

Summary ID#Z019

Clinical Study Summary: Study B9R-JE-6001

Title of Study: Evaluation of Growth Promoting Effect and Safety of Growth Hormone in Achondroplasia	
Investigator(s): This multicenter study included 33 principal investigators.	
Study Center(s): This study was conducted at 33 study centers in one country.	
Length of Study: 4 years, 4 months Date of clinical study start: March 1993 Date of clinical study completion: June 1997	Phase of Development: 3
Objectives: The primary objective of the study was to assess the efficacy of 0.5 versus 1.0 IU/kg/wk of somatropin in improving growth rates and height standard deviation scores (SDS) after 12, 24, and 36 months of treatment in achondroplasia. Secondary objectives included additional efficacy and safety analyses.	
Study Design: The present study was carried out as a multicenter, open-label study in patients divided into 2 dosage groups (0.5 and 1.0 IU/kg/wk). Patients were allocated to the 2 groups by the minimization method to avoid group-related differences in the main background factors (chronological age, bone age, and height SDS). Measurements were obtained before the start of treatment and after 1, 2, 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, and 36 months of treatment. If one or both of the following criteria were not met after completion of one-year administration, the dose was increased from 0.5 IU to 1.0 IU for patients in the 0.5 IU Group, while growth hormone (GH) therapy was suspended for one year for patients in the 1.0 IU Group: a) growth rate in the one year of treatment was more than 4 cm/year, b) difference between the growth rate in the year before treatment and that in the year of treatment was more than 1.0 cm.	
Number of Patients: A total of 46 patients were randomized in this study. 0.5 IU/kg/wk group: 22 1.0 IU/kg/wk group: 24	
Diagnosis and Main Criteria for Inclusion: Patients were included if they had been diagnosed with achondroplasia (with no history of GH therapy), had a height less than or equal to 2 standard deviations below the standard value of persons of the same sex and age, had a chronological age of 4 to 10 years (males) or 4 to 9 years (female) at the start of treatment, had not yet developed secondary sex characteristics, had normal thyroid function, and had height data for 1 year prior to start of treatment.	
Test Product, Dose, and Mode of Administration: Somatropin 0.5 IU/kg/wk, administered subcutaneously in 6 to 7 divided doses. (4 IU of recombinant human GH per vial) Somatropin 1.0 IU/kg/wk, administered subcutaneously in 6 to 7 divided doses. (4 IU of recombinant human GH per vial)	
Duration of Treatment: 3 years	
Reference Therapy, Dose, and Mode of Administration: None	

Variables:Efficacy:

The growth rate (cm/y) and height SDS at the start of treatment and after 12, 24, and 36 months of treatment were calculated from the height recorded 1 year before the start of treatment, and after 12, 24, and 36 months of treatment. Additional efficacy measures were: body weight, distance between both digital tips, length of both legs, sitting height, circumference of the head, chronological age and bone age.

Safety:

Safety was evaluated through the reporting of adverse events and laboratory tests (hematology, biochemistry, endocrinology and antibody tests, and urinalysis).

Evaluation Methods:

Statistical: The significance of differences in the following parameters between before and after treatment was determined by the paired t-test in each group and the significance of differences in the following parameters between the two groups was determined by t-test. The level of significance was 5% (two-sided test).

Parameters regarding Height:

- Growth rate (cm/y)
- Height SDS in the standard of normal children
- Height SDS in the standard of children with achondroplasia

Parameters regarding Bone Age:

- Bone age/height age in the standard of normal children
- Bone age/height age in the standard of children with achondroplasia

Other Parameters:

- Distance between both digital tips and the ratio of distance between both digital tips to height
- Leg length and the ratio of leg length to height
- Sitting height and the ratio of sitting height to height
- Head circumference and the ratio of head circumference to height

Drug safety was assessed in all 46 patients. Patients whose administration of drug was suspended (from 12 months to 24 months), whose dose was increased after 12 months (from 0.5 to 1.0 IU/kg/wk), who showed poor compliance, or who dropped out were excluded from the efficacy analysis.

Summary:**Patient Disposition and Demographics:**

Forty-six pediatric patients with achondroplasia were divided into two groups (0.5 IU Group: 22 patients; 1.0 IU Group: 24 patients). Table 6001.1 lists demographic data for these patients. Growth hormone deficiency (GHD) was detected in 2 patients in the 0.5 IU Group and 5 patients in the 1.0 IU Group. Baseline characteristics were similar between the two groups.

Table 6001.1. Demographic Data of Patients at the Start of Treatment

		No. of Patients		
		0.5 IU Group	1.0 IU Group	Total
Number of Patients		22	24	46
Sex	Male	11 (50.0%)	12 (50.0%)	23 (50.0%)
	Female	11 (50.0%)	12 (50.0%)	23 (50.0%)
Growth hormone secretion stimulating test*	Normal	20 (90.9%)	19 (79.2%)	39 (84.8%)
	Insufficient	2 (9.1%)	5 (20.8%)	7 (15.2%)
Chronologic age (years)		6.7±0.4	6.8±0.4	6.7±0.3
Bone age (years) 20 bones		5.5±0.4	5.6±0.5	5.5±0.3
Bone age (years) RUS		5.8±0.5	6.0±0.6	5.9±0.4
Height (cm)		92.4±1.8	93.1±2.	92.8±1.3
Height SDS (standard of normal children)		-5.0±0.2	-5.1±0.2	-5.1±0.1
Height SDS (standard of children with achondroplasia)		-0.2±0.2	-0.2±0.1	-0.2±0.1
Body weight (kg)		18.3± 1.0	17.8±1.0	18.0±0.7
Obesity index (%)		34.9±3.8	29.3±3.4	31.9±2.6
Growth rate at the start of treatment (cm/year)		4.2±0.2	3.9±0.3	4.0±0.2
Growth rate SDS in the standard of normal children		-2.4±0.4	-2.7±0.4	-2.5±0.3

Abbreviations: RUS = Radius, ulnar, short bones; SDS = standard deviation score.

Note: Values are Mean±standard error (SE).

* GH secretion was classified as "insufficient" only when the peak value in at least 2 GH secretion stimulating tests was ≤10 ng/ml.

Thirty-four patients (n=16, 0.5 IU Group; n=18, 1.0 IU Group) were evaluated for the growth-promoting effect and utility. Twelve patients were excluded from the efficacy evaluation: 4 patients whose growth hormone therapy was suspended after 12 months; 3 patients whose dose was increased after 12 months (from 0.5 to 1.0 IU/kg/wk); 3 patients who showed poor compliance or who dropped out; and 2 patients who violated criteria for continuation of treatment.

Primary Efficacy Measures:

Results for the primary efficacy measures of growth rate (cm/y) and height SDS are provided in Table 6001.2.

Table 6001.2. Efficacy Results

	0.5 IU Group	p-value	1.0 IU Group	p-value (within-group)	p-value (between groups)
Growth rate (cm/y)					
0 months	4.0±0.2		3.8±0.3		
12 months	5.9±0.2	<0.001	6.9±0.2*	<0.001	<0.01
24 months	4.7±0.2	<0.05	4.9±0.3*	<0.05	NS (p=0.609)
36 months	3.8±0.2	NS	4.8±0.2*	< 0.05	<0.05
Height SDS (standard of normal children)					
0 months	-4.98±0.30		-5.07±0.20		
12 months	-4.63±0.29	<0.01	-4.47±0.20	<0.01	NS
24 months	-4.51±0.30	<0.01	-4.25±0.21	<0.01	NS
36 months	-4.50±0.26	<0.001	-4.30±0.23	<0.01	NS
Height SDS (standard of patients with achondroplasia)					
0 months	-0.16±0.29		0.25±0.17		
12 months	0.18±0.28	<0.01	0.33±0.17	<0.01	NS
24 months	0.24±0.28	<0.01	0.46±0.18	<0.01	NS
36 months	0.20±0.25	<0.001	0.44±0.21	<0.001	NS

Abbreviations: NS = Not significant; SDS = standard deviation score.

Note: Values are mean±standard error (SE)

* The growth rate at 12 and 36 months was significantly larger in the 1.0 IU Group than in the 0.5 IU Group (p<0.01 and p<0.05, respectively).

Between the two groups, there was no statistically significant difference in the height SDS (standard of patients with achondroplasia) recorded at 12, 24, or 36 months of treatment.

Secondary Efficacy Measures:

In the 0.5 IU Group, the ratio of bone age to the height age relative to that of normal children (referred to as BA/HA[normal]) showed no statistically significant changes compared with that recorded at the start of treatment. In the 1.0 IU Group, the ratio recorded at the start of treatment (1.78±0.09) decreased to 1.66±0.09 after 6 months of treatment (p<0.001) and further decreased to 1.65±0.10 after 12 months of treatment (p<0.05), but there were no statistically significant changes after 24 months of treatment.

In the 0.5 IU Group, the ratio of bone age to the height age relative to that of children with achondroplasia (BA/HA[achondro]) recorded at the start of treatment was 0.89±0.04, and increased to 0.93±0.03 after 12 months of treatment, to 0.99±0.04 after

24 months of treatment, and to 1.01 ± 0.03 after 36 months of treatment; the increase was statistically significant after 12, 24 and 36 months of treatment ($p < 0.05$, $p < 0.01$ and $p < 0.05$, respectively). In the 1.0 IU Group, compared with the value recorded at the start of treatment (0.83 ± 0.05), a statistically significant ($p < 0.01$) decrease was noted after 6 months (0.79 ± 0.05) and a statistically significant ($p < 0.05$) increase was noted after 24 months (0.89 ± 0.04) of treatment. After 36 months of treatment, the change was not statistically significant.

When the two groups were compared, both the BA/HA (normal) and BA/HA (achondro) were statistically significantly ($p < 0.05$) smaller in the 1.0 IU Group after 36 months of treatment.

Table 6001.3 lists the ratio of distance between both digital tips (arm span), leg length, sitting height, and head circumference to height. The ratio of distance between both digital tips, that of leg length, and that of sitting height to height showed no statistically significant difference compared with the start of treatment in either group. The ratio of head circumference to height at 36 months was statistically significantly decreased compared with that of the start of treatment in both groups ($p < 0.001$).

Table 6001.3. Ratio of Each Physical Parameter to Height

		0.5IU Group	1.0IU Group	t-test (0.5IU vs 1.0IU)
Arm Span (Distance between both digital tips)	At the start of treatment	0.90±0.02(15)	0.92±0.01(17)	P=0.4058
	At 12 months	0.91±0.01(14)	0.91±0.01(18)	P=0.8365
	At 24 months	0.92±0.02(12)	0.91±0.01(17)	P=0.8062
	At 36 months	0.91±0.01(15)	0.91±0.01(15)	P=0.7111
	Paired test (0M vs 12M)	P=0.3370	P=0.6684	
	Paired test (0M vs 24M)	P=0.3409	P=0.6692	
	Paired test (0M vs 36M)	P=0.3356	P=1.0000	
Length of both lower legs	At the start of treatment	0.39±0.01(15)	0.41±0.01(15)	P=0.0868
	At 12 months	0.40±0.00(13)	0.41±0.01(17)	P=0.2139
	At 24 months	0.40±0.00(12)	0.41±0.01(16)	P=0.3966
	At 36 months	0.41±0.01(14)	0.41±0.01(15)	P=0.9614
	Paired test (0M vs 12M)	P=0.3370	P=0.3343	
	Paired test (0M vs 24M)	P=0.3388	P=0.1648	
	Paired test (0M vs 36M)	P=0.1648	P=0.3370	
Sitting height	At the start of treatment	0.68±0.01(14)	0.67±0.01(14)	P=0.6765
	At 12 months	0.67±0.01(13)	0.67±0.01(15)	P=0.8900
	At 24 months	0.68±0.01(12)	0.66±0.01(16)	P=0.3235
	At 36 months	0.68±0.01(13)	0.66±0.01(12)	P=0.1560
	Paired test (0M vs 12M)	P=0.1661	P=0.3356	
	Paired test (0M vs 24M)	P=0.1669	P=0.1654	
	Paired test (0M vs 36M)	P=1.0000	P=0.0811	
Circumference of the head	At the start of treatment	0.58±0.01(13)	0.57±0.02(15)	P=0.8589
	At 12 months	0.54±0.01(13)	0.57±0.01(18)	P=0.1276
	At 24 months	0.53±0.01(12)	0.53±0.02(15)	P=0.9367
	At 36 months	0.51±0.01(13)	0.53±0.01(15)	P=0.2050
	Paired test (0M vs 12M)	P=0.0172	P=0.1643	
	Paired test (0M vs 24M)	P=0.0162	P=0.0024	
	Paired test (0M vs 36M)	P=0.0007	P=0.0007	

Note: Values are Means±SE (n), where SE = Standard Error and n = number of patients in analysis.

Safety:

Table 6001.4 provides a summary of abnormal laboratory test findings. During the treatment period, there were 47 incidents (21 patients) of abnormal laboratory findings whose causal relationship with growth hormone could not be ruled out (positive or indefinite): 5 patients in 0.5 IU, 13 patients in 1.0 IU, and 1 patient in 0.5 IU→1.0 IU, in addition 2 patients suspended treatment and/or dropped out in 1.0 IU group.

The causal relationship was judged “positive” in 6 incidents (1 patient in 0.5 IU: positive anti-hGH antibodies; 3 patients in 1.0 IU: increased triiodothyronine (T3), positive anti-hGH antibodies, and abnormal oral glucose tolerance test (OGTT); 1 patient in 0.5→1.0 IU: abnormal OGTT; 1 patient suspended treatment in 1.0 IU→0 IU: positive anti-hGH antibodies), with 2 incidents out of the 6 showing no normalization (1 patient in 0.5→1.0 IU: abnormal OGTT; 1 suspended patient: positive anti-hGH antibodies). With regard to abnormal OGTT, no follow-up testing was conducted because the patients failed to visit the hospital after discontinuation of the growth hormone administration.

Regarding the patients who tested positive for anti-hGH antibodies, the investigators judged it unnecessary to follow up with them because they showed no particular clinical symptoms. The five positive anti-hGH antibody laboratory tests were judged to have a “positive” or “indefinite” causal relationship with growth hormone administration. Three of these patients subsequently tested negative for anti-hGH antibodies while continuing to receive growth hormone. Although two patients continued to have a positive test for anti-hGH antibodies, the investigator did not believe it was necessary to continue to follow-up with the patients because the titer of the antibody was less than 100-fold dilution.

Table 6001.4. Abnormal Laboratory Tests

Dosage (Pts.)	0.5IU group (18)*		1.0IU group (21)		0.5IU-1.0IU group (3)		Suspended/dropped out patients in 1.0IU group (3)	
	Positive or Indefinite	Negative	Positive or Indefinite	Negative	Positive or Indefinite	Negative	Positive or Indefinite	Negative
Relationship	5 (27.8%)	10 (55.6%)	13 (61.9%)	11 (52.4%)	1 (33.3%)	2 (66.7%)	2 (66.7%)	1 (33.3%)
Patients with Abnormal Laboratory Test	5 (27.8%)	10 (55.6%)	13 (61.9%)	11 (52.4%)	1 (33.3%)	2 (66.7%)	2 (66.7%)	1 (33.3%)
Counts of Abnormal Laboratory Test	9	27	34	23	1	3	3	1
RBC↓	1	0	0	0	0	0	0	0
WBC↑	0	3	1	3	0	1	0	0
WBC↓	0	1	1	0	0	0	0	0
Eosinophil↑	1	3	5	2	0	0	0	0
Neutrophil↑	0	3	0	3	0	1	0	0
Neutrophil↓	0	3	2	1	0	0	0	0
Lymphocyte↑	0	2	2	0	0	0	0	0
Lymphocyte↓	0	1	0	2	0	0	0	0
Monocyte↓	0	0	1	1	0	0	0	0
ATL	0	2	3	0	0	0	0	0
Plt↑	0	1	0	1	0	0	0	0
Hb↓	1	0	1	0	0	0	0	0
Ht↓	1	0	0	0	0	0	0	0
GOT↑	0	1	1	1	0	0	0	0
GPT↑	0	2	0	1	0	0	0	0
Al-p↑	0	0	1	0	0	0	0	0
BUN↑	0	0	0	1	0	0	0	0
BUN↓	0	1	0	0	0	0	0	0
Total Cholesterol↑	0	1	1	1	0	0	0	0
Cl↑	0	0	0	1	0	0	0	0
Ca↓	0	0	2	0	0	0	0	0
HbA1c↑	2	0	3	0	0	0	1	0
T3↑	0	1	1	0	0	0	0	0
T4↑	0	0	0	0	0	1	0	0
Anti-hGH Antibody	1	0	3	0	0	0	1	0
Urinary Protein Positive	0	0	0	2	0	0	0	1
Urine Sugar Positive	0	0	0	1	0	0	0	0
Urinary Occult Blood	0	1	0	1	0	0	0	0
OGTT	2	1	6	1	1	0	1	0

* One patient in the 0.5 IU group had treatment discontinued due to an adverse event unrelated to growth hormone treatment, and is not included in the group total.

There were 53 adverse events reported from 28 patients during the growth hormone treatment period. A causal relationship could not be ruled out in 11 incidents (11 patients), but none of the events were considered positively related to growth hormone administration. These 11 events were handled as adverse reactions (Table 6001.5).

Table 6001.5. Number of Adverse Reactions (Subjective Symptoms and Objective Findings)

Symptom	0.5 IU Group N=18*	1.0 IU Group N=21	5 IU→1.0 IU Group N=3	Suspended/ dropped out patient in 1.0 IU group N=3	Total
aggravation of bowleg	0	2	0	0	2
glucose tolerance abnormal	1	0	0	0	1
hearing decreased	0	1	0	0	1
pain of the injection site	1	0	0	0	1
sudden weight increase	0	1	0	0	1
headache	1	0	0	0	1
venous angioma	1	0	0	0	1
epileptic seizure	1	0	0	0	1
progression of deformity of the joint	0	1	0	0	1
necrosis of the femoral head	0	1	0	0	1
Total	5	6	0	0	11

Abbreviation: N = Number of patients in the group.

* One patient in the 0.5 IU group had treatment discontinued due to an adverse event unrelated to growth hormone treatment, and is not included in the group total.

There were 2 patients who had the preexisting condition of “bowleg” at baseline, whose condition worsened during the growth hormone treatment period. In both cases, the causal relationship with growth hormone was rated as “indefinite” because it was impossible to completely rule out the possibility that the growth hormone exerted some effects on bowleg. “Glucose tolerance abnormal,” which was noted in one patient, was transient and resolved without treatment. Because it could not be clarified whether the event was due to administration of hGH or attributable to some other cause, the causal relationship with the growth hormone was rated as “indefinite.” The one patient in whom “venous angioma” was reported showed no clinical symptoms or worsening of the disease even after continuation of growth hormone administration. Although it was suspected that the disease was congenital, the causal relationship was rated as “indefinite” since the cause was unknown. In one patient, growth hormone treatment was discontinued (after 1036 days of administration) and orthopedic treatment was given because radiographic diagnosis indicated the possibility of “necrosis of the head of the right femur.” In the one patient who reported “epileptic seizures”, the seizures disappeared as a result of oral administration of an antiepileptic and the patient continued receiving growth hormone. This patient had a history of febrile convulsions, but there

were no other predispositions relating to epilepsy, and thus the causal relationship was classified as “indefinite.”

Of the 42 events where the causal relationship with growth hormone was judged “negative”, 3 incidents of “cerebral infarction”, “aggravation of obesity”, and “atlantoaxial subluxation” were classified as severe. In the one patient in whom “cerebral infarction” was reported, although stenosis of the internal carotid artery, which was presumably the cause of the disease, was considered congenital, the causal relationship with growth hormone was classified as “indefinite” and growth hormone treatment was discontinued. In the one patient in whom “atlantoaxial subluxation” was reported, the causal relationship was rated as “indefinite”, growth hormone was discontinued, and the patient was hospitalized for treatment (extension and application of brace). However, a specialist of atlantoaxial subluxation diagnosed that the disease was accidental and had no causal relationship with growth hormone. Therefore, the causal relationship was changed to “negative”, and growth hormone treatment was resumed with no recurrence of the disease.