CENTER FOR DRUG EVALUATION AND RESEARCH

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MEDICAL REVIEW(S)

CLINICAL REVIEW

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Established Name	Genotropin
(Proposed) Trade Name	Genotropin
Therapeutic Class	rhGH (recombinant human growth hormone)
Applicant	Pfizer, Inc.
Priority Designation	S
Formulation	Lyophilized Genotropin
Dosing Regimen	0.33 mg/kg per week
Indication	Short stature in girls with Turner Syndrome
Intended Population	Girls with Turner Syndrom

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

THE SUPPLEMENT SHOULD BE APPROVED.

1.1.1 Efficacy

- No additional efficacy studies are required to obtain approval for this indication.
- As will be described in more detail in Section 1.3.2.2 of the Executive Summary, the short-term efficacy data from Studies 055 and 092 presented in this application describing the significant linear growth response of short children with Turner Syndrome (TS) after 12 months of treatment with Genotropin **is sufficient by itself** to warrant approval of this supplement and the requested labeling change. A comparison of the efficacy findings in Studies 055 and 092 with the results of 4 published short-term controlled studies **strongly supports** the validity of the sponsor's findings. A review of published final height (FH) studies supported by the sponsor wherein short TS children were treated with Genotropin until FH was achieved provides **modest additional support** for the application. A review of published FH studies not supported by the sponsor wherein short TS children were treated with rhGH formulations other than Genotropin until FH was achieved **is not necessary** for approval of this application and is contained in this Medical Officer's review **only to provide context**.
- The Sponsor's proposed additional language to the Clinical Studies section of the Genotropin Package Insert describing the effects of Genotropin on linear growth in Studies 055 and 092 was carefully reviewed and then edited (in collaboration with the Division's Statistical Reviewers). The most consequential edits involved 1) presentation of results from the Genotropin only arms from each study and exclusion of (b) (4) (b) (4) (b) (4) (see Section 6.1.2 ahead regarding the rationale for this decision); 2) reformatting of Table 5 in order to present the results from Studies 055 and 092 in a more comprehensive but user-friendly fashion; and 3) expressing results as means as opposed to medians (the means and medians were very similar, and the other studies described in the Genotropin Package Insert use means); and 4) editing of the text describing Table 5 for purposes of clarity and to clearly indicate that the response to Genotropin 0.33 mg/kg per week in Study 055 (the proposed dosage in the Package Insert) was more robust than the response to Genotropin 0.13-0.23 mg/kg per week in Study 092. The sponsor agreed with all of the Division's suggested edits. No edits were required for the sponsor's proposed additions to the Indications and Usage, and Dosing and Administration sections.

1.1.2 Safety

- No additional safety data are required to obtain approval for this indication.
- No edits were required for the sponsor's proposed additions to the Precautions, and Adverse Reactions sections.

- In the very near future, Pfizer (as well as the other 5 sponsors approved to market rhGH) will be requested to make a number of class labeling changes. Amongst these changes will be language in the Precautions section indicating **"glucose levels should be monitored periodically in all patients treated with somatropin, especially in those with risk factors for diabetes mellitus, such as obesity (including obese patients with PWS), Turner syndrome, or a family history of diabetes mellitus."**
- See Section 1.2.3 below.

1.1.3 Risk-Benefit Statement

As discussed in Sections 1.3.2.2, 1.3.2.3 and 1.1.1 of the EXECUTIVE SUMMARY, the **efficacy data** submitted in support of Genotropin for the treatment of short stature associated with TS is **substantial and sufficient**. As discussed in Sections 1.3.3 and 1.1.2, the **safety data** submitted reveal that Genotropin is **safe and well tolerated** in TS children. As discussed in Section 1.2.3 below, the Division is requesting that the sponsor gather additional long-term data regarding the incidence of certain AEs in TS patients vs. non-TS patients after treatment with Genotropin. **All things considered, a review of the efficacy and safety data submitted by the sponsor demonstrates a favorable benefit to risk ratio, and supports the proposed indication for Genotropin as a long-term treatment of growth failure associated with TS in patients who have open epiphyses**.

1.2 Recommendation on Postmarketing Action

1.2.1 Risk Management Activity

None.

1.2.2 Required Phase 4 Commitments

None.

1.2.3 Other Phase 4 Requests

- In that 1) TS patients are inherently prone to develop type 2 diabetes mellitus, scoliosis, hypertension and otitis media, and may be more prone to develop slipped capital femoral epiphysis (SCFE) and benign intracranial hypertension (BIH); 2) type 2 diabetes mellitus, aggravation of preexisting scoliosis, SCFE and BIH are currently labeled potential adverse effects associated with rhGH treatment, and hypertension (via rhGH-induced salt retention) and otitis media (related to rhGH-induced adenoidal hypertrophy) are plausible adverse effects of rhGH (though currently unlabeled); and 3) a comparison of the **reporting rates** of adverse events (AEs) in TS patients vs. non-TS patients treated with Genotropin reported to the sponsor's Early Alert Safety Databases (ARGUS and NovAlert [including serious AEs {SAEs} from the Kabi International Growth Study {KIGS} and ongoing clinical studies]) revealed that SCFE, BIH, diabetes mellitus, hypertension and otitis media occurred ≥3 times as often in TS patients compared with

non-TS patients, **the Division recommends that the sponsor add an additional section to its annual Periodic Safety Update Report (PSUR) wherein the incidence of all AEs (in particular the 6 listed above) are compared in TS patients and non-TS patients treated with Genotropin.**

- If possible, an attempt should be made to capture FH data on the TS patients who were treated with Genotropin alone during Studies 055 and 092. The Division realizes that this may be a very difficult undertaking and therefore not feasible.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

As summarized and referenced in detail in Section 2.6.1, TS occurs in approximately 1 in every 1,900 live female births and is caused by a loss or abnormality of the second X chromosome in at least 1 major cell line in the body. The 2 principal features of TS are short stature and ovarian dysgenesis. Absent treatment with rhGH, girls with TS attain a FH approximately 21 cm (~8") shorter than the normal female population. In a classic study reflecting the results of 4 European studies, the historical FH observed in untreated girls with TS was **143.2 cm**. Ovarian failure occurs in the vast majority of girls, mandating lifelong estrogen therapy beginning in adolescence.

Numerous studies conducted during the past 15 years have demonstrated that treatment with rhGH accelerates short-term growth in girls with TS. More recently, published studies have shown that treatment of TS children with rhGH results in an increase in FH (compared with concurrent untreated controls, historical untreated controls and/or predicted final adult height at baseline), and normalization of FH (i.e., FH >5 feet) in many patients. Therefore, the **standard of care guideline** for the clinical use of rhGH published by the American Association of Clinical Endocrinologists (AACE) in 2003 recommends initiation of rhGH as soon as the height of a TS girl is below the 5th percentile of the normal growth curve. The recommendations published by Saenger et al in 2001 following an international multidisciplinary workshop on the management of patients with TS held in March 2000 are essentially identical. Furthermore, the Lawson Wilkins Pediatric Endocrinology Society (LWPES) Drug and Therapeutics Committee cites rhGH as an important pharmacological agent to increase linear growth in children with TS. Dosing guidelines for rhGH for the treatment of TS patients with short stature are discussed at length in Section 1.3.4 of the Executive Summary and Section 2.6.3. The potential merits of oxandrolone as adjunctive therapy, and the lack of value of estrogen as a growth promoting agent in TS children are also discussed in Section 2.6.3.

In 1997, Humatrope and Nutropin were approved by the Agency for the treatment of short stature associated with TS (with an orphan designation). When the period of orphan exclusivity for those 2 products expired in 2004, the sponsor for Genotropin requested a pre-sNDA meeting which was held on 16Feb05. It was agreed at that time that the sponsor would submit the results

of Studies 055 and 092 (in addition to a review of the literature) in support of an indication to treat short children with TS with Genotropin.

1.3.2 Efficacy

1.3.2.1 Brief Description of Study Design

Two randomized, open-label, clinical trials (Studies 055 and 092) were conducted that evaluated the efficacy and safety of Genotropin in TS patients with short stature. TS patients were treated with Genotropin alone or Genotropin plus adjunctive hormonal therapy (ethinyl estradiol [Study 055] or oxandrolone [Study 092]). The focus of this review was on the 38 patients who were treated with Genotropin alone in the 2 studies, and the results from the adjunctive therapy arms are not presented (see Section 6.1.2 ahead for the rationale for this decision). In Study 055, 22 patients were treated for 12 months, and in Study 092, 16 patients were treated for 12 months. Patients received Genotropin 0.33 mg/kg per week in Study 055, and 0.13 to 0.23 mg/kg per week in Study 092. The primary efficacy variables shared by both studies were height velocity (HV), height standard deviation score (SDS), and HV SDS (and their changes from baseline). SDS for HV and height were expressed using either the Tanner (Study 055) or Sempe (Study 092) standards for age-matched normal children, as well as the Ranke standard (both studies) for age-matched, untreated TS patients. An additional primary efficacy variable in Study 092 was the predicted final adult height measured by the Bayley-Pinneau predicted adult height (B-P PredAH) method as well as the modified projected adult height (mProjAH) method. The Division's Statistical Reviewer utilized both the paired t-test and Wilcoxon's signed rank test in performing within goup analyses. Safety endpoints included adverse events and measures of glucose tolerance.

1.3.2.2 Efficacy Results

- **In Studies 055 and 092, height SDS (Tanner/Sempe or Ranke standard) increased significantly at Month 12.**

After 12 months of Genotropin treatment, in Study 055, mean height SDS (Tanner) significantly increased from a mean baseline value of -3.08 by **0.41**, and in Study 092, mean height SDS (Sempe) also significantly increased from a mean baseline value of -3.19 by **0.26**. After 12 months of Genotropin treatment, in Study 055, mean height SDS (Ranke) significantly increased from a mean baseline value of -0.24 by **0.79**, and in Study 092, mean height SDS (Ranke) also significantly increased from a mean baseline value of -0.31 by **0.46**. In Study 055, a substantial height SDS response was also evident at Month 6, and continued to increase at Month 12.

- **In Studies 055 and 092, HV and HV SDS (Tanner/Sempe or Ranke standard) increased significantly at Month 12.**

After 12 months of Genotropin treatment, in Study 055, **the mean HV (7.79 cm/year) was significantly increased from baseline (change in HV = 3.68 cm/year)**, and in Study 092, **the mean HV (6.09 cm/year) was also significantly increased from baseline (change in HV =**

2.19 cm). However, the magnitude of these significant increases from baseline was greater in Study 055 than in Study 092, more than likely because the patients were treated with a larger and more appropriate dosage of Genotropin. In Study 055, after 6 months of treatment with Genotropin, the annualized mean HV (8.19 cm/year) was also significantly increased from baseline **and had doubled the baseline HV** (change in HV = 4.01 cm).

- In Studies 055 and 092, as expected, HV SDS and height SDS were smaller at baseline and after treatment with Genotropin using the normative standards as opposed to the TS standard. Irrespective of the standard utilized, each of these variables significantly increased from baseline in both studies. **However, the magnitude of these significant increases from baseline for each of these variables was greater in Study 055 than in Study 092, more than likely because the patients were treated with a larger and more appropriate dosage of Genotropin.**

- The change in HV after treatment with Genotropin for 12 months was >0 in every patient in both studies, and >1 cm/year in 21/22 patients (95%) in Study 055 and 11/16 patients (69%) in Study 092. The change in height SDS (Tanner or Sempe) after treatment with Genotropin for 12 months was >0 in 20/22 patients (91%) in Study 055 and 13/16 patients (81%) in Study 092, **i.e. 2 patients in Study 055 and 3 patients in Study 092 did not grow in response to Genotropin when their heights were expressed as SDS derived from the growth patterns of healthy non-TS children.** The change in height SDS was >0.1 in 77% of patients in Study 055 and 75% of patients in Study 092.

- After 12 months of treatment with Genotropin alone, the mean B-P PredAH (147.4 cm) of the TS girls was significantly increased from baseline (144.6 cm). Similarly, the mean mProjAH also significantly increased (from 144.4 cm at baseline to 147.2 cm at Month 12).

1.3.2.3 Efficacy Conclusions

- **The significant HV, HV SDS and height SDS change from baseline results in both studies indicate a consistent linear growth response to Genotropin at Month 12 in TS children with short stature, which was apparent even at Month 6 in Study 055.**
- **The more robust HV, HV SDS and height SDS responses observed in Study 055 compared with Study 092 more than likely reflects the fact that the TS children in Study 092 were treated with a lower and less optimal dose of Genotropin (0.33 mg/kg per week in Study 055 vs. 0.13 to 0.23 mg/kg per week in Study 092). Of note, the dosage previously approved for the treatment of short stature associated with TS was up to 0.375 mg/kg per week.**
- **Two patients in Study 055 (9%) and 3 patients in Study 092 (19%) did not grow in response to Genotropin when their heights were expressed as SDS derived from the growth patterns of healthy non-TS children (i.e., the change in height SDS was <0), and 1 patient in Study 055 (5%) and 5 patients in Study 092 (31%) grew less than 1 cm after 1 year of Genotropin treatment. These findings are consistent with**

previous observations that the linear growth response of TS girls with short stature to treatment with rhGH is less consistent and more variable than the response of short children with growth hormone deficiency. In addition, these results provide further evidence that the TS children in Study 092 were suboptimally dosed.

- **The positive post-treatment HV SDS values (using the Tanner/Sempe standards for healthy non-TS children or the Ranke standard for TS children) achieved in both studies indicate that Genotropin treatment of TS girls induced rates of growth which were greater than that of either normal children or untreated TS children of the same age.**
- **The similar significant increases in B-P PredAH and mProjAH (~3 cm) (2 totally different methodologies) in Study 092 indicate that treatment with Genotropin for 1 year definitively increased the predicted final adult height of TS girls. The sponsor reports that continued treatment with Genotropin for an additional 1, 2 or 3 years resulted in greater increases in predicted final adult height.**
- **In Study 055, the significant increases in height SDS (Ranke, 0.79; Tanner, 0.41) were robust. Ranke et al have reported that first year growth of TS patients after treatment with rhGH is a powerful predictor of height gain (i.e., FH compared with mProjAH at baseline) in TS children who continue to receive rhGH until FH is attained.**
- **The focus of this Medical Officer's review was on the Month 12 efficacy results. The sponsor reports that long-term treatment with Genotropin in Study 092 resulted in a progressive increase from baseline in height SDS (Ranke) from 0.4 at Month 12, to 0.9, 1.2 and 1.4 at Months 24, 36, and 48, respectively.**

- **With respect to published short-term (12 month) studies:**

The HV results at Month 12 in Studies 055 and 092 (open label studies without an untreated or placebo-treated concurrent control group) compare very favorably with the 12 month results of the 4 concurrently controlled studies. The similar results observed during the controlled studies support the validity of the significant increases in HV observed during Studies 055 and 092.

Furthermore, considering the results of all 6 short-term studies, it is clear that treatment with 0.30 – 0.36 mg/kg per week of Genotropin for 12 months results in a greater linear growth response (~1 cm/year more) than treatment with 0.13 – 0.27 mg/kg per week for 12 months. In this regard, Genotropin dosages of 0.30 – 0.36 mg/kg per week more closely approximate the dosage of Genotropin previously approved for the treatment of short stature associated with TS (i.e., up to 0.375 mg/kg per week).

- **With respect to published FH studies:**

The results of 4 FH studies in Genotropin-treated children with TS supported by the sponsor have been published. The most consequential of these was a retrospective review of 188 TS patients in the German subset of the KIGS database - wherein a median

Genotropin dose of **0.29 mg/kg per week** resulted in a median FH was **152.2 cm**, a 6 cm gain over mProjAH at baseline, and a 1 unit change from baseline in height SDS (Ranke). **Although these 4 Pfizer/Pharmacia-sponsored FH studies were flawed in that 1) 3 of them were not controlled; 2) 2 of them were retrospective analyses; and 3) 1 of them was concurrently controlled but the Genotropin dosage utilized was suboptimal, they do provide a *small* degree of support for the sponsor's current application, in particular, the large study described above.** ***However, it should be noted that, in the opinion of this Medical Officer, the short-term data presented in the preceding bullets are sufficient to grant approval for this indication.***

The results of 12 FH studies (3 concurrently controlled and 9 uncontrolled) in rhGH-treated children with TS supported by other sponsors were reviewed by this Medical Officer. ***It is important to note once again that, in the opinion of this Medical Officer, referral to these FH studies supported by other sponsors is not necessary for the approval of the current submission, i.e. the short-term data described in the preceding bullets are sufficient to grant approval for this indication. The intent of this Medical Officer in summarizing the results of these FH studies supported by other sponsors is only to provide context.*** On the other hand, given that multiple review articles by highly regarded organizations recommend rhGH treatment for TS children with short stature as the **standard of care**, it would **not** be inappropriate to use this FH literature to directly support the current application.

The most consequential of the 3 concurrently controlled FH studies not supported by the sponsor of this submission was the large (n=104), randomized Canadian study which demonstrated a robust, highly significant treatment difference in response to 0.3 mg/kg per week of rhGH, i.e. the mean difference between the rhGH-treated group and the untreated control group by ANCOVA was 7.2 cm (p<0.001). The other 2 concurrently controlled studies were not randomized, and the treatment differences were less substantial (4.4-5.3 and 5.4 cm).

As a group, the 9 uncontrolled studies not supported by the sponsor further indicate a beneficial effect of rhGH treatment on FH in TS patients with short stature (mean FHs ranged from 147 to 152.3 cm when the dosage of rhGH ranged from 0.27 to 0.43 mg/kg per week, and treatment arms including oxandrolone were excluded). Furthermore, when the dosage of rhGH ranged from 0.45 to 0.70 mg/kg per week, mean FHs were clearly larger ranging from 154.3 to 163.6 cm (~64"). To put all of these FH results in context, it is important to restate that 1) the historical FH observed in untreated girls with TS reported by Lyon et al in 1985 (13 and see Section 2.6.2.1) was 143.2 cm; and 2) some investigators believe that the so-called Lyon curve may not be currently applicable, i.e. Sybert et al recently reported an untreated FH of 148 cm in untreated TS girls in Washington state.

It appears that the first year growth of TS patients after treatment with rhGH is a powerful predictor of height gain (i.e., FH compared with mProjAH at baseline) in TS children who continue to receive rhGH until FH is attained. It has also been reported that decreased CA, BA and height SDS (Turner standard) correlate negatively with height gain,

while rhGH dose, duration of treatment with rhGH and overall prepubertal height gain correlate positively with height gain.

The fact that there is current literature indicating that treatment of non-TS non-growth hormone deficient short children with rhGH (i.e., chronic renal insufficiency [CRI], small for gestational age [SGA], idiopathic short stature [ISS]) significantly improves FH indirectly also supports the use of rhGH for the long-term treatment of short stature associated with TS.

1.3.3 Safety Results/Conclusions

- The safety analyses of Studies 055 and 092 were satisfactory. Respiratory infections were the most common AEs. There was an ~12% incidence of otitis media in Study 092. **In that rhGH may induce lymphatic/adenoidal hypertrophy, and TS patients are inherently predisposed to recurrent otitis media, it is possible that Genotropin contributed to the incidence of otitis media in this study. It is not at all surprising that joint pain/arthralgia was the most frequent treatment-related AE reported in Study 055 (an expected consequence of rhGH-induced fluid retention).**

- During Studies 055 and 092, glucose tolerance remained essentially normal and no patient developed diabetes mellitus. However, as has been observed in previous studies, treatment with Genotropin did result in progressive elevation of median insulin levels, which remained within the normal range. **In that 1) treatment with rhGH can result in overt diabetes mellitus/impaired glucose tolerance in some patients; and 2) TS patients are inherently prone to develop type 2 diabetes mellitus, TS patients should be monitored extremely carefully for evidence of overt diabetes mellitus and any other form of glucose intolerance after treatment with rhGH is initiated.**

- The analyses of TS vs. non-TS AEs in the sponsor's Early Alert Safety Databases (ARGUS and NovAlert) (including SAEs from KIGS) reveals:

  BIH, epiphysiolysis/SCFE, diabetes mellitus, systemic hypertension and otitis media were all reported ≥3 times as often in TS patients (vs. non-TS patients). Given the inherent predisposition of TS children definitely for 3, and probably for 2, of these AEs, and the fact that rhGH is labeled for 3 of these AEs and potentially could cause the other 2, these observations are not at all surprising. However, it is important to note that the denominators used to calculate the reporting rates in the TS cohorts were relatively small, so that a relatively small number of AEs in the numerator was able to generate a reporting rate percentage ≥3 times that observed in TS cases, i.e. much more data will need to be accrued to validate the observations described above.

- **Genotropin is generally well tolerated in patients with TS.**

1.3.4 Dosing Regimen and Administration

As noted in Section 1.3.2.2 above, **the more robust HV, HV SDS and height SDS responses observed in Study 055 compared with Study 092** more than likely reflects the fact that the TS children in Study 092 were treated with a **lower and less optimal dose of Genotropin (0.33 mg/kg per week in Study 055 vs. 0.13 to 0.23 mg/kg per week in Study 092)**. This is further evidenced by the fact that 2 patients in Study 055 **(9%) compared with 3 patients in Study 092 (19%)** did not grow in response to Genotropin when their heights were expressed as SDS derived from the growth patterns of healthy non-TS children (i.e., the change in height SDS was <0), and 1 patient in Study 055 **(5%) compared with 5 patients in Study 092 (31%)** grew less than 1 cm after 1 year of Genotropin treatment. Of note, the dosage previously approved for the treatment of short stature associated with TS was **up to 0.375 mg/kg per week**, and the dose recommended by the AACE recently is **0.35 mg/kg per week**.

Therefore, this Medical Officer strongly agrees with the sponsor's proposed dosing regimen of 0.33 mg/kg per day.

It is important to note that there is Scandanavian literature which suggests that treatment of TS children with rhGH at dosages greater than 0.35 mg/kg per week (i.e., **as much as 0.45-0.7 mg/kg per week**) results in a greater increase in FH, and no apparent increase in adverse events. Therefore, the AACE guideline also recommends that providers should consider individualized dosing of rhGH in girls with TS in accordance with each patient's response.

To amplify further, the AACE recommends therapy with rhGH alone in TS girls younger than 9 to 12 years of age (and treatment of TS girls as young as 2 years of age - although at present only limited experience is available with rhGH treatment for children of this age), and continuation of rhGH treatment until FH or epiphyseal closure has been documented.

1.3.5 Drug-Drug Interactions

Nothing new to report derived from this submission.

1.3.6 Special Populations

Not applicable to this supplement.

2 INTRODUCTION AND BACKGROUND

2.1 PROCDUCT INFORMATION, CURRENTLY APPROVED INDICATIONS AND PROPOSED INDICATION

Genotropin (somatropin [rDNA origin] for injection) is a lyophilized formulation of rhGH.

It is currently indicated for the long-term treatment of pediatric patients who have growth failure due to an inadequate secretion of endogenous GH, the long-term treatment of pediatric patients who have growth failure due to Prader-Willi syndrome (PWS), the long-term treatment of growth failure in children born SGA who fail to manifest catch-up growth by age 2, and long-term replacement therapy in adults with growth hormone deficiency (GHD) of either childhood- or adult-onset etiology (1).

The sponsor has submitted this supplement in support of the following proposed indication:

Genotropin is indicated for long-term treatment of growth failure associated with Turner Syndrome in patients who have open epiphyses.

2.2 Currently Available Treatment for Approved Indications and Proposed Indication

- The rhGH formulations of 4 other sponsors are approved for the treatment of adult GHD.
- The rhGH formulations of 5 other sponsors are approved for the treatment of pediatric GHD.
- The rhGH formulation of no other sponsor is approved for the treatment of short stature associated with PWS or growth failure in children born SGA who fail to manifest catch-up growth by age 2.

- **The rhGH formulations of 2 other sponsors are approved for the treatment of short stature associated with TS.**

2.3 Availability of Proposed Active Ingredient in the United States

The rhGH formulations of 5 other sponsors are available in the United States.

2.4 Important Issues with Pharmacologically Related Products

Not applicable to this supplement.

2.5 Presubmission Regulatory Activity Regarding Current Submission

At a pre-sNDA teleconference held with the sponsor on 16Feb05, it was agreed that the TS submission would be based upon the results of 2 open label Genotropin studies in TS patients - a multicenter clinical trial conducted in Belgium, Protocol TRN 87-055 (Study 055) (2), and a multicenter clinical trial in France, Protocol TRN 86-092 (Study 092) (3). Additionally, it was agreed that the sponsor would review the literature with regard to the short-term and long-term treatment of patients with TS with rhGH.

2.6 Turner Syndrome - Product Development Rationale; Epidemiology & Clinical Manifestations; Current Treatment Guidelines Including the Use of Recombinant Human GH

2.6.1 Product Development Rationale for TS

Pituitary-derived GH in TS was first administered to patients with TS over 40 years ago (4), and in Europe, Genotropin has been approved to treat TS since 1987. In 1997, Humatrope and Nutropin were approved in the USA for the treatment of short stature associated with TS (with an orphan designation). Since that time, a large amount of literature has been published demonstrating the short-term and long-term benefits of rhGH therapy in TS patients (see Section 2.6.3.1 ahead). When the period of orphan exclusivity ended in 2004, the sponsor requested the pre-sNDA meeting described in Section 2.5 above.

2.6.2 Epidemiology and Clinical Manifestations of TS (see Review References 5–8)

TS occurs in approximately 1 in every 1,900 live female births (9) and is caused by a loss or abnormality of the second X chromosome in at least 1 major cell line in the body. The 2 principal features of TS are short stature and ovarian dysgenesis. Absent treatment with rhGH, girls with TS attain a final height (FH) approximately 21 cm shorter than the normal female population (10). Ovarian failure occurs in the vast majority of girls, mandating lifelong estrogen therapy beginning in adolescence. Other TS stigmata include may include neck webbing, cubitus valgus, hyperconvex nails, ptosis, facial nevi, and peripheral lymphedema. In addition, left-sided congenital cardiac anomalies (i.e., coarctation of the aorta, bicuspid aortic valve, higher risk for aortic root dilatation/aortic dissection), renal anomalies (i.e., horseshoe kidney and duplication of the collecting system), middle ear anomalies, type 2 diabetes mellitus, scoliosis, slipped capital femoral epiphysis, thyroid dysfunction and autoimmune disorders are more common in TS than in unaffected girls. Although the distribution of intelligence in TS is similar to the general population, girls with TS may have specific cognitive difficulties (i.e., mathematics, spatial tasks). As a result of these cognitive difficulties, as well as other behavioral issues and their short stature per se, girls with TS often times have significant socialization issues.

2.6.2.1 Growth of Untreated Children with TS

In a study (11, 12; Ranke et al) of 150 untreated TS patients at 3 sites in Germany, the mean height at age 5 years was 95.7 cm ± 4.6 (~38 inches), at age 14 years was 134.0 cm ± 4.6 (~53 inches=4'5") and **at 16 years was 141.1 cm** ± 5.4 (~56 inches=4'8"), i.e. the pubertal growth spurt (~3 inches) was minimal. Compared with age-matched non-TS girls, an increase in height deficit was apparent until age 14 years when the deficit slowed, i.e. it is well known that the HV of the average non-TS girl decreases after menarche due to the enhancement of epiphyseal closure by estrogen. In another study reflecting the results of 4 European studies (13; Lyon et al), the historical FH observed in untreated girls with TS was similar (i.e., **143.2 cm**). Finally, in a study conducted in Italy, the mean FH of untreated girls with TS was **142.5 ± 7.0** (14). It should be noted that some investigators question the current validity and applicability of these earlier estimations of the FH of untreated girls with TS by Lyon (13) and Ranke (11, 12). The mean adult height of 149 of the untreated TS patients followed by Sybert and McCauley in Washington state is **148 cm** (5), and the mean adult height of 69 untreated TS patients in a recent European study published by Massa et al was **147 cm** (15).

In younger children, the reduction in height and weight was of the same relative magnitude; however, with increasing age, weight increased more relative to height. This relative weight increase was primarily due to truncal obesity (11).

In younger children, bone age (BA) was decreased compared to chronological age (CA), but BA progressed at the same rate observed in non-TS children until ~age 12 years. Thereafter, BA progression fell below 1 year per each chronological year; closure of the epiphyses may not occur until ~age 19 years. Thus, there is retardation in BA compared to CA in TS children at all ages, especially after ~age 12 years (11).

2.6.2.1.1 Predicting Final Adult Height/FH in Untreated Children with TS

Prediction methods for estimating final adult height have been utilized for approximately 60 years, and are generally considered accurate for most purposes (16, 17). The most common procedure utilized to predict adult height in children with short statue (including girls with TS) are the B-P PredAH method (wherein the percentage of FH reflected by the patient's current achieved height at an observed Greulich & Pyle BA (18) is read from a table constructed on the basis of the growth data of healthy children, and then used to calculate the B-P PredAH (19). An alternate commonly used adult height prediction method is referred to as the projected adult height (ProjAH). The ProjAH method assumes that the FH SDS will be equivalent to the height SDS at the current actual CA of the subject, i.e. the patient's height SDS at the time of the initial evaluation is extrapolated. The ProjAH method was modified by Lyon et al by applying linear regression to the results of 4 European studies, resulting in the so-called mProjAH method (13).

Zachmann et al reported that in children with TS, the B-P PredAH method was as accurate as in healthy, unaffected children (20). On the other hand, van Teunenbroek et al **concluded that the ProjAH method was superior to methods incorporating BA assessment, such as the B-P PredAH method** (21). Depending on the age and cohort studied, the B-P PredAH method

yielded a mean error ranging from 8.0 to 12.1 cm. In contrast, the ProjAH method yielded a mean error of 0.4-2.7 cm, and the mProjAH method 0.1-2.0 cm (21).

The potential greater utility of the mProjAH and unmodified ProjAH methods as compared with the B-P PredAH method in predicting final adult height in TS children is not surprising. BA determinations are commonly felt to be misleading in pathological states such as TS, since BA references are obtained in healthy subjects who presumably manifest normal physiological bone maturation. In TS, the maturation of the wrist and hand bones is frequently discordant which may distort BA measurements. Additionally, in girls with TS, HV decreases with advancing age, and the adolescent growth spurt is minimal, which may also result in less accurate BA-based height prediction methods (e.g., the B-P PredAH method).

Using the mProjAH and ProjAH methods, Lyon (13) retrospectively compared the predicted adult heights (performed at age 3-12 years) with the actual final adult heights (obtained at ages 19-24 years) in untreated girls with TS, and found a correlation coefficient of 0.95 ($p<0.01$). However, the mean error of the unmodified ProjAH was 3.3 cm and that of the mProjAH was 0.6 cm, suggesting a greater utility for the mProjAH method. The mProjAH method appeared to be least useful when the BA was significantly delayed (13).

Confirming the accuracy of the mProjAH, Rosenfeld et al found that the mean error in an untreated control group of 25 American girls with TS was 0.0 cm (22). Lin et al studied a cohort of girls with TS who were naive to rhGH, but treated with low dose estrogen and oxandrolone; in this study, the mProjAH differed from actual final adult height by only 0.37 cm (23). Finally, Dacou-Voutetakis et al evaluated 27 untreated TS girls and found that mProjAH correlated well with FH, with a mean error of only 0.7 cm (24), and Pasquino et al reported that the mProjAH in 18 untreated Italian girls with TS correlated well with actual adult height, with a mean error of only 0.26 SD (25).

In conclusion, it would appear that all of the methods used to predict final adult height in untreated girls with TS have utility, but that the ProjAH and mProjAH methods appear to be more accurate than the BA-based B-P PredAH method, and that the mProjAH method appears to be somewhat more accurate than the unmodified ProjAH method.

In that both the B-P PredAH and mProjAH methods were used to predict final adult height at baseline and following rhGH treatment in Study 092 (France), and in that this Medical Officer will be reviewing the results of published FH studies in TS patients (wherein final adult heights after treatment with rhGH were compared with predicted adult heights at baseline) in the Efficacy Summary/Discussion section ahead (see Section 6.1.5.1), the preceding section provides appropriate and necessary background information.

2.6.3 Current Treatment Guidelines

2.6.3.1 rhGH

Numerous studies conducted during the past 15 years have demonstrated that treatment with rhGH accelerates short-term growth in girls with TS. More recently, published studies have shown that treatment of TS children with rhGH results in an increase in FH (compared with concurrent untreated controls, historical untreated controls and/or predicted adult height at baseline), and normalization of FH (i.e., FH >5 feet) in many patients. **The most important of these studies will be tabulated, discussed and referenced in the Efficacy Summary/Discussion section ahead** (see Section 6.1.5.1).

Therefore, the **standard of care guideline** for the clinical use of rhGH published by the AACE in 2003 recommends initiation of rhGH as soon as the height of a TS girl is below the 5th percentile of the normal growth curve (26). The recommendations published by Saenger et al in 2001 following an international multidisciplinary workshop on the management of patients with TS held in March 2000 are essentially identical (27). Furthermore, the LWPES Drug and Therapeutics Committee cites rhGH as an important pharmacological agent to increase linear growth in children with TS (28). Sybert and McCauley (5) reviewed the University of Washington experience with 532 children and adults with TS; they recommend that rhGH should be considered for every girl with TS (but that parents and children should be told of the limitations of current knowledge about treatment [i.e., their uncertainty regarding the current applicability of the 1985 Lyon growth curve in untreated TS patients] and be given realistic expectations with respect to the resulting gain in height, so that they can make informed decisions).

The AACE recommends therapy with rhGH alone in TS girls younger than 9 to 12 years of age, and treatment of TS girls as young as 2 years of age (although at present only limited experience is available with rhGH treatment for children of this age) (26). The AACE guideline **recommends a starting dose of 0.05 mg/kg per day** (0.35 mg/kg per week; ~equal to the dose recommended in the Package Inserts of the rhGH formulations previously approved for the treatment of short stature associated with TS [up to 0.375 mg/kg per week]), and continuation of rhGH treatment until FH or epiphyseal closure has been documented. It is important to note that there is Scandanavian literature which suggests that treatment of TS children with rhGH at dosages greater than 0.35 mg/kg per week (i.e., as much as 0.45-0.7 mg/kg per week) results in a greater increase in FH, and no apparent increase in adverse events (29–31). Therefore, the AACE guideline also recommends that providers should consider individualized dosing of rhGH in girls with TS in accordance with each patient's response.

2.6.3.2 Oxandrolone as Adjunctive Therapy to rhGH

A number of publications during the last 15 years indicate that the addition of oxandrolone to rhGH results in improved short-term height increases (32; **also see Tables 9 and 10**) and FH outcomes (22, 33, 34) (compared to treatment with rhGH alone). Oxandrolone seems to be particularly suited for the promotion of growth because, uniquely among the anabolic steroids, it

is not aromatized into substances with estrogenic properties (26). The AACE guideline therefore recommends that providers consider the addition of a nonaromatizable anabolic steroid, such as oxandrolone, to rhGH therapy in TS girls older than 9 to 12 years of age, or in girls older than 8 years of age in whom therapy was instituted when the patient already was far below the 5th percentile of the normal growth curve (26). TS girls treated with anabolic steroids (including oxandrolone) should be monitored for signs of virilization and overly rapid skeletal maturation. Anabolic steroids should not be used alone for the promotion of growth. **Also see Section 6.1.2 ahead**.

2.6.3.3 Estrogen Therapy in Girls with TS

Current data indicate that estrogen (administered alone or in conjunction with rhGH) has **no role as a growth promoting agent** in TS girls at any age (26, 35) (i.e., no enhancement of growth/ possible detrimental effect). On the other hand, estrogen therapy (including ethinyl estradiol) is **appropriately used to promote feminization**/puberty in TS girls. However, when used to induce puberty, estrogen therapy may cause fusion of the epiphyses, thereby limiting longitudinal bone growth. In this regard, Chernausek et al reported that rhGH-treated TS patients in whom estrogen replacement was delayed until age 15 gained ~8.4 cm over their projected height at baseline (Lyon; mProjAH method), whereas those starting estrogen at age 12 years gained ~5.1 cm (36). Multivariate analysis revealed that the number of years of rhGH therapy before estrogen treatment was a strong factor in predicting height gained, **indicating that the timing of estrogen replacement therapy may be an important determinant of FH in rhGH-treated girls with TS** (36). In contrast, other investigators have reported that the use of a very low initial dose of ethinyl estradiol (i.e., 2.5 μg) at ~age 13 yrs to induce puberty does not adversely impact the final adult height achieved with rhGH treatment (37, 38). **Also see Section 6.1.2 ahead**.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

This Medical Officer collaborated extensively and frequently with the Division's Statistical Reviewer/Statistical Team Leader in the preparation of the clinical review. The most important findings of the Division's Statistical Reviewer have been incorporated into this Medical Officer's review.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 SOURCES OF CLINICAL DATA AND REVIEW STATEGY

The electronically submitted Clinical Overview and individual Clinical Study Reports for Studies 055 and 092 submitted by the sponsor on 27Jun05, as well as the additional information submitted electronically (and by email) by the sponsor at the request of this Medical Officer on 2Aug05, 25Jan06, 26Jan06, 6Feb06, **21Feb06** (written response to questions posed during

formal teleconference held on 8Feb06), 17Mar06 and 24Mar06 were thoroughly and comprehensively reviewed by this Medical Officer.

4.2 Tables of Clinical Studies

Only Studies 055 and 092 were contained in the Sponsor's submission.

4.4 Data Quality and Integrity

Monitoring visits by the sponsor were adequate. Case report forms (CRFs) were compared with source documents and checked for completeness and accuracy. Ongoing audits of the database were conducted to ensure that the data entered were a true representation of the original CRF entries. In addition, the Division's Statistical Reviewer expressed confidence in the raw SAS data provided by the sponsor.

4.5 Compliance with Good Clinical Practices

The sponsor appeared to adhere to appropriate clinical practices in conducting Studies 055 and 092.

4.6 Financial Disclosures

Complete financial disclosure information was submitted by the sponsor and reviewed by this Medical Officer. None of the 25 investigators who participated in Studies 055 or 092 had any financial information to disclose. More specifically, none of these investigators 1) had compensation potentially affected by the outcome of the studies; 2) received significant payments of other sorts by the sponsor of the studies; 3) had proprietary interest in the tested products; or 4) had significant equity interest in the sponsor of the tested product.

6 INTEGRATED REVIEW OF EFFICACY

6.1 INDICATION

Long-term treatment of growth failure associated with Turner Syndrome in patients who have open epiphyses.

6.1.1 Methods

See Section 4.1 above.

6.1.2 General Discussion of Endpoints and Treatment Arms

The focus of this Medical Officer's review was on the change in HV, HV SDS, and height SDS

in young girls with TS after 1 year of treatment with Genotropin alone in 2 Phase III, open label, multicenter studies. In Study 055 (Belgium), children were randomized to a second treatment arm (Genotropin and ethinyl estradiol); however, as stated earlier, in that estrogen has no role as a growth promoting agent in TS girls of prepubertal or pubertal age (35, 36) (b) (4) (b) (4) (b) (4) In Study 092 (France), children were randomized to a second treatment arm (Genotropin and oxandrolone). As stated earlier, it is recommended by the AACE that concomitant treatment with rhGH and oxandrolone should be considered in girls older than 8 years of age in whom no therapy was instituted until the patient was already far below the 5th percentile of the normal growth curve (26). However, (b) (4) (b) (4)

6.1.3 Study Designs (see Table 1 for a side by side comparison of both study designs)

6.1.3.1 Study Design for TRN 87-055 (Study 055) (Belgium; June 1987 – February 1989)

6.1.3.1.1 General Description (including dosing)

Study 055 was a randomized, open label, multicenter study conducted in young girls with TS at 6 sites in Belgium to demonstrate the effect of Genotropin and the combination of Genotropin and ethinyl estradiol on linear growth and bone maturation. Each site enrolled 2-14 patients. Patients were randomized to 12 months of treatment with Genotropin alone or the combination of Genotropin and ethinyl estradiol. In order to achieve gross balance on CA, a stratified randomization with 2 strata (<11 years of age and ≥11 years of age) was used. Daily subcutaneous injections of Genotropin (~0.05 mg/kg per day) were administered to patients in both treatment arms (i.e., 0.33 mg/kg per week divided into 7 equal injections). To prevent lipoatrophy, the injection site was varied. Ethinyl estradiol was administered orally to the adjunctive therapy group at a daily dose of 25 ng/kg.

6.1.3.1.2 Major Inclusion/Exclusion Criteria

- Prepubertal girls >5 years of age (pubertal stage was estimated from breast development (Tanner score 1 - 5) and pubic hair (Tanner score 1 - 5)
- TS proven by karyotype
- BA <12 years
- Height SDS <-1 (39; Tanner standard for healthy children)
- HV <25th percentile (corresponding to HV SDS <-0.7) for CA (39; Tanner standard for healthy children). HV at baseline was derived from the difference in pre-treatment height (obtained at least 6 months before the start of treatment) and the height at the start of treatment.
- Normal GH response (>10 ng/mL) after standard pharmacological or physiological stimulation test

- Patients receiving thyroid hormone replacement therapy must have been on stable treatment for at least 3 months
- Patients with previous or ongoing treatment with any GH formulation, anabolic steroids or estrogen excluded
- Patients with serious chronic diseases (e.g., diabetes mellitus or other endocrinopathy, renal disease or major cardiovascular abnormalities) excluded

6.1.3.1.3 Efficacy Endpoints

The primary efficacy parameters reflecting linear growth were:

- Height SDS and change in height SDS (39; Tanner standard based on the growth patterns of non-TS girls)
- Height SDS and change in height SDS (11; Ranke standard based on the growth patterns of untreated TS girls)
- HV and change in HV (cm/yr)
- HV SDS and chance in HV SDS (39; Tanner standard based on the growth patterns of non-TS girls)
- HV SDS and change in HV SDS (11; Ranke standard based on the growth patterns of untreated TS girls)

Standing height was measured with a Harpenden stadiometer or comparable wall-mounted device, and the mean of 3 measurements was recorded at baseline, 6 and 12 months.

Secondary efficacy parameters included weight and BA. BA was determined using the Tanner-Whitehouse method (39); wrist radiographs were read by the same examiner without knowledge of the age of the patients.

6.1.3.1.4 Safety Evaluations

Blood samples were drawn at baseline, 6 months and 12 months for the safety parameters listed in Table 1. All adverse events and concomitant drug therapy were recorded at each clinic visit.

6.1.3.1.5 Statistical Methods

The sponsor used paired t-tests for within-group analyses to determine if patients grew faster after treatment than before, and two-sample t-tests for between-group comparisons. **Since the focus of this Medical Officer's review was on the Genotropin only treatment arm and not the Genotropin/ethinyl estradiol treatment arm (see Section 6.1.2 above), the Division's Statistical Reviewer was requested to focus her review on the results observed after treatment with Genotropin alone**. Accordingly, the Division's Statistical Reviewer performed paired t-tests (a parametric method) and Wilcoxon's signed rank tests (a non-parametric method) to determine if height SDS (Tanner and Ranke standards), HV, and HV SDS (Tanner and Ranke standards) were significantly improved from baseline after 12 months of treatment with

Genotropin alone (within group). Patients were excluded from the Tanner SDS analyses if they were too old for the Tanner standard to be applied accurately (i.e., non-TS healthy patients undergo spontaneous puberty whereas the vast majority of TS girls do not). In addition, there was no imputation of missing values.

Safety results were presented utilizing descriptive statistics.

6.1.3.2 Study Design for TRN 86-092 (Study 092) (France; October 1986 – January 1992)

6.1.3.2.1 General Description (including dosing)

Study 092 was a randomized, open label, multicenter study conducted in young girls with TS at 7 sites in France to demonstrate the effect of Genotropin and the combination of Genotropin and oxandrolone on linear growth and bone maturation. Each site enrolled 3-8 patients. Patients were randomized to 18 months of treatment with Genotropin alone or the combination of Genotropin and oxandrolone. If the investigator considered the patient to have benefited from the study, the patient could continue to receive treatment for as long as 60 months. Subcutaneous injections of Genotropin (~0.02-0.04 mg/kg) were administered to patients in both treatment arms 6 days a week (i.e., 0.13-0.23 mg/kg per week). To prevent lipoatrophy, the injection site was varied. Oxandrolone was administered orally at a daily dose of 1.25 mg (<25 kg) or 2.5 mg (>25 kg) for 2 months out of 3, or in some cases, 2 weeks out of 3, to the adjunctive therapy group. If, after 1 year of treatment, BA was ≥12 years, 5 μg/day of ethinyl estradiol (21 days of each month) was added to promote pubertal development.

6.1.3.2.2 Major Inclusion/Exclusion Criteria

- Prepubertal (B1P1) girls ≥4 years of age (pubertal stage was estimated from breast development (Tanner score 1 - 5) and pubic hair (Tanner score 1 - 5)
- TS proven by karyotype (45X, 45X/46XX mosaic, various partial X deletions)
- BA ≤11 years
- Height SDS <-2 (39; Sempe standard for healthy children)
- HV SDS <-1 for CA (40; Sempe standard for healthy children). HV at baseline was derived from the difference in pre-treatment height (obtained not <9 months but not >15 months before the start of treatment) and the height at the start of treatment.
- Normal GH response (>7.5 ng/mL=15μIU/mL) after standard pharmacological stimulation test
- Total or Free T4 normal
- Basal FSH or LHRH-stimulated FSH in prepubertal range
- Patients with previous or ongoing treatment with estrogen or glucocorticoids (>10 days/year) excluded. Previous anabolic treatment must have been stopped for at least 6 months.
- Patients with serious chronic diseases (e.g., diabetes mellitus, asthma, celiac disease, heart disease, impaired renal function, constitutional bone disease, major cardiovascular abnormalities) excluded

6.1.3.2.3 Efficacy Endpoints

The primary efficacy parameters reflecting linear growth were:

- Height SDS and change in height SDS (40; Sempe standard based on the growth patterns of non-TS girls in France)
- Height SDS and change in height SDS (11; Ranke standard based on the growth patterns of untreated TS girls)
- HV and change in HV (cm/yr)
- HV SDS and chance in HV SDS (39; Sempe standard based on the growth patterns of non-TS girls in France)
- HV SDS and change in HV SDS (11; Ranke standard based on the growth patterns of untreated TS girls)
- B-P PredAH and change in B-P PredAH to predict adult height (19)
- mProjAH and change in mProjAH to predict adult height (13)

Standing height was measured with a Harpenden stadiometer or comparable wall-mounted device, and the mean of 3 measurements was recorded at **baseline**, 1 month, 3 months, 6 months, 9 months, **12 months**, 15 months and 18 months.

Secondary efficacy parameters included weight and BA. BA was determined every 6 months using the Tanner-Whitehouse method (39); wrist radiographs were read by the same examiner without knowledge of the age of the patients. Psychological effects were assessed based on school attendance and evaluations by psychologists.

6.1.3.2.4 Safety Evaluations

Blood samples were drawn at baseline, 6 months, 12 months and 18 months for the safety parameters listed in Table 1. All adverse events and concomitant drug therapy were recorded at each clinic visit. If fasting blood glucose levels ≥120.6 mg/dL (6.7 mmol/L) or HbA1c levels ≥7% were obtained, patients were to have an oral glucose tolerance test performed (glucose and insulin levels).

6.1.3.2.5 Statistical Methods

The sponsor used paired t-tests for within-group analyses to determine if patients grew faster after treatment than before, and two-sample t-tests for between-group comparisons. **Since the focus of this Medical Officer's review was on the Genotropin <u>only</u> treatment arm and <u>not</u> the Genotropin/oxandrolone treatment arm (see Section 6.1.2 above), the Division's Statistical Reviewer was requested to focus her review on the results observed after treatment with Genotropin <u>alone</u>.** Accordingly, the Division's Statistical Reviewer performed paired t-tests (a parametric method) and Wilcoxon's signed rank tests (a non-parametric method) to determine if height SDS (Sempe and Ranke standards), HV, and HV SDS (Sempe and Ranke standards) were significantly improved from baseline **after 12 months of treatment*** with

Genotropin alone (within group). Patients were excluded from the Sempe SDS analyses if they were too old for the Sempe standard to be applied accurately (i.e., non-TS healthy patients undergo spontaneous puberty whereas the vast majority of TS girls do not). In addition, there was no imputation of missing values.

***In order to better compare the results of Studies 092 and 055, and the results of both studies with the 4 concurrently controlled 12 month duration studies in the literature (see Section 6.1.5.1 ahead), and because the number of evaluable patients treated for 2 (71% of those enrolled), 3 (53% of those enrolled) and 4 (41% of those enrolled) years during Study 092 was substantially less than the number treated for 1 year (94% of those enrolled), the Division's Statistical Reviewer was requested to focus exclusively on the 12 month results from Study 092. Therefore, the 2, 3 and 4 year results from Study 092 will not be presented in this review.** Note: Many patients became **"non-evaluable"** after the first 12 months of treatment because they switched from 1 treatment group to the other.

Safety results were presented utilizing descriptive statistics.

6.1.3.3 Comparison of Study Designs for Studies 055 and 092

See Table 1 (copied from the sponsor's submission) for a tabular comparison of study medication, duration of treatment, inclusion criteria, and efficacy/safety endpoints for Studies 055 and 092. As discussed in Sections 6.1.3.1 and 6.1.3.2 above, and as can be seen in Table 1, the overall study designs were similar.

Table 1
Comparison of Study Designs for Studies 055 and 092

	Study 055	Study 092
Study Medication	Genotropin 0.33 mg/kg/week, divided in 7 SC injections given once daily	Genotropin 0.13 – 0.23 mg/kg per week, divided in 6 SC injections given once daily (once a week, no injection was administered)
	Genotropin (as above) plus ethinylestradiol tablets 25 ng/kg/day, orally	Genotropin (as above) plus oxandrolone tablets 1.25 mg/day (<25kg) or 2.5 mg/day (>25kg), orally
Duration of Treatment	12 months	18 months extended up to 60 months
Inclusion Criteria	Turner Syndrome Pre-pubertal CA >5 years BA <12 years Height SDS less than -1 chronological age (CA) Height velocity SDS less than -0.7 (Tanner standard) Normal GH response (>10 ng/mL) Euthyroid	Turner Syndrome Pre-pubertal CA ≥4 years BA age ≤11 years Height SDS below -2 SD Height velocity below -1 SD established over the 12 months before the start of the treatment No anabolic treatment for at least 6 months Normal GH secretion (>7.5 ng/mL) Normal T4 or free T4
Efficacy Endpoint	Height (cm) Height SDS* Height velocity (cm/yr) Height velocity SDS* Weight (kg) Bone age (year)	Height (cm) Height SDS† Height velocity (cm/yr) Height velocity SDS† Weight (kg) Bone age (year) Prognosis of FH Psychological effects
Safety Endpoint	Glucose Insulin HbAlc T4 Anti-hGH antibodies Adverse Events	Hematology Liver Function Tests Alk-Phos Calcium Glucose Urea Insulin HbA1c IGF-1 Antibodies Lipids Adverse Events

* Tanner standard and Ranke standard
† Sempe standard and Ranke standard

6.1.4 Efficacy Findings

6.1.4.1 Enrollment and Disposition

6.1.4.1.1 Study 055

A total of 42 subjects were randomized into the study: 22 treated with Genotropin alone and 20 treated with Genotropin + ethinyl estradiol. All 22 patients treated with Genotropin alone **completed the study** and were included in the 6 and 12 month ITT analyses performed by the Division's Statistical Reviewer.

6.1.4.1.2 Study 092

A total of 34 subjects were randomized into the study: 17 treated with Genotropin alone and 17 treated with Genotropin + oxandrolone. No patients withdrew from the study prior to Month 12 (or Month 18). In that Subject No. 2 in the Genotropin alone arm changed her treatment at Month 9 to Genotropin + oxandrolone, only 16 subjects were included in the 12 month ITT analyses performed by the Division's Statistical Reviewer. Two other subjects in the Genotropin alone arm changed to the other treatment group between Month 12 and Month 18, but that obviously did not impact the 12 month ITT analyses.

6.1.4.2 Demographics and Baseline Characteristics

6.1.4.2.1 Study 055

As seen in Tables 2 (provided by the Division's Statistical Reviewer) and 4 (copied from the sponsor), the 2 treatment groups in Study 055 were very comparable with respect to demographics and baseline characteristics (including CA, BA, height, height SDS (Tanner or Ranke standard), HV and HV SDS (Tanner or Ranke standard). The children randomized **to the treatment arm of interest (Genotropin alone)** were growing very slowly (mean pre-treatment HV 4.1 cm/yr and mean HV SDS -2.3 [Tanner standard for healthy girls]), and were very short (mean height 119.8 cm and mean height SDS -3.08 [Tanner standard for healthy girls]). As expected, mean BA (9.7) was ~1 year behind the mean CA (10.5). 73% had a 45X karyotype.

Note: Mean and median values closely approximated each other.

Table 2 – Study 055
Demographics and Baseline Characteristics of Subjects Randomized to Genotropin Alone

	Age (yrs)	Height (cm)	Height SDS Ranke	Height SDS Tanner	Weight (kg)	Bone Age (yrs)	Height Velocity (cm/yr)	HV SDS Ranke	HV SDS Tanner
Treatment: Genotropin (Group 1)									
N	22	22	22	22	22	20	22	22	20
Mean	**10.5**	**119.8**	**-0.24**	**-3.08**	**25.6**	**9.7**	**4.1**	**-0.1**	**-2.3**
Std	3.3	14.4	0.82	1.01	7.4	1.9	1.5	1.1	2.1
Min	3.2	83.9	-1.25	-5.11	11.3	5.2	1.0	-2.9	-5.7
Median	11.5	122.3	-0.45	-3.18	26.6	9.9	3.8	-0.1	-2.5
Max	14.8	134.7	2.05	-0.37	36.8	11.8	7.7	2.8	-0.3
Treatment: Genotropin + ethinyl estradiol (Group 2)									
N	20	20	20	18	20	20	20	20	16
Mean	11.6	124.3	-0.24	-3.12	27.8	9.4	3.8	0.2	-2.3
Std	2.9	12.0	0.98	1.04	8.4	2.4	1.2	1.6	1.7
Min	6.2	99.1	-2.12	-4.94	15.0	3.8	2.1	-1.8	-4.8
Median	11.6	125.7	0.09	-3.04	27.0	9.8	3.5	-0.3	-2.2
Max	16.5	144.0	1.54	-1.86	50.5	12.7	6.4	5.2	0.7

6.1.4.2.2 Study 092

As seen in Tables 3 (provided by the Division's Statistical Reviewer) and 4 (copied from the sponsor), the 2 treatment groups in Study 092 were also very comparable with respect to the same demographic and baseline characteristics listed in Section 6.1.4.2.1 above. The children randomized **to the treatment arm of interest (Genotropin alone)** were also growing very slowly (mean pre-treatment HV 3.9 cm/yr and mean HV SDS -1.52 [Sempe standard for healthy French girls]), and were very short (mean height 118.1 cm and mean height SDS -3.2 [Sempe standard for healthy French girls]). As expected, mean BA (8.4) was ~1.5 years behind the mean CA (10.0). 65% had a 45X karyotype.

Note: Mean and median values closely approximated each other.

Table 3 – Study 092
Demographics and Baseline Characteristics of Subjects Randomized to Genotropin Alone

	Age (yrs)	Height (cm)	Height SDS Ranke	Height SDS Sempe	Weight (kg)	Bone Age (yrs)	Height Velocity (cm/yr)	HV SDS Ranke	HV SDS Sempe
Treatment: Genotropin (Group 1)									
N	17	17	17	17	17	17	17	17	17
Mean	**10.0**	**118.1**	**-0.24**	**-3.20**	**25.4**	**8.4**	**3.90**	**-0.32**	**-1.52**
Std	2.9	12.4	0.85	0.97	10.4	2.3	1.00	0.67	0.63
Min	5.5	97.5	-1.98	-4.78	12.0	4.0	1.83	-1.63	-2.77
Median	9.7	117.2	-0.09	-2.86	22.0	7.8	3.85	-0.14	-1.51
Max	14.5	139.0	0.91	-1.92	52.0	12.0	5.40	0.66	-0.56
Treatment: Genotropin + oxandrolone (Group 2)									
N	17	17	17	17	17	17	17	17	17
Mean	11.0	120.5	-0.50	-3.59	27.0	8.6	3.47	-0.54	-2.08
Std	2.5	10.4	0.68	0.84	6.8	2.1	0.86	0.78	0.56
Min	4.3	93.0	-1.82	-4.87	12.9	3.5	1.51	-2.14	-2.97
Median	12.0	123.0	-0.29	-3.70	26.0	8.8	3.57	-0.58	-2.11
Max	14.2	133.5	0.60	-2.34	36.4	11.0	4.87	0.67	-0.56

Note: In Study 092, the start of treatment with Genotropin in both treatment arms was delayed in some patients for nearly 5 months after the pre-treatment baseline height had been obtained. **Focusing on the treatment arm of greatest interest, the start of treatment was delayed for 7 subjects in the Genotropin only arm, including 2 patients whose treatment was delayed nearly 4 months**. As a result, during a teleconference held on 8Feb06, the Division questioned whether the difference between the pre-treatment and post-treatment heights might be **overestimated**, i.e. even a slowly growing untreated child with TS (~4 cm/year) might have grown somewhat during the treatment delay. **On 21Feb06, the sponsor submitted a detailed explanation as to why treatment delays less than 120 days would not meaningfully impact the results from this study**. The most compelling argument presented by the sponsor was that since HV was conservatively calculated as the difference between the height obtained after 1 year of treatment and the baseline height divided by the time between the 2 visits, the duration of the treatment delay (i.e., in 2 instances, ~4 months=120 days=0.33 years) was combined with the 1 year period of treatment in the denominator, thus **diminishing** the true therapeutic effect of the Genotropin. The sponsor also noted that for a slowly growing child with TS, an ~120 day interval between height measurements is necessary to allow actual statural growth to appreciably exceed the well known error which can occur in measurement.

6.1.4.2.3 Comparison of Demographics and Baseline Characteristics of Subjects Randomized to Both Treatment Arms for Studies 055 and 092

As discussed in Sections 6.1.4.2.1 and 6.1.4.2.2 above, and as can be seen in Table 4, demographics and baseline characteristics were very similar in Studies 055 and 092. The children randomized **to the treatment arms of interest (Genotropin alone) in the 2 studies** had comparable mean ages (10.5 vs. 10 years), mean baseline heights (119.8 vs. 118.1 cm), mean height SDS (-3.1 [Tanner] vs. -3.2 [Sempe]) and mean pre-treatment HV (4.1 vs. 3.9 cm/year). The only discernible differences of note were: 1) pre-treatment HV SDS (-2.3 [Tanner] in Study 055 vs. -1.5 [Sempe] in Study 092; and 2) a slightly more retarded BA in Study 092.

Table 4 – Studies 055 and 092
Demographics and Baseline Characteristics of Subjects Randomized to Both Treatment Arms

	Study 055		Study 092	
Parameters	Genotropin + ethinylestradiol N=20	Genotropin N=22	Genotropin N=17	Genotropin + oxandrolone N=17
Karyotype, n (%)				
45,X	13 (65%)	16 (73%)	11 (65%)	12 (71%)
Variants	7 (35%)	6 (27%)	6 (35%)	5 (29%)
Age (yrs)				
mean	11.6	10.5	10.0	11.0
Median	11.6	11.5	9.7	12.0
Range	(6.2 – 16.5)	(3.2 – 14.8)	(5.5 – 14.5)	(4.3 – 14.2)
Height (cm)				
mean	124.3	119.8	118.1	120.5
Median	125.7	122.3	117.2	123.0
Range	(99.1 – 144.0)	(83.9 – 134.7)	(97.5 – 139.0)	(93.0 – 133.5)
Height SDS Ranke,				
Mean	-0.2	-0.2	-0.2	-0.5
Median	0.1	-0.5	-0.1	-0.3
Range	(-2.1 – 1.5)	(-1.3 – 2.1)	(-2.0 – 0.9)	(-1.82 – 0.60)
Height SDS Tanner				
Mean	-3.1*	-3.1		
Median	-3.0*	-3.2	NA	NA
Range	(-4.9 - -1.9)	(-5.1 - -0.4)		
Height SDS Sempe				
Mean			-3.2	-3.6
Median	NA	NA	-2.9	-3.7
Range			(-4.8 - -1.9)	(-4.9 - -2.3)
Height Velocity HV				
Mean (cm/yr)	3.8	4.1	3.9	3.5
Median	3.5	3.8	3.9	3.6
Range	(2.1 – 6.4)	(1.0 – 7.7)	(1.8 – 5.4)	(1.5 – 4.9)
HV SDS Ranke				
Mean	0.2	-0.1	-0.3	-0.5
Median	-0.3	-0.1	-0.1	-0.6
Range	(-1.8 – 5.2)	(-2.9 – 2.8)	(-1.6 – 0.7)	(-2.1 – 0.7)
HV SDS Tanner				
Mean	-2.3†	-2.3*	NA	NA
Median	-2.2†	-2.5*		
Range	(-4.8 – 0.7)	(-5.7 – -0.3)		
HV SDS Sempe				
Mean	NA	NA	-1.5	-2.1
Median			-1.5	-2.1
Range			(-2.8 - -0.6)	(-3.0 - -0.6)
Weight (kg)				
Mean	27.8	25.6	25.4	27.0
Median	27.0	26.6	22.0	26.0
Range	(15.0 – 50.5)	(11.3 – 36.8)	(12.0 – 52.0)	(12.9 – 36.4
Bone Age (yrs)				
Mean	9.4	9.7‡	8.4	8.6
Median	9.8	9.9‡	7.8	8.8
Range	(3.8 – 12.7)	(5.2 – 11.8)	(4.0 – 12.0)	(3.5 – 11.0)
Study Drug mg/kg/wk				
Genotropin	(0.3 – 0.37)	(0.14 – 0.41)	(0.15 – 0.23)	(0.10 – 0.23)

6.1.4.3 Dosing

As noted earlier, patients in Study 055 were treated with 0.33 mg/kg per week, and patients in Study 092 were treated with 0.13-0.23 mg/kg per week. The dose utilized in Study 055 closely approximates the dose approved for Humatrope and Nutropin AQ/Nutropin for the treatment of short stature associated with TS (up to 0.375 mg/kg per week).

6.1.4.4 **Efficacy Results**

6.1.4.4.1 **Study 055** (see Table 5 from Statistical Reviewer)

Height SDS:

Height SDS (Tanner or Ranke standard) increased significantly at Month 6 and Month 12. Height SDS (Tanner) significantly increased from a mean baseline value of -3.08 by 0.24 units after 6 months of Genotropin treatment, and by **0.41 units after 12 months of Genotropin treatment**. Height SDS (Ranke) significantly increased from a mean baseline value of -0.24 by 0.44 units after 6 months of Genotropin treatment and **0.79 units after 12 months of Genotropin treatment. These data are consistent with a highly significant linear growth response to Genotropin which was apparent at Month 6, and continued to increase at Month 12.** The mean height SDS (Ranke) values at 6 months (+0.20) and 12 months (+0.55) indicate that more of these TS children were taller than their age-matched untreated peers after treatment with Genotropin.

HV and HV SDS:

After 6 months of treatment with Genotropin alone, the annualized mean HV (**8.19 cm/year**) of the TS girls was significantly increased from baseline (4.11 cm/year; **change in HV = 4.01 cm**); after 12 months of treatment with Genotropin alone, the mean HV (7.79 cm/year) remained significantly increased from baseline (**change in HV = 3.68 cm/year**). **Once again, these data are consistent with a highly significant linear growth response to Genotropin which was apparent even at Month 6.** Note: It is well known that the annualized 6 month HV overestimates the actual annual HV in children with many forms of short stature treated with rhGH, i.e. the response to rhGH between Month 6 and Month 12 is less than the response between Month 0 and Month 6.

The fact that the mean HV SDS (Tanner or Ranke standard) changed from negative values at baseline to positive values at both 6 and 12 months (all changes from baseline >4 units and HV SDS between +2.23 and +4.42) **indicates that Genotropin treatment of TS girls induced rates of growth which were greater than that of either normal children or untreated TS children of the same age.**

Distribution of Response:

In Study 055, the change in HV after treatment with Genotropin for 12 months was >0 in all patients, and >1 cm/year in 21/22 patients (95%). The change in height SDS (Tanner) after treatment with Genotropin for 12 months was >0 in 20/22 patients (91%), and >0.1 in 77% of patients. See Table 8 ahead.

In general, the results calculated by the Division's Statistical Reviewer's results verified those of the sponsor. The results of the parametric paired t-tests (means) and the non-parametric Wilcoxon's signed rank tests (medians) were very similar.

Table 5 – Study 055

Efficacy Results for Genotropin Alone Group

	Month 0 vs. Month Follow-up (6 or 12)			Diff1* Diff2*	p-value1* p-value2*
Height SDS (Tanner)	0 vs. 6	**-3.08 ± 1.01 (22)** Median = -3.18	**-2.84 ± 1.07 (22)** Median = -2.99	**0.2419** 0.1841	**0.0001** <0.0001
	0 vs. 12	**-3.08 ± 1.01 (22)** Median = -3.18	**-2.67 ± 1.09 (22)** Median = -2.87	**0.4101** 0.3474	**<0.0001** <0.0001
Height SDS (Ranke)	0 vs. 6	**-0.24 ± 0.82 (22)** Median = -0.45	**0.20 ± 0.85 (22)** Median = 0.08	**0.4385** 0.4059	**<0.0001** <0.0001
	0 vs. 12	**-0.24 ± 0.82 (22)** Median = -0.45	**0.55 ± 0.89 (22)** Median = 0.44	**0.7889** 0.7073	**<0.0001** <0.0001
Height Velocity (cm/year)	0 vs. 6	**4.11 ± 1.50 (22)** Median = 3.76	**8.19 ± 2.10 (22)** Median = 7.69	**4.0788** 4.1130	<0.0001 <0.0001
	0 vs. 12	**4.11 ± 1.50 (22)** Median = 3.76	**7.79 ± 1.55 (22)** Median = 7.37	**3.6760** 3.7804	<0.0001 <0.0001
Height Velocity SDS (Tanner)	0 vs. 6	**-2.33 ± 1.37 (20)**** Median = -2.52	**2.23 ± 2.34 (20)**** Median = 2.23	**4.5645** 4.9322	<0.0001 <0.0001
	0 vs. 12	**-2.33 ± 1.37 (20)**** Median = -2.52	**2.23 ± 2.27 (20)**** Median = 2.20	**4.5558** 4.5504	<0.0001 <0.0001
Height Velocity SDS (Ranke)	0 vs. 6	**-0.05 ± 1.15 (22)** Median = -0.07	**4.42 ± 1.58 (22)** Median = 4.28	**4.4704** 4.4045	<0.0001 <0.0001
	0 vs. 12	**-0.05 ± 1.15 (22)** Median = -0.07	**4.21 ± 1.24 (22)** Median = 4.27	**4.2662** 4.1832	<0.0001 <0.0001

*Diff1 and p-value1 are from paired t-test; diff2 and p-value2 are from Wilcoxon's signed rank test.

**According to the sponsor, 2 patients (Nos. 1 and 12) were too old to be compared using the Tanner standard and, therefore, were excluded from the analysis.

BA:

As per the sponsor (data not displayed), median BA increased from a baseline value of 9.9 to 11.2 years at Month 12. **The median increase in the BA over the treatment year was 1.1 year.**

6.1.4.4.2 **Study 092** (see Table 6 from Statistical Reviewer)

Height SDS:

Height SDS (Sempe or Ranke standard) increased significantly at Month 12. Height SDS (Sempe) significantly increased from a mean baseline value of -3.19 by **0.26 units after 12 months of Genotropin treatment.** Height SDS (Ranke) significantly increased from a mean baseline value of -0.31 by **0.46 units after 12 months of Genotropin treatment. These data are consistent with a highly significant linear growth response to Genotropin at Month 12.** The mean height SDS (Ranke) value at 12 months (+0.14) indicates that more of these TS children were taller than their age-matched untreated peers after treatment with Genotropin.

HV and HV SDS:

After 12 months of treatment with Genotropin alone, the mean HV (**6.09 cm/year**) of the TS girls was significantly increased from baseline (3.90 cm/year; **change in HV = 2.19 cm**). **Once again, these data are consistent with a significant linear growth response to Genotropin at Month 12.**

During the second year of Genotropin treatment the median HV was 5.1 cm/year (as per the sponsor; data not shown). **Note**: It is well known from observations in children with many forms of short stature treated with rhGH that the HV response progressively declines after the first year of therapy.

The fact that the mean HV SDS (Sempe or Ranke standard) changed from negative values at baseline to positive values at 12 months (both changes from baseline >2 units and HV SDS between +2.23 and +2.66) **indicates that Genotropin treatment of TS girls induced rates of growth which were greater than that of either normal children or untreated TS children of the same age.**

Distribution of Response:

In Study 092, the change in HV after treatment with Genotropin for 12 months was >0 in all patients, and >1 cm/year in 11/16 patients (69%). The change in height SDS (Sempe) after treatment with Genotropin for 12 months was >0 in 13/16 patients (81%), and >0.1 in 75% of patients. See Table 8 ahead.

B-P PredAH and mProjAH:

After 12 months of treatment with Genotropin alone, the mean B-P PredAH (147.4 cm) of the TS girls was significantly increased from baseline (144.6 cm). Similarly, the mean mProjAH also significantly increased from baseline (from 144.4 cm at baseline to 147.2 cm at Month 12). These comparable results (derived by 2 totally different methodologies – see Section 2.6.2.1.1 above) indicate that treatment with Genotropin for 1 year significantly increased the predicted final adult height of TS girls.

In general, the results calculated by the Division's Statistical Reviewer's results verified those of the sponsor. The results of the parametric paired t-tests (means) and the non-parametric Wilcoxon's signed rank tests (medians) were very similar.

Table 6 – Study 092

Efficacy Results for Genotropin Alone Group

	Month 0	Month 12	Diff1* Diff2*	p-value1* p-value2*
Height SDS (Sempe)	**-3.19 ± 1.00 (16)** Median = -2.83	**-2.94 ± 1.03 (16)** Median = -2.57	**0.2566** 0.2896	**0.0021** 0.0052
Height SDS (Ranke)	**-0.31 ± 0.82 (16)** Median = -0.14	**0.14 ± 0.84 (16)** Median = 0.33	**0.4559** 0.4898	**<0.0001** <0.0001
Height Velocity (cm/year)	**3.90 ± 1.03 (16)** Median = 3.83	**6.09 ± 0.89 (16)** Median = 6.02	**2.1933** 2.5029	**<0.0001** <0.0001
Height Velocity SDS (Sempe)	**-1.55 ± 0.64 (16)** Median = -1.60	**0.68 ± 1.31 (16)** Median = 0.57	**2.2292** 2.2883	**<0.0001** <0.0001
Height Velocity SDS (Ranke)	**-0.38 ± 0.64 (16)** Median = -0.22	**2.28 ± 1.16 (16)** Median = 2.24	**2.6650** 2.5720	**<0.0001** <0.0001
B-P Predicted Adult Height (cm)	**144.6 ± 6.75 (14)** Median = 143.6	**147.4 ± 7.59 (14)** Median = 147.2	**2.8486** 2.2890	**0.0002** 0.0002
Projected Adult Height (cm)	**144.4 ± 5.02 (16)** Median = 145.5	**147.2 ± 5.12 (16)** Median = 148.3	**2.7812** 2.9879	**<0.0001** <0.0001

* Diff1 and p-value1 are from paired t-test; diff2 and p-value2 are from Wilcoxon's signed rank test.

Longer term efficacy of Genotropin in Study 092:

As discussed in Section 6.1.3.2.5 above, the focus of this Medical Officer's review was on the Month 12 efficacy results. The sponsor reports significant median increases from baseline for height SDS (Ranke) and HV SDS (Ranke) after 2, 3 and 4 years of treatment with Genotropin alone (0.9 and 2.6, 1.2 and 2.4, and 1.4 and 1.4, respectively).

BA:

As per the sponsor (data not displayed), median BA increased from a baseline value of 7.8 to 8.7 years at Month 12. **The median increase in the BA over the first treatment year was 1.0 year**.

6.1.4.4.3 Subgroup Analyses

6.1.4.4.3.1 Gender, Race, and Age

Since the 2 studies were conducted in European female children, subgroup analyses for race and gender were not performed. In that randomization was stratified by age in Study 055, subgroups of <11 years of age and ≥11 years of age were analyzed in both studies by the Division's Statistical Reviewer at the request of this Medical Officer. With the exception of the subgroup ≥11 years of age in Study 092 (n=5; inadequate sample size), the growth parameters of the TS girls in either age group were significantly improved after 12 months of Genotropin treatment (data not shown).

6.1.5 Efficacy Summary/Discussion, Conclusions and Recommendations

6.1.5.1 Efficacy Summary/Discussion

6.1.5.1.1 Consolidated Summary/Discussion of Results from Studies 055 and 092

Since Studies 055 and 092 differed with respect to the **dosage of Genotropin administered**, the study location, and the standard utilized to calculate height SDS and HV SDS in TS children compared to healthy non-TS children (i.e., Tanner vs. Sempe), this Medical Officer and the Division's Statistical Reviewer agreed that the data from the 2 clinical trials should not be combined. **Therefore, the results from the 2 studies are presented side-by-side in Table 7 below and row-by-row in Table 8 below, <u>and the text preceding Tables 7 and 8 recapitulates the most salient findings and provides commentary when appropriate</u>** (see Section 6.1.4.4 above for a more detailed discussion of the results).

- **In Studies 055 and 092, height SDS (Tanner/Sempe or Ranke standard) increased significantly at Month 12** (see Table 7).
    - After 12 months of Genotropin treatment, in Study 055, mean height SDS (Tanner) significantly increased from a mean baseline value of -3.08 by **0.41**, and

in Study 092, mean height SDS (Sempe) also significantly increased from a mean baseline value of -3.19 by **0.26**.

- After 12 months of Genotropin treatment, in Study 055, mean height SDS (Ranke) significantly increased from a mean baseline value of -0.24 by **0.79**, and in Study 092, mean height SDS (Ranke) also significantly increased from a mean baseline value of -0.31 by **0.46**.

- In Study 055, a substantial height SDS response was also evident at Month 6, and continued to increase at Month 12 (see Table 5 above).

- The mean height SDS (Ranke) values at 6 months (+0.20) and 12 months (+0.55) in Study 055, and the mean height SDS (Ranke) value at 12 months (+0.14) in Study 092 indicate that more of these TS children were taller than their age-matched untreated TS peers after treatment with Genotropin.

- **In Studies 055 and 092, HV and HV SDS (Tanner/Sempe or Ranke standard) increased significantly at Month 12** (see Table 7).

  - After 12 months of Genotropin treatment, in Study 055, **the mean HV (7.79 cm/year) was significantly increased from baseline (change in HV = 3.68 cm/year)**, and in Study 092, **the mean HV (6.09 cm/year) was also significantly increased from baseline (change in HV = 2.19 cm). <u>However, the magnitude of these significant increases from baseline was greater in Study 055 than in Study 092, more than likely because the patients were treated with a larger and more appropriate dosage of Genotropin</u>** (see Table 7).

  - In Study 055, after 6 months of treatment with Genotropin, the annualized mean HV (8.19 cm/year) was also significantly increased from baseline **and had doubled the baseline HV** (change in HV = 4.01 cm) (see Table 5 above). Note: It is well known that the annualized 6 month HV (in this instance 8.19 cm/year) overestimates the actual annual HV (in this instance 7.79 cm/year) in children with many forms of short stature treated with rhGH, i.e. the response to rhGH between Month 6 and Month 12 is less than the response between Month 0 and Month 6.

  - In both studies, the fact that the mean HV SDS (Tanner/Sempe or Ranke standard) changed from negative values at baseline to positive values at both 6 and 12 months **indicates that Genotropin treatment of TS girls induced rates of growth which were greater than that of either normal children or untreated TS children of the same age** (see Table 7).

- In Studies 055 and 092, as expected, HV SDS and height SDS were smaller at baseline and after treatment with Genotropin using the normative standards as opposed to the TS standard. As stated above, irrespective of the standard utilized, each of these variables

significantly increased from baseline in both studies. **<u>However, the magnitude of these significant increases from baseline for each of these variables was greater in Study 055 than in Study 092, more than likely because the patients were treated with a larger and more appropriate dosage of Genotropin</u>** (see Table 7).

- Table 8 summarizes the distribution of response for HV and height SDS (Tanner or Sempe) in Studies 055 and 092. The change in HV after treatment with Genotropin for 12 months was >0 in every patient in both studies, and >1 cm/year in 21/22 patients (95%) in Study 055 and 11/16 patients (69%) in Study 092. The change in height SDS (Tanner or Sempe) after treatment with Genotropin for 12 months was >0 in 20/22 patients (91%) in Study 055 and 13/16 patients (81%) in Study 092, **i.e. 2 patients in Study 055 and 3 patients in Study 092 did not grow in response to Genotropin when their heights were expressed as SDS derived from the growth patterns of healthy non-TS children.** The change in height SDS was >0.1 in 77% of patients in Study 055 and 75% of patients in Study 092.

- After 12 months of treatment with Genotropin alone, the mean B-P PredAH (147.4 cm) of the TS girls was significantly increased from baseline (144.6 cm). Similarly, the mean mProjAH also significantly increased from baseline (from 144.4 cm at baseline to 147.2 cm at Month 12) (see Section 6.1.4.4.2 above).

- In Studies 055 and 092, the median increases in BA between baseline and Month 12 were 1.1 and 1.0 years, respectively, i.e. **there was no increase in BA compared to CA after 1 year of treatment with Genotropin in either study**.

- The focus of this Medical Officer's review was on the Month 12 efficacy results. The sponsor reports significant increases from baseline for height SDS (Ranke) and HV SDS (Ranke) after 2, 3 and 4 years of treatment with Genotropin alone (0.9 and 2.6, 1.2 and 2.4, and 1.4 and 1.4, respectively).

Table 7 – Studies 055 and 092
Growth Parameters (mean ± SD) after 12 Months of Treatment with Genotropin Alone in Pediatric Patients with Turner Syndrome

	Genotropin 0.33 mg/kg/week (Study 055^ n=22)	Genotropin 0.13-0.23 mg/kg/week (Study 092# n=16)
Height velocity (cm/yr)		
Baseline	4.11 ± 1.50	3.90 ± 1.03
Month 12	7.79 ± 1.55	6.09 ± 0.89
Change from baseline (95% CI)	3.68 (3.01, 4.34)	2.19 (1.53, 2.86)
Height Velocity SDS (Tanner^/Sempe# Standards)	(n=20)	
Baseline	-2.33 ± 1.37	-1.55 ± 0.64
Month 12	2.23 ± 2.27	0.68 ± 1.31
Change from baseline (95% CI)	4.56 (3.52, 5.59)	2.23 (1.44, 3.02)
Height Velocity SDS (Ranke Standard)		
Baseline	-0.05 ± 1.15	-0.38 ± 0.64
Month 12	4.21 ± 1.24	2.28 ± 1.16
Change from baseline (95% CI)	4.27 (3.52, 5.01)	2.67 (1.81, 3.52)
Height SDS (Tanner^/Sempe# Standards)		
Baseline	-3.08 ± 1.01	-3.19 ± 1.00
Month 12	-2.67 ± 1.09	-2.94 ± 1.03
Change from baseline (95% CI)	0.41 (0.26, 0.56)	0.26 (0.11, 0.40)
Height SDS (Ranke Standard)		
Baseline	-0.24 ± 0.82	-0.31 ± 0.82
Month 12	0.55 ± 0.89	0.14 ± 0.84
Change from baseline (95% CI)	0.79 (0.68, 0.89)	0.46 (0.37, 0.54)

Ranke standard based on age-matched, untreated TS patients
Tanner^/Sempe# standards based on age-matched healthy non-TS children
P<0.05 for all changes from baseline (paired t-test)

Table 8 – Studies 055 and 092
Response Rates for HV and height SDS Change from Baseline*

	Height Velocity (cm/yr)		Height SDS (Tanner/Study 055 or Sempe/Study 092)	
	# responders (change >0)	# responders (change >1)	# responders (change >0)	# responders (change >0.1)
Study 055 (n=22)	**22 (100%)**	**21 (95%)**	**20 (91%)**	**17 (77%)**
Study 092 (n=16)	**16 (100%)**	**11 (69%)**	**13 (81%)**	**12 (75%)**

*Change from baseline = value after 1 year of Genotropin treatment minus baseline value

In summary with respect to Section 6.1.5.1.1:

1) **The significant HV, HV SDS and height SDS change from baseline results from both studies are consistent with a highly significant linear growth response to Genotropin at Month 12 in TS children with short stature, which was apparent even at Month 6 in Study 055.**
2) **The more robust HV, HV SDS and height SDS responses observed in Study 055 compared with Study 092 more than likely reflects the fact that the TS children in Study 092 were treated with a lower and less optimal dose of Genotropin (0.33 mg/kg per week in Study 055 vs. 0.13 to 0.23 mg/kg per week in Study 092). Of note, the dosage previously approved for the treatment of short stature associated with TS was up to 0.375 mg/kg per week.**
3) **Two patients in Study 055 (9%) and 3 patients in Study 092 (19%) did not grow in response to Genotropin when their heights were expressed as SDS derived from the growth patterns of healthy non-TS children (i.e., the change in height SDS was <0), and 1 patient in Study 055 (5%) and 5 patients in Study 092 (31%) grew less than 1 cm after 1 year of Genotropin treatment. These findings are consistent with previous observations that the linear growth response of TS girls with short stature to treatment with rhGH is less consistent and more variable than the response of short children with growth hormone deficiency (25, 41). In addition, these results provide further evidence that the TS children in Study 092 were suboptimally dosed (see bullet 2 just above).**
4) **The positive post-treatment HV SDS values (using the Tanner/Sempe standards for healthy non-TS children or the Ranke standard for TS children) achieved in both studies indicate that Genotropin treatment of TS girls induced rates of growth which were greater than that of either normal children or untreated TS children of the same age.**
5) **The similar significant increases from baseline in B-P PredAH and mProjAH (~3 cm) (2 totally different methodologies) in Study 092 indicate that treatment with Genotropin for 1 year definitively increased the predicted final adult height of TS girls. The sponsor reports that continued treatment with Genotropin for an**

additional 1, 2 or 3 years resulted in greater increases in predicted final adult height.

6) **In Study 055, the significant increases from baseline in height SDS (Ranke, 0.79; Tanner 0.41) were robust. Ranke et al (41) and other investigators have reported that the first year growth of TS patients after treatment with rhGH is a powerful predictor of height gain (i.e., FH compared with mProjAH at baseline) in TS children who continue to receive rhGH until FH is attained. Other predictors of height gain at FH in rhGH-treated children with TS will be discussed in Section 6.1.5.1.3 ahead.**
7) **There was no increase in BA compared to CA after 12 months of treatment with Genotropin in either study.**
8) **The focus of this Medical Officer's review was on the Month 12 efficacy results. In Study 092, the sponsor reports significant increases from baseline for height SDS (Ranke) and HV SDS (Ranke) after 2, 3 and 4 years of treatment with Genotropin alone (0.9 and 2.6, 1.2 and 2.4, and 1.4 and 1.4, respectively).**

6.1.5.1.2 Comparison of the Results Observed in Studies 055 and 092 with the Results of Four Concurrently Controlled Short-Term Published Studies Wherein rhGH was Administered to TS Children with Short Stature

A review of the literature reveals 4 concurrently controlled short-term studies wherein rhGH was administered for at least 1 year to TS children with short stature. Sample size, rhGH dosage, potential duration of therapy, mean baseline CA and mean baseline BA are summarized in Table 9, and compared with the same parameters in Studies 055 and 092. Three of the 4 studies had untreated concurrent control groups and 1 study (35; Quigley et al) was placebo controlled. The amount of rhGH administered during the 4 controlled studies ranged from 0.26 to 0.375 mg/kg per week, very similar to the range of doses in Study 092 (0.13-0.23 mg/kg per week) and Study 055 (0.33 mg/kg per week). The mean baseline CAs across all of the studies were similar (~9-11 years). The mean baseline BAs were ~2 years behind the mean baseline CAs across the 4 controlled studies (as expected in TS), compared with an ~1 year delay in Study 055 and an ~1.5 year delay in Study 092.

Table 10 compares the results observed during the 4 concurrently controlled studies and Studies 055 and 092. Although some patients in the controlled studies were treated with rhGH for multiple years, the intent of this section is to focus on the HV response after 1 year of treatment. Baseline HVs were remarkably consistent across all 6 studies (~4 cm/year). During the first year of the 4 concurrently controlled studies, HV remained essentially unchanged from baseline (3.8-4.4 cm/year) in the control groups. **A comparison of HVs and the changes from baseline in HV after 1 year of rhGH treatment between Studies 055 and 092, and the 4 concurrently controlled published studies reveals an apparent dose-response**.* Treatment with **0.33 mg/kg per week of Genotropin in Study 055** resulted in a HV of **7.8 cm/year** and a change from baseline in HV of **3.7 cm/year**, while treatment with **0.36 (35) and 0.30 (42) mg/kg per week** in 2 of the 4 controlled studies resulted in very similar HVs of **7.2 and 7.6 cm/year**, respectively, and very similar changes from baseline in HV of **3.4 and 3.3 cm/year**, respectively. On the other hand, treatment with **0.13-0.23 mg/kg per week of Genotropin in Study 092**

resulted in a HV of **6.1 cm/year** and a change from baseline in HV of **2.2 cm/year**, while treatment with **0.27 (35) and 0.26 (24) mg/kg per week** in 2 of the 4 controlled studies resulted in very similar HVs of **6.4 and 6.3 cm/year**, respectively, and very similar changes from baseline in HV of **2.5 and 2.3 cm/year**, respectively. *The relatively poor response (change in HV = 2.1 cm/year) published by Rosenfeld et al (32), in spite of treatment with 0.375 mg/kg per week of Genotropin, possibly relates to the fact that Genotropin was administered TIW rather than daily. It is well known that children with short stature due to GHD demonstrate a substantially improved response when rhGH is administered daily as opposed to TIW.

Table 9
Treatment of Turner Syndrome with Recombinant Human Growth Hormone: Comparison of Four Controlled Short-Term Published Studies with Pfizer's Two Open Label Studies – Baseline Data

Publication	Quigley 2002[35]	Dacou-Voutetakis 1998[24]	Stephure Canadian Growth Hormone Advisory Group 1993[42]	Rosenfeld 1990[32]	Pfizer French Study 86-092[3]	Pfizer Belgian Study 87-055[10]
Number of patients	224*	123	111	71	34	42
Control Group	Placebo (n=41)	Untreated (n=41)	Untreated (n=55)	Untreated (n=18)†	-	-
rhGH dosage mg/kg per week	0.27 (n=92) 0.36 (n=91)	0.26 (n=82)	0.3 (n=56)	0.375 (n=17) 0.375 (n=54)‡ Initially divided 3 times a week, intra-muscularly, then daily	0.13 – 0.23 (n=16)	0.33 (n=22)
Potential Duration of Therapy	>18 months	2.2 years	2 years	4 – 5 years	4 years	1 year
Mean Baseline CA (Controls / Treated)	9.4 – 9.9§	11.4 / 11.5	10.5 / 10.8	4.4 – 12.4§	10	10.5
Mean Baseline BA (Controls / Treated)	7.6 – 7.9	NA / 9.7	8.8 / 9.0	NA	8.4	9.7

*232 enrolled - 224 received rhGH for at least 180 days and evaluable for efficacy
†untreated for 12 – 21 months; ‡treated with oxandrolone + rhGH during Year 1

§mean not available, only range provided

Table 10
Treatment of Turner Syndrome with Recombinant Human Growth Hormone: Comparison of Four Controlled Short-Term Published Studies with Pfizer's Two Open Label Studies – HV Results

Publication	Baseline HV (cm/yr) Control Somatropin	1st Year HV (cm/yr) Control Somatropin	Change in HV (cm/yr) Control Somatropin
Quigley+ 2002[35] Placebo Control	4.1 3.7 – 4.3	4.0++ 6.4 – 7.2#	-0.1++ 2.5 – 3.4#
Dacou-Voutetakis 1998[24] Untreated control	4.0 4.0	4.4 6.3	0.4 2.3
Stephure Canadian Growth Hormone Advisory Group 1993[42] Untreated Control	4.2 4.3	3.8 7.6	-0.4 3.3
Rosenfeld+ 1990[32] Untreated Control	4.2 4.1 – 4.5	3.8 6.6 – 9.8†	-0.4 2.1 – 5.5†*
Pfizer Study 87-055[2]	– 4.1	– 7.8	– 3.7
Pfizer Study 86-092[3]	– 3.9	– 6.1	– 2.2

*All values represent the mean.
+The change in HV may not be readily calculated from the preceding columns as this reflects the range of changes, and not the changes in the range.
++1 year data calculated from the reference (which provided 18 month data).
†treated with oxandrolone + rhGH during Year 1

In summary with respect to Section 6.1.5.1.2:

The HV results at Month 12 in Studies 055 and 092 (open label studies without an untreated or placebo-treated concurrent control group) compare very favorably with the 12 month results of the 4 concurrently controlled studies. The similar results observed during the controlled studies support the validity of the significant increases in HV observed during Studies 055 and 092.

Furthermore, considering the results of all 6 short-term studies, it is clear that treatment with 0.30 – 0.36 mg/kg per week of Genotropin for 12 months results in a greater linear growth response (~1 cm/year more) than treatment with 0.13 – 0.27 mg/kg per week for 12 months. In this regard, Genotropin dosages of 0.30 – 0.36 mg/kg per week more closely approximate the dosage of Genotropin previously approved for the treatment of short stature associated with TS (i.e., up to 0.375 mg/kg per week). In addition, as noted earlier, it

has been reported that treatment of TS children with rhGH at dosages greater than 0.30–0.36 mg/kg per week (i.e., as much as 0.45-0.70 mg/kg per week) results in a greater increase in FH, and no apparent increase in adverse events (29-31). A brief but thorough review of the FH literature follows in Section 6.1.5.1.3 ahead.

6.1.5.1.3 A Limited Review of Published FH Studies Wherein rhGH was Administered to TS Children with Short Stature (as well as non-TS non-growth hormone deficient children with short stature)

Background statement:

During the last 10-15 years, most of the published studies reporting FH results in TS children treated with rhGH did not have a concurrent control group. Absent a concurrent control group, these authors have evaluated their FH results in several ways: **1) by comparing their FH results with historical data, i.e. the FH attained by untreated TS children** (141.1–143.2 cm/year; see references 11-14 and Section 2.6.2.1 above); 2) **by comparing their FH results with the mProjAH at baseline** (13; see Section 2.6.2.1.1 above); and 3) by comparing their FH results with mid-parental target height.

6.1.5.1.3.1 Published FH Studies Supported by the Sponsor in rhGH-Treated Children with TS

In this section, this Medical Officer will briefly describe 4 published FH studies (3 uncontrolled and 1 concurrently controlled) in TS children treated with Genotropin supported by the sponsor of this submission (Pfizer/formerly Pharmacia). Please refer to the first 4 rows of Table 11 below.

Ranke et al (41) recently retrospectively reviewed the FH response of **188** TS patients treated with Genotropin; this information was contained in the German subset of the KIGS database. KIGS is a very large postmarketing surveillance database established by Pharmacia many years ago to monitor the safety and efficacy of Genotropin administered to children with short stature. The median dose of Genotropin was **0.29 mg/kg per week**. Median FH was **152.2 cm**, gain over mProjAH at baseline was **6 cm**, and change from baseline in height SDS (Ranke) was 1. He also performed a detailed analysis of factors predictive of substantial height gain (please see Section 6.1.5.1.3.3 below).

Betts et al (43) retrospectively reviewed the FH response of 52 TS girls treated with Genotropin; this information was contained in the United Kingdom subset of the KIGS database. The median dose of Genotropin was **0.24 mg/kg per week**. Median FH was **148 cm** and the gain over mProjAH at baseline was **5.2 cm**. Less than optimal dosing may account for the lesser growth response in this study compared with the Ranke study described in the preceding paragraph.

Johnston et al (44) reported the results of 49 TS girls in the UK treated with **0.3 mg/kg per week** of Genotropin until FH was attained. The mean near final height (NFH) was **146.8 cm** and height gain over mProjAH at baseline was **4.6 cm**. NFH was greater than 152.4 cm (60") in 31% of these TS children compared with the expected 5-10% of untreated historical controls.

Dacou-Voutetakis et al (24) reported the results of a non-randomized, concurrently controlled study; 35 TS children were treated with 0.23 mg/kg per week of Genotropin and 27 TS children were untreated. FH in the treated group (146.1 cm) was only **2.1 cm greater** than FH in the untreated group, more than likely because of suboptimal dosing.

Although these 4 Pfizer/Pharmacia-sponsored FH studies were flawed in that 1) 3 of them were not controlled; 2) 2 of them were retrospective analyses; and 3) 1 of them was concurrently controlled but the Genotropin dosage utilized was suboptimal, they do provide a small degree of support for the sponsor's current application, in particular the large study published by Ranke et al (41). However, it should be noted that, in the opinion of this Medical Officer, the short-term data discussed in Sections 6.1.5.1.1 and 6.1.5.1.2 above are sufficient to grant approval for this indication.

6.1.5.1.3.2 Selected Published FH Studies **Not** Supported by the Sponsor

Important background statement:

In this section, this Medical Officer will briefly describe 3 concurrently controlled and 9 uncontrolled published FH studies in TS children treated with Genotropin not supported by the sponsor of this submission (Pfizer/formerly Pharmacia). Please refer to rows 5 through 16 in Table 11 below.

These FH studies include the 4 label-enabling studies which led to the original approval of Humatrope and Nutropin AQ/Nutropin for the treatment of short stature associated with TS. **It is important to note once again that, in the opinion of this Medical Officer, referral to these FH studies supported by other sponsors is not necessary for the approval of the current submission, i.e. the short-term data discussed in Sections 6.1.5.1.1 and 6.1.5.1.2 above are sufficient to grant approval for this indication. The intent of this Medical Officer in summarizing the results of these FH studies supported by other sponsors is only to provide context**. On the other hand, given that multiple review articles by highly regarded organizations (26-28) recommend rhGH treatment for TS children with short stature as the **standard of care**, it would **not** be inappropriate to use this FH literature to directly support the current application.

6.1.5.1.3.2.1 Concurrently Controlled FH Studies **Not** Supported by the Sponsor

In this section, this Medical Officer will briefly describe 3 concurrently controlled published FH studies in TS children treated with Genotropin not supported by the sponsor of this submission (Pfizer/formerly Pharmacia). Please refer to rows 5 through 7 in Table 11 below.

The largest study was published **in 2005** by the Canadian Growth Hormone Advisory Committee (37). Sixty one prepubertal TS patients (mean age 10.3) were **randomized to treatment** with **0.3 mg/kg per week** of rhGH, and 43 prepubertal TS patients (mean age 10.9) were randomized to no rhGH treatment, i.e the untreated control group. **The mean difference between the**

rhGH-treated group and the untreated control group by ANCOVA was 7.2 cm (p<0.001) (FH in the treated group was 147.5 cm). Hochberg et al (45) and Pasquino et al (25) published the results of **smaller, non-randomized**, concurrently controlled FH studies; mean FH in the rhGH-treated groups (**0.3 mg/kg per week in each study**) exceeded mean FH in the untreated control groups by 4.4 (5.3 when corrected for mProjAH at baseline) and 5.4 cm, respectively (FHs in the treatment groups were 147.3 and 147.6, respectively).

The most consequential of these 3 concurrently controlled FH studies was the large, randomized Canadian study which demonstrated a robust highly significant treatment difference, i.e. the mean difference between the rhGH-treated group and the untreated control group by ANCOVA was 7.2 cm (p<0.001). The other 2 concurrently controlled studies were not randomized, and the treatment differences were less substantial (4.4-5.3 and 5.4 cm).

6.1.5.1.3.2.2 Uncontrolled FH Studies **Not** Supported by the Sponsor

In this section, this Medical Officer will very briefly and selectively describe 9 uncontrolled published FH studies in TS children treated with Genotropin not supported by the sponsor of this submission (Pfizer/formerly Pharmacia). Please refer to rows 8 through 16 in Table 11 below.

Quigley et al (35) (dose of rhGH = 0.27-0.36 mg/kg per week) reported that the mean NFH of 99 treated girls (whose BA was ≥14 years) was **148.7 cm**, a mean **increase of 1.3 SDS from baseline** (TS standard); **NFH was >152.4 cm (60") in 29% compared with the expected 5-10% of untreated historical controls.** Chernausek et al (36) (dose of rhGH = 0.375 mg/kg per week) reported FHs of **150.4 cm** (height gain over mProjAH at baseline = **8.4 cm**) when estrogen therapy was delayed until age 15, and **147 cm** (height gain over mProjAH at baseline = **5.1 cm**) when estrogen therapy was started at age 12. Massa et al (15) (dose of rhGH = 0.27-0.43 mg/kg per week) reported that the mean NFH of 45 TS patients completing the treatment protocol was **152.3 cm, 5.3 cm greater than the final adult height of 63 historically untreated TS patients.** These 3 studies have already been referenced in Section 2.6.3.3 above – a discussion of the use of estrogen in TS syndrome patients.

The FHs observed by Rosenfeld et al (22), Nilsson et al (33) and Attanasio et al (44) were similar to those described above (please refer to Table 11 for details). These 3 studies have already been referenced in Section 2.6.3.2 above – a discussion of the potential value of oxandrolone as adjunctive therapy in TS patients with short stature.

Sas et al (29), von Pareren et al (30) and Carel et al (31) reported mean FHs of **154.3 to 163.6 cm** after treatment with larger dosages of rhGH (**0.45 to 0.70 mg/kg per week**).

As a group, these uncontrolled studies further support a beneficial effect of rhGH treatment on FH in TS patients with short stature (mean FHs ranged from 147 to 152.3 cm when the dosage of rhGH ranged from 0.27 to 0.43 mg/kg per week, and treatment arms including oxandrolone were excluded). Furthermore, when the dosage of rhGH ranged

from 0.45 to 0.70 mg/kg per week, mean FHs were clearly larger ranging from 154.3 to 163.6 cm (~64"!!). To put all of these FH results in context, it is important to restate that 1) the historical FH observed in untreated girls with TS reported by Lyon et al in 1985 (13 and see Section 2.6.2.1) was 143.2 cm; and 2) some investigators believe that the so-called Lyon curve may not be currently applicable, i.e. Sybert et al recently reported a FH of 148 cm in untreated TS girls in Washington state (5).

6.1.5.1.3.3 Predictors of FH After Treatment of TS Children with rhGH

As stated in Section 6.1.5.1.1, **Ranke et al (41) and other investigators have reported that the first year growth of TS patients after treatment with rhGH is a powerful predictor of height gain (i.e., FH compared with mProjAH at baseline) in TS children who continue to receive rhGH until FH is attained**. It has also been reported that height gain over mProjAH 1) correlates inversely with CA (35, 36, 37, 41), BA (41) and height SDS (Turner standard) (41) at baseline, and 2) correlates positively with rhGH dose (41), duration of treatment with rhGH (37, 41), and overall prepubertal height gain (41). As discussed earlier in Section 2.6.3.3 above, years of rhGH treatment prior to the initiation of estrogen to induce puberty remains a somewhat controversial issue.

6.1.5.1.3.4 FH Results After Treatment of non-TS, non-Growth Hormone Deficient Children with rhGH

Various formulations of rhGH have been previously approved to treat short stature in non-growth hormone deficient target populations **other than TS girls**. Several recent publications have reported that treatment with rhGH results in significantly improved FH in short children with CRI (pre-transplantation) (46), SGA (47, 48) and ISS (49-51). In that TS children and the abovementioned target populations are **all non-growth hormone deficient**, these findings indirectly support the use of rhGH for the long-term treatment of short stature associated with TS.

In summary with respect to Section 6.1.5.1.3:

The results of 4 FH studies in Genotropin-treated children with TS supported by the sponsor have been published. The most consequential of these was a retrospective review of 188 TS patients in the German subset of the KIGS database - wherein a median Genotropin dose of **0.29 mg/kg per week** resulted in a median FH was **152.2 cm**, a 6 cm gain over mProjAH at baseline, and a 1 unit change from baseline in height SDS (Ranke). **Although these 4 Pfizer/Pharmacia-sponsored FH studies were flawed in that 1) 3 of them were not controlled; 2) 2 of them were retrospective analyses; and 3) 1 of them was concurrently controlled but the Genotropin dosage utilized was suboptimal, they do provide a *small* degree of support for the sponsor's current application, in particular, the large study alluded described above (41). *However, it should be noted that, in the opinion of this Medical Officer, the short-term data discussed in Sections 6.1.5.1.1 and 6.1.5.1.2 above are sufficient to grant approval for this indication*.**

The results of 12 FH studies (3 concurrently controlled and 9 uncontrolled) in rhGH-treated children with TS supported by other sponsors have been reviewed by this Medical Officer. ***It is important to note once again that, in the opinion of this Medical Officer, referral to these FH studies supported by other sponsors is not necessary for the approval of the current submission, i.e. the short-term data discussed in Sections 6.1.5.1.1 and 6.1.5.1.2 above are sufficient to grant approval for this indication. The intent of this Medical Officer in summarizing the results of these FH studies supported by other sponsors is only to provide context.*** On the other hand, given that multiple review articles by highly regarded organizations (26-28) recommend rhGH treatment for TS children with short stature as the **standard of care**, it would **not** be inappropriate to use this FH literature to directly support the current application.

The most consequential of the 3 concurrently controlled FH studies not supported by the sponsor of this submission was the large (n=104), randomized Canadian study which demonstrated a robust highly significant treatment difference in response to 0.3 mg/kg per week of rhGH, i.e. the mean difference between the rhGH-treated group and the untreated control group by ANCOVA was 7.2 cm ($p<0.001$). The other 2 concurrently controlled studies were not randomized, and the treatment differences were less substantial (4.4-5.3 and 5.4 cm).

As a group, these uncontrolled studies further support a beneficial effect of rhGH treatment on FH in TS patients with short stature (mean FHs ranged from 147 to 152.3 cm when the dosage of rhGH ranged from 0.27 to 0.43 mg/kg per week, and treatment arms including oxandrolone were excluded). Furthermore, when the dosage of rhGH ranged from 0.45 to 0.70 mg/kg per week, mean FHs were clearly larger ranging from 154.3 to 163.6 cm (~64"!!). To put all of these FH results in context, it is important to restate that 1) the historical FH observed in untreated girls with TS reported by Lyon et al in 1985 (13 and see Section 2.6.2.1) was 143.2 cm; and 2) some investigators believe that the so-called Lyon curve may not be currently applicable, i.e. Sybert et al recently reported a FH of 148 cm in untreated TS girls in Washington state (5).

It appears the first year growth of TS patients after treatment with rhGH is a powerful predictor of height gain (i.e., FH compared with mProjAH at baseline) in TS children who continue to receive rhGH until FH is attained (41). It has also been reported decreased CA, BA and height SDS (Turner standard) correlate negatively with height gain, while rhGH dose, duration of treatment with rhGH and overall prepubertal height gain correlate positively with height gain.

The fact that there is current literature indicating that treatment of non-TS non-growth hormone deficient short children with rhGH (i.e., CRI, SGA, ISS) significantly improves FH indirectly supports the use of rhGH for the long-term treatment of short stature associated with TS.

Table 11
Treatment of Turner Syndrome with Recombinant Human Growth Hormone
Review of Consequential Final Height Studies in the Literature

Author Year	Control group	GH/Manuf	n	GH dose (mg/kg/wk)	Aver age at GH start (yrs)	Concomitant medications	Final Height or Near Final Height (NFH) (cm)	Notes
Ranke 2002[41]	None	**Genotropin/ Pfizer**	188	0.29	11.7	E2 started at age 14	**152.2 Height gain c/w projected height at baseline was 6 cm**	Data are from a **retrospective analysis** of the German subset of the KIGS surveillance study
Betts 1999[43]	None	**Genotropin/ Pfizer**	52	0.24	10.7	E2 added at various times	**148[@] Height gain c/w projected height at baseline was 5.2 cm**	Data are from a retrospective analysis of the UK subset of the KIGS surveillance study; [@]given as +0.42 SDS, and converted by the sponsor from the Lyon curves
Johnston 2001[44]	Concurrent untreated for 1 yr only	**Genotropin/ Pfizer**	12	0 for 1 yr, then 0.3	9.1	E2 started at entry	**145.5** (NFH)	
			17	0.3	9.0	E2 started after age 12	**146.2** (NFH)	**The mean NFH of all 49 girls was 146.8 cm; height gain c/w projected height at baseline was 4.6 cm; NFH >152.4 cm (60") in 31% c/w the expected 5-10% of untreated historical controls**
			20	0.3	9.1	E2 started at entry	**148.2** (NFH)	
Dacou-Voutetakis 1998[24]	**Concurrent untreated; Non-Randomized**	**Genotropin/ Pfizer** ---	35 27	**0.23** 0	12.0 NA	E2 started age 15.6 E2 started age 14.2	**146.1** **144.0**	**GH group – untreated control group = 2.1 cm**
Stephure 2005[37]	**Concurrent untreated; Randomized**	Humatrope/ Eli Lilly ---	61 43	0.3 0	10.3 10.9	E2 added age 13	**147.5** **141.0**	**The mean difference between the rhGH-treated group and the untreated control group by ANCOVA was 7.2 cm (p<0.001)**

Hochberg 1999[45]	**Concurrent untreated; Non-Randomized**	Humatrope/ Eli Lilly and Biotropin/ BTG ---	25 24	0.3 0	10.7 NA	E2 added age 13.2 E2 added age 13.4	**147.3** **142.9**	**GH group minus untreated control group = 4.4 cm**; In the untreated group, the projected height ~final height in almost all subjects
Pasquino 1996[25]	**Concurrent untreated; Non-Randomized**	Sponsor not specified ---	18 18	0.15 for 1 year, then 0.3 0	13.0 NA	E2 started age 15.7	**147.6** **142.2**	**GH group minus untreated control group = 5.4 cm**
Quigley 2002[35]	Placebo controlled for 18 mos only Historical untreated for NFH	Humatrope/ Eli Lilly	15 24 38 22 41	0.27 0.27 0.36 0.36 placebo	10.6 10.4 11.2 11.1 NA	placebo E2 (low dose) after age 8 placebo E2 (low dose) after age 8 placebo	149.9 (NFH) 145.1 (NFH) 150.4 (NFH) 149.1 (NFH) NA*	**The mean NFH of 99 treated girls whose bone age was ≥14 was 148.7 cm - a mean increase of 1.3 SDS from baseline (TS standard); NFH >152.4 cm (60") in 29% c/w the expected 5-10% of untreated historical controls** *merged into Group 3 after 18 mos
Chernausek 2000[36]	Historical untreated for FH	Nutropin/ Genentech	30	0.375	9.6	E2 added at 12 yrs of age	**147.0**	**Height gain** c/w projected height at baseline was **8.4 cm** when estrogen treatment was delayed until age 15 yrs, and **height gain** c/w projected height at baseline was **5.1 cm** when estrogen treatment was started at age 12 yrs
			30		9.4	E2 added at 15 yrs of age	**150.4**	
		---	69	0	NA	E2 added at mean age 15-16.2 yrs	144.1	
Massa 1995[15]	Historical untreated for FH	Humatrope/ Eli Lilly	19 35	0.27 0.27 for 2 yrs, then 0.43	<12 >12	E2 added after age 12 yrs E2 added from beginning	**151.3** **152.0**	The NFH of the 45 patients completing the treatment protocol was **152.3 cm, 5.3 cm greater than the final adult height of 63 historically untreated TS patients**
		---	63	0	NA	0	**147.0**	

Rosenfeld 1998[22]	Concurrent untreated for 1 yr only	Protropin/ Genentech	17	0.375 from the beginning	9.1	E2**	**150.4**	**E2 added to all groups after age 14
			43*	0 for 1-2 yrs, then 0.375 0.375 from the beginning	9.7	Oxandrolone, E2** Oxandrolone, E2**	**152.1**	
	Historical untreated for FH	---	25	0	9.2	---	144.2	
Nilsson 1996[33]	None	Somatonorm/ Kabi, then Genotropin/ Pfizer	6	0 for 1year, then 0.23	12.3	Oxandrolone from beginning	151.0	
			7	0 for 1year, then 0.23		Oxandrolone from beginning, and E2 after 1 year	151.1	
			17	0.23	12.1	Oxandrolone from beginning	**154.2**	
			15	0.23	12.3	Oxandrolone and E2 from beginning	**151.1**	
Attanasio 1995[34]	None	Humatrope/ Eli Lilly	6	Between 0.15 and 0.3	11#	E2 started after BA 12.5 yrs	150.9	FH data collected as part of the NCGS surveillance study; #Age at start not expressly stated, but calculated by the sponsor; some subjects may have received no GH for the first year of the study

Sas 1999[29]	None	Norditropin/ Novo Nordisk	9 10	**0.46** given qHS **0.46**, given as 1/3 qAM, 2/3 qHS	13.3 13.8	E2 from the beginning	**154.3** **156.5**	
van Pareren 2003[30]	None	Norditropin/ Novo Nordisk	19 20 21	0.3 0.3 for 1 year and **0.45 thereafter** 0.3 for 1 year and **0.45 for the second year, and 0.60 thereafter**	6.5 6.9 6.5	17β E2 started in all girls at average age 12.7 yrs	157.6 **162.9** **163.6**	
Carel 1998[31]	None	Maxomat/ Sanofi	17	0.3	11.0	E2 added at 14 yrs	148.3	Treatment stopped when BA ≥13.5 yrs; Data from 0.3 group was a retrospective analysis
			14	**0.23 increasing to 0.7 over 4 yrs**	10.2	E2 added at 15.3 yrs	**155.3**	

6.1.5.3 Efficacy Conclusions

- **The significant HV, HV SDS and height SDS change from baseline results in both studies indicate a consistent linear growth response to Genotropin at Month 12 in TS children with short stature, which was apparent even at Month 6 in Study 055.**
- **The more robust HV, HV SDS and height SDS responses observed in Study 055 compared with Study 092 more than likely reflects the fact that the TS children in Study 092 were treated with a lower and less optimal dose of Genotropin (0.33 mg/kg per week in Study 055 vs. 0.13 to 0.23 mg/kg per week in Study 092). Of note, the dosage previously approved for the treatment of short stature associated with TS was up to 0.375 mg/kg per week.**
- **Two patients in Study 055 (9%) and 3 patients in Study 092 (19%) did not grow in response to Genotropin when their heights were expressed as SDS derived from the growth patterns of healthy non-TS children (i.e., the change in height SDS was <0), and 1 patient in Study 055 (5%) and 5 patients in Study 092 (31%) grew less than 1 cm after 1 year of Genotropin treatment. These findings are consistent with previous observations that the linear growth response of TS girls with short stature to treatment with rhGH is less consistent and more variable than the response of short children with GHD (41). In addition, these results provide further evidence that the TS children in Study 092 were suboptimally dosed (see bullet 2 just above).**
- **The positive post-treatment HV SDS values (using the Tanner/Sempe standards for healthy non-TS children or the Ranke standard for TS children) achieved in both studies indicate that Genotropin treatment of TS girls induced rates of growth which were greater than that of either normal children or untreated TS children of the same age.**
- **The similar significant increases from baseline in B-P PredAH and mProjAH (~3 cm) (2 totally different methodologies) in Study 092 indicate that treatment with Genotropin for 1 year definitively increased the predicted final adult height of TS girls. The sponsor reports that continued treatment with Genotropin for an additional 1, 2 or 3 years resulted in greater increases in predicted final adult height.**
- **In Study 055, the significant increases from baseline in height SDS (Ranke, 0.79; Tanner 0.41) were robust. Ranke et al (41) and other investigators have reported that first year growth of TS patients after treatment with rhGH is a powerful predictor of height gain (i.e., FH compared with mProjAH at baseline) in TS children who continue to receive rhGH until FH is attained.**
- **There was no increase in BA compared to CA after 12 months of treatment with Genotropin in either study.**
- **The focus of this Medical Officer's review was on the Month 12 efficacy results. In Study 092, the sponsor reports significant increases from baseline for height SDS (Ranke) and HV SDS (Ranke) after 2, 3 and 4 years of treatment with Genotropin alone (0.9 and 2.6, 1.2 and 2.4, and 1.4 and 1.4, respectively). In other words, long-term treatment with Genotropin resulted in a progressive increase from baseline in**

height SDS (Ranke) from 0.4 at Month 12, to 0.9, 1.2 and 1.4 at Months 24, 36, and 48, respectively.

- **With respect to published short-term (12 month) studies:**

The HV results at Month 12 in Studies 055 and 092 (open label studies without an untreated or placebo-treated concurrent control group) compare very favorably with the 12 month results of the 4 concurrently controlled studies. The similar results observed during the controlled studies support the validity of the significant increases in HV observed during Studies 055 and 092.

Furthermore, considering the results of all 6 short-term studies, it is clear that treatment with 0.30 – 0.36 mg/kg per week of Genotropin for 12 months results in a greater linear growth response (~1 cm/year more) than treatment with 0.13 – 0.27 mg/kg per week for 12 months. In this regard, Genotropin dosages of 0.30 – 0.36 mg/kg per week more closely approximate the dosage of Genotropin previously approved for the treatment of short stature associated with TS (i.e., up to 0.375 mg/kg per week). In addition, as noted earlier, it has been reported that treatment of TS children with rhGH at dosages greater than 0.30–0.36 mg/kg per week (i.e., as much as 0.45-0.70 mg/kg per week) results in a greater increase in FH, and no apparent increase in adverse events (29-31).

- **With respect to published FH studies:**

The results of 4 FH studies in Genotropin-treated children with TS supported by the sponsor have been published. The most consequential of these was a retrospective review of 188 TS patients in the German subset of the KIGS database - wherein a median Genotropin dose of **0.29 mg/kg per week** resulted in a median FH was **152.2 cm**, a 6 cm gain over mProjAH at baseline, and a 1 unit change from baseline in height SDS (Ranke). **Although these 4 Pfizer/Pharmacia-sponsored FH studies were flawed in that 1) 3 of them were not controlled; 2) 2 of them were retrospective analyses; and 3) 1 of them was concurrently controlled but the Genotropin dosage utilized was suboptimal, they do provide a *small* degree of support for the sponsor's current application, in particular, the large study described above (41). *However, it should be noted that, in the opinion of this Medical Officer, the short-term data discussed in Sections 6.1.5.1.1 and 6.1.5.1.2 above are sufficient to grant approval for this indication*.**

The results of 12 FH studies (3 concurrently controlled and 9 uncontrolled) in rhGH-treated children with TS supported by other sponsors have been reviewed by this Medical Officer. *It is important to note once again that, in the opinion of this Medical Officer, referral to these FH studies supported by other sponsors is not necessary for the approval of the current submission, i.e. the short-term data discussed in Sections 6.1.5.1.1 and 6.1.5.1.2 above are sufficient to grant approval for this indication. The intent of this Medical Officer in summarizing the results of these FH studies supported by other sponsors is only to provide context*. On the other hand, given that multiple review articles by highly regarded organizations

(26-28) recommend rhGH treatment for TS children with short stature as the **standard of care**, it would **not** be inappropriate to use this FH literature to directly support the current application.

The most consequential of the 3 concurrently controlled FH studies not supported by the sponsor of this submission was the large (n=104), randomized Canadian study which demonstrated a robust highly significant treatment difference in response to 0.3 mg/kg per week of Genotropin, i.e. the mean difference between the rhGH-treated group and the untreated control group by ANCOVA was 7.2 cm (p<0.001). The other 2 concurrently controlled studies were not randomized, and the treatment differences were less substantial (4.4-5.3 and 5.4 cm).

As a group, these uncontrolled studies further support a beneficial effect of rhGH treatment on FH in TS patients with short stature (mean FHs ranged from 147 to 152.3 cm when the dosage of rhGH ranged from 0.27 to 0.43 mg/kg per week, and treatment arms including oxandrolone were excluded). Furthermore, when the dosage of rhGH ranged from 0.45 to 0.70 mg/kg per week, mean FHs were clearly larger ranging from 154.3 to 163.6 cm (~64"!!). To put all of these FH results in context, it is important to restate that 1) the historical FH observed in untreated girls with TS reported by Lyon et al in 1985 (13 and see Section 2.6.2.1) was 143.2 cm; and 2) some investigators believe that the so-called Lyon curve may not be currently applicable, i.e. Sybert et al recently reported a FH of 148 cm in untreated TS girls in Washington state (5).

It appears that the first year growth of TS patients after treatment with rhGH is a powerful predictor of height gain (i.e., FH compared with mProjAH at baseline) in TS children who continue to receive rhGH until FH is attained (41). It has also been reported decreased CA, BA and height SDS (Turner standard) correlate negatively with height gain, while rhGH dose, duration of treatment with rhGH and overall prepubertal height gain correlate positively with height gain.

The fact that there is current literature indicating that treatment of non-TS non-growth hormone deficient short children with rhGH (i.e., CRI, SGA, ISS) significantly improves FH indirectly supports the use of rhGH for the long-term treatment of short stature associated with TS.

6.1.5.4 Efficacy Recommendations

- No additional efficacy studies are required to obtain approval.
- The short-term efficacy data from Studies 055 and 092 presented in this application describing the significant linear growth response of short children with TS after 12 months of treatment with Genotropin **is sufficient by itself** to warrant approval of this supplement and the requested labeling change. A comparison of the efficacy findings in Studies 055 and 092 with the results of 4 published short-term controlled studies **strongly supports** the validity of the sponsor's findings. A review of published FH studies supported by the sponsor wherein short TS children were treated with Genotropin until FH was achieved provides very modest additional support for the application. A review

of published FH studies not supported by the sponsor wherein short TS children were treated with rhGH formulations other than Genotropin until FH was achieved **is not necessary** for approval of this application and is contained in this Medical Officer's review **only to provide context**.

- The Sponsor's proposed additional language to the Clinical Studies section of the Genotropin Package Insert describing the effects of Genotropin on linear growth in Studies 055 and 092 was carefully reviewed and then edited (in collaboration with the Division's Statistical Reviewers). The most consequential edits involved 1) presentation of results from the Genotropin only arms from each study and exclusion (b) (4) (b) (4) (b) (4) 2) reformatting of Table 5 so as to present the results from Studies 055 and 092 in a more comprehensive but user-friendly fashion; and 3) expressing results as means as opposed to medians (the means and medians were very similar, and the other studies described in the Genotropin Package Insert use means); and 4) editing of the text describing Table 5 for purposes of clarity and to clearly indicate that the response to Genotropin 0.33 mg/kg per week in Study 055 (the proposed dosage in the Package Insert) was more robust than the response to Genotropin 0.13-0.23 mg/kg per week in Study 092. The sponsor agreed with all of the Division's suggested edits. No edits were required for the sponsor's proposed additions to the Indications and Usage, and Dosing and Administration sections.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

In addition to a safety analysis of the clinical trial data from Studies 055 and 092 (including safety data from all patients who were randomized to **either treatment arm** and dispensed study medication), a comparison of the AEs occurring in TS patients (vs. non-TS patients) treated with Genotropin reported through October 15, 2004 to the sponsor's Early Alert Safety Databases (ARGUS and NovAlert) was provided for review (see Section 7.1.17.1 ahead).

7.1.1 Deaths

None in either study.

7.1.2 Other Serious Adverse Events (SAEs)

Study 055:

One patient in the Genotropin alone arm experienced sinusitis/orbital cellulites and 1 patient experienced a petit mal seizure. One patient in the Genotropin + ethinyl estradiol arm experienced a grand mal seizure.

Study 092:

One patient in the Genotropin alone experienced flushing and 1 patient had ear tubes inserted because of recurrent otitis media. One patient in the Genotropin + oxandrolone arm experienced a sprained knee and 1 patient experienced a traumatic liver injury.

In the opinion of this Medical Officer, with the possible exception of recurrent otitis media, none of the SAEs reported in Studies 055 and 092 were related to Genotropin therapy. In that rhGH may induce lymphatic/adenoidal hypertrophy, and TS patients are inherently predisposed to recurrent otitis media (small, dysfunctional eustachian tubes and palatal dysfunction)**, it is possible that Genotropin contributed to the recurrent otitis media in this patient.**

7.1.3 Discontinuations

All of the patients in Study 055 completed the 12 month study. None of the patients in Study 092 discontinued prior to Month 18.

7.1.5 Common Adverse Events (AEs)

7.1.5.3 Incidence of Common AEs

Study 055:

See Table 12 below. Fifteen patients reported 1 or more common AEs during Study 055. The majority of these AEs were considered mild to moderate. **The most frequently reported common AE in both treatment arms was transient joint pain (16.7%). This is a well known adverse effect associated with the use of rhGH and relates to its fluid retaining effects.** The other AEs occurred very infrequently, and, in the opinion of this Medical Officer, it is very unlikely that these events were related to treatment with Genotropin

Table 12 – Study 055
Summary of Adverse Events (AE) - All Causality

WHO Dictionary Term	Genotropin n=22	Genotropin + ethinyl estradiol n=20
Joint Pain	**4 (18.2%)**	**3 (15.0%)**
Epilepsy	1 (4.5%)	1 (5.0%)
Sinusitis	1 (4.5%)	1(5.0%)
Cellulitis	1 (4.5%)	0
Urinary Tract Infection	0	1 (5.0%)
Dysfunctional voiding	0	1 (5.0%)
Menarche	1 (4.5%)	0
Varicella	1 (4.5%)	0
Measles	1 (4.5%)	0
Herpes Zoster	1 (4.5%)	0
Total AEs	11 (50.0%)	7 (35.0%)

Study 092:

See Table 13 below. A total of 29 common AEs were reported in 13 patients in the Genotropin alone group, and 33 common AEs were reported in 11 patients in the Genotropin + oxandrolone group. The majority of these AEs were considered mild to moderate. **Joint pain was reported by 5.9% of 34 randomized patients (less than in Study 055 probably because the amount of Genotropin administered was smaller).** Upper respiratory tract infections were the most frequently reported common AEs. **Otitis media was reported by 11.8% of 34 randomized patients. Once again, in that rhGH may induce lymphatic/adenoidal hypertrophy, and TS patients are inherently predisposed to recurrent otitis media** (small, dysfunctional eustachian tubes and palatal dysfunction)**, it is possible that Genotropin contributed to the incidence of otitis media in this study.**

Table 13 – Study 092
Summary of AEs that Occurred in at Least 2 Patients - All Causality

WHO dictionary term	Genotropin n=17	Genotropin + oxandrolone n=17
Otitis media	**3 (17.6%)**	**1 (5.9%)**
Tonsillitis	2 (11.8%)	3 (17.6%)
Sinusitis	2 (11.8%)	1 (5.9%)
Influenza	1 (5.9%)	4 (23.5%)
Bronchitis	0	2 (11.8 %)
Urinary Tract Infection	3 (17.6%)	0
Epistaxis	2 (11.8%)	0
Joint Pain	**1 (5.9%)**	**1 (5.9%)**
Increased Appetite	0	2 (11.8 %)

7.1.7 Laboratory Findings

7.1.7.3 Standard analyses and explorations of laboratory data

7.1.7.3.1 Measures of Glucose Tolerance

The median values for fasting blood glucose and insulin are described in Table 14 below. **Median glucose values remained unchanged and normal.** All glucose values obtained during both studies were within or transiently slightly above the normal range. **Median insulin levels increased progressively at each time point in both treatment arms in each study, but remained within the normal range. In study 092, the median insulin value after 18 months of Genotropin treatment was statistically greater than the baseline value in both treatment arms ($p<0.05$). Insulin values above the normal range occurred in 22/76 (28.9%) patients in Studies 055 and 092.** Median HbA1c levels did not change and remained normal in both studies. **No patients developed overt diabetes mellitus or were treated for hyperglycemia in these 2 studies.**

Table 14 – Studies 055 and 092
Median Fasting Blood Glucose and Insulin Values

	Study 055				Study 092			
	Genotropin + ethinyl estradiol		Genotropin		Genotropin		Genotropin + oxandrolone	
	Glucose mg/dl	Insulin µU/mL	Glucose mg/dl	Insulin µU/mL	Glucose mg/dl	Insulin µU/mL	Glucose mg/dl	Insulin µU/mL
Baseline	76.5	10	81.0	8.0	88.2	6.1	81.5	6.8
6 months	76.0	19	84.0	17.0	81.0	6.3	78.3	8.3
12 months	84.0	15.5	80.0	13.0	83.7	9.2	82.8	9.3
18 months	NA	NA	NA	NA	78.7	12	80.6	12

7.1.7.3.2 Thyroid Function Tests

No clinically significant changes occurred in either study.

7.1.10 Immunogenicity

No significant immunogenicity was detected in either study.

7.1.17 **Postmarketing Experience**

7.1.17.1 **Early Alert Safety Databases**

The sponsor's **Early Alert Safety Databases** are **ARGUS** (Pfizer's **current** Early Alert Safety Database) and NovAlert (Pharmacia's **original** Early Alert Safety Database). These Early Alert Safety Databases **contain AEs reported spontaneously, by health authorities, and published in the medical literature, as well as SAEs reported from ongoing clinical studies and KIGS.** KIGS is an open label, postmarketing, non-interventional safety surveillance study established by Pharmacia many years ago to follow children who are treated with Genotropin for a variety of growth disorders. It is important to note that these databases are designed to capture reporting rates rather than true incidence rates. The ARGUS database identifies cases using the MedDRA (version 7.1) dictionary with the preferred term Turner's syndrome, and NovAlert identified cases using the Who-ART drug dictionary with the preferred term gonadal dysgenesis.

7.1.17.1.1 **ARGUS Database**

A summary of AEs reported in ≥4% of Genotropin-treated patients with/without TS in the Argus database is provided in Table 15. The percentages of TS vs. non-TS cases are compared in the ARGUS database without KIGS data included (2 columns on the left), and with KIGS data included (2 columns on the right).

Patient outcomes were similar in the TS cases and non-TS cases (see top of Table 15).

BIH and SCFE were both reported ≥3 times as often in TS patients (vs. non-TS patients). TS patients are known to have abnormalities of lymphatic drainage (5) which may inherently predispose them to the development of BIH, and BIH is a labeled adverse event associated with rhGH treatment. Similarly, TS is characterized by generalized skeletal dysplasia (5) which may inherently predispose them to the development of SCFE, and SCFE is a labeled adverse event associated with rhGH treatment. Therefore, these findings are not at all surprising.

Otherwise, no consequential reporting differences between the TS and non-TS patients existed in the Argus database.

Table 15
Summary of AEs Reported in ≥4% of Genotropin-Treated Patients in the ARGUS Database With/Without KIGS Patients – All Causality

	ARGUS without KIGS		ARGUS with KIGS	
Case Outcome/ MedDRA Term	**TS Cases n=27**	**Non-TS Cases n=811**	**TS Cases n=58**	**Non-TS Cases n=751**
Case Outcome				
Death	1 (3.7%)	44 (5.4%)	6 (10.3%)	105 (14%)
Recovered	10 (37.0%)	273 (33.7%)	34 (58.6%)	317 (42.2%)
Recovered w/sequelae	1 (3.7%)	13 (1.6%)	3 (5.2%)	78 (10.4%)
Not recovered	6 (22.2%)	162 (20.0%)	13 (22.4%)	179 (23.8%)
Unknown	9 (33.3%)	319 (39.3%)	2 (3.4%)	72 (9.6%)
MedDRA Term				
Benign intracranial hypertension (BIH)	--	--	**3 (5.2%)**	**7 (0.9%)**
Slipped capital femoral epiphysis (SCFE)	**1 (3.7%)**	**4 (0.5%)**	**5 (8.6%)**	**15 (2.0%)**
Scoliosis	--	16 (2.0%)	1 (1.7%)	34 (4.5%)
Craniopharyngioma	--	--	--	30 (4.0%)
Neoplasm recurrence	--	--	--	100 (13.3%)
Exanthem	2 (7.4%)	1 (0.1%)	--	--
Vomiting	1 (3.7%)	11 (1.4%)	3 (5.2%)	16 (2.1%)
Headache	1 (3.7%)	44 (5.4%)	2 (3.4%)	22 (2.9%)
Drug ineffective	--	43 (5.3%)	--	--
Radius Fracture	--	--	3 (5.2%)	1 (0.1%)

7.1.17.1.2 NovAlert Database

A summary of AEs reported in ≥4% of Genotropin-treated patients with/without TS in the NovAlert database is provided in Table 16. The percentages of TS vs. non-TS cases are compared in the NovAlert database without KIGS data included (2 columns on the left), and with KIGS data included (2 columns on the right).

Patient outcomes were similar in the TS cases and non-TS cases (see top of Table 15). The 4 deaths that were reported in TS patients occurred in the KIGS study (reported as aortic aneurysm, aortic coarctation, surgical intervention and suicide attempt). Aortic coarctation and aortic root dilatation/aortic dissection are all well known serious sequealae of TS (5).

BIH, epiphysiolysis/SCFE, diabetes mellitus, systemic hypertension and otitis media were all reported ≥3 times as often in TS patients (vs. non-TS patients). As stated in Section 7.1.17.1.1 above, 1) TS patients are known to have abnormalities of lymphatic drainage (5) which may inherently predispose them to the development of BIH, and BIH is a labeled adverse event associated with rhGH treatment; and 2) TS is characterized by generalized skeletal dysplasia (5) which may inherently predispose them to the development of SCFE, and SCFE is a labeled adverse event associated with rhGH treatment. It is well known that TS patients are predisposed to diabetes mellitus (type 2) and systemic hypertension (5), and treatment with rhGH can result in glucose intolerance (labeled) and potentially could result in hypertension (i.e., rhGH-induced salt retention) (unlabeled). As stated earlier, TS patients are inherently predisposed to recurrent otitis media (small, dysfunctional eustachian tubes and palatal dysfunction)**, and rhGH can result in lymphatic/adenoidal hypertrophy which could aggravate a propensity for otitis media (unlabeled). Therefore, all of these observations are not at all surprising.**

Scoliosis is another disease entity that TS patients are inherently prone to develop; in addition, it is well known and **labeled** that treatment with rhGH resulting in rapid growth can aggravate preexisting scoliosis. Nonetheless, scoliosis was reported in less than 3% of the patients in the NovAlert database (data not shown) (and in only 1 TS patient in the ARGUS database [see Table 16]).

Hyperthyroidism was reported in 8.8% of TS cases (vs. 1.1% on non-TS cases). The fact that TS patients are also inherently prone to autoimmune thyroid disease may explain this observation.

The significance of the more frequent reports of neoplasm (NOS) in TS patients (n=3) (vs. non-TS patients) is unclear.

Table 16
Summary of AEs Reported in ≥4% of Genotropin-Treated Patients in the NovAlert Database With/Without KIGS Patients – All Causality

	NovAlert without KIGS		NovAlert with KIGS	
Case Outcome/ Who-ART Term	**TS Cases n=34**	**Non-TS Cases n=348**	**TS Cases n=93**	**Non-TS Cases n=830**
Case Outcome				
Death	--	51 (14.7%)	4 (4.3%)	67 (8.0%)
Recovered	13 (38.2%)	92 (26.4%)	35 (37.6%)	301 (36.3%)
Recovered w/sequelae	1 (2.9%)	24 (6.9%)	14 (15.1%)	113 (13.6%)
Not recovered	15 (44.1%)	74 (21.3%)	26 (28.0%)	248 (29.9%)
Unknown	5 (14.7%)	105 (30.2%)	14 (15.1%)	100 (12.0%)
Not applicable	--	2 (0.6%)	--	1 (0.1%)
Who-ART Term				
Hypertension Intracranial (BIH)	**2 (5.9%)**	**5 (1.4%)**	**3 (3.2%)**	**12 (1.4%)**
Epiphysiolysis (SCFE)	--	--	**4 (4.3%)**	**9 (1.1%)**
Diabetes Mellitus	**2 (5.9%)**	**5 (1.4%)**	**4 (4.3%)**	**23 (2.8%)**
Hypertension	**2 (5.9%)**	**4 (1.1%)**	**4 (4.3%)**	**8 (1.0%)**
Otitis Media	--	--	**4 (4.3%)**	**1 (0.1%)**
Hyperthyroidism	3 (8.8%)	4 (1.1%)	1 (1.1%)	--
Neoplasm NOS	3 (8.8%)	3 (0.9%)	3 (3.2%)	9 (1.1%)
Relapse of CNS Tumor	--	11 (3.2%)	--	52 (6.3%)
Relapse of Craniopharyngioma	--	9 (2.6%)	--	67 (8.1%)
Surgical Intervention	--	--	12 (12.9%)	49 (5.9%)
Headache	2 (5.9%)	9 (2.6%)	3 (3.2%)	14 (1.7%)
Paralysis	2 (5.9%)	1 (0.3%)	1 (1.1%)	3 (0.4%)
Convulsions	2 (5.9%)	8 (2.3%)	1 (1.1%)	31 (3.7%)
Injection site reactions	1 (2.9%)	14 (4.0%)	--	--

7.3 Safety Summary/Discussion, Conclusions and Recommendations

7.3.1 Safety Summary/Discussion

Adverse events during Studies 055 and 092:

In Study 055, the most frequently reported common AE in both treatment arms was transient joint pain (16.7%) (this was observed to a lesser extent in Study 092 because a smaller amount of Genotropin was administered). **Joint pain/arthralgia is a well known, labeled AE associated with the use of rhGH and relates to its fluid retaining effects.**

In Study 092, upper respiratory tract infections were the most frequently reported common AEs. **Otitis media was reported by 11.8% of 34 randomized patients. In that rhGH may induce lymphatic/adenoidal hypertrophy, and TS patients are inherently predisposed to recurrent otitis media** (small, dysfunctional eustachian tubes and palatal dysfunction)**, it is possible that Genotropin contributed to the incidence of otitis media in this study.**

No patients discontinued from either study during 12 months of treatment with Genotropin alone.

Glucose tolerance during Studies 055 and 092:

Median glucose values remained unchanged and normal. In contrast, median insulin levels increased progressively at each time point in both treatment arms in each study, but remained within the normal range (maximum median insulin level was ~12 μU/mL). **No patients developed overt diabetes mellitus or were treated for hyperglycemia in these 2 studies**. These findings are entirely consistent with the literature, i.e. in most patients, rhGH treatment increases circulating levels of insulin but not glucose (26). In some patients, however, treatment with rhGH has resulted in glucose intolerance, i.e. impaired glucose tolerance/impaired fasting glucose and overt diabetes mellitus; Cutfield et al recently reported that the incidence of type 2 diabetes mellitus in rhGH-treated children was 6 fold greater than that in age-matched normal children (52). von Pareren et al have reported improvement of insulin resistance/carbohydrate tolerance (and for that matter hypertension), when multiyear rhGH treatment was discontinued in TS children (53). However, it should be noted that there is no long-term data regarding rhGH exposure and the lifetime risk of diabetes mellitus in any population of children, including TS girls (5).

In that 1) treatment with rhGH can result in overt diabetes mellitus/impaired glucose tolerance in some patients; and 2) TS patients are inherently prone to develop type 2 diabetes mellitus (5), TS patients should be monitored extremely carefully for evidence of overt diabetes mellitus and any other form of glucose intolerance after treatment with rhGH is initiated.

Analyses of TS vs. non-TS AEs in the sponsor's Early Alert Safety Databases (ARGUS currently, and NovAlert in the past):

Considering data from both analyses together:

BIH, epiphysiolysis/SCFE, diabetes mellitus, systemic hypertension and otitis media were all reported ≥3 times as often in TS patients (vs. non-TS patients):

- **TS patients are known to have abnormalities of lymphatic drainage (5) which may inherently predispose them to the development of BIH, and BIH is a labeled adverse event associated with rhGH treatment**
- **TS is characterized by generalized skeletal dysplasia (5) which may inherently predispose them to the development of SCFE, and SCFE is a labeled adverse event associated with rhGH treatment.**
- **It is well known that TS patients are predisposed to diabetes mellitus (type 2) and systemic hypertension (5), and treatment with rhGH can result in glucose intolerance (labeled) and potentially could result in hypertension (i.e., rhGH-induced salt retention) (unlabeled).**
- **TS patients are inherently predisposed to recurrent otitis media** (small, dysfunctional eustachian tubes and palatal dysfunction), **and rhGH can result in lymphatic/adenoidal hypertrophy which could aggravate a propensity for otitis media (unlabeled).** In

addition, it has been reported that otitis media occurred or worsened in a greater number of TS patients receiving rhGH (vs. no rhGH) (5, 26).

- **Therefore, all of these observations are not at all surprising. However, it is important to note that the denominators used to calculate the reporting rates in the TS cohorts were relatively small, so that a relatively small number of AEs in the numerator was able to generate a reporting rate percentage ≥3 times that observed in TS cases, i.e. much more data will need to be accrued to validate the observations described above.**

Scoliosis is another disease entity that TS patients are inherently prone to develop; in addition, it is well known and **labeled** that treatment with rhGH resulting in rapid growth can aggravate preexisting scoliosis. Nonetheless, scoliosis was reported in less than 3% of the patients in the NovAlert database (and in only 1 TS patient in the ARGUS database).

Finally, the analyses of the ARGUS and NovAlert databases shed no light on the **absence of long-term data regarding rhGH exposure on cardiovascular status, especially aortic root diameter (54).**

7.3.2 Safety Conclusions

- The safety analyses of Studies 055 and 092 were satisfactory. Respiratory infections were the most common AEs. There was an ~12% incidence of otitis media in Study 092. **In that rhGH may induce lymphatic/adenoidal hypertrophy, and TS patients are inherently predisposed to recurrent otitis media, it is possible that Genotropin contributed to the incidence of otitis media in this study. It is not at all surprising that joint pain/arthralgia was the most frequent treatment-related AE reported in Study 055 (an expected consequence of rhGH-induced fluid retention).**

- During Studies 055 and 092, glucose tolerance remained essentially normal and no patient developed overt diabetes mellitus. However, as has been observed in previous studies, treatment with Genotropin did result in progressive elevation of median insulin levels, which remained within the normal range. **In that 1) treatment with rhGH can result in overt diabetes mellitus/impaired glucose tolerance in some patients; and 2) TS patients are inherently prone to develop type 2 diabetes mellitus (5), TS patients should be monitored extremely carefully for evidence of overt diabetes mellitus and any other form of glucose intolerance after treatment with rhGH is initiated.**

- The analyses of TS vs. non-TS AEs in the sponsor's Early Alert Safety Databases (ARGUS and NovAlert) (including SAEs from KIGS) reveals:

  BIH, epiphysiolysis/SCFE, diabetes mellitus, systemic hypertension and otitis media were all reported ≥3 times as often in TS patients (vs. non-TS patients). Given the inherent predisposition of TS children definitely for 3, and probably for 2, of these AEs, and the fact that rhGH is labeled for 3 of these AEs and potentially could cause the other 2, these observations are not at all surprising.

However, it is important to note that the denominators used to calculate the reporting rates in the TS cohorts were relatively small, so that a relatively small number of AEs in the numerator was able to generate a reporting rate percentage ≥3 times that observed in TS cases, i.e. much more data will need to be accrued to validate the observations described above.

- **Genotropin is generally well tolerated in patients with TS.**

7.3.3 Safety Recommendations

- No additional safety data is required to obtain approval.
- In that 1) TS patients are inherently prone to develop type 2 diabetes mellitus, scoliosis, hypertension and otitis media, and may be more prone to develop SCFE and BIH; 2) type 2 diabetes mellitus, aggravation of preexisting scoliosis, SCFE and BIH are currently labeled potential AEs associated with rhGH treatment, and hypertension (via rhGH-induced salt retention) and otitis media (related to rhGH-induced adenoidal hypertrophy) are plausible AEs of rhGH (though currently unlabeled); and 3) a comparison of the **reporting rates** of AEs in TS patients vs. non-TS patients treated with Genotropin reported to the sponsor's Early Alert Safety Databases (ARGUS and NovAlert [including SAEs from KIGS and ongoing clinical studies]) revealed that SCFE, BIH, diabetes mellitus, hypertension and otitis media occurred ≥3 times as often in TS patients compared with non-TS patients, **the Division recommends that the sponsor add an additional section to its annual PSUR wherein the incidence of all AEs (in particular the 6 listed above) are compared in TS patients and non-TS patients treated with Genotropin.** See Section 1.2.3 in the **EXECUTIVE SUMMARY**.
- No edits were required for the sponsor's proposed additions to the Precautions, and Adverse Reactions sections.
- In the very near future, Pfizer (as well as the other 5 sponsors approved to market rhGH) will be requested to make a number of class labeling changes. Amongst these changes will be language in the Precautions section indicating **"glucose levels should be monitored periodically in all patients treated with somatropin, especially in those with risk factors for diabetes mellitus, such as obesity (including obese patients with PWS), Turner syndrome, or a family history of diabetes mellitus."**

9 OVERALL ASSESSMENT

9.1 Conclusions

9.1.1 Efficacy Conclusions

See Efficacy Conclusions in the Executive Summary.

9.1.2 Safety Conclusions

See Safety Conclusions in the Executive Summary.

9.2 Recommendation on Regulatory Action

APPROVAL

9.2.1 Efficacy Recommendations

See Efficacy Recommendations in the Executive Summary.

9.2.2 Safety Recommendations

See Safety Recommendations in the Executive Summary.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

None.

9.3.2 Required Phase 4 Commitments

None.

9.3.3 Other Phase 4 Requests

See Other Phase 4 Requests in the Executive Summary.

9.4 Labeling Review

The sponsor proposed additions to the Package Insert in 5 places: Clinical Studies section, Indications and Usage section, General subsection of the Precautions section, Adverse Reactions section, and Dosing and Administration section.

The proposed addition to the Clinical Studies section was edited by the Division and agreed to by the sponsor, as follows:

Pediatric Patients with Turner Syndrome (TS)

Two randomized, open-label, clinical trials were conducted that evaluated the efficacy and safety of GENOTROPIN in Turner Syndrome patients with short stature. Turner Syndrome patients were treated with GENOTROPIN alone or GENOTROPIN plus adjunctive hormonal therapy (ethinyl estradiol or oxandrolone). A total of 38 patients were treated with GENOTROPIN alone in the two studies. In Study 055, 22 patients were treated for 12 months, and in Study 092, 16 patients were treated for 12 months. Patients received GENOTROPIN at a dose between 0.13 to 0.33 mg/kg/week.

SDS for height velocity and height are expressed using either the Tanner (Study 055) or Sempe (Study 092) standards for age-matched normal children as well as the Ranke standard (both studies) for age-matched, untreated Turner Syndrome patients. As seen in Table 5, height velocity SDS and height SDS values were smaller at baseline and after treatment with Genotropin when the normative standards were utilized as opposed to the Turner Syndrome standard.

Both studies demonstrated statistically significant increases from baseline in all of the linear growth variables (i.e., mean height velocity, height velocity SDS, and height SDS) after treatment with Genotropin (see Table 5). The linear growth response was greater in Study 055 wherein patients were treated with a larger dose of Genotropin.

Table 5. Growth Parameters (mean ± SD) after 12 Months of Treatment with Genotropin in Pediatric Patients with Turner Syndrome in Two Open Label Studies

	Genotropin 0.33 mg/kg/week (Study 055^ n=22)	Genotropin 0.13-0.23 mg/kg/week (Study 092# n=16)
Height velocity (cm/yr)		
Baseline	4.1 ± 1.5	3.9 ± 1.0
Month 12	7.8 ± 1.6	6.1 ± 0.9
Change from baseline (95% CI)	3.7 (3.0, 4.3)	2.2 (1.5, 2.9)
Height Velocity SDS (Tanner^/Sempe# Standards)	(n=20)	
Baseline	-2.3 ± 1.4	-1.6 ± 0.6
Month 12	2.2 ± 2.3	0.7 ± 1.3
Change from baseline (95% CI)	4.6 (3.5, 5.6)	2.2 (1.4, 3.0)
Height Velocity SDS (Ranke Standard)		
Baseline	-0.1 ± 1.2	-0.4 ± 0.6
Month 12	4.2 ± 1.2	2.3 ± 1.2
Change from baseline (95% CI)	4.3 (3.5, 5.0)	2.7 (1.8, 3.5)
Height SDS (Tanner^/Sempe# Standards)		
Baseline	-3.1 ± 1.0	-3.2 ± 1.0
Month 12	-2.7 ± 1.1	-2.9 ± 1.0
Change from baseline (95% CI)	0.4 (0.3, 0.6)	0.3 (0.1, 0.4)
Height SDS (Ranke Standard)		
Baseline	-0.2 ± 0.8	-0.3 ± 0.8
Month 12	0.6 ± 0.9	0.1 ± 0.8
Change from baseline (95% CI)	0.8 (0.7, 0.9)	0.5 (0.4, 0.5)

SDS = Standard Deviation Score
Ranke standard based on age-matched, untreated Turner Syndrome patients
Tanner^/Sempe# standards based on age-matched normal children
$P<0.05$ for all changes from baseline

The proposed addition to the Indications and Usage section was agreed to by the Division, as follows:

Long-term treatment of growth failure associated with Turner Syndrome in patients who have open epiphyses.

The proposed addition to the General subsection of the Precautions section was agreed to by the Division, as follows:

Treatment with GENOTROPIN Lyophilized Powder, as with other growth hormone preparations, should be directed by physicians who are experienced in the diagnosis and management of patients with GHD, Prader-Willi syndrome (PWS), Turner Syndrome (TS) or those who were born small for gestational age (SGA).

The proposed addition to the Adverse Reactions section was agreed to by the Division, as follows:

In two clinical studies with GENOTROPIN in pediatric patients with Turner Syndrome, the most frequently reported adverse events were respiratory illnesses (influenza, tonsillitis, otitis, sinusitis), joint pain and urinary tract infection. The only treatment-related adverse event that occurred in more than 1 patient was joint pain.

The proposed addition to the Dosing and Administration section was agreed to by the Division, as follows:

Pediatric TS Patients: Generally, a dose of 0.33 mg/kg body weight/week is recommended.

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