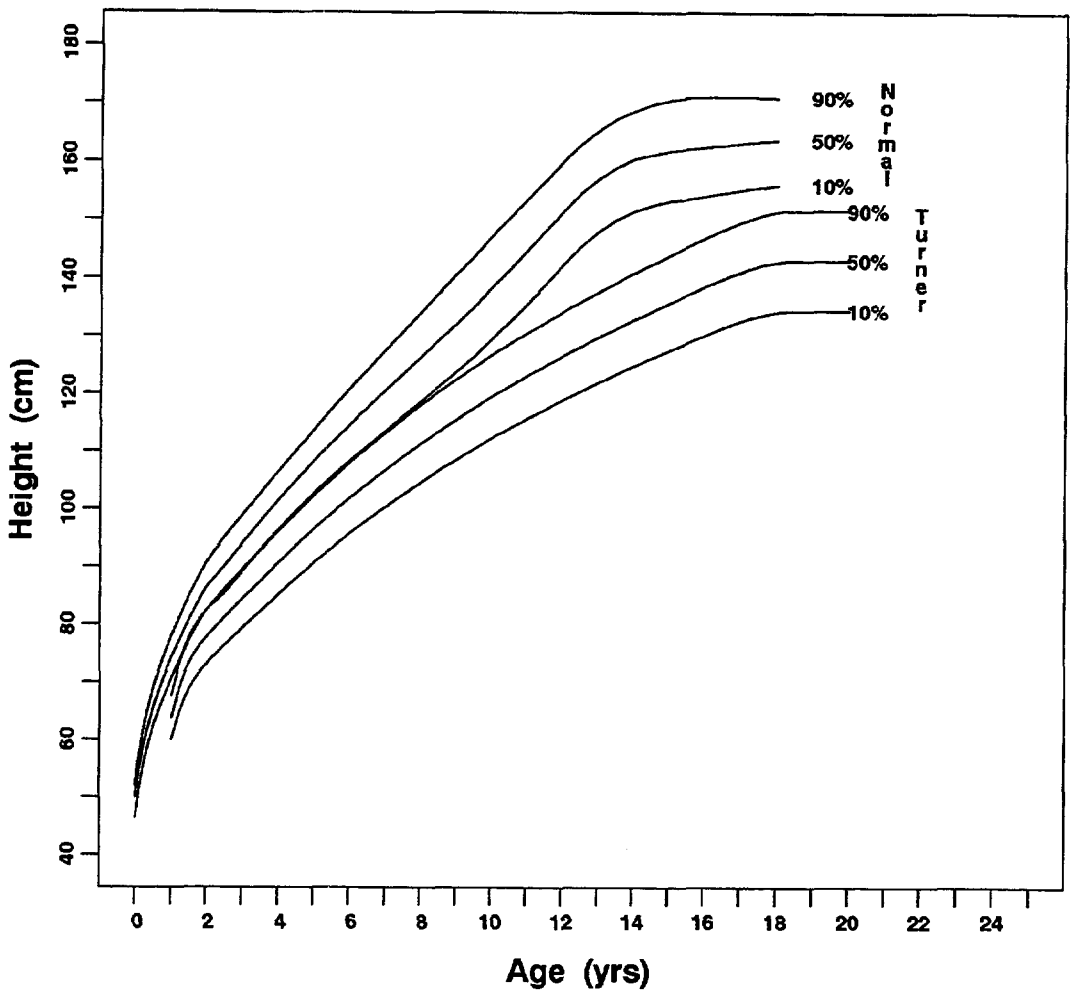

Figure 2: Height Standards for Turner Syndrome and Normal Females (Lyon AJ et al. 1985)

The question of comparability of the data gathered by the European investigators described above to the spontaneous growth of girls with Turner syndrome in North America was analyzed and reviewed by Lippe et al. (Lippe B 1991, 1993), using the U.S. untreated Turner database compiled by Genentech investigators. This study determined that the growth of untreated North American patients with Turner syndrome closely followed the growth curves previously published by Lyon et al., and that the initial degree of height deficit strongly predicted the eventual deficit in adult height. The mean adult height of patients who received no growth hormone or anabolic steroids but received variable estrogen therapy was 144.0 ± 6.3 cm (mean ± SD) (Lippe 1993), similar to the cumulative published U.S. experience of approximately 143 cm. It was noted that the adult heights of women with Turner syndrome were not influenced, either positively or negatively, by estrogen treatment (Lippe B 1991).

Thus the average adult height of women with Turner syndrome in the United States who did not receive growth promoting therapy is about 4'8", with a range (±2 standard deviations) of 4'4" to 5'0". This contrasts with the average normal adult female height of 5'4" (range 4'11" to 5'9"). Thus, the mean height deficit in Turner syndrome in the U.S. is also approximately 20 cm (8"), identical to the deficit reported for European women with Turner syndrome.

The short adult stature typical of Turner syndrome is notable for both ethnic and parental influences on adult height in a pattern similar to that observed for non-Turner syndrome women. Final height has been reported for young women with Turner syndrome from a number of different countries and ethnic backgrounds (see Table 1). Adult height of women from Scandinavian countries (mean 145–147 cm) is greater than that of women from Mediterranean countries (mean 142–144 cm) and those from Oriental countries (Japan, mean 138 cm). A consistent finding is the fact that the mean height of adult women with Turner syndrome is approximately 87%–88% of the mean adult height of women of the same ethnic background (see Table 2). Additionally, adult height of women with Turner syndrome correlates strongly with mid-parental height in most studies, such that girls with taller parents achieve greater adult heights than those with shorter parents. Regardless of ethnic background, there is an approximate difference of 20 cm (8") between mid-parental target height and the adult height attained by women with Turner syndrome.

Table 1

Final Height of Patients with Turner Syndrome Not Treated with Growth Hormone

Country	n	Final Height (cm) Mean ± SD (Range)	Concomitant Treatments	Comments
Belgium Massa 1990	34	143.4 ± 5.6	Estrogen (some)	No difference in FH between patients with spontaneous vs. induced puberty.
Canada Park 1983	28	142 ± 7.6	Estrogen	Growth below but parallel to percentiles from 5 to 12 yr then declined.
Denmark Naeraa 1990 a, b	76 16	146.8 ± 5.8 147.6 ± 4.4	Estrogen Androgen	FH correlated with MPH.
UK Brook 1974	64	142.5	Estrogen	FH correlated with MPH. No estrogen effect on FH.
Europe Ranke 1994	661	144.3 ± 6.7	Estrogen and/or oxandrolone > 14 yr or > 20 yr	No difference between patients treated with ox > 14 yr vs > 20 yr. Strong correlation between FH and MPH.
Finland Lenko 1988	76	145.5 ± 5.7	Estrogen, androgen, or combined	No significant FH differences between estrogen, androgen or both. FH corr. with MPH.
France Rochiccioli 1994	216	141.5	Possible estrogen	FH correlated with MPH.
Germany Ranke 1988	14	146.8 ± 5.8	None	Loss of growth potential observed between 3–14 yr.
Israel Lev-Ran 1977	12 15 13	143.2 143.3 144.1	None Androgen Estrogen	No FH differences between groups.
Israel and Italy Cohen 1995	45 30		Estrogen Estrogen	FH correlated with MPH. Subgroup (n = 4) with Xq– taller than other karyotypes.
Italy Bernasconi 1994	105	142.4 ± 7.0	Possible estrogen	Strong correlation between FH and MPH. No significant diff. in FH in spontaneous, induced, or no puberty.
Japan Hibi 1991	45 11	141.9 ± 3.6 137.5 ± 3.7	Androgen None	Spontaneous puberty group shorter than no spont. puberty-androgen group.
Netherlands Rongen-Westerlaken 1991	46	146.9	Estrogen	No difference in FH with or without estrogen.
United States Lippe 1993	84	144.0 ± 6.3	Estrogen after 18 yr	No effect of estrogen on FH. Strong correlation between initial and final height SDS.

FH = final height.
MPH = mid-parental height.

Table 2

Comparison by Country of Turner
Adult Height with Average Female Adult Height[a]
Mean (cm)

Country	Turner Syndrome	Average Female	Ratio[b]
Germany	146.8	169.0	0.87
Denmark	146.8	166.8	0.88
Switzerland	143.3	166.0	0.86
Sweden	143.6	165.5	0.87
Finland	146.8	165.3	0.88
U.S. (Database)	144.0	163.7	0.88
U.S. (Sybert)	146.9	163.8	0.90
England	143.0	162.2	0.88
France	141.4	163.0	0.87
Japan	136.4	156.0	0.87

[a] Derived from Rochiccioli.

[b] Ratio of mean adult height of Turner syndrome women to mean height of non-Turner syndrome women.

ETIOLOGY OF SHORT STATURE IN TURNER SYNDROME

The cause of the growth failure in Turner syndrome has not been fully elucidated. It is likely that the poor growth beginning early in life is multifactorial.

A few patients with simultaneous occurrence of growth hormone deficiency and Turner syndrome have been reported (Brook CGD 1978; Faggiano M et al. 1975). However, the general consensus of studies available to date indicates that the majority of patients with Turner syndrome do not have clearly demonstrable defects of growth hormone secretion. Comprehensive evaluation of growth hormone secretion in patients with Turner syndrome has produced varied results, which may in part reflect methodological differences between studies. The published data indicate reduced, normal, or even increased growth hormone secretion in patients with Turner syndrome, highlighting the fact that there is no obvious and reproducible endocrine defect in these patients. For example, the study of Ross et al. revealed normal spontaneous growth hormone secretion in patients with Turner syndrome aged 2 to 8 years, but significantly reduced spontaneous growth hormone secretion in patients aged 9 to 20 years, compared with controls matched for bone age (Ross JL et al. 1985). This study demonstrated a significant age-related reduction in mean 24-hour spontaneous growth hormone concentration, however responses to arginine and insulin stimulation were within the normal range. Other studies also have demonstrated

normal responses to growth hormone provocative testing. In a limited number of patients who demonstrated reduced growth hormone secretion in response to provocative testing, repeat testing after estrogen priming produced normal results. In addition, Mauras et al. demonstrated significant increases in spontaneous growth hormone secretion in response to low dose ethinyl estradiol therapy in these patients (Mauras N et al. 1989). Thus, it seems likely that there may be a relative growth hormone insufficiency during the pubertal years at a time when estrogen deficiency is common. Similarly, serum IGF-I concentrations are reduced in adolescents with Turner syndrome and increase in response to estrogen replacement therapy.

The studies described above do not explain the poor prepubertal growth or the reduced pubertal growth spurt in the patients with Turner syndrome who do undergo spontaneous puberty. Factors other than estrogen deficiency likely also influence growth hormone secretion in Turner syndrome. One study noted an inverse relationship between spontaneous growth hormone levels and percentage of ideal body weight of patients with Turner syndrome at the time that puberty would be expected to occur (Cianfarani S et al. 1994), suggesting that the reduced growth hormone secretion seen in some patients with Turner syndrome may in part be due to obesity. In this study the mean nocturnal growth hormone concentrations of patients with Turner syndrome were intermediate between those of controls and a group of patients with classical growth hormone deficiency.

The above studies underscore the uncertainty regarding the pathogenesis of short stature in Turner syndrome. Other defects proposed to contribute to the growth disorder of these patients include their well-recognized but subtle skeletal dysplasia (perhaps related to the prenatal lymphedema) (Horton WA 1990; Lubin MB et al. 1990). There are a number of well described skeletal abnormalities, in addition to a number of less common defects, including thinning of the parietal bones, pectus excavatum (in addition to the more classical "shield chest"), "drumstick" appearance of the distal phalanges, short 4 and/or 5th metacarpals and/or metatarsals, pes cavus, midfacial hypoplasia and irregular tibial metaphyses (Lubin MB et al. 1990). There is evidence that long bone growth may be more impaired than vertebral growth, resulting in short-leggedness.

The growth defect of patients with Turner syndrome appears to be generalized, since not only the bones, but also other tissues and organs, are small. This

finding suggests a generalized growth retardation affecting all tissues, including the skeleton. Many of these seemingly disparate defects may in fact be attributable to lymphatic system malformations and obstruction with associated intrauterine edema (van der Putte SJC 1977). Lymphatic distention can cause compression of surrounding tissues, potentially leading to a restrictive effect on developing ossification centers, resulting in the skeletal dysplasia and defective growth of other tissues characteristic of the syndrome.

Some of the somatic features of Turner syndrome, including the short stature, may result from absence or dysfunction of specific genes. Deletions in the Xp21→Xpter region are associated with short stature (Disteche CM et al. 1986). Such possible "stature-determining" genes located on the distal short arm of the X chromosome likely escape inactivation and have Y chromosomal homologues, so that normal males and females have two active copies of these genes. The absence of the second active copy in patients with Turner syndrome may explain some of the characteristic abnormalities. The concept that there are growth determining genes on the X and Y chromosomes is supported by a number of clinical observations, including the fact that individuals with 46,XY gonadal dysgenesis are of normal stature and that those with 47,XXY and 47,XYY karyotypes have tall stature.

In summary, although there is low secretion of growth hormone and IGF-I in adolescent girls with Turner syndrome, this likely reflects their estrogen deficiency, rather than a defect in the neuroendocrine regulation of growth hormone secretion. Since growth failure typically precedes the decline in growth hormone and IGF-I concentrations, the defective childhood growth in Turner syndrome is not fully explained by abnormalities of the growth hormone/IGF-I axis. Available data suggest that short stature in Turner syndrome is due to multiple causes, including skeletal dysplasia, lymphedema, and genetic abnormalities. These are compounded by insufficiency of growth hormone secretion during the peripubertal period. It is notable that although there may be subtle alterations of growth hormone secretion, girls and women with Turner syndrome are uniformly short, regardless of their growth hormone secretion status.

GROWTH HORMONE THERAPY IN TURNER SYNDROME

EARLY TRIALS OF GROWTH HORMONE THERAPY IN TURNER SYNDROME

Because of the extreme short stature characteristic of Turner syndrome, the condition has long been considered a natural target for growth promoting

therapies, including the use of growth hormone. Treatment of Turner syndrome with human pituitary growth hormone began in the 1960's (Tzagouris M 1969; Wright JC et al. 1965; Hutchings JJ et al. 1965; Soyka LF et al. 1964), and by the early 1970's, it was clear that growth hormone could increase growth rate in these patients (Escamilla R 1973; Tanner JM et al. 1971). However, due to limited supplies of human pituitary-derived growth hormone, experience with growth hormone therapy in Turner syndrome was limited. This situation changed dramatically with the availability of somatrem (recombinant methionyl human growth hormone) and somatropin (recombinant human growth hormone). Clinical trials were initiated in 1983 to address the issues of safety and efficacy of treatment with somatrem or somatropin in girls with Turner syndrome.

RATIONALE FOR GROWTH HORMONE THERAPY IN TURNER SYNDROME

Since patients with Turner syndrome do not have a clear deficiency of endogenous growth hormone secretion, the questions arise as to why consider GH therapy in this population and why an increase in growth rate occurs with GH treatment. Perhaps the most compelling reason to test the hypothesis that GH treatment would improve the growth of girls with Turner syndrome was the demonstrated ability of GH to promote statural growth in a variety of growth disorders.

However, there was reason to believe that the response to GH would be less in Turner syndrome than that seen in other patient groups. A feature of the multifactorial growth disturbance in Turner syndrome is a defect at the peripheral level, in the tissue response to growth hormone, as opposed to an insufficiency of growth hormone secretion. This defective tissue response, perhaps representing a degree of end organ resistance, may be due to the mild epiphyseal dysplasia, as discussed above. It would thus be expected that these patients would demonstrate a reduced response to administration of standard doses of exogenous growth hormone, an expectation which was confirmed in the earliest clinical trials.

The clinical and scientific rationale for long-term growth hormone treatment of patients with Turner syndrome to adult height arose from studies documenting a significant increase in growth rate with the use of somewhat higher doses of GH than those used in classical GH deficiency. These clinical observations led to the expectation that growth hormone therapy could potentially increase the final height of patients with Turner syndrome to within the lower end of the normal female reference range. Carefully monitored clinical trials were initiated by

Genentech, Eli Lilly, and others to assess safety and efficacy of such GH therapy in Turner syndrome.

EFFICACY OF GROWTH HORMONE IN INCREASING FINAL HEIGHT IN TURNER SYNDROME

Several reports now describe the benefits of growth hormone with respect to final height in Turner syndrome. It is notable that there is substantial variation in the mean final heights achieved by treated patients in these studies. Factors that may contribute to the variability of the results include age of initiation of GH therapy, duration of GH therapy, GH dose and injection schedule, age of initiation of estrogen replacement, estrogen dose, and the use of oxandrolone co-therapy.

Most of the reported studies have used the pretreatment adult height projection method, often applied to the Lyon curves, to assess the gain in adult height due to GH treatment. Occasional studies have used alternative height projection methods, some of which have been shown to be less accurate (see Appendix A).

In published reports on the effect of GH treatment in Turner syndrome, the definition of final height varies, with most studies reporting "final" height for patients with further growth potential. Many reports are incomplete and describe only the small subset of enrolled patients who reach adult height first. These patients generally begin GH treatment at an older age and therefore complete therapy after only a relatively short duration of treatment. Therefore, extrapolation of these results to the more optimal treatment approach of beginning GH therapy at a younger age may lead to misleading conclusions about the potential benefit of GH therapy.

The effect of growth hormone treatment on final heights of patients treated at younger ages and for longer duration of therapy is addressed in the Genentech and Lilly studies in this report. As described below, the results of these studies are consistent with each other as well as those in the literature when studies with similar study protocols are compared.

The studies in the literature, summarized in Table 3 by country, can be categorized according to study design factors affecting outcome. Only a few studies (e.g., Germany and Japan) involved patients treated at an early age, as in the Genentech and Lilly studies (i.e., mean < 11 years). These studies, with

several years of GH therapy prior to the initiation of estrogen replacement, have demonstrated the best adult height outcomes (mean increases of 6–9 cm).

Several studies specified initiation of estrogen at an early age relative to the initiation of GH therapy (Australia, Canada, Netherlands). These studies reported the least increases in adult height; however, some of these results may have been underestimated due to the inaccurate projection methods used (discussed in Appendix A).

A large number of studies report data for patients treated at a later age with GH, in some cases representing only the first patients to complete the protocols. These include studies from Belgium, France, Italy, Scotland, and several pooled European countries. These studies are notable for having a shorter mean duration of therapy. Nonetheless, mean increases of 5 or more cm in adult height were reported in most studies.

A number of studies have more than one factor impacting outcome. One example is the UK study which had limited duration of GH therapy, relatively early initiation of estrogen, and a substantially lower dose of GH than that used in other studies. Not surprisingly, these patients showed minimal gains. Interestingly, other patients in the same study, treated earlier and longer with GH but not yet at final height, have already achieved a mean adult height increase of >5 cm.

The cumulative results of these studies suggest that increases in adult height of 5 cm or more are generally achieved, and can even be exceeded if factors affecting outcome are optimized. The data from large registries (National Cooperative Growth Study, Kabi International Growth Study) confirm that these results are readily achieved in general practice.

Table 3

Studies with Adult Height Results in GH-Treated Turner Syndrome (Mean)

Study	Adult Height Gain (cm)	GH Age (yr)	Estrogen Age (yr)	GH Dose (mg per kg weekly)
Early GH, Later E				
U.S. Genentech 85-023	7.4 M, 8.4 L	9.1	15	0.375
U.S. Genentech 85-044	8.3 M, 8.4 L	9.4	15	0.375
Germany (some + Ox)	4.5–9 L	10–11	NA	0.185–0.33
Japan	6–8 NS	10	NA	0.185, 0.37
Earlier E				
U.S. Genentech 85-044	5.9 M, 5.1 L	9.6	12	0.375
U.S. Lilly GDCI	NA	11.1	8 or 13.5	0.27, 0.36
Canada Lilly GDCT	5.4 C	11.7	13	0.3
Australia	3.7 L	11	11	0.44
	5.5 L	11	13	0.44
Canada	NA	12	13	0.3
Netherlands	2.6 R	NA	12	0.3–0.44
Late GH				
U.S. Genentech 85-044	5.0 M, 4.7 L	12.7	14	0.375
Belgium	8.5 L	12	14	0.37
	6.9 L	15	16.5	0.3
France (some + Ox)	5–6 H	13	NA	0.28
Italy	5.9 H	13	NA	0.37
Scotland	0.7 NS	NA	NA	NA
Europe—Lilly	3.5 R	12	14.5	0.289
Low Dose GH				
United Kingdom	1.7 L	12	13	0.22
	5.3 L	11	13	0.26
Registries				
U.S. NCGS (some + Ox)	5.3 L	12	NA	NA
Europe KIGS (some + Ox)	6.1 L	12	14	0.26
GH + Ox				
U.S. Genentech 85-023	9.8 L	9.9	15	0.375
Sweden	6.6 L	12	NA	0.26
	5.1 L	12	13	0.26
	8.9 L	12	NA	0.26
	3.8 L	12	12	0.26

GH: growth hormone
E: estrogen
OX: oxandrolone
C: vs. randomized controls (ANCOVA)
M: vs. matched controls (ANCOVA)
L: vs. projected adult height using Lyon standards
R: vs. projected adult height using Ranke standards
H: vs. historical data for untreated Turner syndrome
NS: vs. projected adult height, standards not specified
NA: not available

USE OF RANDOMIZED AND HISTORICAL CONTROLS

Randomized Studies

The use of randomized controlled trials is generally accepted as the desirable approach for the evaluation of therapeutic effect, especially in short term clinical trials. In such a study, either concurrent non-treated controls or placebo-treated controls would form the comparison group.

Unique circumstances relevant to this point exist for the issue of growth hormone therapeutic effects in Turner syndrome when final height is used as the endpoint. Growth studies tend to be prolonged, especially if adult height is the primary endpoint and treatment is begun at an early age. Recruiting and maintaining patients in such prolonged studies, especially those involving placebo injections, is extremely difficult. In addition, the necessity for careful matching of treated and control groups for important baseline characteristics can be jeopardized by excessive dropout rates in placebo-controlled studies. For these reasons, it has been difficult to recruit placebo-controlled trials of GH use in children to adult height and maintain them successfully to completion.

The Food and Drug Administration Endocrine Advisory Committee, in September 1987, recommended that final height should be the primary endpoint for efficacy and that the randomized, controlled trial, preferably placebo-controlled, was the ideal study design. In response to this recommendation, Genentech extended two previously initiated clinical trials of GH in Turner syndrome to adult height. These trials had randomized untreated controls for the initial 12–21 months. Eli Lilly initiated several trials of GH treatment in Turner syndrome to adult height. Of the three North American Lilly-sponsored studies, the two nearing completion are presented in this briefing document. These include one study using randomized non–GH-treated controls and one dose-response study in which there were placebo-treated controls for the initial 18 months. The third study, which still has open enrollment, continues under the supervision of an independent data monitoring board.

Historical Controls

Another valid method of analyzing outcomes of long-term studies is the use of historical controls, provided they are properly obtained and are comparable to the test group. A systematic and comprehensive study of historical control subjects from the U.S. Turner syndrome population was undertaken. The purpose of building this national, multicenter database of untreated Turner

syndrome was to serve as a source of historical controls, as well as to address through careful analysis issues regarding the use of the Lyon standard curves for Turner syndrome in the U.S. for plotting heights and calculating projected adult height.

The use of the standards developed by Lyon et al. for the analysis of growth of American girls with Turner syndrome is dependent upon showing that the standards are accurate for the height of American girls with Turner syndrome at any age, including adult height. The Genentech U.S. Untreated Turner Database was assembled using historical control data from fourteen institutions throughout the United States, with additional data obtained from the two Genentech clinical trials and the Genentech National Cooperative Growth Study. The resultant database contains 3448 height measurements from 1363 patients, including adult height measurements for 84 patients. Their mean adult height was 144.0 ± 6.3 cm, which was not statistically different from the Lyon average of 143.0 ± 6.7 cm. The mean height standardized for age (i.e., SD score) was 0.05 ± 0.97, remarkably close to the expected 0.0 ± 1.0. These data confirmed that the Lyon Turner standards are appropriate for use in the U.S.

It is important to recognize that ethnic background and parental heights still have a strong influence on height, as noted above. The effect of these factors with respect to the standard curves is to place a subject on a higher or lower percentile, both for childhood and adult heights. Analysis of the U.S. Turner database indicated that most of the effect of the parents' heights on adult height is already accounted for the childhood height. In other words, a Turner child of tall patients would not only be expected to be a relatively tall adult by Turner standards, but also to be tall for Turner syndrome standards as a child at all ages.

The question is often raised regarding the possibility of secular trend affecting the applicability of these curves to present-day patients. Secular trend refers to changes in average heights, which can be positive or negative, due to changes in environmental or other factors over time. According to data from the National Health Survey (National Health Survey Series 11, No. 238. DHHS Publication No. [PHS] 87-1688, October 1987), a mean increase in adult height of the general population of only 0.3 cm was found over one decade, which was not statistically significant. Similarly, heights for 1296 untreated Turner patients in the U.S. database showed no significant trend in height over a four decade period. The mean year of birth for subjects used as matched controls was only

10 years earlier than the mean year of birth for treated subjects in the Genentech studies.

For the analysis of the Genentech clinical trials, historical controls were used for comparison with treated patients. Guidelines for the use of such controls are specified in the FDA Information Sheet for IRBs and Clinical Investigators on Drug Study Designs. These guidelines specify that the "use of historical controls has been reserved for special circumstances, notably cases where the disease treated has a predictable mortality (a large difference from this usual course would be easy to detect) and those in which the effect is self-evident...[investigators] need to be sure that historical controls are comparable to the treated subjects with respect to variables that could effect outcome." Accordingly, historical controls were used in the adult height analyses for the Genentech studies in Turner syndrome, provided they never received growth-promoting therapy and were matched to patients in the treated groups for baseline age, with careful consideration of the age at which estrogen therapy was first given.

A second method of adult height analysis used in the Genentech studies involved comparisons of adult heights with each patient's pretreatment projected adult height, as is often used in the published literature. In order for projected heights to be accurate, the shape of the standard curves needs to be accurate, for the method relies on data showing that patients' percentiles in childhood are highly correlated with their percentile as an adult.

Analysis of the U.S. Genentech Turner database indicated that using the Lyon curves, the mean childhood height (SD score) accurately predicted the observed adult height after age 18 (SD score) with a mean change of -0.4 ± 0.6 SD, which was not statistically significant. The mean baseline projected adult height for 56 subjects followed longitudinally was 144.1 cm, while the mean observed adult height was 143.8 cm. The strong correlation ($r = 0.80$) validated the projection method as a way of using a group of patients as their own controls.

The accuracy of the projection method suggests that there is no bias in the curves generated by Lyon et al. Bias might occur in the generation of standard curves if shorter or taller cases are omitted at either younger or older ages. This appears to be the case with the standard curves of Ranke et al., in which systematic error in the curves leads to consistent overprediction of projected height when using these curves. It should be noted that the tendency of certain

methods to overpredict leads to, if anything, an underestimation of the effect of therapy when comparing final height with pretreatment projected adult height. None of the Turner projection methods analyzed to date have shown evidence of downward bias.

Other Height Prediction Methods

The use of bone aged-based height prediction methods, such as those of Bayley-Pinneau, Tanner-Whitehouse, or Roche-Wainer-Thissen, is widely regarded as the least reliable way of predicting adult height for girls with Turner syndrome. This is contrary to the case for normal statured subjects or certain short-statured populations, where these methods have been found to be accurate. Since the skeletal maturation of girls with Turner syndrome appears qualitatively different from that of normal girls, and there are no reference standards for skeletal maturation in Turner syndrome, it is not surprising that predicted heights based on bone age are unreliable.

Controls Summary

Randomized controls and validated historical controls are accepted methods for the assessment of increase in adult height of GH-treated subjects with Turner syndrome. Consideration of important factors such as mid-parental height and baseline height and age are important for both types of studies. The projection methods commonly used for non-randomized controlled trials must employ an appropriate method and appropriate standards to be acceptable. The lack of secular trend and downward or upward bias supports the use of the Lyon standards for patients with Turner syndrome in the U.S.

BACKGROUND SUMMARY

Turner syndrome is a relatively common congenital disorder caused by deficiency of X-chromosomal material. The growth disturbance of patients with Turner syndrome begins in utero, worsens during childhood and continues through adolescence. The etiology of growth failure likely includes the absence of X-chromosomal stature-determining genes, the effects of prenatal lymphedema due to abnormal development of lymphatic vessels, some degree of skeletal dysplasia, and a contribution from reduced growth hormone secretion during adolescence, likely influenced by the estrogen deficiency prevalent at this time of life in these patients.

Short stature is virtually universal in this condition, with the mean adult height of affected women being approximately 20 cm (8") less than the mean for

unaffected women of similar ethnic background. The accompanying documents address the efficacy and safety of recombinant human growth hormone in the treatment of short stature in patients with Turner syndrome.

Background References

Bernasconi S, Larizza D, Benso L, Volta C, Vannelli S, Milani S, Aicardi G, Berardi R, Borrelli P, Boscherini B, Pasquino AM, Buzi F, Cacciari E, Mazzanti L, Cavallo L, Chiumello G, Nizzoli G, Dammacco F, Deluca F, De Matteis F, de Sanctis C, Matarazzo P, de Sanctis V, DiMaio S, Gabrielli O, Giovanelli G, Balestrazzi P, Klain U, Morabito F, Mazzilli G, Pintor C, Radetti G, Rigon F, Licursi A, Saggese G, Severi F, Lamanna S, Spada A, Stoppoloni G, Tato L, Tonini G. 1994. Turner's syndrome in Italy: familial characteristics, neonatal data, standards for birth weight and for height and weight from infancy to adulthood. Acta Paediatr Scand 83:292-298.

Brook CGD, Murset G, Zachmann M, Prader A. 1974. Growth in children with 45,X0 Turner's syndrome. Arch Dis Child 49:789-795.

Brook CGD. 1978. Growth hormone deficiency in Turner's syndrome. N Engl J Med 298:1203-1204.

Cianfarani S, Vaccaro F, Pasquino AM, Marchione SA, Passeri F, Spadoni GL, Bernardini S, Spagnoli A, Boscherini B. 1994. Reduced growth hormone secretion in Turner syndrome: is body weight a key factor? Horm Res 41:27-32.

Cohen A, Kauli R, Pertzelan A, Lavagetto A, Roitmano Y, Romano C, Laron A. 1995. Final height of girls with Turner's syndrome: correlation with karyotype and parental height. Acta Pediatrica 85(5):550-554.

Disteche CM, Casanove M, Saal H, Friedman C, Sybert V, Graham J, et al. 1986. Growth hormone therapy in Turner's syndrome: one versus two daily injections. J Clin Endocrinol Metab 79:489-494.

Escamilla R. 1973. Non-hypopituitary dwarfs and human growth hormone therapy. In: Advances in human growth hormone research, edited by Raiti, S.Washington, D.C.U.S. Department of Health, Education and Welfare p 766-785.

Faggiano M, Minozzi M, Lombardi G, Carella G, Criscuolo T. 1975. Two cases of the chromatin positive variety of ovarian dysgenesis (XO/XX mosaicism) associated with hGH deficiency and marginal impairment of other hypothalamic-pituitary functions. Clin Genet 8:324-329.

Grunerio de Papendieck L, Iorcansky S, Coco R, Rivarola M, Bergada C. 1987. High incidence of thyroid disturbances in 49 children with Turner syndrome. J Pediatr 111(2):258-261.

Hall JG, Gilchrist DM. 1990. Turner syndrome and its variants. Pediatric Clinics of North America 37(6):1421-1440.

Hibi I, Tanae A, Tanaka T, Yoshizawa A, Miki Y, Ito J. 1991. Spontaneous puberty in Turner syndrome: its influence, influence on final height and endocrinological features. In: Ranke MD, Rosenfeld RG, editors. Turner syndrome: growth promoting therapies. Amsterdam:Elsevier Science Publisher 75-81.

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.

Hook EB, Warburton D. 1983. The distribution of chromosomal genotypes associated with Turner's syndrome: livebirth prevalence rates and evidence for diminished fetal mortality and severity in genotypes associated with structural X abnormalities or mosaicism. Hum Genet 64:24-27.

Horton WA. 1990. Growth place biology and the Turner syndrome. In: Rosenfeld RG, Grumback MM, editors. Turner syndrome. New York:Marcel Dekker, Inc. p 259-266.

Hultcrantz M, Sylven L. 1995. Hearing problems in women with Turner syndrome. In: Turner syndrome in a life-span perspective. Albertsson-Wikland K, Ranke MB, editors. New York:Elsevier Science,B.V. p 249-257.

Hutchings JJ, Escanilla RF, Li CH, Forsham PF. 1965. Human growth hormone administration in gonadal dysgenesis. Am J Dis Child 109:318.

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.

Lev-Ran A. 1977. Androgens, estrogens, and the ultimate height in XO gonadal dysgenesis. Am J Dis Child 131:648-649.

Lippe B, Frane J, Genentech National Cooperative Study Group. 1991. Growth in Turner syndrome: the United States experience. In: Turner Syndrome: Growth promoting therapies, Ranke MB, Rosenfeld RG, editors. Elsevier Science Publishers B.V. (Biomedical Division) p 59-65.

Lippe B, Plotnick L, Attie K, Frane J. 1993. Growth in Turner syndrome: Updating the United States Experience et al. In: Basic and clinical approach to Turner Syndrome. Hibi I, Takano K, editors. Elsevier Science Publishers B.V. (Biomedical Division) p 77-82.

Lubin MB, Gruber HE, Rimoin DL, Lachman RS. 1990. Skeletal abnormalities in the Turner syndrome. In: Rosenfeld RG, Grumbach MM, editors. Turner syndrome. New York:Marcel Dekker, Inc. p 281-292.

Lyon AJ, Preece MA, Grant DB. 1985. Growth curve for girls with Turner syndrome. Arch Dis Child 60:932-935.

Massa G, Vanderschueren-Lodeweyckx M, Malvaux P. 1990. Linear growth in patients with Turner syndrome: influence of spontaneous puberty and parental height. Eur J Pediatr 149:246-250.

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, Nielsen J. 1990a. Standards for growth and final height in Turner's syndrome. Acta Paediatr Scand 79:182-190.

Naerra RW, Eiken M, Legarth EG, Nielsen J. 1990b. Prediction of final height in Turner's syndrome. A comparative study. Acta Paediatr Scan 79:776-783.

Palmer CG, Reichmann A. 1976. Chromosomal and clinical findings in 110 females with Turner syndrome. Hum Genet 35:35-49.

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

Ranke MB, Pfluger H, Rosendal W, Stubbe P, Enders H, Bierich JR, et al. 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.

Ranke MB. 1995. Growth hormone therapy in Turner syndrome. Horm Res 4 (suppl 3):35-41.

Rochiccioli P, Battin J, Bertrand AM, Bost M, Cabrol S, Le Bouc Y, et al. 1994. Final stature in cases of Tuner's syndrome treated with growth hormone. Arch Pediatr 1:359-362.

Rongen-Westerlaken C. 1991. The Effect of Growth Hormone Treatment on the Craniofacial Complex in Turner Syndrome.153-161.

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

Sculerati N, Ledesma-Medina J, Finegold DN, Stool SE. 1990. Otitis media and hearing loss in Turner syndrome. Arch Otolaryngol 116(6):704-707.

Silbert A, Wolff PH, Lilienthal J. 1977. Spatial and temporal processing in patients with Turner's syndrome. Behavior Genetics 7(1):11-21.

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.

Tanner JM, Davies PSW. 1985. Clinical longitudinal standards for height and height velocity for North American children. J Pediatr 107:317-329.

Tanner JM, Whitehouse RH, Hughes PCR, Vince FP. 1971. Effect of human growth hormone treatment for 1 - 7 years on growth of 100 children with growth hormone deficiency, low birth weight, inherited smallness, Turner's syndrome and other complaints. Arch Dis Child 46:745.

Turner HH 1938. A syndrome of infantilism, congenital webbed neck, and cubitus valgus. Endocrinology 23:566-574.

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

Ullrich O. 1930. Uber typische Kombinationsbilder multipler Abartung. Z Kinderheik 49:271-276.

Van der Putte SJC. 1977. Lymphatic malformation in human fetuses. A study of fetuses with Turner's syndrome or status Bonnevie-Ullrich. Virchows Arch A Pathol Anat Histopathol 376:233-246.

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

ADVISORY COMMITTEE MEETING: **TABLE OF CONTENTS**
NAME OF DRUG: **Growth Hormone—Turner Syndrome**

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ADVISORY COMMITTEE MEETING: **ITEM B**
NAME OF DRUG: **Growth Hormone—Turner Syndrome**

A. GENENTECH CLINICAL TRIAL OVERVIEW

CONTROLLED CLINICAL TRIALS

Genentech has sponsored two long-term, multicenter, historically controlled studies of the use of recombinant GH for the treatment of short stature associated with Turner syndrome (see Table 1). The primary endpoint of these studies is adult height. In the first study, all patients who completed at least 12 months under Protocol 83-002 were studied under Protocol 85-023. In the following discussions, 83-002 and 85-023 are treated as one study, referred to as Study 85-023. This second study is Study 85-044.

Genentech conducted the above trials to support Nutropin® [somatropin (rDNA original) for injection] for treatment of growth failure associated with Turner syndrome, NDA 20-656.

Nutropin® is a recombinant DNA-derived single chain protein of 191 amino acids which is biologically and chemically identical to human growth hormone of pituitary origin. Nutropin® is currently being marketed for children with growth hormone deficiency and also for growth failure associated with chronic renal insufficiency. Genentech has submitted an NDA for the use of Nutropin® in the long-term treatment of girls who have short stature associated with Turner syndrome. This NDA was submitted to FDA on September 29, 1995. This document is submitted to the Endocrine and Metabolism Advisory Committee in support of this NDA.

Table 1

Turner Syndrome Clinical Trials

Protocol No.	Enrollment Dates	Treatment End Date	Total Weekly Dose (mg/kg)	Treatment Group	n	Mean Baseline Age yr (range)	Maximum Length of Treatment (years) (As of 4/1/95)	Mean Exposure to Drug (years) (As of 4/1/95)
83-002[a]	8/83–6/84	10/85	0.375	Untreated	18	9 (5–12)	NA	NA
				oxandrolone	19	9 (4–12)	1.9	1.4
				GH + ox[b]	17	9 (5–12)	1.9	1.5
				GH	17	9 (5–12)	2.0	1.6
85-023[a]	4/85–10/85	11/94	0.375	Protropin	17	9 (5–12)	8.9	6.0
				GH + ox[b]	49	9 (4–12)	9.6	4.9
85-044	2/87–5/88	7/96	0.375	Untreated	9	11 (9–14)	NA	NA
				GH TIW	36	12 (8–16)	7.6	4.7
				GH daily[c]	81	11 (8–15)	7.5	4.6

[a] After all patients had completed at least 12 months in Study 83-002, continuing patients were studied under 85-023.

[b] GH + ox = GH plus oxandrolone.

[c] Includes previously untreated controls.

NA = Not applicable.

Study 85-023 used Protropin® (somatrem for injection). Study 85-044 used Nutropin® [somatropin (rDNA origin) for injection]. The FDA has agreed that a study using Protropin® in conjunction with a study using Nutropin® would satisfy the NDA requirement of two clinical studies, as Protropin® and Nutropin® have been shown to be substitutable.

The adult heights of the treated patients were analyzed according to treatment regimen (see Table 2) and compared with appropriate historical controls (described below). The most important differences between the treatment groups were the ages of initiation of GH and estrogen therapies (i.e., early vs. late). The terms "early" and "late" when applied to estrogen therapy are meant to be interpreted as relative to each other and not relative to common practice or any other standard. Subjects in Study 85-044 who were < 11 when starting GH therapy were prospectively randomized to receive estrogen therapy at either age 12 or age 15.

Table 2

Patient Groups in Studies 85-023 and 85-044

Group Study	Mean Baseline Age (yr)	Treatment Regimen	N Enrolled
Early Protropin			
85-023	9.1	Early GH+ late estrogen (at age > 14)	17
85-023	9.1	Early GH+ late estrogen (at age > 14) + oxandrolone	50
Early Nutropin (age < 11 years)			
85-044	9.6	Early GH+ early estrogen (at age 12)	27
85-044	9.4	Early GH, randomized to early estrogen, but received estrogen after age 14	3
85-044	9.4	Early GH+ late estrogen (at age 15)	30
Late Nutropin (age > 11 years)			
85-044	12.7	Late GH+ estrogen after 12 months	51
85-044	14.2	Late GH, only in study one year	6

The two clinical trials were restricted to patients with Turner syndrome confirmed by karyotype and a GH response of ≥ 7 ng/mL on a stimulation test. Other inclusion criteria included a height of ≥ 1 standard deviation (SD) below the mean for normal females, a pretreatment growth rate of < 6 cm/yr, and bone age ≤ 12 years.

Actual mean baseline height standardized for U.S. norms (height SD score) was –3.1 in Study 85-023 and –3.2 in Study 85-044. In both studies, baseline heights standardized for the Turner norms of Lyon et al. (Lyon AJ et al. 1985) were very close to the expected mean of zero with an SD close to 1.0 (-0.1 ± 0.8, $n = 188$). This close matching between the height distribution of the study population and the Turner norms indicates the lack of biased selection and supports the appropriateness of these standards for American Turner subjects. Patients with signs of puberty and those previously treated with GH or sex steroids therapy were excluded.

The age range in the two clinical studies represents the ages at which most Turner patients present clinically. In Study 85-023 the mean age was 9.2 years (range: 4.4 to 12.4 years). Approximately three-fourths of the girls in that study were 45,X, with the remainder having an abnormal X chromosome or mosaicism. The subjects in Study 85-044 had a mean age of 11.0 years (range: 7.8 to 16.4 years), and three-fifths of those girls had monosomy X.

STATISTICAL ANALYSIS OF ADULT HEIGHT

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 possible in the adult height analysis, all patients with a height measured after age 13.5 are used in the analysis of adult height regardless of whether they still had more growth potential as reflected by open epiphyses on X-ray. Since only measured heights are used in these analyses, this represents a conservative estimate of ultimate height.

The first analysis of adult height involved comparison of the actual achieved adult heights for treated subjects with actual adult heights of matched American untreated historical controls. The source of these control subjects was the Genentech U.S. untreated Turner syndrome database, obtained from primarily the same clinical investigators who participated in the clinical trials.

All available historical controls who had baseline ages within the same range as the patients from Study 85-023 were included. In each analysis, controls were required to be of appropriate age for the initiation of estrogen therapy. In addition, no subject was used as a control who had ever received androgen therapy. Finally, each control used was also required to have a height measurement after age 18 (to be compared with the most recent height of the

treated patients after age 13.5). As a result, the control patients were followed until they were notably older than the treated patients, which makes the estimates of the effects of GH treatment on adult height conservative. Note that all eligible control subjects were included without consideration of adult height outcome.

The comparisons were made using analysis of covariance, where the covariates were baseline age and height, karyotype, and mid-parental target height. In Study 85-044, two control groups were used to match the treated groups according to baseline age: under age 11 for the early GH group and over age 11 for the late GH group.

A second analysis of adult height compared the actual adult heights of treated subjects with their respective pretreatment projected adult heights. In this analysis, each patient serves as their own control. The pretreatment projected adult height of a patient is based on norms for height from a pool of untreated Turner syndrome subjects from four Western European studies (Lyon AJ et al. 1985). The use of these norms for projected adult height was first cross-validated by Lyon et al. using additional data from England. Subsequently, the use of the Western European norms for projected adult height was validated using the Genentech U.S. untreated Turner database (see Appendix A).

Comparisons of adult height (for this analysis defined conservatively as most recent height measured after age 13.5) were 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 for those who received GH alone and those who received the combination of GH plus oxandrolone. In Study 85-044, the comparison is between patients treated with early GH who were randomized to and received estrogen at age 12 and those who received estrogen at age 15.

ADVISORY COMMITTEE MEETING: **ITEM C**
NAME OF DRUG: **Growth Hormone—Turner Syndrome**

B. EFFICACY SUMMARY

B.1 STUDY 85-023

STUDY 83-002/85-023: THE EFFICACY AND SAFETY OF PROTROPIN® (SOMATREM FOR INJECTION) ALONE AND IN COMBINATION WITH OXANDROLONE IN ALLEVIATING GROWTH RETARDATION ASSOCIATED WITH TURNER SYNDROME

STUDY DESIGN

Study 83-002 was an open-label, randomized, controlled study to assess the safety and growth-promoting effects of GH 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 four study groups: untreated control, oxandrolone alone, GH alone, and the combination of GH and oxandrolone (GH + ox). The dose of GH 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 (Study 85-023) began April 2, 1985, and consisted of two treatment arms: GH alone and GH in combination with oxandrolone (GH + ox). As per a commitment to patients and investigators at the start of the study, the original untreated control and oxandrolone alone groups from Study 83-002 were switched to combination therapy (GH + ox), which provided the greatest short-term growth response in Study 83-002. The original combination (GH + ox) and GH alone groups continued with the same therapy as before. There was no interruption of therapy during the transition between studies. With the initiation of Study 85-023, the dose of oxandrolone was decreased from 0.125 to 0.0625 mg/kg/day orally due to excessive virilization on the higher dose.

Amendments to the study provided for the switch from intramuscular (IM) to subcutaneous (SC) injections; the change from TIW to daily injections in all patients in the GH group and one-half of the patients in the combination (GH + ox) group (randomly selected); and estrogen replacement therapy, which was withheld until patients were at least age 14 and treated with GH for at least 3 years. Estrogen was given as Premarin® (conjugated estrogens) 0.3 mg/day for 6 months, followed by 0.625 mg/day, with progesterone added at one year.

The protocol was further amended to provide for treatment and follow-up of patients until final adult height is achieved. American untreated Turner subjects were used as controls in adult height analyses.

EFFICACY RESULTS

Growth Rate vs. Concurrent Randomized Controls

Table 3 shows the growth rate results for the first year of Study 83-002/85-023 for each of the four treatment groups. Using analysis of covariance with baseline age as covariate, all differences between the four groups in first year growth rate were statistically significant ($p < 0.0001$, except GH versus oxandrolone $p = 0.0016$). Combination (GH + ox) therapy resulted in the greatest first year growth rate.

Table 3

Study 83-002/85-023
Growth Rate (cm/yr) and Bone Age Change (yr)
Mean ± SD (n)

Treatment Group	Growth Rate		Bone Age Change
	Prestudy	0–12 Month	Month 0–12
Control	4.2 ± 1.1 (16)	3.8 ± 0.9 (16)	0.6 ± 0.5 (16)
GH	4.5 ± 0.8 (17)	6.6 ± 1.2 (17)	1.0 ± 0.5 (16)
Oxandrolone	4.1 ± 1.0 (18)	7.8 ± 1.1 (18)	1.3 ± 0.5 (17)
GH + ox	4.3 ± 0.9 (17)	9.8 ± 1.4 (17)	1.6 ± 0.8 (16)

The mean change in bone age during the first year was significantly greater in the oxandrolone group (1.3 yr) and the combination (GH + ox) group (1.6 yr) compared with the untreated control group (0.6 yr) ($p \leq 0.001$ in both cases). The bone age advancement was significantly greater in the combination (GH + ox) group than in the GH group ($p = 0.012$) and was nearly significantly greater in the oxandrolone group than in the GH group ($p = 0.07$).

Thus, the increase in growth rate with combination (GH + ox) therapy was largely offset by the advancement in bone-age. In addition, the dose of oxandrolone used during the first phase of the study was associated with frequent virilization (see Safety Section). As a consequence, the dose was halved for the remainder of the study.

Analysis Populations for Adult Height Analyses

Table 4 summarizes the numbers of patients available for analysis in Study 85-023. Four patients were enrolled under the first study phase (Protocol 83-002) but were not studied under Protocol 85-023 and never received GH. One patient received combination (GH+ox) therapy in the first study phase, but did not enroll in Study 85-023. Nevertheless, this patient is included in this report as if she had entered Study 85-023 in order to include all patients who received GH or combination (GH+ox) therapy in either study. Patients with height after age 13.5 are used in the analysis of adult height. This age limit was used in order to include as many patients as possible, even though this makes the adult height analysis conservative.

Table 4

Study 85-023
Analysis Populations for Adult Height (n)

Treatment Regimen	Patients Enrolled	Patients with Height after Age 13.5
GH	17	17
GH+ox[a]	50	46
Total	67	63

[a] GH plus oxandrolone.

A total of 63/67 (94%) were at least age 13.5 when last measured and thus were used in adult height analyses. The four patients in Study 85-023 without a height measurement after age 13.5 were all in the combination (GH+ox) group.

Baseline and Estrogen Therapy Characteristics

Baseline (pretreatment) characteristics are presented in Table 5 for the 63 patients with heights measured after age 13.5. Table 5 also contains results for a group of American control patients (n=25). The controls used here were matched on the basis of baseline age with the GH group (and thus closely matched the combination (GH+ox) group). No patient in the GH group or the control group received estrogen therapy before age 14. As shown in Table 5, not all patients received estrogen therapy as of their last clinic visit.

Table 5

Study 85-023
Baseline and Estrogen Treatment Characteristics[a]
Mean ± SD (Range)

	American Controls n = 25	GH n = 17	GH + Ox n = 46
Baseline age (yr)	9.2 ± 1.7 (5.8 to 12.1)	9.1 ± 2.1 (5.4 to 12.4)	9.9 ± 2.3 (4.7 to 13.9)
Baseline height (cm)	117.1 ± 8.9 (101.1 to 138.0)	114.6 ± 9.5 (101.1 to 136.5)	117.5 ± 10.2 (91.4 to 141.0)
Mid-parental target height (cm)	164.2 ± 5.0	164.5 ± 3.7	162.4 ± 3.9
Karyotype (% 45,X)	60%	76%	78%
Age at estrogen treatment initiation (yr)	15.8 ± 1.8 (14.0 to 21.3) n = 22	15.2 ± 0.9 (14.0 to 17.0) n = 13	14.9 ± 0.9 (13.2 to 17.3) n = 32

[a] Treated patients have a height measurement after age 13.5; historical control patients have a height measurement after age 18.

There were no statistically significant differences between groups with respect to any of the characteristics in Table 5 except for age at initiation of estrogen therapy, which was greater in the controls than in either treated group. The greater age at estrogen therapy initiation in the control group results in a conservative assessment of the benefit of GH therapy.

Adult Height: Comparison with Matched Untreated American Controls

Table 6 summarizes the efficacy results of therapy for patients at least 13.5 years old when last measured. Using analysis of covariance for adult height as endpoint and baseline height and age, mid-parental height, and karyotype as covariates, the increase in adult height in the GH alone group in comparison with the control group was **7.4 cm** ($p < 0.0001$) with a 95% confidence interval (CI) from 4.6 to 10.2 cm. The increase in adult height in the combination (GH + ox) group by ANCOVA in comparison with the control group is **10.1 cm** ($p < 0.0001$) with a 95% CI from 7.8 to 12.4 cm.

Table 6

Study 85-023
Efficacy Results[a]
Mean ± SD (Range)

	American Controls n = 25	GH n = 17	GH + ox n = 46
Duration of GH therapy (yr)	NA	7.6 ± 2.2 (4.3 to 10.5)	5.9 ± 2.0 (2.4 to 10.8)
Most recent age (yr)	22.1 ± 3.1 (18.1 to 29.7)	18.0 ± 2.2 (15.1 to 23.4)	17.3 ± 1.7 (14.0 to 22.5)
Most recent height (cm)	144.2 ± 6.0 (135.1 to 156.7)	150.4 ± 5.5 (138.7 to 158.0)	151.5 ± 6.1 (140.4 to 164.9)
Pretreatment projected adult height (cm)	144.2 ± 5.6	142.0 ± 5.9	141.7 ± 5.8
Most recent height minus pretreatment projected adult height (cm)	0.0 ± 4.4 95% CI: −1.8 to 1.8	8.4 ± 4.5 95% CI: 6.3 to 10.6	9.8 ± 5.1 95% CI: 8.3 to 11.3
Most recent height: treated vs. U.S. controls by ANCOVA (cm)	NA	7.4 95% CI: 4.6 to 10.2	10.1 95% CI: 7.8 to 12.4

[a] Treated patients have a height measurement after age 13.5. Historical control patients have a height measurement after age 18.

Figure 1 shows the pretreatment and most recent heights for all patients in Study 85-023, including the four patients in the combination group who did not have a height measured after age 13.5. Figure 1 also shows that the pretreatment heights in both groups were primarily between the 10th and 90th percentiles for girls with Turner syndrome and were generally consistent with the norms for girls with Turner syndrome.

Eleven of 17 (65%) patients in the GH alone group and 29/46 (63%) patients in the combination group have most recent heights taller than 2.5 standard deviations below the mean for normal adult women. This contrasts with the fact that only 18% of untreated American women with Turner syndrome have heights taller than 2.5 standard deviations below the normal mean (149 cm).

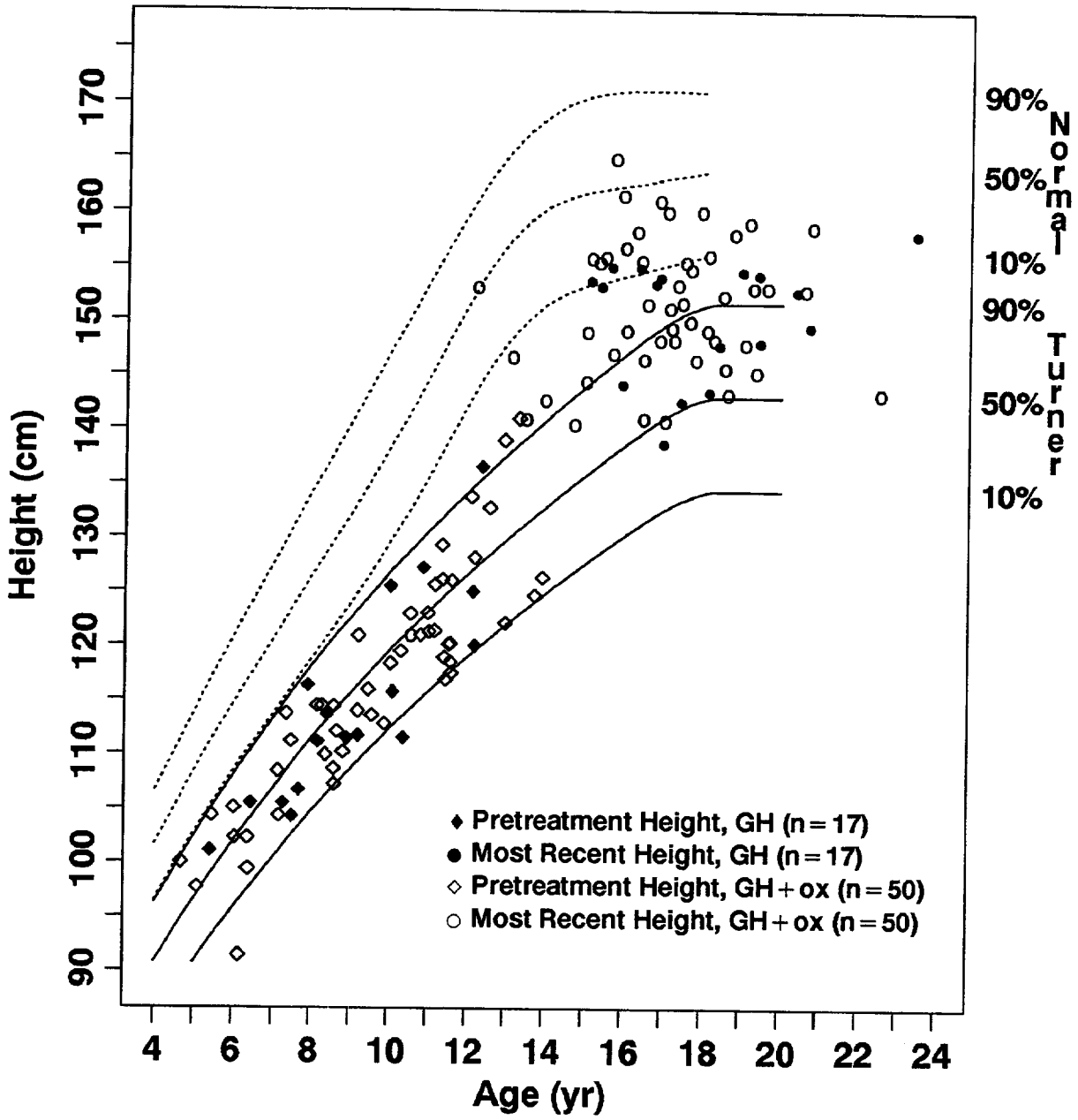

Figure 1: Pretreatment and Most Recent Heights for Study 85-023

Adult Height: Comparison with Pretreatment Projected Adult Height

For the patients who received GH alone, the mean difference between the most recent height and their pretreatment projected adult height is **8.4 cm**, with a 95% CI from 6.3 to 10.6 cm. For the patients who received combination (GH+ox) therapy who were at least age 13.5 when last measured, the mean difference between the most recent height and the pretreatment projected adult height is **9.8 cm**, with a 95% CI from 8.3 to 11.3 cm. These changes are similar to those found comparing with matched American controls (described above), of 7.4 and 10.1 cm, respectively. On the other hand, in the American control group, there was no statistically significant mean difference between the measured adult height after age 18 (144.2 cm) and the projected adult height (144.8 cm), as determined from heights obtained at ages 6 to 12 years (which confirms the height projection method using the Lyon standards).

Adult Height: Comparison of GH and Combination (GH+ox) Therapy

Using analysis of covariance with adult height as endpoint and baseline height and age, mid-parental height, and karyotype as covariates, the mean increase in adult height is 2.7 cm greater in the combination (GH+ox) group than in the GH group ($p = 0.037$), with a 95% CI for the difference between groups from 0.2 to 5.2 cm.

Adult Height Summary

The mean adult height achieved in the GH and GH+ox groups (150.4 cm, 151.5 cm, respectively) were significantly increased compared with matched controls. The mean increase by analysis of covariance was 7.5 cm and 10.1 cm, respectively.

Figure 2 shows the differences between the most recent height and the pretreatment projected adult height for each of the 63 patients treated with GH or combination (GH+ox) therapy who have height measurements after age 13.5. Figure 2 also shows these differences in the control group, who had most recent height measurements after age 18. Significant increases from projected heights were seen in both treated groups ($p < 0.0001$), while there was no significant difference in the control group.

Most recent height has exceeded the pretreatment projected adult height in 16/17 (94%) patients in the GH group and 42/46 (91%) patients in the combination (GH+ox) group who were over age 13.5. Some of the girls have further growth potential, as judged by their most recent bone age. A net gain of

greater than 5 cm (or 2 inches) was achieved in 14/17 (82%) patients in the GH group and in 38/46 (83%) patients in the combination (GH+ox) group. The majority of patients (63%) measured after age 13.5 attained heights within or near the normal range for adult women, which is rarely seen in untreated subjects with Turner syndrome.

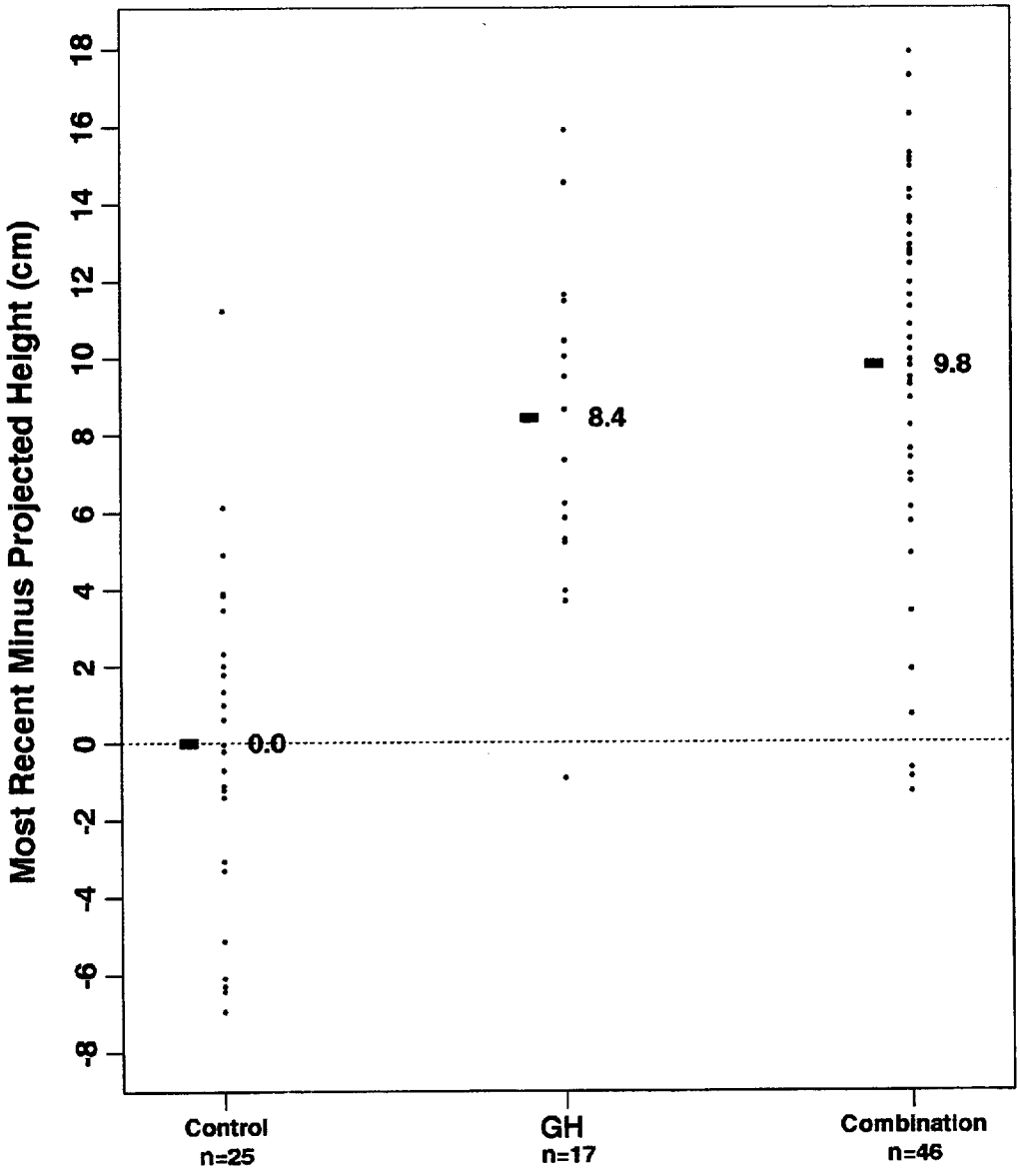

Figure 2: Most Recent Height Minus Baseline Projected Adult Height for Study 85-023 (Treated Patients > Age 13.5, Controls ≥ Age 18); "–" Indicates Mean

B.2 STUDY 85-044

STUDY 85-044: A PHASE III, MULTICENTER, OPEN-LABEL, RANDOMIZED STUDY OF THE EFFICACY AND SAFETY OF NUTROPIN® [SOMATROPIN (rDNA ORIGIN) FOR INJECTION] IN TWO DOSAGE SCHEDULES IN ALLEVIATING GROWTH RETARDATION ASSOCIATED WITH TURNER SYNDROME

STUDY DESIGN

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 GH in girls with Turner syndrome. The first 45 patients in the study were randomized to either the control group (n=9) or GH-treatment 3 times/week (TIW, n=36). All subsequent patients enrolled were treated with GH daily (n=72). The cumulative weekly dose of GH 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 GH daily during the second and subsequent study years. Thus, the total number of patients who received GH daily was 81. Patients initially enrolled in the TIW and daily groups continued with their original GH 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 estrogen replacement regimens depending on their baseline age (listed in Table 7). Patients under age 11 at the beginning of the study were randomized to begin estrogen therapy either at age 15 or at age 12. Three patients randomized to receive estrogen at age 12 but who did not receive estrogen until after age 14 were analyzed separately. Patients over age 11 at the beginning of the study were assigned estrogen therapy at Month 12 of GH therapy. Six patients who were over age 11 at baseline did not continue in the study beyond Year 1. Estrogen dosing was the same as in Study 85-023 (see p. 9).

The protocol was further amended to provide for treatment and follow-up of patients until final adult height was achieved. American untreated Turner subjects were used as controls in adult height analyses.

Efficacy Results

First Year Growth Rate

Patients in the Control and TIW groups were randomized; patients in the daily group were enrolled subsequently. There were no significant differences in the pretreatment growth rate among the three groups ($p > 0.05$). There was no significant difference between the prestudy and Year 1 growth rates for the untreated control group ($p = 0.36$). In contrast, there were significant increases in growth rate between pretreatment and Year 1 for both the TIW and daily groups ($p < 0.0001$). The mean growth rate for Year 1 was significantly greater in both the TIW (6.7 cm) and daily (8.1) treatment groups than in the control group (4.0 cm) ($p < 0.0001$). The 1.4 cm/yr difference in first year growth rate between the daily and TIW groups was statistically significant ($p < 0.0001$).

Analysis Populations for Adult Height Analysis

Study 85-044 examined both the effects of daily or TIW GH therapy and the age at initiation of estrogen therapy in patients with Turner syndrome. Patients treated daily with GH had a greater mean growth rate than patients treated TIW. Although treatment schedule did not have a significant effect on adult height in analysis of covariance, there was a significantly shorter duration of therapy in the daily treated group. The analyses below focus on groups according to GH and estrogen treatment therapy.

Table 7 summarizes the number of patients enrolled and the number available for the adult height analysis by treatment regimen. One-hundred-nine patients of 117 (94%) were available for adult height analysis.

Table 7

Study 85-044
Analysis Populations for Adult Height (n)

Treatment Regimen	Enrolled	Height after Age 13.5 and >1 yr GH
Early GH (age <11 years)		
Randomized to estrogen at age 12 (early estrogen)[a]	27	26
Randomized to estrogen at age 12 but received estrogen after age 14	3	3
Randomized to estrogen at age 15 (late estrogen)[b]	30	29
Late GH (age >11 years)		
Assigned estrogen after 12 months of GH therapy	51	51
≤ 1 year in study; no estrogen therapy	6	0
Total	117	109

[a] Includes 3 patients with spontaneous puberty.
[b] Includes 8 patients with spontaneous puberty.

Three patients randomized to receive estrogen at age 12 did not receive estrogen before age 13, but experienced spontaneous puberty before age 12. These patients are included in the estrogen at age 12 group. Three additional patients randomized to receive estrogen at age 12 did not receive estrogen until after age 14 and are analyzed separately. One patient randomized to receive estrogen at age 15 started estrogen therapy before age 14 (at age 13.6), but was not excluded. Eight patients in the estrogen at age 15 group experienced spontaneous puberty before estrogen therapy but were not excluded from that group.

One patient in the estrogen at age 12 group and one patient in the estrogen at age 15 group were less than age 13.5 when last measured. Only patients with height measurements after age 13.5 years are included in the analysis of adult height. Comparisons are made with matched American controls, as described beginning on page 6.

Baseline and Estrogen Treatment Characteristics

The baseline characteristics of those treated patients with heights measured after age 13.5 and their corresponding matched control groups are summarized in Table 8. There were no statistically significant differences in the early

GH-treated groups between the two treatment groups and their age-matched control group for any of the baseline characteristics in Table 8 except for age at initiation of estrogen therapy. Similarly, there were no statistically significant differences between the late GH group and its control group for any of the characteristics in Table 8 except for age at initiation of estrogen therapy, which was later in the control group.

Table 8

Study 85-044
Baseline and Estrogen Treatment Characteristics[a]
Mean ± SD (Range)

	Patients under Age 11 at Baseline			Patients over Age 11	
		Early GH			Late GH
	American Controls n = 14	Estrogen at Age 12 n = 26	Estrogen at Age 15 n = 29	American Controls n = 55	Estrogen at Month 12 n = 51
Baseline age (yr)	9.3 ± 0.8 (8.0 to 11.0)	9.6 ± 1.0 (7.8 to 11.0)	9.4 ± 0.9 (7.9 to 10.7)	13.2 ± 1.7 (11.1 to 16.2)	12.7 ± 1.3 (11.0 to 16.4)
Baseline height (cm)	117.9 ± 6.7 (108.0 to 128.0)	116.8 ± 6.3 (104.3 to 128.7)	116.4 ± 6.4 (106.9 to 131.2)	131.6 ± 8.8 (116.0 to 148.6)	129.4 ± 6.9 (115.3 to 140.8)
Mid-parental target height (cm)	163.6 ± 2.7	161.9 ± 4.2	163.6 ± 4.6	162.8 ± 5.5	162.9 ± 4.6
	n = 12	n = 21	n = 29	n = 42	
Karyotype (% 45,X)	57%	62%	62%	53%	65%
Age at estrogen treatment initiation (yr)	16.2 ± 1.9 (14.7 to 21.3) n = 13	12.3 ± 0.3 (11.9 to 13.2) n = 22	15.0 ± 0.5 (13.6 to 16.0) n = 19	15.0 ± 1.8 (12.1 to 21.3) n = 51	13.7 ± 1.3 (12.0 to 17.8) n = 49

[a] GH-treated patients have a height measurement after age 13.5 and ≥ 1 yr GH treatment; historical control patients have a height measurement after age 18.

Adult Height: Comparison of Treated Patients with Untreated American Historical Controls

Table 9 summarizes the efficacy results of the study. Using baseline age (i.e., at the start of GH therapy), baseline height, karyotype, and mid-parental target height as covariates in analysis of covariance (ANCOVA), the mean difference in adult height between the early GH/estrogen at age 12 group and the American historical controls (under age 11) was **5.9 cm** with a 95% confidence interval (CI) from 3.3 to 8.5 cm ($p < 0.0001$). In contrast, the mean difference in adult height

by ANCOVA between the early GH/estrogen at age 15 group and the American controls was **8.3 cm** with a 95% CI from 5.3 to 11.3 cm ($p < 0.0001$).

The difference in adult height by ANCOVA in the late GH group compared to the American controls (over age 11) was **5.0 cm** with a 95% CI from 3.7 to 6.3 cm ($p < 0.0001$).

Table 9

Study 85-044
Efficacy Results[a]
Mean ± SD (Range)

	Patients under Age 11 at Baseline			Patients over Age 11	
		Early GH			Late GH
	American Controls n = 14	Estrogen at Age 12 n = 26	Estrogen at Age 15 n = 29	American Controls n = 55	Estrogen at Month 12 n = 51
Duration of GH therapy (yr)		5.6 ± 1.1 (3.5 to 7.1)	6.1 ± 1.3 (2.4 to 7.6)	NA	3.8 ± 1.1 (1.1 to 6.5)
Most recent age (yr)	21.9 ± 2.6 (18.1 to 26.4)	15.8 ± 1.0 (13.6 to 17.4)	16.3 ± 0.9 (14.7 to 17.8)	21.5 ± 2.7 (18.1 to 27.8)	17.6 ± 1.3 (14.3 to 20.5)
Most recent height (cm)	144.1 ± 6.0 (135.5 to 156.7)	147.0 ± 6.1 (135.0 to 155.4)	150.4 ± 6.0 (141.1 to 162.0)	144.1 ± 6.2 (131.5 to 160.0)	148.5 ± 5.5 (135.6 to 159.2)
Pretreatment projected adult height (cm)	144.6 ± 5.8	141.9 ± 5.4	142.0 ± 6.1	144.7 ± 7.3	143.8 ± 5.3
Most recent height minus pretreatment projected adult height (cm)	−0.5 ± 4.5 (−7.0 to 6.1) 95% CI: −2.9 to 1.9	5.1 ± 3.6 (−0.9 to 13.2) 95% CI: 3.7 to 6.5	8.4 ± 4.3 (−0.2 to 15.8) 95% CI: 6.8 to 10.0	−0.5 ± 3.6 (−8.6 to 6.7) 95% CI: −1.5 to 0.4	4.7 ± 4.0 (−6.3 to 14.4) 95% CI: 3.6 to 5.9
Most recent height: Treated vs. controls by ANCOVA (cm)	NA	5.9 95% CI: 3.3 to 8.5	8.3 95% CI: 5.3 to 11.3	NA	5.0 95% CI: 3.7 to 6.3

[a] GH-treated patients have a height measurement after age 13.5 and ≥ 1 yr GH treatment. Historical control patients have a height measurement after age 18.

Figures 3 and 4 show that the majority of the baseline heights of the girls were between the 10th and 90th percentiles for Turner syndrome and were generally consistent with the norms for Turner syndrome. GH therapy conferred substantial increases in growth in all three treated groups. Note that Figure 3

contains all 60 patients randomized to estrogen at age 12 or 15 years, including those who were less that 13.5 years old when last measured. The figure illustrates that the girls treated with later estrogen (filled symbols) achieved greater heights than those given earlier estrogen (open symbols). Figure 4 demonstrates that on average the girls treated late with GH (age > 11 years old) had adult heights that were not as great as those seen with early GH and later estrogen, but nonetheless were significantly increased.

Figures 3 and 4 show that many of the subjects are now above the Turner standard curves and within the normal range for American girls (an objective of GH therapy). Over 50% of the girls > 13.5 years of age treated for more than 1 year with GH are above minus 2.5 SD (149 cm) on the growth chart for the general population, compared with an expected prevalence of 18%.

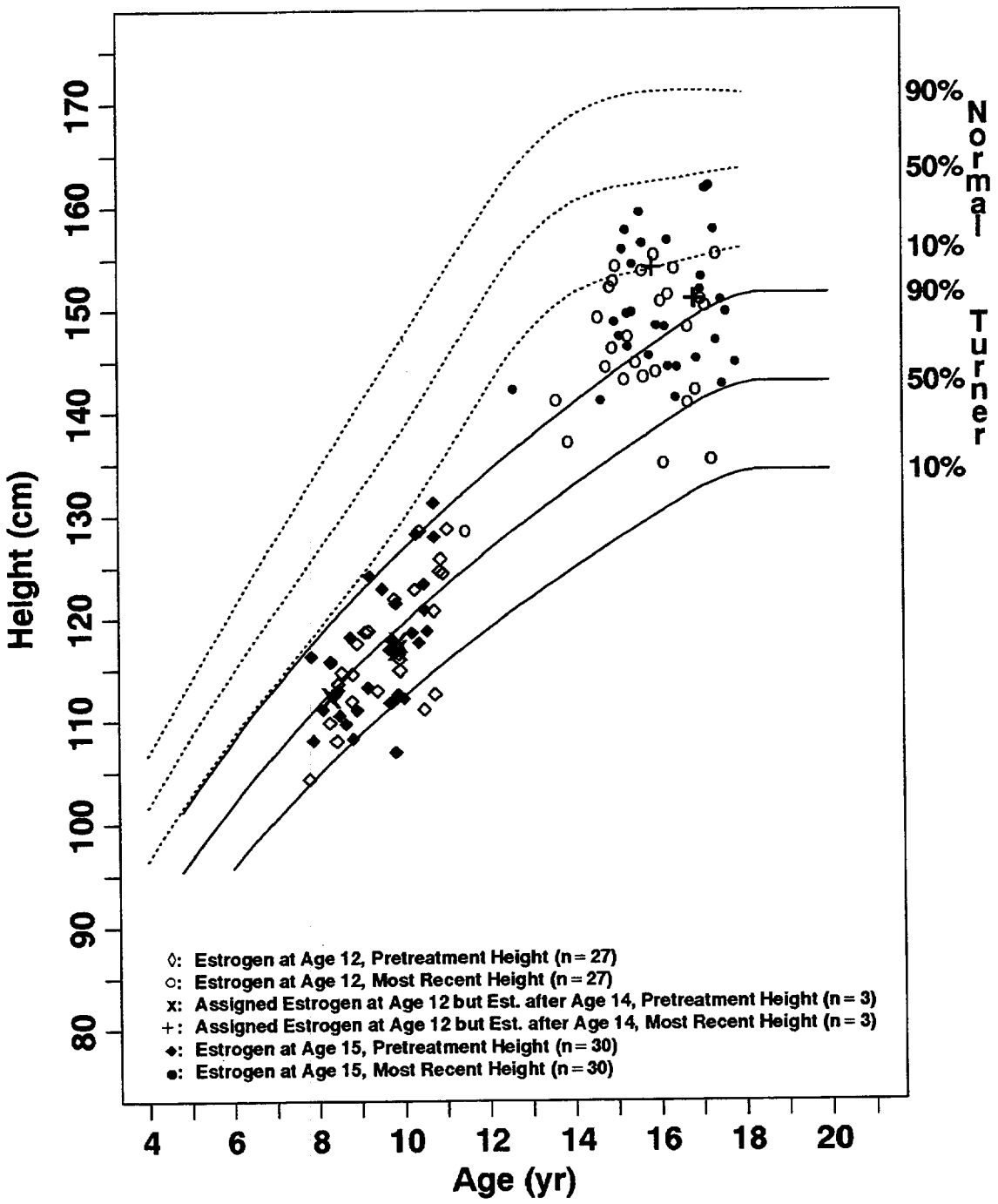

Figure 3: Pretreatment and Most Recent Heights for Early GH Patients Randomized to Early versus Late Estrogen in Study 85-044

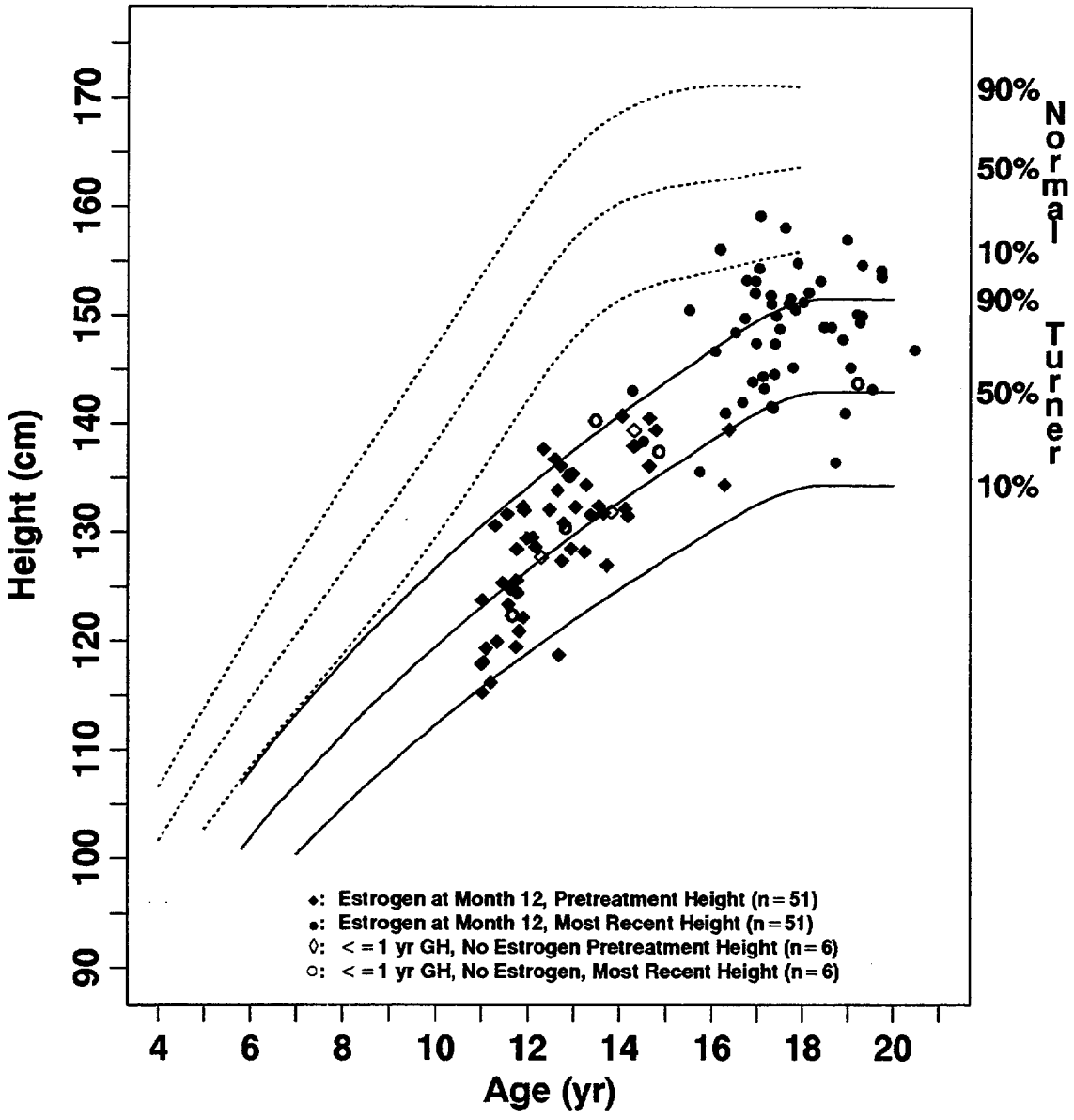

Figure 4: Pretreatment and Most Recent Heights for the Late GH Patients in Study 85-044

Adult Height: Comparison with Pretreatment Projected Adult Heights

The mean difference between most recent height and the pretreatment projected adult height in the early GH/estrogen at age 12 was 5.1 cm, with a 95% CI from 3.7 to 6.5 cm ($p < 0.0001$). The mean difference in the early GH/estrogen at age 15 group was 8.4 cm, with a 95% CI from 6.8 to 10.0 cm, ($p < 0.0001$).

The mean difference between adult height and the pretreatment projected adult height in late GH group was 4.7 cm ($p < 0.0001$) with a 95% CI from 3.6 to 5.9 cm.

These values for increase in adult height are similar to those obtained using comparisons of adult height with matched American untreated controls (5.9 cm and 8.3 cm, respectively), as previously described. As before, the group receiving early GH and estrogen at age 15 achieved the greatest adult height with GH therapy.

Comparison of Estrogen Therapy at Age 12 and at Age 15

Using analysis of covariance with age at the start of GH therapy, height and bone age at age 12, karyotype, and mid-parental target height as covariates, the estimated mean adult height was 2.4 cm greater in the early GH/later estrogen group than in the early GH/earlier estrogen group ($p = 0.0083$). Although both groups had improved adult height compared to the untreated controls, there was a statistically significant difference in the groups treated with estrogen at different ages.

Annual growth rates by chronological age for the earlier and later estrogen groups are illustrated in Figure 5, which shows that patients treated with estrogen at age 12 had an initial increase in mean growth rate followed by a sharp decline in mean growth rate. After age 14, growth in this group was significantly less than expected from the Lyon Turner curves, while growth in the later estrogen group continued to significantly exceed that expected for untreated Turner syndrome girls.

Figure 6 shows the yearly increase of bone age in these two groups and indicates a consistently more rapid advance of bone age in the girls receiving estrogen therapy. The cumulative increase in bone age relative to the increase in chronological age was significantly greater in the estrogen at age 12 group ($+0.4$ yr) than in the estrogen at age 15 group (-0.3 yr) ($p = 0.0004$). The more rapid advancement of bone age in girls treated with this regimen of estrogen explains the decline in growth rate and impact on adult height.

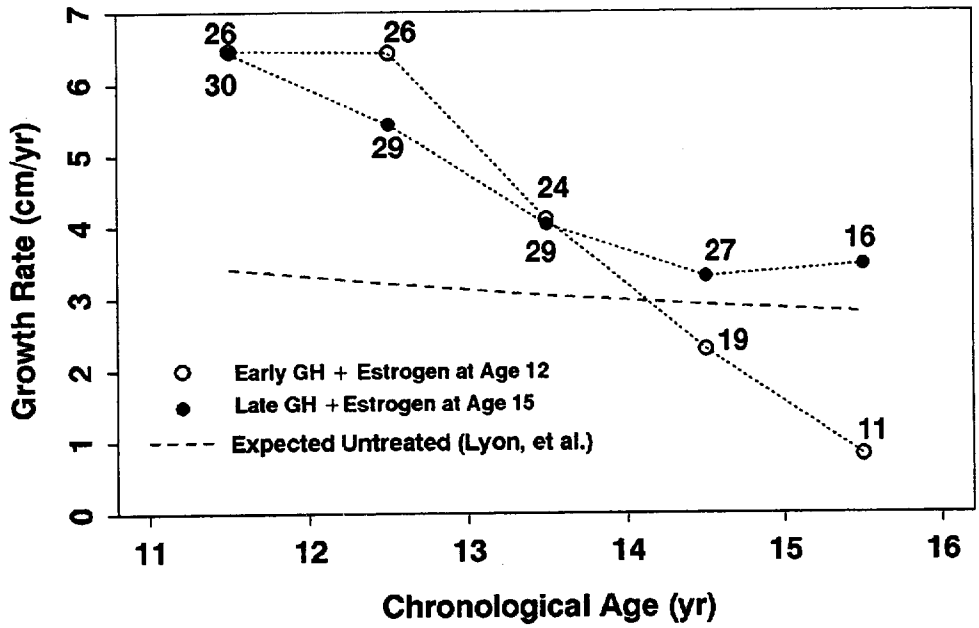

Figure 5: Mean Growth Rates by Chronological Age for GH Patients Randomized to Early versus Late Estrogen (n)

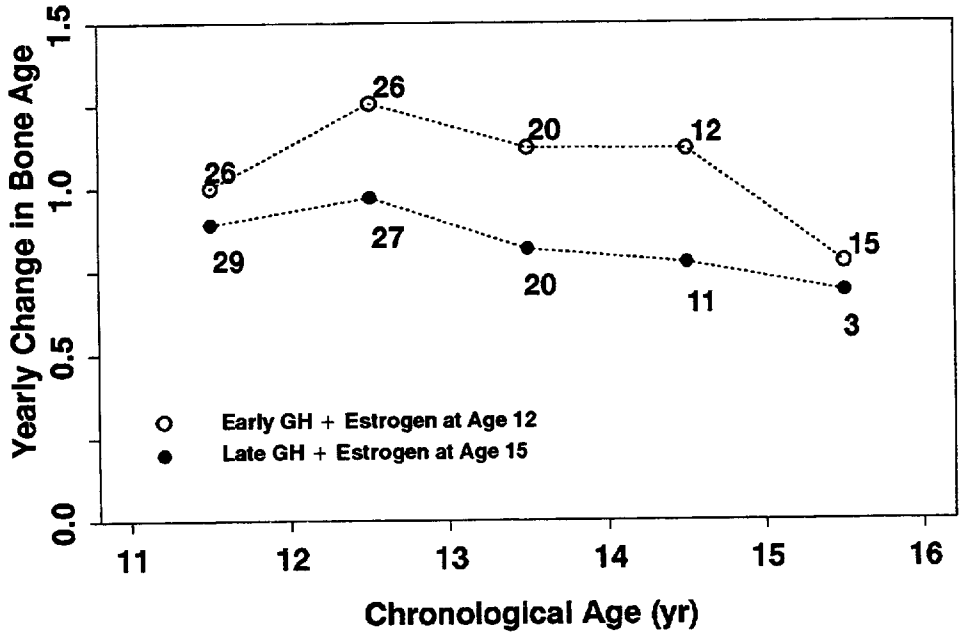

Figure 6: Mean Yearly Change in Bone Age by Chronological Age for GH Patients Randomized to Estrogen at Age 12 vs. Age 15 (n)

Adult Height Summary

The comparisons of actual measured adult heights in GH treated patients with Turner syndrome with matched U.S. untreated controls demonstrate that use of GH results in significant increases in adult height. This was greatest in girls who began GH therapy before age 11 and who had later initiation of estrogen therapy.

Figure 7 shows the differences between the most recent height and the projected adult height for all 109 of the patients treated more than one year who have height measurements after age 13.5. Figure 7 also shows these differences in the patients in the control groups, with the most recent height measurement at age 18. Significant increases from projected heights were seen in all treated groups ($p < 0.0001$), while there was no significant difference for either control group. The 29 patients randomized to later estrogen therapy showed the greatest increase in adult height with a mean increase over pretreatment projection of 8.4 cm (3.3 inches).

Overall, 102 of the 109 patients (94%) treated with GH for more than one year with a height measured after age 13.5 exceeded their pretreatment projected adult height. Fifty-six patients are within 2.5 SDs of the mean for normal adult women. Thus, the majority of these patients attained heights within or near the normal range for adult women, which is rarely seen in untreated subjects with Turner syndrome.

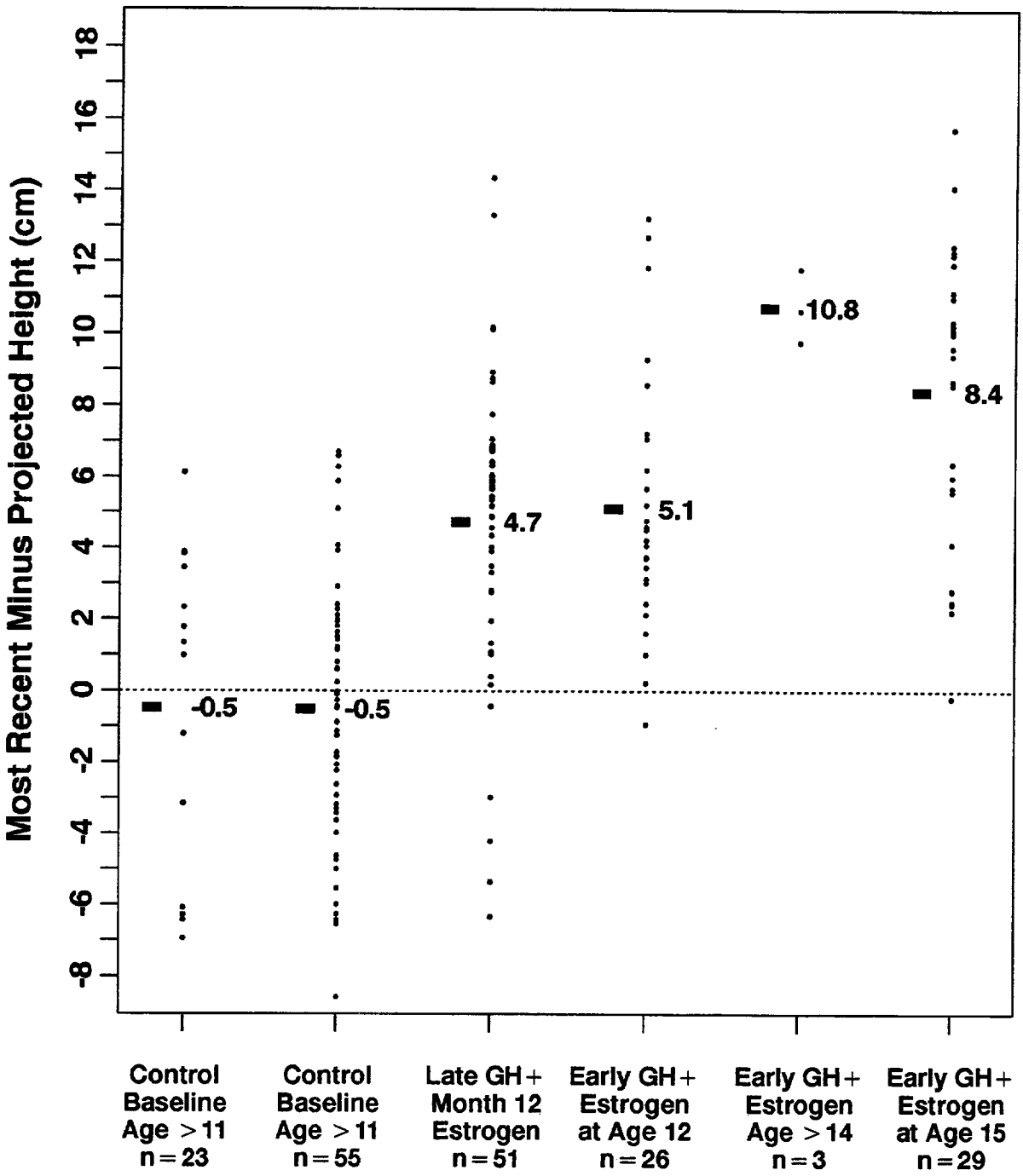

Figure 7: Most Recent Height Minus Baseline Projected Adult Height in Study 85-044; "–" Indicates Mean

B.3 EFFICACY CONCLUSIONS

The primary endpoint of the studies was the effect of GH therapy on adult height. All treated groups showed a significant increase in mean adult height compared to matched cohorts of American controls as well as to their own pretreatment projected adult heights. The increase was greatest for patients with early GH therapy and estrogen therapy after age 14 (the mean improvement in adult height for these patients compared to their own projected adult height without treatment was 8.6 cm and the median was 9.6 cm). As adults, they increased their stature on average from an expected 143 cm to over 150 cm, which is at the lower end of the normal adult female height range.

Both Genentech studies show that in direct comparison with matched controls, adult height is significantly increased in all treatment groups. Genentech's Study 85-044 demonstrated in a randomized manner that the age of estrogen therapy has an impact on adult height outcome. The study also shows greater gains in patients treated with GH at a younger age (i.e., < 11 yrs).

Figure 8a focuses on the patients from both studies with early GH and late estrogen therapy ($n = 49$), who had a mean increase in adult height over pretreatment projection of 8.6 cm (3.4 inches). Forty-four of these 49 patients (90%) had height increases over 5 cm (approximately 2 inches) and all but two of these patients (96%) had a height increase of at least 2 cm. The median increase for these 49 patients was 9.6 cm. These results confirm the results seen in comparisons with matched controls.

Figure 8b shows the relationship between the increase in adult height and the duration of GH therapy. Included in this figure are the 49 subjects shown in Figure 8a plus the 19 patients in the Late GH group who did not receive estrogen before age 14. The positive correlation ($r = 0.53$, $p < 0.0001$) demonstrates the importance of duration of GH therapy on adult height.

Most of the patients treated with GH or GH + oxandrolone who were at least age 13.5 attained heights within 2.5 SDs of the mean for normal adult women ($58/95 = 61\%$). This occurs in only 18% of untreated Turner syndrome subjects, whose mean adult height is 3.5 SDs below the mean for normal adult women.

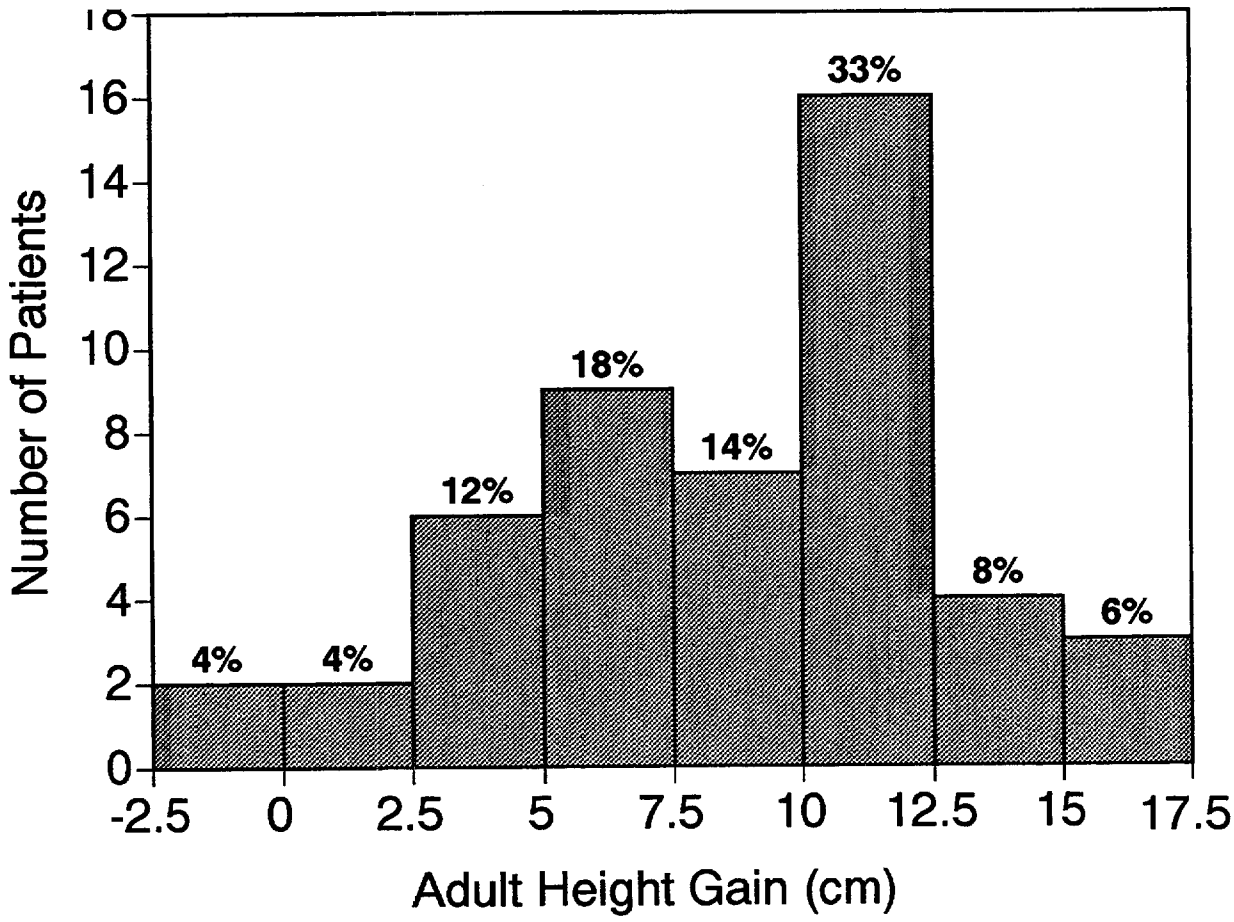

Figure 8a: Adult Height Gain (Most Recent Weight Minus Pretreatment Projected Adult Height) for Subjects in Studies 85-023 and 85-044 Treated with Early GH and Later Estrogen (n = 49)

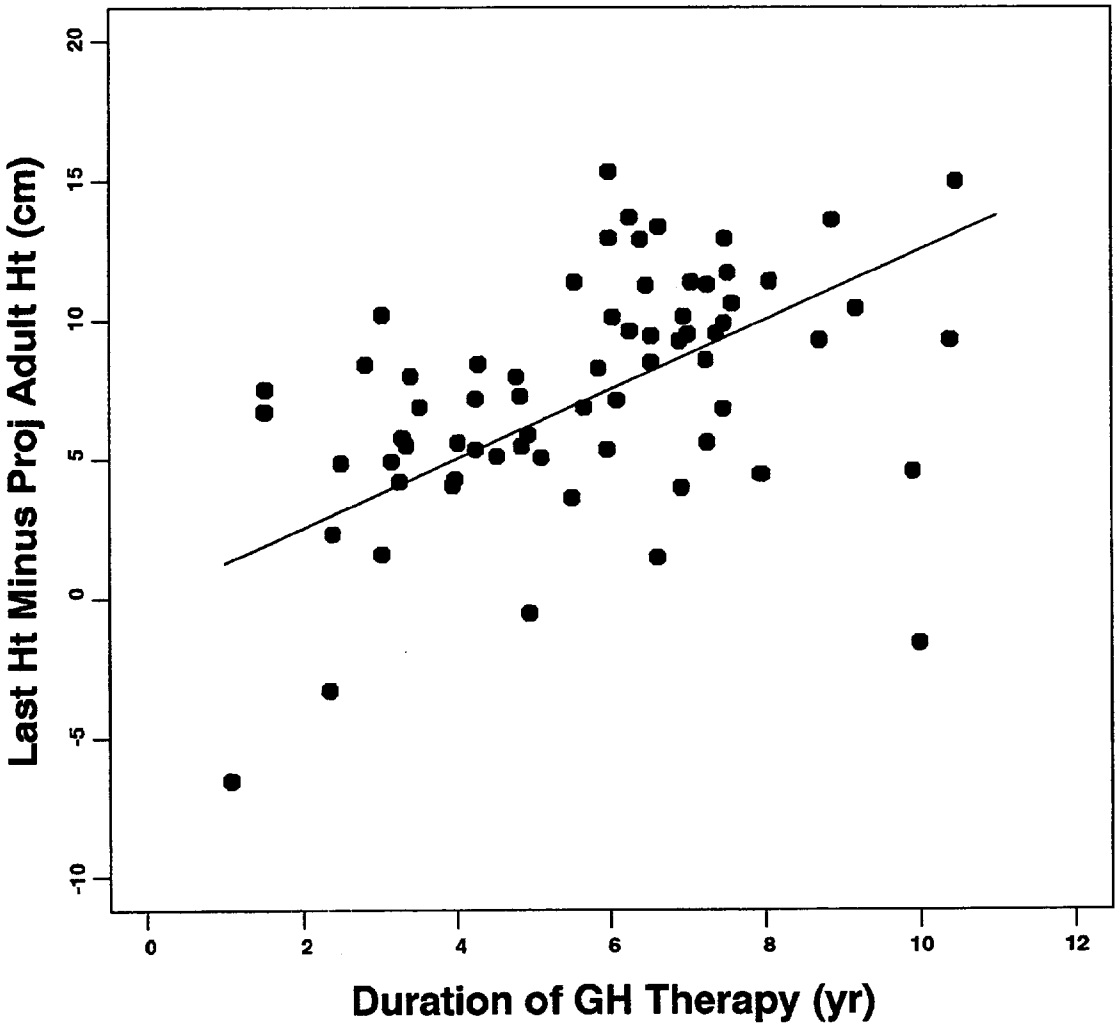

Figure 8b: Adult Height Gain (Most Recent Minus Pretreatment Projected Adult Height) for Subjects in Studies 85-023 and 85-044 without Estrogen Before Age 14 ($n = 68$, $r = 0.53$, $p < 0.0001$)

ADVISORY COMMITTEE MEETING: **ITEM D**
NAME OF DRUG: **Growth Hormone—Turner Syndrome**

C. SAFETY SUMMARY

INTRODUCTION

This summary includes all safety information involving children with Turner syndrome treated with Genentech's formulations of recombinant GH: Nutropin® [somatropin (rDNA origin) for injection] and Protropin® (somatrem for injection). The safety data information was collected from study initiation through April 1, 1995 from the two Genentech, Inc. clinical trials (Studies 85-023 and 85-044). In addition, all data for Turner patients enrolled in a major post-marketing surveillance study of GH therapy (the National Cooperative Growth Study, Protocol 85-036) and from spontaneous reports for patients treated with commercial GH as of December 31, 1994 are included. Additionally, any serious adverse events noted as of May 31, 1996 and described in the August 15, 1996 Safety Update to the NDA are included in this Safety Summary.

The Genentech National Cooperative Growth Study (NCGS) is a multicenter, open-label, surveillance study of Protropin® and Nutropin® in the U.S. and Canada, in which 2216 patients with Turner syndrome have been identified. As such, the study provides valuable safety information for Turner patients treated with GH in a clinical setting. Patients reported in this survey have received Protropin® or Nutropin® at a variety of dosages, schedules, and routes (IM or SC), and have a variety of concomitant medical conditions and/or medications. Although not a controlled trial, the NCGS data are included in this summary because they add to the safety data observed in the controlled clinical trials.

DURATION OF EXPOSURE TO RECOMBINANT GH

The overall duration of exposure to GH in the Genentech Turner syndrome studies as well as the NCGS 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 document, with close to 1000 patient-years of exposure to GH. An additional 5700 patient-years of experience are provided through the NCGS database.

Table 10

Extent of Exposure to GH (yr)
in Studies 85-023 and 85-044

Treatment Group	n	Mean	Minimum	Maximum	Patient Years
85-023					
GH	17	7.5	4.3	10.5	127
GH + ox[a]	50	5.3	1.0	10.8	265
85-044					
TIW GH	36	4.7	0.5	7.6	169
Daily[b] GH	81	4.6	0.0	7.5	373
NCGS	2216	2.6	0.0	8.5	5762
Total	2400				6696

[a] Includes patients previously in the control and oxandrolone only groups.
[b] Includes patients previously in the control group.

PATIENT ACCOUNTABILITY

Study 85-023

Table 11 summarizes patient accountability.

Between August 1983 and June 1984, 71 patients were enrolled in the first phase of Study 85-023 (initially referred to as Study 83-002).

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).

Four patients (two in the control group and two in the oxandrolone group) discontinued from the study during the first phase of the study having never received Protropin® therapy. These patients are not included in Table 11. One patient in the combination group requested removal from the first phase of the study because of concern with potential side effects.

Of the 66 patients enrolled in Study 85-023, 46 patients completed the protocol and 20 patients discontinued prior to completing the protocol (see Table 11).

Four patients discontinued due to adverse events. One patient in the GH group discontinued because of elbow pain due to overgrowth of the right ulnar head, which an orthopedist felt might be increased by GH therapy. Another patient in the GH group discontinued because of right foot cellulitis and right knee pain. A patient on combination (GH + ox) therapy was discontinued for "acromegalic" features. Upon further evaluation, the investigator determined that these coarse facial features were familial and not due to acromegaly. Another combination patient discontinued due to an abnormal glucose tolerance test; a subsequent glucose tolerance test performed 6 months after discontinuing the medications was normal.

Five patients were discontinued due to noncompliance with the protocol, and 11 patients requested removal for other reasons. Eight of these 11 patients were reported satisfied with the height they had achieved at the time of discontinuation, and three patients discontinued as a result of a decision by the patient and/or family.

Study 85-044

As of the New Drug Application, 102 patients had discontinued treatment (see Table 11) 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).

Two patients in the daily treatment group discontinued due to adverse events. One patient discontinued therapy after one month due to an injection site reaction (subcutaneous bumps); skin testing revealed an allergy to the excipient. The second patient was diagnosed with a cerebrovascular accident when symptoms of progressive right-sided weakness and slurred speech were reported after 44 months of GH treatment. GH, Premarin®, and Provera® were discontinued; the incident was considered to be not related to GH therapy and possibly related to Turner syndrome or estrogen therapy.

Thirteen patients were noncompliant with the protocol, including irregularities with injections or visit schedule. Three patients were lost to follow-up.

Table 11

Accountability for Patients Treated
with GH in Studies 85-044 and 85-023

	Study 85-023		Study 85-044		
	Protropin	GH + ox	TIW	Daily	Total
Patients completing protocol	13	33	23	40	109
Patients discontinued prior to completing protocol	4	17	11	28	60
Adverse event	2	2	0	2	6
Noncompliance	1	4	4	9	18
Lost to follow-up	0	0	1	2	3
Requested removal	1	11[a]	6	15	33
Patients currently on study	0	0	2	13	15
Total	17	50	36	81	184

[a] Includes one patient who discontinued from Study 83-002.

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% (Lippe B 1991). Other commonly described clinical findings in Turner syndrome include 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 are evaluated in consideration of these conditions.

Adverse events reported during GH therapy in these studies were primarily those expected for this pediatric age group or were those associated with Turner syndrome. Although some of these events, such as hypothyroidism or edema, may also have been partially related to GH, oxandrolone, and/or estrogen therapy it is not possible to assess the relative contributions of the underlying syndrome and the medication(s).

Deaths

There were no deaths reported in the two clinical trials. In NCGS, there were 5 deaths reported, including one which occurred during the period of the Safety Update. All deaths occurred in patients with pre-existing cardiovascular

anomalies. No deaths were considered related to GH therapy. Three patients had discontinued GH prior the event. One nonstudy patient with cystic fibrosis and severe steroid-dependent asthma died at home during an acute asthma attack. A non-study patient treated with GH for 4 years was diagnosed with metastatic angiosarcoma of the liver and later died. The physician felt that the malignancy was not related to GH therapy.

ABNORMALITIES ASSOCIATED WITH TURNER SYNDROME

Glucose Metabolism

Abnormalities in carbohydrate metabolism are frequently observed in patients with Turner syndrome, and although not fully understood, may be related to impaired insulin secretion and/or reduced insulin sensitivity (see Appendix C). Glucose tolerance tests were performed during treatment in both Genentech clinical studies.

In Study 85-023, one patient in the combination group (GH + ox) discontinued due to a "diabetic" glucose tolerance test as discussed above in the Patient Accountability Section. 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 hyperglycemia were reported as adverse events during Study 85-044. Reactive hypoglycemia was reported as an adverse event in one patient that was considered to be probably related to therapy at Month 27, and not related at Months 54, 60, and 66.

No cases of sustained diabetes mellitus were reported in either clinical trial.

Glucose intolerance was reported in five NCGS and two non-study Turner patients. Four of these patients were diagnosed with type II diabetes mellitus and one patient was diagnosed with type I diabetes mellitus. This incidence is consistent with the expected incidence in Turner syndrome patients.

Lipid Metabolism

Abnormal lipid metabolism has been reported in untreated Turner patients (see Appendix C). Cholesterol and triglyceride measurements were followed in the 2 clinical trials.

In Study 85-023, increased triglycerides were reported in one patient and hypercholesterolemia in another.

Bone Metabolism

A number of skeletal abnormalities may be seen in patients with Turner syndrome (see Appendix C).

In Study 85-023, progression of scoliosis was reported in one patient treated with combination (GH + ox) therapy and in another combination therapy patient on a post-study follow-up visit. 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. Scoliosis or kyphosis was reported in 11 NCGS Turner patients. Progression was noted in two of these patients.

Cardiovascular Anomalies

Cardiovascular anomalies occur in approximately 55% of Turner patients and can be associated with fatal outcomes. In a selected group of females with Turner syndrome, Price et al. (Price DA et al. 1993) found a reduction in life expectancy, particularly because of death due to cardiovascular malformations. In this series, 156 Turner patients who survived infancy were followed for an average of 17 years; there were a total of 15 deaths. Sixteen of the patients had a congenital heart anomaly and five of the deaths occurred in this group, including two children.

Hypertension, which occurs in approximately 7% of Turner patients, may be due to coarctation of the aorta, bicuspid aortic valve, or renovascular abnormalities or essential hypertension.

In Study 85-023, one patient on GH and Premarin® was diagnosed with a cerebrovascular accident with left-sided weakness. This was considered to be due to bacterial endocarditis (*Staphylococcus aureas*) associated with pre-existing aortic stenosis and possibly with eczema.

In Study 85-044, one patient in the daily treatment group was diagnosed as having had a cerebrovascular accident as described above in the Patient Accountability Section.

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 with up to 11 years of follow-up.

Deaths associated with cardiovascular disease were reported in 5 NCGS Turner patients, as previously discussed. All 5 cases were reported as unrelated to GH therapy. In 3 of the 5 cases, GH therapy had been discontinued for some time prior to the event.

Thyroid Function

The incidence of Hashimoto's thyroiditis in Turner syndrome is approximately 34% (Lippe BM 1990). While thyroid autoantibodies may be present in over 50% of Turner subjects, the incidence of clinical hyperthyroidism is probably closer to 10% (Lippe BM 1991).

In Study 85-023, 15 patients were reported with hypothyroidism, thyroiditis, or with elevated TSH during the study. Four patients were on thyroxine at baseline; 4 patients had elevated TSH (indicative of hypothyroidism) at baseline; and 8 became hypothroid during the protocol, one of whom had "compensated" hypothyroidism and did not receive treatment.

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).

The incidence of patients on thyroid replacement therapy (24% in Study 85-023, 13% in Study 85-044) is within the range expected for untreated Turner girls.

Edema

Edema, resulting from lymphatic malformations and obstruction, is the cause of many of the physical findings of Turner syndrome and may persist postnatally as recurrent peripheral edema. This is often seen following institution of estrogen therapy (see Appendix C).

Peripheral edema was reported in 11 patients in 85-023 and in five patients during Study 85-044, including two patients prior to receiving GH therapy. Increased edema was considered to be possibly or probably related to therapy in some patients. Edema was reported in nine NCGS and two non-study patients treated for 2 weeks to 7 months.

Hearing Loss/Otitis Media

Hearing loss was reported in five patients during Study 85-044 and one patient during Study 85-023 within the expected incidence. Hearing loss was reported in one non-study and two NCGS patients.

Chronic recurrent otitis media is a frequent problem in Turner syndrome. Therefore, patients with Turner syndrome should be evaluated carefully for otitis media and other ear disorders. Thirteen (13) of 184 girls with Turner syndrome studied in two randomized controlled trials had otitis media at study entry. During the first year of GH treatment, 19% of GH-treated girls who had not had otitis media on enrollment had otitis media and 18% of girls in the control group had otitis media.

Pigmented Nevi

Approximately 25% of Turner syndrome patients develop multiple pigmented nevi (Lippe BM 1991; Borroni G et al. 1994). Bourguignon et al. (Bourguignon J-P et al. 1993) noted a faster rate of nevi growth with GH therapy. Similar results were reported in a group of eight patients with Turner syndrome (Pierardge et al. 1993). Three patients in Study 85-044 and two patients in the NCGS were reported with pigmented nevi, including two reports of surgical removal.

Alopecia

Alopecia areata and diffuse hypotrichosis have been reported in untreated Turner syndrome patients (Tebbe B et al. 1993). One patient in Study 85-023 and two NCGS patients were reported with alopecia while on GH. Alopecia

areata was also reported in one patient in Study 85-023 during therapy with oxandrolone alone.

ADVERSE EVENTS ASSOCIATED WITH GH THERAPY

Slipped Capital Femoral Epiphysis

The occurrence of slipped capital femoral epiphysis (SCFE) during GH treatment appears to be no more frequent than would be expected in rapidly growing children in general, and may be related to the rapid growth induced by GH (Hintz RL 1992). One patient in Study 85-023 developed SCFE after 21 months of GH therapy, which was not interrupted. In NCGS there were 3 Turner patients with SCFE before they received GH. Four patients developed SCFE while being treated with GH, including 1 secondary to pelvic tumor. SCFE was also reported in one non-study patient.

Leukemia

No cases of leukemia were reported in any of the studies, including NCGS, among Turner syndrome patients.

Carpal Tunnel Syndrome

No cases of carpal tunnel syndrome were reported in any of the studies, including NCGS, among Turner syndrome patients.

Intracranial Hypertension

Intracranial hypertension (IH) has been identified as a rare complication of GH therapy, including patients with Turner syndrome (Malozowski S et al. 1993; Price DA et al. 1995). Castillo et al. (Castillo L et al. 1994) have reported a case of IH in a Turner syndrome patient that was managed with GH discontinuation and acetazolamide.

No cases of IH were reported in the two Turner syndrome clinical trials. IH was reported in one non-study and four NCGS Turner patients. The GH dosages were reported in four of these patients (0.25, 0.31, 0.35, and 0.36 mg/kg/week). The duration of therapy with GH prior to diagnosis of IH was 29 days, 3 months, 5 months, 7 months, and 3 years, respectively. The latter case was associated with initiation of estrogen therapy and was confirmed with estrogen dechallenge and rechallenge.

Pancreatitis

No cases of pancreatitis were reported in any of the studies with Turner syndrome patients.

Acromegaly

Kollman et al. (Kollman F et al. 1991) reported one of 55 GH-treated Turner patients with "acromegalic" changes. Abnormal craniofacial and tooth growth in Turner syndrome have been reported (Rongen-Westerlaken C et al. 1993).

One patient in Study 85-023 was discontinued for "acromegalic" features which were felt to be familial as described previously in the Patient Accountability Section.

Ankle and feet thickening were reported in one NCGS patient; bone X-rays revealed no acromegalic changes. One patient was reported with disproportionately enlarged hands and feet, and another patient with large feet.

The hand-wrist X-rays for all patients treated in Study 85-023 were analyzed by two independent authorities for possible acromegalic changes. Both reviewers concluded that 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.

Neoplasm

Two new neoplasms were reported in NCGS Turner patients: one case each of metastatic papillary thyroid cancer, and mucoepidermoid carcinoma of the mouth. Only the latter was considered to be possibly related to GH by the reporting investigator. A patient with a fibrosarcoma of the left pelvis, pretreatment, later developed a chondrosarcoma in the same location.

As previously described, one non-study patient treated with GH for 4 years was diagnosed with metastatic angiosarcoma of the liver and later died (date of death not reported). The physician felt that the malignancy was not related to GH therapy.

Reported in the NDA safety update was one report of a hemangioma in an NCGS Turner patient. A hemangioma is a congenital anomaly in which a proliferation of vascular endothelium leads to a mass that resembles neoplastic

tissue. The 16-year old patient had a mild hemangioma develop on her right foot which enlarged over a one-month period and resolved over another month. The event was reported as possibility related to GH therapy which was continued.

ADVERSE EVENTS BY BODY SYSTEM

Adverse events and intercurrent illnesses are summarized by treatment group in Table 12. The table contains an integrated summary of adverse events for the two controlled Turner studies (Studies 85-044 and 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, and were not considered by the investigator to be related to GH therapy. Noteworthy events are described below for the endocrine, hematology and musculoskeletal, nervous and respiratory categories.

Certain events, such as cyst surgery, abdominal pain, paronychia, otitis, bronchitis, flu, and chicken pox, were described as severe by the investigator. These were found to be related to either underlying aspects of the disease or expected childhood illnesses.

Table 12

Integrated Summary of Adverse Events
in Studies 85-023 and 85-044

Treatment Group:	Control[a]	Oxandrolone	GH + ox	Growth Hormone[a]
Average Duration[b]:	**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.

[b] **Note:** The duration of the GH-treated group is approximately four times as long as that for the control group. Hence, one would expect a higher number of events for the GH-treated group.

Endocrine

Virilization 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.

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.

Musculo/Skeletal

In Study 85-023, two patients discontinued for reasons associated with joint pain. One patient in the GH group discontinued due to elbow pain associated with overgrowth of the right ulnar head which an orthopedist felt might be increased by GH therapy. This pain was mild and was not considered to be related to therapy by the investigator. Another patient in the GH group discontinued due to right foot cellulitis and right knee pain. One patient on combination (GH + ox) 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.

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.

One case each of syncope, dizziness, behavioral problems, sleep disturbances, left-sided facial and eyelid drooping (resolved spontaneously with continued GH therapy), and increased pressure in the retina (IH was not diagnosed) were reported in NCGS Turner patients.

See the Intracranial Hypertension section above a discussion of intracranial hypertension.

Respiratory

A 10-year-old non-NCGS Turner patient treated for cystic fibrosis and steroid-dependent asthma died at home of an acute asthma attack, as described previously. Relation to Protropin® therapy (given for 2 months) was felt to be unlikely by the reporting physician.

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.

LABORATORY EVALUATIONS

There were no unexpected abnormal laboratory measurements, including liver function tests. At baseline, serum cholesterol and triglyceride levels were elevated in some patients. Increases in mean inorganic phosphorus and alkaline phosphatase levels were seen with GH therapy, as expected. Long-term GH therapy was accompanied by increases in mean triglyceride levels and decreases in mean BUN and cholesterol levels. There were no significant changes in calcium, creatinine, or other electrolyte or chemistry measurements.

Sporadic instances of increased TSH and/or T_4 levels occurred, although mean levels did not change significantly.

Fasting insulin and postprandial glucose and insulin levels were elevated in some treated patients; however, fasting glucose and HbA_{1c} levels were normal in nearly all treated patients with no significant changes in mean values (Table 13). No instances of diabetes mellitus were reported.

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 GH+ox	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 GH+ox	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 GH+ox	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 GH+ox	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 GH+ox	22	NA	5.2 ± 0.5	4.3 ± 0.9	NA	NA

[a] Medians.
NA = Not Available.

Antibodies to GH

The incidence of antibodies to GH in patients treated with Nutropin® was maximal at 12 months (15%) and declined thereafter with continued therapy. There were no patients with antibodies associated with a binding capacity of 2.0 mg/L or greater and there was no growth attenuation seen in patients with antibodies to GH. While the potential for developing an antibody with high binding capacity exists, it is a very rare event and was not seen in the GH study reviewed in this document or in studies in GH deficiency and chronic renal insufficiency in previous NDA submissions.

SUMMARY

The use of GH in the treatment of short stature associated with Turner syndrome has been studied since 1960. A considerable body of experience has emerged from the clinical literature which helps to support the safety of GH therapy in this population. GH has not been shown to worsen or complicate underlying conditions common to patients with Turner syndrome.

Prospective studies of the use of GH for the treatment of short stature associated with Turner syndrome have confirmed the long record of safety accorded exogenous GH therapy. Careful surveillance of over 2000 Turner syndrome patients followed in the NCGS have further established this safety profile with data from actual clinical usage.

Serious adverse events associated with GH therapy in Turner syndrome were rare. Two cases of cerebrovascular accident occurred in the studies, one attributed by the investigator to complications of Turner syndrome and estrogen therapy, and the other related to bacterial endocarditis. Five deaths associated with underlying cardiovascular anomalies were reported in patients in the NCGS surveillance study that were all considered unrelated to GH therapy. Serial echocardiograms performed on 12 patients in Study 85-023 revealed no changes in left ventricular mass or aortic root diameter as a result of GH therapy.

Two patients reported with glucose intolerance had normal follow-up tests off medication. The prevalence of thyroid replacement therapy in the two studies was within the expected range for a group of Turner girls.

One patient was reported with mild elbow pain due to overgrowth of the right ulnar head. Another patient was discontinued for "acromegalic" features which were similar to those of her mother and thus not clearly distinguishable as due to acromegaly. Detailed examinations of hand/wrist X-rays were undertaken by two outside specialists, who concluded that long-term (six years) GH therapy did not result in any acromegalic effects on bone.

Certain events, such as cyst surgery, abdominal pain, paronychia, otitis, bronchitis, flu, and chicken pox, were described as severe by the investigator. These were found to be related to either underlying aspects of the disease or expected childhood illnesses. Adverse events expected in Turner syndrome, such as glucose intolerance, scoliosis, hypertension, hypothyroidism, edema, otitis, hearing loss, and alopecia, were reported in either expected or

less-than-expected frequencies. Although some events may have been related to GH therapy, such as edema or hypothyroidism, it is not possible to assess the relative contributions of the underlying syndrome and GH or other medications.

Certain rare adverse drug reactions known to be associated with GH administration in children with GH deficiency, such as intracranial hypertension, were also seen in Turner syndrome patients treated with GH. Slipped capital femoral epiphysis occurred in a few patients, possibly due to accelerated growth. No cases of allergy to GH, leukemia, carpal tunnel syndrome, or pancreatitis were reported. Several reports of virilism, including clitoromegaly, were associated with oxandrolone therapy.

There were no unexpected abnormal laboratory measurements. Sporadic instances of increased TSH and/or T_4 levels occurred, although mean levels did not change significantly. Fasting insulin and postprandial glucose and insulin levels were elevated in some treated patients; however, fasting glucose and HbA_{1c} levels were normal in nearly all treated patients. In patients treated with GH, the incidence of antibodies to GH was maximal at 12 months (15%) and declined thereafter with continued therapy. There was no growth attenuation seen in patients with antibodies to GH.

There are no other known severe toxicities of GH. Although there is little experience with regard to the use of GH during pregnancy, this is a negligible concern in this patient population due to the finding of ovarian dysgenesis in nearly all subjects and the extremely rare occurrence of conception.

CONCLUSION

Long-term treatment with GH in two clinical trials was found to be safe and well tolerated. This finding is further supported by a large post-marketing surveillance study and numerous studies of GH use in Turner syndrome reported in the literature. The total experience with GH in Turner syndrome in these studies is over 12,000 patient-years. No adverse events were observed that would preclude the recommendation of 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.

Based on these data, GH is a safe and well-tolerated therapy when used for the treatment of growth failure in children with Turner syndrome.

ADVISORY COMMITTEE MEETING: **ITEM E**
NAME OF DRUG: **Growth Hormone—Turner Syndrome**

D. BENEFITS/RISKS

The Genentech-sponsored clinical trials of the use of recombinant GH in Turner syndrome have achieved the primary endpoint of these studies: increase of adult height. A careful analysis of the adult heights achieved by patients treated with GH compared with matched untreated American Turner girls, the majority of whom were followed by the same investigators, demonstrated a significant increase in adult height as a result of GH therapy.

Patients who begin GH therapy before age 11 and who have estrogen therapy delayed until after age 14 can expect a mean increase in adult height of about 8–9 cm, with 80% having increases of at least 5 cm or approximately 2 inches, bringing them closer to or into the normal female height range.

The data from the 2 Genentech clinical trials are consistent with other published studies (Appendix B) which indicate that patients treated with GH at an earlier age and/or estrogen at a later age will achieve greater benefit.

The extensive experience accumulated by Genentech regarding the safety of GH therapy has revealed no unexpected serious adverse events or clinically significant laboratory changes attributable to GH. The risk of a serious adverse event related to GH therapy is small. Long-term treatment with GH in two clinical trials was well tolerated and this finding is supported by the safety data from the NCGS and by numerous studies of GH use in Turner syndrome reported in the literature (see Appendix C). No adverse events were observed that would preclude long-term GH therapy of patients with Turner syndrome.

Optimal GH therapy in patients with Turner syndrome should improve their stature on average from an expected 143 cm to greater than 150 cm, with most patients achieving heights close to the lower end of the height range for females in the general population. Based on the accumulated safety information in these clinical trials, the risks of GH therapy in this population are small in comparison to the expected benefits. These data show that Nutropin® [somatropin (rDNA origin) for injection] is a safe, well-tolerated, and efficacious therapy for the treatment of short stature and growth failure in children with Turner syndrome.

ADVISORY COMMITTEE MEETING: **APPENDICES**
NAME OF DRUG: **Growth Hormone—Turner Syndrome**

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APPENDIX A

American Turner Syndrome Database

1. U.S. UNTREATED TURNER SYNDROME DATABASE

The studies of Ranke et al. (Ranke MB et al. 1983) and Lyon et al. (Lyon AJ et al. 1985) have provided thorough analyses of the growth of untreated girls with Turner syndrome. Numerous other reports from around the world have served to confirm the basic patterns illustrated by these two studies. Data from a large number of American girls with Turner syndrome are described below, showing the utility and applicability of the standards of Lyon et al. (Lyon AJ et al. 1985) for the analysis of growth studies performed in the United States. These standards can be used to project adult height for individual patients in the absence of GH or androgen treatment.

The use of the mixed longitudinal and cross-sectional standards developed by Lyon et al. for the analysis of the growth of American girls with Turner syndrome is dependent upon the following conditions being met:

1. that the standards are accurate for the height of American girls with Turner syndrome at any age, including adult height;
2. that the effect of delayed low-dose estrogen treatment on growth is transient and minimally affects adult stature;
3. that a childhood percentile can be used to project height at a later age, including adult height, if the girls are not treated with GH, androgen, or inappropriate estrogen therapy;
4. that there is no significant secular trend in the final heights of girls with Turner syndrome;
5. that the effect of parental height on final height is accounted for in the childhood standardized height.

Satisfying these conditions allows the use of the Turner standards of Lyon et al. to evaluate the effect of growth-promoting therapy in girls with Turner syndrome. Analyses addressing these conditions are discussed in detail below.

Lyon et al. (Lyon AJ et al. 1985) generated growth curves from four Continental European studies (see Figure 2 in the Background section). Standard height

curves for Turner syndrome derived from Lyon et al. are in widespread use today.

To assess the applicability of the curves based on the data of Lyon et al. for the childhood and adult heights of American girls with Turner syndrome, a database was assembled using American historical control data. Fourteen institutions throughout the United States (primarily those institutions that participated in Genentech GH studies in Turner syndrome) contributed data for untreated Turner patients using report forms designed to capture all information available for height, bone age, estrogen age and dose, parental height, and karyotype. Additional pretreatment data were obtained from the two Genentech clinical trials (Protocols 85-023 and 85-044) and the Genentech National Cooperative Growth Study.

The historical data used in the following analyses are derived from 3448 height measurements from 1363 patients, including adult height measurements for 84 patients.

The heights of Turner subjects in this country were compared with the standards derived from the European population (Lyon et al.). This was done to determine whether the Turner standards currently in use in this country (i.e., from Lyon et al.) are appropriate or whether new standards should be derived from the American data.

Figure 9 shows 2959 height measurements from 1300 untreated American Turner patients plotted vs. age. This figure contains only heights of patients before estrogen therapy (if any) was initiated, plus all heights obtained after age 18. These measurements are superimposed on curves representing the 10th, 50th, and 90th percentiles based on the results of Lyon et al.

Figure 10 shows a spline fit to the American heights (solid curve) together with a dashed curve showing the spline fit to the Lyon European data. The fits at all ages, including age 18, are extremely close. The data clearly show that the Turner standards of Lyon et al. are applicable to the U.S. Turner syndrome population at all ages.

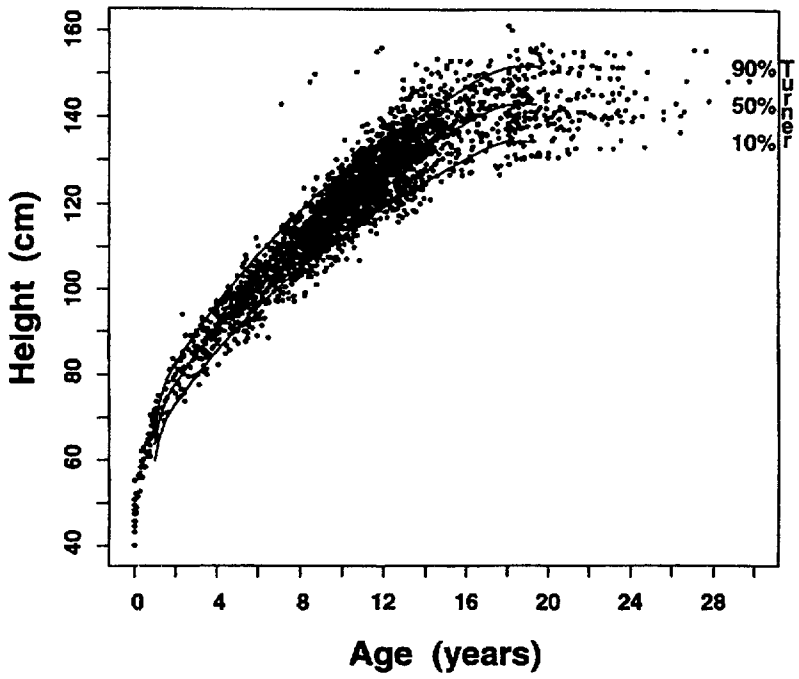

Figure 9: Heights of American Patients with Turner Syndrome Before Treatment with Estrogen or Other Medication Affecting Height Plus Heights for Patients Over 18 Years Old on Estrogen (2959 Points from 1300 Patients) with Standard Curves from Lyon et al.

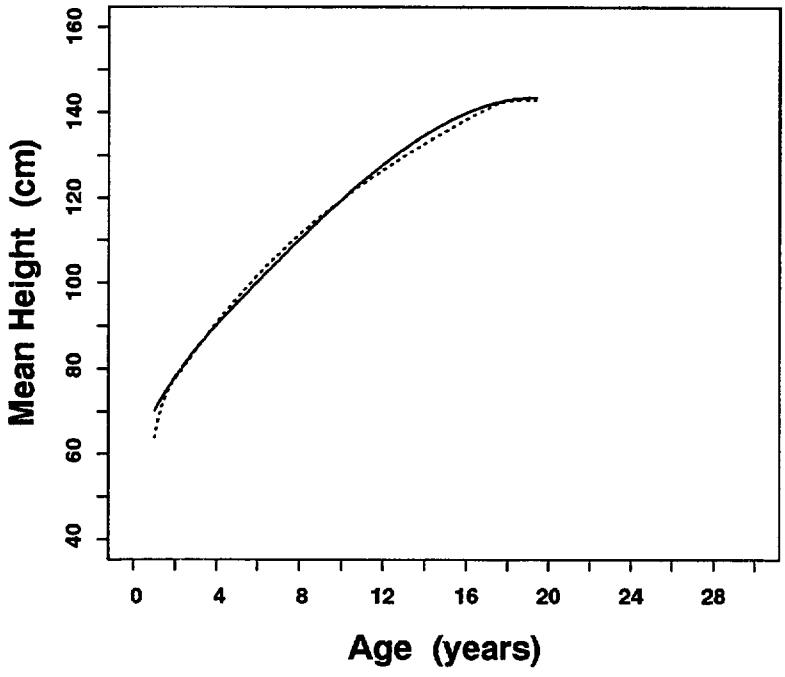

Figure 10: Spline Fit for American Patients (Solid Curve) Compared with Lyon Smoothed Mean Height (Dashed Curve)

Eighty-four patients had one or more height measurements after the age of 18. Their last heights averaged 144.0 ± 6.3 cm (mean ± SD), which is not statistically significantly different from either the Lyon average of 143.0 ± 6.7 cm from four continental European studies or the pooled average from the U.S. literature of 143.1 cm. These results demonstrate the applicability of the Lyon standards to the American Turner population with respect to adult height.

The heights of these American girls were standardized using Lyon standards. The mean of 2686 Turner-standardized heights for 1296 children at least one year of age who had not yet received estrogen was + 0.05, i.e., close to the expected mean of zero if the American population was exactly equivalent to the European population. The standard deviation was 0.97, which is close to the expected standard deviation of 1.0. Figure 11 shows the Lyon standardized heights vs. patient age. This figure shows that the conformity of the standards is uniform across the age range.

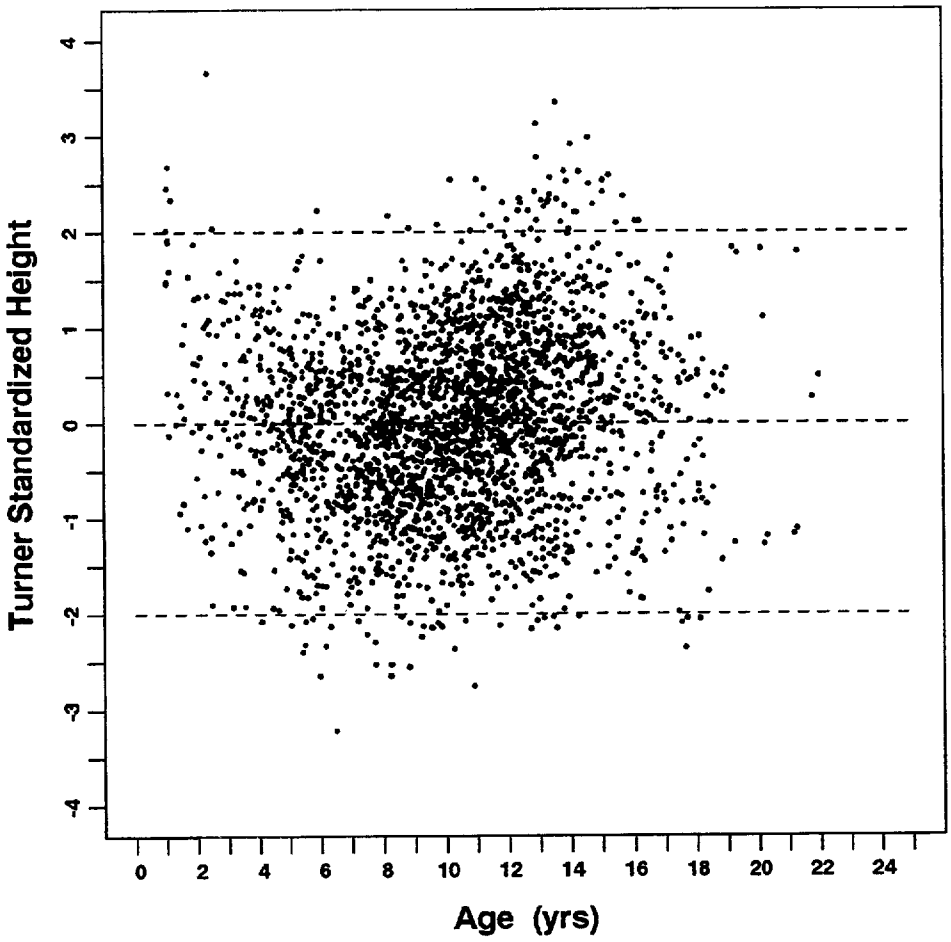

Figure 11: Turner Standardized Heights of American Subjects with Turner Syndrome Before Treatment with Estrogen or Other Medication Affecting Height (2686 Points from 1296 Patients)

APPENDIX A (cont'd)

American Turner Syndrome Database

2. KARYOTYPE

The incidence of sex chromosome mosaicism (e.g., 45,X/46,XX) in liveborns is unknown, since the presence of stigmata may vary with the percentage of cells with a normal karyotype (Anglani F et al. 1984). In one study, 60% of Turner girls in a screening program of newborns were found to be mosaics (Robinson A 1990). Early reports of Turner syndrome implied that those patients with mosaicism were more likely to be taller than 45,X patients, whereas most studies have concluded that there are no significant differences in adult height (Rochiccioli P et al. 1994; Massa G et al. 1990; Haeusler G et al. 1994).

Table 14 shows mean adult heights reported in the U.S. (Park E et al. 1983; Conte FA et al. 1978; Demetriou E et al. 1984; Engel E et al. 1965; Haddad HM et al. 1959; Johanson AJ et al. 1969; Lippe BM 1982; Moore DC et al. 1977; Rodens KP in prep; Snider ME 1974; Sybert VP 1984; Talbot NB 1947; Urban MD 1979) and other countries (Lyon AJ et al. 1985; Massa G et al. 1990; Benker G et al. 1979; Bernasconi S et al. 1991; Bosze P et al. 1980; Brook CED et al. 1974; Joss E et al. 1984; Lenko HL et al. 1988; Lev-Ran A et al. 1977; Lindsten J et al. 1973; Mattevi MS et al. 1971; Muritand MR et al. 1985; Naeraa RW et al. 1991; Pelz L et al. 1982; Ranke MB et al. 1991; Takano K et al. 1988) for patients with karotype 45,X compared with patients with other Turner karyotypes (non-45,X). The table also shows mean adult height data reported for all Turner patients, including those for whom karyotype information was not provided. The table contains data only for patients who never received androgen or GH therapy. However, some of the patients did receive estrogen therapy for varying durations prior to attaining final height.

The pooled U.S. mean adult height was 142.8 cm ($n = 89$) for 45,X patients and 143.6 cm ($n = 69$) for non-45,X patients. Assuming an approximate SD of 5 cm, the difference of the pooled means was not statistically significant ($p = 0.33$). The pooled non-U.S. data, primarily from Western Europe, showed even closer mean adult heights (144.0 cm for 45,X, $n = 203$; 144.1 cm for non-45,X, $n = 95$, $p = 0.88$). When all U.S. and non-U.S. data were pooled, the difference was again not significant ($p = 0.61$). Thus, karyotype does not appear to be a major factor in ultimate adult stature in Turner syndrome. In addition, there was no statistically significant difference in final height between U.S. and non-U.S. patients with 45,X ($p = 0.08$) or other karyotypes ($p = 0.58$).

Table 14

Mean Adult Height by Karyotype for Turner Patients not Treated with Androgen or GH from U.S. and non-U.S. Published Studies

U.S. Studies	Age of Estrogen Initiation (yr)	45,X Height (n)	non-45,X Height (n)	Total[a]
Conte	NR	NA	NA	141.4 (53)
Demetriou	16	142.6 (17)	142.6 (20)	142.6 (37)
Engel	NR	142.2 (13)	139.6 (12)	140.9 (25)
Haddad	NR	NA	NA	142.0 (24)
Johanson	15	NA	NA	140.2 (21)
Lippe	NR	140.9 (18)	144.8 (14)	142.6 (32)
Moore	NR	140.3 (10)	NA	140.3 (10)
Park	17	NA	NA	142.0 (28)
Rodens	NR	NA	NA	142.7 (56)
Snider	NR	141.6 (10)	147.2 (8)	144.1 (18)
Sybert	NR	146.9 (21)	145.2 (15)	146.3 (37)
Talbot	NR	NA	NA	141.1 (11)
Urban	NR	NA	NA	140.6 (21)
TOTAL (U.S.)		142.8 (89)	143.6 (69)	142.3 (373)
Non-U.S. Studies		**45,X Height (n)**	**non-45,X Height (n)**	**Total[a]**
Benker	NR	NA	NA	142.7 (13)
Bernasconi	NR	NA	NA	142.5 (23)
Bosze	NR	142.4 (12)	141.2 (10)	141.9 (22)
Brook	NR	142.9 (18)	NA	142.9 (18)
Joss	13	NA	NA	139.4 (15)
Lenko	15	NA	NA	146.8 (26)
Lev-Ran	NR	143.2 (12)	NA	143.2 (12)
Lindsten	15	142.4 (8)	145.4 (5)	143.6 (13)
Lyon	>15	NA	NA	143.2 (22)
Massa	NR	142.5 (51)	147.1 (7)	143.1 (58)
Mattevi	NR	NA	NA	143.0 (8)
Muritano	NR	140.9 (14)	139.0 (11)	140.1 (25)
Naeraa	18	147.0 (47)	146.4 (29)	146.8 (76)
Pelz	NR	143.1 (14)	141.2 (5)	142.6 (19)
Ranke	NR	147.0 (24)	146.9 (20)	146.9 (44)
Takano	NR	135.5 (3)	137.3 (8)	136.8 (11)
TOTAL (non-U.S.)		144.0 (203)	144.1 (95)	143.8 (405)
TOTAL (all data)		143.6 (292)	143.9 (164)	143.1 (778)

[a] Includes patients with no karyotype information available.

NA = Not available.

NR = Not reported.

APPENDIX A (cont'd)

American Turner Syndrome Database

3. SPONTANEOUS PUBERTY

Spontaneous puberty is observed in 5%–33% of Turner patients (Lippe BM et al. 1990; Park E et al. 1983; Lyon AJ et al. 1985; Hibi I et al. 1991; Haeusler G et al. 1992; Mazzanti L et al. 1994) and is typically associated with some breast development, occasional initiation of menses, and a small growth spurt (Park E et al. 1983; Massa G et al. 1990). Spontaneous puberty may be seen in 45,X cases as well as in mosaics and, in rare instances, pregnancy may occur (King CR et al. 1978; Reyes FL et al. 1976; Philip J et al. 1976). A small, delayed adolescent growth spurt can be detected in Turner syndrome, even in the absence of physical signs of puberty (Massa G et al. 1990; Ranke MB et al. 1991; Haeusler G et al. 1992; Pelz L et al. 1991). In those girls with spontaneous puberty, the average age of onset (age 12–13) appears to coincide with the timing of the small growth spurt (Massa G et al. 1990; Haeusler G et al. 1992; Mazzanti L et al. 1994). Mean adult height in girls who have had spontaneous puberty was not significantly different from adult height in other Turner patients in several studies (Park E et al. 1983; Massa G et al. 1990; Naerra RW et al. 1990). However, others have reported that spontaneous puberty may adversely affect mean final height in Turner syndrome (Hibi I et al. 1991; Rosenfield RL et al. 1990; Page LA et al. 1992).

In summary, spontaneous puberty, though not frequent among Turner girls, is not a predictor of improved final height but may, in some instances, compromise adult stature. The effect of this would be an underestimation of the adult height gain attributable to therapy in patients with spontaneous puberty when using the projection method.

APPENDIX A (cont'd)

American Turner Syndrome Database

4. PARENTAL HEIGHT/ETHNIC ORIGIN

Studies have shown that just as in the unaffected population, the heights of untreated adult Turner women correlate with the heights of their parents (Rocchiccioli P et al. 1994; Massa G et al. 1990). In these studies, the correlation has been found to be better with a combined target height than with either the mother's height or father's height alone. Thus, Turner patients with tall parents are correspondingly tall Turner children; this provides them with relatively tall projected adult heights (Lyon et al.) during childhood, and they will end up as correspondingly tall Turner adults.

As with parental height, the effect of ethnic background on height would be expected to be as apparent throughout childhood as it is for adult height. Thus, the growth curves for various countries are shifted up or down relative to each other proportionately at all ages (Haeusler G et al. 1994) (see Figure 12). Once the childhood height is known, the contribution of ethnic origin to adult height is largely accounted for.

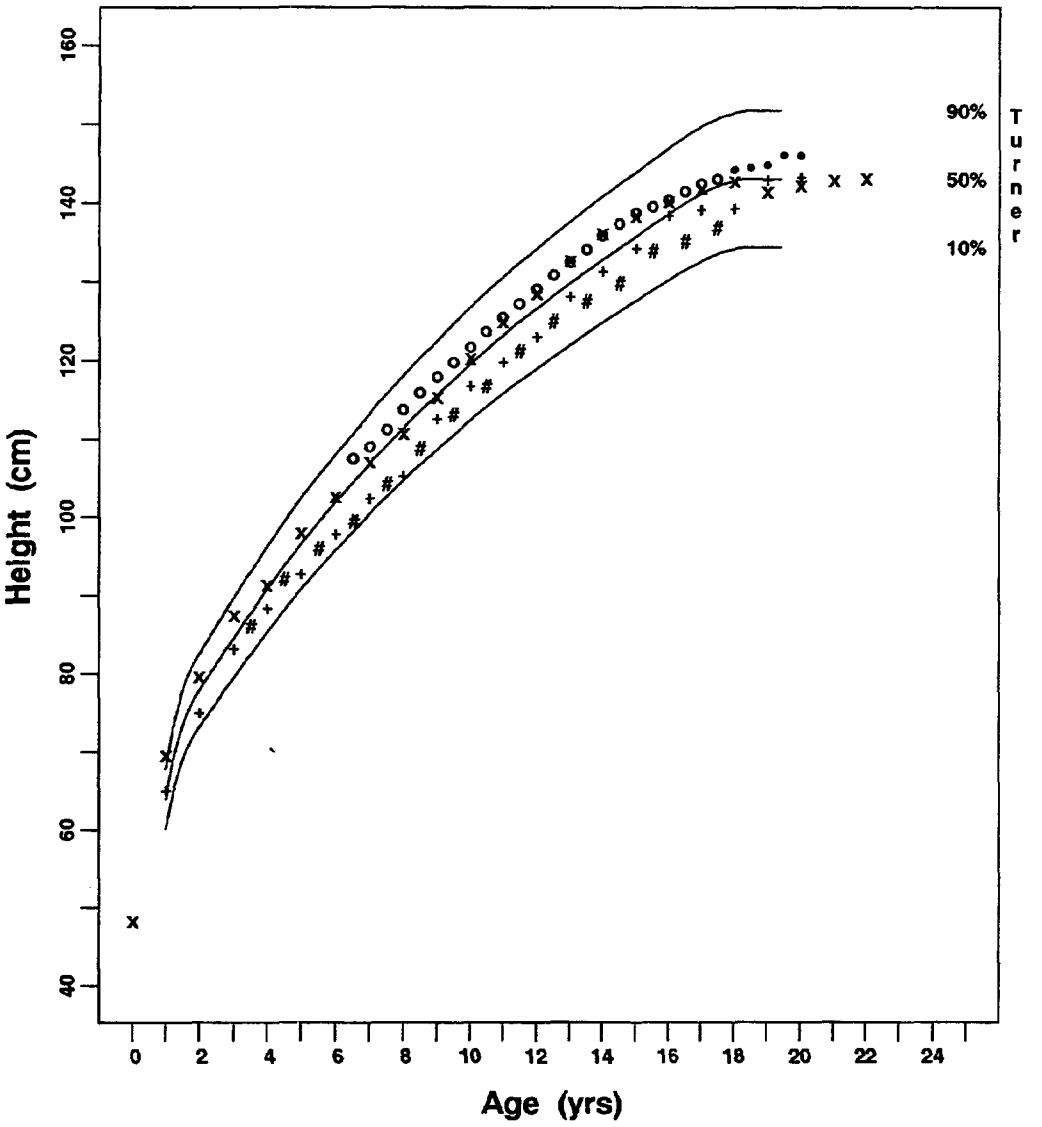

Figure 12: Mean Heights from Lyon et al.; England (+), Massa et al.; Belgium (x), Naeraa et al.; Denmark (o pre-estrogen, • post-estrogen), and Takano et al.; Japan (#) with Turner Percentile Curves Derived by Lyon et al.

The mean adult height for American Turner women is approximately 143 cm, compared with the normal female adult mean of 163.7 cm (Hamill PW et al. 1979). Although there is some variation in mean adult height in studies from around the world, the differences appear to correlate with differences seen in the normal female populations (see Table 15). The ratio of mean Turner adult height to mean normal female adult height is consistent across ethnic populations. Using mean height values for Denmark (147/167 cm), the U.S. (143/164 cm), and Japan (137/157 cm), each case results in a ratio of approximately 0.88. A review of the world literature consistently reveals that Turner women can be

expected on average to reach approximately 88% of the mean adult height for normal females of the same ethnic origin. The sole exception to this rule in the literature is the data reported by Sybert et al.

Table 15

Comparison by Country of Turner
Adult Height with Normal Female Adult Height[a]

Country	Turner Syndrome	Normal Female	Ratio[b]
Germany	146.8	169.0	0.87
Denmark	146.8	166.8	0.88
Switzerland	143.3	166.0	0.86
Sweden	143.6	165.5	0.87
Finland	146.8	165.3	0.88
U.S. (Database)	144.0	163.7	0.88
U.S. (Sybert)	146.9	163.8	0.90
England	143.0	162.2	0.88
France	141.4	163.0	0.87
Japan	136.4	156.0	0.87

[a] Derived from Rocchiccioli.

[b] Ratio of mean adult height of Turner syndrome women to mean height of non-Turner syndrome women.

EFFECT OF PARENTAL HEIGHT ON TURNER PATIENT HEIGHT—U.S. DATABASE

The relationship of the parental heights with the heights of untreated Turner patients in the historical database was examined. The mid-parental target height for these 1031 patients was 162.9 ± 4.6 cm (mean $\pm$ SD). This is close to the average adult stature of normal American females of 163.7 ± 5.86 cm (Tanner JM et al. 1985). The mean standardized mid-parental height is -0.14 ± 0.78. Thus, the heights of the parents of Turner subjects are like those of the normal population.

Figure 13 shows the initial standardized height for 1031 untreated American Turner patients at various ages vs. their sex-adjusted, mid-parental height. No heights after estrogen therapy are included. There was a modest correlation of childhood height SDS and sex-adjusted, mid-parental height SDS ($r = 0.358$), which is highly statistically significant ($p = 0.0001$) due to the large sample size. Figure 14 shows the last adult height for 58 patients vs. their sex-adjusted, mid-parental height. The correlation of adult height and mid-parental target height ($r = 0.35$, $p = 0.007$) is similar to that shown in Figure 13. Since the

heights of the parents influence the childhood and adult heights similarly, once the childhood height is known, the contribution of parental heights to adult height is largely accounted for.

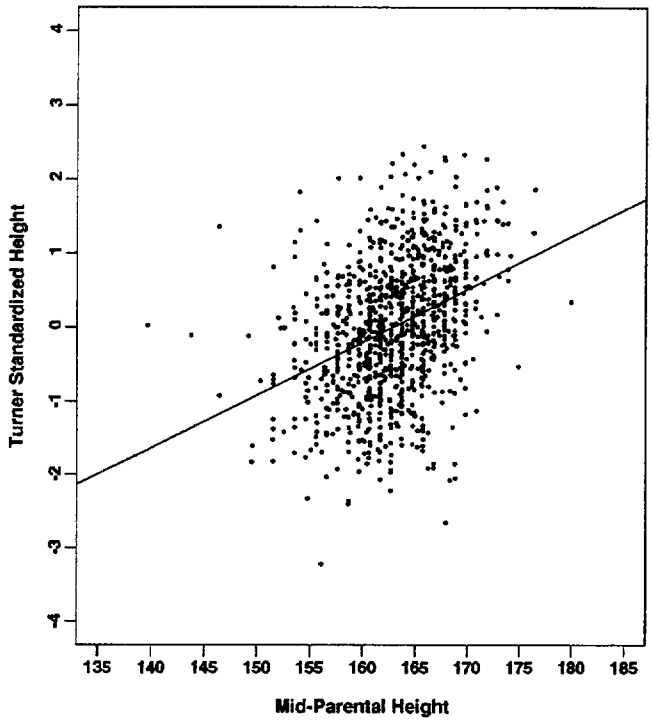

Figure 13: Initial Turner Standardized Height vs. Mid-Parental Target Height for Untreated American Turner Patients, Pre-Estrogen, n = 1031, r = 0.36, p = 0.0001

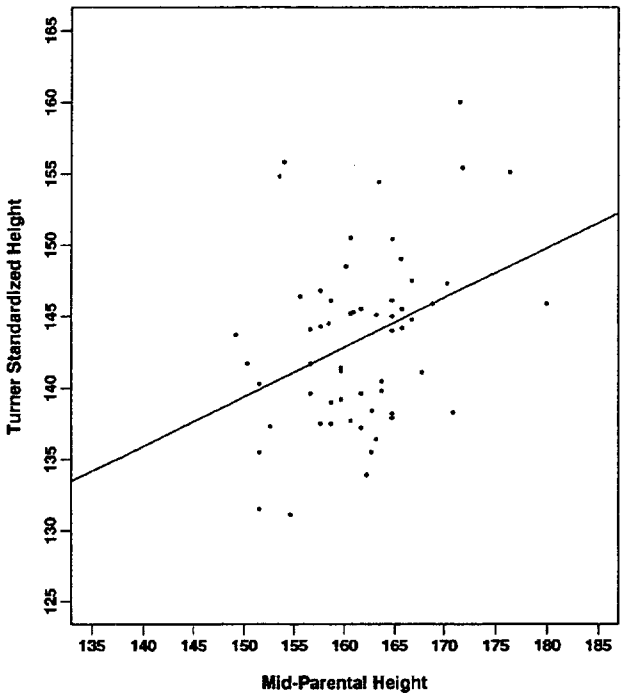

Figure 14: Adult Height (Age > 18) vs. Mid-Parental Target Height for American Turner Patients, n = 58, r = 0.35, p = 0.007

The above data illustrate that the heights of a Turner subject's parents influence childhood height and adult height similarly. Multiple regression analysis showed that including mid-parental height in addition to childhood standardized height reduced the variance of the prediction by less than 3%. Thus, most of the effect of the parent's height on adult height is already accounted for in the childhood height.

APPENDIX A (cont'd)

American Turner Syndrome Database

5. SECULAR TREND

It has been postulated that there is an ongoing secular trend in height, suggesting that children born in recent decades may be expected to be taller than children born earlier. Whereas this may be true in some developing countries, this does not appear to be significant in the U.S. during recent history. A complete report regarding the secular trends in stature for normal females in the United States has been provided by Dr. Alex F. Roche of the Fels Institute, a renowned expert in this field. Using data from three surveys conducted by The National Center for Health Statistics, he has found no notable trends in the height of normal American girls during the last few decades. Using height measurements for 11,585 girls aged 5–17 years, born from the late 1940s to the mid 1970s, there were minor differences in mean height over time, generally less than 1.5 cm.

From the National Health Series 11, No. 238[1], there was only a mean difference of 0.3 cm between the mean height of 1066 normal females aged 25–34 years. This difference is not statistically significant.

Figure 15 shows 2686 standardized heights for 1296 untreated Turner patients at all ages plotted against the year of birth of the patient. A simple regression analysis demonstrates that there is almost no correlation ($r = -0.076$). Figure 16 shows a similar plot for all untreated (except for estrogen) American Turner patients for whom height measurements at age ≥ 18 are available ($n = 84$). The last recorded height measurement for each subject was used. As before, no trend in adult height is apparent ($r = 0.068$, $p = 0.54$). We conclude that there has not been any clinically or statistically significant trend in height in Turner syndrome over the last four decades.

[1] (Ref: Vital and Health Statistics: Anthropometric Reference Data and Prevalence of Overweight, United States, 1976–80. Data from the National Health Survey Series 11, No. 238. DHHS Publication No. (PHS) 87–1688, October 1987.)

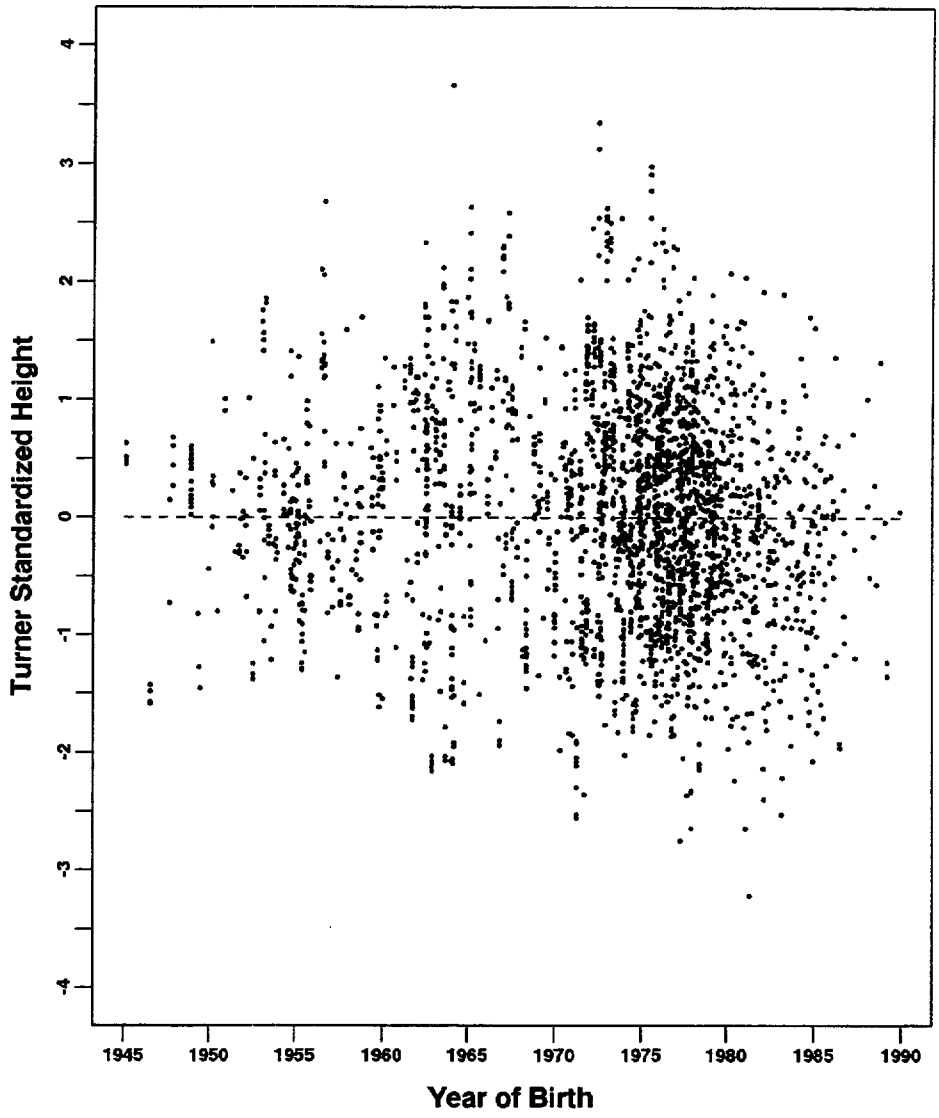

Figure 15: Turner Standardized Height vs. Year of Birth for American Turner Patients Before Treatment with Estrogen or Other Medication Affecting Height (2686 Points from 1296 Patients, r=–0.076)

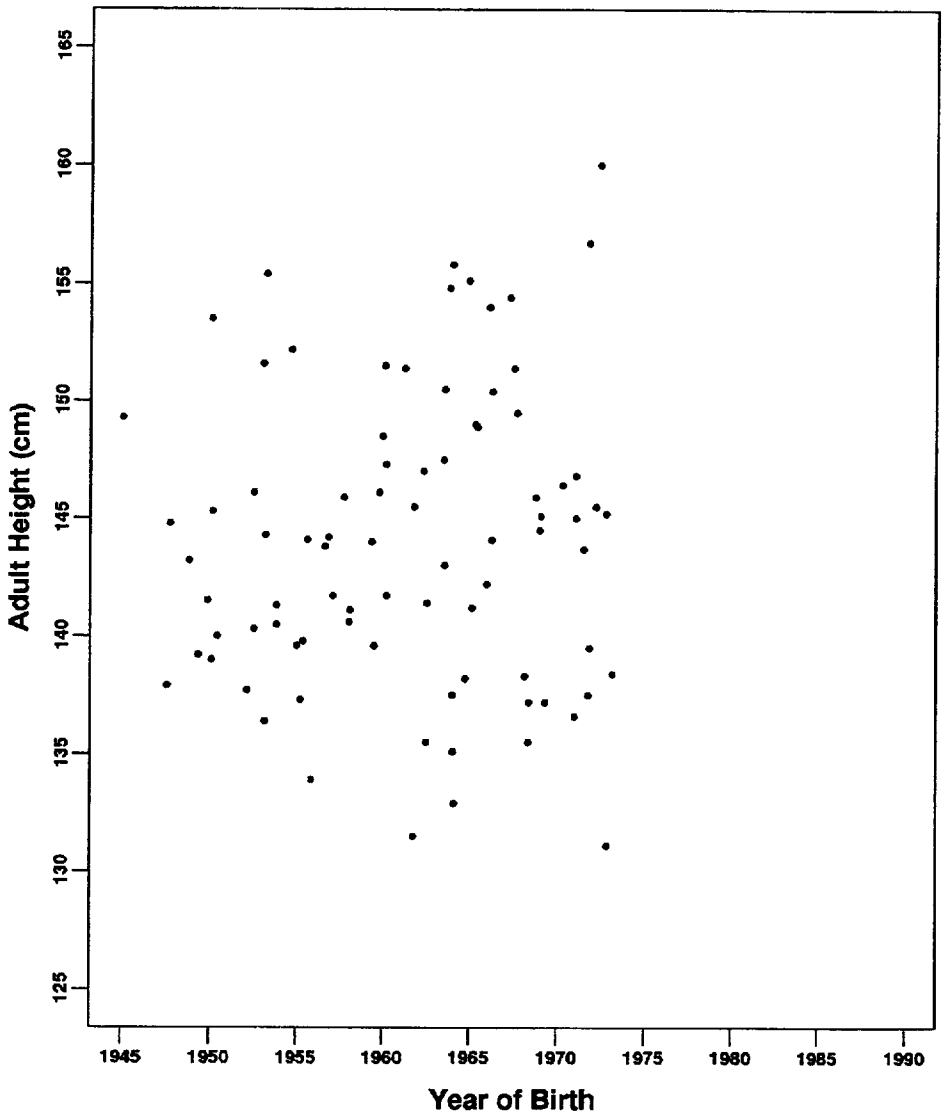

Figure 16: Adult Height vs. Year of Birth for American Turner Patients Including Patients who May Have Received Estrogen but Not Androgen or Growth Hormone, n = 84, r = 0.068, p = 0.5398

APPENDIX A (cont'd)

American Turner Syndrome Database

6. ESTROGEN

Heights from the U.S. database after the initiation of estrogen therapy (but before any growth hormone or androgens) are presented in Figure 17 (n = 682). This figure shows a tendency for the pre-adult heights to be slightly greater than the Lyon standards, as would be expected since the Lyon data excluded patients with estrogen therapy and estrogen is known to stimulate growth. Lyon noted similar findings in 29 girls whose mean height SD scores went from –0.55 before estrogen was started, to –0.15 after one year of estrogen, and back to –0.50 at final height. Thus, estrogen therapy caused a transient increase in standardized height and no significant change in adult height.

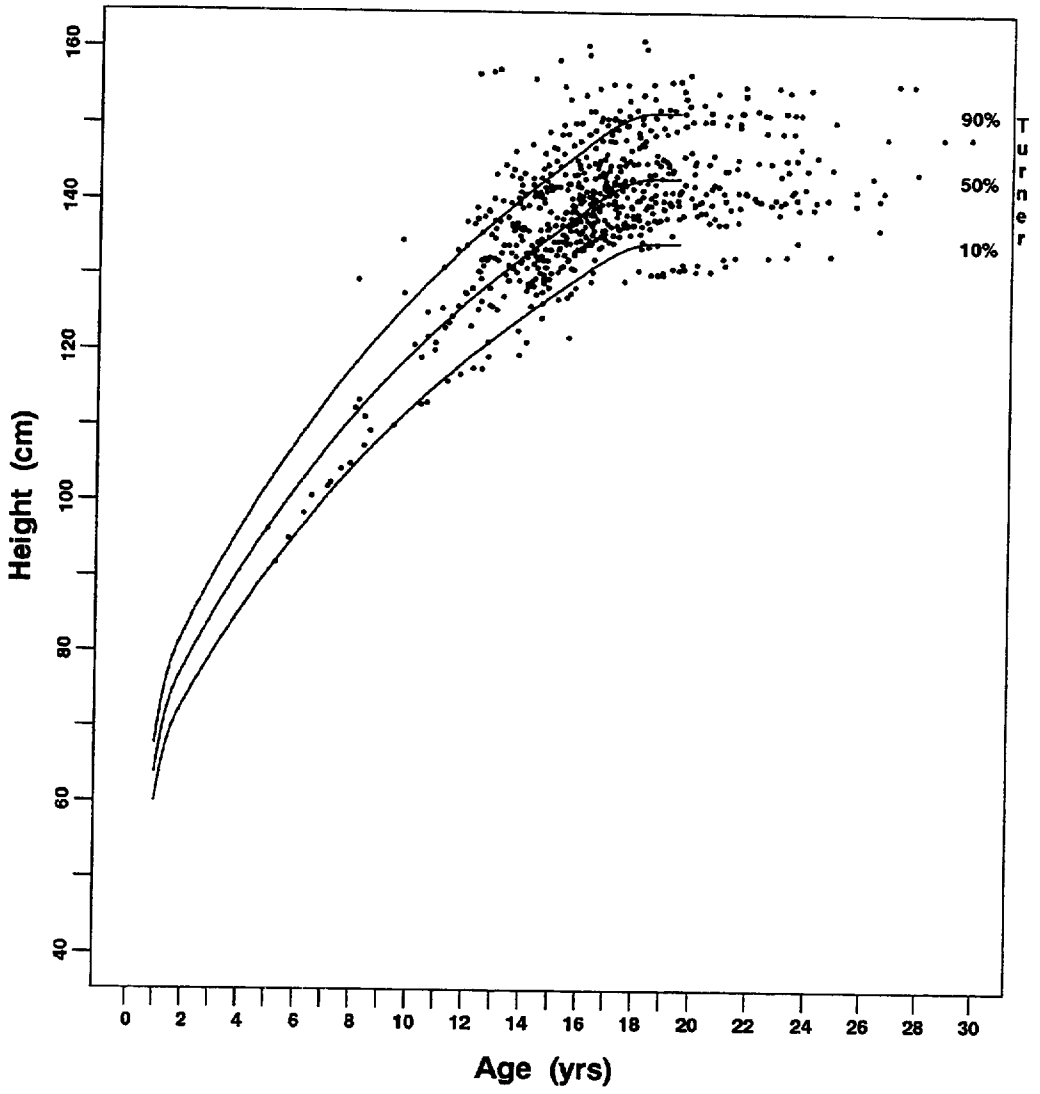

Figure 17: Heights of American Subjects with Turner Syndrome After Beginning Treatment with Estrogen but Before Treatment with Any Other Medication Affecting Height (682 points from 172 patients)

APPENDIX A (cont'd)

American Turner Syndrome Database

7. ACCURACY OF THE PROJECTED ADULT HEIGHTS

Although the standard curves constructed by Lyon et al. (Lyon AJ et al. 1985) are largely from cross-sectional data, they were demonstrated in the original paper to be useful in predicting adult stature. Although the authors provide a regression equation for prediction, they point out that simply calculating the height SD score at presentation and using the standards to project final height is fairly accurate.

Lyon provided the first validation of this method by comparing the childhood (ages 3–12) height SD scores of 29 girls with Turner syndrome with their own adult (ages 19–24) height SD score. A strong correlation was found ($r = 0.95$, $p < 0.001$), with a residual SD of 0.3% and 95% confidence limits of approximately ± 2.0 cm. The mean initial height SD score for the 29 patients was –0.60, while their mean final height SD score was –0.50, a change of 0.7 cm from their mean projected final height.

Further evaluation of the prediction method was performed by Naeraa et al. (Naeraa RW et al. 1990), who found little difference between mean childhood and adult SD scores in 78 Turner subjects. The correlation between childhood and adult standardized heights was 0.80.

Using our American Turner historical database, we evaluated 56 untreated patients for whom we had pre-estrogen heights at ages between 5 and 16, and adult heights after age 18 (adult heights include those on estrogen). These heights come from 13 centers throughout the United States.

Figure 18 shows the last adult Turner standardized height for each patient versus the corresponding earliest childhood height (minimum age 5). The mean childhood standardized height (and thus the mean projected adult standardized height) for the 56 patients was $+0.16 \pm 0.91$. The mean actual adult standardized height was $+0.12 \pm 0.92$. There was no significant change in Turner standardized height over time (mean change -0.04 ± 0.58, paired t-test, $p = 0.59$). Similar results were found when the analysis was restricted to patients who did not receive estrogen before age 15.

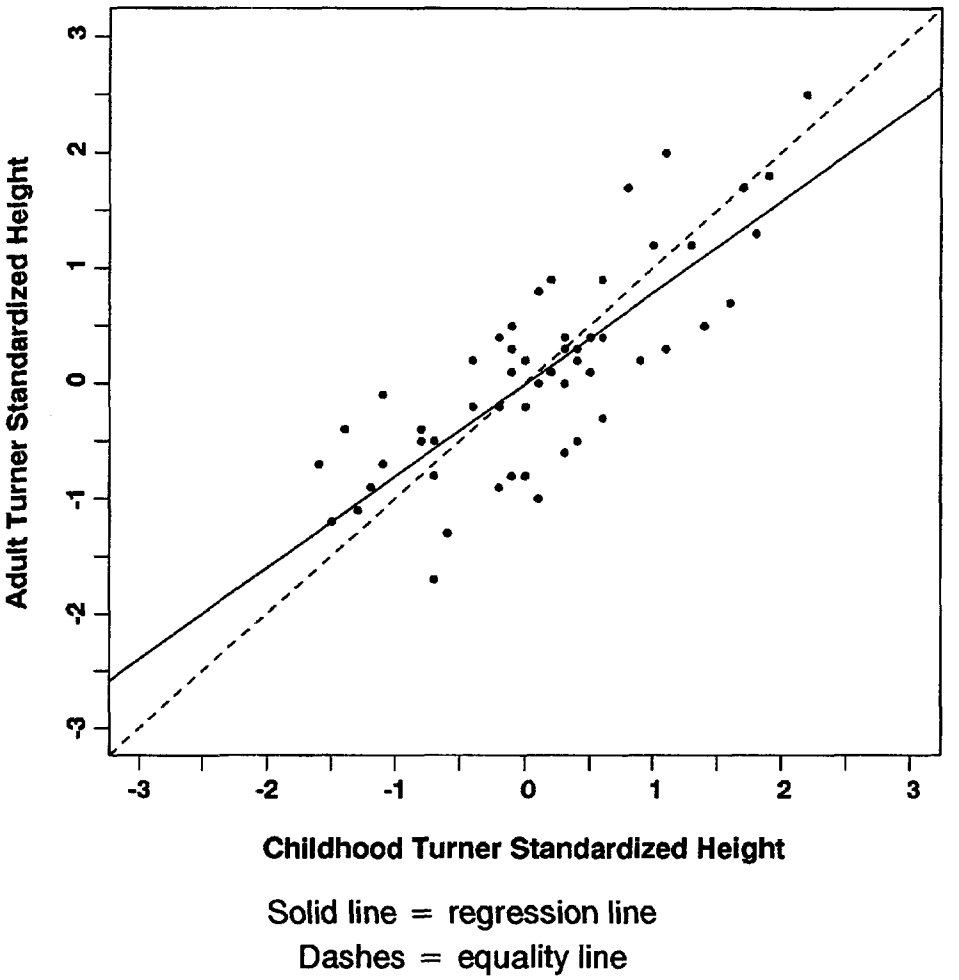

Figure 18: Adult Standardized Heights (Age > 18) Versus Childhood Standardized Heights (Ages 5 to 16) for American Turner Patients, $n = 56$, $r = 0.80$, $p < 0.0001$

A strong correlation was found for childhood and adult height SD score ($r = 0.80$, $p < 0.0001$), in agreement with the findings of Lyon et al. (Lyon AJ et al. 1985) and Naeraa et al. (Naeraa RW et al. 1990).

Projected final heights for the earliest childhood heights were compared with actual adult heights for the 56 patients plotted in Figure 18. The mean projected height was 144.1 ± 6.1 cm, while the observed adult height was 143.8 ± 6.2 cm. The mean difference was -0.3 ± 3.9 cm (range: -7.0 cm to 6.6 cm). We conclude that the longitudinal data for untreated Turner patients validate the pretreatment projected final height method.

The projected height method for Turner syndrome is actually independent of the mean adult Turner height of a particular population and thus is universally applicable (Frane JW et al. 1990). For example, using the data for Danish girls (Crock P et al. 1990), one could project the mean final height of the 69 ten-year-old Turner girls with a mean height of 121.6 cm. The mean projected adult height is 145.9 cm, which is similar to the observed mean adult height of 146.8 cm for the 53 Turner subjects in that study.

APPENDIX A (cont'd)

American Turner Syndrome Database

8. COMPARISON OF PROJECTION METHODS

Several methods of predicting adult height are available from the published literature. The methods are of two kinds. The first kind of method is the simple projection of adult height SD score as equal to the childhood height SD score, as first recommended by Lyon et al. These methods all use the simple formula:

subject's adult height SDS = subject's childhood height SDS

Thus, these methods all require norms for childhood and adult Turner height. Following Rosenfeld et al. (1992), we refer to all of these as "projection methods."

The second kind of method is also based on regression and also requires norms for childhood and adult Turner height, but it uses a more general equation of the form

adult height SDS = a + b * childhood height SDS

For example, Lyon et al. obtained the regression equation

adult height SDS = 0.21 + 1.13 * childhood height SDS

Using results from Naeraa et al., one obtains the equation

adult height SDS = 0.8 * childhood height SDS.

To distinguish these methods from the projections discussed above, we call them "equation methods." It is particularly important to distinguish the Lyon projection method from the Lyon equation method.

For both kinds of methods, to obtain the adult height projection in cm from the adult height SDS, as calculated above, the following formula is used:

projected adult height (cm = mean Turner adult height + adult height SDS * Turner adult standard deviation

where the mean Turner adult height and Turner adult standard deviation are obtained using the Turner norms for height.

All of these methods were derived using European data. Table 16 shows the accuracy of each of these methods using the same 56 U.S. untreated Turner patients, from the database discussed above. In this table, the Lyon and Naeraa equations are applied using the Lyon norms for height.

Table 16

Comparison of Adult Height Projections
Mean + SD

	Lyon Projection	Karlberg Projection	Ranke Projection	Lyon Equation	Naeraa Equation
Childhood Height SDS	0.16 ± 0.91	−0.39 ± 1.02	−0.02 ± .03	0.16 ± 0.91	0.16 ± 0.91
Projected Adult Height SDS	0.16 ± 0.91	−0.39 ± 1.02	−0.02 ± 1.03	0.39 ± 1.03	0.13 ± 0.73
Observed Adult Height SDS	0.12 ± 0.92	−0.49 ± 0.97	−0.29 ± 1.04	0.12 ± 0.92	0.12 ± 0.92
Projected Adult Height (cm)	144.1 ± 6.1	144.4 ± 6.5	146.2 ± 6.3	145.7 ± 6.9	143.9 ± 4.9
Observed Adult Height (cm)	143.8 ± 6.2	143.8 ± 6.2	143.8 ± 6.2	143.8 ± 6.2	143.8 ± 6.2
Observed Minus Projected Adult Height (cm)	−0.3 ± 1.0	−0.6 ± 4.0	−2.4 ± 4.0	−1.8 ± 4.2	−0.1 ± 3.7

The ranking of methods in decreasing order of mean accuracy were the Naeraa equation, Lyon projection, Karlberg projection, Lyon equation, and Ranke projection. Use of the Naeraa equation and the Lyon projection showed a high degree of accuracy. The Karlberg projection differed from observed adult height by less than one cm. However, both the Lyon equation and the Ranke projection markedly overpredicted adult height.

The Ranke projection overpredicted by about an inch. Since this is a simple projection, it suggests a systematic inaccuracy in the standard curves. Use of the Ranke projection as a method of assessing gain in adult height can thus lead to serious underestimate of benefit from GH therapy.

The error noted with the Lyon equation stems from the fact that it was based in part on a set of 29 English girls who were on average quite short in comparison with the norms that were composed by Lyon et al. from European continental data. In particular, none of their subjects had a childhood height SD score above 1.

Examination of the standard errors for the Lyon regression coefficients showed that their equation was not notably different from the simple projection. From the purely statistically point of view, the Lyon equation (adult height SDS = 0.21 + 1.13 * childhood height SDS) also suffers first from the fact that since SD scores are used, their intercept term 0.21 would be expected to be equal to zero. Second, their slope term 1.13 would be expected to be equal to the correlation of childhood and adult height SD scores and therefore would not exceed 1. The nature of the problems with the Lyon equation results in a substantial overprediction of adult height pretreatment and therefore a serious underestimate of adult height gain from GH therapy.

The good results for Naeraa et al. are expected from Figure 20 and its discussion, where it was shown that the regression for the U.S. data was the same (i.e., adult height SDS = 0.8 * childhood height SDS). Thus, the Naeraa equation could just as well be called the American equation.

In conclusion, evaluation of the differences in adult height gain reported in the literature that are based on projection methods must take into account the methods used. It should also be remembered that the projection method used to evaluate the Genentech Turner studies was derived on the basis of European data and validated using U.S. Turner subjects. Analyses could also have been reported made using the Naeraa (or American) equation, but essentially the same results are obtained when the Lyon projection or the Naeraa equation is used.

Since the Lyon projection method is validated with the U.S. data here and elsewhere in this report, and is in widespread use throughout the world, the Lyon projection method is used exclusively in this report.

APPENDIX A (cont'd)

American Turner Syndrome Database

9. POTENTIAL BIAS OF HISTORICAL CONTROLS

Since the Lyon data as well as the American database contain both cross-sectional and longitudinal data, there is the possibility that a bias entered into the generation of the standard growth chart. In particular, if taller patients are less likely to have follow-up data, then the estimate of adult height could be biased downward. This issue has been addressed by comparing the pre-estrogen childhood heights of patients for whom adult height is available with those for whom adult height is not available.

Table 17 shows the mean pre-estrogen Turner standardized heights at each chronological age year beginning with age 5. These means are reported separately according to whether there was an adult height available (column 3) or not (column 2). There was no statistically significant difference between these groups at any age except between the ages of 16 and 17 ($p = 0.03$) (column 4); in fact, there was a tendency for adult height to be available for taller rather than shorter children (column 3 > column 2). These results show that it is unlikely that the standard curves were subject to any downward bias for adult heights due to suspected dropouts of taller patients. A similar analysis showed that there was no consistent statistically significant relationship between height at any age and whether or not a height was available at any other age.

Table 17 also shows the mean adult standardized heights associated with each chronological age group (column 5). In all but two of the age groups, there was no statistically significant difference between the mean childhood standardized height (column 3) and the mean standardized adult height (column 6).

The general trend, however, was for the mean childhood standardized height to be greater than the mean adult height. If anything, the American subjects tended to be somewhat shorter as adults than the Lyon Turner curves predict. Thus, prediction of adult height using the Lyon Turner curves is somewhat conservative. Also shown in Table 17 are the correlations (column 7) and p-values (column 8) for childhood and adult heights in each age group. These correlations are all very high (range 0.77 to 0.99) and highly significant ($p \leq 0.006$ in all groups). Thus, the correlation of childhood and adult standardized heights are high at all childhood ages, consistent with the correlations observed by Lyon et al. (Lyon AJ et al. 1985) and Naeraa et al. (Naeraa RW et al. 1990).

Table 17

Turner Standardized Heights (n) for American Turner Patients Not Treated with Androgen or GH

1	2	3	4	5	6	7	8
Chronological Age	Mean Childhood Height SDS (No Adult Ht. Available)	Mean Childhood Height SDS (Adult Ht. Available)	t-test p-value between groups	Mean Adult Height SDS	t-test p-value Adult vs. Childhood	Correlation Childhood with Adult	Correlation p-value
5–6	–0.28	0.14	0.11	–0.01	0.40	0.90	0.0001
	(122)	(12)		(12)			
6–7	–0.29	–0.16	0.68	–0.02	0.47	0.93	0.0007
	(103)	(8)		(8)			
7–8	–0.25	0.06	0.46	0.01	0.75	0.95	0.0043
	(151)	(6)		(6)			
8–9	–0.20	–0.16	0.90	–0.01	0.49	0.77	0.006
	(196)	(11)		(11)			
9–10	–0.14	0.14	0.21	–0.02	0.31	0.83	0.0001
	(186)	(15)		(15)			
10–11	0.02	0.44	0.08	0.10	0.0082	0.91	0.0001
	(220)	(18)		(18)			
11–12	0.10	0.19	0.67	–0.11	0.016	0.84	0.0001
	(220)	(21)		(21)			
12–13	0.29	0.33	0.86	0.21	0.24	0.91	0.0001
	(206)	(25)		(25)			
13–14	0.32	0.00	0.16	–0.07	0.51	0.90	0.0001
	(151)	(25)		(25)			
14–15	0.56	0.28	0.21	0.08	0.10	0.86	0.0001
	(86)	(19)		(19)			
15–16	0.26	0.36	0.75	0.20	0.20	0.91	0.0001
	(41)	(19)		(19)			
16–17	–0.04	0.60	0.03	0.59	0.88	0.95	0.0001
	(38)	(15)		(15)			
17–18	–0.08	–0.09	0.98	–0.06	0.53	0.99	0.0001
	(14)	(12)		(12)			
18+				0.07			
				(84)			

APPENDIX A (cont'd)

American Turner Syndrome Database

10. SUMMARY

To evaluate the application of the Lyon Turner height standards for U.S. Turner subjects, a large database of untreated American Turner subjects consisting of approximately 3000 height measurements of 1300 patients was established. These data validate the use of these standards as well as the projection method used for predicting adult height.

The database also shows that there has been no secular trend in height for Turner syndrome subjects over the past 4 decades. Whereas factors such as karyotype and spontaneous puberty have minimal effect on adult stature, parental height and ethnic origin do. However, since these influences affect childhood height and adult height equally, the projection method is still valid for any Turner subject regardless of genetic background. In addition to validating the projection method, the U.S. untreated Turner database contains 56 untreated subjects with both childhood and adult height, from whom matched cohorts were derived for comparison with patients treated in the two Genentech clinical studies of GH in Turner syndrome, as presented in the Efficacy section of this document.

APPENDIX B

Literature Review—Growth Promoting Therapies

ANDROGEN THERAPY

Numerous attempts have been made by investigators in many countries to improve the growth of girls with Turner syndrome, with the primary objective of improving adult stature. Many of these studies have used androgens (e.g., oxandrolone, fluoxymesterone), a class of drugs with both anabolic and virilizing effects. Virtually all of these studies have demonstrated short-term improvements in growth rate, whereas those studies carried out to near final height have shown either no effect or modest gains (Table 18).

Table 18

Effect of Androgen Therapy on Adult Height in Published Studies of Turner Syndrome

Reference	No. Treated	Drug[a]	Mean Adult Height (cm)	Mean Control Height (cm)	Type of Control
Moore	9	ox	146.4	140.3	estrogen
Lev-Ran	15	nan/me	143.3	143.2	untreated
Urban	25	ox and/or flu	146.5	140.6	estrogen
Joss	15	ox	143.3	139.4	untreated
Sybert	29	ox or flu	148.1	146.3	untreated
Muritano	37	nor or met	142.0	140.1	untreated
Lenko	47	flu	145.5	145.6	untreated
Naeraa	22	ox	147.5	144.5	predicted ht.
Crock	23	ox	145.5	140.5	predicted ht.

[a] ox = oxandrolone; nan = nandrolone; me = methandrostenolone; flu = fluoxymesterone; nor = norethandrolone; met = metandienone.

The results of the above studies are in general agreement that the net gain in adult stature is on the order of 0–3.9 cm when compared with untreated controls, and approximately 6 cm when compared with controls who received early estrogen therapy.

ESTROGEN THERAPY

Studies using estrogen therapy alone for growth promotion in Turner syndrome have been fewer in number, although it should be noted that many of the control populations mentioned in other studies have received estrogen replacement therapy. As discussed previously, it is unlikely that estrogen deficiency accounts

significantly for the growth failure in Turner syndrome; however estrogen replacement is eventually prescribed in these patients anyway for the treatment of ovarian failure. The prevailing practice has been to delay estrogen replacement therapy until age 14 or beyond to prevent early epiphyseal closure. Ranke and Grauer (Ranke MB et al. 1994) concluded that estrogen begun at that time is highly unlikely to interfere with final height attainment. However, this does result in a delay of pubertal development in these children relative to their unaffected peers.

Some investigators have attempted to use low-dose estrogen therapy at an earlier age for the treatment of growth failure in Turner syndrome. Ross et al. (Ross JL et al. 1983) studied the short-term response (using ulnar length) to ethinyl estradiol and showed an increase in growth rate at a low dose that was not observed at higher doses. A subsequent 6-month placebo-controlled trial in 16 Turner girls showed a 70% greater growth rate in the treated group, with a slight increase in predicted adult height (Ross JL et al. 1986).

Bohnet (Bohnet HG et al. 1986) reported improved growth rates in 33 girls aged 12–17 treated for 1–4 years. However, growth rates quickly declined to pretreatment levels and adult bone age was reached following 2–4 years of treatment. Lenko et al. (Lenko HL et al. 1988) also reported increased short-term growth rates in patients receiving estrogen alone.

Kastrup et al. (Kastrup KW et al. 1988; Kastrup KW et al. 1986; Kastrup KW et al. 1991) reported the effects of low-dose estrogen in 35 girls with Turner syndrome. While an increase in first year growth rate was observed, bone maturation was noted to be accelerated, especially in the younger girls, with no improvement in final height noted in the older girls (mean 144.2 cm vs. pretreatment predicted mean of 142.2 cm, n = 12). Demetriou et al. (Demetriou E et al. 1984) noted a small increase in growth rate in 19 patients treated at a mean age of 14.3 years, but no increase in 18 patients treated at a mean age of 17.2 years. They report that neither dose nor duration of therapy with estrogen was correlated with final height.

Martinez et al. (Martinez A et al. 1987) gave ethinyl estradiol to nine patients for 18 months and showed similar early gains in growth rate, but showed no significant change in predicted adult height due to accelerated bone maturation. Ranke et al. (Ranke MB et al. 1986) observed a marginal increase in growth rate in 33 girls receiving estrogen therapy, again accompanied by undue advancement of bone age. Pasquino and Boscherini (Pasquino AM et al. 1991)

treated 11 subjects with a lower dose of ethinyl estradiol than previous studies, and found a small increase in growth rate in 8 of the 11 patients.
Lin et al. (Lin TH et al. 1994) investigated the use of low-dose estrogen plus androgen therapy in 9 patients and found no effect on adult height.

The above studies employing low-dose estrogen for the purpose of promoting growth in Turner syndrome are consistent in showing a modest transient acceleration of growth, invariably accompanied by significant skeletal maturation. Most investigators agree that no improvement in final height can be achieved with estrogen treatment alone, however low the estrogen dose utilized.

GH THERAPY

The use of growth hormone (GH) in the treatment of short stature associated with Turner syndrome has been studied since 1960, when Escamilla et al. (Escamilla RF et al. 1960) treated one patient for 3.5 months with pituitary (cadaveric) GH and showed a doubling of her growth rate. Since then, GH administration in Turner syndrome has been the subject of many clinical trials. Efficacy and safety with GH has been described in sizable cohorts from numerous countries. These are summarized below, with specific discussion of dose-response relationship and adult height results.

GH DOSING REGIMENS

Early evaluations with pituitary GH showed that, compared with children with GH deficiency, Turner syndrome patients had an inherent tendency for poorer response to GH therapy. For this reason, a slightly higher dose (0.375 mg/kg/wk) was selected for Protocol 83-002/85-023 and subsequently for Protocol 85-044. At no time was the total weekly dose altered in either study, although the growth response in Turner syndrome to this higher dose remained less than that seen in GH-deficient patients at 0.3 mg/kg/wk. The efficacy and safety demonstrated for this dose suggest that it is appropriate for the treatment of this population.

The use of recombinant GH in the management of short stature associated with Turner syndrome has been the subject of numerous clinical trials. Table 19 summarizes the first year growth response results of clinical trials from the literature. Studies that used only pituitary GH are not included since treatment was often intermittent. A total of 22 clinical trials using daily GH dosage regimens in the absence of oxandrolone or estrogen therapy have resulted in 32 mean first-year growth responses.

Table 19

Literature Experience with Recombinant GH
in Turner Syndrome First-Year Growth Response

Baseline Age (yrs)	n	Dose[a]	Pre-GH Growth (cm/yr)	0–12 mo. Growth (cm/yr)	0–12 mo. Increase (cm/yr)	GH Duration (months)	Reference
10.0[b]	29	0.179[D]	4.2[c]	6.4	2.2	48	Attanasio,
9.0[b]	26	0.269[D]	4.2[c]	8.5	4.3	48	Kollman,
							Weise
9.2[b]	15	0.370[D]	4.0	8.4	~4.4	36	Bergmann,
12.0[b]	4	0.370[D]	3.5	8.9	~5.4	36	Massa,
12.9[b]	17	0.370[D,E]	4.1	7.4	~3.3	36	Vanderschueren-Lodeweyckx
NA	232	0.270[D,E]	NA	NA	NA	36	Chipman
4–14	17	0.308[D]	3.5	8.4	4.9	12	Crowne
3–16	19	NA	3.5	7.4	~3.9	12	Ferrandez
6–19	51	0.308[D,E]	NA	5.9	NA	24	Gerver
NA	68	0.256[D]	5.9	7.9	~2.0	36	Hakeem
		0.385[D]	4.9	9.1	~4.2		
7–13	11	0.256[D,E]	3.4	3.8	~0.4	24	Haeusler & Frisch
10.1[b]	10	0.269[D]	3.5	6.3	~2.8	36	Job
11.4[b]	12	0.269[D,ox]	3.3	7.4	~4.1	36	
11.1[b]	46	0.173[D]	3.9	5.5	~1.6	12	Job
	49	0.346[D]	3.8	6.7	~2.9	12	
	28	0.173[D,E]	3.3	6.8	~3.5	12	
	26	0.346[D,E]	3.7	7.0	~3.3	12	
7–16	33	0.269[D]	3.3	6.2	2.9	24	Knudtzon
6–11	10	0.385[D]	3.7	8.3	~4.6	12	Lebl
7–14	25	0.269[D]	3.8	7.3	~3.5	24	Lenko
12–14	5	0.354[ox]	3.2	8.6	~5.4	24	Lu & Cowell
4–9	11	0.269[D]	NA	NA	NA	12	Lyson-Wojciechowska
	22	0.538[D]					
8–13	8	0.346[D]	3.4	5.9	~2.5	12	Merola
8–14	8	0.346[D,E]	2.8	6.1	~3.3	12	
7–11	13	0.269[D]	3.7	6.8	~3.1	24	Naeraa
9–13	8	0.000[D,E]	3.2	5.8	~2.6	24	
11–18	18	0.269[D,E]	2.4	5.8	~2.4	24	
6–12	9	0.296[T]	4.0	6.8	~2.8	48	Nienhuis,
6–12	11	0.296[D]	4.3	7.9	~3.6	48	Rongen-Westerlaken
12–19	16	0.296[E,T]	3.2	4.9	~1.7	48	
12–19	16	0.296[D,E]	4.0	6.9	~3.9	48	
8–17	15	0.240[D]	3.6	5.4	~2.8	36	Pasquino
3–12	17	0.346[D]	NA	NA	NA	24	Pavia
9–15	14	0.346[D,E]				24	
10.5[b]	32	0.327[D]	4.0	6.1	~2.1	48	Pienkowski
11.0[b]	653	0.288[D]	4.1	6.8	~2.7	48[d]	Price
12.9[b]	99	0.288[D]	NA	NA	NA	36	Rocchiccioli

Table 19 (cont'd)

Literature Experience with Recombinant GH
in Turner Syndrome First-Year Growth Response

Baseline Age (yrs)	n	Dose[a]	Pre-GH Growth (cm/yr)	0–12 mo. Growth (cm/yr)	0–12 mo. Increase (cm/yr)	GH Duration (months)	Reference
NA	16	0.354[D]	3.4	7.6	~4.2	48	Rongen-Westerlaken
10.9[b]	12	0.354[D]	NA	NA	NA		
14.1[b]	4	0.354[D,E]	NA	NA	NA		
NA	106	0.300[E,T]	NA	NA	NA	60	Ross
7–12	51	0.300[D,E]	4.3	8.2	~3.9	24	Rovet, Holland
7–10	8	0.330[D]	NA	NA	NA	12	Saggese
7–13	9	0.288[D]	3.3	6.5	~3.2	12	Sato
8.8[b]	22	0.321[D]	4.6	8.2	3.6	12	de Schepper
9.1[b]	22	0.321[B]	4.7	7.4	2.7	12	
5–16	29	0.385[D]	3.9	7.6	~3.7	12	Sippell
10.2[b]	47	0.231[D]	4.0	6.3	~2.3	24	Stahnke
10.5[b]	44	0.231[D,ox]	4.2	8.5	~4.3	24	
3–17	47	0.192[D]	3.7	5.2	1.5	36	Takano
	39	0.192[D]	3.6	6.9	2.3	36	
	43	0.192[D]	3.6	5.7	2.1	36	
	47	0.385[D]	3.5	6.3	2.8	36	
	43	0.385[D]	3.6	6.9	3.5	36	
	51	0.385[D]	3.5	6.4	2.9	36	
9.9[b]	16	0.269[D]	4.0	6.1	~2.1	36	Toublanc
10.9[b]	18	0.269[D,ox]	3.5	7.5	~4.0	36	
2–10	54	0.315[D]	NA	NA	NA	12	van Teunenbroek
11.1[b]	21	0.462[D]	3.8	NA	4.5	12	Werther
	20	0.462[D,E]					
4–9	15	0.404[D]	4.7	NA	NA	24	Wisniewski & Romer
3–9	15	0.404[D]					
		0.269[D,ox]					Nilsson
12.1[b]	17	0.269[D,ox],	3.9	NA	NA	48	
12.3[b]	15	E	3.8	NA	NA	48	
11.3[b]	22	0.269[D,E]	3.8	NA	NA	48	

[a] Dose in mg/kg/wk; where applicable, 2.6 IU/mg and 30 kg/m^2 assumed.
[b] Mean results provided; range not published.
[c] Untreated control group; pretreatment growth rates not reported.
[d] Actual breakdown: n = 457 × 1 yr; n = 285 × 2 yrs; n = 156 × 3 yrs; n = 47 × 4 yrs.
[B] Twice-daily injections.
[D] Daily injections.
[T] Three injections weekly.
[E] Estrogen given concomitantly with GH therapy during the first year.
[ox] Oxandrolone given concomitantly with GH therapy during the first year.
~ Increase was estimated using the difference of means.
NA = Not available.

Regression analysis of first-year responses by total weekly GH dose (weighted by the number of patients in each study) resulted in a significant relationship ($p < 0.001$) and is illustrated in Figure 19. The point derived from Genentech's trial (85-044) is also plotted as a diamond.

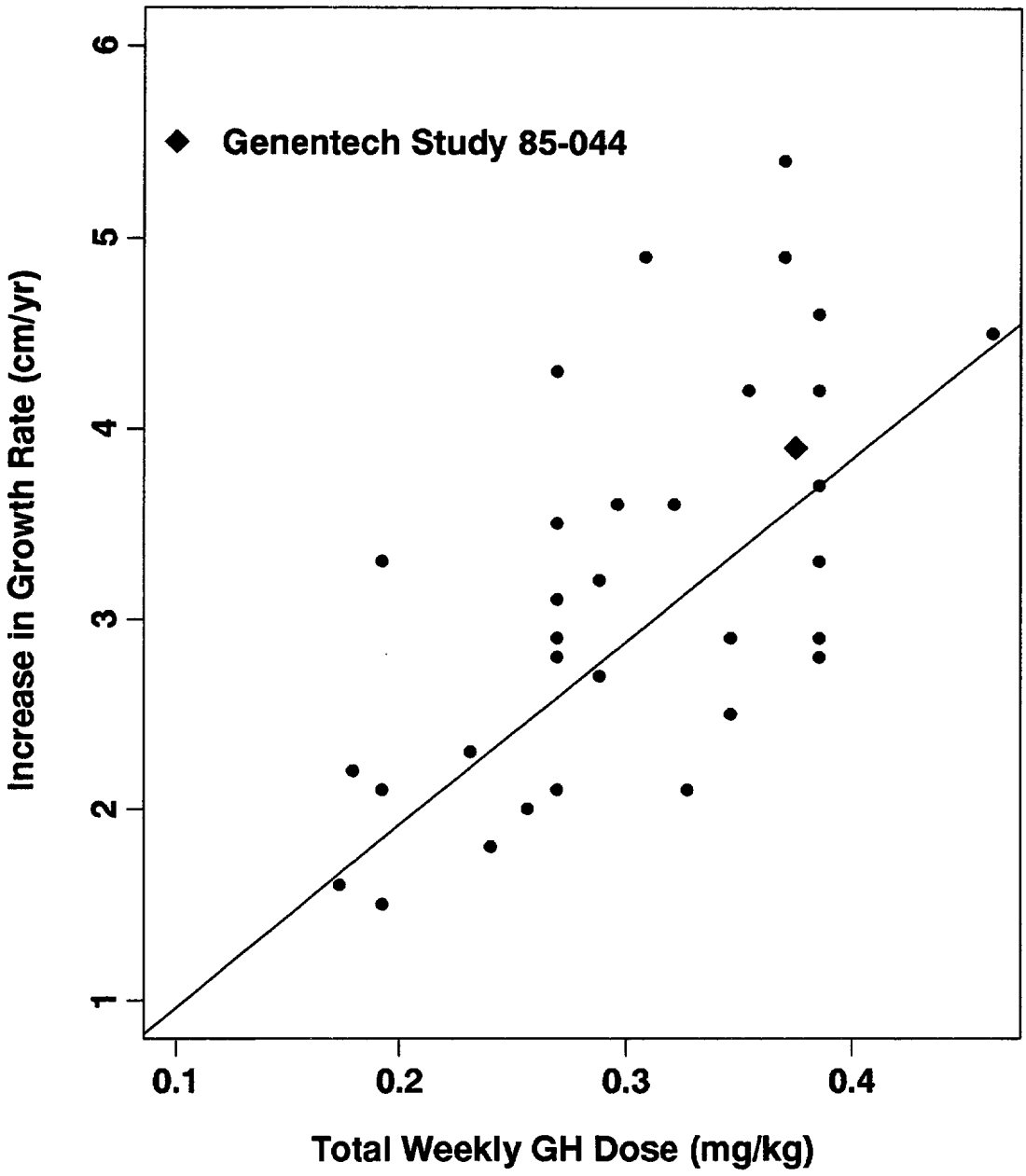

Figure 19: Increase in Growth Rate Versus Total Weekly Dose in Turner Syndrome. Each symbol represents a treatment group reported in a published study. The diamond represents data from Genentech Study 85-044.

The line of regression obtained is described by the following equation:

Increase in growth rate (cm/year) = 9.6 × total weekly dose (mg/kg/week)

For example, a dose of 0.15 mg/kg/week would be expected to increase first-year growth rate by 1.5 cm/year. The weekly dose of 0.375 mg/kg would be expected to increase the first-year growth rate by 3.6 cm/year, which is very close to the increase in rate of 3.9 cm/year observed in the Genentech trial 85-044.

Table 20 describes four studies in Turner syndrome which evaluated more than one dose of GH in the absence of estrogen or androgen treatment. Examination of these first-year growth responses substantiates a less robust response to GH in Turner syndrome patients compared with GH-deficient patients on similar doses. However, higher doses uniformly resulted in greater growth responses.

Table 20

Responses to Various Doses of Recombinant GH
in Prepubertal Turner Syndrome Patients

Reference	GH Dose (mg/kg/wk)[a]	n	Growth Rate (cm/yr)		
			Baseline	1st-Year	Increase
Hakeem	0.26	68	5.9	7.9	~2.0
	0.39		4.9	9.1	~4.2
Job	0.17	46	3.9	4.4	~1.6
	0.27	10	3.5	6.3	~2.8
	0.35	49	3.8	6.7	~2.9
Kollmann	0.18	29	NR	6.4	2.2
	0.27	26	NR	8.5	4.3
Takano	0.19	47	3.7	5.2	1.5
	0.19	39	3.6	6.9	2.3
	0.19	43	3.6	5.7	2.1
	0.39	47	3.5	6.3	2.8
	0.39	43	3.6	6.9	3.5
	0.39	51	3.5	6.4	2.9

[a] Where applicable, 2.6 IU/mg GH and 30 kg/m^2 assumed.
~ Increase was estimated using the difference of means.
NR = Not reported.

ADULT HEIGHT

Several studies of the use of GH in Turner syndrome and its effect on adult height have now been published or otherwise reported (Table 21). These studies vary with regard to important aspects of study design, such as the age of initiation of GH, duration of GH therapy, the dose and schedule of GH, the age of initiation and dose of estrogen, and the use of oxandrolone co-therapy. Nonetheless, the results are consistent with each other and with the Genentech Turner syndrome clinical trials when studies with similar designs are compared.

As with the Genentech studies, the "adult" heights reported in most of these studies are conservative estimates of efficacy, as the patients usually have potential for further growth at the end of the studies. In addition, a number of studies report incomplete adult height data, lacking data for the subjects who were youngest at baseline. Finally, estimates of adult height gain are affected by the choice of method used, as discussed in Appendix A. For consistency, mean net gains in adult height are reported relative to pretreatment projection based on Lyon curves if available.

Table 21

Studies with Adult Height Results
in GH-Treated Turner Syndrome
(Mean)

Study	N at Adult Ht	Adult Ht (cm)	Adult Height Gain (cm)	GH Age (yr)	Estrogen Age (yr)	GH Dose (mg per kg weekly)
EARLY GH, LATER E						
U.S. Genentech 85–023	17	150.4	7.4 M, 8.4 L	9.1	15	0.375
U.S. Genentech 85–044	29	150.4	8.3 M, 8.4 L	9.4	15	0.375
Germany (some + Ox)	47	148.5–152.0 152.0–154.6 (Ox)	4.5–9 L	10–11	NA	0.185–0.33
EARLIER E						
U.S. Genentech 85-044	26	147.0	5.9 M, 5.1 L	9.6	12	0.375
U.S.—Lilly GDCI	31	148.7	NA	11.1	8, 13.5	0.27, 0.36
Canada—Lilly GDCT	27	146.0	5.4 C	11.7	13	0.3
Australia	18 15	147.3 148.1	3.7 L 5.5 L	11 11	11 13	0.44 0.44
Canada	17	148.0	NA	12	13	0.3
Netherlands	45	152.3	2.6 R	NA	12	0.3–0.44
Japan	41	144.0	6–8 NS	10	NA	0.185, 0.37
LATE GH						
U.S. Genentech 85-044	51	148.5	5.0 M, 4.7 L	12.7	14	0.375
Belgium	31 15	151.3 153.8	8.5 L 6.9 L	12 15	14 16.5	0.37 0.3
France (some + Ox)	93	147.4 148.1 (Ox)	5–6 H	13	NA	0.28
Italy (some Ox, pre-GH)	18 10	148.4 143.0 (Ox)	5.9 H 0.5 H	13	NA	0.37
Scotland	26	141.7	0.7 NS	NA	NA	NA
Europe—Lilly	117	150.4	3.5 R	12	14.5	0.289
LOW DOSE GH						
United Kingdom	21 17	147.5 148.0	1.7 L 5.3 L	12 11	13 13	0.22 0.26
REGISTRIES						
U.S. NCGS (some + Ox)	230	147.8	5.3 L	12	NA	NA
KIGS (some + Ox)	82	149.6	6.1 L	12	14	0.26

Table 21 (cont'd)

Studies with Adult Height Results
in GH-Treated Turner Syndrome
(Mean)

Study	N at Adult Ht	Mean Adult Ht (cm)	Adult Height Gain (cm)	GH Age (yr)	Estrogen Age (yr)	GH Dose (mg per kg weekly)
GH + OX						
Genentech 85-023	46	151.5	9.8 L	9.9	15	0.375 mg
Sweden	6	151.0	6.6 L	12	NA	0.26
	7	151.1	5.1 L	12	13	0.26
	17	154.2	8.9 L	12	NA	0.26
	15	151.1	3.8 L	12	12	0.26

GH: growth hormone.
E: estrogen.
OX: oxandrolone.
C: vs. randomized controls (ANCOVA)
M: vs. matched historical controls (ANCOVA)
L: vs. projected adult height using Lyon standards.
R: vs. projected adult height using Ranke standards.
H: vs. historical data for untreated Turner syndrome.
NS: vs. projected adult height, standards not specified.
NA: Not available.

STUDIES WITH EARLY GH AND LATER ESTROGEN THERAPY

Some of the published studies of GH use in Turner syndrome utilized GH therapy at an early age (mean age < 12 years) and delayed estrogen therapy. This is similar to two of the treatment groups in the Genentech clinical trials, as well as the group treated with GH plus oxandrolone, discussed later.

Several studies conducted in **Germany** were summarized by Stahnke et al. (book), utilizing a variety of GH products and dosages. Adult height was reported in 47 of 228 enrolled patients. The mean age of initiating GH was between 10 and 11 years in each study. Mean final heights in the various study groups were 150.0, 152.0, 148.5, 154.6, and 152.0, with the latter two groups including some patients treated with oxandrolone co-therapy. Mean increases in adult height compared with Lyon projected heights, were between approximately 4.5 and 9.0 cm.

A multicenter study in **Japan** has been reported by Takano et al. (3 sources), with 41 of 341 enrolled patients at adult height. Patients received early GH therapy and delayed estrogen therapy. The patients received either 0.5 or 1.0 U/kg/wk and achieved mean adult heights of 144.6 and 143.5 cm

respectively. A significantly greater increase in standardized height was found in the higher dose group. Relative to the mean projected height of 137 cm (for all enrolled patients, standards used not specified), the mean net gain was estimated by the authors to be 6–8 cm.

In the Genentech clinical trials, one treatment group in each of the studies had early GH and late estrogen therapy. In Genentech study **85-023**, 17 patients initiated treatment with GH at a mean age of 9.1 years and were treated for a mean duration of 7.6 years. Estrogen therapy was begun at a mean age of 15.2 years. GH dose was 0.375 mg/kg/wk. Mean adult height was 150.4 cm, representing a net gain of 8.4 cm compared with pretreatment Lyon projected height.

In Genentech study **85-044**, a similar group of 29 patients were treated with GH starting at a mean age of 9.4 years and for a mean duration of 6.1 years. Estrogen therapy was begun at a mean age of 15.0 years. GH dose was 0.375 mg/kg/wk. Mean adult height was 150.4 cm, representing a net gain of 8.4 cm (vs. Lyon projection), identical to the results of the previous study.

The third treatment group to receive early GH and late estrogen in a Genentech study is discussed below under studies with oxandrolone co-therapy.

STUDIES WITH LATE ONSET OF GH THERAPY

Several studies have been reported in which GH therapy was begun at a relatively late age (mean age > 12 years), often resulting in a decreased duration of GH therapy, especially prior to the onset of estrogen therapy. This is similar to one of the treatment groups in Genentech study 85-044.

Two multicenter studies conducted in **Belgium** were summarized by Heinrichs et al. (1995). Adult height was reported in 46 of 88 enrolled patients. GH therapy was begun at a mean age of 12.2 years in one study and 14.9 years in the second study. Mean duration of GH therapy was 5.2 and 3.6 years, respectively. Mean adult heights were 151.3 cm and 153.8 cm, representing mean net gains of 8.5 cm and 6.9 cm, respectively, compared with Lyon projected heights.

Final height results have been reported by Rochiccioli et al. (3 refs) for 117 patients in a multicenter study in **France**. Mean age of onset of GH therapy was 12.9 years, with the mean duration of therapy only 3.8 years. Mean GH

dose was relatively low at 0.74 U/kg/week. Mean final height was 147.4 cm with GH alone and 148.1 cm in those treated with oxandrolone co-therapy (n=24). Greater adult heights were achieved in patients treated >3 years than in those treated for shorter duration. The mean net gain was estimated to be approximately 5–6 cm based on data for untreated French girls with Turner syndrome. It is noteworthy that the girls in this study were shorter than average Turner girls at baseline (mean baseline height SDS=–0.3 by Ranke standards).

Limited data for a study in **Scotland** was reported in an abstract, which was subsequently referenced in a recent Lancet paper and editorial. Mean "final" height was reported for 26 of 58 enrolled patients, treated for a mean duration of 3.5 years, with a number of subjects treated for only 1 year. Mean "final" height for these 26 patients was 141.7 cm compared with a mean projection of 141 cm (method not specified). The age at "final" height was not reported.

The results of **5 European studies** sponsored by Eli Lilly were reported by Massa et al. and Van den Broeck et al. (1995). Adult height was reported for 117 of 229 enrolled patients. Mean GH dose was relatively low at 0.79 U/kg/wk. Mean baseline age was 12.3 years. Mean final height was 150.4 cm. The mean net gain was reported as 3.5 cm in the abstract compared with baseline projections using the Ranke standards (see Appendix A regarding use of these standards). A presentation of the same data at the 1996 International Congress of Endocrinology meeting included a revised calculation using validated projection methods, resulting in mean net gains of approximately 6 cm (Van den Broeck et al. [1996]).

Taken together, these studies suggest that late onset and limited duration of GH therapy will result in gains of approximately 5 cm in adult height. These are consistent with the 51 patients in Genentech study **85-044** treated with GH after age 11 (mean age 12.7 years) and for a mean duration of 3.8 years. Estrogen therapy was begun 12 months after GH therapy, at a mean age of 13.7 years. Mean final height was 148.5 cm, for a mean net gain of 4.7 cm compared with Lyon projected heights.

STUDIES WITH EARLIER ONSET OF ESTROGEN THERAPY

Several studies have reported lesser benefits of GH therapy associated with the use of estrogen replacement therapy at a relatively early age. In most of these studies, GH was initiated at a relatively late age, resulting in a shortened period

of GH therapy prior to estrogen replacement. These studies are comparable to one of the treatment groups in Genentech study 85-044.

Werther et al., 1995, reported data from a multicenter study in **Australia** with adult height reported in 33 of 41 enrolled patients. Mean baseline age for GH therapy (1.2 μg/kg/week) was 11 years. One group of patients started estrogen at that time, while another group received on placebo for 2 years before starting estrogen at a mean age of 13 years. Mean adult height was 147.3 cm in the first group and 148.1 in the second group, with mean net gains of 3.7 cm and 5.3 cm, respectively, compared with Lyon projected heights.

Data for 17 patients in an uncontrolled study in **Canada** were reported by Taback et al. 1995. Mean GH dose was 0.3 mg/kg/wk, median age of initiation of GH therapy was 12.4 years, with estrogen therapy begun at a median age of 13.3 years. Median adult height was 148.0 cm, compared with 140.7 cm in a group of non-randomized controls (n = 14). Mean data were not reported. Comparisons were made using projected adult heights based on an equation calculated by Lyon et al., which is known to overpredict, as demonstrated by the control data in this study (see Appendix A).

A multicenter study in the **Netherlands** has been reported by Massa et al. and Nienhuis et al. Adult height was available for 45 of 54 patients. Most patients were over age 12 at the start of GH therapy (1.2 μg/kg/week) and started estrogen therapy either at age 12 or at the onset of GH therapy. Mean adult height was 152.3 cm, which was compared with 147.6 cm in a report of untreated Dutch Turner patients. Comparisons with the Ranke projection suggested a mean gain of only 2.6 cm, although this method has subsequently been shown to overpredict the adult height of untreated subjects (see Appendix A).

These results confirm the observation made in Genentech study **85-044** that early estrogen therapy compromises the effect of GH therapy. The 26 patients who started GH therapy at a mean age of 9.6 years and estrogen at 12.3 years had a mean adult height of 147.0 cm, for a mean net gain of 5.1 cm. A comparison by ANCOVA of patients randomized to estrogen therapy at age 12 or age 15 showed a mean difference in net gain of 2.4 cm, which was statistically significant in favor of delayed estrogen therapy.

STUDIES WITH LOW GH DOSE

Several studies are remarkable for the use of a substantially lower dose of GH than that used in the two Genentech clinical trials (0.375 mg/kg/week) and most other studies.

Tillman et al. (1995) reported a study conducted in the **United Kingdom** with adult height for 21 patients. The mean GH dose was 0.6 U/kg/wk (approximately 0.22 μg/kg/wk, or less than two-thirds of the dose used in Genentech trials). GH therapy was started at a mean age of 11.8 years and mean duration was 4.1 years. Estrogen was started at a median age of 13.0 years and five patients received oxandrolone co-therapy. The mean final height of 147.5 cm was reported to represent a mean net gain of 1.7 cm compared with Lyon projected heights. Another cohort of patients in this study was presented consisting solely of patients who received ≥ 4 years of GH therapy. These 17 patients began GH at a mean age of 10.9 years and estrogen at a median age of 12.6 years with 7 patients receiving oxandrolone co-therapy. Mean GH dose was 0.7 U/kg/wk and mean duration of GH therapy 5.2 years. Mean adult height for this cohort was 148.0 cm, with a mean net gain of 5.3 cm, although 6 of these patients were still receiving GH therapy.

REGISTRY STUDIES

Two large, post-marketing surveillance studies have reported data regarding Turner patients treated with GH.

A report of the U.S. **National Cooperative Growth Study (NCGS)** by Hintz et al.. (1995) included adult data for 230 Turner patients of 1658 enrolled. Mean baseline age was 12.2 years and mean duration of GH therapy was 4.3 years. Mean final height was 147.8 cm, for a mean net gain of 5.3 cm compared with Lyon projected heights.

In a report of the **Kabi International Growth Study (KIGS)** by Ranke et al. (1995), adult height was reported for 82 of 1632 Turner patients enrolled. Mean GH dose was 0.7 U/kg/wk, median age of starting GH was 12.0, and median age of starting estrogen was 13.8 years ($n=75$). Thirty-one of the patients were treated with oxandrolone co-therapy at a mean age of 13.6 years. Mean adult height was 149.6 cm, with an estimated potential for further growth of 1.9 cm. The mean net gain in adult height was 6.1 cm compared with Lyon projected heights.

The patients in these registries started GH at a relatively late age, and received a relatively low dose.

STUDIES WITH OXANDROLONE CO-THERAPY

In addition to the studies above from France, Germany, UK, KIGS, and NCGS, in which some patients received oxandrolone co-therapy, a multicenter study in **Sweden** has been reported by Nilsson et al. (JCEM, book), in which all patients received both GH and oxandrolone. These patients were treated similarly to one of the treatment groups in Genentech study 85-023. In the Swedish study, GH at a dose of 0.7 U/kg/wk was started at a mean age of 12.3 years. Mean adult heights using various regimens were 151.0, 151.1, 154.2, and 151.1 cm, representing gains of 6.6, 5.1, 8.9, and 3.8 cm respectively compared with Lyon projected heights. It is noteworthy the latter group was the one with early estrogen therapy, suggesting that early estrogen compromises the effect of combination therapy, similar to its effect on GH therapy alone.

In Genentech study **85-023**, a group of 46 patients received combination GH + oxandrolone. The GH dose was 0.375 mg/kg/wk and GH therapy was started at a mean age of 9.9 years, with a mean duration of therapy of 5.9 years. Estrogen therapy was begun at a mean age of 14.9 years. The patients achieved a mean adult height of 151.5 cm for a mean net gain of 9.8 cm. A comparison by ANCOVA of the combination group with the group treated with GH alone resulted in a mean difference of 2.7 cm. However, as in the Swedish study, these data reflect the use of a high initial dose of oxandrolone which was associated with excessive virilization.

SUMMARY

The results of the studies reported in the literature are consistent with the 5 treatment groups in the 2 Genentech studies included in this submission. The data show that mean gains in adult height of 8–10 cm can be achieved with early GH therapy alone (or in combination with oxandrolone) and that this increase will be lower by several cm if estrogen therapy is started at a relatively early age.

Further examination of these data show that the effect of GH dose shown above for initial growth response may also be evident in the adult height data, with lower doses associated with lesser net benefit. More importantly, the age of onset of GH therapy, and thus the duration of GH therapy are critical to the overall outcome, with delayed onset of therapy resulting in mean net gains closer to 5 cm.

A minority of studies have suggested net gains of less than 5 cm. These can be attributed in some cases to more than one element of the study design (for example, low GH dose or late age of GH therapy, combined with early estrogen use). In addition, analysis using the Lyon equation or Ranke projection methods provide erroneously low estimates of net gain in adult height.

The experience summarized here has led investigators to speculate that earlier identification of patients leading to early initiation of GH therapy might allow for the institution of low-dose estrogen therapy at a more age-appropriate time. The limited data on oxandrolone co-therapy at an appropriate dose preclude a recommendation regarding the combination regimen.

In conclusion, the Genentech clinical trials are exceptional for the large proportion of patients achieving adult height. Nonetheless, the results of these studies are consistent with other published studies, which generally contain data for a smaller proportion of patients who have completed therapy. Comparisons which account for various study design characteristics highlight the similarity of the results and confirm the conclusions drawn from the Genentech studies regarding recommended guidelines for growth-promoting therapy, namely early GH and delayed estrogen therapy.

APPENDIX C

Safety Experience from the Literature

Table 18 summarizes the published literature regarding treatment of Turner syndrome with recombinant GH. In addition to Genentech-sponsored trials and postmarketing surveillance, 37 studies from 16 countries have published efficacy and/or safety data of recombinant GH treatment of more than 2500 Turner syndrome patients. The largest of these studies was an experiential database that followed 653 girls up to 4 years (Price DA et al. 1993). The estimated exposure was 1683 patient-years. The total exposure described in the literature was approximately 6500 patient years.

SAFETY ISSUES ARISING FROM CONCURRENT MEDICAL CONDITIONS

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 13%, and hypertension 7% (Lippe B 1991). Other commonly described clinical findings in Turner syndrome include 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.

More than 100 articles describing controlled and uncontrolled clinical studies of GH in Turner patients have appeared in the literature over the past decade and are another source of safety and efficacy data. Salient information from the literature is presented in the summaries below.

GLUCOSE METABOLISM

Abnormalities in carbohydrate metabolism are frequently observed in patients with Turner syndrome and, although not fully understood, may be related to impaired insulin secretion and/or reduced insulin sensitivity (Tamborlane W et al. 1988; Stoppoloni G et al. 1990). The insulin resistant state may be due to an insulin receptor defect in muscle (Caprio S et al. 1992).

Increased insulin response to glucose has been observed in Turner syndrome patients treated with GH, and may be further aggravated by concomitant administration of estrogen or androgen therapy (Caprio S et al. 1992; Chiumello G et al. 1991; Wilson DM et al. 1988). Most long-term clinical trials

and detailed metabolic studies with GH have described mildly elevated insulin concentrations without commensurate changes in glucose or hemoglobin A_{1C} concentrations (Caprio S et al. 1992; Chiumello G et al. 1991; Wilson DM et al. 1988; Crowne EC et al. 1990; Kollman F et al. 1991; Price DA et al. 1993; Sato T et al. 1988; Takano K et al. 1992; Toublanc JE et al. 11991). Changes reported in oral glucose tolerance tests, while sometimes statistically significant, have remained within the normal range (Butenandt O et al. 1992; Stahnke N et al. 1991; Weise M et al. 1993; Weise M et al. 1993).

Possible exceptions were Stahnke et al. (Stahnke N et al. 1991), who reported inconsistently abnormal glucose tolerance tests in 14/91 patients, and Haeusler and Frisch (Haeusler G et al. 1992), who observed impaired glucose tolerance in 2/11 patients pretreatment and 5/11 during combined GH and ethinyl estradiol therapy. In one study, 3 of 52 Turner patients had abnormal glucose tolerance tests, which may have been due to their weight being above the 95th percentile for height (Raiti S 1987).

Some investigative groups have not observed any abnormalities in carbohydrate metabolism, including insulin concentrations, despite detailed laboratory analyses (Bergmann P et al. 1990; Giordano P et al. 192; Holland J et al. 1991). Oxandrolone, alone or in combination with GH, can reduce glucose tolerance (Wilson DM et al. 1988; Haeusler G et al. 1992).

LIPID METABOLISM

Adolescent girls with Turner syndrome may have significantly increased cholesterol levels prior to GH, androgen, or estrogen treatment (Ross JL et al. 1995). Neither GH nor oxandrolone appear to have clinically important effects on either cholesterol or triglyceride serum concentrations in most studies of Turner patients (Crowne EC et al. 1990; Price DA et al. 1993; Butenandt O et al. 1992; Stahnke N et al. 1991; Stahnke N et al. 1992; Wilson DM et al. 1991). However, Toublanc et al. (Toublanc JE et al.) reported that combination GH plus oxandrolone therapy resulted in transiently elevated triglyceride concentrations and a sustained reduction in cholesterol concentrations; GH alone did not induce these changes. In one study, combined therapy was associated with a 20% increase in LDL-cholesterol, although concentrations remained within the normal range (Stahnke N et al. 1992). In one study with GH treatment alone, Ferrandez et al. (Ferrandez A et al. 1991) reported 2/54 patients with elevated cholesterol and triglyceride levels.

BONE METABOLISM

A number of skeletal abnormalities may be seen in patients with Turner syndrome, including an "osteoporosis-like" bone dysplasia, shortness of the fourth metacarpal, a diminished carpal angle, hypoplasia of cervical vertebrae, scoliosis, and others (Ferrandez A et al. 1991). Bone mineral content has been reported to be decreased in as many as 90% of children with Turner syndrome (Mora S et al. 1992), which may be due to increased bone resorption in the presence of decreased bone formation (Schonau E et al. 1992).

During GH therapy, some of the abnormalities of bone metabolism have been reported to be positively influenced, including restoration of phosphorus balance, an increase in mineral deposition, and enhanced cellular proliferation (Ferrandez A et al. 1991). Alkaline phosphatase serum concentrations, usually normal in untreated Turner syndrome patients, often increase during GH therapy, reflecting an increase in bone formation (Butenandt O et al. 1992). In a study of Turner syndrome patients, Bergmann et al. (Bergmann P et al. 1990) reported that serum concentrations of procollagen-III and osteocalcin were increased after 1–3 months of GH treatment. The authors also reported that untreated patients with Turner syndrome had a 25% lower bone mineral content of the spine before treatment than age-matched controls that was partially restored to normal after one year of GH treatment. In another study in adolescents with Turner syndrome, bone mineral values after treatment with GH were found to be normal, including measurements of the lumbar spine (Neely EK et al. 1993).

Slipped capital femoral epiphyses (SCFE) may occur more frequently in patients with endocrine disorders. The incidence of SCFE in untreated Turner syndrome patients is unknown.

Scoliosis, sometimes associated with hemivertebra, is also common in Turner syndrome, occurring in approximately 13% of patients (Lippe BM et al. 1990). Scoliosis typically progresses with the pubertal growth spurt in normal girls, and thus worsening of scoliosis may also be expected following the institution of estrogen therapy or during periods of rapid growth. The influence of GH on the progression of scoliosis is not well characterized.

One feature of Turner syndrome is the relative lack of growth of the lower extremities, and a disproportionately wide hip (Gerver WJM et al. 1992; van Teunenbroek A et al. 1992). Results of two clinical trials have yielded

conflicting data concerning hip width. van Teunenbroek et al. (van Teunenbroek A et al. 1992) found that a one-year course of GH therapy at 4 IU/m^2/day (0.045 mg/kg/day) resulted in a normalization of hip width. In a similar trial of Turner syndrome patients given 24 IU/m^2/week for 2 years, Gerver et al. (Gerver WJM et al. 1992) reported that GH caused a worsening in pelvis proportions.

Kollmann et al. (Kollmann F et al. 1991) reported one of 55 patients treated with GH with "acromegalic" changes. Abnormal craniofacial and tooth growth in Turner syndrome in the absence of GH therapy have been previously reported (Rongen-Westerlaken C et al. 1993).

CARDIOVASCULAR STATUS

Hypertension occurs in about 7% of Turner syndrome patients, cardiovascular anomalies in 55%, renal and renovascular anomalies in 37% (Lippe BM 1991). Coarctation of the aorta occurs in about 15%–20% of patients with Turner syndrome, many of whom also have bicuspid aortic valve (Lippe BM 1990). Hypertension may be due to coarctation of the aorta, bicuspid aortic valve, renovascular abnormalities, or essential hypertension. GH has not been reported to influence blood pressure in Turner patients (Crowne EC et al. 1990).

In a selected group of patients with Turner syndrome, Price et al. (Price DA et al. 1993) found a reduction in life expectancy, particularly because of death due to cardiovascular malformations. In this series, 156 Turner patients who survived infancy were followed for an average of 17 years; there were a total of 15 deaths. Sixteen of the patients had a congenital heart anomaly and five of the deaths occurred in this group, including two children.

PIGMENTED NEVI AND ALOPECIA

Approximately 25% of Turner syndrome patients develop multiple-pigmented nevi (Lippe BM 1991; Borroni G et al. 1994). Bourguignon et al. (Bourguignon J-P et al. 1993) have performed standardized photographic evaluations of 33 children with pigmented nevi, 14 of whom were treated with GH (up to 0.85 IU/kg/week). Nevi grew 8%–11% during the 6-month observation period in control patients, and approximately twice this rate in GH-treated patients. Nevi growth was not influenced by pubertal status or GH dose, nor was it correlated with the statural response to GH. Importantly, biopsy results detected no neoplastic growths or premalignant nevi transformations. In a follow-up article, Pierard & Pierard-Franchimont (Pierard GE et al. 1993)

reported similar results in a group of 8 patients with Turner syndrome. Naeraa et al. (Naeraa RW et al. 1994) reported that the number and size of nevi increased in one girl with Turner syndrome during the first 3 months of combination therapy with GH and estradiol. The moles apparently disappeared during the following 3 months, despite continued therapy.

Alopecia areata and diffuse hypotrichosis have been reported in untreated Turner syndrome patients (Tebbe B et al. 1993).

THYROID FUNCTION

The incidence of Hashimoto's thyroiditis in Turner syndrome is approximately 34% (Lippe BM et al. 1990). While thyroid autoantibodies may be present in over 50% of Turner subjects, the incidence of clinical hypothyroidism is probably closer to 10% (Lippe BM 1991).

In normal and GH-deficient adults, short-term GH administration causes an increased turnover of T_4 to T_3 (Grunfeld C et al. 1988; Jorgenson JOL et al. 1989). This has been confirmed in long-term studies of children with GH deficiency or Turner syndrome (Massa G et al. 1991; Pirazzoli P et al. 1992). In Turner syndrome patients, Massa et al. (Massa G et al.) reported only a transient decline in T_4 levels at 6 months that returned to baseline levels. Pirazzoli et al. (Pirazzoli P et al. 1992) reported that changes in thyroid hormones were sustained in GH-deficient children treated up to a year and, in addition, changes in T_3/T_4 ratios correlated positively with growth rate. However, observed changes in concentrations of T_3 and T_4 were relatively small. Massa et al. (Massa G et al. 1991) and Pirazzoli et al. (Pirrazoli P et al. 1992) reported statistically significant changes of 15% or less, and all values remained within the normal range during GH treatment.

EDEMA

Edema, resulting from lymphatic malformations and obstruction, is the cause of many of the physical findings of Turner syndrome in utero, and may persist postnatally as recurrent peripheral edema. This is often aggravated following institution of estrogen therapy. GH has been reported to cause expansion of extracellular volume (Moller J et al. 1992). Dean (Dean H 1991) reported that transient peripheral edema occurs in 2%–3% of patients with Turner syndrome that are treated with GH. Price et al. (Price DA et al. 1993) observed three girls with lymphedema of the dorsum of the feet of 47 Turner syndrome patients treated with GH. Edema has also been reported with combined therapy of GH

and estrogen (Tebbe B et al. 1993). Lebl et al. (Lebl J et al. 1994) have described two patients that developed persistent edema during the first year of GH therapy.

ALLERGY/IMMUNOLOGY

Minor abnormalities in immune function without clinical manifestations (with the exception of autoimmune thyroid disease) have been reported in girls with Turner syndrome, as well as in GH-deficient children (Bozzola M et al. 1989; Cacciari E et al. 1981). The GH-induced changes in immune function reported in GH-deficient children have not been associated with changes in immune competency; individual absolute B- and T-cell responses reported thus far have been within normal limits (Ammann AJ et al. 1987; Yoshida A et al. 1992). Transient changes of minimal clinical significance have also been observed in Turner patients treated with GH (Rongen-Westerlaken C et al. 1991). As stated by Church et al. (Church JA et al. 1989), many of the immunologic findings with GH treatment in GH-deficient patients may reflect the variable nature of these tests when they are performed sequentially. In an uncontrolled study, Nienhuis et al. (Nienhuis H et al. 1993) found that the prevalence of antithyroid autoantibodies increased after 4 years of GH therapy. The authors could not conclude that the GH therapy had any influence on this increase and the prevalence of autoantibodies at the end of the study was no higher than that found in earlier studies without GH treatment. Kollmann et al. (Kollmann F et al. 1991) reported 2/55 GH-treated Turner patients with injection site reactions, and 1/55 with skin hypertrophy.

ANTIBODIES TO GH

Varying frequencies of antibodies to exogenously administered GH have been reported, although the majority were associated with a low binding capacity. One study reported 9 of 16 girls with Turner syndrome with antibodies to methionyl GH (not Genentech's Protropin), one of whom had a high binding capacity during the first year of treatment that was associated with a poor growth response (Rongen-Westerlaken C et al. 1990). During the second year of treatment, binding capacity gradually decreased. This group also reported transient rises in concentrations of circulating immune complexes (after 3 months) in 3/16 patients. Raiti et al. (Raiti S et al. 1987) reported significant antibodies to pituitary GH in one of 52 Turner patients, and Takano et al. (Takano K et al. 1992) observed antibodies to terminal methionine-free GH in 1/46 patients during a 3-year trial. Takano et al. (Takano K et al. 1989) earlier reported on a larger cohort of 203 patients with Turner syndrome and observed

the presence of antibodies to GH in 71.4% of patients treated with terminal methionine-containing GH and in 11.9% of patients receiving terminal methionine-free GH; antibodies were not sufficient to reduce growth response in any patients. Antibodies were not associated with any adverse events.

INTRACRANIAL HYPERTENSION

Intracranial hypertension (with papilledema, visual changes, headache, nausea, and/or vomiting) has been reported in a small number of patients treated with GH (Malozowski S et al. 1993). Castillo et al. (Castillo L et al. 1994) have reported a case of intracranial hypertension in a Turner syndrome patient that was managed with GH discontinuation and acetazolamide.

LIVER FUNCTION

Two authors have described changes in liver function tests (LFTs) in Turner patients treated with GH. Kollmann et al. (Kollmann F et al. 1991) reported one patient (out of a cohort of 55) who had "abnormal liver function" and another with "organomegaly." Tonini and Marinoni (Tonini G et al. 1990) described elevated LFTs in two Turner patients receiving GH. Stahnke et al. (Stahnke N et al. 1992) found no abnormalities on ultrasound after 2 years of GH therapy.

SUMMARY

The use of GH in the treatment of short stature associated with Turner syndrome has been studied since 1960. A considerable body of experience has emerged from the clinical literature which helps to support its efficacy and safety. In addition to Genentech-sponsored trials, other groups have confirmed GH enhancement in adult height. GH has not been shown to worsen or complicate underlying conditions common to patients with Turner syndrome.

APPENDIX D

Nutropin® [somatropin (rDNA origin) for injection]

Bar Code to Appear Here

Nutropin®
[somatropin (rDNA origin) for injection]

DESCRIPTION

Nutropin® [somatropin (rDNA origin) for injection], is a human growth hormone (hGH) produced by recombinant DNA technology. Nutropin has 191 amino acid residues and a molecular weight of 22,125 daltons. The amino acid sequence of the product is identical to that of pituitary-derived human growth hormone. The protein is synthesized by a specific laboratory strain of *E. coli* as a precursor consisting of the rhGH molecule preceded by the secretion signal from an *E. coli* protein. This precursor is directed to the plasma membrane of the cell. The signal sequence is removed and the native protein is secreted into the periplasm so that the protein is folded appropriately as it is synthesized.

Nutropin is a highly purified preparation. Biological potency is determined by measuring the increase in body weight induced in hypophysectomized rats.

Nutropin is a sterile, white, lyophilized powder intended for subcutaneous administration after reconstitution with Bacteriostatic Water for Injection, USP (benzyl alcohol preserved). The reconstituted product is nearly isotonic at a concentration of 5 mg/mL growth hormone and has a pH of approximately 7.4.

Each 5 mg Nutropin vial contains 5 mg (approximately 15 IU) somatropin, lyophilized with 45 mg mannitol, 1.7 mg sodium phosphates (0.4 mg sodium phosphate monobasic and 1.3 mg sodium phosphate dibasic), and 1.7 mg glycine.

Each 10 mg Nutropin vial contains 10 mg (approximately 30 IU) somatropin, lyophilized with 90 mg mannitol, 3.4 mg sodium phosphates (0.8 mg sodium phosphate monobasic and 2.6 mg sodium phosphate dibasic), and 3.4 mg glycine.

Deleted unapproved portion of labeling

Bacteriostatic Water for Injection, USP is sterile water containing 0.9 percent benzyl alcohol per mL as an antimicrobial preservative packaged in a multidose vial. The diluent pH is 4.5–7.0.

CLINICAL PHARMACOLOGY

General

In vitro and in vivo preclinical, and clinical testing have demonstrated that Nutropin is therapeutically equivalent to pituitary-derived human growth hormone. Treatment of patients who lack adequate endogenous growth hormone secretion, patients with chronic renal insufficiency, and patients with Turner syndrome that were treated with Nutropin resulted in an increase in growth rate and an increase in insulin-like growth factor-I levels similar to that seen with pituitary-derived human growth hormone.

Actions that have been demonstrated for Nutropin, somatrem and/or pituitary-derived human growth hormone include:

A. **Tissue Growth**—1) Skeletal Growth: Nutropin stimulates skeletal growth in patients with growth failure due to a lack of adequate secretion of endogenous growth hormone or secondary to chronic renal insufficiency and in patients with Turner syndrome. Skeletal growth is accomplished at the epiphyseal plates at the ends of a growing bone. Growth and metabolism of epiphyseal plate cells are directly stimulated by growth hormone and one of its mediators, insulin-like growth factor-I. Serum levels of insulin-like growth factor-I are low in children and adolescents who are growth hormone deficient, but increase during treatment with Nutropin. New bone is formed at the epiphyses in response to growth hormone. This results in linear growth until these growth plates fuse at the end of puberty. 2) Cell Growth:

Treatment with pituitary-derived human growth hormone results in an increase in both the number and the size of skeletal muscle cells. 3) Organ Growth: Growth hormone of human pituitary origin influences the size of internal organs, including kidneys, and increases red cell mass. Treatment of hypophysectomized or genetic dwarf rats with Nutropin results in organ growth that is proportional to the overall body growth. In normal rats subjected to nephrectomy-induced uremia, Nutropin promoted skeletal and body growth.

B. **Protein Metabolism**—Linear growth is facilitated in part by growth hormone–stimulated protein synthesis. This is reflected by nitrogen retention as demonstrated by a decline in urinary nitrogen excretion and blood urea nitrogen during growth hormone therapy.

C. **Carbohydrate Metabolism**—Growth hormone is a modulator of carbohydrate metabolism. For example, patients with inadequate secretion of growth hormone sometimes experience fasting hypoglycemia that is improved by treatment with growth hormone. Growth Hormone therapy may increase glucose intolerance. There is an increased incidence of glucose intolerance in untreated patients with chronic renal insufficiency or Turner syndrome. Administration of Nutropin to normal adults, patients with chronic renal insufficiency, patients who lack adequate secretion of endogenous growth hormone, and patients with Turner syndrome resulted in increases in mean serum fasting and postprandial insulin levels. However, mean glucose and hemoglobin A_{1c} levels remained in the normal range.

D. **Lipid Metabolism**—Acute administration of pituitary-derived human growth hormone to humans resulted in lipid mobilization. Nonesterified fatty acids increased in plasma within two hours of pituitary-derived human growth hormone administration. In growth hormone deficient patients, long-term growth hormone administration often decreases body fat. Mean cholesterol levels decreased in patients treated with Nutropin.

E. **Mineral Metabolism**—The retention of total body potassium in response to growth hormone administration apparently results from cellular growth. Serum levels of inorganic phosphorus may increase slightly in patients with inadequate secretion of endogenous growth hormone, chronic renal insufficiency, or patients with Turner syndrome after growth hormone therapy

due to metabolic activity associated with bone growth as well as increased tubular reabsorption of phosphate by the kidney. Serum calcium is not significantly altered in these patients. Sodium retention also occurs. (See PRECAUTIONS: Laboratory Tests.)

F. **Connective Tissue Metabolism**—Growth hormone stimulates the synthesis of chondroitin sulfate and collagen as well as the urinary excretion of hydroxyproline.

Pharmacokinetics

Subcutaneous absorption—The absolute bioavailability of recombinant human growth hormone (rhGH) after subcutaneous administration in healthy adult males has been determined to be 81% ± 20. The mean terminal $t_{1/2}$ after subcutaneous administration is significantly longer than that seen after intravenous administration (2.1 ± 0.43 hrs vs. 19.5 ± 3.1 min) indicating that the subcutaneous absorption of the compound is slow and rate-limiting.

Distribution—Animal studies with rhGH showed that growth hormone localizes to highly perfused organs, particularly the liver and kidney. The volume of distribution at steady state for rhGH in healthy adult males is about 50 mL/kg body weight, approximating the serum volume.

Metabolism—Both the liver and kidney have been shown to be important metabolizing organs for pituitary-derived growth hormone. Animal studies suggest that the kidney is the dominant organ of clearance. Growth hormone is filtered at the glomerulus and reabsorbed in the proximal tubules. It is then cleaved within renal cells into its constituent amino acids, which return to the systemic circulation.

Elimination—The mean terminal $t_{1/2}$ after intravenous administration of rhGH in healthy adult males is estimated to be 19.5 ± 3.1 minutes. Clearance of rhGH after intravenous administration in healthy adults and children is reported to be in the range of 116–174 mL/hr/kg.

Bioequivalence of Formulations—Nutropin has been determined to be bioequivalent to Nutropin AQ™ [somatropin (rDNA origin) injection] based on the statistical evaluation of AUC and C_{max}.

Special Populations

Pediatric—Available literature data suggest that rhGH clearances are similar in adults and children.

Gender—No data are available for exogenously administered rhGH. Available data for methionyl recombinant growth hormone, pituitary-derived growth hormone, and endogenous GH suggest no consistent gender-based differences in GH clearance.

Race—Reported values for half-lives for endogenous GH in normal adult black males are not different from observed values for normal adult white males. No data for other races are available.

Growth Hormone Deficiency (GHD)—Reported values for clearance of rhGH in adults and children with GHD range from 138–245 mL/hr/kg and are similar to those observed in healthy adults and children. Mean terminal $t_{1/2}$ values following intravenous and subcutaneous administration in adult and pediatric GHD patients are also similar to those observed in healthy adult males.

Renal Insufficiency—Children and adults with chronic renal failure (CRF) and end-stage renal disease (ESRD) tend to have decreased clearance as compared to normals. Endogenous GH production may also increase in some individuals with ESRD. However, no rhGH accumulation has been reported in children with CRF or ESRD dosed with current regimens.

Turner Syndrome—No pharmacokinetic data is available for exogenously administered rhGH. However, reported half-lives, absorption and elimination rates for endogenous GH in this population are within the ranges observed for normal subjects and GHD populations.

Hepatic Insufficiency—A reduction in rhGH clearance has been noted in patients with severe liver dysfunction. The clinical significance of this decrease is unknown.

Efficacy Studies

Effects of Nutropin on Growth Failure Due to Chronic Renal Insufficiency (CRI)

Two multicenter, randomized, controlled clinical trials were conducted to determine whether treatment with Nutropin prior to renal transplantation in patients with chronic renal insufficiency could improve their growth rates and height deficits. One study was a double-blinded, placebo-controlled trial and the other was an open-label, randomized trial. The dose of Nutropin in both controlled studies was 0.05 mg/kg/day (0.35 mg/kg/wk) administered daily by subcutaneous injection. Combining the data from those patients completing two years in the two controlled studies results in 62 patients treated with Nutropin and 28 patients in the control groups (either placebo-treated or untreated). The mean first year growth rate was 10.8 cm/yr for Nutropin-treated patients, compared with a mean growth rate of 6.5 cm/yr for placebo/untreated controls ($p < 0.00005$). The mean second year growth rate was 7.8 cm/yr for the Nutropin-treated group, compared with 5.5 cm/yr for controls ($p < 0.00005$). There was a significant increase in mean height standard deviation (SD) score in the Nutropin group (–2.9 at baseline to –1.5 at Month 24, $n = 62$) but no significant change in the controls (–2.8 at baseline to –2.9 at Month 24, $n = 28$). The mean third year growth rate of 7.6 cm/yr in the Nutropin-treated patients ($n = 27$) suggests that Nutropin stimulates growth beyond two years. However, there are no control data for the third year because control patients crossed over to growth hormone treatment after two years of participation. The gains in height were accompanied by appropriate advancement of skeletal age. These data demonstrate that Nutropin therapy improves growth rate and corrects the acquired height deficit associated with chronic renal insufficiency. Currently there are insufficient data regarding the benefit of treatment beyond three years. Although predicted final height was improved during Nutropin therapy, the effect of Nutropin on final adult height remains to be determined.

Post-Transplant Growth

The North American Pediatric Renal Transplant Cooperative Study (NAPRTCS) has reported data for growth post-transplant in children who did not receive growth hormone. The average change in height SD score during the initial two years post-transplant was 0.18 ($n = 300$, J Ped 1993;122:397–402).

Controlled studies of growth hormone treatment for the short stature associated with CRI were not designed to compare the growth of treated or untreated patients after they received renal transplants. However, growth data are

available from a small number of patients who have been followed for at least 11 months. Of the 7 control patients, 4 increased their height SD score and 3 had either no significant change or a decrease in height SD score. The 13 patients treated with Nutropin prior to transplant had either no significant change or an increase in height SD score after transplantation, indicating that the individual gains achieved with growth hormone therapy prior to transplant were maintained after transplantation. The differences in the height deficit narrowed between the treated and untreated groups in the post-transplant period.

Turner Syndrome

One long-term, randomized, multicenter, clinical trial and two long-term, open-label historically controlled multicenter clinical trials were conducted to evaluate the efficacy of growth hormone for the treatment of patients with short stature due to Turner syndrome (see table below).

In the randomized study comparing growth hormone-treated patients to a concurrent control group who received no growth hormone, the growth hormone-treated patients who received a dose of 0.3 mg/kg/week from a mean age of 11.7 years attained a mean near final height of 146.0 cm (n=27) as compared to the control group who attained a near final height of 142.1 cm (n=19). By analysis of covariance, the effect of growth hormone therapy was a height increase of 5.4 cm ($p = 0.001$).

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

In the second study, patients were randomized to receive estrogen replacement therapy (conjugated estrogens, 0.3 mg escalating to 0.625 mg daily) at either age 12 or 15 years. Compared with matched historical controls, early GH therapy combined with estrogen replacement at age 12 years resulted in an adult height gain of 5.9 cm (n=26), compared to 8.3 cm (n=29) in patients initiating estrogen at age 15 years.

Study/Group	N at Adult Height	GH Age (yr)	Estrogen Age (yr)	GH Duration (yr)	Adult Height Gain (cm)*
GDCT	27	11.7	13	4.7	5.4
85-023	17	9.1	15.2	7.6	7.4
85-044: A	29	9.4	15.0	6.1	8.3
B	26	9.6	12.3	5.6	5.9
C	51	12.7	13.7	3.8	5.0

* Analysis of covariance vs controls

These studies confirm that when patients with short stature associated with Turner syndrome are treated appropriately with growth hormone, there is a significant gain in adult height.

INDICATIONS AND USAGE

Nutropin® [somatropin (rDNA origin) for injection] is indicated for the long-term treatment of growth failure due to a lack of adequate endogenous growth hormone secretion.

Nutropin® [somatropin (rDNA origin) for injection] is also indicated for the treatment of growth failure associated with chronic renal insufficiency up to the time of renal transplantation. Nutropin therapy should be used in conjunction with optimal management of chronic renal insufficiency.

Nutropin® [somatropin (rDNA origin) for injection] is also indicated for the long-term treatment of short stature associated with Turner syndrome.

CONTRAINDICATIONS

Nutropin should not be used in subjects with closed epiphyses.

Nutropin should not be used in patients with active neoplasia. Growth hormone therapy should be discontinued if evidence of neoplasia develops.

Nutropin, when reconstituted with Bacteriostatic Water for Injection, USP (benzyl alcohol preserved) should not be used in patients with a known sensitivity to benzyl alcohol.

WARNINGS

Benzyl alcohol as a preservative in Bacteriostatic Water for Injection, USP has been associated with toxicity in newborns. When administering Nutropin to newborns, reconstitute with Sterile Water for Injection, USP. USE ONLY ONE DOSE PER NUTROPIN VIAL AND DISCARD THE UNUSED PORTION.

PRECAUTIONS

General: Nutropin should be prescribed by physicians experienced in the diagnosis and management of patients with growth failure due to GH deficiency, Turner syndrome or chronic renal insufficiency. No studies have been completed of Nutropin therapy in patients who have received renal transplants. Currently, treatment of patients with functioning renal allografts is not indicated.

Because Nutropin may reduce insulin sensitivity, patients should be monitored for evidence of glucose intolerance.

Patients with a history of an intracranial lesion should be examined frequently for progression or recurrence of the lesion. Patients with growth failure secondary to chronic renal insufficiency should be examined periodically for evidence of progression of renal osteodystrophy. Slipped capital femoral epiphysis or avascular necrosis of the femoral head may be seen in children with advanced renal osteodystrophy, and it is uncertain whether these problems are affected by growth hormone therapy. X-rays of the hip should be obtained prior to initiating therapy. Physicians and parents should be alert to the development of a limp or complaints of hip or knee pain in patients treated with Nutropin.

Slipped capital femoral epiphysis may occur more frequently in patients with endocrine disorders or in patients undergoing rapid growth.

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

Patients with Turner syndrome should be evaluated carefully for otitis media and other ear disorders since these patients have an increased risk of ear or hearing disorders. In a randomized-controlled trial, there was a statistically significant increase, as compared to untreated controls, in otitis media (43% vs. 26%) and ear disorders (18% vs. 5%) in patients receiving growth hormone. In addition, patients with Turner syndrome should be monitored closely for cardiovascular disorders (e.g., stroke, aortic aneurysm, hypertension) as these patients are also at risk for these conditions.

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

See WARNINGS for use of Bacteriostatic Water for Injection, USP (benzyl alcohol preserved) in newborns.

As with any protein, local or systemic allergic reactions may occur. Parents/patient should be informed that such reactions are possible and that prompt medical attention should be sought if allergic reactions occur.

Laboratory Tests: Serum levels of inorganic phosphorus, alkaline phosphatase, and parathyroid hormone (PTH) may increase with Nutropin therapy.

Untreated hypothyroidism prevents optimal response to Nutropin. Patients with Turner syndrome have an inherently increased risk of developing autoimmune thyroid disease. Changes in thyroid hormone laboratory measurements may develop during Nutropin treatment in patients who lack adequate endogenous growth hormone secretion. Therefore, patients should have periodic thyroid function tests and should be treated with thyroid hormone when indicated.

Drug Interaction: The use of Nutropin in patients with chronic renal insufficiency receiving glucocorticoid therapy has not been evaluated. Concomitant glucocorticoid therapy may inhibit the growth promoting effect of Nutropin. If

glucocorticoid replacement is required, the glucocorticoid dose should be carefully adjusted.

There was no evidence in the controlled studies of Nutropin's interaction with drugs commonly used in chronic renal insufficiency patients. Limited data indicate that growth hormone treatment increases cytochrome P450 (CP450) mediated antipyrine clearance in man. These data suggest that GH administration may alter the clearance of compounds known to be metabolized by CP450 liver enzymes (e.g., corticosteroids, sex steroids, anticonvulsants, cyclosporin). Careful monitoring is advisable when GH is administered in combination with other drugs known to be metabolized by CP450 liver enzymes.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenicity, mutagenicity and reproduction studies have not been conducted with Nutropin.

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

Nursing Mothers: It is not known whether Nutropin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Nutropin is administered to a nursing mother.

Information for Patients: Patients being treated with growth hormone and/or their parents should be informed of the potential benefits and risks associated with treatment. If home use is determined to be desirable by the physician, instructions on appropriate use should be given, including a review of the contents of the Patient Information Insert. This information is intended to aid in the safe and effective administration of the medication. It is not a disclosure of all possible adverse or intended effects.

If home use is prescribed, a puncture resistant container for the disposal of used syringes and needles should be recommended to the patient. Patients and/or parents should be thoroughly instructed in the importance of proper disposal and cautioned against any reuse of needles and syringes (see Patient Information Insert).

ADVERSE REACTIONS

As with all protein pharmaceuticals, a small percentage of patients may develop antibodies to the protein. Growth hormone antibody binding capacities below 2 mg/L have not been associated with growth attenuation. In some cases when binding capacity exceeds 2 mg/L, growth attenuation has been observed. In clinical studies of patients that were treated with Nutropin for the first time, 0/107 growth hormone deficient (GHD) patients, 0/125 CRI patients, and 0/112 Turner syndrome patients screened for antibody production developed antibodies with binding capacities ≥ 2 mg/L at six months.

Additional short-term immunologic and renal function studies were carried out in a group of patients with chronic renal insufficiency after approximately one year of treatment to detect other potential adverse effects of antibodies to growth hormone. Testing included measurements of C1q, C3, C4, rheumatoid factor, creatinine, creatinine clearance and BUN. No adverse effects of growth hormone antibodies were noted.

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

In studies in patients treated with Nutropin, injection site pain was reported infrequently.

Leukemia has been reported in a small number of growth hormone deficient patients treated with growth hormone. It is uncertain whether this increased risk is related to the pathology of growth hormone deficiency itself, growth hormone therapy, or other associated treatments such as radiation therapy for intracranial tumors. On the basis of current evidence, experts cannot conclude that growth hormone therapy is responsible for these occurrences. The risk to GHD, CRI or Turner syndrome patients, if any, remains to be established.

Other adverse drug reactions that have been reported in growth hormone–treated patients include the following: 1) Metabolic: Infrequent, mild and transient peripheral edema. 2) Musculoskeletal: Arthralgias; rare carpal tunnel syndrome. 3) Skin: Rare increased growth of pre-existing nevi; patients should be

monitored carefully for malignant transformation. 4) Endocrine: Rare gynecomastia. Rare pancreatitis.

OVERDOSAGE

The recommended dosage for growth hormone deficiency is up to 0.30 mg/kg (approximately 0.90 IU/kg) of body weight weekly. The recommended dosage for chronic renal insufficiency is up to 0.35 mg/kg (approximately 1.05 IU/kg) of body weight weekly. The recommended dosage for Turner syndrome is up to 0.375 mg/kg (approximately 1.125 IU/kg) of body weight weekly. Long-term overdosage could result in signs and symptoms of gigantism and/or acromegaly consistent with the known effects of excess human growth hormone.

DOSAGE AND ADMINISTRATION

The Nutropin dosage and administration schedule should be individualized for each patient. Therapy should not be continued if ~~final height is achieved or~~ epiphyseal fusion has occurred. Patients who fail to respond adequately while on Nutropin therapy should be evaluated to determine the cause of unresponsiveness.

Dosage

Growth Hormone Deficiency (GHD)

A weekly dosage of up to 0.30 mg/kg (approximately 0.90 IU/kg) of body weight administered by daily subcutaneous injection is recommended.

Chronic Renal Insufficiency (CRI)

A weekly dosage of up to 0.35 mg/kg (approximately 1.05 IU/kg) of body weight administered by daily subcutaneous injection is recommended.

Nutropin therapy may be continued up to the time of renal transplantation.

In order to optimize therapy for patients who require dialysis, the following guidelines for injection schedule are recommended:

1. Hemodialysis patients should receive their injection at night just prior to going to sleep or at least 3–4 hours after their hemodialysis to prevent hematoma formation due to the heparin.
2. Chronic Cycling Peritoneal Dialysis (CCPD) patients should receive their injection in the morning after they have completed dialysis.
3. Chronic Ambulatory Peritoneal Dialysis (CAPD) patients should receive their injection in the evening at the time of the overnight exchange.

Turner Syndrome

A weekly dosage of up to 0.375 mg/kg (approximately 1.125 IU/kg) of body weight administered 3 to 7 times per week by subcutaneous injection is recommended.

Administration

After the dose has been determined, reconstitute as follows: each 5 mg vial should be reconstituted with 1–5 mL of Bacteriostatic Water for Injection, USP (benzyl alcohol preserved); or each 10 mg vial should be reconstituted with 1–10 mL of Bacteriostatic Water for Injection, USP (benzyl alcohol preserved) only. For use in newborns see WARNINGS. The pH of Nutropin after reconstitution with Bacteriostatic Water for Injection, USP (benzyl alcohol preserved) is approximately 7.4.

To prepare the Nutropin solution, inject the Bacteriostatic Water for Injection, USP (benzyl alcohol preserved) into the Nutropin vial, aiming the stream of liquid against the glass wall. Then swirl the product vial with a **GENTLE** rotary motion until the contents are completely dissolved. **DO NOT SHAKE.** Because Nutropin is a protein, shaking can result in a cloudy solution. The Nutropin solution should be clear immediately after reconstitution. Occasionally, after refrigeration, you may notice that small colorless particles of protein are present in the Nutropin solution. This is not unusual for solutions containing proteins. If the solution is cloudy immediately after reconstitution or refrigeration, the contents **MUST NOT** be injected.

Before needle insertion, wipe the septum of both the Nutropin and diluent vials with rubbing alcohol or an antiseptic solution to prevent contamination of the

contents by microorganisms that may be introduced by repeated needle insertions. It is recommended that Nutropin be administered using sterile, disposable syringes and needles. The syringes should be of small enough volume that the prescribed dose can be drawn from the vial with reasonable accuracy.

STABILITY AND STORAGE

Before Reconstitution—Nutropin® [somatropin (rDNA origin) for injection], and Bacteriostatic Water for Injection, USP (benzyl alcohol preserved), must be stored at 2–8°C/36–46°F (under refrigeration). **Avoid freezing the vials of Nutropin and Bacteriostatic Water for Injection, USP (benzyl alcohol preserved).** Expiration dates are stated on the labels.

After Reconstitution—Vial contents are stable for 14 days when reconstituted with Bacteriostatic Water for Injection, USP (benzyl alcohol preserved) and stored at 2–8°C/36–46°F (under refrigeration). Store the unused portion of Bacteriostatic Water for Injection, USP (benzyl alcohol preserved) at 2–8°C/36–46°F (under refrigeration). **Avoid freezing the reconstituted vial of Nutropin and the Bacteriostatic Water for Injection, USP (benzyl alcohol preserved).**

HOW SUPPLIED

Nutropin is supplied as 5 mg (approximately 15 IU) or 10 mg (approximately 30 IU) of lyophilized, sterile somatropin per vial.

Each 5 mg carton contains two vials of Nutropin® [somatropin (rDNA origin) for injection] (5 mg per vial) and one 10 mL multiple dose vial of Bacteriostatic Water for Injection, USP (benzyl alcohol preserved). NDC 50242-072-02

Each 10 mg carton contains two vials of Nutropin® [somatropin (rDNA origin) for injection] (10 mg per vial) and two 10 mL multiple dose vials of Bacteriostatic Water for Injection, USP (benzyl alcohol preserved). NDC 50242-018-20

Nutropin® [somatropin (rDNA origin) for injection] manufactured by:

Genentech, Inc.
460 Point San Bruno Boulevard
South San Francisco, CA 94080-4990

Bacteriostatic Water for Injection, USP (benzyl alcohol preserved) manufactured for:
Genentech, Inc.

Nutropin® G48086-R3

[somatropin (rDNA origin) for injection] Revised October,1996

APPENDIX E

Bibliography

Ammann AJ, Sherman BM. Effect of growth hormone therapy on immune function [letter]. J Pediatr 1987;110:663–5.

Anglani F, Baccichetti C, Artifoni L, Lenzinzi E, Tenconi R. Frequency of abnormal karyotypes in relation to the ascertainment method in females referred for suspected sex chromosome abnormality. Clin Genet 1984;25:242–7.

Anhalt H, Wilson DM, Bachrach LK, Hintz RL, Olney RC, Eckert KL, et al. A prospective randomized trial of growth response to two dosages of rhGH [abstract]. Pediatr Res 1994;35:93A.

Attanasio A, James D, Reinhardt R, Rekers-Mombarg L. Final height and long-term outcome after growth hormone therapy in Turner syndrome: results of a German multicentre trial. Horm Res 1995;43:147–9.

Attie KA, Chernausek S, Frane J, Rosenfeld RG for the Genentech Study Group. Growth hormone use in Turner syndrome: a preliminary report on the effect of early vs delayed estrogen. In: Albertsson-Wikland and Ranke M, editors. Turner syndrome in a life-span perspective. Elsevier Science BV Publishers, 1995;175–81.

Benker G, Spira G, Zah W, Tharandt L, Hackenberg K, Reinwein D. Immunoreactive somatomedin B in acromegaly and in Turner's syndrome. Clin Endocrinol 1979;11:357–65.

Bergmann P, Valsamis J, Van Perborgh J, De Schepper J, Van Vliet G. Comparative study of the changes in insulin-like growth factor-I, procollagen-III N-terminal extension peptide, bone Gla-protein, and bone mineral content in children with Turner's syndrome treated with recombinant growth hormone. J Clin Endocrinol Metab 1990;71:1461–7.

Bernasconi S, Giovannelli G, Volta C, Aicardi G, Balestrazzi P, Benso L, et al. Spontaneous growth in Turner syndrome: preliminary results of an Italian multicenter study. In: Ranke MB, Rosenfeld RG, editors. Turner syndrome: growth promoting therapies. Amsterdam: Elsevier Science Publishers, 1991:53–7.

Bohnet HG. New aspects of oestrogen/gestagen-induced growth and endocrine changes in individuals with Turner syndrome. Eur J Pediatr 1986;145:275–9.

Borroni G, Larizza D, Vignati G, Zaccone C, Zanetta R, Vignoli GP, et al. The dermatological spectrum of Turner syndrome. J Eur Acad Dermatol Venereol 1994;3:334–40.

Borroni G, Larizza D, Vignati G, Zaccone C, Zanetta R, Vignoli GP, et al. The dermatological spectrum of Turner syndrome. J Eur Acad Dermatol Venereol 1994;3:334–40.

Bosze P, Eiben OG, Gaal M, Laszlo J. Body measurements of patients with streak gonads and their bearing upon the karyotype. Hum Genet 1980;54:355–60.

Bourguignon J-P, Pierard GE, Ernould C, Heinrichs C, Craen M, Rochiccioli P, et al. Effects of human growth hormone therapy on melanocytic naevi. Lancet 1993;341:1505–6.

Bozzola M, Cisternino M, Valtorta A, Moretta A, Biscaldi I, Maghnie M, et al. Effect of biosynthetic methionyl growth hormone (GH) therapy on the immune function in GH-deficient children. Horm Res 1989;31:153–6.

Brook CGD. Growth hormone deficiency in Turner's syndrome. N Engl J Med 1978;298:1203–4.

Brook CGD, Murset G, Zachmann M, Prader A. Growth in children with 45,XO Turner's syndrome. Arch Dis Child 1974;49:789–95.

Butenandt O, Schmitt S. Metabolic aspects in growth hormone treatment of Ullrich-Turner syndrome. J Pediatr Endocrinol 1992;5:95–9.

Cacciari E, Masi M, Fantini MP, Licastro F, Cicognani A, Pirazzoli P, et al. Serum immunoglobulins and lymphocyte subpopulations derangement in Turner's syndrome. J Immunogenet 1981;8:337–44.

Caprio S, Boulware SD, Press M, Sherwin RS, Rubin K, Carpenter TO, et al. Effect of growth hormone treatment on hyperinsulinemia associated with Turner syndrome. J Pediatr 1992;120:238–43.

Castillo L, Sedano MJ. Pseudotumor cerebri following treatment with growth hormone [abstract]. Eur J Endocrinol 1994;130(Suppl 2):194.

Chipman JJ, Holcombe JH, Tamura RN, Whitaker NG, Olovich KG. Three year efficacy results of a placebo-controlled to dose response study of human growth hormone in Turner's syndrome [abstract]. Pediatr Res 1993;33(Suppl):S46.

Chiumello G, Bognetti E, Bonfanti R, Ciralli F, Cofano D. Glucose metabolism in Turner syndrome. In: Ranke MB, Rosenfeld RG, editors. Turner syndrome: growth promoting therapies. Amsterdam: Elsevier Science Publishers, 1991:47–9.

Church JA, Costin G, Brooks J. Immune functions in children treated with biosynthetic growth hormone. J Pediatr 1989;115:420–3.

Church JA, Costin G, Brooks J. Immune functions in children treated with biosynthetic growth hormone. J Pediatr 1989;115:420–3.

Chuce, Paterson WF, Kelnar CJH, Smail PH, Green SA, Donaldson MDC Response to growth hormone and final height in patients with Turner syndrome [abstract]. Horm Res 1995;44:73.

Crawford JD. Management of children with Turner's syndrome. In: Papadatos CJ, Bartsocas CS, editors. The management of genetic disorders. New York: Alan R. Liss, Inc., 1979:94–109.

Crock P, Werther GA, Wettenhall HNB. Oxandrolone increases final height in Turner syndrome. J Pediatr Child Health 1990;26:221–4.

Crowne EC, Price DA, Clayton PE, Wallace WHB, Addison GM. Growth hormone treatment in Turner's syndrome: the absence of undesired side-effects [abstract]. Acta Paediatr Scand 1990;370(Suppl):192.

Cutler GB Jr, Ross JL. Estrogen therapy in Turner syndrome. Acta Paediatr Jpn 1992;34:195–205.

Dean H. Growth hormone therapy in girls with Turner syndrome. Birth Defects 1991;26:229–34.

Demetriou E, Emans SJ, Crigler JF Jr. Final height in estrogen-treated patients with Turner syndrome. J Obstet Gynecol 1984;64:459–64.

De Muinck Keizer-Schrama S, Rikken B, Hokken-Koelega A, Wit JM, Drop S, and the Dutch Growth Hormone Working Group. Comparative effect of two doses of growth hormone for growth hormone deficiency. Arch Dis Child 1994;71:12–8.

De Muinck Keizer-Schrama SMPF, Rikken B, Wynne HJ, Hokken-Koelega ACS, Wit JM, Bot A, et al. Dose-response study of biosynthetic human growth hormone (GH) in GH-deficient children: effects on auxological and biochemical parameters. J Clin Endocrinol Metab 1992;74:898–905.

de Schepper J, Craen M, Massa G, Heinrichs C, Maes M, du Caju M, et al. Growth hormone therapy in Turner's syndrome: one versus two daily injections. J Clin Endocrinol Metab 1994;79:489–4.

Disteche CM, Casanova M, Saal H, Friedman C, Sybert V, Graham J, et al. Small deletions of the short arm of the Y chromosome in 46,XY females. Proc Natl Acad Sci USA 1986;83:7841–4.

Duke EMC, Hussein DM, Hamilton W. Turner syndrome associated with growth hormone deficiency. Scott Med J 1981;26:240–4.

Escamilla RF, Hutchings JJ, Deamer WC, Li CH. Clinical experiences with human growth hormone in pituitary infantilism and in gonadal dysgenesis [abstract]. Acta Endocrinol 1960;35(Suppl 51):253.

Faggiano M, Minozzi M, Lombardi G, Carella G, Criscuolo T. Two cases of the chromatin positive variety of ovarian dysgenesis (XO/XX mosaicism) associated with hGH deficiency and marginal impairment of other hypothalamic-pituitary functions. Clin Genet 1975;8:324–9.

Ferguson-Smith MA. Karyotype-phenotype correlations in gonadal dysgenesis and their bearing on the pathogenesis of malformations. J Med Genet 1965;2:142–55.

Ferrandez A, Mayayo E, Castillo JA, Beltran F, Vargas ME on behalf of the Spanish Study Group. Growth response in Turner syndrome after one year of rhGH therapy. In: Ranke MB, Rosenfeld RG, editors. Turner syndrome: growth promoting therapies. Amsterdam: Elsevier Science Publishers, 1991:209–14.

Ferrandez A, Mayayo E, Castillo JA, Lalana MP, Olivan MP, Navarro MC, on behalf of the Spanish Study Group. Bone effects of rhGH in Turner syndrome. In: Ranke MB, Rosenfeld RG, editors. Turner syndrome: growth promoting therapies. Amsterdam: Elsevier Science Publishers, 1991:119–23.

Ford CE, Jones KW, Polani PE, de Almeida JC, Briggs JH. A sex-chromosome anomaly in a case of gonadal dysgenesis (Turner's syndrome). Lancet 1959;1:711–3.

Frane JW, Sherman BM, and the Genentech Collaborative Group. Predicted adult height in Turner syndrome. In: Rosenfeld RG, Grumbach MM, editors. Turner syndrome. New York: Marcel Dekker, Inc., 1990:405–19.

Frasier D, Costin G, Lippe BM, Aceto T, Funder PF. A dose-response curve for human growth hormone. J Clin Endocrinol Metab 1981;53:1213–7.

Gerver WJM, Drayer NM, van Es A. Does growth hormone treatment of patients with Turner's syndrome cause an abnormal body shape? Acta Paediatr 1992;81:691–4.

Goad WB, Robinson A, Puck TT. Incidence of aneuploidy in a human population. Am J Hum Genet 1976;28:62–8.

Giordano P, Tammaro P, Giancola A, Furfaro C. Effects on carbohydrate tolerance in patients with Turner's syndrome treated with rGH (three-year follow-up). Rass Int Clin Ther 1992;72:540–2.

Grunfeld C, Sherman BM, Cavalieri RR. The acute effects of human growth hormone administration on thyroid function in normal men. J Clin Endocrinol Metab 1988;67:1111–4.

Haeusler G, Frisch H. Methods for evaluation of growth in Turner's syndrome: critical approach and review of the literature. Acta Paediatr 1994;83:309–14.

Haeusler G, Frisch H. Growth hormone treatment in Turner's syndrome: short and long-term effects on metabolic parameters. Clin Endocrinol 1992;36:247–53.

Haeusler G, Schemper M, Frisch H, Blumel P, Schmitt K, Plochl E. Spontaneous growth in Turner syndrome: evidence for a minor pubertal growth spurt. Eur J Pediatr 1992;151:283–7.

Hakeem V, Spoudeas HA, Massarano AA, Stanhope R, Hindmarsh PC, Brook CGD. Therapeutic options for promoting growth in the Turner syndrome [abstract]. Horm Res 1992;37:25.

Hamerton JL. Population cytogenetics: a perspective. In: Adinolfi M, Benson P, Giannelli F, Seller M, editors. Pediatric research: a genetic approach. London: Spastics International Medical Publications, 1982:99–121.

Hamill PVV, Drizd TA, Johnson CL, Reed RB, Roche AF, Moore WM. Physical growth: National Center for Health Statistics percentiles. Am J Clin Nutr 1979;32:607–29.

Heinrichs C, DeSchepper J, Thomas M, Massa G, Craen M, Malvaux P, et al., for Pediatric Endocrinology. Final height in 46 girls with Turner syndrome treated with growth hormone in Belgium: evaluation of height recovery and predictive factors. In: Albertsson-Wikland K and Ranke M, editors. Turner

syndrome in a life-span perspective. Elsevier Science BV Publishers, 1995;137–47.

Hibi I, Tanae A, Tanaka T, Yoshizawa A, Miki Y, Ito J. Spontaneous puberty in Turner syndrome: its incidence, influence on final height and endocrinological features. In: Ranke MB, Rosenfeld RG, editors. Turner syndrome: growth promoting therapies. Amsterdam: Elsevier Science Publishers, 1991:75–81.

Hintz RL. Untoward events in patients treated with growth hormone in the USA. Horm Res 1992;38(Suppl 1):44–9.

Hintz RL, Attie KM. Compton PG, Rosenfeld RG. Multifactorial studies of GH treatment of Turner syndrome: the Genentech National Cooperative Growth Study. In: Albertsson-Wikland and Ranke M, editors. Turner syndrome in a life-span perspective. Elsevier Science BV Publishers, 1995;167–73.

Holland J, Brnjac L, Alexander D, Bailey J, Bala M, Best T, et al. Turner syndrome and final adult stature: a randomized controlled trial using human growth hormone and low dose ethinyl estradiol. In: Ranke MB, Rosenfeld RG, editors. Turner syndrome: growth promoting therapies. Amsterdam: Elsevier Science Publishers, 1991:195–200.

Hook EB, Warburton D. The distribution of chromosomal genotypes associated with Turner's syndrome: livebirth prevalence rates and evidence for diminished fetal mortality and severity in genotypes associated with structural X abnormalities or mosaicism. Hum Genet 1983;64:24–7.

Horton WA. Growth plate biology and the Turner syndrome. In: Rosenfeld RG, Grumbach MM, editors. Turner syndrome. New York: Marcel Dekker, Inc., 1990:259–66.

Job J-C. How sex steroids can modify the effect of growth hormone on growth in Turner syndrome. In: Hibi I, Takano K, editors. Basic and clinical approach to Turner syndrome. Amsterdam: Elsevier Science Publishers, 1993;279–86.

Jorgensen JOL, Pedersen SA, Laurberg P, Weeke J, Skakkebaek NE, Christiansen JS. Effects of growth hormone therapy on thyroid function of growth hormone-deficient adults with and without concomitant thyroxine-substituted central hypothyroidism. J Clin Endocrinol Metab 1989;69:1127–32.

Joss E, Zuppinger K. Oxandrolone in girls with Turner's syndrome. A pair-matched controlled study up to final height. Acta Paediatr Scand 1984;73:674–9.

Karlberg J et al. Growth in infancy and childhood in girls with Turner's syndrome. Acta Paediatr Scand 80:1158–1165, 1991.

Kastrup KW and the Turner Study Group. Oestrogen therapy in Turner's syndrome. Acta Paediatr Scand 1988;343(Suppl):43–6.

Kastrup KW and Turner Study Group. Growth and development in girls with Turner's syndrome during early therapy with low doses of estradiol. Acta Endocrinol (Copenh) 1986;279(Suppl):157–63.

Kastrup KW, Naeraa R, Nielsen J. Treatment with natural estrogens in Turner syndrome. In: Ranke MB, Rosenfeld RG, editors. Turner syndrome: growth promoting therapies. Amsterdam: Elsevier Science Publishers, 1991:175–9.

King CR, Magenis E, Bennett S. Pregnancy and the Turner syndrome. Obstet Gynecol 1978;52:617–24.

Knudtzon J, Aarskog D and The Norwegian Turner Study Group. Results of two years of growth hormone treatment followed by combined growth hormone and oestradiol in Turner syndrome. Horm Res 1993;39(Suppl 2):7–17.

Kollmann F, Damm M, Reinhardt D, Stover B, Heinrich U, Brendel L, et al. Growth promoting effects of human recombinant growth hormone in subjects with Ullrich-Turner syndrome (UTS). In: Ranke MB, Rosenfeld RG, editors. Turner syndrome: growth promoting therapies. Amsterdam: Elsevier Science Publishers, 1991:201–7.

Kosowicz J. The roentgen appearance of the hand and wrist in gonadal dysgenesis. Am J Radiol 1965;93:354–61.

Laczi F, Julesz J, Janaky T, Laszlo FA. Growth hormone reserve capacity in Turner's syndrome. Horm Metab Res 1979;11:664–6.

Lebl J, Zemkova D. Oedema in two girls with Turner's syndrome on growth hormone treatment. Cs Pediat 1994;49:204–5.

Lebl J, Zemkova D, Kolouskova M, Snajderova M. Growth hormone therapy in girls with Turner's syndrome. Cs Pediat 1994;49:131–6.

Lenko HL, Hakulinen A, Kaar M-L, Maenpaa J, Makela A-L, Sipila I. Effect of conventional dose growth hormone therapy for two years on height velocity

and height prognosis in girls with Turner syndrome. Horm Res 1993;39(Suppl 2):3–6.

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

Leszczynski S, Kosowicz J. Radiological changes in the skeletal system in Turner's syndrome. Review of 102 cases. Prog Radiol 1965;1:510–17.

Lev-Ran A. Androgens, estrogens, and the ultimate height in XO gonadal dysgenesis. Am J Dis Child 1977;131:648–9.

Lin TH, Kirkland RT, Kirkland JL. Adult height in girls with Turner syndrome treated with low-dose estrogens and androgens. Ann Pharmacother 1994;28:570–1.

Lindsten J, Cerasi E, Luft R, Hultquist G. The occurrence of abnormal insulin and growth hormone (HGH) responses to sustained hyperclycaemia in a disease with sex chromosome aberrations (Turner's syndrome). Acta Endocrinol 1967;56:107–31.

Lindsten J, Filipsson R, Hall K, Leikrans S, Gustavson K-H, Ryman N. Body height and dental development in patients with Turner's syndrome. Helv Pediatr Acta 1974;34(Suppl):33–46.

Lippe B. Turner syndrome. Endocrinol Metab Clin North Am 1991;20:121–52.

Lippe BM. Primary ovarian failure. In: Kaplan SA, editor. Clinical pediatric endocrinology. Philadelphia: WB Saunders, 1990:325–66.

Lubin MB, Gruber HE, Rimoin DL, Lachman RS. Skeletal abnormalities in the Turner syndrome. In: Rosenfeld RG, Grumbach MM, editors. Turner syndrome. New York: Marcel Dekker, Inc., 1990:281–92.

Lyon AJ, Preece MA, Grant DB. Growth curve for girls with Turner syndrome. Arch Dis Child 1985;60:932–5.

Lyson-Wojciechowska G, Romer TE, Wisniewski A, Majcher A. Body build and proportions of girls up to 10 years of age with Turner's syndrome after 12 months of growth hormone treatment. Pediatria Polska 1993;48:23–9.

Lu PW, Cowell CT. Combined therapy with growth hormone and oxandrolone in adolescent girls with Turner syndrome. J Paediatr Child Health 1993;29:40–2.

Malozowski S, Tanner LA, Wysowski D, Flemming GA. Growth hormone, insulin-like growth factor I, and benign intracranial hypertension [letter]. N Engl J Med 1993;329(9):665–6.

Martinez A, Heinrich JJ, Domene H, Escobar ME, Jasper H, Montuori E, et al. Growth in Turner's syndrome: long term treatment with low dose ethinyl estradiol. J Clin Endocrinol Metab 1987;65:253–7.

Massa G, Otten BJ, de Muinck Keizer-Schrama SMPF, Delemarre-van de Waal HA, Jansen M, Vulsma T, et al. Treatment with two growth hormone regimens in girls with Turner syndrome: final height results. Horm Res 1995;43:144–6.

Massa G, Maes M, Heinrichs C, Vandeweghe M, Craen M, Vanderschueren-Lodeweyckx M. Influence of spontaneous or induced puberty on the growth promoting effect of treatment with growth hormone in girls with Turner's syndrome. Clin Endocrinol 1993;38:253–60.

Massa G, Maes M, Malvaux P, Craen M, Ernould C, Heinrichs C, et al. Growth promoting effect of growth hormone and low dose ethinyl estradiol in girls with Turner syndrome: final height results [abstract]. Pediatr Res 1993;33(Suppl):S56.

Massa G, van den Broek J, Wit JM on behalf of the Lilly European Turner Study Group. Final height results of the LIlly European Turner Studies. In: Albertsson-Wikland and Ranke M, editors. Turner syndrome in a life-span perspective. Elsevier Science BV Publishers, 1995;155–9.

Massa G, Vanderschueren-Lodeweyckx M, Malvaux P. Linear growth in patients with Turner syndrome: influence of spontaneous puberty and parental height. Eur J Pediatr 1990;149:246–50.

Massa G, de Zegher F, Vanderschueren-Lodeweyckx M. Effect of growth hormone therapy on thyroid status of girls with Turner's syndrome. Clin Endocrinol 1991;34:205–9.

Mattevi MS, Wolff H, Salazano FM, Mallmann MC. Cytogenetic, clinical and genealogical analyses in a series of gonadal dysgenesis patients and their families. Humangenetik 1971;13:126–43.

Mauras N, Rogol AD, Veldhuis JD. Increased hGH production rate after low-dose estrogen therapy in prepubertal girls with Turner's syndrome. Pediatr Res 1990;28:626–30.

Mazzanti L, Nizzoli G, Tassinari D, Bergamaschi R, Magnani C, Chiumello G, et al. Spontaneous growth and pubertal development in Turner's syndrome with different karyotypes. Acta Paediatr 1994;83:299–304.

Merola B, Rossi E, Colao A, Longobardi S, Selleri A, Sarnacchiaro F, et al. rGH and very low doses of estrogen in the treatment of Turner's syndrome. Acta Med Auxol 1992;24:49–54.

Moller J, Jorgensen JOL, Ovesen P, Moller N, Laursen T, Christiansen JS. Effects of growth hormone on body fluid homeostasis. J Pediatr Endocrinol 1992;5:79–83.

Mora S, Weber G, Guarneri MP, Nizzoli G, Pasolini D, Chiumello G. Effect of estrogen replacement therapy on bone mineral content in girls with Turner syndrome. Obstet Gynecol 1992;79:747–51.

Muritano MR, Job JC. Effects of weakly androgenic steroids on growth in patients with Turner syndrome. Arch Fr Pediatr 1985;42:265–71.

Naeraa RW, Nielsen J. Standards for growth and final height in Turner's syndrome. Acta Paediatr Scand 1990;79:182–90.

Naeraa RW, Eiken M, Legarth EG, Nielsen J. Spontaneous growth, final height and prediction of final height in Turner syndrome. In: Ranke MB, Rosenfeld RG, editors. Turner syndrome: growth promoting therapies. Amsterdam: Elsevier Science Publishers, 1991:113–6.

Naeraa RW, Eiken M, Legarth EG, Nielsen J. Prediction of final height in Turner's syndrome. A comparative study. Acta Paediatr Scand 1990;79:776–83.

Naeraa RW, Nielsen J, Kastrup KW. Growth hormone and 17β-oestradiol treatment of Turner girls—2-year results. Eur J Pediatr 1994;153:72–7.

Neely EK, Marcus R, Rosenfeld RG, Bachrach LK. Turner syndrome adolescents receiving growth hormone are not osteopenic. J Clin Endocrinol Metab 1993;76:861–6.

Nienhuis HE, Rongen-Westerlaken C, Wit JM, Otten BJ, de Muinck Keizer-Schrama SMPF, Drayer NM, et al. Results of long-term therapy with growth hormone in two dose regimens in Turner syndrome. Horm Res 1993;39(Suppl 2):31–6.

Nienhuis HE, Rongen-Westerlaken C, Geertzen HGM, Rijkers GT, Zegers BJM, Wit JM, et al. Long-term effect of human growth hormone therapy on the

prevalence of autoantibodies in Turner syndrome. Horm Res 1993;39(Suppl 2):49–53.

Nilsson KO, Albertsson-Wikland K, Aronson S, Gustafsson J, Hagenäs L, Hager A, et al. Long-term results of combination treatment with growth hormone, oxandrolone and ethinyl estradiol in girls with Turner syndrome. In: Hibi I, Takano K, editors. Basic and clinical approach to Turner syndrome. Amsterdam: Elsevier Science Publishers, 1993:303–10.

Nilsson KO, Albertsson-Wikland K, Alm J, Aronson S, Gustafsson J, Hagenäs L, et al. Growth promoting treatment in girls with Turner syndrome: final height results according to three different Turner syndrome growth standards. In: Albertson-Wikland K and Ranke M, editors. Turner syndrome in a life-span perspective. Elsevier Science BV Publishers, 1995;89–94.

Nilsson KO, Albertsson-Wikland K, Alm J, Aronson S, Gustafsson J, Hagenäs L, et al. Improved final height in girls with Turner's syndrome treated with growth hormone and oxandrolone. J Clin Endocrinol Metab 1996;81:635–40.

Page LA. Final heights in 45,X Turner's syndrome with spontaneous sexual development. Review of European and American reports. J Pediatr Endocrinol 1993;6:153–8.

Pai GS, Leach DC, Weiss L, Wolf C, Van Dyke DL. Thyroid abnormalities in 20 children with Turner syndrome. J Pediatr 1977;91:267–9.

Palmer CG, Reichmann A. Chromosomal and clinical findings in 110 females with Turner syndrome. Hum Genet 1976;35:35–49.

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

Pasquino AM, Boscherini B. Effect of low-dose estrogen on growth in Turner syndrome. In: Ranke MB, Rosenfeld RG, editors. Turner syndrome: growth promoting therapies. Amsterdam: Elsevier Science Publishers, 1991:181–5.

Pasquino AM, Bernardini S, Cianfarani S, Mancuso G, Marchione SA, Passeri F, et al. GH assessment and three years' hGH therapy in girls with Turner syndrome. Horm Res 1992;38:120–4.

Pavia C, Vilaplana RM, Valls C. Effect of GH alone or in combination with EE_2 on the growth of Turner syndrome. In: Ranke MB, Rosenfeld RG, editors. Turner syndrome: growth promoting therapies. Amsterdam: Elsevier Science Publishers, 1991;169–73.

Pelz L, Sager G, Hinkel GK, Kirchner M, Kruger G, Verron G. Delayed spontaneous pubertal growth spurt in girls with the Ullrich-Turner syndrome. Am J Med Genet 1991;40:401–5.

Pelz L, Timm D, Eyermann E, Hinkel GK, Kirchner M, Verron G. Body height in Turner's syndrome. Clin Genet 1982;22:62–6.

Philip J, Sele V. 45,XO Turner's syndrome without evidence of mosaicism in a patient with two pregnancies. Acta Obstet Gynecol Scand 1976;55:283–6.

Pienkowski C, Tauber MT, Sporer G, Elefterion M, Dechaux E, Rochiccioli P. Search for factors influencing growth velocity in Turner syndromes treated by GH [abstract]. Horm Res 1992;37:26.

Pierard GE, Pierard-Franchimont C. Morphometric evaluation of the growth of nevi. Ann Dermatol Venereol 1993;120:605–9.

Pirazzoli P, Cacciari E, Mandini M, Sganga T, Capelli M, Cicognani A, et al. Growth and thyroid function in children treated with growth hormone. J Pediatr 1992;121:210–3.

Price DA, Albertsson-Wikland K on behalf of the International Board of the Kabi Pharmacia International Growth Study. Demography, auxology and response to recombinant human growth hormone treatment in girls with Turner's syndrome in the Kabi Pharmacia International Growth Study. Acta Paediatr 1993;391(Suppl):69–74.

Price DA, Clayton PE, Crowne EH, Roberts CR. Safety and efficacy of human growth hormone treatment in girls with Turner syndrome. Horm Res 1993;39(Suppl 2):44–8.

Price DA, Clayton PE, Lloyd IC. Benign intracranial hypertension induced by growth hormone treatment [letter]. Lancet 1995;345:458–9.

Raiti S. Statistical aspects of hGH therapy for hypopituitarism. Pediatr Adolesc Endocrinol 1987;16:1–12.

Ranke MB, Blum WF, Haug F, Rosendahl W, Attanasio A, Enders H, et al. Growth hormone, somatomedin levels and growth regulation in Turner's syndrome. Acta Endocrinol (Copenh) 1987;116:305–13.

Ranke MB, Chavez-Meyer H, Blank B, Frisch H, Hausler G. Spontaneous growth and bone age development in Turner syndrome: results of a multicentric study 1990. In: Ranke MB, Rosenfeld RG, editors. Turner syndrome: growth promoting therapies. Amsterdam: Elsevier Science Publishers, 1991:101–6.

Ranke MB, Grauer M-L. Adult height in Turner syndrome: results of a multinational survey 1993. Horm Res 1994;42:90–4.

Ranke MB, Haug F, Blum WF, Rosendahl W, Attanasio A, Bierich JR. Effect on growth of patients with Turner's syndrome treated with low estrogen doses. Acta Endocrinol (Copenh) 1986;279(Suppl):153–6.

Ranke MB, Pfluger H, Rosendahl W, Stubbe P, Enders H, Bierich JR, et al. Turner syndrome: spontaneous growth in 150 cases and review of the literature. Eur J Pediatr 1983;141:81–8.

Ranke MB, Price DA, Maes M, Albertsson-Wikland K, Lindberg A. Factors influencing final height in Turner syndrome following GH treatment: results of the Kabi International Growth Study (KIGS). In: Albertsson-Wikland and Ranke M, editors. Turner syndrome in a life–span perspective. Elsevier Science BV Publishers, 1995;161–5.

Ranke M. Growth in Turner's syndrome. Acta Paediatr 83:343–4,1994.

Ranke MB, et al. Spontaneous adult height in idiopathic short stature. Horm. Res. 1995: 44:152–7.

Reschini E, D'Alberton A, Catania A, Motta T. Growth hormone and ACTH secretory dynamics in Turner's syndrome. Gynecol Endocrinol 1990;4:119–25.

Reyes FI, Koh KS, Faiman C. Fertility in women with gonadal dysgenesis. Am J Obstet Gynecol 1976;126:668–70.

Robinson A. Demography and prevalence of Turner syndrome. In: Rosenfeld RG, Grumbach MM, editors. Turner syndrome. New York: Marcel Dekker, Inc., 1990:93–9.

Rocchiccioli P, Battin J, Bertrand AM, Bost M, Cabrol S, Le Bouc Y, et al. Final stature in cases of Turner's syndrome treated with growth hormone. Arch Pediatr 1994;1:359–62.

Rocchiccioli P, Battin J, Bertrand AM, Bost M, Cabrol S, Le Bouc Y, et al. Final height in Turner syndrome patients treated with growth hormone. Horm Res 1995;44:172–6.

Rocchiccioli P, Chaussain JL. Final height in patients with Turner syndrome treated with growth hormone (n = 117). In Albertsson-Wikland K and Ranke M, editors. Turner syndrome in a life-span perspective. Elsevier Science BV Publishers, 1995;123–8.

Rochiccioli P, David M, Malpuech G, Colle M, Limal JM, Battin J, et al. Study of final height in Turner's syndrome: ethnic and genetic influences. Acta Paediatr 1994;83:305–8.

Rongen-Westerlaken C, Wit JM, De Muinck Keizer-Schrama SMPF, Otten BJ, Oostdijk W, Delemarre-van der Waal HA, et al. Growth hormone treatment in Turner syndrome accelerates growth and skeletal maturation. Eur J Pediatr 1992;151:477–81.

Rongen-Westerlaken C, Rijkers GT, Scholtens EJ, van Es A, Wit JM, van den Brande JL, et al. Immunologic studies in Turner syndrome before and during treatment with growth hormone. J Pediatr 1991;119:268–72.

Rongen-Westerlaken C, Fokker MH, Wit JM, De Muinck Keizer-Schrama SMPF, Otten BJ, Oostdijk W, et al. Two-year results of treatment with methionyl human growth hormone in children with Turner syndrome. Acta Paediatr Scand 1990;79:658–63.

Rongen-Westerlaken C, van der Born E, Prahl-Andersen B, van Teunenbroek A, Manesse P, Otten BJ, et al. Effect of growth hormone treatment on craniofacial growth in Turner's syndrome. Acta Paediatr 1993;82:364–8.

Rongen-Westerlaken C, van Es A, Wit J-M, Otten BJ, De Muinck Keizer-Schrama SMPF, Drayer NM, et al. Growth hormone therapy in Turner's syndrome. Impact of injection frequency and initial bone age. Am J Dis Child 1992;146:817–20.

Rosenfeld RG. Reply. J Pediatr 1993;122(4):671–2.

Rosenfield RL. Spontaneous puberty and fertility in Turner syndrome. In: Rosenfeld RG, Grumbach MM, editors. Turner syndrome. New York: Marcel Dekker, Inc., 1990:131–48.

Rosenfeld RG, Frane J, Attie KM, Brasel JA, Burstein S, Cara JF, et al. Six-year results of a randomized, prospective trial of human growth hormone and oxandrolone in Turner syndrome. J Pediatr 1992;121:49–55.

Ross JL, Cassorla FG, Skerda MC, Valk IM, Loriaux DL, Cutler GB Jr. A preliminary study of the effect of estrogen dose on growth in Turner's syndrome. N Engl J Med 1983;309:1104–6.

Ross JL, Feuillan P, Long LM, Kowal K, Kushner H, Cutler GB Jr. Lipid abnormalities in Turner syndrome. J Pediatr 1995;126:242–5.

Ross JL, Long LM, Loriaux DL, Cutler GB Jr. Growth hormone secretory dynamics in Turner syndrome. J Pediatr 1985;106:202–6.

Ross JL, Long LM, Skerda M, Cassorla F, Kurtz D, Loriaux DL, et al. Effect of low doses of estradiol on 6-month growth rates and predicted height in patients with Turner syndrome. J Pediatr 1986;109:950–3.

Ross JL, McCauley E, Freund L, Cutler GB Jr. Long-term effects of growth hormone, estrogen, or placebo on self-image and behavior in Turner syndrome [abstract]. Pediatr Res 1993;33(Suppl):S50.

Rovet J, Holland J, Members of the Canadian Growth Hormone Advisory Group. Psychological aspects of the Canadian randomized controlled trial of human growth hormone and low-dose ethinyl oestradiol in children with Turner syndrome. Horm Res 1993;39(Suppl 2):60–4.

Rudman D, Goldsmith M, Kutner M, Blackston D. Effect of growth hormone and oxandrolone singly and together on growth rate in girls with X chromosome abnormalities. J Pediatr 1980;96:132–5.

Saggese G, Federico G, Cinquanta L. Plasma growth hormone-binding protein activity, insulin-like growth factor I, and its binding protein levels in patients with Turner's syndrome: effect of short- and long-term recombinant human growth hormone administration. Pediatr Res 1995;37:106–11.

Sato T, Miyamori C, Kajiwara S, Miyagawa K, Shimizu M. Factors attenuating growth promoting effect of growth hormone therapy for Turner's syndrome. Endocrinol Japon 1988;35:725–31.

Schober E, Frisch H, Waldhauser F, Bieglmayr C. Influence of estrogen administration on growth hormone response to GHRH and L-Dopa in patients with Turner's syndrome. Acta Endocrinol (Copenh) 1989;120:442–6.

Schonau E, Kruse K, de Bernard B, Moro L. Further evidence of elevated bone resorption in Ullrich-Turner syndrome by measuring urinary galactosyl-hydroxylysine. Acta Paediatr 1992;81:633–4.

Sippell WG, Partsch CJ, Steinkamp H on behalf of the German Pfrimmer-Kabi UTS Study Group. Biosynthetic growth hormone (Genotropin) therapy in girls with the Ullrich-Turner-syndrome (UTS). In: Ranke MB, Rosenfeld RG, editors. Turner syndrome: growth promoting therapies. Amsterdam: Elsevier Science Publishers, 1991;237–40.

Stahnke N, Attanasio A, Van den Broek J, Partsch CJ, Zeisel HJ. GH treatment studies to final height in girls with Turner syndrome—the German experience. In: Albertsson-Wikland K and Ranke M, editors. Turner syndrome in a life-span perspective. Elsevier Science BV Publishers, 1995;95–103.

Stahnke N, Stubbe P, Keller E, and Study Participants. Recombinant human growth hormone and oxandrolone in treatment of short stature in girls with Turner syndrome. Horm Res 1992;37(Suppl 2):37–46.

Stahnke N, Stubbe P, Keller E, Zeisel HJ and Serono Study Group Hamburg. Effects and side-effects of GH plus oxandrolone in Turner syndrome. In: Ranke MB, Rosenfeld RG, editors. Turner syndrome: growth promoting therapies. Amsterdam: Elsevier Science Publishers, 1991:241–7.

Stoppoloni G, Prisco F, Alfano C, Iafusco D, Marrazzo G, Paolisso G. Characteristics of insulin resistance in Turner syndrome. Diabete Metab 1990;16:267–71.

Taback SD, Collu R, Deal CL, Guyda HJ, Salisbury S, Dean HJ, et al. Does growth-hormone supplementation affect adult height in Turner's syndrome? Lancet 1996;348:25–7.

Takano K, Ogawa M, Okada Y, Tanaka T, Tachibana K, Hizuka N. Final height and long-term effects after growth hormone therapy in Turner syndrome: results of a 6-year multicentre study in Japan. In: Albertsson-Wikland K and Ranke M, editors. Turner syndrome in a life-span perspective. Elsevier Science BV Publishers, 1995;113–21.

Takano K, Shizume K, Hibi I, and the members of the Committee for the Treatment of Turner Syndrome. Turner's syndrome: treatment of 203 patients with recombinant human growth hormone for one year. A multicentre study. Acta Endocrinol (Copenh) 1989;120:559–68.

Takano K, Shizume K, Hibi I and the members of the Committee for the Treatment of Turner Syndrome. GH treatment in Turner syndrome: the result of a multicentric study in Japan. In: Ranke MB, Rosenfeld RG, editors. Turner syndrome: growth promoting therapies. Amsterdam: Elsevier Science Publishers, 1991;249–55.

Takano K, Shizume K, Hibi I and the members of the Committee for the Treatment of Turner Syndrome. GH treatment in Turner syndrome: the result of a multicentric study in Japan. In: Ranke MB, Rosenfeld RG, editors.

Turner syndrome: growth promoting therapies. Amsterdam: Elsevier Science Publishers, 1991;249–55.

Takano K, Shizume K, Hibi I, and the members of the committee for the treatment of Turner's syndrome. Treatment of 46 patients with Turner's syndrome with recombinant human growth hormone (YM-17798) for three years: a multicentre study. Acta Endocrinol 1992;126:296–302.

Takano K, Shizume K, Hibi I, Suwa S, Okada Y. Cross-sectional growth study in patients with Turner's syndrome. Endocrinol Japan 1988;35:631–8.

Takano K, Shizume K, Hibi I, Ogawa M, Okada Y, Suwa S, et al. Growth hormone treatment in Turner syndrome: results of a multicentre study in Japan. Horm Res 1993;39(Suppl 2):37–41.

Takano K, Shizume K, Hibi I, Ogawa M, Okada Y, Suwa S, et al. Long-term effects of growth hormone treatment on height in Turner syndrome: results of a 6-year multicenter study in Japan. Horm Res 1995;43:141–3.

Tamborlane W, Caprio S, Press M, Carpenter T, Plewe G, Sherwin R. Insulin resistance and compensatory hyperinsulinaemia in Turner's syndrome [abstract]. Diabetologia 1988;31:548A.

Tanner JM, Davies PSW. Clinical longitudinal standards for height and height velocity for North American children. J Pediatr 1985;107:317–29.

Tillmann V, Price DA, Bucnall JL, Clayton PE. Experience within the Manchester growth clinic of growth hormone treatment of girls with Turnder syndrome: the influence of duration of treatment on final height. In: Albertsson-Wikland and Ranke M, editors. Turner syndrome in a life-span perspective. Elsevier Science BV Publishers, 1995;149–54.

Tonini G, Marinoni S. Elevation of serum aminotransferase and γ-glutamyltranspeptidase levels in three patients receiving recombinant human growth hormone therapy [abstract]. Acta Paediatr Scand 1990;370(Suppl):193.

Toublanc JE, Job JC, Rappaport R, Colle M, Battin J, Rochiccioli P, et al. The French experience of treatment of Turner syndrome with growth hormone (GH) versus GH + oxandrolone. In: Ranke MB, Rosenfeld RG, editors. Turner syndrome: growth promoting therapies. Amsterdam: Elsevier Science Publishers, 1991:231–6.

Turner HH. A syndrome of infantilism, congenital webbed neck, and cubitis valgus. Endocrinology 1938;23:566–74.

Ullrich O. Uber typische Kombinationsbilder multipler Abartung. Z Kinderheilk 1930;49:271–6.

Van den Broek J, Massa GG, Attanasio A, Matranga A, Chassain J-L, Price DA, et al. Final height after long-term growth hormone treatment in Turner syndrome. J Pediatr 1995;127:729–35.

van der Putte SCJ. Lymphatic malformation in human fetuses. A study of fetuses with Turner's syndrome or status Bonnevie-Ullrich. Virchows Arch A Pathol Anat Histopathol 1977;376:233–46.

Vanderschueren-Lodeweyckx M, Massa G, Maes M, Malvaux P, Heinrichs C, Craen M. Growth promoting effect of growth hormone in low dose ethinyl estradiol in girls with Turner syndrome: 2 year results. In: Ranke MB, Rosenfeld RG, editors. Turner syndrome: growth promoting therapies. Amsterdam: Elsevier Science Publishers, 1991;257–61.

van Teunenbroek A, Gerver W, de Muinck Keizer-Schrama S, Stijnen T, Drop S, and the Dutch Working Group on Growth Hormone. Body proportions before and during GH treatment in Turner syndrome [abstract]. Horm Res 1992;37:25.

Van Vliet G, Collu R. Treatment of Turner syndrome with growth hormone [letter]. J Pediatr 1993;122(4):671–2.

Villadolid MCR, Takano K, Hizuka N, Asakawa K, Sukegawa I, Horikawa R, et al. Twenty-four hour plasma GH, FSH and LH profiles in patients with Turner's syndrome. Endocrinol Japon 1988;35:71–81.

Weise M, James D, Leitner CH, Hartmann KKP, Bohles HJ, Attanasio A, et al. Glucose metabolism in Ullrich Turner syndrome: long-term effects of therapy with human growth hormone. Horm Res 1993;39:36–41.

Weise M, James D, Leitner CH, Hartmann KKP, Bohles HJ, Attanasio A, et al. Glucose metabolism in Ullrich Turner syndrome: long-term effects of therapy with human growth hormone. Horm Res 1993;39:36–41.

Werther G on behalf of the Australasian Paediatric Endocrine Group. A multi-centre double-blind study of growth hormone and low-dose estrogen in Turner syndrome: an interim analysis. In: Ranke MB, Rosenfeld RG, editors.

Turner syndrome: growth promoting therapies. Amsterdam: Elsevier Science Publishers, 1991;263–8.

Werther G, Dietsch S for the Australasian Paediatric Endocrine Group. Multicentre trial of synthetic growth hormone and low dose oestrogen in Turner syndrome: analysis of final height. In: Albertsson-Wikland K and Ranke M, editors. Turner syndrome in a life-span perspective. Elsevier Science BV Publishers, 1995;105–12.

Wilson DM, Rosenfeld RG and the Genentech Turner Collaborative Group. Effect of GH and oxandrolone on carbohydrate and lipid metabolism. In: Ranke MB, Rosenfeld RG, editors. Turner syndrome: growth promoting therapies. Amsterdam: Elsevier Science Publishers, 1991;269–74.

Wilson DM, Frane JW, Sherman B, Johanson AJ, Hintz RL, Rosenfeld RG, et al. Carbohydrate and lipid metabolism in Turner syndrome: effect of therapy with growth hormone, oxandrolone, and a combination of both. J Pediatr 1988;112:210–7.

Wisniewski A, Romer TE. Growth retardation in patients with Turner's syndrome: efficiency of rhGH treatment as a function of dose. Pediatria Polska 1993;48:17–22.

Wilton P. Growth hormone treatment in girls with Turner's syndrome. Acta Paediatr Scand 1987;76:193–200.

Yoshida A, Ishioka C, Kimata H, Mikawa H. Recombinant human growth hormone stimulates B cell immunoglobulin synthesis and proliferation in serum-free medium. Acta Endocrinol 1992;126:524–9.

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