CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-280/S-031

STATISTICAL REVIEW(S)

Statistical Review and Evaluation
Clinical Studies

NDA#:	20-280/SE1-031/Priority
APPLICANT:	Pharmacia and Upjohn Company.
NAME OF DRUG:	Genotropin (somatropin [rDNA origin]) for injection
INDICATION:	Treatment of Growth Deficiency in children small for their gestational age
DOCUMENTS REVIEW:	Volumes 1.1-1.41 and SAS data dated January 25, 2001. Volume dated March 21,2001.

This review pertains to four untreated-control studies of Genotropin in children small for their gestational age.

The medical officers for this submission were R. Perlstein and S. Malozowski, M.D. (HFD-510), with whom this review was discussed.

I. Background

Genotropin is an approved growth hormone. This submission covers its use in children small for their gestational age but not having growth hormone deficiency.

These studies had a two-year untreated control phase and an uncontrolled continuation phase. This review will not discuss the uncontrolled data except to say that the uncontrolled data showed that patients continuing on Genotropin maintained their height SDS up to 6 years on treatment.

II. Study CTN 89-041 (France)

A. Study Description and Method of Analysis

This was a randomized, parallel group, no treatment control study comparing Genotropin 0.033 mg/kg/day, Genotropin 0.067 mg/kg/day, and no treatment in children small for their gestational age. The children at screening had to have a height SDS<-2.0 for their chronological age and gender. The height velocity SDS at screening had to be less than 0 during the 12-month observation period before inclusion into the study. The birth length SDS had to be below –2. The children could not be GH deficient. (They had to have a GH level at least 10 mg/ml during a provocation test.)

The randomization scheme assigned half as many patients to the untreated group as to each of the active treatments. Sealed envelopes from the randomization, stored at Pharmacia & Upjohn, France, were opened in consecutive order by the clinical monitor (the date of randomization and initials were to be written on the envelope at the opening). The responsible investigator was then informed of the study group allocation.

After one year the untreated children could choose to start Genotropin treatment or remain untreated. [This was unique to this study.]

The primary efficacy variable in the study report was height velocity SDS [(height velocity-mean)/SD] where mean and SD are expected mean and standard deviation of height for the patient's age and sex. {The protocol for this study stated that height velocity not height velocity SDS was the primary variable but height velocity SDS was analyzed to be consistent with the other studies in the submission.} The protocol did not specify the time period that was primary or how missing values would be handled. The sponsor analyzed height velocity SDS from months 0 to 12 and height velocity SDS from months 12 to 24. The sponsor did a Bonferroni correction for the yearly analyses and used Dunnett's multiple comparison procedure within each yearly analysis to compare the two Genotropin doses with the untreated group. The sponsor assigned usually a value of 0 if the 12-month or 24-month value was missing. A value of –3 was assigned at month 24 if there was indication the patient was off Genotropin treatment because the sponsor stated that growth usually slows if the patient doesn't continue treatment after a year.

Patients completing the first 24 months without major protocol deviations were included in the PP 0-24 population. The sponsor analyzed changes from baseline in both height SDS and parental adjusted height SDS at 24 months using the per protocol population. The sponsor's p-values are from a t-test using only the two treatments tested.

B. Results

A total of 140 patients (60 on Genotropin 0.033 mg/kg/day, 52 on Genotropin 0.067 mg/kg/day and 28 untreated) started the study at 22 centers. Three patients (1 on Genotropin 0.033 mg/kg/day, 1 on Genotropin 0.067 mg/kg/day and 1 untreated) failed to complete the first year. An additional 7 patients (4 on Genotropin 0.033 mg/kg/day and 3 on Genotropin 0.067 mg/kg/day) did not continue into the second year. Two additional patients on Genotropin 0.033 mg/kg/day withdrew during the second year. The per protocol 0-24 month population included 108 patients (43 on Genotropin 0.033 mg/kg/day, 42 on Genotropin 0.067 mg/kg/day, 9 untreated for the full two years and 14 patients untreated for only one year).

The treatment groups were not comparable at baseline in mean age and height with the Genotropin 0.067 mg/kg/day group being older and of greater height. These differences are not too important since this group's height SDS and growth velocity were comparable.

Table 1 provides the results of the analysis of the three treatment groups for the first year of treatment. Both Genotropin groups were significantly different in height velocity SDS during that year. The higher dose gave significantly more growth than the lower dose.

Table 1. Effects of Genotropin on height velocity SDS during first 12 months. ITT population.

Treatment group	Pretreatment N Mean (SD)	Month 0-12 N Mean (SD)
0.033 mg/kg/day	60 -1.3 (1.5)	60 2.6 (1.6)
0.067 mg/kg/day	52 -1.3 (1.0)	52 4.1 (1.9)
Untreated	28 -1.1 (0.8)	28 -0.4 (1.4)
Primary analysis (Dunnett's test)*:		
0.033 mg/kg/day vs. untreated		p=0.0001 S
0.067 mg/kg/day vs. untreated		p=0.0001 S
Sec. Analysis (Student's t-test):		
0.067mg/kg/day vs. 0.033 mg/kg/day		p=0.0001

* The p-values in the tables are not adjusted for multiple comparisons. The "S" implies statistical significance even after corrections for multiple comparisons.

Table 2 below provides the results of the analysis of the treatment groups during the second year. There are more treatment groups in this analysis because some of the untreated patients were randomized to Genotropin during the second year. Only the higher dose group was significantly different (after adjusting for multiple comparisons and Bonferroni adjustment) in height velocity SDS during that year compared to the untreated group. The higher dose gave significantly more growth than the lower dose. The untreated patients who were switched to Genotropin during the second year showed more growth during their first year of Genotropin treatment than the Genotropin patients in their second year of treatment.

Table 2. Effects of Genotropin on height velocity SDS during 24 months of treatment. ITT population.

Treatment group	Pretreatment N Mean (SD)	Month 0-12 N Mean (SD)	Month 12-24 N Mean (SD)
0.033 mg/kg/day	60 -1.3 (1.5)	60 2.6 (1.6)	60 0.8 (1.7)
0.067 mg/kg/day	52 -1.3 (1.0)	52 4.1 (1.9)	52 1.8 (1.9)
Untreated/0.033 mg/kg/day	9 -1.0 (0.8)	9 -0.9 (0.7)	9 2.6 (2.0)
Untreated/0.067 mg/kg/day	8 -1.5 (0.6)	8 -0.8 (1.4)	8 3.4 (1.4)
Untreated	11 -0.8 (0.7)	11 0.2 (1.6)	11 -0.6 (1.1)
Primary analysis (Dunnett's test)*:			
0.033 mg/kg/day vs. untreated			p=0.0164 NS
0.067 mg/kg/day vs. untreated			p=0.0001 S
Sec. Analysis (Student's t-test):			
0.067mg/kg/day vs. 0.033 mg/kg/day			p=0.0015

* The p-values in the tables are not adjusted for multiple comparisons. The "S" implies statistical significance even after corrections for multiple comparisons.

Although the comparison of Genotropin 0.033 mg/kg/day and untreated was not significant at month 24 (because of multiple comparison correction), it was significant at Month 12 because of the larger increase in growth velocity during the first year compared to the second year.

Table 14 of the sponsor (Volume 2, page 97) presents the results of the analysis of changes from baseline for height SDS at 24 months in the per protocol population. This

analysis showed each dose of Genotropin significantly better than no treatment with the larger dose more effective than the lower dose.

Table 14. Height SDS Values at Baseline and Month 24 - PP 0-24 Population

Treatment Group	Baseline Mean (SD)	Month 24 Mean (SD)	Change From Baseline to Month 24 Mean (SD)
Untreated (N = 9)	-2.5 (0.4)	-2.3 (0.5)	0.2 (0.3)
Somatropin 0.033 mg/kg/day (N = 43)	-3.0 (0.7)	-2.0 (0.8)	1.1 (0.4)
Somatropin 0.067 mg/kg/day (N = 42)	-3.0 (0.7)	-1.7 (0.8)	1.3 (0.5)
Untreated / 0.033 mg/kg/day (N = 8)	-3.0 (0.6)	-2.3 (0.5)	0.7 (0.3)
Untreated / 0.067 mg/kg/day (N = 6)	-3.4 (1.5)	-2.4 (1.7)	1.0 (0.4)
			P-value*
0.033 mg/kg/day vs untreated 0.067 mg/kg/day vs untreated 0.033 mg/kg/day vs 0.067 mg/kg/day			0.0001 0.0001 0.0016

* Student t test; significance defined as $p \leq 0.05$.
Abbreviations: SDS = standard deviation score, PP = per protocol

C. Reviewer's Comments

The sponsor has demonstrated that Genotropin has increased height velocity SDS compared to placebo in the study population. This reviewer verified the sponsor's analyses from the data sets provided.

The protocol did not specify the time frames for the analyses. Since some of the untreated group took Genotropin during the second year, the sponsor's analysis of separate analyses for year one and two seems appropriate. Since the data indicates that the first year on Genotropin gives greater growth than the second year, it furnishes another reason for separate yearly analyses. The sponsor's Bonferroni adjustment for year one and year two analyses and then doing Dunnett's test for multiple comparisons within the yearly analyses is acceptable from a statistical perspective but may be too conservative.

This reviewer analyzed height velocity during the first year and got significant results. The sponsor's argument for using height velocity SDS for consistency with the other studies rather than height velocity is therefore reasonable and was not done because the original protocol specified analyses would fail to show significance.

The sponsor's handling of missing values for the primary efficacy analysis for the ITT population seems reasonable. The protocol did not specify how missing values would be handled. The method chosen by the sponsor, if anything, seems to bias the analysis in favor of the untreated group.

This reviewer investigated whether there was a relationship between the height velocity at one year and two years in the two groups given Genotropin and the level of growth hormone at testing during screening. Because more than one type of test could be used, this reviewer did two analyses. One of the analyses used only the test having the most usage. The other analysis used the lowest assessment of growth hormone irrespective of which type of test was used. No significant relationship between height velocity under treatment and group hormone level at baseline was seen in either analysis.

The protocol did not specify how the per protocol analyses would be analyzed. Since changes from baseline were analyzed in each study and in most studies similar results would be obtained in analyzing the values themselves as was obtained from analyzing changes from baseline, this is not a critical issue.

This reviewer noticed that the analysis of changes from baseline in parental adjusted height SDS and changes from baseline in height SDS are similar because the values were identical except for rounding and, in a few cases, parental adjusted height SDS was not defined. Therefore, this review has not given the results of changes in parental adjusted height SDS.

This reviewer noticed that the randomization packets were not used in sequential order. This was true of all treatments and not just the untreated group. The sponsor in their March 21,2001 submission stated that randomization numbers were given between the initial visit and baseline visit. Thus, there was no direct relationship between the randomization numbers and baseline dates.

III. Study CTN 90-079 (Germany)

A. Study Description and Method of Analysis

This study was similar to study CTN 89-041 during the first two years with the exception that no patient in the untreated group was allowed to switch to Genotropin at the end of the first year.

The randomization was (4: 5: 5) in this study, where the untreated group had the fewest patients. Sealed envelopes from the randomization, stored at Pharmacia & Upjohn, Germany, were opened, signed and dated in consecutive order by the clinical monitor.

The coordinating investigator and the responsible investigator were then informed of the study group allocation.

B. Results

A total of 69 patients (24 on Genotropin 0.033 mg/kg/day, 25 on Genotropin 0.067 mg/kg/day and 20 untreated) started the study at 25 centers. An additional 4 patients were randomized but never entered the study. Twelve patients (4 on Genotropin 0.033 mg/kg/day, 6 on Genotropin 0.067 mg/kg/day and 2 untreated) failed to complete 24 months. The per protocol 0-24 month population included 42 patients (17 on Genotropin 0.033 mg/kg/day, 16 on Genotropin 0.067 mg/kg/day, 9 untreated).

The treatment groups were comparable at baseline in demographic and baseline efficacy variables.

Table 3 provides the results of the analysis of the three treatment groups for the first and second year of treatment. Both Genotropin groups were significantly different in height velocity SDS during the first year. The higher dose gave significantly more growth than the lower dose during that year. During the second year only the higher dose was significantly different from placebo after adjusting for multiple testing.

Table 3. Effects of Genotropin on height velocity SDS during 24 months of treatment.

ITT population.

Treatment group	Pretreatment N Mean (SD)	Month 0-12 N Mean (SD)	Month 12-24 N Mean (SD)
0.033 mg/kg/day	23 -0.9 (1.4)	24 2.5 (2.3)	24 1.0 (2.4)
0.067 mg/kg/day	25 -1.3 (1.5)	25 4.4 (2.9)	25 1.9 (2.6)
Untreated	16 -1.5 (1.7)	20 -0.8 (1.2)	20 -0.4 (0.8)
Primary analysis (Dunnett's test)*:			
0.033 vs. untreated		p=0.0001 S	p=0.0233 NS
0.067 vs. untreated		p=0.0001 S	p=0.0004 S
Sec. Analysis (Student's t-test):			
0.067 mg/kg/day vs. 0.033 mg/kg/day		P=0.0059	P=0.1540

* The p-values in the tables are not adjusted for multiple comparisons. The "S" implies statistical significance even after corrections for multiple comparisons.

Table 13 of the sponsor (Volume 17, page 51) presents the results of the analysis of changes from baseline in height SDS at 24 months in the per protocol population. This analysis showed each dose of Genotropin significantly better than no treatment with the larger dose more effective than the lower dose.

Table 13. Height SDS Values After 24 Months of Treatment - PP 0-24 Population

Treatment Group	Baseline Mean (SD)	Month 24 Mean (SD)	Change From Baseline to Month 24 Mean (SD)
Untreated (N = 9)	-3.6 (1.1)	-3.5 (1.1)	0.1 (0.3)
Somatropin 0.033 mg/kg/day (N = 17)	-3.2 (0.7)	-2.1 (0.6)	1.1 (0.6)
Somatropin 0.067 mg/kg/day (N = 16)	-4.5 (1.4)	-2.5 (1.4)	2.0 (0.7)
			P-value*
0.033 mg/kg/day vs untreated 0.067 mg/kg/day vs untreated 0.033 mg/kg/day vs 0.067 mg/kg/day			0.0001 0.0001 0.0004

* Student t test; significance defined as $p \leq 0.05$.
Abbreviations: PP = per protocol, SDS = standard deviation score

C. Reviewer's Comments

Although the comparison of Genotropin 0.033 mg/kg/day and untreated for height velocity SDS in the ITT population was not significant at month 24 (because of multiple comparison correction), it was significant at Month 12 because of the larger increase in growth velocity during the first year compared to the second year.

IV. Study CTN 89-070/89-071 (Sweden, Denmark, Norway, Finland)

A. Study Description and Method of Analysis

This study was similar to study CTN 89-041 during the first two years with the exception that no patient in the untreated group was allowed to switch to Genotropin at the end of the first year.

This study was a pooling of Studies CTN 89-070, which excluded patients with growth - related syndromes, and CTN 89-071, which included patients only with Silver-Russell syndrome. Only ten patients (3 untreated, 6 on Genotropin 0.033 mg/kg/day, and 1 on Genotropin 0.067 mg/kg/day) had Silver-Russell syndrome.

Randomization was done within 2 age strata: younger than 4 years 7 months, and 4 years 7 months and older. The randomization scheme was somewhat complex. It was (1: 2: 2) among Silver-Russell patients and (10:14:14) otherwise where fewer patients were in the

untreated groups. Sealed envelopes from the randomization, stored at Pharmacia & Upjohn, Stockholm, were opened, signed and dated in consecutive order. The coordinating investigator received information about the study group allocation and subsequently informed the different centers.

B. Results

There were 56 patients who started the trial at 23 centers in Sweden, Denmark, Norway and Finland. Six additional patients were randomized but did not start the study and are not included in the ITT population. Three patients (1 on Genotropin 0.067 mg/kg/day and 2 untreated) failed to complete 24 months. The per protocol 0-24 month population included 45 patients (16 on Genotropin 0.033 mg/kg/day, 18 on Genotropin 0.067 mg/kg/day, 11 untreated).

The ITT treatment groups were comparable at baseline in demographic and baseline height velocity SDS.

Table 4 provides the results of the analysis of the three treatment groups for the first and second year of treatment. Both Genotropin groups were significantly different in height velocity SDS during both years. The higher dose gave significantly more growth than the lower dose during both years.

Table 4. Effects of Genotropin on height velocity SDS during 2 years of treatment. ITT population.

Treatment group	Pretreatment N Mean (SD)	Month 0-12 N Mean (SD)	Month 12-24 N Mean (SD)
0.033 mg/kg/day	21 -1.4 (0.9)	21 2.4 (1.7)	21 0.9 (1.6)
0.067 mg/kg/day	20 -1.0 (0.9)	20 4.3 (1.6)	20 2.3 (1.9)
Untreated	15 -1.0 (1.0)	15 -1.1 (0.9)	15 -1.2 (0.8)
Primary analysis (Dunnett's test):			
0.033 mg/kg/day vs. untreated		p=0.0001 S	p=0.0002 S
0.067 mg/kg/day vs. untreated		p=0.0001 S	p=0.0001 S
Sec. Analysis (Student's t-test):			
0.067 mg/kg/day vs .0.033 mg/kg/day		p=0.0002	P=0.0044

* The p-values in the tables are not adjusted for multiple comparisons. The "S" implies statistical significance even after corrections for multiple comparisons.

Table 13 (Volume 14, page 49) of the sponsor presents the results of the analysis of height SDS at 24 months for the per protocol population. This analysis showed each dose of Genotropin significantly better than no treatment with the larger dose more effective than the lower dose.

Table 13 Height SDS Values After 24 Months of Treatment – PP 0-24 Population

	Baseline Mean (SD)	Month 24 Mean (SD)	Change From Baseline to Month 24 Mean (SD)
Untreated (N = 11)	-2.9 (0.5)	-2.9 (0.4)	0.1 (0.2)
Somatropin 0.033 mg/kg/day (N = 16)	-3.5 (0.8)	-2.0 (1.0)	1.5 (0.5)
Somatropin 0.067 mg/kg/day (N = 18)	-3.1 (0.8)	-1.2 (0.8)	1.9 (0.4)
			P-value*
0.033 mg/kg/day vs untreated 0.067 mg/kg/day vs untreated 0.067 mg/kg/day vs 0.033 mg/kg/day			<0.0001 <0.0001 0.0161

* Student t test, significance defined as $p \leq 0.05$
Abbreviations: PP = per protocol, SDS = standard deviation score

V. CTN 90-080 (Belgium)

A. Study Description and Method of Analysis

This study was similar to study CTN 89-041 during the first two years with the exceptions that no patient in the untreated group was allowed to switch to Genotropin at the end of the first year, and the doses of Genotropin studied were 0.067 mg/kg/day and 0.10 mg/kg/day.

The randomization scheme was (2: 3: 3) with the untreated group having fewer patients. Sealed envelopes from the randomization, stored at Pharmacia & Upjohn, Stockholm, were opened, signed and dated in consecutive order. Information about the randomization was sent to the Pharmacia & Upjohn Market Company in Belgium. The principal investigator received information about the study group allocation from the Market Company and subsequently informed the different centers.

B. Results

There were 54 patients who started the trial at 8 centers in Belgium. Two additional patients were randomized but did not start the study and are not included in the ITT population. Two patients (1 on Genotropin 0.067 mg/kg/day, 1 on Genotropin 0.10 mg/kg/day) failed to complete 24 months. The per protocol 0-24 month population

included 46 patients (17 on Genotropin 0.067 mg/kg/day, 18 on Genotropin 0.1 mg/kg/day, 11 untreated).

The ITT treatment groups were comparable at baseline in demographic and baseline height velocity SDS.

Table 5 provides the results of the analysis of the three treatment groups for the first and second year of treatment. Both Genotropin groups were significantly different in height velocity SDS during both years. The higher dose gave significantly more growth than the lower dose during the second year but not the first.

Table 5. Effects of Genotropin on height velocity SDS during 24 months of treatment. ITT population.

Treatment group	Pretreatment N Mean (SD)	Month 0-12 N Mean (SD)	Month 12-24 N Mean (SD)
0.1 mg/kg/day	19 -0.8 (1.2)	19 5.8 (2.0)	19 4.3 (1.7)
0.067 mg/kg/day	20 -0.9 (0.9)	20 5.3 (1.5)	20 2.7 (1.7)
Untreated	13 -0.6 (1.0)	13 -1.1 (0.9)	13 -0.7 (1.3)
Primary analysis (Dunnett's test)*: 0.1 mg/kg/day vs. untreated		p=0.0001 S	p=0.0001 S
0.067 mg/kg/day vs. untreated		p=0.0001 S	p=0.0001 S
Sec. Analysis (Student's t-test):			
0.1 mg/kg/day vs. 0.067 mg/kg/day		p=0.3318	p=0.0033

*The p-values in the tables are not adjusted for multiple comparisons. The "S" implies statistical significance even after correction for multiple comparisons.

The sponsor stated in the study report that an interim analysis was to be performed when all patients had completed the 12-month visit. The sponsor's method of analysis (using a 0.025 significance level to test year 1 and year 2 results) adequately adjusts for this interim analysis, even though no formal adjustment was specified.

Table 12 of the sponsor (Volume 25, page 52) presents the results of the analysis of changes from baseline in height SDS at 24 months in the per protocol population. This analysis showed each dose of Genotropin significantly better than no treatment. The higher dose was not significantly more effective than the lower dose.

Table 12. Height SDS Values After 24 Months of Treatment - PP 0-24 Population

Treatment Group	Baseline Mean (SD)	Month 24 Mean (SD)	Change From Baseline to Month 24 Mean (SD)
Untreated (N = 11)	-3.3 (1.0)	-3.1 (1.1)	0.2 (0.3)
Somatropin 0.067 mg/kg/day (N = 17)	-3.6 (0.8)	-1.4 (0.7)	2.2 (0.6)
Somatropin 0.1 mg/kg/day (N = 18)	-3.7 (0.8)	-1.1 (0.8)	2.6 (0.7)
			P-value*
0.067 mg/kg/day vs untreated 0.1 mg/kg/day vs untreated 0.1 mg/kg/day vs 0.067 mg/kg/day			0.0001 0.0001 0.1100

* Student t test; significance defined as $p \leq 0.05$.
Abbreviations: PP = per protocol, SDS = standard deviation score

VI. Overall Conclusions

This reviewer duplicated the sponsor's analyses of Height Velocity SDS for the ITT population and changes from baseline in Height SDS for the per protocol population from the data files provided. Most analyses showed both doses to be effective with the larger doses more effective than the lower doses. Some of the lack of significance was attributable to the conservative multiple comparison procedures used.

James R. Gebert, Ph.D.
Mathematical Statistician HFD-715

Concur: Dr. Sahlroot

Dr. Nevius

This review contains 12 pages of text.
cc:
Archival NDA 20-280/SE1-031
HFD-510
HFD-510/Dr. Malozowski
HFD-510/Dr. Perlstein

Addendum to Statistical Review
Clinical Studies

NDA#: 20-280/SE1-031/Priority
APPLICANT: Pharmacia and Upjohn Company
NAME OF DRUG: Genotropin (somatropin [rDNA origin]) for injection
INDICATION: Treatment of Growth Deficiency in children small for their gestational age
DOCUMENTS REVIEWED: Amendment and datasets dated June 19, 2001 and amendment dated July 3, 2001.

This reviewer was informed by the Division of Scientific Investigations that its investigations for this submission were satisfactory. They informed me, however, that they could not check height velocity SDS values, the primary efficacy measure, because these were centrally calculated. This reviewer requested information on how height velocity SDS was calculated by the sponsor in a May 30, 2001 information request. The method used was provided in the sponsor's June 19, 2001 submission. In reviewing that submission this reviewer found that the values were calculated correctly except for studies 89-070/071 and 90-080/98-8122-011. In those studies a table from was incorrectly used. The sponsor had used the lower age of an age range (e.g. 6 for ages 6-7) to extrapolate height velocity SDS values. Elsewhere, the mid-range (e.g. 6.5 for ages 6-7) was used in the calculations for similar tables in the other studies. The sponsor agreed that the table had been incorrectly used and recalculated the analyses of height velocity SDS in those studies. Tables 4 and 5 of this review are the corrected tables for Tables 4 and 5 for the Statistical Review of March 21, 2001. These results differed only slightly from the original tables and do not change the conclusions of that review that Genotropin showed efficacy in all four studies for changes from baseline in height velocity SDS.

Corrected Table 4. Effects of Genotropin on height velocity SDS during 2 years of treatment. ITT population. Nordic Study 89-070/071

Treatment group	Pretreatment N Mean (SD)	Month 0-12 N Mean (SD)	Month 12-24 N Mean (SD)
0.033 mg/kg/day	21 -1.4 (0.9)	21 2.6 (1.7)	21 1.2 (1.6)
0.067 mg/kg/day	20 -0.9 (0.9)	20 4.5 (1.8)	20 2.6 (1.9)
Untreated	15 -0.8 (1.0)	15 -0.9 (0.9)	15 -1.1 (0.7)
Primary analysis (Dunnett's test):			
0.033 mg/kg/day vs. untreated		p=0.0001 S	p=0.0001 S
0.067 mg/kg/day vs. untreated		p=0.0001 S	p=0.0001 S
Sec. Analysis (Student's t-test):			
0.067 mg/kg/day vs .0.033 mg/kg/day		p=0.0003	P=0.0049

* The p-values in the tables are not adjusted for multiple comparisons. The "S" implies statistical significance even after corrections for multiple comparisons.

Corrected Table 5. Effects of Genotropin on height velocity SDS during 24 months of treatment. ITT population. Belgium Study 90-080/98-8122-011

Treatment group	Pretreatment N Mean (SD)	Month 0-12 N Mean (SD)	Month 12-24 N Mean (SD)
0.1 mg/kg/day	19 -0.7 (1.2)	19 6.1 (2.2)	19 4.5 (1.7)
0.067 mg/kg/day	20 -0.8 (0.8)	20 5.6 (1.6)	20 2.8 (1.8)
Untreated	13 -0.5 (1.0)	13 -1.0 (0.8)	13 -0.6 (1.3)
Primary analysis (Dunnett's test)*: 0.1 mg/kg/day vs. untreated		p=0.0001 S	p=0.0001 S
0.067 mg/kg/day vs. untreated		p=0.0001 S	p=0.0001 S
Sec. Analysis (Student's t-test):			
0.1 mg/kg/day vs. 0.067 mg/kg/day		p=0.3316	p=0.0031

*The p-values in the tables are not adjusted for multiple comparisons. The "S" implies statistical significance even after correction for multiple comparisons.

This reviewer asked the sponsor whether the height SDS values in the proposed label were affected by a similar error. The sponsor stated in their July 3, 2001 submission that height SDS was calculated correctly.

James R. Gebert, Ph.D.
Mathematical Statistician HFD-715

Concur: Dr. Sahlroot

This review contains 2 pages of text.
cc:
Archival NDA 20-280/SE1-031
HFD-510
HFD-510/Dr. Malozowski
HFD-510/Dr. Perlstein
HFD-510/Ms. King
HFD-700/Dr. Anello
HFD-715/Dr. Gebert
HFD-715/Dr. Nevius
HFD-715/Dr. Sahlroot

Addendum to Statistical Review
Clinical Studies

NDA#:	20-280/SE1-031/Priority
APPLICANT:	Pharmacia and Upjohn Company
NAME OF DRUG:	Genotropin (somatropin [rDNA origin]) for injection
INDICATION:	Treatment of Growth Deficiency in children small for their gestational age

DOCUMENTS REVIEWED: Label dated July 12, 2001

I find the Clinical Studies section of the label of July 12, 2001 pertaining to children born small for gestational age acceptable from a statistical perspective.

James R. Gebert, Ph.D.
Mathematical Statistician HFD-715

cc:
Archival NDA 20-280/SE1-031
HFD-510
HFD-510/Dr. Malozowski
HFD-510/Dr. Perlstein
HFD-510/Ms. King
HFD-700/Dr. Anello
HFD-715/Dr. Gebert
HFD-715/Dr. Nevius
HFD-715/Dr. Sahlroot