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PROPRIETARY DRUG NAME® / GENERIC DRUG NAME: Genotropin® / Somatropin (PNU-180307)

PROTOCOL NO.: GENASG-0021-007 (A6281225)

PROTOCOL TITLE: Long-Term Study of PNU-180307 for Short Children Born Small for Gestational Age (SGA) Without Epiphyseal Closure (Extension of the Study 307-MET-0021-002)

Study Centers: Twenty (20) centers in Japan took part in the study and enrolled subjects.

Study Initiation Date and Final Completion Date: 14 October 2002 to 20 August 2015

Phase of Development: Phase 4

Study Objectives:

Primary: The primary objective was to evaluate safety (laboratory test parameters and adverse events [AEs]) of long-term administration of somatropin until a final height was reached in short children born small for gestational age (SGA) without epiphyseal closure.

Secondary:

- To examine height velocity, height velocity Standard Deviation Score (SDS) for chronological age, height SDS for chronological age and Δ height SDS for chronological age.
- To comprehensively evaluate height velocity SDS for bone age, height SDS for bone age and Δ height SDS for bone age to examine the relationship between bone age and height increase.
- To examine changes in day-to-day activities of children treated with somatropin by means of questionnaires.

METHODS

Study Design: This study was a multi-center, long-term extension (LTE) study in subjects who participated in the previous study (Examination of Effects on Growth Promoting and Safety of PNU-180307 in Short Children Born Small for Gestational Age Without Epiphyseal Closing). During this LTE, growth hormone therapy was approved for the indication of short stature due to SGA; therefore, this study continued as a post-marketing clinical study after approval. After entering this study, subjects who had been treated with

somatropin 0.033 mg/kg/day in the previous study received a dose of 0.067 mg/kg/day as the 'dose-increasing' group. However, if any AE occurred and the dose increase was not well tolerated, the dose could be reduced to 0.033 mg/kg/day.

Subjects in the 0.067 mg/kg/day dose group in previous study were maintained on the same dose as the 'dose-remaining' group.

The schedule of activities is presented in Table 1.

Table 1. Schedule of Activities

Observation Time Point Observation Item	During the Period of the Study							
	At the Start of Treatment (12 Months After the Start of the Previous Study)	Every 3 Months of Treatment	Every 12 Months of Treatment	At the End of the Study/ Discontinuation	At the time of Proceeding to the Post-Marketing Study	Every 6 Months After the Start of the Study	Every 12 Months After the Start of the Study	At the End of the Study/ Discontinuation
Time window (day)[a]	-	±14	±14	-	±14	±14	±14	-
Informed consent	X				X			
Inclusion/exclusion criteria	X				X			
Height/body weight	X	X	X	X	X	X	X	X
Physical changes (secondary sex characteristics etc)	X	X	X	X	X	X	X	X
Bone age (left-hand X-P)	X		X	X	X		X	X
Questionnaires (APSASS)	X		X	X	X			
Questionnaires at the End of Treatment (or at the time of discontinuation)				X				X
IGF-I	X	X	X	X	X	X	X	X
Change in treatment (injection) compliance/injection site	X	X	X	X	X	X	X	X
Concomitant therapy/medication	X	X	X	X	X	X	X	X
Laboratory[b]	X	X	X	X	X	X	X	X
Anti-GH antibody	X		X	X	X	X		X
Pregnancy test	X						X	X
Oral glucose tolerance test	X		X	X	X			X
Adverse events	X	X	X	X	X	X	X	X

Table 1. Schedule of Activities

The specified test day was based on the start day of treatment, namely Day 0 in this study.
Every 6 months: height/body weight, physical changes (secondary sex characteristics etc), IGF-I, laboratory tests, and concomitant therapy/medication.
Every 12 months: bone age (left-hand X-P), anti-GH antibody and pregnancy test (for a woman of childbearing potential).
During the treatment period: change in the treatment (injection) compliance/injection site, concomitant therapy/medication, and adverse events.
APSASS = Assessment of Psycho-Social Activities on Short Stature; IGF-I = insulin-like growth factor I; GH = growth hormone.

a. The time window was expressed as the difference from the specified test day. Observations/examinations immediately before the start of treatment was to be performed on the start day of treatment as much as possible.
b. Among laboratory tests, follicle stimulating hormone was measured for female subjects only, and androgenic hormone was measured for male subjects only.

Number of Subjects (Planned and Analyzed): Target sample size was not determined as this was an extension study. Sixty-two (62) subjects (29 subjects in the dose-increasing group and 33 subjects in the dose-remaining group) were enrolled in the study.

Diagnosis and Main Criteria for Inclusion and Exclusion: Children with short stature due to SGA who had completed the 1-year treatment in the previous study and who were deemed eligible for enrolment by the Investigators.

Exclusion Criteria: Subjects who had any chronic disease requiring treatment with steroid hormone that could affect growth promotion including estrogen, androgen, anabolic hormone, and corticosteroids (except those for external use), and who received the treatment; received radiotherapy or chemotherapy; had serious cardiac disease, renal disease, or hepatic disease; had diabetes mellitus with a manifestation of abnormal glucose metabolism; had serious chronic disease; had a malignant tumor; or were allergic to m-cresol were excluded from the study.

Subjects who had achieved a height SDS for chronological age of 0; experienced puberty, and showed height velocity of <2 cm/year; reached bone age of 17 years for male subjects and 15 years for female subjects were also excluded from the study.

Study Treatment: Somatropin 5.3 mg or somatropin 12 mg for two-chamber cartridge (TC) injection (marketed formula) were supplied by the Sponsor. Somatropin 5.3 mg and somatropin 12 mg for TC injection both contained, in a 2-compartment cartridge, the lyophilized and sterilized recombinant somatropin powder and a diluent.

Subjects received a dose corresponding to their body weight once daily before bedtime. Somatropin was administered to either buttock (the study drug could be injected into the femoral region) using a special injection device. The administered dose was adjusted according to body weight, which was measured at each hospital visit.

Somatropin was administered at a dose of 0.067 mg/kg/day or 0.033 mg/kg/day. As the Japanese guideline for growth hormone (GH) treatment recommends a dose of 0.033 mg/kg/day, the dose could be changed to 0.033 mg/kg/day depending on age, puberty, growth rate, and safety.

The study treatment was to be stopped if either of the following items applied:

- If the height SDS for chronological age achieved 0 during the treatment period.
- If height velocity for chronological age was <1 cm/year.
- If the period of maximum growth during puberty ends, and height velocity decreases to <2 cm/year.
- If the subject has reached bone age of 17 years for male subjects and 15 years for female subjects.

Efficacy and Safety Endpoints:

Primary Endpoint: Laboratory test abnormalities and AEs.

Secondary Endpoints:

- Height velocity SDS for chronological age,
- Height velocity,
- Height SDS for chronological age,
- Height velocity SDS for bone age,
- Height SDS for bone age.

Safety Evaluations: AEs were recorded from when subjects received at least 1 dose of the study drug until the last visit. Serious adverse events (SAEs) were reported from the time of obtaining informed consent through 28 days after the last administration of the study drug. Laboratory tests were performed every 3 months before the entry into the post-marketing study, at the entry into the post-marketing study, and every 6 months starting from the initiation of the this study and at the completion of the study drug (discontinuation) after the entry into the post-marketing study (for anti-human GH antibody, every 12 months, at the entry into the post-marketing study, and at the completion of the study drug [discontinuation]). Changes in injection site were examined at each visit and the results were recorded. Bone age was evaluated based on radiographs of carpal bones in the left hand performed every 12 months, at the entry into the post-marketing study, and at the completion of the study drug (discontinuation). Oral glucose tolerance test (OGTT) was performed every 12 months before the entry into the post-marketing study, at the entry into the post-marketing study, and at the completion of the study drug (discontinuation).

Statistical Methods: The full analysis set (FAS) was comprised of subjects who met the inclusion/exclusion criteria and were enrolled in the study except for subjects who were never given any administration of study medication after enrollment and who had no study assessment data after enrollment. Efficacy and safety analyses were performed on the FAS.

Summary statistics were calculated by treatment group in observed values at the start of treatment in the previous study and at the evaluation time points, and in their changes from the start of treatment for the efficacy parameters.

Shift tables were prepared for scores in each Assessment of Psycho-Social Activities on Short Stature (APSASS) questionnaire item at the start of treatment in the previous study and at the evaluation time points every 12 months of treatment. In addition, changes (improved, unchanged, worsened, and other) in scores in each APSASS item at the evaluation time points every 12 months of treatment from the start of treatment in the previous study were tabulated.

Safety Analysis: The incidence of AEs by treatment group was tabulated by system organ class and by preferred term of the World Health Organization (WHO) Adverse Reaction Terminology (ART), the glossary for WHO adverse reaction reporting system. In addition, the incidence of abnormal changes in laboratory tests was tabulated by treatment group.

Changes in injection site and bone age were listed by treatment group. Shift tables were prepared by treatment group for OGTT results at the start of treatment in the previous study and at the evaluation time points every 12 months of treatment up to entry into the post-marketing study.

RESULTS

Subject Disposition and Demography: Sixty-two (62) subjects (29 subjects in the dose-increasing group and 33 subjects in the dose-remaining group) were enrolled. One (1) subject in the dose-remaining group did not receive study drug during the study period, therefore, 61 subjects were analyzed for efficacy and safety as the FAS. One (1) subject who received the 0.033 mg/kg/day dose in the previous study was included in the dose-increasing group in this study. Because the Investigator considered that this subject would benefit from the 0.033 mg/kg/day dose, the dose was not increased in the entry.

Subject disposition is shown in Table 2. The mean duration of treatment with somatropin including the duration of treatment in previous study (including discontinued cases) was 2612.7 days (range: 545 to 4942 days) in the dose increasing group and 2352.2 days (range: 658 to 4469 days) in the dose-remaining group.

Table 2. Subject Disposition

Number of Subjects	0.033/0.067 mg	0.067/0.067 mg
Enrolled	29	33
Treated	29	32
Completed until the date of marketing approval (not entered the post-marketing study)	5	5
Completed	2	0
Reaching a height SDS for chronological age of 0 SD during treatment	3	5
Discontinued until the date of marketing approval (not entered the post-marketing study)	8	12
Adverse events	0	1
Protocol deviation	0	1
Withdrawn consent	8	8
Others	0	2
Entered the post-marketing study	16	15
Completed	10	10
Reaching a height SDS for chronological age of 0 SD during treatment	2	0
Height velocity for chronological age <1.0 cm/year	0	1
Annual height velocity <2 cm after achieving peak velocity at puberty	0	1
Reaching a bone age of 17 years in male or 15 years in female	8	8
Discontinued	6	5
Protocol deviation	1	0
Withdrawn consent	3	2
Others	2	3
Efficacy analysis set: full analysis set	29	32
Safety analysis set: full analysis set	29	32

SD = standard deviation; SDS = standard deviation score.

The discontinuations from this study is presented in Table 3.

Table 3. Discontinuations From the Study

Number of Subjects	0.033/0.067 mg	0.067/0.067 mg	Total
	29	32	61
Clinical trial:			
Subject died	0	0	0
Discontinuations			
Relation to study drug not defined	8 (27.6)	11 (34.4)	19 (31.1)
Protocol violation	0	1 (3.1)	1 (1.6)
No longer willing to participate in study	8 (27.6)	8 (25.0)	16 (26.2)
Lost to follow-up	0	0	0
Other	0	2 (6.3)	2 (3.3)
Related to study drug	0	1 (3.1)	1 (1.6)
Adverse event	0	1 (3.1)	1 (1.6)
Not related to study drug	0	0	0
Adverse event	0	0	0
Transition to post-marketing clinical trial:			
Subject died	0	0	0
Discontinuations			
Relation to study drug not defined	6 (20.7)	5 (15.6)	11 (18.0)
Protocol violation	1 (3.4)	0	1 (1.6)
No longer willing to participate in study	3 (10.3)	2 (6.3)	5 (8.2)
Lost to follow-up	0	0	0
Other	2 (6.9)	3 (9.4)	5 (8.2)
Related to study drug	0	0	0
Adverse event	0	0	0
Not related to study drug	0	0	0
Adverse event	0	0	0

Safety analysis set was used.

The dose-increasing group consisted of 15 males and 14 females, and the dose-remaining group consisted of 18 males and 14 females. The sex ratio was similar between these groups. The mean age at the start of treatment in previous study was 5.20 years in the dose-increasing group and 5.4 years in the dose-remaining group. The demographic characteristics are presented in Table 4.

The mean height velocity SDS for chronological age at the start of treatment in previous study was −1.866 standard deviation (SD) in the dose-increasing group and −1.450 SD in the dose-remaining group. The mean height SDS for chronological age at the start of treatment in previous study was −3.14 SD in the dose-increasing group and −3.09 SD in the dose-remaining group. There was no obvious imbalance between the treatment groups regarding those values.

Table 4. Demographic Characteristics – All Subjects

Number of Subjects	0.033/0.067 mg	0.067/0.067 mg	Total
	29	32	61
Age (SD)	5.20 (1.64)	5.40 (1.27)	5.31 (1.45)
Gender	0	0	0
Female	14	14	28
Male	15	18	33

SD = standard deviation.

Efficacy Results: In the dose-increasing group, the mean height velocity SDS for chronological age from Month 12 to Month 24 indicated that the growth-promoting effect was similar to that observed from Month 0 to Month 12. In the dose-remaining group, the mean height velocity SDS for chronological age from Month 12 to Month 24 indicated that the growth-promoting effect was similar to that observed in the dose-increasing group from Month 0 to Month 12 and from Month 12 to Month 24. From Month 24, the mean height velocity SDS for chronological age decreased gradually in both groups up until Month 72 to Month 84, remaining at positive values up until Month 36 to Month 48 in the dose-increasing group and Month 48 to Month 60 in the dose-remaining group. From Month 84, when numbers of evaluable subjects fell by half or less in both groups, the mean height velocity SDS for chronological age showed a leveling-off or slightly increasing trend. Throughout the entire study period, the mean change from the start of treatment in height velocity SDS for chronological age was positive (Table 5).

Table 5. Height Velocity SDS for Chronological Age and Change Over Time (SD)

		Start of Treatment (Previous Study) Mean ± SD (n)	Months 0 to 12 (Previous Study) Mean ± SD (n)	Months 12 to 24 (Current Study) Mean ± SD (n)	Months 24 to 36 (Current Study) Mean ± SD (n)	Months 36 to 48 (Current Study) Mean ± SD (n)	Months 48 to 60 (Current Study) Mean ± SD (n)	Months 60 to 72 (Current Study) Mean ± SD (n)
0.033/0.067 mg	Score	−1.866±1.221 (29)	2.520±1.790 (29)	2.782±1.978 (28)	1.812±1.526 (26)	1.480±1.543 (24)	−0.041±2.081 (21)	−0.293±1.585 (20)
	Change	—	4.383±1.992 (29)	4.647±2.029 (28)	3.758±1.710 (26)	3.438±1.926 (24)	2.072±2.111 (21)	1.887±1.779 (20)
0.067/0.067 mg	Score	−1.450±1.600 (32)	4.768±2.056 (32)	2.595±1.731 (32)	1.696±2.111 (28)	0.824±1.527 (23)	0.480±1.651 (20)	−0.046±2.434 (16)
	Change	—	6.218±2.193 (32)	4.046±2.015 (32)	3.220±2.356 (28)	2.276±1.650 (23)	1.995±2.257 (20)	1.651±2.862 (16)
		Months 72 to 84 (Current Study) Mean ± SD (n)	**Months 84 to 96 (Current Study) Mean ± SD (n)**	**Months 96 to 108 (Current Study) Mean ± SD (n)**	**Months 108 to 120 (Current Study) Mean ± SD (n)**	**Months 120 to 132 (Current Study) Mean ± SD (n)**	**Months 132 to 144 (Current Study Mean ± SD (n))**	**Months 144 to 156 (Current Study) Mean ± SD (n)**
0.033/0.067 mg	Score	−0.488±3.117 (15)	0.263±1.802 (11)	0.521±2.058 (9)	−0.668±2.126 (6)	1.080±1.953 (5)	2.655±4.329 (4)	3.373±1.995 (3)
	Change	2.003±3.738 (15)	2.730±2.204 (11)	3.104±1.749 (9)	1.892±2.106 (6)	1.438±2.425 (5)	5.390±4.332 (4)	6.707±2.188 (3)
0.067/0.067 mg	Score	−1.511±2.692 (16)	−0.114±1.964 (14)	−0.466±2.055 (8)	−0.590±2.693 (6)	1.173±3.042 (4)	0.730±2.022 (2)	—
	Change	0.189±3.147 (16)	1.804±3.107 (14)	1.029±2.511 (8)	1.022±2.469 (6)	2.645±2.372 (4)	2.215±0.757 (2)	—

— = not applicable; n = number of subjects; SD = standard deviation; SDS = standard deviation score.

In both groups, the mean height velocity peaked between Month 0 and Month 12, thereafter decreased and remained constant from Month 24 to Month 72. The mean height velocity further decreased from Month 72 to Month 84, and thereafter remained constant (Table 6).

Table 6. Height Velocity and Change Over Time (cm/year)

		Start of Treatment (Previous Study) Mean ± SD (n)	Months 0 to 12 (Previous Study) Mean ± SD (n)	Months 12 to 24 (Current Study) Mean ± SD (n)	Months 24 to 36 (Current Study) Mean ± SD (n)	Months 36 to 48 (Current Study) Mean ± SD (n)	Months 48 to 60 (Current Study) Mean ± SD (n)	Months 60 to 72 (Current Study) Mean ± SD (n)
0.033/0.067 mg	Score	5.36±0.99 (29)	8.09±1.27 (29)	7.83±1.33 (28)	6.88±0.94 (26)	6.68±0.98 (24)	6.06±1.49 (21)	6.08±1.45 (20)
	Change	—	2.75±1.51 (29)	2.49±1.50 (28)	1.59±1.31 (26)	1.44±1.51 (24)	0.91±1.84 (21)	0.93±1.94 (20)
0.067/0.067 mg	Score	5.45±1.21 (32)	9.72±1.45 (32)	7.70±1.19 (32)	6.75±1.52 (28)	6.08±1.14 (23)	6.30±1.24 (20)	6.49±1.37 (16)
	Change	—	4.28±1.61 (32)	2.26±1.43 (32)	1.35±1.63 (28)	0.64±1.20 (23)	0.91±1.70 (20)	1.18±2.17 (16)

		Months 72 to 84 (Current Study) Mean ± SD (n)	Months 84 to 96 (Current Study) Mean ± SD (n)	Months 96 to 108 (Current Study) Mean ± SD (n)	Months 108 to 120 (Current Study) Mean ± SD (n)	Months 120 to 132 (Current Study) Mean ± SD (n)	Months 132 to 144 (Current Study) Mean ± SD (n)	Months 144 to 156 (Current Study) Mean ± SD (n)
0.033/0.067 mg	Score	4.89±2.18 (15)	5.16±1.20 (11)	5.18±2.16 (9)	5.72±2.24 (6)	4.84±1.30 (5)	4.38±1.10 (4)	3.10±1.92 (3)
	Change	−0.19±2.58 (15)	−0.11±1.23 (11)	−0.09±1.95 (9)	0.10±2.24 (6)	−0.94±2.15 (5)	−1.25±2.11 (4)	−2.07±2.51 (3)
0.067/0.067 mg	Score	4.88±1.86 (16)	4.82±2.12 (14)	5.55±2.42 (8)	5.03±1.86 (6)	4.30±1.84 (4)	2.60±0.14 (2)	—
	Change	−0.45±2.28 (16)	−0.38±2.36 (14)	−0.21±2.17 (8)	−0.93±1.92 (6)	−1.75±1.86 (4)	−3.40±0.28 (2)	—

— = not applicable; n = number of subjects; SD = standard deviation.

The mean height SDS for chronological age was higher up to Month 36 in the dose-remaining group than in the dose-increasing group, but, from Month 48, remained similar between the groups. The mean height SDS for chronological age increased as the treatment period increased up to Month 48 in the dose-increasing group and up to Month 72 in the dose-remaining group, but thereafter remained at around −1.5 SD up to Month 156 in the dose-increasing group and up to Month 120 in the dose-remaining group. The mean height SDS for chronological age exceeded −2.0 SD at Month 36 in the dose-increasing group and at Month 24 in the dose-remaining group (Table 7). Throughout the entire study period, the mean changes from the start of treatment in height SDS for chronological age at each observation time point were 0.60 SD to 2.50 SD in both groups.

Table 7. Height SDS for Chronological Age and Change Over Time (SD)

		Start of Treatment (Previous Study) Mean ± SD (n)	Month 12 (Previous Study) Mean ± SD (n)	Month 24 (Current Study) Mean ± SD (n)	Month 36 (Current Study) Mean ± SD (n)	Month 48 (Current Study) Mean ± SD (n)	Month 60 (Current Study) Mean ± SD (n)	Month 72 (Current Study) Mean ± SD (n)
0.033/0.067 mg	Score	−3.14±0.76 (29)	−2.53±0.92 (29)	−2.02±0.97 (28)	−1.80±0.99 (26)	−1.48±1.05 (24)	−1.53±1.06 (21)	−1.56±1.11 (20)
	Change	—	0.60±0.29 (29)	1.11±0.40 (28)	1.37±0.48 (26)	1.70±0.56 (24)	1.79±0.66 (21)	1.80±0.72 (20)
0.067/0.067 mg	Score	−3.09±0.83 (32)	−2.17±0.96 (32)	−1.70±1.03 (32)	−1.53±1.10 (28)	−1.49±1.15 (23)	−1.44±1.10 (20)	−1.43±1.06 (16)
	Change	—	0.93±0.34 (32)	1.40±0.44 (32)	1.65±0.54 (28)	1.82±0.58 (23)	1.91±0.51 (20)	2.06±0.44 (16)
		Month 84 (Current Study) Mean ± SD (n)	**Month 96 (Current Study) Mean ± SD (n)**	**Month 108 (Current Study) Mean ± SD (n)**	**Month 120 (Current Study) Mean ± SD (n)**	**Month 132 (Current Study) Mean ± SD (n)**	**Month 144 (Current Study) Mean ± SD (n)**	**Month 156 (Current Study) Mean ± SD (n)**
0.033/0.067 mg	Score	−1.73±1.13 (15)	−1.52±0.89 (11)	−1.52±1.01 (9)	−1.52±1.20 (6)	−1.96±1.11 (5)	−1.73±0.87 (4)	−1.77±0.76 (3)
	Change	1.78±0.87 (15)	1.99±0.46 (11)	2.01±0.63 (9)	1.83±0.89 (6)	1.48±0.82 (5)	1.63±0.73 (4)	1.73±0.67 (3)
0.067/0.067 mg	Score	−1.58±1.17 (16)	−1.87±1.36 (14)	−1.63±1.48 (8)	−1.25±0.59 (6)	−0.98±0.51 (4)	−0.70±0.42 (2)	—
	Change	1.91±0.57 (16)	1.73±0.81 (14)	2.01±0.92 (8)	2.25±0.45 (6)	2.28±0.32 (4)	2.50±0.14 (2)	—

— = not applicable; n = number of subjects; SD = standard deviation; SDS = standard deviation score.

The mean height velocity SDS for bone age was generally similar to the mean height velocity SDS for chronological age up until Month 48 to Month 60 in both groups. Thereafter, the mean height velocity SDS for bone age was slightly higher than the mean height velocity SDS for chronological age in both groups, except from Month 72 to Month 84, from Month 96 to Month 108 and after Month 132 in the dose-increasing group (Table 8).

Table 8. Height Velocity SDS for Bone Age and Change Over Time (SD)

		Start of Treatment (Previous Study) Mean ± SD (n)	Months 0 to 12 (Previous Study) Mean ± SD (n)	Months 12 to 24 (Current Study) Mean ± SD (n)	Months 24 to 36 (Current Study) Mean ± SD (n)	Months 36 to 48 (Current Study) Mean ± SD (n)	Months 48 to 60 (Current Study) Mean ± SD (n)	Months 60 to 72 (Current Study) Mean ± SD (n)
0.033/0.067 mg	Score	−1.836±1.386 (27)	2.105±2.066 (27)	2.586±2.268 (26)	1.503±1.830 (24)	1.196±1.409 (22)	−0.062±1.775 (20)	0.281±2.814 (16)
	Change	—	3.941±2.089 (27)	4.431±2.144 (26)	3.430±1.687 (24)	3.090±1.930 (22)	1.979±2.239 (20)	2.209±3.172 (16)
0.067/0.067 mg	Score	−1.635±1.734 (31)	4.479±2.190 (31)	2.461±1.990 (31)	1.091±1.852 (27)	0.510±1.809 (22)	0.913±2.146 (19)	0.949±2.729 (14)
	Change	—	6.114±2.159 (31)	4.096±2.064 (31)	2.745±1.977 (27)	2.079±1.641 (22)	2.584±2.947 (19)	3.101±3.442 (14)

		Months 72 to 84 (Current Study) Mean ± SD (n)	Months 84 to 96 (Current Study) Mean ± SD (n)	Months 96 to 108 (Current Study) Mean ± SD (n)	Months 108 to 120 (Current Study) Mean ± SD (n)	Months 120 to 132 (Current Study) Mean ± SD (n)	Months 132 to 144 (Current Study) Mean ± SD (n)	Months 144 to 156 (Current Study) Mean ± SD (n)
0.033/0.067 mg	Score	−1.249±2.558 (13)	0.804±3.440 (10)	−0.634±2.419 (8)	−0.070±4.120 (5)	1.553±3.019 (4)	2.310±1.711 (3)	2.710±2.942 (2)
	Change	1.449±3.280 (13)	3.047±3.355 (10)	1.816±2.741 (8)	2.286±4.650 (5)	3.528±3.651 (4)	3.907±2.034 (3)	5.080±3.776 (2)
0.067/0.067 mg	Score	0.932±2.545 (13)	0.286±2.351 (13)	−0.223±1.352 (7)	0.532±1.809 (5)	2.718±0.864 (4)	2.185±0.304 (2)	—
	Change	2.969±2.107 (13)	2.540±2.626 (13)	1.879±1.533 (7)	2.926±2.486 (5)	4.993±0.740 (4)	4.630±1.513 (2)	—

— = not applicable; n = number of subjects; SD = standard deviation; SDS = standard deviation score.

The mean height SDS for bone age was slightly higher than the mean height SDS for chronological age up to Month 60 in the dose-increasing group and up to Month 48 in the dose-remaining group. Thereafter, the mean height SDS for bone age was slightly lower than the mean height SDS for chronological age in both groups, except at Month 108 and after Month 144 in the dose-increasing group and at Month 144 in the dose-remaining group. Throughout the entire study period, the mean changes from the start of treatment in height SDS for bone age at each observation time point ranged between 0.10 SD to 1.60 SD in both groups (Table 9).

Table 9. Height SDS for Bone Age and Change Over Time (SD)

		Start of Treatment (Previous Study) Mean ± SD (n)	Month 12 (Previous Study) Mean ± SD (n)	Month 24 (Current Study) Mean ± SD (n)	Month 36 (Current Study) Mean ± SD (n)	Month 48 (Current Study) Mean ± SD (n)	Month 60 (Current Study) Mean ± SD (n)	Month 72 (Current Study) Mean ± SD (n)
0.033/0.067 mg	Score	−2.24±1.32 (27)	−1.19±1.20 (27)	−1.15±1.15 (26)	−1.20±1.35 (24)	−0.74±1.32 (22)	−1.16±1.21 (20)	−1.78±1.02 (16)
	Change	—	1.06±0.96 (27)	1.04±1.18 (26)	1.06±1.08 (24)	1.56±1.29 (22)	1.09±1.15 (20)	0.80±1.23 (16)
0.067/0.067 mg	Score	−2.10±1.20 (31)	−0.68±1.54 (31)	−0.88±1.79 (31)	−1.17±1.62 (27)	−1.46±1.01 (22)	−1.80±0.97 (19)	−1.70±0.77 (14)
	Change	—	1.42±0.77 (31)	1.19±1.18 (31)	1.09±1.09 (27)	1.00±0.88 (22)	0.66±0.99 (19)	0.71±0.90 (14)
		Month 84 (Current Study) Mean ± SD (n)	**Month 96 (Current Study) Mean ± SD (n)**	**Month 108 (Current Study) Mean ± SD (n)**	**Month 120 (Current Study) Mean ± SD (n)**	**Month 132 (Current Study) Mean ± SD (n)**	**Month 144 (Current Study) Mean ± SD (n)**	**Month 156 (Current Study) Mean ± SD (n)**
0.033/0.067 mg	Score	−1.85±1.17 (13)	−1.77±1.12 (10)	−1.41±0.97 (8)	−1.58±1.50 (5)	−2.10±1.21 (4)	−1.40±0.17 (3)	−1.55±0.92 (2)
	Change	0.21±1.59 (13)	0.55±1.51 (10)	0.71±1.51 (8)	0.46±2.12 (5)	0.35±2.25 (4)	1.60±0.46 (3)	1.25±0.49 (2)
0.067/0.067 mg	Score	−2.15±0.92 (13)	−2.27±1.06 (13)	−1.94±1.37 (7)	−1.38±0.98 (5)	−0.98±0.74 (4)	−0.65±0.64 (2)	—
	Change	0.38±0.92 (13)	0.15±0.79 (13)	0.10±0.74 (7)	0.26±0.66 (5)	0.38±0.53 (4)	0.25±0.92 (2)	—

— = not applicable; n = number of subjects; SD = standard deviation; SDS = standard deviation score.

The mean bone age increased by approximately 1 year per 12 months in both groups. The mean ratio of bone age to chronological age remained at approximately 1 throughout the study period in both groups, and as a whole, there was no trend indicating excessive bone maturation.

In both groups, the mean predicted adult height SDS was higher than the mean height SDS for chronological age, except Month 144 in the dose-remaining group, when the number of evaluable subjects was 2, although the values remained negative.

Safety Results:

SAEs: All-causality SAEs were observed in 15 subjects. Treatment-related SAEs were observed in 1 subject in the dose-increasing group (adenoidal hypertrophy) and in 1 subject in the dose-remaining group (tonsillar hypertrophy, adenoidal hypertrophy, and disease progression). Except for these events, the causal relationship to the study drug was ruled out for all SAEs. Treatment-emergent SAEs by system organ class, and preferred term (all-causality) are presented in Table 10.

Table 10. Treatment-Emergent Serious Adverse Events by System Organ Class, and Preferred Term (All-Causality)

Number (%) of Subjects With Adverse Events by: System Organ Class and WHOART Preferred Term	0.033/0.067 mg		0.067/0.067 mg		Total	
	Number of Adverse Events	n (%)	Number of Adverse Events	n (%)	Number of Adverse Events	n (%)
Evaluable for adverse events	-	29	-	32	-	61
With adverse events	16	10 (34.5)	9	5 (15.6)	25	15 (24.6)
Vision disorders	0	0	1	1 (3.1)	1	1 (1.6)
Retinal detachment	0	0	1	1 (3.1)	1	1 (1.6)
Hearing and vestibular disorders	1	1 (3.4)	0	0	1	1 (1.6)
Deafness	1	1 (3.4)	0	0	1	1 (1.6)
Gastro-intestinal system disorders	2	2 (6.9)	0	0	2	2 (3.3)
Gastroenteritis	2	2 (6.9)	0	0	2	2 (3.3)
Liver and biliary system disorders	1	1 (3.4)	0	0	1	1 (1.6)
Hepatic function abnormal	1	1 (3.4)	0	0	1	1 (1.6)
Endocrine disorders	1	1 (3.4)	2	2 (6.3)	3	3 (4.9)
Adenoid hypertrophy	1	1 (3.4)	2	2 (6.3)	3	3 (4.9)
Respiratory system disorders	5	4 (13.8)	2	2 (6.3)	7	6 (9.8)
Pharyngitis	1	1 (3.4)	2	2 (6.3)	3	3 (4.9)
Pneumonia	1	1 (3.4)	0	0	1	1 (1.6)
Upper respiratory tract infection	1	1 (3.4)	0	0	1	1 (1.6)
Bronchitis	1	1 (3.4)	0	0	1	1 (1.6)
Asthma	1	1 (3.4)	0	0	1	1 (1.6)
Reproductive disorders, male	1	1 (3.4)	1	1 (3.1)	2	2 (3.3)
Hernia inguinal	1	1 (3.4)	1	1 (3.1)	2	2 (3.3)
Reproductive disorders, female	1	1 (3.4)	0	0	1	1 (1.6)
Ovarian disorder	1	1 (3.4)	0	0	1	1 (1.6)
Foetal disorders	2	2 (6.9)	0	0	2	2 (3.3)
Hypospadias	1	1 (3.4)	0	0	1	1 (1.6)
Cryptorchism	1	1 (3.4)	0	0	1	1 (1.6)
Resistance mechanism disorders	1	1 (3.4)	3	3 (9.4)	4	4 (6.6)
Infection viral	0	0	1	1 (3.1)	1	1 (1.6)
Otitis media	1	1 (3.4)	1	1 (3.1)	2	2 (3.3)
Healing impaired	0	0	1	1 (3.1)	1	1 (1.6)
Secondary terms	1	1 (3.4)	0	0	1	1 (1.6)
Inflicted injury	1	1 (3.4)	0	0	1	1 (1.6)

Table 10. Treatment-Emergent Serious Adverse Events by System Organ Class, and Preferred Term (All-Causality)

Subjects were only counted once per treatment for each row.
Included all data collected during study.
n = number of subjects; WHOART = World Health Organization Adverse Reaction Terminology.

Non-serious AEs: Table 11 presents the summary of treatment-emergent non-serious adverse events (all-causalities) in ≥5% subjects.

The most common all-causality non-serious AEs were upper respiratory tract infection in 53 subjects (86.9%), influenza-like symptoms in 31 subjects (50.8%), otitis media in 27 subjects (44.3%), gastroenteritis in 27 subjects (44.3%), conjunctivitis in 20 subjects (32.8%), and rhinitis in 20 subjects (32.8%) based on the total of both treatment groups as shown in Table 11.

Table 11. Treatment-Emergent Non-Serious Adverse Events (All Causality) in ≥5% of Subjects

Number (%) of Subjects With Adverse Events by: System Organ Class and WHOART Preferred Term	0.033/0.067 mg		0.067/0.067 mg		Total	
	Number of Adverse Events	n (%)	Number of Adverse Events	n (%)	Number of Adverse Events	n (%)
Evaluable for adverse events		29		32		61
With adverse events	586	27 (93.1)	538	31 (96.9)	1124	58 (95.1)
Skin and appendages disorders	56	17 (58.6)	38	18 (56.3)	94	35 (57.4)
Acne	2	2 (6.9)	3	3 (9.4)	5	5 (8.2)
Dermatitis	12	3 (10.3)	3	2 (6.3)	15	5 (8.2)
Eczema	20	6 (20.7)	10	5 (15.6)	30	11 (18.0)
Pruritus	0	0	2	2 (6.3)	2	2 (3.3)
Rash	4	3 (10.3)	1	1 (3.1)	5	4 (6.6)
Rash erythematous	2	2 (6.9)	1	1 (3.1)	3	3 (4.9)
Rash pustular	4	4 (13.8)	2	2 (6.3)	6	6 (9.8)
Skin disorder	3	3 (10.3)	1	1 (3.1)	4	4 (6.6)
Urticaria	2	2 (6.9)	4	2 (6.3)	6	4 (6.6)
Dermatitis contact	0	0	2	2 (6.3)	2	2 (3.3)
Otitis externa	3	3 (10.3)	2	2 (6.3)	5	5 (8.2)
Bullous eruption	3	2 (6.9)	2	2 (6.3)	5	4 (6.6)
Verruca	1	1 (3.4)	5	4 (12.5)	6	5 (8.2)
Musculo-skeletal system disorders	4	4 (13.8)	7	5 (15.6)	11	9 (14.8)
Arthralgia	4	4 (13.8)	7	5 (15.6)	11	9 (14.8)
Central & peripheral nervous system disorders	5	4 (13.8)	4	3 (9.4)	9	7 (11.5)
Headache	5	4 (13.8)	4	3 (9.4)	9	7 (11.5)
Vision disorders	24	10 (34.5)	24	15 (46.9)	48	25 (41.0)
Conjunctivitis	17	8 (27.6)	16	12 (37.5)	33	20 (32.8)
Eye abnormality	5	4 (13.8)	8	5 (15.6)	13	9 (14.8)
Myopia	2	2 (6.9)	0	0	2	2 (3.3)
Gastro-intestinal system disorders	65	22 (75.9)	47	18 (56.3)	112	40 (65.6)
Constipation	5	3 (10.3)	6	4 (12.5)	11	7 (11.5)
Diarrhoea	5	5 (17.2)	2	2 (6.3)	7	7 (11.5)
Vomiting	7	5 (17.2)	3	3 (9.4)	10	8 (13.1)
Abdominal pain	0	0	2	2 (6.3)	2	2 (3.3)
Gastroenteritis	34	17 (58.6)	22	10 (31.3)	56	27 (44.3)
Nausea	1	1 (3.4)	2	2 (6.3)	3	3 (4.9)
Stomatitis	6	2 (6.9)	3	1 (3.1)	9	3 (4.9)
Tooth caries	6	4 (13.8)	2	2 (6.3)	8	6 (9.8)

Table 11. Treatment-Emergent Non-Serious Adverse Events (All Causality) in ≥5% of Subjects

Number (%) of Subjects With Adverse Events by: System Organ Class and WHOART Preferred Term	0.033/0.067 mg		0.067/0.067 mg		Total	
	Number of Adverse Events	n (%)	Number of Adverse Events	n (%)	Number of Adverse Events	n (%)
Tooth disorder	1	1 (3.4)	3	3 (9.4)	4	4 (6.6)
Enterocolitis	0	0	2	2 (6.3)	2	2 (3.3)
Liver and biliary system disorders	6	3 (10.3)	2	1 (3.1)	8	4 (6.6)
SGOT increased	3	3 (10.3)	1	1 (3.1)	4	4 (6.6)
SGPT increased	3	3 (10.3)	1	1 (3.1)	4	4 (6.6)
Metabolic and nutritional disorders	1	1 (3.4)	3	3 (9.4)	4	4 (6.6)
Glucose tolerance abnormal	1	1 (3.4)	3	3 (9.4)	4	4 (6.6)
Endocrine disorders	3	3 (10.3)	2	2 (6.3)	5	5 (8.2)
Sialoadenitis	3	3 (10.3)	2	2 (6.3)	5	5 (8.2)
Cardiovascular disorders, general	2	2 (6.9)	1	1 (3.1)	3	3 (4.9)
Hypotension postural	2	2 (6.9)	1	1 (3.1)	3	3 (4.9)
Respiratory system disorders	295	25 (86.2)	272	29 (90.6)	567	54 (88.5)
Coughing	0	0	2	2 (6.3)	2	2 (3.3)
Pharyngitis	9	7 (24.1)	16	9 (28.1)	25	16 (26.2)
Pneumonia	1	1 (3.4)	3	2 (6.3)	4	3 (4.9)
Rhinitis	14	8 (27.6)	29	12 (37.5)	43	20 (32.8)
Sinusitis	6	5 (17.2)	6	4 (12.5)	12	9 (14.8)
Upper respiratory tract infection	214	25 (86.2)	157	28 (87.5)	371	53 (86.9)
Bronchitis	31	9 (31.0)	25	10 (31.3)	56	19 (31.1)
Asthma	20	6 (20.7)	34	6 (18.8)	54	12 (19.7)
White cell and RES disorders	13	4 (13.8)	12	9 (28.1)	25	13 (21.3)
Eosinophilia	7	2 (6.9)	4	3 (9.4)	11	5 (8.2)
Leukocytosis	3	2 (6.9)	5	4 (12.5)	8	6 (9.8)
Lymphadenopathy	1	1 (3.4)	3	3 (9.4)	4	4 (6.6)
Lymphocytes atypical	2	2 (6.9)	0	0	2	2 (3.3)
Platelet, bleeding & clotting disorders	8	8 (27.6)	8	5 (15.6)	16	13 (21.3)
Purpura	6	6 (20.7)	8	5 (15.6)	14	11 (18.0)
Haematoma	2	2 (6.9)	0	0	2	2 (3.3)
Urinary system disorders	2	2 (6.9)	6	3 (9.4)	8	5 (8.2)
Urinary incontinence	2	2 (6.9)	0	0	2	2 (3.3)
Haematuria	0	0	6	3 (9.4)	6	3 (4.9)
Reproductive disorders, female	4	3 (10.3)	0	0	4	3 (4.9)
Ovarian disorder	4	3 (10.3)	0	0	4	3 (4.9)

Table 11. Treatment-Emergent Non-Serious Adverse Events (All Causality) in ≥5% of Subjects

Number (%) of Subjects With Adverse Events by: System Organ Class and WHOART Preferred Term	0.033/0.067 mg		0.067/0.067 mg		Total	
	Number of Adverse Events	n (%)	Number of Adverse Events	n (%)	Number of Adverse Events	n (%)
Foetal disorders	2	2 (6.9)	3	3 (9.4)	5	5 (8.2)
Skeletal malformation	0	0	2	2 (6.3)	2	2 (3.3)
Tooth malformation	2	2 (6.9)	1	1 (3.1)	3	3 (4.9)
Body as a whole-general disorders	42	20 (69.0)	42	18 (56.3)	84	38 (62.3)
Allergic reaction	0	0	9	3 (9.4)	9	3 (4.9)
Fever	18	11 (37.9)	3	1 (3.1)	21	12 (19.7)
Pain	0	0	2	2 (6.3)	2	2 (3.3)
Influenza-like symptoms	24	16 (55.2)	28	15 (46.9)	52	31 (50.8)
Application site disorders	2	2 (6.9)	0	0	2	2 (3.3)
Injection site bleeding	2	2 (6.9)	0	0	2	2 (3.3)
Resistance mechanism disorders	44	16 (55.2)	47	19 (59.4)	91	35 (57.4)
Infection bacterial	8	4 (13.8)	9	6 (18.8)	17	10 (16.4)
Infection viral	2	2 (6.9)	0	0	2	2 (3.3)
Otitis media	32	13 (44.8)	31	14 (43.8)	63	27 (44.3)
Herpes zoster	2	2 (6.9)	4	1 (3.1)	6	3 (4.9)
Abscess	0	0	3	2 (6.3)	3	2 (3.3)
Secondary terms	7	6 (20.7)	16	11 (34.4)	23	17 (27.9)
Varicella	3	3 (10.3)	2	2 (6.3)	5	5 (8.2)
Inflicted injury	2	2 (6.9)	5	4 (12.5)	7	6 (9.8)
Molluscum contagiosum	0	0	4	2 (6.3)	4	2 (3.3)
Scoliosis	1	1 (3.4)	2	2 (6.3)	3	3 (4.9)
Laceration	1	1 (3.4)	3	3 (9.4)	4	4 (6.6)
Poison specific terms	1	1 (3.4)	4	4 (12.5)	5	5 (8.2)
Sting	1	1 (3.4)	4	4 (12.5)	5	5 (8.2)

Subjects were only counted once per treatment for each row.
Includes all data collected during the study.
n = number of subjects; RES = reticuloendothelial system; SGOT = Serum glutamic oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase; WHOART = World Health Organization Adverse Reaction Terminology.

Treatment-emergent non-serious AEs by system organ class and preferred term (treatment-related) are presented in Table 12.

Table 12. Treatment-Emergent Non-Serious Adverse Events by System Organ Class and Preferred Term (Treatment-Related) in ≥5% of Subjects

Number (%) of Subjects With Adverse Events by: System Organ Class and WHOART Preferred Term	0.033/0.067 mg n (%)	0.067/0.067 mg n (%)	Total n (%)
Evaluable for adverse events	29	32	61
With adverse events	5 (17.2)	5 (15.6)	10 (16.4)
Central & peripheral nervous system disorders	2 (6.9)	0	2 (3.3)
Headache	2 (6.9)	0	2 (3.3)
Metabolic and nutritional disorders	1 (3.4)	3 (9.4)	4 (6.6)
Glucose tolerance abnormal	1 (3.4)	3 (9.4)	4 (6.6)
Body as a whole – general disorders	2 (6.9)	2 (6.3)	4 (6.6)
Fever	2 (6.9)	0	2 (3.3)
Pain	0	2 (6.3)	2 (3.3)
Application site disorders	2 (6.9)	0	2 (3.3)
Injection site bleeding	2 (6.9)	0	2 (3.3)

Subjects were only counted once per treatment for each row.
Included all data collected during study.
n = number of subjects; WHOART = World Health Organization Adverse Reaction Terminology.

Discontinuation due to AE: AEs leading to permanent discontinuation were reported in 1 subject in the dose-increasing group (sex chromosome disorder [verbatim term: turner syndrome]) and in 1 subject in the dose-remaining group (jaw malformation [verbatim term: mandibular protrusion]). The event jaw malformation was considered treatment-related; both events were mild in severity and reported to be stable although the outcome was reported as 'not resolved'. For the 1 subject who discontinued the study treatment due to sex chromosome disorder, the event was considered to meet the specified exclusion criterion (subjects who were considered ineligible by the Investigators) and the subject was discontinued from the study due to this protocol deviation.

Deaths: No deaths were reported during this study.

Laboratory Abnormalities: Forty-nine (49) abnormal changes in laboratory test results were reported as AEs in 23 subjects (37.7%); most of these events resolved. An increased hemoglobin A1c (HbA1c) was reported as an AE of mild hyperglycemia in 1 subject in the dose-increasing group, but resolved. No notable changes in HbA1c levels were observed in either group, and the levels remained generally within the reference range.

Based on OGTT, 1 subject in dose-remaining group was judged to be diabetic at Month 36, but recovered to normal at Month 48. The evaluation at Month 72 showed borderline diabetes for this subject.

No clinically significant changes were observed for other safety parameters, such as changes in injection site and bone age.

CONCLUSIONS:

Most of the observed AEs were mild to moderate in severity. AEs leading to permanent discontinuation were reported in 1 subject in the dose-increasing group (sex chromosome disorder [verbatim term: turner syndrome]) and in 1 subject in the dose-remaining group (jaw malformation [verbatim term: mandibular protrusion]). The event jaw malformation was considered treatment-related; both events were mild in severity and reported to be stable although the outcome was reported as 'not resolved'. Treatment-related SAEs were observed in 1 subject in the dose-increasing group (adenoidal hypertrophy) and in 1 subject in the dose-remaining group (tonsillar hypertrophy, adenoidal hypertrophy, and disease progression). All of these treatment-related SAEs were moderate in severity and reported to have resolved.

No new safety concerns or information arose from this LTE study.

The mean height velocity SDS for chronological age peaked from Month 12 to Month 24 in the dose-increasing group and from Month 0 to Month 12 in the dose-remaining group. Although the values gradually decreased up until Month 72 to Month 84 in both groups, positive values were maintained over a long period of time, until Month 36 to Month 48 in the dose-increasing group and until Month 48 to Month 60 in the dose-remaining group. From Month 84, when numbers of evaluable subjects fell by half or less in both groups, the mean height velocity SDS for chronological age showed a leveling-off or slightly increasing trend.

In both groups, the mean height velocity peaked between Month 0 and Month 12, thereafter decreased and remained constant from Month 24 to Month 72. The mean height velocity further decreased from Month 72 to Month 84, and thereafter remained constant.

The mean height SDS for chronological age exceeded −2.0 SD at Month 36 in the dose-increasing group and at Month 24 in the dose-remaining group. Throughout the entire study period, the mean changes from the start of treatment in height SDS for chronological age at each observation time point were 0.60 SD to 2.50 SD in both groups.

The mean height velocity SDS for bone age was generally similar to the mean height velocity SDS for chronological age up until Month 48 to Month 60 in both groups. Thereafter, the mean height velocity SDS for bone age was slightly higher than the mean height velocity SDS for chronological age in both groups, except from Month 72 to Month 84, from Month 96 to Month 108 and after Month 132 in the dose-increasing group.

The mean height SDS for bone age was slightly higher than the mean height SDS for chronological age up to Month 60 in the dose-increasing group and up to Month 48 in the dose-remaining group. Thereafter, the mean height SDS for bone age tended to be slightly lower than the mean height SDS for chronological age in both groups, except at Month 108 and after Month 144 in the dose-increasing group and at Month 144 in the dose-remaining group. Throughout the entire study period, the mean changes from the start of treatment in height SDS for bone age at each observation time point ranged between 0.10 SD to 1.60 SD in both groups.

The mean ratio of bone age to chronological age remained at levels around 1 throughout the study period in both groups, and as a whole, there was no trend indicating excessive bone maturation.

Thus, the long-term treatment data demonstrated that somatropin at a dose of 0.067 mg/kg/day was safe and the growth-promoting effect of somatropin was maintained.