

Effects of Astragalus Extract Mixture HT042 on Height Growth in Children with Mild Short Stature: A Multicenter Randomized Controlled Trial

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HT042 is a standardized functional food ingredient approved by Korean Food and Drug Administration with a claim 'HT042 can help height growth of children'. We aimed to evaluate the safety and efficacy of HT042 on height growth in children with mild short stature. A multicenter, randomized, double-blind, placebo-controlled parallel study was performed on children aged 6–8 years with height ranked below the 25th percentile. In 129 children, height gain was significantly higher in HT042 group than placebo group after 24 weeks (mean difference, 0.29 cm; 95% CI, 0.01 to 0.57 cm; $p = 0.027$). The difference was elevated when the efficacy analysis was restricted to children below the 10th percentile (mean difference, 0.45 cm; 95% CI, 0.04 to 0.87 cm; $p = 0.031$). Because bone age advancement was lower in HT042 group, height standard deviation score gain for bone age was higher in HT042 group and the difference was significant in children below the 10th percentile (mean difference, 0.20 score; 95% CI, 0.00 to 0.39 points; $p = 0.045$). Serum IGF-1 and IGFBP-3 levels were significantly increased compared with baseline within HT042 group, but group difference was not significant. HT042 supplementation helped to increase height growth in children without skeletal maturation and was more effective in much shorter children. The effects might be mediated by increases in serum IGF-1 and IGFBP-3 levels. Copyright © 2017 John Wiley & Sons, Ltd.

Keywords: Astragalus extract mixture; clinical trial; mild short stature; children.

INTRODUCTION

Height growth of children is affected by multiple factors besides heredity, such as nutrition and environment. Growth hormone (GH) deficiency, systemic diseases, or malnutrition are the pathologic causes of growth retardation, and most of others are idiopathic (Cohen *et al.*, 2008). Especially, malnutrition in the early days of life causes a stunting child, which is a serious problem in developing countries (Owino *et al.*, 2016). Short children with evidence of endocrine or chromosomal abnormalities can be recovered by GH therapy, and malnutrition can be supplemented by nutrition, but in some cases, nutritional supplement alone does not fully recover (de Onis and Branca, 2016). Some oral agents that are known to stimulate GH secretion such as aromatase inhibitors, arginine, and zinc have been studied to stimulate bone growth or GH secretion.

However, these oral agents showed limited efficacy or safety (Alba-Roth *et al.*, 1988; Hamza *et al.*, 2012; Hero *et al.*, 2006; Stammers *et al.*, 2015).

Astragalus extract mixture HT042, consisting of the roots of *Astragalus membranaceus* (Fisch.) Bunge and *Phlomis umbrosa* Turcz. and the stem of *Eleutherococcus senticosus* (Rupr. and Maxim.) Maxim., is an herbal mixture that has been used to strengthen bones and muscles from traditional Korean medicine. HT042 enhances longitudinal bone growth in *in vivo* models by stimulating cell proliferation in the epiphyseal plate and inducing the expression of insulin-like growth factor-1 (IGF-1) without estrogenic response (Kim *et al.*, 2013; Kim *et al.*, 2012; Kim *et al.*, 2010). HT042 is approved by Korean Food and Drug Administration with a claim 'HT042 can help height growth of children' (KFDA, 2016) because it was effective in the unpublished randomized controlled trial for 12 weeks in school-aged children with mild short stature.

In the present study, we conducted a randomized controlled trial for 24 weeks to evaluate the efficacy of HT042 on height gain in younger children with mild short stature aged 6–8 years whose height was ranked below the 25th percentile for their age and gender on the Korean population-based reference growth chart (KPS and KDCA, 2007). We also measured

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anthropometric parameters, bone age, and serum levels of GH, IGF-1, IGFBP-3, and luteinizing hormone (LH).

METHODS

Subjects and sample size calculation. One hundred and forty children were enrolled between 2013 and 2014 from the pediatric clinic of Kyung Hee University Hospital and the pediatric clinic of Kyung Hee University Korean Medicine Hospital at Gangdong. We planned a sample size of 140 subjects, which provided 80% power, after allowing for dropouts, to detect a 0.33 cm difference in height gain between the two supplement groups at a significance level of 0.05 based on a previous clinical trial (unpublished). To be eligible for the study, children had to be aged 6–8 years and their height had to be ranked below the 25th percentile for their age and gender according to the Korean population-based reference growth chart at the time of screening (KPS and KDCP, 2007). Children were excluded if they had a GH deficiency, hypothyroidism, type 1 diabetes, precocious puberty (LH > 0.6 IU/L), infection, tumor, renal impairment (more than twice normal creatinine level), or liver impairment (more than twice normal aspartate aminotransferase or alanine aminotransferase levels). No evidence of malnutrition was found in children based on body weight, BMI, serum albumin and total protein levels, and dietary intake data obtained at baseline. None had any endocrine or systemic disease.

Design. This study was designed as a multicenter, randomized, double-blind, placebo-controlled parallel study. The protocol was reviewed and approved by the Institutional Review Board at both participating centers, and all children and parents gave written informed consent for the study. Eligible children were randomly assigned by a clinical pharmacist in a 1:1 ratio to receive either 750 mg of HT042 or an identical-looking placebo twice daily for 24 weeks. Each HT042 and placebo preparation was assigned a code from a randomization list by block randomization (block size 4). The randomization list was generated by an external statistician with SAS, version 9.4 (SAS Institute, Cary, NC, USA). Allocation was masked in subjects, pediatric providers, and assessor by central allocation and sequentially numbered, opaque, sealed envelopes. This study was conducted in accordance to the Declaration of Helsinki and ICH-GCP guidelines and was registered at CRIS in 02/05/2013 (Registration identifier: KCT0000736).

The primary outcome was height gain during the 24-week supplementation period. Height was measured at the analogous time of day in the range of ± 1 h by using a portable stadiometer (Seca 213, Seca GmbH, Hamburg, Germany) and recorded to the nearest 0.1 cm. The height standard deviation score (SDS) expressed the anthropometric value as the number of standard deviations below or above the mean value of the reference and was calculated by using Korean reference data. The children were dressed in light clothing and were barefoot when these measurements were

recorded. The following evaluations were performed: height, weight, vital signs, physical exam, and verifying prescription drug use; bone age radiograph of both hands and wrists by calculating the TW3-RUS score; and lab tests including serum GH, IGF-1, and IGFBP-3 levels at the baseline and end point. Blood samples were collected after children had fasted overnight.

Preparation of HT042. HT042, a proprietary product of NeuMed, was manufactured by NeuMed Inc. (Seoul, Korea). HT042 consists of the lyophilized 70% ethanolic extracts of three medicinal plants: the roots of *A. membranaceus*, the stems of *E. senticosus*, and the roots of *P. umbrosa*. Standardized HT042 contains formononetin (a marker compound of *A. membranaceus*) 0.006–0.010%, eleutheroside E (a marker compound of *E. senticosus*) 0.2–0.5%, and 6,9-epi-8-*O*-acetylshanzhiside methyl ester (a marker compounds of *P. umbrosa*) 0.2–0.6%. For the quality verification, the quantitative analysis of HT042 performed by high-performance liquid chromatography for measuring concentrations of marker compounds. The analysis was conducted in accordance with the standard analytical method of Korean Food and Drug Administration. The result showed that the concentrations of marker compounds were in the standard range.

For the clinical trial, HT042 was prepared in a liquid form containing 750 mg of the standard extract in 50 mL of solution and was packed in a pouch. The placebo solution did not appear to differ from the HT042 solution in terms of its color, size, odor, or taste but contained oligosaccharides, caramels, and other materials and was presented in a similar pouch. Supplements in the form of either the placebo or HT042 were given to the study participants after a 2-week screening process. The pouches were issued to the children's parents at baseline. Parents were instructed to give their child one pouch after breakfast and one pouch after dinner for the 24-week study period and to record whether the child had consumed the supplement. Children, parents, researchers, and referring physicians were blinded until the statistical analysis was complete.

Statistical analysis. Safety analyses included all children who received the study drug ($n = 140$). The full-analysis set (FAS) included 129 subjects whose height was measured at baseline and end point. After randomization, three children were excluded because of violation of eligibility, and one child was lost during follow-up in the placebo group. In the HT042 group, six children withdrew consent (one due to diarrhea) and one child took a contraindicated drug. Per-protocol (PP) efficacy analyses included 115 subjects who completed the supplementation without protocol violation or intercurrent illness. In the placebo group, four children exhibited low compliance (less than 70%), two children violated the visit window protocol, and one child showed abnormal serum LH levels, assumed to indicate precocious puberty. In the HT042 group, three children exhibited low compliance (less than 70%), one child withdrew consent, three children violated the visit window protocol, and one child exhibited intercurrent illness that interfered with the trial (Fig. 1).

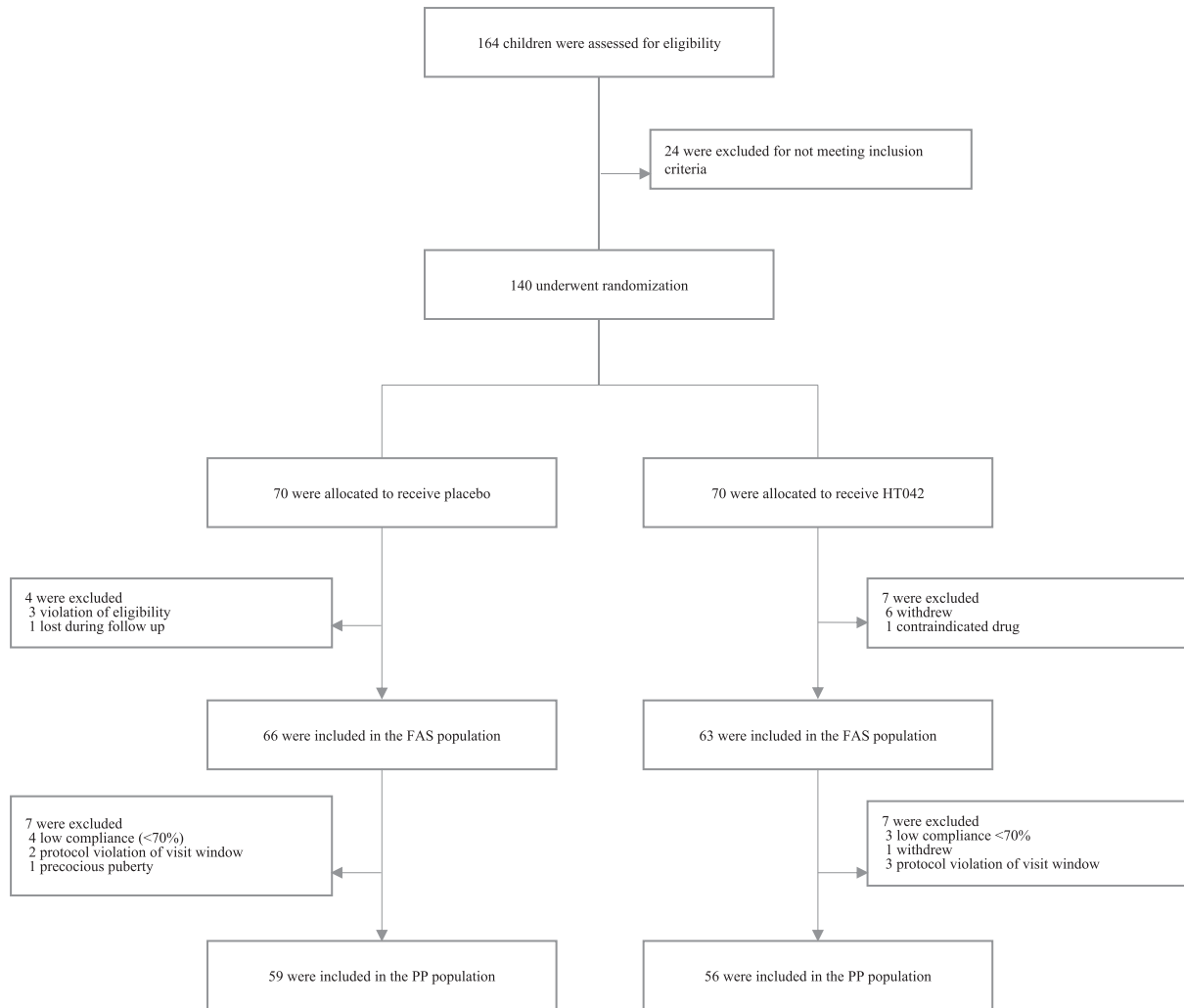


Figure 1. Randomization and analysis populations.

The primary efficacy analysis was an independent two-sample *t*-test of height gain between the groups. If the normality assumption was not met, a Wilcoxon rank sum test was used. A paired *t*-test was used for the analyses of changes within groups. If the normality assumption was not met, a Wilcoxon signed rank test on difference was used. For the analysis of categorical variables, a Fisher's exact test was used. One sample *t*-tests were conducted to test the null hypothesis that the change in the change in height SDS equals zero. All statistical analyses were performed by using SAS. Results were expressed as mean $\pm$ SD for continuous variables and frequency for categorical variables. All statistical tests were two-sided. A *p*-value smaller than 0.05 was considered statistically significant.

RESULTS

Table 1 displays baseline participant characteristics. There were no significant differences between the groups in gender distribution, maternal height, paternal height, gestational age, birth weight, sleeping hours, time spent exercising, chronological age, bone age, height, weight, BMI, and mean levels of serum GH, IGF-1, IGFBP-3, and LH at the start of the study. Both paternal height and maternal height were within the

normal range, and bone age was delayed approximately 0.8 year from the chronological age in both groups.

Efficacy

The primary efficacy analysis demonstrated that the HT042 group showed a significant increase in height gain compared with the placebo group after 24 weeks in the FAS population (mean difference, 0.29 cm; 95% CI, 0.01 to 0.57 cm, *p* = 0.027; Table 2). In the placebo group, height increased from 115.4 to 118.4 cm (*p* < 0.001), whereas in the HT042 group, it increased from 115.2 to 118.5 cm (*p* < 0.001) after 24 weeks. Because some subjects exhibited low compliance or protocol violation, PP analyses were also performed. Mean height gain was significantly greater in the HT042 group compared with the placebo group during the 24-week supplementation period in the PP population (mean difference, 0.29 cm; 95% CI: 0.01 to 0.57 cm, *p* = 0.036).

The Δ height SDS (end point height SDS minus baseline height SDS) was higher in the HT042 group but was not significantly different from the placebo group in both FAS (mean difference, 0.04 score; 95% CI, -0.02 to 0.09, *p* = 0.077) and PP (mean difference, 0.04 score; 95% CI, -0.02 to 0.09, *p* = 0.111) populations. Bone age was not significantly progressed in the

Table 1. Subject characteristics of the FAS and PP populations at baseline and at end point

Characteristic	FAS population (<i>n</i> = 129)			PP population (<i>n</i> = 115)		
	Placebo (<i>n</i> = 66)	HT042 (<i>n</i> = 63)	<i>p</i> -value*	Placebo (<i>n</i> = 59)	HT042 (<i>n</i> = 56)	<i>p</i> -value*
General characteristics						
Sex (M/F)	31/35	36/27	0.248	29/30	32/24	0.391
Gestational age (<37/37–42/>42 weeks)	3/60/3	3/57/3	>0.999	2/55/2	3/50/6	0.691
Birth weight (<2.5/2.5–4.0/>4.0 kg)	7/56/3	11/50/2	0.564	7/49/3	10/44/2	0.101
Sleeping hours (<7/7–9/9–11/>11 h)	0/29/37/0	0/26/37/0	0.759	0/24/35/0	0/23/33/0	0.243
Time spent exercising (0–1/1–2/2–3/>3 h per day)	41/23/2/0	35/26/2/0	0.798	34/23/2/0	31/23/2	0.256
Maternal height (cm)	157.4 ± 3.7	158.0 ± 4.0	0.353	157.4 ± 3.7	158.2 ± 4.1	0.267
Paternal height (cm)	171.1 ± 5.0	170.1 ± 4.8	0.355	171.1 ± 4.8	169.9 ± 4.9	0.197
Baseline						
Chronological age (years)	7.3 ± 0.9	7.2 ± 0.9	0.462	7.3 ± 0.9	7.2 ± 0.9	0.444
Bone age (years)	6.4 ± 1.1	6.4 ± 1.0	0.810	6.5 ± 1.0	6.4 ± 1.0	0.764
Height (cm)	115.4 ± 5.5	115.2 ± 5.1	0.710	115.4 ± 5.3	115.2 ± 5.2	0.665
Height SDS	−1.3 ± 0.6	−1.3 ± 0.4	0.747	−1.3 ± 0.6	−1.3 ± 0.4	0.693
Height SDS for bone age	−0.3 ± 1.2	−0.4 ± 1.0	0.887	−0.3 ± 1.2	−0.3 ± 1.0	0.963
Weight (kg)	21.3 ± 3.0	20.9 ± 3.1	0.364	21.4 ± 3.1	20.9 ± 3.0	0.389
BMI (kg/m ²)	16.0 ± 1.7	15.7 ± 1.6	0.292	16.1 ± 1.7	15.7 ± 1.5	0.315
GH level (ng/mL)	2.9 ± 4.8	2.8 ± 4.6	0.294	2.9 ± 4.9	2.9 ± 4.9	0.553
IGF-1 level (ng/mL)	154.4 ± 43.6	150.9 ± 42.4	0.640	154.4 ± 45.1	150.8 ± 42.6	0.669
IGFBP-3 level (ng/mL)	3825.5 ± 845.4	3712.7 ± 875.1	0.391	3801.9 ± 880.2	3708.2 ± 885.3	0.497
LH level (ng/mL)	0.22 ± 0.18	0.21 ± 0.17	0.704	0.22 ± 0.18	0.22 ± 0.17	0.983
End point						
Chronological age (years)	7.8 ± 0.9	7.7 ± 0.9	0.515	7.8 ± 0.9	7.7 ± 0.9	0.490
Bone age (years)	7.0 ± 1.1	6.9 ± 1.1	0.507	7.0 ± 1.0	6.9 ± 1.1	0.465
Height (cm)	118.4 ± 5.4	118.5 ± 5.1	0.913	118.4 ± 5.3	118.4 ± 5.2	0.827
Height SDS	−1.2 ± 0.6	−1.1 ± 0.4	0.803	−1.2 ± 0.6	−1.2 ± 0.4	0.836
Height SDS for bone age	−0.4 ± 1.1	−0.3 ± 0.9	0.697			
Weight (kg)	22.7 ± 3.2	22.3 ± 3.5	0.394	22.8 ± 3.2	22.2 ± 3.3	0.422
BMI (kg/m ²)	16.2 ± 1.8	15.8 ± 1.7	0.186	16.2 ± 1.8	15.8 ± 1.5	0.176
GH level (ng/mL)	2.3 ± 3.9	2.2 ± 3.2	0.682	2.4 ± 4.1	2.3 ± 3.4	0.509
IGF-1 level (ng/mL)	165.5 ± 56.1	171.6 ± 51.3	0.478	166.7 ± 58.7	171.8 ± 52.7	0.585
IGFBP-3 level (ng/mL)	3903.1 ± 877.8	3931.3 ± 777.6	0.880	3911.7 ± 914.2	3902.7 ± 801.2	0.955
LH level (ng/mL)	0.32 ± 0.49	0.33 ± 0.40	0.854	0.29 ± 0.40	0.32 ± 0.39	0.755

*± values are mean ± SD. *p*-values for comparisons of mean values between two groups are based on two-sample *t*-test. If the normality assumption is not met, a Wilcoxon rank sum test was used.

†For the analysis of categorical variables, a Fisher's exact test was used.

SDS = (measured value – mean value of the reference population)/standard deviation of the reference population.

Abbreviations: SDS, standard deviation score; BMI, body mass index; GH, growth hormone; IGF-1, insulin-like growth factor-1; IGFBP-3, insulin-like growth factor binding protein-3; LH, luteinizing hormone; FAS, full-analysis set; PP, per-protocol.

HT042 group compared with the placebo group. The mean difference between bone age and chronological age (BA-CA) was increased in both groups compared with baseline, but the difference was greater in the placebo group in both FAS (1.61 ± 3.80 vs. 1.05 ± 3.50 months) and PP populations (1.46 ± 3.66 vs. 0.91 ± 3.12 months). The Δ height SDS for bone age was higher in the HT042 group; the difference of Δ height SDS for bone age between HT042 and placebo groups increased more than twice that of the Δ height SDS (0.10 vs. 0.04 score). Mean levels of serum IGF-1 and IGFBP-3 were significantly increased compared with baseline only within the HT042 group [IGF-1, 11.06 ± 45.03 (*p* = 0.059) vs. 20.74 ± 35.39 ng/mL (*p* < 0.001); IGFBP-3, 83.64 ± 778.96 (*p* = 0.232) vs. 218.57 ± 583.19 ng/mL (*p* = 0.004)], but group difference was not significant due to large standard deviation (IGF-1, *p* = 0.080; IGFBP-3, *p* = 0.436). There were no

significant differences in serum GH or LH levels between groups. An analogous pattern was seen in the PP population.

A greater effect of HT042 was seen when the efficacy analysis was restricted to children whose starting height was less than the 10th percentile at baseline (Table 3). Mean height gain was significantly higher in the HT042 group compared with the placebo group during the 24-week supplementation period (mean difference, 0.45 cm; 95% CI, 0.04 to 0.87 cm; *p* = 0.031; Table 4). In the placebo group, height increased from 113.1 to 116.1 cm (*p* < 0.001), which is analogous to the height gain of the placebo groups in the total FAS population, whereas in the HT042 group, height increased from 111.7 to 115.2 cm (*p* < 0.001). Height SDS for bone age was significantly increased in the HT042 group compared with the placebo group in the children whose starting height was below the

Table 2. Group comparison of change in parameters after 24 weeks of supplementation

Characteristic	FAS population (n = 129)			PP population (n = 115)		
	Placebo (n = 66)	HT042 (n = 63)	p-value	Placebo (n = 59)	HT042 (n = 56)	p-value*
Height gain from baseline (cm)	3.01 ± 0.67	3.30 ± 0.94	0.027	2.95 ± 0.63	3.24 ± 0.88	0.036
95% CI	(2.85 to 3.18)	(3.07 to 3.54)		(2.78 to 3.11)	(3.00 to 3.48)	
p-value [#]	<0.001	<0.001		<0.001	<0.001	
ΔHeight SDS	0.11 ± 0.12	0.15 ± 0.18	0.077	0.11 ± 0.12	0.15 ± 0.17	0.111
95% CI	(0.08 to 0.14)	(0.10 to 0.19)		(0.08 to 0.14)	(0.10 to 0.19)	
p-value	<0.001	<0.001		<0.001	<0.001	
ΔHeight SDS for bone age	−0.07 ± 0.40	0.03 ± 0.38	0.164	−0.07 ± 0.37	0.02 ± 0.36	0.191
95% CI	(−0.17 to 0.03)	(−0.07 to 0.12)		(−0.16 to 0.03)	(−0.07 to 0.12)	
p-value	0.724	0.879		0.758	0.902	
ΔBA-CA (months)	1.61 ± 3.80	1.03 ± 3.47	0.433	1.46 ± 3.66	0.91 ± 3.12	0.598
95% CI	(0.67 to 2.54)	(0.16 to 1.94)		(0.51 to 2.41)	(0.08 to 1.78)	
p-value	0.007	0.039		0.018	0.051	
ΔGH	−0.67 ± 6.24	−0.62 ± 5.59	0.473	−0.56 ± 6.42	−0.60 ± 5.92	0.538
95% CI	(−2.21 to 0.86)	(−2.03 to 0.78)		(−2.23 to 1.12)	(−2.19 to 0.99)	
p-value	0.112	0.425		0.214	0.686	
ΔIGF-1	11.06 ± 45.03	20.74 ± 35.39	0.080	12.28 ± 46.52	20.91 ± 35.30	0.133
95% CI	(−0.01 to 22.13)	(11.83 to 29.66)		(0.16 to 24.41)	(11.46 to 30.37)	
p-value	0.059	<0.001		0.047	<0.001	
ΔIGFBP-3	83.64 ± 778.96	218.57 ± 583.19	0.406	109.83 ± 784.39	194.46 ± 585.69	0.699
95% CI	(−107.85 to 275.13)	(71.70 to 365.45)		(−94.58 to 314.24)	(37.62 to 351.31)	
p-value	0.232	0.004		0.287	0.016	
ΔLH	0.10 ± 0.45	0.11 ± 0.40	0.834	0.07 ± 0.36	0.10 ± 0.40	0.862
95% CI	(−0.01 to 0.21)	(0.01 to 0.21)		(−0.02 to 0.17)	(−0.01 to 0.21)	
p-value	0.283	0.182		0.078	0.046	
ΔBMI	0.16 ± 0.75	0.10 ± 0.61	0.353	0.18 ± 0.76	0.09 ± 0.59	0.293
95% CI	(−0.02 to 0.34)	(−0.05 to 0.26)		(−0.01 to 0.38)	(−0.06 to 0.25)	
p-value	0.036	0.132		0.067	0.241	

*A paired *t*-test was used for the analyses of changes within groups. If normality assumption was not met, a Wilcoxon signed rank test on difference was used.

BA-CA = bone age minus chronological age.

Abbreviations: SDS, standard deviation score; BMI, body mass index; GH, growth hormone; IGF-1, insulin-like growth factor-1; IGFBP-3, insulin-like growth factor binding protein-3; LH, luteinizing hormone; FAS, full-analysis set; PP, per-protocol.

10th percentile (mean difference 0.20 score; 95% CI, 0.00 to 0.39; *p* = 0.046; Fig. 2).

Safety

The safety population consisted of 70 subjects who received HT042 supplementation and 70 who received placebo. No serious adverse events (AEs) were attributed to HT042 supplementation. Mean compliance was 89% for subjects receiving HT042 and 89% for those receiving placebo. No statistically significant differences between the two groups were detected in the incidence of adverse effects. Eighty-seven AEs were reported by 44 children in the HT042 group (62.86%), and 86 AEs were reported by 43 children in the placebo group (61.43%). The most common AE was nasopharyngitis, which was reported in 29 AEs in the HT042 group (33.33%) and 40 AEs in the placebo group (46.51%; Table 5). All AEs were considered mild in severity and unlikely or definitely not likely to be associated with the treatment, according to the judgment of pediatric providers. The changes in blood and urine biomarkers, vital signs, and electrocardiogram readings during treatment were not statistically different between the HT042 and placebo groups.

DISCUSSION

This study, which shows a positive effect of herbal extracts on height gain in children with mild short stature, is distinctive in utilizing a multicenter, randomized, double-blind, placebo-controlled design. This design reduces selection bias and allocation bias throughout the whole process (Sacks *et al.*, 1982); avoids possible errors generated from the use of historical control trials, reference growth chart, or predicted height gain (Sacks *et al.*, 1982; Zachmann *et al.*, 1978; Bramswig *et al.*, 1990); and controls for potential placebo effects (Boulton *et al.*, 1992).

Children who received HT042 supplementation for 24 weeks showed a significant increase in height gain compared with children who received a placebo by 0.29 cm. While an approximate 0.3-cm-greater growth in 6 months may seem small, the findings may still be clinically meaningful as well as statistically significant. HT042 group increased their height by 0.14 SDS, albeit a moderate but statistically significant improvement (extrapolated 1-year increment of 0.28 SDS). This magnitude of improvement in height is 60–90% of the successful first year response to GH treatment (height SDS of 0.3–0.5) expected in idiopathic short stature (Cohen *et al.*, 2008). The positive impact of the HT042

Table 3. Subject characteristics of the baseline height <10th or ≥10th percentile subgroup at baseline and at end point

Characteristic	Baseline height < 10th percentile (n = 55)			Baseline height ≥ 10th percentile (n = 74)		
	Placebo (n = 30)	HT042 (n = 25)	p-value*	Placebo (n = 36)	HT042 (n = 38)	p-value*
General characteristics						
Sex (M/F)	15/15	15/10	0.458	16/20	21/17	0.352
Gestational age (<37/37–42/>42 weeks)	0/27/3	2/22/1	0.283	3/33/0	1/35/2	0.362
Birth weight (<2.5/2.5–4.0/>4.0 kg)	4/25/1	5/20/0	0.846	3/31/2	6/30/2	0.800
Sleeping hours (<7/7–9/9–11/>11 h)	0/13/17/0	0/12/13/0	0.729	0/24/12/0	0/25/23/0	0.936
Time spent exercising (0–1/1–2/2–3/>3 h per day)	20/9/1/0	10/15/0/0	0.042	21/14/1/0	25/11/2/0	0.589
Maternal height (cm)	157.0 ± 3.4	157.3 ± 4.2	0.784	157.4 ± 3.7	158.2 ± 4.1	0.376
Paternal height (cm)	170.0 ± 5.3	170.2 ± 4.8	0.899	171.1 ± 4.8	169.9 ± 4.9	0.174
Baseline						
Chronological age (years)	7.4 ± 0.9	6.9 ± 0.8	0.069	7.3 ± 0.9	7.4 ± 0.9	0.644
Bone age (years)	6.3 ± 1.1	6.1 ± 1.0	0.424	6.5 ± 1.0	6.6 ± 0.9	0.768
Height (cm)	113.1 ± 5.7	111.7 ± 4.4	0.332	117.3 ± 4.7	117.5 ± 4.3	0.861
Height SDS	−1.8 ± 0.6	−1.7 ± 0.3	0.946	−0.9 ± 0.2	−1.0 ± 0.2	0.040
Height SDS for bone age	−0.7 ± 1.4	−0.7 ± 1.0	0.860	−0.0 ± 1.0	−0.1 ± 1.0	0.758
Weight (kg)	20.4 ± 2.5	19.8 ± 3.0	0.190	22.1 ± 3.2	21.6 ± 2.9	0.626
BMI (kg/m ²)	15.9 ± 1.3	15.8 ± 1.7	0.319	16.1 ± 2.0	15.6 ± 1.5	0.556
GH level (ng/mL)	3.6 ± 6.1	2.9 ± 3.4	0.483	2.4 ± 3.2	2.7 ± 5.3	0.492
IGF-1 level (ng/mL)	145.0 ± 43.0	136.3 ± 43.1	0.459	162.3 ± 43.0	160.5 ± 39.7	0.825
IGFBP-3 level (ng/mL)	3806.7 ± 922.0	3538.8 ± 986.6	0.214	3841.1 ± 788.8	3827.1 ± 786.2	0.804
LH level (ng/mL)	0.22 ± 0.18	0.22 ± 0.16	>0.999	0.23 ± 0.18	0.21 ± 0.17	0.636
End point						
Chronological age (years)	7.9 ± 0.9	7.4 ± 0.8	0.071	7.8 ± 0.9	7.9 ± 0.9	0.578
Bone age (years)	7.0 ± 1.1	6.7 ± 1.1	0.275	7.1 ± 1.1	7.2 ± 1.0	0.749
Height (cm)	116.1 ± 5.5	115.2 ± 4.3	0.505	120.3 ± 4.6	120.7 ± 4.3	0.746
Height SDS	−1.7 ± 0.6	−1.5 ± 0.3	0.412	−0.8 ± 0.2	−0.9 ± 0.3	0.224
Height SDS for bone age	−0.8 ± 1.2	−0.7 ± 0.9	0.633	−0.1 ± 0.9	−0.1 ± 0.8	0.798
Weight (kg)	21.6 ± 2.7	21.0 ± 3.8	0.237	23.6 ± 3.3	23.1 ± 3.1	0.548
BMI (kg/m ²)	16.0 ± 1.4	15.8 ± 2.0	0.250	16.3 ± 2.0	15.8 ± 1.5	0.254
GH level (ng/mL)	2.7 ± 4.9	1.9 ± 2.7	0.691	1.9 ± 2.9	2.4 ± 3.6	0.475
IGF-1 level (ng/mL)	151.9 ± 58.3	154.3 ± 39.8	0.855	176.9 ± 52.4	183.0 ± 55.1	0.574
IGFBP-3 level (ng/mL)	3770.7 ± 945.7	3801.2 ± 818.0	0.900	4024.4 ± 812.3	4016.8 ± 748.4	0.967
LH level (ng/mL)	0.38 ± 0.53	0.13 ± 0.43	0.971	0.28 ± 0.47	0.31 ± 0.39	0.768

*± values are mean ± SD. p-values for comparisons of mean values between two groups are based on two-sample *t*-test. If the normality assumption was not met, a Wilcoxon rank sum test was used.

†For the analysis of categorical variables, two-tailed Fisher's exact test was used.

Abbreviations: SDS, standard deviation score; BMI, body mass index; GH, growth hormone; IGF-1, insulin-like growth factor-1; IGFBP-3, insulin-like growth factor binding protein-3; LH, luteinizing hormone.

on growth rate is in accordance with previous study reporting an improved growth of school-aged Korean children with mild short stature following 12-week administration. Recently, meta-analysis of nine RCTs revealed that micronutrient-fortified supplemented children grew an average of 0.27 cm and 0.15 SDS over 6 months than those who were not supplemented in low-income and middle-income countries, but there was no significant difference in high-income country (Kristjansson *et al.*, 2015). Meanwhile, the present study showed positive effect in healthy children of developed country, which means that HT042 does not act like a nutrient but functionally stimulates height growth.

Interestingly, HT042 was more effective when the efficacy analysis was restricted to children whose height was less than the 10th percentile at baseline. Mean

height gain increased by 0.45 cm in the HT042 group compared with the placebo group, while the children whose height was above the 10th percentile increased by only 0.17 cm. This tendency is similar to that of GH treatment, which the children who are shortest relative to target height have the best growth response (Cohen *et al.*, 2008). The result suggests that the growth stimulating effect of HT042 is distinct in much shorter children.

Bone age was advanced in both groups, but the advancement was lower within the HT042 group (1.61 vs. 1.05 months), which gives an indication that the growth potential was preserved in the HT042 group. From these results, the difference of Δ height SDS for bone age between HT042 and placebo groups increased more than twice that of the Δ height SDS (0.10 vs. 0.04 score). Accordingly, 0.3-cm-difference

Table 4. Subgroup comparison of change in parameters after 24 weeks of supplementation

Characteristic	Baseline height < 10th percentile (n = 55)			Baseline height ≥ 10th percentile (n = 74)		
	Placebo (n = 30)	HT042 (n = 25)	p-value*	Placebo (n = 36)	HT042 (n = 38)	p-value*
Height gain from baseline (cm)	2.95 ± 0.65	3.41 ± 0.87	0.031	3.06 ± 0.68	3.24 ± 0.99	0.262
95% CI	(2.71 to 3.20)	(3.13 to 3.82)		(2.83 to 3.29)	(2.91 to 3.56)	
p-value [#]	<0.001	<0.001		<0.001	<0.001	
ΔHeight SDS	0.12 ± 0.12	0.18 ± 0.15	0.070	0.11 ± 0.13	0.12 ± 0.19	0.336
95% CI	(0.07 to 0.16)	(0.13 to 0.26)		(0.07 to 0.15)	(0.06 to 0.19)	
p-value	<0.001	<0.001		<0.001	<0.001	
ΔHeight SDS for bone age	−0.13 ± 0.42	0.07 ± 0.26	0.045	−0.02 ± 0.39	0.00 ± 0.44	0.839
95% CI	(−0.28 to 0.03)	(−0.04 to 0.18)		(−0.15 to 0.11)	(−0.15 to 0.14)	
p-value	0.979	0.797		0.863	<0.993	
ΔBA-CA	2.23 ± 3.83	0.84 ± 2.32	0.103	1.08 ± 3.75	1.16 ± 4.08	0.931
95% CI	(0.80 to 3.66)	(−0.12 to 1.87)		(−0.18 to 2.35)	(−0.18 to 2.50)	
p-value	0.003	0.083		0.217	0.089	
ΔGH	−0.91 ± 8.05	−1.06 ± 4.33	0.987	−0.48 ± 4.30	−0.33 ± 6.32	0.369
95% CI	(−3.92 to 2.10)	(−3.00 to 0.73)		(−1.93 to 0.98)	(−2.41 to 1.74)	
p-value	0.349	0.264		0.223	0.919	
ΔIGF-1	6.86 ± 31.03	18.02 ± 31.90	0.196	14.56 ± 54.22	22.54 ± 37.81	0.198
95% CI	(−4.73 to 18.45)	(4.89 to 32.30)		(−3.79 to 32.90)	(10.11 to 34.97)	
p-value	0.236	0.009		0.093	0.001	
ΔIGFBP-3	−36.00 ± 825.66	262.40 ± 588.92	0.136	183.33 ± 734.52	189.74 ± 585.49	0.996
95% CI	(−344.31 to 272.31)	(11.47 to 519.36)		(−65.19 to 431.86)	(−2.71 to 382.18)	
p-value	0.813	0.036		0.164	0.053	
ΔLH	0.16 ± 0.43	0.13 ± 0.43	0.908	0.05 ± 0.47	0.10 ± 0.38	0.631
95% CI	(0.00 to 0.32)	(−0.05 to 0.31)		(−0.11 to 0.21)	(−0.03 to 0.23)	
p-value	0.124	0.377		0.886	0.312	
ΔBMI	0.07 ± 0.80	−0.01 ± 0.71	0.370	0.24 ± 0.71	0.17 ± 0.54	0.589
95% CI	(−0.23 to 0.37)	(−0.33 to 0.27)		(0.00 to 0.48)	(0.00 to 0.35)	
p-value	0.629	0.840		0.051	0.076	

*A paired *t*-test was used for the analyses of changes within groups. If normality assumption is not met, a Wilcoxon signed rank test on difference was used.

BA-CA = bone age minus chronological age

Abbreviations: SDS, standard deviation score; BMI, body mass index; GH, growth hormone; IGF-1, insulin-like growth factor-1; IGFBP-3, insulin-like growth factor binding protein-3; LH, luteinizing hormone.

seems to be attenuated and the actual effect on final height would be greater considering the fact that bone age is less advanced in the HT042 group (Kawai *et al.*, 1997; Hintz *et al.*, 1999). In the HT042 group whose starting height was below the 10th percentile, height SDS for bone age was significantly increased by 0.20 compared with the placebo group. This magnitude is comparable with the successful first year response of height SDS to GH treatment when extrapolated to 1 year. The result suggests that HT042 supplementation increases height growth rate in children with mild short stature without skeletal maturation, and this effect is likewise more distinct in much shorter children.

Height growth is the outcome of chondrocyte proliferation and hypertrophy of the growth plates, primarily caused by IGF-1 stimulation of GH. Insulin-like growth factor-1 transport is mediated mainly by IGFBP-3 (Costalonga *et al.*, 2009). Insulin-like growth factor-1 and IGFBP-3 are considered a biochemical index of GH levels because they are GH-dependent and maintain a regular daily concentration, whereas GH exhibits large diurnal fluctuation (Firth and Baxter, 2002). Serum levels of IGF-1 and IGFBP-3 increased significantly in the HT042 group during the supplementation period but did not increase significantly in the placebo

group. This result is consistent with previous *in vivo* findings in rats, where the HT042 group displayed higher IGF-1 expression in the growth plate and serum IGF-1 and IGFBP-3 levels (Kim *et al.*, 2012; Kim *et al.*, 2010). The effect of HT042 on height growth may be mediated by the increase in serum IGF-1 and IGFBP-3 levels stimulated by GH.

A limitation of our study is that we could not restrict parents' external efforts to promote the children's growth, so confounding bias from nonsanctioned activities is possible. In that the volunteers who are interested in promoting their height growth generally participate in these kinds of clinical trials, several factors including taking dietary supplement or herbal medicine seem to have affected catch-up growth in placebo group (Lee *et al.*, 2012). It is a limitation that these factors cannot be completely controlled in the trial on the height growth rate of children. However, there were no differences between the groups in major factors, including demographic distribution, parental height (which can reflect genetic factors), and sleeping hours and mean time spent exercising (which can influence GH secretion) even though we did not perform a stratified randomization.

In conclusion, HT042 supplementation helped to increase growth rate in children without skeletal

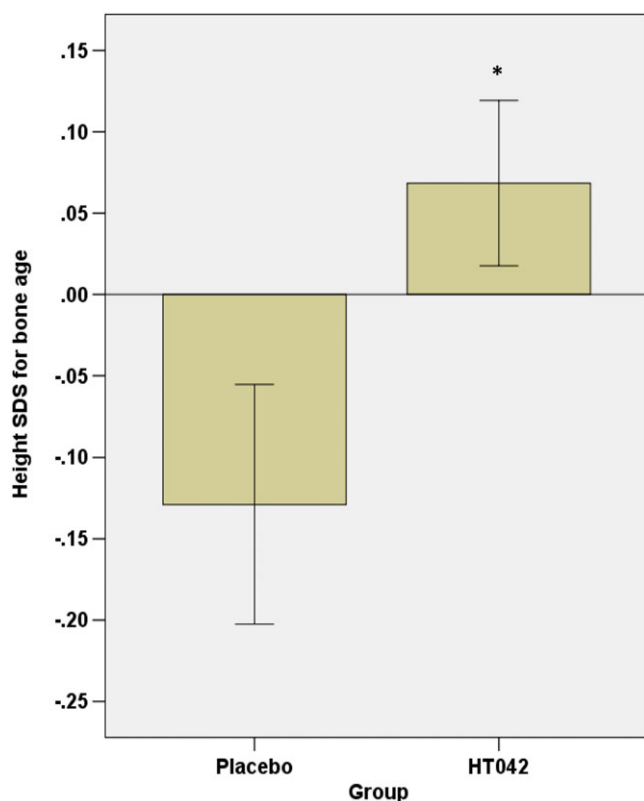


Figure 2. Change in height standard deviation score (SDS) for bone age in the HT042 group and the placebo group after 24 weeks of supplementation whose baseline height was <10th percentile. [Colour figure can be viewed at [wileyonlinelibrary.com](#)]

maturation, which can be considered preserved growth potential, and it was more effective in much shorter children below 10th percentile. Based on hematologic findings, we surmise that the effects of HT042 on height growth may be mediated by increases in serum IGF-1 and IGFBP-3 levels stimulated by GH.

Table 5. Adverse events

Variable	Placebo (n = 70)	HT042 (n = 70)
Symptoms and signs, n (%)	43 (61.4%)	44 (62.9%)
Nasopharyngitis, n	40	29
Rhinitis, n	4	7
Gastroenteritis, n	2	6
Abdominal pain, n	4	5
Allergic rhinitis, n	4	7
Acute otitis media, n	2	4
Atopic dermatitis, n	0	3
Pharyngitis, n	4	2
Others, n	26	24
Mean no of adverse events, n/n	86/70 (1.23)	87/70 (1.24)
Determination, overall		
Severity		
Mild	86/86	87/87
Moderate	0	0
Severe	0	0
Degree of association ($p > 0.999^{\dagger}$)		
Definitely not, n/n (%)	79/86 (91.86)	80/87 (91.95)
Unlikely, n/n (%)	7/86 (8.14)	7/87 (8.05)
Possible, n	0	0
Probable, n	0	0
Certain, n	0	0

[†]For the analysis of categorical variables, a two-tailed Fisher's exact test was used.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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