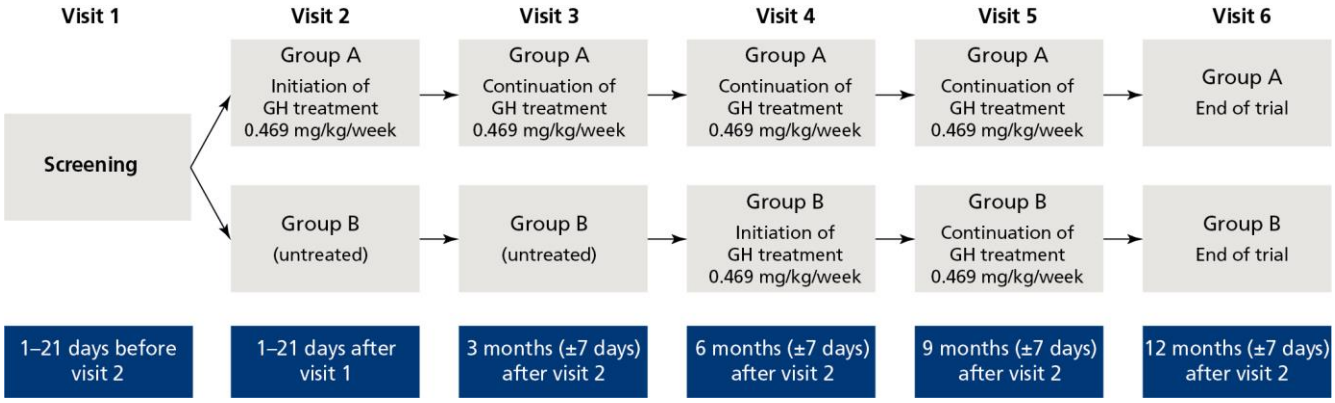
Supplementary Material

Manuscript Title: **Efficacy and Safety Evaluation of Human Growth Hormone Therapy in Patients with Idiopathic Short Stature in Korea: A Randomized Controlled Trial**

Authors: Min Ho Jung, Byung-Kyu Suh, Cheol Woo Ko, Kee-Hyoung Lee, Dong-Kyu Jin, Han-Wook Yoo, Jin Soon Hwang, Woo Yeong Chung, Heon-Seok Han, Vinay Prusty and Ho-Seong Kim

Supplementary Figure 1. Trial design.



GH, growth hormone

Supplementary Table 1. Inclusion and exclusion criteria.

Inclusion criteria:	
Patients were required, at screening, to fulfil all the criteria below:	
1	Informed consent obtained from patient's parents or legally acceptable representative before any trial-related activities (trial-related activities are any procedure that would not have been performed during normal management of the patient)
2	Pre-pubertal status (males aged from 4 to 11 [both inclusive], females aged from 4 to 9 [both inclusive]): an absence of breast development in females (Tanner 1 only) and testicular volume <4 mL in males
3	Height below 3rd percentile (according to the 2007 Korean National growth chart)
4	Epiphyses confirmed as open in patients ≥10 years of age
5	Normal thyroid function
6	Growth hormone level above 10 ng/mL following a stimulation test (test results within 6 months from screening can be used)
7	Normal karyotype (assessed only female patients)
8	Bone age ≤12 years
Exclusion criteria:	
Eligible patients were not allowed to meet any of the exclusion criteria below:	
1	Known presence of one or more pituitary hormone deficiencies (adrenocorticotropic hormone), antidiuretic hormone [ADH], follicle-stimulating hormone [FSH], luteinizing hormone [LH], thyroid-stimulating hormone [TSH])
2	Known primary hypothyroidism, adrenal insufficiency or hypogonadism (treated or untreated)
3	Specific types of growth failure including, but not limited to, known chromosomal abnormalities associated with growth failure and altered sensitivity to GH, e.g. Turner

	syndrome, Noonan syndrome, Prader–Willi syndrome, chromosomal trisomies, chronic renal failure, type 1 diabetes mellitus, osteo- and chondrodystrophies, hypochondroplasia, achondroplasia, small gestational age, chronic inflammatory states (e.g. inflammatory bowel disease, rheumatoid arthritis, systemic lupus, cystic fibrosis), mitochondrial myopathies, intrauterine growth retardation (defined as a birth height and weight both below the 5th percentile and not exhibiting catch up growth by age 3), and syndromes known to be associated with growth failure
4	Bone age is advanced over chronological age more than 3 years (inclusive)
5	Active malignancy, central nervous system trauma, active chemotherapy or radiation therapy for neoplasia within 5 years prior to screening (visit 1)
6	Treatment with any GH at least for 12 months prior to the screening visit (visit 1)
7	Concurrent therapy with substances known or suspected to be associated with alterations in growth including: methylphenidate, Adderall, dexedrine and other substances used for the treatment of attention deficit disorder; anti-inflammatory doses of glucocorticoids; oxandrolone, testosterone, estrogens and Lupron
8	Prior history of intracranial hypertension
9	Significant abnormality in clinical screening laboratories as determined by the physician
10	Any other social or medical condition, which, in the opinion of the physician, would be detrimental to either the patient or the trial
11	Hypertrophic cardiomyopathy
12	Known or suspected any chronic disease or nutritional disease
13	Mental incapacity, psychiatric disorder, unwillingness or language barrier precluding adequate understanding or cooperation
14	Known or suspected allergy to any of the trial products or related products

15	Participation in any other trial within 3 months prior to visit 1. Participation is defined as randomized

Removal of patients from therapy and assessment	
1	Pregnancy or intention of becoming pregnant
2	Withdrawal of informed consent or assent
3	Detection of an active malignancy
4	Commencement of medications as described in exclusion criteria
5	Failure to take more than 80% of scheduled Norditropin® NordiLet® injections
6	Onset of synostosis
7	Pubertal status defined as, for girls, Tanner breast, pubes score ≥2 and presence of menses, and, for boys, testicular volume ≥4 mL and Tanner pubes, penis score ≥2 for each testis
8	Patient with safety concern at the discretion of the investigator

Supplementary Table 2. Patient disposition.

	Group A n (%)	Group B n (%)	Total n (%)
Screened	NA	NA	70
Screening failures	NA	NA	16
Withdrawn before randomization			0
Randomized	36 (100.0)	18 (100.0)	54 (100.0)
Exposed	36 (100.0)	15 (83.3)	51 (94.4)
Withdrawn after randomization			
Withdrawal criteria[†]	0 (0.0)	3 (16.7)	3 (5.6)
Completed	36 (100.0)	15 (83.3)	51 (94.4)

[†]Three patients in group B were allocated but withdrew informed consent before trial product administration.

n, number of patients; NA, not applicable.