CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-280/S-031

MEDICAL REVIEW

MEDICAL OFFICER REVIEW

DIVISION OF METABOLIC AND ENDOCRINE DRUG PRODUCTS (HFD-5 I O)

APPLICATION #:	20-280/S-031	**APPLICATION TYPE:**	Commercial NDA
SPONSOR:	Pharmacia &Upjohn	**PROP. BRAND NAME:**	Genotropin
	C.Blanchard & G. Brier	**GENERIC NAME:**	Somatropin (recombinant DNA [rDNA]) origin
	616-833-6717/3670	**CHEMICAL NAME:**	Recombinant human growth hormone (rhGH)
CATEGORY OF DRUG:	rhGH	**USAN / Established Name:**	
		ROUTE:	Subcutaneous Injection (SC)
MEDICAL REVIEWER:	Robert S. Perlstein MD, FACP, FACE	**REVIEW DATE:**	16Jul01

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date:	CDER Stamp Date:	Submission Type:	Comments:
25Jan01	26Jan01	Supplemental NDA for new indication	

RELATED APPLICATIONS: All NDAs/INDs pertaining to somatropin therapy for short stature in children.

Overview: A comprehensive review of 4 pivotal studies indicates that somatropin 0.067 mg/kg/day (and 0.033 mg/kg/day) are effective short-term therapies (2 years; compared to an untreated control group), for the treatment of children born small for gestational age (SGA) who fail to manifest spontaneous catch-up growth by age 2 years. Somatropin (0.067 mg/kg/day) was significantly more effective than somatropin (0.033 mg/kgday) . These results were based on analyses of height velocity (HV) standard deviation score (SDS), height SDS for chronological age (CA) (height SDS_{CA}), and parental adjusted height (PAH) SDS during the 24 month controlled portion of these studies. During the 24-72 month uncontrolled portion of the 4 pivotal clinical trials, both dosages were shown to have a sustained effect on linear growth (e.g., with a trend suggesting greater efficacy for the 0.067 mg/kg/day doseage as per comparative descriptive statistics). The failure of the bone age/chronological age (BA/CA) ratio to increase >1, and the increase in height SDS for BA (height SDS_{BA}), during both the 0-24 month, and the 0-72 month treatment periods suggest that BA did not advance too rapidly and that the effect on final height (FH) will be favorable. Somatropin products have been administered to literally many thousands of children with different etiologies of short stature during the last 15 years, and, in general, have an excellent safety profile. The adverse events observed during **these** clinical studies of SGA children were the expected and well established side effects of somatropin therapy in children (e.g, 9 patients with scoliosis). A possible trend towards more glucose intolerance was observed in the 0.067 mg/kg/day treatment group (compared to the 0.033 mg/kg/day group) during the first 2 years of therapy; however, in all other respects, the 2 dosages were equally safe and well tolerated. Of note, there was 1 patient reported with benign intracranial hypertension at Month 84 in 1 of the studies (which resolved completely without sequelae once somatropin was discontinued, and 1 definite and 1 possible report of apparent precocious puberty. The relationship between somatropin administration and precocious puberty is unclear at this time. Since the larger dose was more efficacious than the smaller dose in promoting linear growth in this patient population, and the safety profiles of the 2 dosages were "essentially" equivalent, this medical reviewer supports the Sponsor's intention to market the 0.067 mg/kg/day dosage for the long-term treatment of SGA children.

Recommended Regulatory Action:

X Approvable ____ Not Approvable

Signed: **Medical Reviewer:** /S/ **Date:** 16Jul01

Medical Team Leader: _____ **Date:** 07/18/01

EXECUTIVE SUMMARY

I. Recommendations

I.A Risk/Benefit Analysis and Approvability from a Clinical Perspective

I.A.1 Summary of Risk versus Benefit

A comprehensive review of 4 pivotal studies indicates that somatropin 0.067 mg/kg/day (and 0.033 mg/kg/day) are effective short-term therapies (2 years; compared to an untreated control group) for the treatment of children born small for gestational age (SGA) who fail to manifest spontaneous catch-up growth by age 2 years. Somatropin (0.067 mg/kg/day) was significantly more effective than somatropin (0.033 mg/kg/day) . These results were based on analyses of height velocity (HV) standard deviation score (SDS), height SDS for chronological age (CA) (height SDS_{CA}), and parental adjusted height (PAH) SDS during the 24 month controlled portion of these studies.

During the 24-72 month uncontrolled portion of the 4 pivotal clinical trials, both dosages were shown to have a sustained effect on linear growth (e.g., with a trend suggesting greater efficacy for the 0.067 mg/kg/day dosage as per comparative descriptive statistics). The failure of the bone age/chronological age (BA/CA) ratio to increase >1, and the increase in height SDS for BA (height SDS_{BA}), during both the 0-24 month, and the 0-72 month treatment periods suggest that BA did not advance too rapidly and that the effect on final height (FH) will be favorable.

Somatropin products have been administered to literally many thousands of children with different etiologies of short stature during the last 15 years, and, in general, have an excellent safety profile. The adverse events observed during these clinical studies of SGA children were the expected and well established side effects of somatropin therapy in children (e.g., 9 patients with scoliosis; no dose response). A possible trend towards more glucose intolerance was observed in the 0.067 mg/kg/day treatment group (compared to the 0.033 mg/kg/day group) during the first 2 years of therapy; however, in all other respects, the 2 dosages were equally safe and well tolerated. Of note, there was 1 patient reported with benign intracranial hypertension at Month 84 in 1 of the studies (which resolved completely without sequelae once somatropin was discontinued, and 1 definite and 1 possible report of apparent precocious puberty. The relationship between somatropin administration and precocious puberty is unclear at this time.

Since the larger dose was more efficacious than the smaller dose in promoting linear growth in this patient population, and the safety profiles of the 2 dosages were "essentially" equivalent, this medical

reviewer supports the Sponsor's intention to market the 0.067 mg/kg/day dosage for the long-term treatment of SGA children.

I.A.2 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 are accepted by the Sponsor.**

I.B. Efficacy, Safety and Dosing Recommendations (including Labeling Recommendations, Risk/Management Actions, and Phase IV Committments)

I.B.1 Efficacy Recommendations

I.B.1.1 Phase IV Commitment:

- **Every attempt should be made to obtain FH data on all patients who originally enrolled in this study, including patients who prematurely withdrew from the clinical trials for any reason - in order to ensure that somatropin therapy has a favorable impact on FH (applicable to Safety Recommendations as well).**

I.B.1.2 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 could 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}.

I.B.2 Safety Recommendations

I.B.2.1 Phase IV Commitments:

- See **Phase IV Commitment** under Efficacy Recommendations - applicable to Safety Recommendations as well.

- **Periodic Safety Reports – To create a section that describes the spontaneous event reports and the safety information from th Kabi International Growth Study (KIGS) for patients receiving a dose of somatropin greater than or equal to 0.4 mg/kg/week. This section will discuss the safety profile of these patients as compared to patients receiving doses of less than 0.4 mg/kg/week (excluding Turner's syndrome and chronic renal insufficiency patients.**

I.B.2.2 Other Recommendations

- Children born SGA (who fail to manifest spontaneous catch-up growth by age 2) who are treated with 0.067 mg/kg/day of somatropin should be carefully monitored for the well established adverse effects of somatropin therapy, **in particular glucose intolerance, aggravation of pre-existing scoliosis, benign intracranial hypertension and precocious puberty.**

- In addition, somatropin-treated SGA children should be monitored for **acromegaloid features**, excessive growth, and neoplasia, and consideration should be given to obtaining serum IGF-I levels periodically.

I.B.3 Dosing Recommendations

In the submitted label, the Sponsor proposes that each patient receive 0.067 mg/kg/day (0.48 mg/kg/week in 7 divided doses).

II Summary of Clinical Findings

II.A Brief Background and Overview of Clinical Program

Approximately 2.5% of all human infants are born SGA, and 10-15% of these children fail to manifest spontaneous catch-up growth by age 2 (e.g., height SDS_{CA} <-2). Furthermore, if left untreated, the SGA children who have failed to catch-up by age 2 demonstrate persistent growth failure throughout childhood and into adulthood (e.g., ~10% of the entire cohort do not achieve a height SDS_{CA} >-2 by the age of 18).

It is thought by some investigators that there are significant psychosocial disadvantages/consequences for children who are much smaller than their peers during childhood. In addition, it is well known in normal children and GHD children that FH is strongly correlated with height at the onset of puberty. Therefore, any therapy (e.g., somatropin) which could potentially promote catch-up growth prior to puberty would be highly advantageous to SGA children.

With regard to SGA children (who fail to spontaneously catch-up), a large percentage have putative growth hormone (GH) insufficiency (e.g., abnormalities in 24 hour GH profiles and/or low levels of insulin-like growth factor-I (IGF-I); however, only ~10% of these

patients have "true" GH deficiency (GHD) (documented by classical GH provocative testing.

During the last decade, several studies have demonstrated that treatment with somatropin can induce short-term catch-up growth in SGA children, and that these children continue to grow well after 5-7 years of treatment.

In view of 1) the apparently significant prevalence of GH insufficiency in SGA children, 2) the satisfactory short-term and long-term linear growth responses of SGA children observed after somatropin therapy in recent published trials, and 3) the satisfactory growth responses achieved with somatropin therapy in children with GHD, as well as in non-GHD children (e.g., chronic renal insufficiency), the decision of the Sponsor in 1990-1991 to initiate 4 almost identical clinical trials (France, Belgium, German and Nordic countries) to investigate the efficacy, safety and tolerability of somatropin in the treatment of **non-GHD children born SGA (without sufficient spontaneous catch-up growth by age 2)** was appropriate - based on the literature available at that time, and the large amount of relevant data published during the 1990s while these 4 trials were ongoing.

Data closure for efficacy and safety results for the original 25Jan01 submission occurred when every child enrolled in the 4 studies had completed 72 months on-study; data closure for the Safety Update Report (SUR) was 31Dec00.

II.B Summary of Efficacy

II.B.1 Summary/Discussion of 4 Efficacy Studies

Study CTN 89-041 (France) contributed ~44% of the enrolled patients (the intent-to-treat [ITT] population for the French study was 140 and the ITT population for all 4 studies combined was 317), and was therefore reviewed separately in detail (see Section VI.A). All 4 studies are compared in the ISE with respect to study design and efficacy results (presented as both pooled and individual study data) (see Section VI.B).

The study designs of these 4 studies were very similar and in some respects identical. All studies were 6 year, open label, randomized studies with an untreated control group for the first 2 years. During the first 2 years of each study, analyses of HV SDS, height SDS_{CA}, and PAH SDS were utilized to compare the efficacy of 2 doses of somatropin (usually 0.033 and 0.067 mg/kg/day; in the Belgian study, a small number of patients received 0.1 mg/kg/day in addition to 0.067 mg/kg/day) and no treatment in stimulating linear growth in SGA children. BA/CA ratio and height SDS_{BA} were also analyzed during the first 24 months to assess the effect of somatropin

on BA progression. During the uncontrolled 24-72 month portion of these studies, patients were either treated continuously with either dose of somatropin (German and Nordic studies), or were treated continuously and discontinuously (e.g., periodic treatment, intermittent treatment) (French and Belgian studies). The same efficacy parameters described above (with the exception of HV SDS) were followed during this uncontrolled phase of the study.

The Summary of Efficacy for this Executive Summary which follows reflects analyses of the pooled data for all 4 studies.

II.B.1.1 Controlled Portion of the Studies - Months 0-24

II.B.1.1.1 Analysis of HV SDS in the ITT population:

- **Mean HV SDS 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, and Month 12 to Month 24 treatment period.**

- HV SDS 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 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.

II.B.1.1.2 Analysis of Height SDS_{CA} in the Per Protocol (PP) 0-24 Month 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 to Month 24 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.

II.B.1.1.3 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).

II.B.1.1.4 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 0.033 and 0.067 mg/kg/day treatment groups compared with the untreated control group - **suggesting that the increase in linear growth was more substantial than the increase in BA.**

II.B.1.1.5 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.**

II.B.1.1.6 Analysis of IGF-I SDS During the 0-24 Month Treatment Period (information derived from French study only)

- 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.

II.B.1.2 Analyses for Months 0-72 (including the uncontrolled 24-72 month portion of the study)

II.B.1.2.1 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. 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 (information derived from French and Belgian studies only).

II.B.1.2.2 PAH SDS and Weight SDS

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

II.B.1.2.3 Height SDS_{BA}

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

II.B.1.2.4 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.

II.B.2 Conclusions - Efficacy

- **These studies 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.**

- **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).

- Younger age at baseline appears to be an important prognosticator of greater growth (e.g., the change in height SDS_{CA} during the 0-24 month treatment period) in response to somatropin therapy in SGA children (as it is in GHD children).

- 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.

- **The small but constant increases in height SDS_{CA} and PAH SDS (as well as weight SDS) after Month 24 indicates that somatropin has a sustained effect on linear growth in SGA children.**

- **Attempts at withdrawal of somatropin during the 24-72 month treatment period (during 2 of the 4 studies) suggest that many (but not all) patients manifest a significant decrease in height SDS_{CA} off therapy, and may benefit from the reinstitution of somatropin 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]).

- **The findings in each of the 4 studies were almost identical, thereby validating each other; when the data from all 4 studies were pooled and the analyses repeated, the level of significance for certain observations clearly increased further.**

II.C Summary of Safety

II.C.1 Summary/Discussion of Safety Issues

II.C.1.1 Exposure and Dosing During Clinical Trials

The exposure to somatropin during these 4 pivotal studies was substantial:

- Approximately 180 patients were exposed to somatropin 0.033 or 0.067 mg/kg/day during the first 2 years of the study.
- Approximately 100 patients were treated continuously between Month 24 and Month 72 or study termination. Sixty two of these 99 patients were treated continuously for 72 months.
- Approximately 50 patients were treated continuously for 96 months.

Conclusions:

- Somatropin was safe and well tolerated in a large number of SGA children treated for as long as ~8 years.

II.C.1.2 Reasons for Study Discontinuation, Adverse Events and Deaths

Most patients withdrew from the clinical trials because it was the designated end of the protocol at that time. Only 4 patients withdrew from the pivotal studies because of adverse events potentially related to somatropin exposure (1 patient with benign intracranial hypertension, 1 patient with elevated sugar during an oral GTT, 1 patient with type 1 diabetes mellitus [wherein somatropin therapy was most likely an aggravating as opposed to a causative factor], and 1 patient with excessive muscle development in the lower limbs).

There were no deaths during the studies and only 3 SAEs potentially related to somatropin therapy (the abovementioned patient with type 1 diabetes mellitus and 2 patients with aggravation of pre-existing scoliosis). Common childhood infections were the most frequent TEAEs reported during the trials - occurring somewhat more frequently in the somatropin-treated patients (~15-40%) than in untreated control patients (~5-20%).

Conclusions:

- SAEs and adverse events resulting in treatment discontinuation related to somatropin therapy were few in number and not unexpected.

II.C.1.3 Adverse Events Previously Associated with Somatropin Administration

II.C.1.3.1 Benign Intracranial Hypertension

One patient developed benign intracranial hypertension at Month 84. Within 1 month of somatropin discontinuation, the event had completely resolved.

Conclusions:

- Benign intracranial hypertension is a rare, but serious, complication of somatropin therapy.

II.C.1.3.2 Abnormal Glucose Tolerance

The administration of 0.067 mg/kg/day of somatropin (compared with 0.033 mg/kg/day) was associated with 1) a greater increase in mean fasting insulin levels, 2) a larger number of patients with fasting insulin levels >29 μU/mL, and 3) a larger number of patients with sporadic glucose elevations with/without concomitant increases in hemoglobin A1c or insulin levels. **These observations at least suggest that the 0.067**

mg/kg/day dosage may result in more abnormalities in glucose homeostasis than the 0.033 mg/kg/day dosage in children born SGA. This finding may be related to the well known decrease in insulin sensitivity in children born SGA compared with age-matched controls, possibly predisposing SGA children to the development of somatropin-induced alterations of glucose homeostasis, especially in larger amounts.

Conclusions:

- **Glucose intolerance may be increased with the recommended 0.067 mg/kg/day dosage (compared with the 0.033 mg/kg/day dosage).**

II.C.1.3.3 Scoliosis

Scoliosis was observed in 9 somatropin patients (pre-existing in 5 patients).

Conclusions:

- Aggravation of pre-existing scoliosis, a well known adverse effect of somatropin therapy, occurred in a significant number of SGA children during these clinical trials.

II.C.1.3.4 Precocious Puberty

One case of "true" precocious puberty (and 1 possible case of precocious puberty) were reported (successfully treated with a luteinizing hormone releasing hormone [LHRH] agonist while somatropin therapy was continued). As discussed in Section VI.C.6.4.4, 2 recently published studies of SGA children receiving long-term therapy with somatropin revealed a mean age for onset of puberty comparable to untreated non-SGA children.

Conclusions:

- Some pediatric endocrinologists feel that therapy with somatropin accelerates the onset of puberty. The literature is conflicted. One of the abovedescribed patients probably did have "true" precocious puberty. However, the second patient (reported in the SUR) was noted to be Tanner stage II at age 8.8 years, but Tanner stage I at age 8.5 years.

II.C.1.3.5 Change in Pigmented Nevi

Three patients reported increases in the size or number of pigmented nevi - which ceased within the initial 24 month treatment period. A fourth patient reported the same finding at Month 99.

Conclusions:

- Changes in pigmented nevi have been reported in the past as a consequence of somatropin therapy. There is no evidence that such changes lead to melanoma.

II.C.1.3.6 Immunogenicity

No patient developed anti-somatropin antibodies during the trials.

Conclusions:

- There was no evidence of immunogenicity during these trials.

II.C.1.3.7 Injection Site Reactions

Injection site reactions were reported in 6 patients.

Conclusions:

- Mild injection site reactions are an occasional complication of somatropin therapy.

II.C.1.3.8 General

The other rare but severe complications of somatropin treatment (e.g., retinopathy, pancreatitis etc) were not observed.

Conclusions:

- None of these complications were observed.

II.C.1.3.9 Acromegaloid Facial Features

Two patients developed prominence of the chin and jaw (prognathism), respectively, apparently without other acromegaloid symptoms and signs (1 patient treated continuously for 72 months with ~0.033 mg/kg/day, and 1 patient treated continuously with ~0.067 mg/kg/day for 72 months - except for Month 24 to Month 48). Both patients had grown satisfactorily and **NOT excessively** during long-term therapy with somatropin, and other acromegaloid features were apparently not present. Serum IGF-I levels were not obtained. Both patients had begun puberty ~1 year before the adverse event was recorded.

Conclusions:

- In the absence of **any** documented IGF-I levels (in particular IGF-I levels considered excessive even for pubertal children), it

is difficult to definitively relate these complaints of facial prominence to somatropin therapy

- Alternative explanations include the unequal facial growth which occurs in some children during puberty and/or a familial predisposition to these facial characteristics.

II.C.1.4 Other Issues Related to Somatropin Administration

II.C.1.4.1 IGF-I Response - Implications for Safety

Although the mean values for IGF-I SDS were in the high normal range, and not significantly different in the 2 dose groups, many more patients in the 0.067 mg/kg/day dose group had IGF-I SDS above the normal range (>+2) at multiple time points during Study 89-041 (compared with patients in the 0.033 mg/kg/day dose group).

Mean height SDS_{CA} and mean PAH SDS (for patients continuously treated with both 0.067 and 0.033 mg/kg/day of somatropin) slowly increased between baseline and Month 72 approaching 0 (the latter finding [e.g., the change in PAH SDS] indicating a normalization of childhood stature when adjusted for genetic potential - **and conversely not indicating growth well in excess of genetic potential**).

Two patients did develop acromegaloid facial features; however, IGF-I levels were not available for either of these patients, and alternative explanations for these findings were possible (see Section II.C.1.3.9 above)

It has recently been reported in adults that elevated levels of IGF-I may be associated with carcinoma of the breast and prostate. Moreover, it is well known that acromegalic patients (with very high levels of IGF-I) are at risk for neoplasia, in particular colon cancer. Other investigators have not reported a relationship between IGF-I and any type of neoplasia. No cases of neoplasia were reported during these studies.

Conclusions:

- **Treatment with 0.067 mg/kg/day (> than 0.033 mg/kg/day) may result in elevated IGF-I SDS (>+2) in a substantial number of SGA children.**
- **In this regard, the increase in PAH SDS towards 0 between Month 0 and Month 72 in both treatment groups suggests growth not in excess of genetic potential, IGF-I levels were not obtained in the 2 patients with reports of "acromegaloid facial features" after the onset of puberty, and no cases of neoplasia were reported during these clinical trials.**

II.C.1.4.2 Final Height (FH)

During these studies, the BA/CA ratio of both short-term (24 months) and long-term (72 months) somatropin-treated SGA patients **increased but remained less than 1**. In addition, in the short-term, there was a significant improvement in height SDS_{BA}. Taken together with recently published data which indicate improved FH outcome in a **small number** of somatropin-treated SGA children, and satisfactory FH in somatropin-treated children with other non-GHD etiologies of short stature, **these data suggest that treatment with somatropin results in a favorable FH outcome in SGA children. Nonetheless, it is essential that as many somatropin-treated SGA patients as possible be followed until FH is attained in order to definitively resolve this question.**

Conclusions:

- The evidence from these trials (e.g., the increase in BA/CA ratio did not exceed 1 after 24 or 72 months in any treatment group) suggests that somatropin will result in a favorable FH outcome in SGA children.

II.C.1.11 Overall Safety Conclusion

Overall, 0.067 and 0.033 mg/kg/day of somatropin have been demonstrated to have a satisfactory safety profile in the treatment of SGA children.

II.D Proposed Dosing

- In the submitted label, the Sponsor proposes that SGA patients (who fail to manifest catch-up growth by age 2) **receive long-term therapy with 0.067 mg/kg/day** (0.48 mg/kg/week in 7 divided doses).

- In that 1) the **0.067 mg/kg/day dose was more efficacious than the 0.033 mg/kg/day dose in stimulating linear growth in SGA children both in the short-term** (2 years; controlled portion of the trials including formal statistical analyses comparing the 2 dosages), **and the long-term*** (6 years; uncontrolled portion of the trials comparing longitudinal descriptive statistics); and 2) **the safety profile of these 2 dosage were "essentially" comparable in SGA children; this medical reviewer agrees with the Sponsor's proposed dosing regimen.**

***Caveat: Once somatropin therapy has resulted in a significant increase in short-term linear growth in SGA children, therapy could 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} (see Sectins I.B.1.2 and II.B.1.2.1 earlier in this EXECUTIVE SUMMARY.)**

II.E Special Populations

II.E.1 Gender, Racial/Ethnic and Age-Related Differences

There were no apparent gender or age-related differences observed in efficacy or safety. However, the number of patients analyzed were too few to draw definitive conclusions.

II.E.2 Pediatric Studies

These studies were pediatric studies (see Pediatric Exclusivity Page as per Project Manager).

II.E.3 Renal and Hepatic Disease

Patients with clinically significant renal and/or hepatic disease were excluded from these clinical trials. Therefore, appropriate subgroup analyses could not be performed. Furthermore, studies with somatropin have not been conducted in other pediatric populations with short stature with renal or hepatic disease.

II.E.4 Pregnancy/Nursing Use

New preclinical studies were not conducted as part of this NDA supplement submission. Preclinical studies with somatropin in the past have not revealed significant toxicity in pregnant rabbits/rats, or their offspring. However, in that controlled studies have not been conducted in pregnant women, this reviewer agrees with the Sponsor's current labeling that somatropin should be used during pregnancy on a very selective basis when it is clearly necessary.

It is not known whether somatropin is excreted in human milk. Therefore, this reviewwer agrees with the Sponsor's current labeling that somatropin should be administered with caution to a nursing woman.

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CLINICAL REVIEW

I. Introduction and Background

I.A General Information

I.A.1 Chemical; Generic; and Trade Names

Chemical name - Recombinant human growth hormone (rhGH).
Generic name - Somatropin (rDNA origin).
Established trade name - Genotropin.

I.A.2 Drug Class

Recombinant human growth hormone (rhGH).

I.A.3 Related Drugs

All the other approved somatropin (rDNA origin) products.

I.A.4 Sponsor's Proposed Indication

Somatropin is indicated for the long-term treatment of patients with SGA and failure to achieve catch-up growth by age 2.

I.A.5 Dosage Form, Dosage Regimen Recommended by Sponsor, and Route of Administration

Reconstituted injectable suspension. Sponsor's recommended dosage regimen is 0.067 mg/kg/day SC.

I.A.6 Brief Overview of Clinical Section of NDA Review

Efficacy was reviewed separately in detail for Study CTN 89-041 (France) (which contained ~50% of the enrolled patients). The efficacy reviews for the other clinical trials (Study CTN 90-079 [Germany], Study CTN 90-080/98-8122-011 [Belgium], and [Study CTN 89-070/89-071 [Nordic countries]) are contained in the Integrated Summary of Efficacy (ISE). A consolidated safety review for all of the clinical trials is found in the Integrated Summary of Safety (ISS) and the SUR.

I.A.7 Milestones in Product Development

No prior FDA reviews or Advisory Committee meetings.

I.A.8 Foreign Marketing Status

In 1996, the Sponsor applied to the European Agency for the Evaluation of Medicinal Products in an attempt to obtain an indication to treat children born SGA with failure to achieve catch-up growth by age 2. The Sponsor's application was disapproved.

Rapid catch-up growth was observed in most patients (as in the present NDA supplement submission). **However, the European Agency at that time expressed concern about an unacceptable risk/benefit ratio.**

On the 1 hand, there was concern that the FH outcome was too uncertain:

- the BA/CA ratio had advanced too rapidly in some patients;
- published data regarding FH in somatropin-treated SGA children was nonexistent;
- BA-based predictions of FH (e.g., predicted adult height, height SDS_{BA}) in children 2-8 years old were (and are) considered unreliable;
- and 4) published FH data for somatropin-treated patients with other non-GHD etiologies of short stature (e.g., chronic renal insufficiency, Turner's syndrome) was lacking.

On the other hand, the European Agency was concerned about the potential risks associated with administering a supraphysiologic amount of somatropin, in particular glucose intolerance and tumorigenesis.

II. Clinically Relevant Findings from Chemistry, Preclinical Toxicology, Biopharmaceutics and Statistical Reviews

II.A Chemistry

See Chemistry Review in original NDA for Genotropin.

II.B Preclinical Toxicology

See Pharmacology/Toxicology Review in original NDA for Genotropin.

II.C Biopharmaceutics Review and Human Pharmacology, Pharmacokinetics (PK) and Pharmacodynamics (PD)

See Biopharmaceutics Review in original NDA for Genotropin. In addition, see Sections I.B.3 and II.D in the EXECUTIVE SUMMARY for discussion of the proposed dosing regimen,

II.D Statistical Review

See Statistical Review. The Medical Reviewer collaborated appropriately with the Statistical Reviewer, in particular with regard to the primary efficacy analysis for the 2 year controlled portion of the 4 pivotal trials.

Note: The Agency's Statistical Reviewer discovered an error in the extrapolation procedure performed by the Sponsor to calculate the HV SDS values in the Belgian and Nordic studies. Corrected HV SDS values were then recalculated by the Sponsor; the original values were minimally altered. Both the Sponsor and the Agency's Statistical Reviewer then reperformed the HV SDS efficacy analyses for the Belgian and Nordic studies, as well as for data pooled from all 4 studies, using the corrected HV SDS values. The new HV SDS analyses produced the same degree of statistical significance as was observed originally, and therefore did not impact the clinical conclusions.

III. Clincal Pharmacology

See Biopharmaceutics Review in original NDA for Genotropin.

IV. Description of Clinical Data and Sources

IV.A Materials Reviewed

- All clinical data in the original submission received on 26Jan01 (via CDROM reviewer's aid and hard copy)
- Safety Update received on 25Jun01 (via CDROM reviewer's aid).
- CDROMS submitted on 25Ap01, 8Jun01 and 25Jun01 in response to multiple questions posed by this medical officer during telecons with Sponsor's represenatives (see Section IV.A.2) in April, May, June and July 2001.
- Email attachments sent by secure email on 11Jul01 and 13Jul01 in response to questions posed by this medical officer.
- Reviews for related NDAs for other approved somatropin products (see Section IV.A.1).

IV.A.1 Related INDs and NDAs

NDAs and INDs for all of the other approved somatropin (rDNA origin) products.

IV.A.2 Correspondence with Sponsor

Multiple telecons between Gregory Brier and/or Cindy Blanchard, Regulatory Affairs, Pharmacia and Upjohn, Kalamazoo, MI (and on 1 occasion, Dr.Steven Schoenfeld in the United Kingdom), and this medical reviewer occurred in April, May, June and July 2001. During these telecons, various questions regarding the study reports, ISE, ISS and SUR were posed by this reviewer to the Sponsor. Shortly thereafter, the Sponsor provided answers (in the form of text, graphs and figures) to these questions on the CDROMs referred to Section IV.A.

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IV.B Table Summarizing Design of Clinical Trials

Table 1. Pivotal Studies

Clinical Trial No. Coordinating Investigators Study Dates Country	Study Design	Dose & Regimen	Patients			Report Location in sNDA (Vol/Pg)
			No. Randomized/ ITT*/Completed 72 Months	Age (yrs)† Range (Mean)*	M/F*	
CTN 89-041 Pr J.L. Chaussain 26-Mar-90 to 04-Jul-97 France	Multicenter (n=22), randomized, open-label, 3 parallel groups (2 active treatment groups + one untreated control group)	Somatropin 0.033 mg/kg/day Somatropin 0.067 mg/kg/day 6 or 7 SC injections/week	152/140/100	3.0-8.4 (5.7)	75/65	**Volume** 2/page 37
CTN 89-070/89-071 Pr K. Albertsson-Wikland 02-Oct-90 to 10-Jun-99 Sweden, Denmark, Norway, Finland (Nordic countries)	Multicenter (n=23), randomized, open-label, 3 parallel groups (2 active treatment groups + one untreated control group)	Somatropin 0.033 mg/kg/day Somatropin 0.067 mg/kg/day SC injection once daily	61/56/28	2.2-8.0 (4.5)	35/21	**Volume** 14/page 1
CTN 90-079 Dr H.A. Wollman 28-Mar-91 to 11-Sep-98 Germany	Multicenter (n=25), randomized, open-label, 3 parallel groups (2 active treatment groups + one untreated control group)	Somatropin 0.033 mg/kg/day Somatropin 0.067 mg/kg/day SC injection once daily	73/69/25	2.0-7.9 (5.4)	47/22	**Volume** 17/page 1
CTN 90-080/98-8122-011 Dr F. deZegher 15-Jul-91 to 09-Mar-98 Belgium	Multicenter (n=8), randomized, open-label, 3 parallel groups (2 active treatment groups + one untreated control group)	Somatropin 0.067 mg/kg/day Somatropin 0.1 mg/kg/day SC injection once daily	54/52/33	2.0-8.1 (5.2)	26/26	**Volume** 25/page 1

* Patients randomized to active treatment who received at least 1 injection, and patients randomized to the untreated group who attended the baseline visit. Age and sex data are based on the ITT population.

† At study entry

Abbreviations: CTN = clinical trial number; ITT = intent to treat; M/F = male/female; Rep = study report; SC = subcutaneous

IV.C Patient Demographics

See review of Study CTN 89-041 (France), ISE and ISS.

IV.D Extent of Exposure

See ISS.

IV.E Clinical Background

IV.E.1 Post-Marketing Experience

None - domestic or foreign.

IV.E.2 Literature Search

Literature regarding the natural history of children born SGA and the treatment of children born SGA with somatropin were reviewed for the last 10 years. Appropriate references are cited in the text of this review, and a list of these references appears after signature page.

IV.E.3 Background Information/Rationale for Initiating Clinical Trials in 1990-1991, and Summary of Relevant Published Clinical Trials Regarding SGA

Approximately 2.5% of all human infants are born SGA (defined as either weight or length at preterm or term birth <2 standard deviations (SD) below applicable gestational age- and sex-adjusted population means; the normal range is conventionally regarded as the applicable mean ± 2 SD). In the majority of cases, SGA is the result of inadequate nutritional delivery to the fetus (genetic or chromosomal abnormalities and toxins are other important causes) (1).

Ten to fifteen percent of all SGA children fail to manifest spontaneous catch-up growth by age 2 (e.g., height SDS_{CA} is <-2) (2-5). Furthermore, if left untreated, the SGA children who have failed to catch-up by age 2 demonstrate persistent growth failure throughout childhood and into adulthood (e.g., ~10% of all SGA children do not achieve a height SDS_{CA} >-2 by the age of 18) (3-5). In a cohort of 15 untreated Swedish SGA children (without initial catch-up) followed for up to 18 years, mean final height SDS_{CA} was - 1.8 (5).

As a consequence of their short stature during childhood, some investigators believe that SGA children may experience psychosocial problems (e.g., problems with self-concept with ramifications in many areas) (6). In addition, it is well known in normal children and GHD children that FH is strongly correlated with height at the onset of puberty (7-8). Therefore, any therapy which could potentially promote

catch-up growth prior to puberty would be highly advantageous in SGA children, in particular with regard to the observation that the pubertal growth spurt in SGA patients is less than that seen in the general population (9).

With regard to SGA children (who fail to spontaneously catch-up), a large percentage have putative growth hormone (GH) "insufficiency" (e.g., abnormalities in 24 hour GH profiles and/or low levels of insulin-like growth factor-I (IGF-I); however, only ~10% of these patients have "true" GHD as documented by classical GH provocative testing (10-11).

During the last decade, several studies have demonstrated that treatment with somatropin can induce short-term catch-up growth in SGA children (12-14), and 2 other studies have shown that these children continue to grow well after 5-7 years of treatment (15-16). Sas et al reported that treatment of 79 SGA children (including 22 patients with GHD) with somatropin (3 or 6 IU/m^2/day; comparable to 0.033 or 0.067 mg/kg/day) resulted in a change in height SDS_{CA} of ~1.5-2 SDS during the first 2 years of therapy (the larger dose produced a significantly greater change than the lower dose only in prepubertal children), and then a slower but constant increment in height SDS_{CA} between Month 24 and Month 60; height SDS_{BA} and predicted adult height increased during the 5 years of therapy, despite a BA/CA ratio >1 in both dose groups after each year of treatment (15).

In view of 1) the apparently significant prevalence of GH insufficiency in SGA children (who have failed to catch-up spontaneously), 2) the satisfactory short-term and long- term linear growth responses of SGA children observed after somatropin therapy in several recently published trials, and 3) the satisfactory growth responses achieved with somatropin therapy in children with GHD [17], as well as in non-GHD children (e.g., chronic renal insufficiency [18]), the decision of the Sponsor in 1990-1991 to initiate 4 almost identical clinical trials (France, Belgium, German and Nordic countries) to investigate the short-term (2 years) and long-term (6 years) efficacy, safety and tolerability of somatropin in the treatment of **non-GHD children born SGA (without sufficient spontaneous catch-up growth by age 2)** was appropriate - based on literature available at that time, and the large amount of relevant data published during the 1990s while the 4 trials were ongoing.

Data closure for efficacy and safety results for the original 25Jan01 submission occurred when every child enrolled in the 4 studies had completed 72 months on-study; data closure for the Safety Update Report (SUR) was 31Dec00.

V. Clinical Review Methods

V.A Conduct of Review and Materials Consulted

Clinical studies were reviewed in accordance with their relative importance. CTN 89-041 (the largest of the 4 pivotal studies comparing 2 **daily doses of somatropin**, the ISE, and the ISS/SUR were reviewed with the greatest intensity. The other 3 individual study reports were reviewed with moderate intensity.

This reviewer carefully reviewed the individual patient data for a number of selected important safety parameters (e.g., glucose, insulin, hemoglobin A1c, IGF-I), as well as many of the disposition tables and figures. **On several occasions, significant errors were found requiring the Sponsor to resubmit certain tables and graphs.**

The materials consulted during the review were 1) the sources listed in Section V.A; and 2) the current literature noted in Section V.E.2.

V.B Evaluation of Data Quality and Integrity Including DSI Audits/Reports

V.B.1 DSI Audits/Reports

On-site inspections were accomplished at 2 centers in Europe (Hopital St-Vincent de Paul (21 patients enrolled at this site), Paris, France, **Dr. Jean-Louis Chaussain - Primary Investigator for Study 89-041 (France)**; and University Hospital Gasthuisberg, Leuven, Belgium, **Dr. Francis de Zegher MD, PhD – Primary Investigator for Study 90-080/98-8122-011 (Belgium).** The written reports by the Agency's DSI inspector were reviewed by this medical officer.

With regard to Study 89-041, study records were found to be discordant with case report forms for several patients, several informed consent documents were found be missing or inaccurate, and certain drug accountability records were not on file. On the other hand, no adverse events were found in the clinical records that were not reported on the case report forms in the NDA supplement submission. **Within these limitations, the DSI inspector considered the data reviewed acceptable for consideration.**

With regard to Study 90-080/98-8122-011, no data deficiencies or discrepancies were noted and the inspection was classified "No Action Indicated". **The DSI inspector considered the data reviewed acceptable for consideration.**

V.B.2 Medical Officer Observations Regarding Data Quality/Integrity and the General Quality of the Written Individual Study, ISE, ISS and SUR Reports

V.B.2.1 General

The Sponsor acknowledged from the outset in the NDA supplement submission that this study was not primarily intended to produce data in support of a registration. **The study was therefore not managed in complete adherence with the normal standards for registration studies.**

V.B.2.2 Quality of Written Reports

V.B.2.2.1 Misstatements/Errors

CTN 89-041 (France): IGF-I determinations were performed at various center-dependent laboratories using multiple assays **(and NOT at a central laboratory in Stockholm, Sweden as stated in the submission).**

ISE: Several end-of-text tables tabulating investigator-determined clinically significant (CS) and non-clinically significant (NCS) elevations of safety laboratory parameters were inaccurately constructed because of a "programmatic error". The Sponsor submitted corrected tables in a timely fashion.

All Studies: **The reports in general were not written as clearly and comprehensively as they could have been in multiple respects. As a result, many requests for additional information/graphics/analysies by this medical officer were necessary.** For example, the question of how many patients actually received luteinizing hormone releasing hormone (LHRH) agonist therapy (a major protocol violation), and for what reason (e.g., treatment of "true" [n=2] or presumed [n=3] precocious puberty, to prophylactically delay the onset of puberty in order to maximize the response to somatropin [n=6]) was not consistent across study reports and required several communications with the Sponsor to clarify.

V.B.2.2.2 Acknowledgements to the Sponsor

This medical officer would like to thank Ms. Blanchard, Mr. Brier, Dr. Schoenfeld, and the Sponsor's statistical team in Sweden for responding to my many questions in a very timely and informative way once requests were made.

V.B.3 Randomization, Compliance and Drug Accountability Issues

V.B.3.1 Randomization Issues

French study: The patients' initials and dates of birth were not always recorded on the envelope before opening and some of the envelopes are missing from the file, especially those used for the initial randomization. **However, the randomization lists created at the same time as the envelopes show all patient numbers and their corresponding treatment groups, and indicate that the randomization process was satisfactory.**

V.B.3.2 Compliance Issues

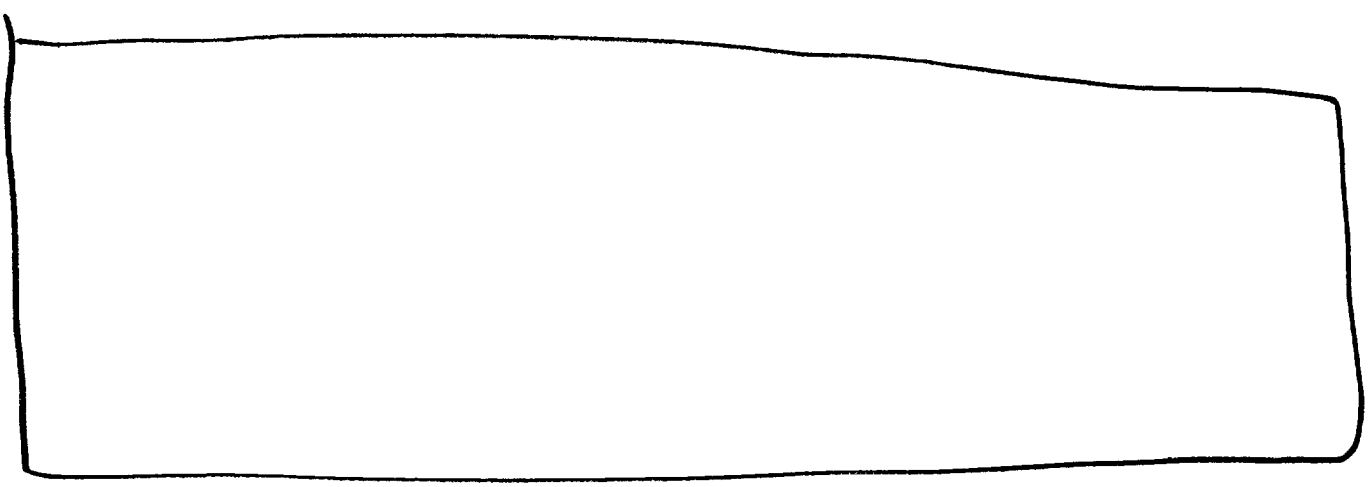
French study: Compliance could not be properly assessed on the basis of the number of cartridges used by each patient because the original protocol failed to stipulate the return of used vials. In addition, compliance problems were not consistently mentioned in the case report forms.

V.B.3.3 Drug Accountability Issues

French study: The Sponsor acknowledged from the outset in the NDA supplement submission that the documentation of product accountability between 1990 and 1996 was less than satisfactory. A certificate validating that products returned from study centers to the Central Pharmacy of the Paris Hospitals (PCH) is missing. This finding is concordant with the observations of the DSI inspector (see Section V.B.1 above).

V.C Quality of Informed Consent/Standard of Patient Care

Several of the informed consent documents were missing or inaccurate at the French hospital inspected by the DSI (see Section V.B.1 above).



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VI. Reviews of Efficacy and Safety for Clinical Studies

VI.A Review of Efficacy for Study CTN 89-041 (France)

VI.A.1 Objectives

The primary objective of this Phase III, open label, randomized, parallel group, multicenter (n=23) clinical trial conducted in France in 140 children born SGA (who subsequently failed to catch-up with their peers by age 2; age range ~2-8) was to compare linear growth in these patients (primary efficacy parameter was HV SDS and secondary efficacy parameters included height SDS_{CA}) with growth in an untreated control group after 2 years of therapy with 2 doses of somatropin. The secondary objectives of the study were to compare the growth promoting effects of the 2 different doses of somatropin after 2 years of therapy (uncontrolled), and to evaluate the safety and tolerability of long-term treatment with somatropin in the SGA patient population.

VI.A.2 Brief Summary of Published Clinical Trials Prior to the Pivotal Phase III Studies

See Section IV.E.3

VI.A.3 Study Design

VI.A.3.1 Description of the Study - Including the Choice of a Control Grouph

Potential study patients were screened to determine eligibility ("background visit"). One hundred and fifty two eligible SGA subjects were then openly* randomized to receive daily SC doses of either 0.033 or 0.067 mg/kg/day of somatropin (begun at the "baseline visit"), or to an untreated control group. After 1 year on study, the untreated patients could choose to remain untreated for 1 more year, or start treatment (in which case they were randomized to either the 0.033 or 0.067 mg/kg/day treatment arms). The first 2 years of study constitute the essential controlled portion of the trial wherein the 2 treatment groups and the untreated control group were statistically compared with regard to the primary and secondary efficacy parameters.** See Figure 1.

The original protocol projected a 2 year study with an untreated control group. Subsequent amendments (4-6, 9-11) extended the study year by year until finally amendment 12 prolonged the study until FH was attained. An untreated control group was no longer maintained after 2 years. In this report, comparative descriptive statistics are presented for various secondary efficacy parameters (in particular height SDS_{CA}**) for the patients who completed 6 years of therapy with

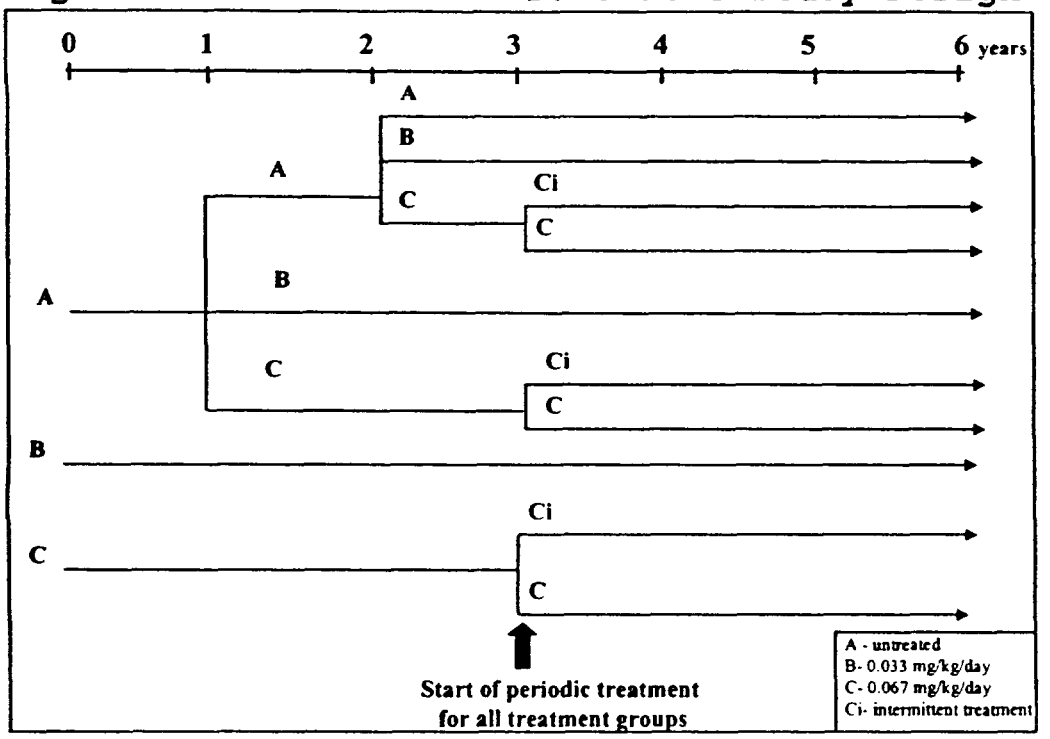
either 0.033 or 0.067 mg/kg/day of somatropin, or discontinuous therapy (defined ahead).

After 2 years on-study, never treated patients could again choose to remain untreated indefinitely, or start treatment (in which case they were again randomized to 1 of the same 2 treatment arms). After 3 years on study, patients who had been receiving somatropin 0.067 mg/kg/day continuously for 1-3 years, were randomized to 2 groups - a continuous treatment group and an intermittent treatment group who thence received therapy cyclically (e.g., 3 months on, 3 months off). In addition, after at least 3 years of therapy, treatment could be stopped if height SDS_{CA} increased to >-1 (see amendment 5 to original protocol). Treatment could be restarted in these patients if 1) height SDS_{CA} decreased to ≤-2, 2) HV SDS decreased to the pretreatment value, and 3) the child had discontinued therapy for at least 1 year (see amendment 8 to original protocol). See Figure 1.

***The study could not be blinded as this would have required injecting children in the control group with placebo – a practice which was considered unethical.**

HV SDS is the most appropriate measure for comparisons among treatment groups during periods of rapid growth such as catch-up growth, and was therefore used as the primary efficacy endpoint and analyzed on a yearly basis from baseline to Month 24. (HV was the primary efficacy variable designated in the original study protocol; however, this primary efficacy variable was later amended to HV SDS **(prior to database closure) so that the primary efficacy endpoints in all 4 pivotal studies would be identical.) Height SDS_{CA} becomes a better discriminator among treatment groups after rapid growth has been completed and the effects of somatropin on height are more constant from year to year. The change in height SDS_{CA} over both 24 and 72 months was therefore chosen as the most important secondary efficacy endpoint.

Figure 1. CTN 89-041 - Schematic Study Design



Study assessments for efficacy and safety were accomplished at the "baseline visit", and then at 3 monthly, 6 monthly and annual visits for the duration of the trial. At 3 monthly visits, growth evaluation was performed and adverse events were recorded. At 6 monthly and annual visits, a more extensive efficacy/safety evaluation was performed including determination of anthropometric measurements, BA, safety laboratory tests, and anti-somatropin antibodies. See Table 2.

VI.A.3.2 Protocol Amendments (overview)

Thirteen amendments were made to the initial protocol. The majority of the amendments extended the study duration year by year (amendments 4-6, 9-12 - see second paragraph of Section VI.A.3.1). Amendments 5 and 8 allowed discontinuation and restart of therapy (see third paragraph of Section VI.A.3.1). Amendment 2 permitted patients initially randomized to the untreated control group to choose to continue without therapy for a second year or to be randomized to 1 of the 2 treatment arms after 1 year on study.

VI.A.4 Materials and Methods

VI.A.4.1 Subjects

VI.A.4.1.1 Subject Selection

The protocol called for the enrollment of 147 SGA patients. In fact, 150 patients were randomized and 142 patients entered the first year of therapy.

VI.A.4.1.2 Inclusion Criteria

- Males and females age 3-8 years old
- Height SDS_{CA} <-2 (as per reference population of French children [19, Sempe et al])
- Birth length SDS <-2 (20, Usher et al)
- Birth weight known
- Gestational age >35 weeks (preferably based on ultrasound measurements during pregnancy)
- HV_{CA} <M (e.g., meaning a HV SDS <0 during the 12 month period prior to inclusion [19, Sempe et al]); during the year prior to randomization, 3 height measurements had to be performed
- GH level >10 ng/ml after a standard provocation test
- Tanner pubertal stage I (prepubertal)

VI.A.4.1.3 Exclusion Criteria

- Endocrine disease including hypopituitarism and Cushing's syndrome (exception: children with well substituted hypothyroidism can be included)
- Previous radiotherapy
- Severe chronic disease
- Chromosomal aberration
- Any known syndrome (e.g., Silver-Russell, Turner's or Seckel syndrome) which possibly could affect growth
- Known intrauterine infection
- Microcephaly, defined as head circumference <-2 SD (Sempe)
- Previous treatment with steroids which have an anabolic effect
- Corticosteroid treatment for more than 1 week per year prior to enrollment

VI.A.4.1.5 Subject Discontinuation

- Serious adverse events (SAEs)
- Verified noncompliance (defined as missing >10% of injections)
- Allergic reaction to somatropin

VI.A.4.2 Study Treatment

VI.A.4.2.1 Formulation/Drug Delivery

The Sponsor's somatropin product is marketed as Genotonorm in France and Genotropin in the United States. Somatropin (Genotonorm) 12 IU* was used until 1994 when it was replaced by somatropin (Genotonorm) 16 IU=5.3 mg. Somatropin (Genotonorm) 36 IU=12 mg was added as an alternative source of somatropin in 1999 (e.g., this presentation was only used after the 0-72 month study period during the safety update reporting period). Somatropin 16 IU=5.3 mg or 36 IU=12 mg were dispensed in a 2 compartment cartridge, with the active substance in 1 compartment and the solvent/preservative in the other. When the cartridge is screwed into the KabiPen or somatropin pen device, reconstitution occurs resulting in concentrations of 16 IU=5.3 mg/mL or 36 IU=12 mg//mL (the well established conversion factor is 1 mg = 3 IU of all somatropin products).

*Genotropin 12 IU (only marketed in Europe), is presented as a sterile powder in a plain vial rather than a two-chambered cartridge, and is then reconstituted to 4 IU/mL corresponding to 1.3 mg/mL.

The excipients in the above formulations include mannitol, sodium dihydrogen phosphate disodium phosphate anhydre, and M-cresol.

Note: Please refer to Section VI.B.4.2.1 in the ISE for a detailed discussion/comparison of all of the somatropin presentations used during the 4 pivotal studies.

VI.A.4.2.2 Treatments Administered - Dosage and Administration

Patients were initially randomized to 1 of 3 study arms - no treatment, 0.033 mg/kg/day SC of somatropin or 0.067 mg/kg/day SC of somatropin. Patients were advised to rotate injection sites to avoid local lipoatrophy. See Section VI.A.3.1 for further detail regarding subsequent treatments.

VI.A.4.2.3 Method of Treatment Assignment - Randomization

Patients were randomized on 3 occasions during the study (in standard fashion utilizing randomization codes and envelopes):

1) Initial randomization to 1 of 3 study arms
2) Randomization to 1 of 2 treatment arms **after patient had received no therapy for 1 or 2 years and had then chosen to be treated with somatropin**
3) After 1-3 years of treatment with 0.067 mg/kg/day of somatropin, randomization to continuous or intermittent therapy

Note: The patients' initials and dates of birth were not always recorded on the envelope before opening and some of the envelopes are missing from the file, especially those used for the initial randomization. However, the randomization lists created at the same time as the envelopes show all patient numbers and their corresponding treatment groups, and indicate that the randomization process was satisfactory.

VI.A.4.2.4 Selection of Doses

For the existing pediatric indications, daily doses of 0.042 mg/kg and 0.033 mg/kg (GHD), and 0.054 mg/kg and 0.050 mg/kg (short stature related to Turner's syndrome and chronic renal insufficiency) are recommended in the United States and Europe, respectively. Therefore, daily doses of 0.033 mg/kg (a "standard" amount) and 0.067 mg/kg (a larger amount with regard to the possibility of resistance to therapy in SGA children) were chosen for this study.

VI.A.4.2.5 Dosage Modification

Dosage modifications (as per individual investigators) were allowed after the initial 24 month controlled portion of the trial was completed.

VI.A.4.2.6 Concomitant Therapy

While on-study, patients could not receive corticosteroid therapy for more than 1 week per year. Medications which were considered necessary for treatment of an intercurrent disease were given at the discretion of the investigator. Therapy with LHRH analogs was prohibited (as per Amendment 13 in 10/99); however, this amendment was effected late in the course of this study and therefore a number of patients were treated with LHRH analogs. These patients were excluded from the per protocol efficacy analyses.

VI.A.4.2.7 Treatment Compliance

Compliance problems were detected but not always mentioned in the case report forms.

VI.A.4.2.8 Product Accountability

Documentation of product accountability between 1990 and 1996 was less than satisfactory. A certificate validating that products returned from study centers to the Central Pharmacy of the Paris Hospitals (PCH) is missing.

VI.A.4.3 Study Assessments

VI.A.4.3.1 Screening/Pre-treatment Assessments (see Table 2)

To confirm subject eligibility and to establish baseline measurements, the following assessments were accomplished at the "background visit" and/or the "baseline visit":

- Complete medical history (including gestational age, birth length/weight, growth history especially during year prior to enrollment)
- Complete physical examination (including standing/sitting height allowing determination of HV/HV SDS during the year prior to enrollment as well as baseline height SDS_{CA})
- Complete blood count (CBC) with differential and platelet count[+]
- Serum chemistry panel, including glucose, hemoglobin A1c, ALT (SGPT), AST (SGOT)[+]
- Free T4[+]
- Anti-somatropin antibodies[+]
- Serum IGF-I[+] (see Section VI.A.4.3.2.2 for calculation of IGF-I SDS)
- **Standard GH provocative test**[+]

[+] Performed at various center-dependent laboratories.

VI.A.4.3.2 Assessments During Treatment

VI.A.4.3.2.1 Efficacy Parameters

VI.A.4.3.2.1.1 Primary Efficacy Parameter (see Table 2)

- HV SDS 0-12 months and 12-24 months after treatment initiation (19, Sempe et al)*

*calculation:

1) HV SDS = (HV - Mean)/SD
HV = the patient's increase in height during the previous 12 months
Mean = the expected HV for patient's age and sex
SD = the standard deviation of HV for patient's age and sex

VI.A.4.3.2.1.2 Secondary Efficacy Parameters (see Table 2)

- Height SDS_{CA} (19, Sempe et al)*
- PAH SDS*
- Height SDS_{BA} (19, Sempe et al)*
- BA (blinded assessment using Greulich-Pyle method [21])
- BA/CA ratio

- Weight SDS
- Body Mass Index (BMI) SDS

*calculations:

1) Height SDS_{CA} = (height - mean)/SD
Height = the patient's actual height
Mean = the expected height for patient's age and sex
SD = the standard deviation of height for patient's age and sex
2) PAH SDS = height SDS_{CA} - target height SDS
Target height SDS = (target height - mean)/SD (Sempe)
Target height (boys) = (ma height$^{\phi}$ + pa height$^{\phi}$)/2 + 6.5 cm
Target height (girls) = (ma height$^{\phi}$ + pa height$^{\phi}$)/2 - 6.5 cm
Mean = the expected FH for patient's sex
SD = the standard deviation of height at FH for patient's sex
$^{\phi}$Parental height preferably measured but may be self-reported.
3) Height SDS_{BA} = (height - mean)/SD
Height = the patient's actual height
Mean = the expected real time height for patient's BA and sex
SD = the standard deviation of expected real time height for patient's BA and sex

Note: All height measurements were to be performed by an experienced investigator using a . The mean of 3 consecutive measurements was recorded.

VI.A.4.3.2.2 Safety Parameters (See Table 2)

- Adverse events
- Physical examinations
- Safety laboratory tests including glucose, hemoglobin A1c, ALT, AST^{+}
- Free or total T4^{+}
- Serum IGF-I^{+} and IGF-I SDS*
- Anti-somatropin antibodies^{+}

$^{+}$Performed at various center-dependent laboratories.

*calculations:

1) IGF-I SDS

Formula for IGF-I SDS:

$$\frac{\text{patient value} - \left(\frac{\text{upper normal range} + \text{lower normal range}}{2}\right)}{\frac{\text{upper normal range} - \text{lower normal range}}{4}}$$

Rationale for IGF-I SDS calculation:

The IGF-I SDS variable was calculated in the same manner as the efficacy endpoints: $\frac{\text{IGF-I value} - \text{population mean}}{\text{population SD}}$.

It was assumed that the normal range at each center was defined as the interval within ± 2 SD from the mean (commensurate with the definition of SGA). Then the population mean is the mean value of the normal range's upper and lower limits. Since there are 4 SD between -2 SD and +2 SD, the population SD was obtained by dividing the difference between the upper limit and the lower limit by 4.

IGF-I determinations were performed at various center-dependent laboratories using multiple assays (and NOT at a central laboratory in Stockholm, Sweden as stated in the submission).

Table 2. CTN 89-041 - Flowchart of Baseline and On Study Efficacy and Safety Parameters*

Evaluations	Screening Period	Treatment Period			
	Background Visit	Baseline Visit	3-Monthly Visits	6-Monthly Visits	Yearly Visits
Informed consent	X				
Onset of treatment		X			
Medical history	X	X			
Concomitant meds & Compliance	X	X	X	X	X
Physical exam	X	X		X!	X!
Growth evaluation**	X	X	X	X	X
Puberty staging	X	X		X	X
BA (blinded)		X		X	X
Adverse events			X	X	X
Safety labs	X	X		X	X
Free or total T4	X	X		X	X
Anti-somatropin antibodies (first 2 yrs only)		X			X
IGF-I		X		X	X
GH provocation test	X				

*Table partially derived from submission
**Height, sitting height and weight

VI.A.4.4 Statistical Analysis

VI.A.4.4.1 General Comments

All statistical methods were rewritten in amendment 1 dated December 1989 – which became valid before any patient entered the study.

VI.A.4.4.2 Sample Size Calculation

The original primary outcome measure was HV. Assuming a 2.0 cm difference in mean HV between the 0.033 mg/kg/day group and the untreated control group (as well as between the 0.033 mg/kg/day group and the 0.067 mg/kg/day group), a SD of 2.0 cm, and 44 subjects in each somatropin dose group and 22 patients in the untreated control

group, there was ~80% power using a two-tailed test at the α=0.05 level. Corrections were made for the unbalanced design and multiple comparisons (Bonferroni).

VI.A.4.4.3 Efficacy Analysis

VI.A.4.4.3.1 Primary Efficacy Variable

The primary efficacy variable was changed from HV to HV SDS to obtain consistency with the other 3 pivotal studies contained in this NDA submission. This decision was made before dataset closure.

HV SDS in the 2 treatment arms and the untreated control group were compared on a yearly basis (0-12 months and 12-24 months) in both the intent to treat (ITT)* and per protocol (PP)** 0-24 month populations. More specifically, a one-way analysis of variance (ANOVA) was carried out with HV SDS as response and treatment as factor in the model. The α-error was chosen to be 0.05. If the ANOVA revealed a treatment effect, Dunnett's test (a t-test with α-correction for multiple comparisons with a control) was performed to assess the differences in HV SDS between the active treatment groups and the untreated control group for each treatment year. To correct for the 2 tests (0-12 months and 12-24 months), the Bonferroni adjustment was used (e.g., α=0.025 in each test). On the other hand, Student's t-test was used to assess the differences in HV SDS between the 2 somatropin treatment groups for each treatment year. No adjustment for multiple comparisons was made. As a result, these latter analyses can only be interpreted in a descriptive way.

*ITT population included all patients randomized to active treatment who received at least 1 injection of study medication, and all patients randomized to the control group who attended at least the baseline visit.
**The PP 0-24 month population included all patients who completed the first 2 years of the study without major protocol violations.

VI.A.4.4.3.2 Secondary Efficacy Variables

The secondary efficacy variables (e.g., height SDS_{CA}, PAH SDS, etc) were only compared in the PP 0-24 month and PP 0-72 month populations. Student's t-test was used to assess the differences in secondary efficacy variables between all 3 study groups for the 0-24 month study period. No adjustment for multiple comparisons was made. As a result, these latter analyses can only be interpreted in a descriptive way. No statistical tests were performed to assess differences in secondary efficacy variables for the 0-72 month study period. Mean and standard error of the mean (SEM) for these variables were visualized graphically over time for each treatment group (in particular, height SDS_{CA}).

VI.A.4.4.3.3 Exploratory Covariate Analyses

Supplementary analyses of HV SDS after 12 and 24 months of somatropin treatment were performed for the ITT and PP 0-24 populations which included age at baseline, sex and HV SDS at baseline as covariates. In addition, supplementary analyses of height SDS after 24 months of somatropin treatment were performed for the PP 0-24 population which included age at baseline, sex and height SDS at baseline as covariates.

VI.A.4.4.3.4 Subgroup Analyses

Comparative analyses between the 3 treatment groups were performed in males/females.

VI.A.4.4.4 Safety Analysis

Laboratory and other safety values (including vital signs) were summarized with simple descriptive statistics, frequency tables or patient data listings for 3 safety populations (0-12 months, 12-24 months, and 24-72 months) by dose group.

VI.A.4.5 Data Quality Assurance

This study was not primarily intended to produce data in support of a registration. The study was therefore not managed in complete adherence with the normal standard for registration studies.

The Sponsor states that accurate, consistent, and reliable data were ensured through the use of standard practices and procedures. Independent audits of this study were conducted by the Sponsor's Clinical Quality Assurance Division in April 1999 and April 2000. [redacted] performed all data management procedures including a series of logic and consistency checks on the database to ensure acceptable accuracy and completeness, and a database audit prior to database lock. The final database was then transferred to [redacted] for analysis and reporting.

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VI.A.5 Results

VI.A.5.1 Patient Disposition and Protocol Violations

VI.A.5.1.1 Study Periods 0-12, 12-24 and 0-24 Months

Of the 152 patients initially randomized, 140 entered the trial One hundred and twenty eight patients completed 2 years on study, and 12 discontinued prior to 2 years on study (7 in the 0.033 mg/kg/day group, 4 in the 0.067 mg/kg/day group and 1 in the untreated control group). Of the 12 patients who discontinued early, 7 discontinued because of major protocol deviations (see Table 4 ahead), 2 patients withdrew informed consent, 1 patient was psychologically intolerant to injections, and 1 patient was non-compliant. See Table 3.

The ITT study population consisted of 140 patients, and the PP 0-24 month study population consisted of 108 patients. See Table 3. Twenty seven of the 32 patients not included in the PP 0-24 month study population were eliminated because of major protocol violations. Twenty four of these patients were inappropriately included in the study: 4 patients with HV SDS >1, 11 patients with baseline height SDS_{CA} >-2 (including 4 in the 0.033 mg/kg/day group and 5 in the 0.067 mg/kg/day group), 2 patients with birth length SDS >-2 and 7 patients with a syndrome which could effect growth (see Table 4).

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