Table 3. CTN 89-042 - Months 0-24: Patient Disposition per Treatment Group & Components of ITT/PP Populations

	Untreated	Somatropin Dose (mg/kg/day)		Untreated 1st Year / Somatropin Dose (mg/kg/day) 2nd Year	
		0.033	0.067	0.033	0.067
Randomized patients	30	63	59		
Total withdrawn prior to treatment	2	3	7		
ITT population n=140	**28**	**60**	**52**		
ITT population (during the 2nd year of treatment) n=140	**11•**	**60**	**52**	**9**	**8**
Total withdrawn first year†	1	1	1		
Completed Month 12 visit	27	59	51		
Total withdrawn at Month 12‡	0	4	3		
Entered second year	10	55	48	9	8
Total withdrawn second year§	0	2	0	0	0
Completed Month 24 visit n=128	10	53	48	9	8
Major protocol deviations in completers¶	1	10	6	1	2
PP 0-24 population n=108	**9**	**43**	**42**	**8**	**6**
Total withdrawn at Month 24	**0**	**2**	**4**	**0**	**0**
Continued after Month 24 n=122	**10**	**51**	**44**	**9**	**8**

• Includes 10 patients in the untreated group who entered the second year of the study plus the 1 patient who was withdrawn during the first year of the study.

† 1/3 patients with major protocol violation.

‡ 6/7 patients with major protocol violation.

¶ 20 patients with major protocol violation

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Table 4. CTN 89-041 - Patients with Major Protocol Violations Months 0-24 (n=27)

Major deviation	Treatment group	No of patients
Height SDS_{CA} >-2	n	11
	untreated	1
	0.033	4
	0.067	5
	untreated/0.067	1
HV SDS > 1.0	n	4
	0.033 mg/kg/day	3
	0.067 mg/kg/day	1
Birth length SDS > -2	n	2
	0.033	1
	untreated/0.033	1
Any known syndrome	n	7
	0.033	4
	0.067	2
	untreated/0.067	1
Month 24 missing	n	1
	untreated	1
Treatment stopped prior to Month 24	n	2
	0.033 mg/kg/day	1
	0.067 mg/kg/day	1

Table partially derived from submission

VI.A.5.1.2 Study Periods 0-72 and 24-72 Months

Of the 122 patients who continued on-study after 2 years of therapy, 100 patients completed 6 years on-study and 22 patients discontinued between Months 24 and 72 (most of these 22 patients withdrew informed consent). See Table 5.

Of the 100 patients who completed 6 years on-study, 69 were included in the PP 0-72 month study population. Thirty one patients were not included in the PP 0-72 month study population because of major protocol violations. Twelve of these 31 patients were observed to have major protocol violation(s) between baseline and Month 24 +/- additional protocol violations between Months 24 and 72 (e.g., 2 patients treated with a LHRH agonist); 19 of these patients were found to have a major protocol violation exclusively between Months 24 and 72 (5 patients were treated with a LHRH analog, 13 patients had a missing 72 month visit and 1 patient changed dosages). See Table 6.

Table 5. CTN 89-042 - Months 0-72: Patient Disposition per Treatment Group

	Month 24 to Month 72 Grouping					
	Untreated*	0.033†	0.067‡	Untreated/ Continuous§	Untreated/ Discontinuous¶	Discontinuous#
Continued after Month 24 n=122	**3**	**16**	**13**	**9**	**15**	**66**
ITT population•• n=140	4	25	21	9	15	66
Total withdrawn n=40	2	10	14	2	4	8
Completed Month 72 n=100	2	15	7	7	11	58
Major protocol deviations in completers n=31	0	5	0	3	5	18
PP 0-72 population n=69	**2**	**10**	**7**	**4**	**6**	**40**

* Patients were untreated from baseline to Month 72.

† Patients were treated continuously from baseline to Month 72 with somatropin 0.033 mg/kg/day.

‡ Patients were treated continuously from baseline to Month 72 with somatropin 0.067 mg/kg/day.

§ Patients were untreated from baseline to Month 12 (or from baseline to Month 24) and then treated continuously through Month 72 with somatropin 0.033 or 0.067 mg/kg/day.

¶ Patients were untreated from baseline to Month 12 (or Month 24) and then treated continuously for some period beginning at Month 12 (or Month 24) with either dose of somatropin, but subsequently not continuously treated (includes intermittent treatment, periodic treatment, or complete cessation of treatment) at some time before Month 72.

Patients who were treated continuously from baseline to Month 24 with either dose of somatropin and then not continuously treated (includes intermittent treatment, periodic treatment, or complete cessation of treatment) at some time before Month 72.

•• Includes patients who withdrew from the study early.

Table 6. CTN 89-041 - Patients with Major Protocol Violations Exclusively Between Months 24-72 (n=19)

Period	Deviation	Group	n
Months 24 to 72	Treatment with LHRH analogue	Total	5
		Discontinuous	3
		Untreated / continuous	1
		Untreated / discontinuous	1
	Dose incorrectly changed	Total	1
		Discontinuous	1
	Missing month 72 visit	Total	13
		Discontinuous	10
		Untreated / discontinuous	3

VI.A.5.2 Patient Demographics and Baseline Characteristics

As depicted in Table 7, patients in the ITT population initially randomized to the 3 study arms were very well matched with respect to demographics and baseline characteristics. Children in the 0.067 mg/kg/day treatment group were slightly older and heavier than the patients in the other 2 study groups. Mean CA was ~5-6, BA ~4-5, height SDS_{CA} ~-3.0, previous year HV ~5-5.5 cm/year, previous year HV SDS ~-1.3, and PAH SDS ~-2.0 in the 3 study groups. See Table 7. In addition, mean birth length, birth weight, and gestational age were quite similar for children in the 3 study arms.

Table 7. ISE - Demographics/Baseline Characteristics of ITT Study Population (0-12 Months)

Variable			Untreated N = 11	Somatropin Dose (mg/kg/day)		Untreated 1st year/ Somatropin Dose (mg/kg/day) 2nd year	
				0.033 N = 60	0.067 N = 52	0.033 N = 9	0.067 N = 8
Sex	Male	n (%)	5 (45)	35 (58)	28 (54)	4 (44)	3 (38)
	Female	n (%)	6 (55)	25 (42)	24 (46)	5 (56)	5 (63)
Chronological age (years)		n	11	60	52	9	8
		Mean (SD)	5.4 (1.1)	5.5 (1.4)	6.2 (1.3)	5.9 (1.7)	4.6 (1.1)
		Range					
Bone age (years)		n	10	52	43	8	8
		Mean (SD)	3.9 (1.2)	4.0 (1.3)	4.8 (1.4)	4.4 (1.6)	3.4 (0.9)
		Range					
Weight (kg)		n	11	60	52	9	8
		Mean (SD)	13.5 (2.3)	14.0 (2.4)	14.9 (2.4)	14.3 (3.0)	11.7 (2.8)
		Range					
Height (cm)		n	11	60	52	9	8
		Mean (SD)	99.3 (6.6)	97.3 (8.8)	100.9 (7.2)	99.2 (9.3)	91.0 (8.6)
		Range					
Height SDS		n	11	60	52	9	8
		Mean (SD)	-2.4 (0.5)	-3.0 (0.8)	-2.9 (0.8)	-2.9 (0.5)	-3.4 (1.5)
		Range					
Height SDS for bone age		n	10	52	43	8	8
		Mean (SD)	0.1 (1.7)	-0.9 (1.8)	-1.1 (1.5)	-0.9 (0.9)	-1.4 (1.4)
		Range					
Height velocity (cm/year)		n	11	60	52	9	8
		Mean (SD)	5.7 (0.8)	5.3 (1.5)	5.1 (1.0)	5.4 (0.8)	5.3 (0.8)
		Range					
HV SDS		n	11	60	52	9	8
		Mean (SD)	-0.8 (0.7)	-1.3 (1.5)	-1.3 (1.0)	-1.0 (0.8)	-1.5 (0.6)
		Range					
PAH SDS		n	11	59	50	9	8
		Mean (SD)	-1.6 (1.5)	-2.0 (1.3)	-1.8 (1.0)	-1.8 (0.8)	-2.2 (1.8)
		Range					

VI.A.5.3 Compliance

The Sponsor reports that lack of compliance was not a significant problem during this study. However, compliance could not be properly assessed on the basis of the number of cartridges used by each patient because the original protocol failed to stipulate the return of used vials.

A small number of patients reported missing isolated doses or taking study medication before clinic visits instead of after visits. There were no apparent differences between treatment groups in the incidence of missed doses. Assessment of the validity of this claim is, however, difficult.

VI.A.5.4 Concomitant Therapy

Seven patients were treated with LHRH analog therapy (e.g., [redacted]). Three of these patients had presumed precocious puberty and 4 were treated "prophylactically" for precocious puberty (see ISS). Therapy was initiated after the Month 24 visit in all of these patients. All 7 of these patients were excluded from the PP 0-72 month study population. One patient received intermittent steroid therapy for asthma subsequent to the Month 48 visit.

No patients were receiving [redacted] replacement therapy for hypothyroidism at study initiation. Two patients began thyroid replacement therapy during the study. One patient was begun on [redacted] day 5 years after discontinuing somatropin therapy - thyroid function test results are not available. A second patient was treated between -Month 15 and -Month 19 with [redacted] day for unclear reasons (Free T4 was normal and TSH was unavailable). Other medications used by patients were generally those prescribed to treat pre-existing conditions or routine childhood ailments.

VI.A.5.5 Efficacy Results

VI.A.5.5.1 Primary Efficacy Results

VI.A.5.5.1.1 HV SDS Months 0-12 and Months 12-24

ITT Population (see Table 8)

- During the baseline to Month 12, and Month 12 to Month 24 treatment periods, mean HV SDS values for the 0.067 mg/kg/day treatment group were significantly greater than the values observed in the untreated group. The mean HV SDS for the 0.033 mg/kg/day treatment group was significantly greater than the value observed in the untreated control group only during the baseline to Month 12 treatment period. (Concordantly, after only 12 months of somatropin therapy, the patients in the untreated/0.033 mg/kg/day and untreated/0.067 mg/kg/day treatment groups manifested an increase in linear growth which was comparable to that seen in the 0.033 and 0.067 mg/kg/day groups during their first 12 months of treatment.)

- HV SDS values for the 0.067 mg/kg/day group were significantly greater than those observed for the 0.033 mg/kg/day group during **both** the baseline to Month 12, and the Month 12 to Month 24 treatment periods.

- The increase in mean HV SDS **was greater during the first 12 months** of treatment than during the second 12 months of treatment for both somatropin treatment groups.

PP 0-24 Month Population (see Table 9)

- During the baseline to Month 12, and Month 12 to Month 24 treatment periods, mean HV SDS values **for both treatment groups** were significantly greater than the values observed in the untreated control group.

- HV SDS for the 0.067 mg/kg/day group was significantly greater than the value observed for the 0.033 mg/kg/day group during both 12 month treatment periods as well.

HV SDS Distribution Analysis - ITT Population

- The distribution of HV SDS during the baseline to Month 12 treatment period was appropriate and devoid of significant outliers (see Figure 2). The HV SDS distribution plot during the Month 12 to Month 24 treatment period was very similar (data not shown).

Table 8. CTN 89-041 - Effects of Somatropin on HV 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	60 -1.3 (1.5)	60 2.6 (1.6)	60 0.8 (1.7)
0.067	52 -1.3 (1.0)	52 4.1 (1.9)	52 1.8 (1.9)
Untreated	28 -1.1 (0.8)	28 -0.4 (1.4)	11 -0.6 (1.1)
Untreated/0.033			9 2.6 (2.0)
Untreated/0.067			8 3.4 (1.4)
Primary analysis (Dunnett's test)*:			
0.033 vs. untreated		p=0.0001 S	p=0.016 NS
0.067 vs. untreated		p=0.0001 S	p=0.0001 S
Sec. analysis (Student's t-test):			
0.067 vs. 0.033		p=0.0001	p=0.0020

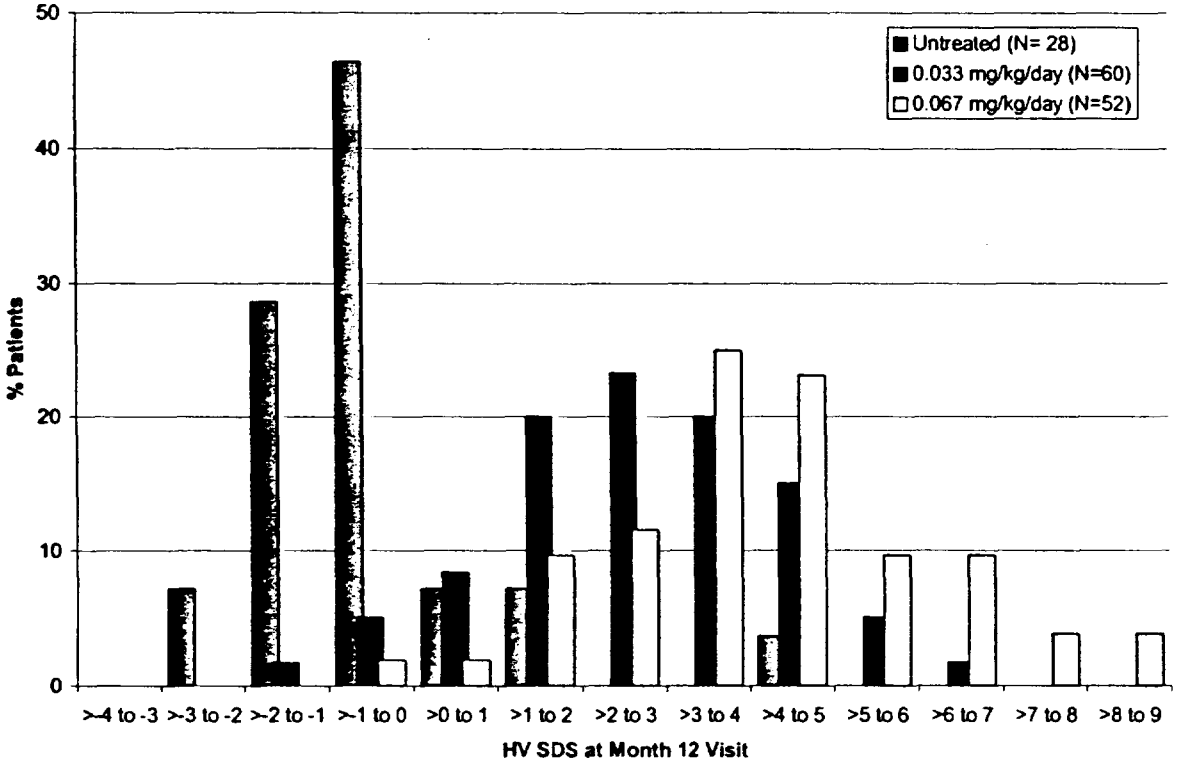
*The p-values in the tables are not adjusted for multiple comparisons. The "S" implies statistical significance even after corrections for multiple comparisons.

Table 9. CTN 89-041 - Effects of Somatropin on HV SDS During 24 months of Treatment (PP 0-24 population)

Treatment group	Pretreatment N Mean (SD)	Month 0-12 N Mean (SD)	Month 12-24 N Mean (SD)
0.033	43 -1.6 (1.3)	43 2.8 (1.4)	43 1.1 (1.3)
0.067	42 -1.4 (1.0)	42 4.1 (1.8)	42 2.2 (1.5)
Untreated/0.033	8 -1.1 (0.7)	8 -0.8 (0.6)	8 2.8 (2.0)
Untreated/0.067	6 -1.6 (0.6)	6 -0.6 (1.5)	6 3.1 (1.6)
Untreated	9 -0.9 (0.6)	9 -0.2 (0.9)	9 -0.8 (1.2)
Primary analysis (Dunnett's test)*:			
0.033 vs. untreated		P=0.0001 S	p=0.0006 S
0.067 vs. untreated		P=0.0001 S	p=0.0001 S
Sec. analysis (Student's t-test):			
0.067 vs. 0.033		P=0.0002	p=0.0006

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

Figure 2. CTN 89-041 - Proportion of Patients at the 12-Month Visit Within Specified HV SDS Categories (ITT Population)



VI.A.5.5.1.1.1 Exploratory Covariate Analyses

Using HV SDS at baseline, age at baseline, and sex as covariates, additional analyses of HV SDS after 12 and 24 months of somatropin treatment were performed for the ITT and PP 0-24 month populations. After adjusting for these prognostic factors, the effect of somatropin on HV SDS was similar to the results obtained in the original analyses. The effect of sex was significant in the Month 24 ITT and PP analyses, but no interaction was seen between sex and treatment (e.g., the effect of sex was similar within each group and did not account for the different HV SDS responses observed in the treatment groups). In addition, regression analyses plotting HV SDS responses against several continuous variables at baseline (e.g., age, HV SDS and height SDS_{CA}) revealed no statistically/clinically significant relationships.

VI.A.5.5.1.1.2 Subgroup Analyses

When the same HV SDS analyses were performed on males and females separately, very similar results were observed.

VI.A.5.5.2 Secondary Efficacy Parameters (Months 0-24)

VI.A.5.5.2.1 Height SDS_{CA} (see Table 10)

- The mean change from baseline to Month 24 in height SDS_{CA} was significantly greater for both the 0.033 mg/kg/day and 0.067 mg/kg/day groups when compared with the untreated group.
- The mean change from baseline in height SDS_{CA} was significantly greater in the 0.067 mg/kg/day group compared with the 0.033 mg/kg/day group.
- As was observed in the HV SDS analyses, the 2 groups of patients who started treatment at Month 12 showed a substantial improvement in mean height SDS_{CA} values as well.

Table 10. CTN 89-041 - Effects of Somatropin on the Change in Height SDS_{CA} After 24 months of Treatment (PP 0-24 Population)

Treatment group	Baseline Mean (SD)	Month 24 Mean (SD)	Change 0-24 months Mean (SD)
0.033 (n=43)	-3.0 (0.7)	-2.0 (0.8)	1.1 (0.4)
0.067 (n=42)	-3.0 (0.7)	-1.7 (0.8)	1.3 (0.5)
Untreated/0.033 (n=8)	-3.0 (0.6)	-2.3 (0.5)	0.7 (0.3)
Untreated/0.067 (n=6)	-3.4 (1.5)	-2.4 (1.7)	1.0 (0.4)
Untreated (n=9)	-2.5 (0.4)	-2.3 (0.5)	0.2 (0.3)
0.033 vs. untreated*			p<0.0001
0.067 vs. untreated*			p<0.0001
0.067 vs. 0.033*			p=0.0016

*Student's t-test

VI.A.5.5.2.1.1 Exploratory Covariate Analyses

Using height SDS_{CA} at baseline, age at baseline, and sex as covariates, additional analyses of height SDS_{CA} after 24 months of somatropin treatment were performed for the PP 0-24 month population. After adjusting for these prognostic factors, the effect of somatropin on height SDS_{CA} was similar to the results obtained in the original analysis. The effect of age at baseline was significant, but no interaction was seen between age and treatment (e.g., the effect of age was similar within each group and did not account for the different height SDS_{CA} responses observed in the treatment groups).

In addition, regression analyses plotting height SDS_{CA} responses against several continuous variables at baseline (e.g., age, height SDS_{CA} and HV SDS) were performed by the Sponsor at the request of this medical officer. **Age at baseline was found to be significantly inversely related to the height SDS_{CA} after 24 months of treatment for both the 0.033 and 0.067 mg/kg/day treatment groups** (see Figures 3 and 4).

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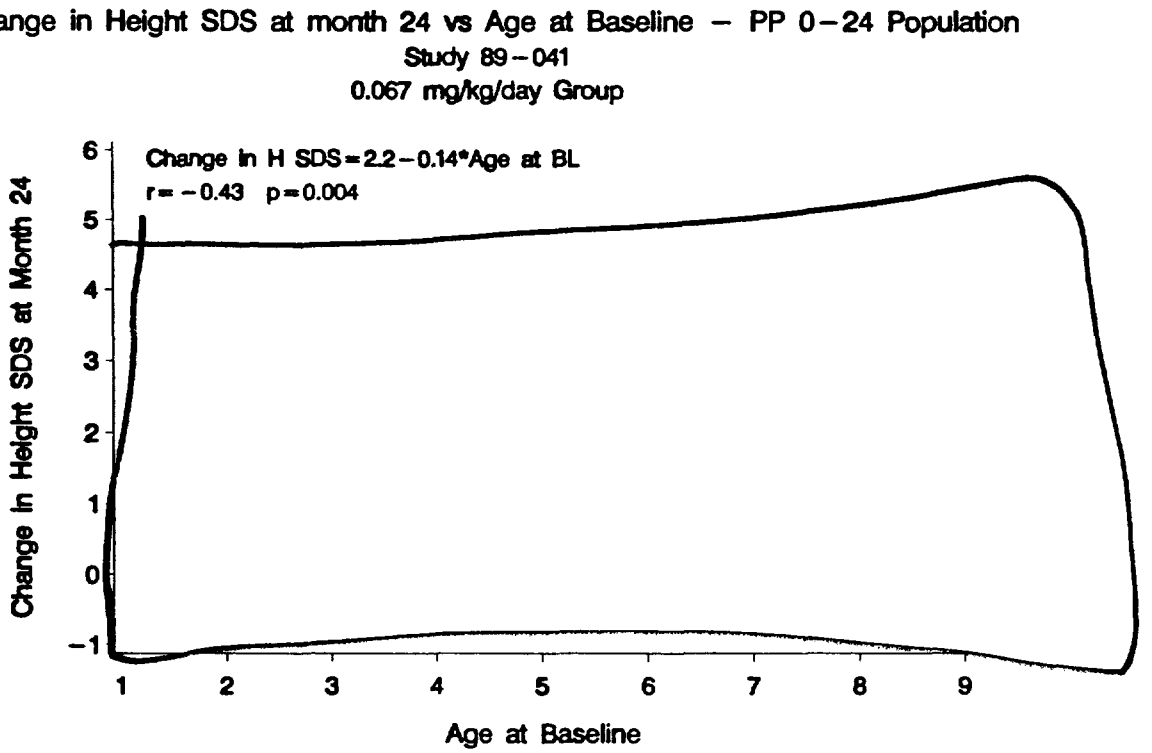
Figure 4. CTN 89-041



VI.A.5.5.2.2 PAH SDS (see Table 11)

- The mean change from baseline to Month 24 in PAH SDS values were significantly greater in the 2 active treatment groups compared with the untreated control group.

- Once again, the administration of 0.067 mg/kg/day of somatropin resulted in a greater PAH SDS response than treatment with 0.033 mg/kg/day.

- Not surprisingly, the changes in PAH SDS were almost identical to the changes in non-parental adjusted height SDS_{CA}.

- When the childrens' mean height SDS_{CA} values were adjusted for mid-parental height, the mean values at Month 24 for all treatment groups were ~1 SDS greater than their respective non-adjusted mean height SDS_{CA} values, reflecting the influence of genetic potential.

Table 11. CTN 89-041 - Effects of Somatropin on the Change in PAH SDS 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)	-1.7 (1.3)	-1.5 (1.3)	0.2 (0.3)
Somatropin 0.033 mg/kg/day (n = 42)	-1.9 (1.4)	-0.9 (1.5)	1.1 (0.4)
Somatropin 0.067 mg/kg/day (n = 40)	-1.9 (1.0)	-0.5 (1.1)	1.4 (0.4)
Untreated / 0.033 mg/kg/day (n = 8)	-1.9 (0.9)	-1.2 (0.8)	0.7 (0.3)
Untreated / 0.067 mg/kg/day (n = 6)	-2.2 (1.9)	-1.2 (2.1)	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 0.0012

VI.A.5.5.2.3 Height SDS_{BA} (see Table 12)

- The mean change from baseline to Month 24 for height SDS_{BA} was significantly greater in the 0.067 mg/kg/day treatment group (but NOT the 0.033 mg/kg/day group) compared with the untreated control group.
- There were NO significant differences between the active treatment groups.
- The greatest increases in mean height SDS_{BA} were seen in the untreated/0.033 mg/kg/day and the untreated/0.067 mg/kg/day treatment groups (who only received active treatment from Month 12 to Month 24).

Table 12. CTN 89-041 - Effects of Somatropin on the Change in Height SDS_{BA} 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 = 8)	-0.1 (1.9)	-0.9 (1.0)	-0.8 (1.6)
Somatropin 0.033 mg/kg/day (N = 41)	-0.9 (1.9)	-1.0 (1.3)	-0.1 (1.5)
Somatropin 0.067 mg/kg/day (N = 36)	-1.1 (1.5)	-0.8 (1.4)	0.3 (1.0)
Untreated / 0.033 mg/kg/day (N = 7)	-1.0 (1.0)	-0.4 (1.1)	0.6 (0.9)
Untreated / 0.067 mg/kg/day (N = 6)	-1.2 (1.6)	-0.7 (1.4)	0.5 (1.3)
			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			0.2714 0.0171 0.1417

IV.A.5.5.2.4 BA and BA/CA Ratio

- The differences in BA between groups were small and not considered clinically important (see Table 13).

- The mean change from baseline to Month 24 for the BA/CA ratio was similar for all of the treatment groups. **The mean BA/CA ratio did not exceed 1.0 in any treatment group after 24 months of somatropin exposure.** See Table 14.

Table 13. CTN 89-041 - Effects of Somatropin on BA (years) 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 = 8)	4.0 (1.2)	6.2 (0.9)	2.3 (0.9)
Somatropin 0.033 mg/kg/day (N = 41)	4.1 (1.2)	6.7 (1.5)	2.6 (1.0)
Somatropin 0.067 mg/kg/day (N = 36)	4.7 (1.4)	7.4 (1.8)	2.7 (0.9)
Untreated / 0.033 mg/kg/day (N = 7)	4.4 (1.7)	6.2 (2.0)	1.8 (0.8)
Untreated / 0.067 mg/kg/day (N = 6)	3.4 (0.9)	5.4 (1.2)	2.0 (0.6)
			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			N/A

Table 14. CTN 89-041 - Effects of Somatropin on BA/CA 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 = 8)	0.7 (0.2)	0.8 (0.1)	0.1 (0.2)
Somatropin 0.033 mg/kg/day (N = 41)	0.8 (0.2)	0.9 (0.1)	0.1 (0.1)
Somatropin 0.067 mg/kg/day (N = 36)	0.8 (0.2)	0.9 (0.2)	0.1 (0.1)
Untreated / 0.033 mg/kg/day (N = 7)	0.8 (0.1)	0.8 (0.1)	0.0 (0.1)
Untreated / 0.067 mg/kg/day (N = 6)	0.7 (0.1)	0.8 (0.1)	0.1 (0.1)
			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			N/A

IV.A.5.5.2.5 Weight SDS and Body Mass Index (BMI) SDS (data not shown)

- The mean change from baseline to Month 24 in weight SDS was significantly greater for both active treatment groups compared with the untreated group.

- The mean change from baseline to Month 24 in weight SDS was significantly greater in the 0.067 mg/kg/day group than in the 0.033 mg/kg/day group.

- Both somatropin-treated groups showed an increase in mean BMI SDS values during the 24 month treatment period, whereas mean BMI SDS decreased in the untreated control group. There were no clinically relevant or statistically significant differences between the 2 somatropin treatment groups.

VI.A.5.5.3 Secondary Efficacy Parameters (Months 0-72) - Uncontrolled Portion of Study

VI.A.5.5.3.1 Height SDS_{CA}

VI.A.5.5.3.1.1 Patients Treated Continuously Between Months 0-72

- After a substantial increment of ~1 SDS after 24 months of continuous therapy with either 0.033 or 0.067 mg/kg/day of somatropin in all 3 treatment groups, the annual increase in height SDS_{CA} between Month 24 and Month 72 was much smaller but nearly constant in patients who continued to receive

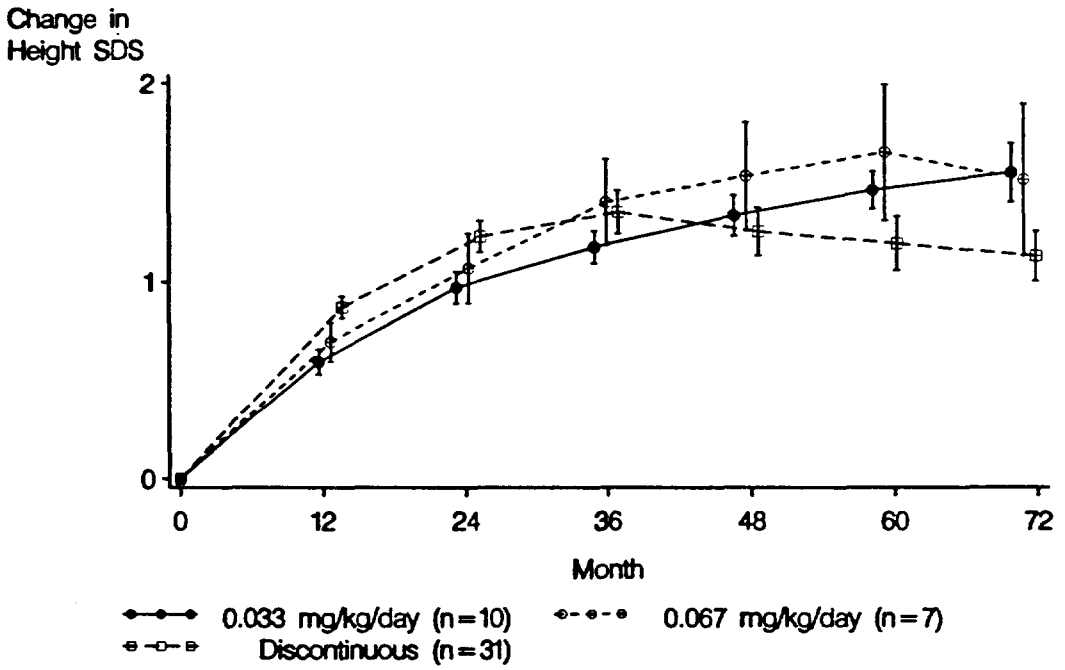
uninterrupted therapy with 0.033 or 0.067 mg/kg/day (see Figure 5)

- On the other hand, linear growth in the discontinuous group (intermittent, periodic, or complete cessation of somatropin therapy between Month 24 and Month 72) stopped at Month 36 and declined slightly thereafter (see Figure 5).

- Mean height SDS_{CA} values per se improved substantially between baseline and Month 24, and then slowly but steadily increased between Month 24 and Month 72 for patients in the 0.033 and 0.067 mg/kg/day treatment groups (see Figure 6).

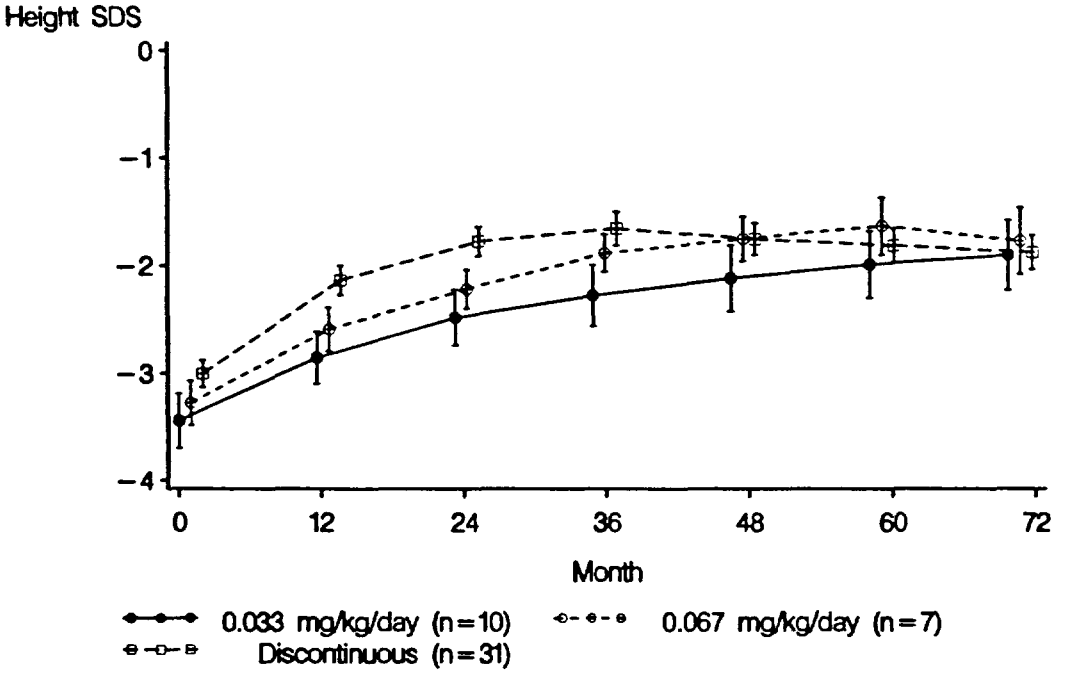
- In the discontinuous group, mean height SDS_{CA} improved substantially between baseline and Month 24, and then stabilized between Month 36 (when the period of discontinuous treatment began) and Month 72; nonetheless, height SDS_{CA} at Month 72 was comparable to the other 2 continuous treatment groups.

Figure 5. CTN 89-041 - Change from Baseline in Mean Height SDS_{CA} (±SEM) - PP 0-72 Population



Note: 9 patients excluded from the discontinuous group due to missing observations.

Figure 6. CTN 89-041 - Mean Height SDS_{CA} (±SEM) - PP 0-72 Population



Note: 9 patients excluded from the discontinuous group due to missing observations.

VI.A.5.5.3.1.2 Height SDS in Patients Treated Discontinuously Between Months 0-72 - **In Particular Patients With Cessation +/- Restart of Somatropin Therapy**

At the request of this medical officer, the Sponsor further analyzed height SDS_{CA} for the PP 0-72 patient population as follows:

1) Patients with a treatment stop at Month 48 or earlier were divided into 2 groups, those with a height SDS_{CA} <-1 at the treatment stop (not recommended by the protocol), and those with a height SDS_{CA} ≥-1 at the treatment stop (as designated in protocol).
2) These 2 "treatment stop" groups were further subcategorized by whether or not the patients restarted treatment.
3) The change in height SDS_{CA} from the cessation of treatment to the restart visit, and the change in height SDS_{CA} from the cessation of treatment to Month 72/study termination (for the patients who did not restart therapy) were then calculated.

- As seen in Figure 7, of the 40 patients in the discontinuous group in the PP 0-72 patient population, 4 patients chose intermittent therapy (0.067 mg/kg/day; 3 months on, 3 months off), and 36 patients had a treatment stop (periodic treatment or study termination).

- Thirty of these 36 patients stopped treatment at Month 48 or earlier: 11/30 had achieved a height SDS_{CA} level >-1 at the time of treatment stop (as per protocol); 19/30 had a height SDS_{CA} <-1 at the time of treatment stop.

- With regard to the 19 patients whose height SDS_{CA} was <-1 at treatment stop:

  1) 8 of these 19 patients had a height SDS_{CA} <-2 at treatment restart, and **the change between mean height SDS_{CA} at treatment stop (-1.83) and the mean height SDS_{CA} at treatment restart (-2.5) was ~-0.7 SDS over a mean duration of 2.2 years off therapy**; when these 8 patients were **restarted on somatropin treatment** for a mean duration of ~1 year until Month 72, **the mean height SDS_{CA} increased 0.3 SDS (and in some individuals as much as 0.7 SDS).**

  2) 6 of these 19 patients (who did not restart somatropin therapy) had a mean height SDS_{CA} <-2 at Month 72/study termination, and **the change between mean height SDS_{CA} at treatment stop (-2.54) and the mean height SDS_{CA} at Month 72/study termination (-3.0) was ~-0.5 SDS over a mean duration of 3.1 years off therapy**

  3) 3 of these 19 patients (who did not restart somatropin therapy) had a height SDS_{CA} between -1 and -2 at Month 72/study termination, and **the change between mean height SDS_{CA} at treatment stop (-1.33) and the mean height SDS_{CA} at Month 72/ study termination (-1.7) was ~-0.4 SDS over a mean duration of 3.0 years off therapy**

- With regard to the 11 patients whose height SDS_{CA} was >-1 at treatment stop:

  1) 6 of these 11 patients (who did not restart somatropin therapy) had a height SDS_{CA} between -1 and -2 at Month 72/study termination, and **the change between mean height SDS_{CA} at treatment stop (-0.54) and the mean height SDS_{CA} at Month 72/study termination (-1.5) was ~-1.0 SDS over a mean duration of 3.3 years off therapy**

  2) 4 of these 11 patients (who did not restart somatropin therapy) had a height SDS_{CA} >-1 at Month 72/study termination, and the change between mean height SDS_{CA} at treatment stop (-0.66) and **the mean height SDS_{CA} at Month 72/study termination (-0.8) was only –0.14 SDS over a mean duration of 2.7 years off therapy**

Conclusions:

- These data demonstrate that following the induction of substantial linear growth with 2-3 years of somatropin therapy in children born SGA, cessation of somatropin treatment (for ~2-3 years) resulted in a significant reduction of height SDS_{CA} (~0.4-1 SDS) in a majority of patients (~23/30) (e.g., so called catch-down growth).

- Restarting somatropin treatment in 8 of these patients (who had previously stopped treatment and experienced catch-down growth) resulted in a significant increase in height SDS_{CA}.

- Four out of the 11 patients who had achieved a height SDS_{CA} >-1 during an initial 2-3 year course of therapy with somatropin did not experience a decrease in height SDS_{CA} when somatropin was discontinued over a period of ~2-3 years.

- It is reasonable to conclude that once somatropin therapy has resulted in a significant increase in short-term linear growth in SGA children, therapy should be continued indefinitely until FH is attained; alternatively, therapy could be discontinued if a height SDS_{CA} >-1 is achieved, but the linear growth of such children should be monitored at least annually and reinitiation of somatropin treatment should be considered if there is a significant decline in height SDS_{CA}.

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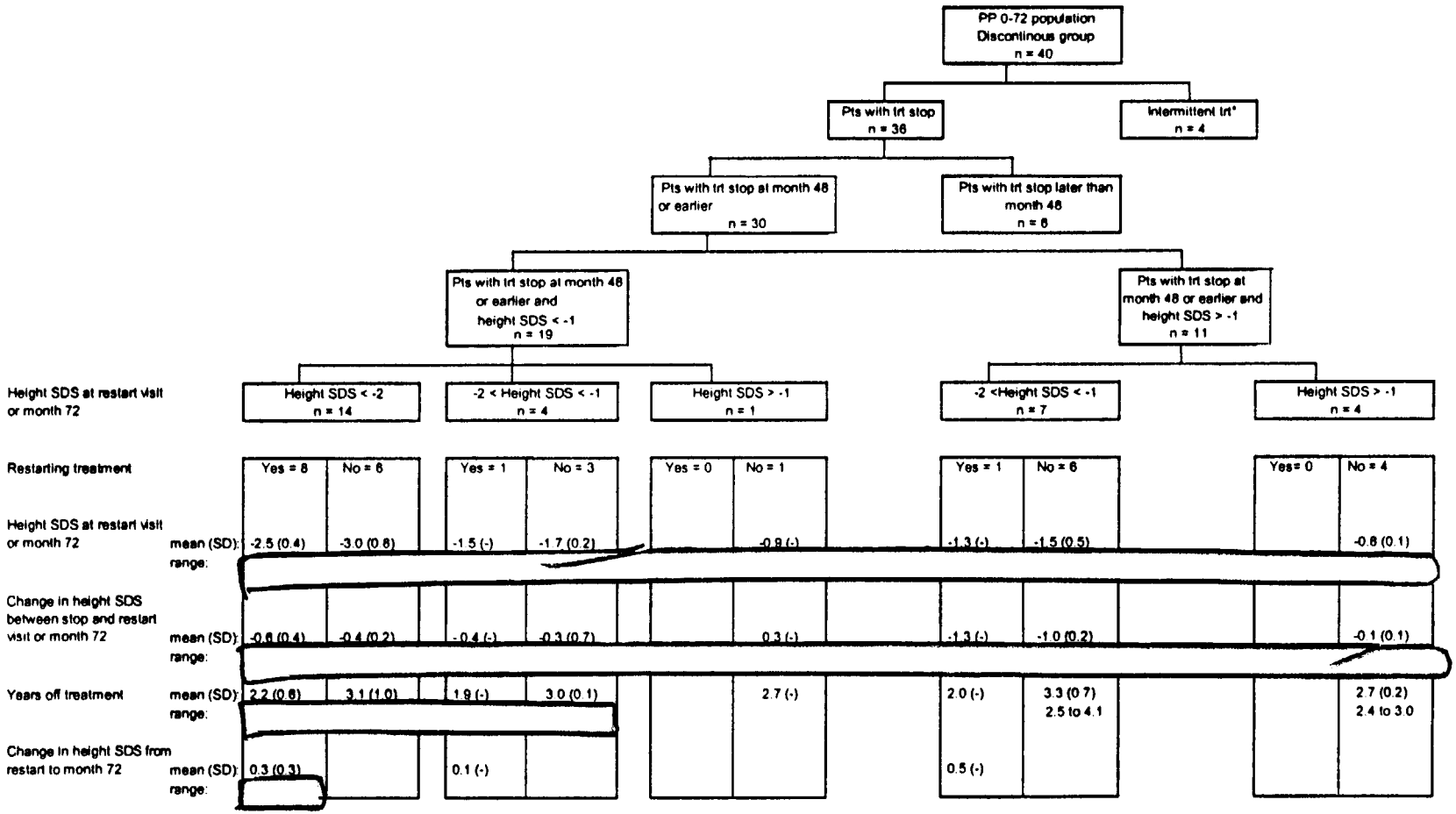
Figure 7. CTN 89-041 - Height SDS_{CA} Values for Discontinuous Patients - PP 0-72 Population



* 3 months on, 3 months off

V.A.5.5.3.2 PAH SDS

Between Month 24 and Month 72, annual increases in PAH SDS values were small but constant (data not shown).

V.A.5.5.3.3 Weight SDS

Between Month 24 and Month 72, annual increases in weight SDS values were small but constant (data not shown).

V.A.5.5.3.4 Height SDS_{BA}

Mean height SDS_{BA} values increased slightly between Month 24 and Month 72 in the 0.067 mg/kg/day group (and decreased somewhat in the 0.033 mg/kg/day group).

V.A.5.5.3.5 BA/CA Ratio

During the 24-72 month treatment period, the BA/CA ratio increased slightly in all 3 treatment groups, but the mean values did not exceed 1.0. See Figure 8.

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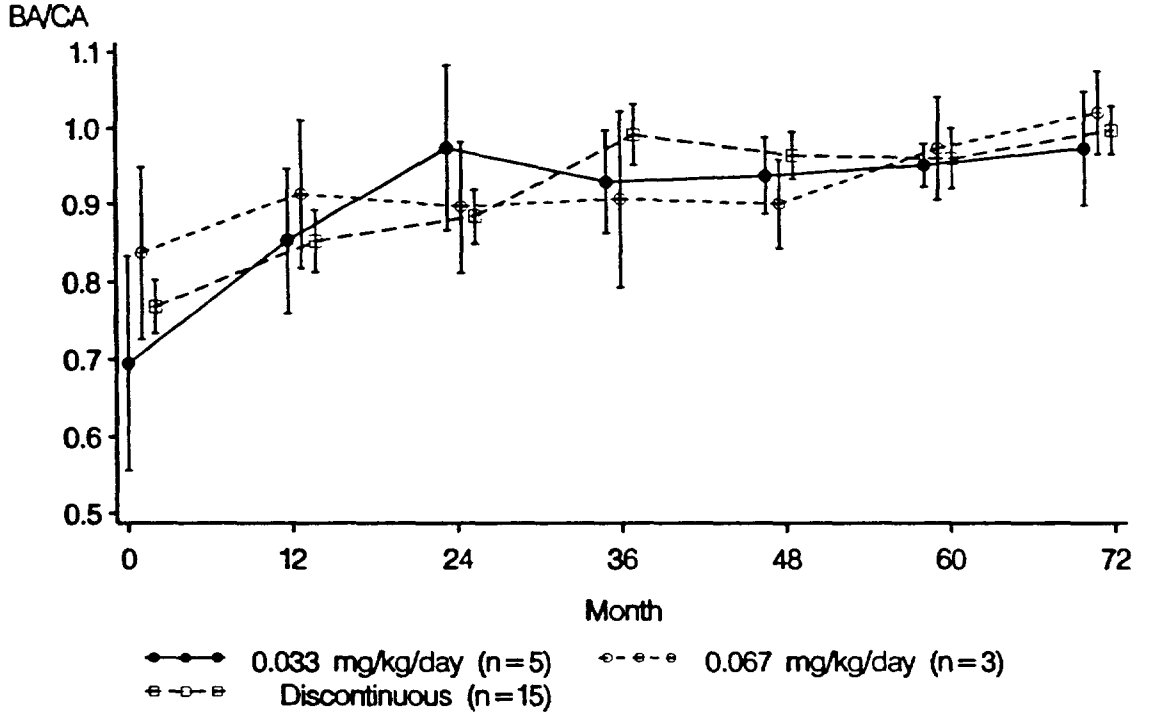
Figure 8. CTN 89-041 - Mean BA/CA Ratio (±SEM) for the PP 0-72 Population



Note: 34 patients excluded (5 in the 0.033 mg/kg/day group, 4 in the 0.067 mg/kg/day group and 25 in the discontinuous group) due to missing observations.

VI.A.5.5.3.6 Changes in IGF-I Levels With Implications for Efficacy

As depicted in Table 15 and Figure 6 below, changes in mean IGF-I SDS (see Section VI.A.4.3.2.2 regarding the calculation of the IGF-I SDS and **caveats regarding its utility discussed in the ISS**) from baseline were not significantly different in either of the 2 treatment groups after 6 - 72 months of somatropin treatment (in particular, after 6, 12, 18 and 24 months of somatropin exposure - when sample sizes were more substantial and meaningful). Mean IGF-I SDS were within the high normal range (between 0 and +1 SDS), and not significantly different in the 2 dose groups during the first 2 years of therapy. This contrasts with the greater efficacy of the 0.067 mg/kg/day treatment group (compared with 0.033 mg/kg/day group) in stimulating linear growth. Therefore, **the greater growth observed in the high dose group cannot then be correlated with a greater IGF-I response.** The lack of correlation between growth parameters and IGF-I response in GHD children treated for many years with conventional amounts of somatropin is well established in the literature (17).

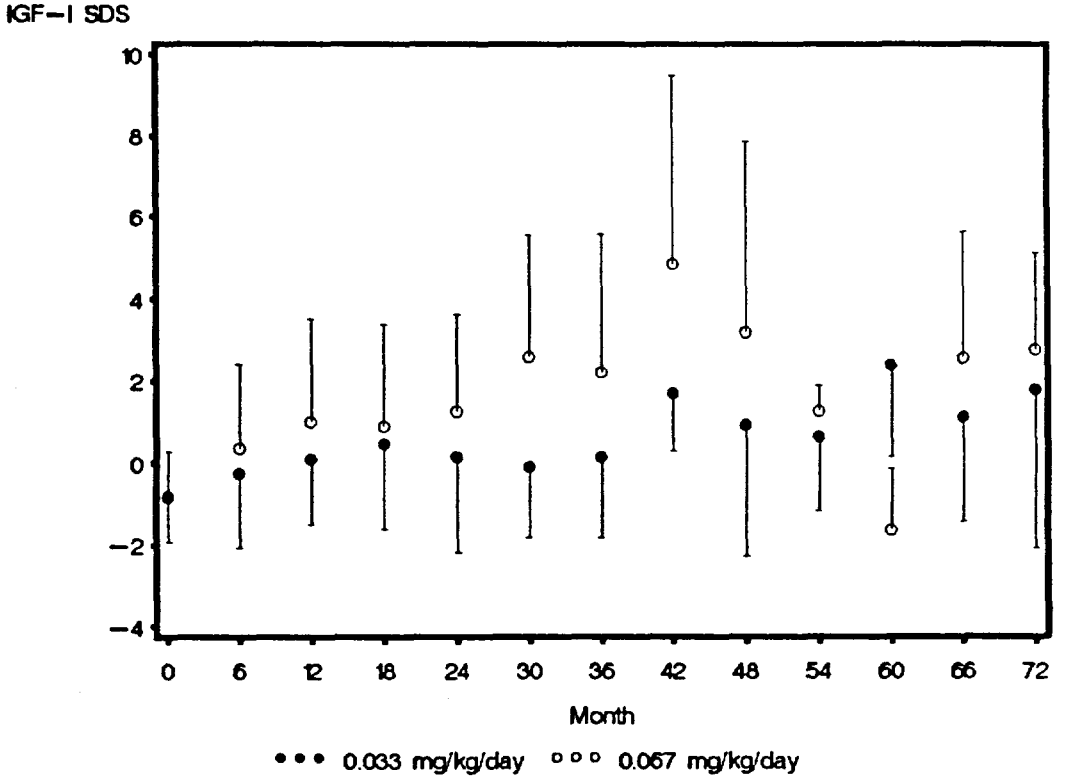
Table 15. CTN 89-041 - Mean IGF-I SDS in the Treatment Groups After 6-72 Months of Somatropin Therapy**

Months	0	6	12	18	24	30	36	42	48	54	60	66	72
	N	N	N	N	N	N	N	N	N	N	N	N	N
Rx group													
0.033*	40	29	38	29	37	11	10	11	9	9	8	6	7
0.067*	31	29	36	29	27	5	4	3	4	5	2	2	3

*mg/kg/day

**Data from patients who received discontinuous therapy after Month 24 are only included through Month 24.

Figure 9. CTN 89-041 - Mean IGF-I SDS in the Treatment Groups After 6-72 Months of Somatropin Therapy (see Table 15 above for sample sizes at different time points)



Furthermore, in this regard, additional analyses was performed by the Sponsor **at the request of this medical reviewer** in order to examine the relationship between IGF-I SDS (and indirectly dose), and HV SDS, height SDS_{CA} and PAH SDS after 2 years of somatropin therapy. All patients with 2 or more IGF-I determinations were divided into 2

cohorts (a "normal" IGF-I group with <2 IGF-I SDS >+2 [containing more patients from the 0.033 mg/kg/day treatment arm as per Section VI.C.6.5.1], and an "abnormal" IGF-I group with ≥2 IGF-I SDS greater than +2 [containing more patients from the 0.067 mg/kg/day treatment arm as per Section VI.C.6.5.1]). A comparison of HV SDS at 12 and 24 months, height SDS_{CA}, and PAH SDS (similar to the efficacy analyses performed for the different treatment arms in the individual study reports and the ISE) revealed no significant differences between these 2 cohorts (data not shown). This suggests that the patients with higher IGF-I levels (who were treated with the larger dose of somatropin [0.067 mg/kg/day] more frequently) manifest increases in linear growth equivalent to patients with lower IGF-I levels (who were treated more often with somatropin 0.033 mg/kg/day). Once again, the lack of correlation between growth parameters and IGF-I responses is not surprising!

VI.A.5.6 CTN 89-041 Efficacy - Summary/Discussion

Controlled Portion of Study - Months 0-24

1) Analysis of HV SDS in the ITT population:

- **Mean HV SDS values for the 0.067 sand 0.033 mg/kg/day treatment groups were significantly greater than the values observed in the untreated control group during the baseline to Month 12 treatment period;** during the Month 12 to Month 24 treatment period, only the 0.067 mg/kg/day group resulted in mean HV SDS values greater than those in the control group.

- Mean HV SDS values for the 0.067 mg/kg/day group were significantly greater than those observed for the 0.033 mg/kg/day group during **both** the baseline to Month 12, and the Month 12 to Month 24 treatment periods.

- The increase in mean HV SDS **was greater during the first 12 months** of treatment than during the second 12 months of treatment for both somatropin treatment groups.

- Similar analyses of mean HV SDS in the PP 0-24 population were confirmatory.

- The distribution of HV SDS during both 12 month treatment periods was appropriate and devoid of significant outliers.

2) Analysis of Height SDS_{CA} in PP 0-24 Population:

- **The mean change from baseline to Month 24 in height SDS_{CA} was significantly greater for both the 0.033 and 0.067 mg/kg/day groups compared with the untreated group.**

- **The mean change from baseline in height SDS_{CA} was significantly greater in the 0.067 mg/kg/day group compared with the 0.033 mg/kg/day group.**

- Age at baseline was found to be significantly inversely related to the height SDS_{CA} after 24 months of treatment for both the 0.033 and 0.067 mg/kg/day treatment groups. Age at baseline has long been known to be an important prognosticator of the extent of somatropin-induced linear growth in GHD children.

3) Analysis of PAH SDS in the PP 0-24 Population:

- The PAH SDS analyses were almost identical to and therefore confirmatory of the analyses of non-parental adjusted height SDS_{CA} (as were the weight SDS analyses).

4) Analysis of Height SDS_{BA} in the PP 0-24 Population

- The mean change from baseline to Month 24 for height SDS_{BA} was significantly greater in the 0.067 mg/kg/day treatment group (but NOT the 0.033 mg/kg/day group) compared with the untreated control group - **suggesting that the increase in linear growth was more substantial than the increase in BA.**

5) BA/CA Ratio in the PP 0-24 Population

- **The mean change from baseline to Month 24 for the BA/CA ratio was similar for both active treatment groups. The mean BA/CA ratio did not exceed 1.0 in any treatment group after 24 months of somatropin exposure.**

6) Analysis of IGF-I SDS During the 0-24 Month Treatment Period

- Mean IGF-I SDS were within the high normal range (between 0 and +1 SDS) in both treatment groups, and not significantly different in the 2 dose groups during the first 2 years of therapy (although many more patients in the 0.067 mg/kg/day treatment group had multiple IGF-I SDS exceeding +2). This contrasts with the greater efficacy of the 0.067 mg/kg/day treatment group (compared with the 0.033 mg/kg/day group) in stimulating linear growth. Therefore, **the greater growth observed in the high dose group cannot be correlated with a greater IGF-I response.** The lack of correlation between growth parameters and IGF-I response in GHD children treated for many years with conventional amounts of somatropin is well established in the literature.

Analyses for Months 0-72 (including the uncontrolled 24-72 month portion of the study)

1) Height SDS_{CA}

- After 24 months of continuous therapy with either 0.033 or 0.067 mg/kg/day of somatropin resulted in a substantial ~1 SDS increment in the mean height SDS_{CA}, **the annual increase in mean height SDS_{CA} between Month 24 and Month 72 was much smaller but constant in patients who continued to receive uninterrupted therapy with either dosage.**

- Following the induction of substantial linear growth with 2-3 years of somatropin therapy in children born SGA, **cessation of somatropin treatment (for ~2-3 years) resulted in a significant reduction of height SDS_{CA} (~0.4-1 SDS)** in a majority of patients (e.g., so called catch-down growth). Restarting somatropin treatment in a small cohort of patients who had previously experienced catch-down growth resulted in a significant increase in height SDS_{CA}. On the other hand, a small but significant percentage of patients achieving a height SDS_{CA} >-1 during an initial 2-3 year course of therapy with somatropin did not experience a decrease in height SDS_{CA} when somatropin was discontinued over a period of ~2-3 years

2) PAH SDS and Weight SDS

- Between Month 24 and Month 72, annual increases in mean PAH SDS and mean weight SDS were small but constant.

3) Height SDS_{BA}

- Mean height SDS_{BA} values increased slightly between Month 24 and Month 72 in the 0.067 mg/kg/day group.

4) BA/CA Ratio

- During the 24-72 month treatment period, the BA/CA ratio increased slightly in both treatment groups, but the mean values did not exceed 1.0.

VI.A.5.7 CTN 89-041 Efficacy - Conclusions

- The 2 year controlled portion of the study demonstrated that somatropin at a dose of 0.033 or 0.067 mg/kg/day for 24 months, improved linear growth in short children born SGA, as assessed by HV SDS analyses in the ITT and PP 0-24 patient populations, and height SDS_{CA} and PAH SDS analyses in the PP 0-24 patient population. These results are very similar to the 5 year findings of Sas et al (15).

- The 0.067 mg/kg/day treatment group was significantly more efficacious than the 0.033 mg/kg/day group during the first 24 months of therapy (as assessed by the same analyses described in the first bullet). These results are very similar to the 5 year findings of Sas et al (15).

- Younger age at baseline appears to be an important prognosticator of greater growth (e.g., the change in mean height SDS_{CA} during the 0-24 month treatment period) in response to somatropin therapy in SGA children (as it is in GHD children). These results are very similar to the findings of Sas et al (15).

- The greater growth observed in the 0.067 mg/kg/day treatment group during the first 24 months of therapy cannot be correlated with a greater IGF-I response. These results are very similar to the findings of Mauras et al in pubertal patients treated with 100 or 42 ug/kg/day of somatropin (24).

- The small but constant increases in mean height SDS_{CA} and mean PAH SDS (as well as weight SDS) after Month 24 indicates that somatropin has a sustained effect on linear growth in SGA children. These results are very similar to the findings of Sas et al (15).

- Attempts at withdrawal of somatotropin during the 24-72 month treatment suggest that many (but not all) patients manifest a significant decrease in height SDS_{CA} off therapy, and may benefit from the reinstitution of somatotropin therapy.

- The failure of the BA/CA ratio to exceed 1, and the increase in height SDS_{BA} after treatment with 0.067 mg/kg/day, during both the 0-24 month and 0-72 month treatment periods suggests that 1) BA is not advancing too rapidly and 2) that the effect of somatropin therapy on FH outcome in SGA children will be favorable (see extensive discussion of FH issue in the review of the ISS [Section VI.C.6.5.1]).

VI.A.5.8 CTN 89-041 Efficacy - Recommendations

VI.A.5.8.1 Phase IV Commitment

- Every attempt should be made to obtain FH data on all patients who enrolled in this study, including patients who prematurely withdrew from the study for any reason.

VI.A.5.8.2 Other Recommendations

- Somatropin 0.067 mg/kg/day can be used as long-term therapy for short children born SGA who fail to manifest catch-up growth by age 2.

- Once somatropin therapy has resulted in a significant increase in short-term linear growth in SGA children, therapy should be continued until FH is attained; alternatively, therapy could be discontinued if a height SDS_{CA} >-1 is achieved, but the linear growth of such children should be monitored at least annually and reinitiation of somatropin treatment should be considered if there is a significant decline in height SDS_{CA}.

VI.A.5.9 CTN 89-041 - Safety Results

Safety results from CTN 89-041 (as well as all other studies) are discussed in the ISS.

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66 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

X.A Specific Revisions to Sponsor's Proposed Label

Relevant sections of the Sponsor's proposed labeling are reproduced below. Suggested revisions by this reviewer appear in red and are underlined as well.

CLINICAL STUDIES

Pediatric Patients Born Small for Gestational Age (SGA) Who Fail to Manifest Catch-up Growth by Age 2

The safety and efficacy of GENOTROPIN in the treatment of children born small for gestational age (SGA) were evaluated in 4 randomized, open-label, controlled clinical trials. Patients (age range of 2 to 8 yearrs) were observed for 12 months before being randomized to receive either GENOTROPIN (2 doses per study, most often 0.24 and 0.48 mg/kg/week) as a daily SC injection, or no treatment, for the first 24 months of the studies. After 24 months in the studies, all patients received GENOTROPIN.

Patients who received any dose of GENOTROPIN showed significant increases in growth during the first 24 months of study compared with patients who received no treatment (see Table 4). Children receiving 0.48 mg/kg/week demonstrated a significant improvement in height standard deviation score (SDS) compared with children treated with 0.24 mg/kg/week. Both of these doses resulted in a slower but constant increase in growth between months 24 to 72 (data not shown).

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Table 4
Efficacy of GENOTROPIN in Children Born Small for Gestational Age (Mean ± SD)

	GENOTROPIN (0.24 mg/kg/week) n=76	GENOTROPIN (0.48 mg/kg/week) n=93	[redacted]	Untreated Control n=40
Height Standard Deviation Score (SDS) Baseline SDS	-3.2 ± 0.8	-3.4 ± 1.0		-3.1 ± 0.9
SDS at 24 months	-2.0 ± 0.8	-1.7 ± 1.0		-2.9 ± 0.9
Change in SDS from baseline to month 24	1.2* ± 0.5	1.7*† ± 0.6		0.1 ± 0.3

* p = 0.0001 vs Untreated Control group
† p = 0.0001 vs group treated with GENOTROPIN 0.24 mg/kg/week

INDICATIONS AND USAGE

GENOTROPIN Lyophilized Powder is indicated for:

- Long-term treatment of pediatric patients who have growth failure due to an inadequate secretion of endogenous growth hormone.
- Long-term treatment of pediatric patients who have growth failure due to Prader-Willi syndrome (PWS). The diagnosis of PWS should be confirmed by appropriate genetic testing.
- Long-term treatment of growth failure in children [redacted] born small for gestational age (SGA) who fail to manifest catch-up growth by age 2.

Other causes of short stature in pediatric patients should be excluded.

- Long-term replacement therapy in adults with growth hormone deficiency (GHD) of either childhood- or adult-onset etiology. GHD should be confirmed by an appropriate growth hormone stimulation test.

CONTRAINDICATIONS

GENOTROPIN Lyophilized Powder should not be used when there is any evidence of neoplastic activity. Intracranial lesions must be inactive and antitumor therapy complete prior to the institution of therapy. GENOTROPIN should be discontinued if there is evidence of tumor growth. Growth hormone should not be used for growth promotion in pediatric patients with fused epiphyses.

Growth hormone should not be initiated to treat patients with acute critical illness due to complications following open heart or abdominal surgery, multiple accidental trauma, or to patients having acute respiratory failure. Two placebo-controlled clinical trials in non-growth hormone deficient adult patients (n=522) with these conditions revealed a significant increase in mortality (41.9% vs 19.3%) among somatropin treated patients (doses 5.3 to 8 mg/day) compared to those receiving placebo (see WARNINGS).

WARNINGS

The 5.8-mg and 13.8-mg presentations of GENOTROPIN Lyophilized Powder contain m-Cresol as a preservative. These products should not be used by patients with a known sensitivity to this preservative. The GENOTROPIN 1.5-mg and GENOTROPIN MINIQUICK presentations are preservative-free (see HOW SUPPLIED).

See CONTRAINDICATIONS for information on increased mortality in patients with acute critical illnesses in intensive care units due to complications following open heart or abdominal surgery, multiple accidental trauma, or with acute respiratory failure. The safety of continuing growth hormone treatment in patients receiving replacement doses for approved indications who concurrently develop these illnesses has not been established. Therefore, the potential benefit of treatment continuation with growth hormone in patients having acute critical illnesses should be weighed against the potential risk.

PRECAUTIONS

General

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 or Prader-Willi syndrome (PWS), or those who were born small for gestational age (SGA).

Patients and caregivers who will administer GENOTROPIN in medically unsupervised situations should receive appropriate training and instruction on the proper use of GENOTROPIN from the physician or other suitably qualified health professional.

Patients with GHD secondary to an intracranial lesion should be examined frequently for progression or recurrence of the underlying disease process. Review of literature reports of pediatric use of somatropin replacement therapy reveals no relationship between this therapy and recurrence of central nervous system (CNS) tumors. In adults, it is unknown whether there is any relationship between somatropin treatment and CNS tumor recurrence.

Patients should be monitored carefully for any malignant transformation of skin lesions.

Caution should be used if growth hormone is administered to patients with diabetes mellitus, and insulin dosage may need to be adjusted. ~~Because growth hormone may induce a state of insulin resistance, patients should be observed for evidence of glucose intolerance.~~ Patients with diabetes or glucose intolerance should be monitored closely during treatment with GENOTROPIN. Patients with risk factors for glucose intolerance, such as obesity (including obese patients with PWS) or a family history of Type II diabetes, should be monitored closely as well. Because growth hormone may induce a state of insulin resistance, patients should be observed for evidence of glucose intolerance.

In patients with hypopituitarism (multiple hormonal deficiencies) standard hormonal replacement therapy should be monitored closely when treatment with GENOTROPIN is instituted.

Hypothyroidism may develop during treatment with GENOTROPIN, and inadequate treatment of hypothyroidism may prevent optimal response to GENOTROPIN. Therefore, patients should have periodic thyroid function tests and be treated with thyroid hormone when indicated.

Pediatric patients with endocrine disorders, including GHD, have a higher incidence of slipped capital femoral epiphyses. Any pediatric patient with the onset of a limp or complaints of hip or knee pain during growth hormone therapy should be evaluated.

Progression of scoliosis can occur in patients who experience rapid growth. Because growth hormone increases growth rate, patients with a history of scoliosis who are treated with growth hormone should be monitored for progression of scoliosis. However, growth hormone has not been shown to increase the incidence of scoliosis. Scoliosis is commonly seen in untreated patients with PWS. Physicians should be alert to this abnormality, which may manifest during growth hormone therapy.

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

Before continuing treatment as an adult, a post-pubertal GHD patient who received growth hormone replacement therapy in childhood should be reevaluated with proper testing as described in INDICATIONS AND USAGE.

If continued treatment is appropriate, GENOTROPIN should be administered at the reduced dose level recommended for adult GHD patients.

ADVERSE REACTIONS

As with all protein drugs, a small number of patients may develop antibodies to the protein. Growth hormone antibody with binding lower than 2 mg/L has not been associated with growth attenuation. In some cases when binding capacity is > 2 mg/L, interference with growth response has been observed.

In 419 pediatric patients evaluated in clinical studies with GENOTROPIN Lyophilized Powder, 244 had been treated previously with GENOTROPIN or other growth hormone preparations and 175 had received no previous growth hormone therapy. Antibodies to growth hormone (anti-hGH antibodies) were present in six previously treated patients at baseline. Three of the six became negative for anti-hGH antibodies during 6 to 12 months of treatment with GENOTROPIN. Of the remaining 413 patients, eight (1.9%) developed detectable anti-hGH antibodies during treatment with GENOTROPIN; none had an antibody binding capacity > 2 mg/L. There was no evidence that the growth response to GENOTROPIN was affected in these antibody-positive patients.

Preparations of GENOTROPIN contain a small amount of periplasmic *Escherichia coli* peptides (PECP). Anti-PECP antibodies are found in a small number of patients treated with GENOTROPIN, but these appear to be of no clinical significance.

In clinical studies with GENOTROPIN in pediatric GHD patients, the following events were reported infrequently: injection site reactions, including pain or burning associated with the injection, fibrosis, nodules, rash, inflammation, pigmentation, or bleeding; lipoatrophy; headache; hematuria; hypothyroidism; and mild hyperglycemia.

Leukemia has been reported in a small number of pediatric patients who have been treated with growth hormone, including growth hormone of pituitary origin and recombinant somatropin. The relationship, if any, between leukemia and growth hormone therapy is uncertain.

In two clinical studies with GENOTROPIN in pediatric patients with Prader-Willi syndrome, the following drug-related events were reported: edema, aggressiveness, arthralgia, benign intracranial hypertension, hair loss, headache, and myalgia.

In clinical studies 273 pediatric patients born small for gestational age, clinically significant events were reported mild transient hyperglycemia, 1 patient with benign intracranial

hypertension, 2 patients with central precocious puberty, 2 patients with jaw prominence, and several patients with aggravation of pre-existing scoliosis, injection site reactions, and self-limited progression of pigmented nevi. Anti-hGH antibodies were not detected in any of the patients treated with Genotropin.

In clinical trials with GENOTROPIN in 1,145 GHD adults, the majority of the adverse events consisted of mild to moderate symptoms of fluid retention, including peripheral swelling, arthralgia, pain and stiffness of the extremities, peripheral edema, myalgia, paresthesia, and hypoesthesia. These events were reported early during therapy, and tended to be transient and/or responsive to dosage reduction.

Table 5 displays the adverse events reported by 5% or more of adult GHD patients in clinical trials after various durations of treatment with GENOTROPIN. Also presented are the corresponding incidence rates of these adverse events in placebo patients during the 6-month double-blind portion of the clinical trials.

Table 5
Adverse Events Reported by ≥ 5% of 1,145 Adult GHD Patients During Clinical Trials of GENOTROPIN and Placebo, Grouped by Duration of Treatment

Adverse Event	Double Blind Phase		Open Label Phase GENOTROPIN		
	Placebo 0-6 mo. n = 572 % Patients	GENOTROPIN 0-6 mo. n = 573 % Patients	6-12 mo. n = 504 % Patients	12-18 mo. n = 63 % Patients	18-24 mo. n = 60 % Patients
Swelling, peripheral	5.1	17.5*	5.6	0	1.7
Arthralgia	4.2	17.3*	6.9	6.3	3.3
Upper respiratory infection	14.5	15.5	13.1	15.9	13.3
Pain, extremities	5.9	14.7*	6.7	1.6	3.3
Edema, peripheral	2.6	10.8*	3.0	0	0
Paresthesia	1.9	9.6*	2.2	3.2	0
Headache	7.7	9.9	6.2	0	0
Stiffness of extremities	1.6	7.9*	2.4	1.6	0
Fatigue	3.8	5.8	4.6	6.3	1.7
Myalgia	1.6	4.9*	2.0	4.8	6.7
Back pain	4.4	2.8	3.4	4.8	5.0

* Increased significantly when compared to placebo, $P \leq .025$: Fisher's Exact Test (one-sided)
n = number of patients receiving treatment during the indicated period.
% = percentage of patients who reported the event during the indicated period.

In expanded post-trial extension studies, diabetes mellitus developed in 12 of 3,031 patients (0.4%) during treatment with GENOTROPIN. All 12 patients had predisposing factors, e.g., elevated glycated hemoglobin levels and/or marked obesity, prior to receiving GENOTROPIN. Of the 3,031 patients receiving GENOTROPIN, 61 (2%) developed symptoms of carpal tunnel syndrome, which lessened after dosage reduction or treatment interruption (52) or surgery (9). Other

adverse events that have been reported include generalized edema and hypoesthesia.

DOSAGE AND ADMINISTRATION

The dosage of GENOTROPIN Lyophilized Powder must be adjusted for the individual patient. The weekly dose should be divided into 6 or 7 subcutaneous injections. GENOTROPIN may be given in the thigh, buttocks, or abdomen; the site of SC injections should be rotated daily to help prevent lipoatrophy.

Pediatric GHD Patients: Generally, a dose of 0.16 to 0.24 mg/kg body weight/week is recommended.

Pediatric PWS Patients: Generally, a dose of 0.24 mg/kg body weight/week is recommended.

Pediatric SGA Patients: Generally, a dose of 0.48 mg/kg body weight/week is recommended.

Adult GHD Patients: The recommended dosage at the start of therapy is not more than 0.04 mg/kg/week. The dose may be increased at 4- to 8-week intervals according to individual patient requirements to a maximum of 0.08 mg/kg/week, depending upon patient tolerance of treatment. Clinical response, side effects, and determination of age-adjusted serum IGF-I may be used as guidance in dose titration. This approach will tend to result in weight-adjusted doses that are larger for women compared with men and smaller for older and obese patients.

XI. Risk/Benefit Analysis

See Section I.A.1 in the EXECUTIVE SUMMARY.

XII. Approvability from a Clinical Perspective

In that somatropin represents a significant advance in the treatment of children born SGA, an entity without an approved therapy at this time, and given the fact that the safety profile of somatropin in this specific patient population (as well as several other pediatric short stature populations) is satisfactory, **the risk/benefit analysis of this NDA supplement submission from a clinical perspective favors drug approval, assuming the 2 Phase IV commitments delineated in Sections I.B.1.1 and I.B.2.1 in the EXECUTIVE SUMMARY are accepted by the Sponsor.**

/S/ 7/18/01

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CC: Original NDA 20-280 - HFD-510; Original IND - HFD-510;
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