Therapeutic Class Overview
Growth Hormone

Therapeutic Class

Overview/Summary: Growth hormone (GH) affects many of the metabolic processes carried out by somatic cells, most notably increasing body mass. Overall growth is stimulated by GH therapy; however, the effects are not evenly distributed among protein, lipid and carbohydrate compartments. Specifically, body protein content and bone mass increase, total body fat content decreases and there is an increase in plasma and liver lipid content due to the mobilization of free fatty acids from peripheral fat stores. Other physiological effects of GH include stimulation of cartilage growth.[1] In pediatric patients, once a diagnosis of growth hormone deficiency (GHD) is confirmed, GH therapy should be initiated immediately and continued at least until liner growth is nearly complete (e.g., decreased to 2.5 cm/year). Therapy should be initiated as soon as possible as evidence demonstrates that growth response is more robust when GH therapy is started at a younger age. Once adult height is achieved, patients should be retested to determine if GH treatment will be required during adulthood.[1] The role of GH therapy in adult patients with GHD is less clear. There is evidence to demonstrate that when used in adult patients with GHD, GH therapy increases muscle mass and decreases body fat. Evidence of other potential beneficial effects of GH therapy in adults are not as established, including improvement in bone mineral density, sense of well-being, muscle strength and lipid profile.[2] Included in this review are the various GH preparations. Specifically, all preparations contain somatropin; otherwise known as recombinant human GH.[3-11] The various preparations are Food and Drug Administration (FDA)-approved for use in a variety of pediatric conditions associated with a failure in growth, including chronic kidney disease, Turner syndrome, being born small for gestational age, Prader-Willi syndrome, mutations in the Short Stature Homeobox gene and Noonan syndrome, as well as for idiopathic short stature.[3-9,11] The majority of preparations are also indicated for the treatment of GHD in adults as well.[3-9] Of note, Serostim® (somatropin) is only FDA-approved for the treatment of human immunodeficiency virus-associated wasting or cachexia in adults.[10] All of the available GH preparations are available for subcutaneous injection and there are currently no generics available within the class.[3-11] Treatment guidelines support the use of GH in FDA-approved indications and they do not distinguish among the various preparations.[12-20]

Table 1. Current Medications Available in Class[3-11]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Somatropin (Genotropin®)	Pediatric indications: growth failure associated with Prader-Willi syndrome, growth failure associated with Turner syndrome, growth failure in children born small for gestational age, growth hormone deficiency, and idiopathic short stature Adult indications: growth hormone deficiency	Cartridge, powder for reconstitution: 5 mg 12 mg Cartridge, powder for reconstitution (preservative-free): 0.2 mg 0.4 mg 0.6 mg 0.8 mg 1.0 mg 1.2 mg 1.4 mg 1.6 mg 1.8 mg 2.0 mg	-
Somatropin (Humatrope®)	Pediatric indications: growth failure associated with short-stature homeobox-containing gene deficiency, growth failure associated	Cartridge, powder for reconstitution: 6 mg 5 mg	-

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
	with Turner syndrome, growth failure in children born small for gestational age, growth hormone deficiency, and idiopathic short stature Adult indications: growth hormone deficiency	12 mg 24 mg Vial, powder for reconstitution: 5 mg	
Somatropin (Norditropin®)	Pediatric indications: growth failure associated with Noonan syndrome, growth failure associated with Turner syndrome, growth failure in children born small for gestational age, and growth hormone deficiency Adult indications: growth hormone deficiency	Prefilled cartridge: 5 mg/1.5 mL Prefilled pen (Norditropin® FlexPro®): 5 mg/1.5 mL 10 mg/1.5 mL 15 mg/1.5 mL Prefilled pen (Norditropin NordiFlex®): 30 mg/3 mL	-
Somatropin (Nutropin®)	Pediatric indications: growth failure associated with chronic renal insufficiency before renal transplant, growth failure associated with Turner syndrome*, growth hormone deficiency*, and idiopathic short stature* Adult indications: growth hormone deficiency	Vial, powder for reconstitution: 5 mg 10 mg Vial, liquid: 10 mg/2 mL Prefilled cartridge: 5 mg/2 mL 10 mg/2 mL 20 mg/2 mL Prefilled pen cartridge: 10 mg/2 mL 20 mg/2 mL	-
Somatropin (Omnitrope®)	Pediatric indications: growth failure associated with Prader-Willi syndrome, growth failure associated with Turner syndrome, growth failure in children born small for gestational age, growth hormone deficiency, and idiopathic short stature Adult indications: growth hormone deficiency	Prefilled cartridge: 5 mg/1.5 mL 10 mg/1.5 mL Vial, powder for reconstitution: 5.8 mg	-
Somatropin (Saizen®)	Pediatric indications: growth hormone deficiency Adult indications: growth hormone deficiency	Cartridge, powder for reconstitution: 8.8 mg Vial, powder for reconstitution: 5 mg (15 IU) 8.8 mg (26.4 IU)	-
Somatropin (Serostim®)	Adult indications: human immunodeficiency virus-associated	Vial, powder for reconstitution: 4 mg (12 IU)	-

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
	wasting or cachexia	Vial, powder for reconstitution (preservative-free): 5 mg (15 IU) 6 mg (18 IU)	
Somatropin (Tev-Tropin®)	Pediatric indications: growth hormone deficiency	Vial, powder for reconstitution: 5 mg (15 IU)	-

IU=International units
*Indicated for long-term treatment.

Evidence-based Medicine

- The evidence demonstrating the safety and efficacy of growth hormone (GH) in Food and Drug Administration approved indications is well established. Overall, treatment with GH is consistently "superior" to no treatment and/or placebo and data suggests that not one specific dosing regimen for each indication is preferred over another. Treatment with GH should be individualized based on growth response and tolerability.
- Of note, limited head-to-head clinical trials exist; therefore, it is difficult to determine if one specific preparation of GH (i.e., somatropin) is "superior" to another.[21-137] Treatment guidelines do not distinguish among the various preparations.[12-20]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
    - Among pediatric patients, growth hormone (GH) (somatropin) is recommended as a treatment option for children with growth failure associated with any of the following: growth hormone deficiency (GHD), Turner syndrome, Prader Willi syndrome, chronic renal insufficiency, born small for gestational age with subsequent growth failure at four years of age or later and short stature homeobox-containing gene deficiency.[12,13,16-18] GH is also a treatment option for pediatric patients with Noonan syndrome.[14,15]
        - The choice of preparation should be individualized after informed discussion between the responsible clinician and the patient and/or caretaker about the advantages or disadvantages of available preparations, taking into consideration therapeutic need and likelihood of adherence to treatment. If more than one preparation is suitable, the least costly should be chosen.
    - Among adult patients, GH is recommended for the approved uses of the preparation in patients with clinical features suggestive of adult GHD and biochemically proven evidence of GHD.[19,20]
- Other Key Facts:
    - No agents in the class are currently available generically.

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Therapeutic Class Review
Growth Hormone

Overview/Summary

Growth hormone (GH) affects many of the metabolic processes carried out by somatic cells, most notably increasing body mass. Overall growth is stimulated by GH therapy; however, the effects are not evenly distributed among protein, lipid and carbohydrate compartments. Specifically, body protein content and bone mass increase, total body fat content decreases and there is an increase in plasma and liver lipid content due to the mobilization of free fatty acids from peripheral fat stores. Other physiological effects of GH include stimulation of cartilage growth.[1]

Growth hormone deficiency (GHD) in pediatric patients is a clinical diagnosis that is confirmed by biochemical testing. A clinical diagnosis is based on auxological features; therefore, a patient's growth patterns are compared to the established norms. The clinical manifestations of GHD will vary depending on whether a patient has complete or partial deficiency. In complete deficiency, pediatric patients will present with early severe growth failure, delayed bone age, central disposition of body fat and very low serum concentrations of GH, insulin growth factor 1 (IGF-1) and IGF binding protein-3. These patients are also more prone to hypoglycemia, prolonged jaundice, microphallus in males and giant cell hepatitis. GHD in pediatric patients with partial deficiency may be more difficult to diagnosis, as these manifestations may not be as obvious. Once a diagnosis of GHD is confirmed in pediatric patients, GH therapy should be initiated and continued until cessation of linear growth. Therapy should be initiated as soon as possible as evidence demonstrates that growth response is more robust when GH therapy is started at a younger age. Several preparations of GH are currently available for use in pediatric patients. Recombinant GH preparations, administered by subcutaneous injection, are currently the most widely utilized. Due to the variability in individual response to therapy, after initial dosing; the dose of GH is adjusted based on growth response and IGF-1 level. While not universally supported, the therapeutic goal of therapy is to achieve a level of IGF-1 that is slightly higher than average, because growth velocity is typically greatest at these levels. A patient's growth velocity, as compared to a similar population, should also be monitored to determine if the growth response is adequate. Possible explanations of an inadequate response to GH therapy include poor adherence, incorrect diagnosis of GHD, subtherapeutic dose of GH or the patient has GHD but with concurrent mild GH insensitivity. In pediatric patients, GH therapy is typically continued at least until linear growth is nearly complete (e.g., decreased to less than 2.5 cm/year). At this point, retesting for GHD should occur to determine if GH therapy should be continued into adulthood. The majority of pediatric patients with idiopathic, isolated GHD in their childhood will have normal GH secretion during late adolescents and young adulthood. In contrast, pediatric patients with genetic GHD, multiple pituitary hormone deficiencies and/or those with structural defects in the hypothalamic-pituitary region, rarely recover the ability to secrete GH as an adult. In these cases; therefore, retesting may not be required.[1]

GHD may also occur in adult patients; however, the role of GH therapy in adults is not as clear as it is in pediatric patients in whom therapy is required for normal growth. There is evidence to demonstrate that when used in adult patients with GHD, GH therapy increases muscle mass and decreases body fat. Evidence of other potential beneficial effects of GH therapy in adults is not as established and includes improvement in bone mineral density, sense of well-being, muscle strength and lipid profile. GH therapy can be considered in adult patients with severe clinical manifestations and unequivocal evidence of GHD due to organic disease of childhood-onset or adult-onset.[2]

All of the GH preparations contain somatropin; otherwise known as recombinant human GH.[3-11] The various preparations are Food and Drug Administration (FDA)-approved for use in a variety of pediatric conditions associated with a failure in growth, including chronic kidney disease, Turner syndrome, being born small for gestational age, Prader-Willi syndrome, mutations in the Short Stature Homeobox gene and Noonan syndrome, as well as for idiopathic short stature.[3-9,11] The majority of preparations are also indicated for the treatment of GHD in adults.[3-9] Of note, Serostim® (somatropin) is FDA-approved solely for the treatment of human immunodeficiency virus-associated wasting or cachexia in adults.[10] Specific

FDA-approved indications for the various GH preparations are outlined in Table 2.[3-11] All of the available GH preparations are available for subcutaneous injection and there are currently no generics available within the class.

For pediatric patients, treatment guidelines recommend the use of GH therapy with somatropin as a treatment option for children with growth failure associated with any of the following: GHD, Turner syndrome, Prader-Willi syndrome, chronic renal insufficiency, born small for gestational age with subsequent growth failure at four years of age or later and Short Stature Homeobox-containing gene deficiency.[12-19] Choice of preparation should be individualized based on potential advantages and disadvantages of therapy, therapeutic need and the likelihood of adherence. If more than one preparation is suitable for a particular patient, the least costly one should be utlized.[12] For adult patients, treatment guidelines recommend the use of GH therapy for the approved indications of the preparations in patients with clinical features suggestive of adult GHD and biochemically proven evidence of adult GHD.[20] Therapy should be individualized independent of body weight. The dose of GH should be low initially and gradually increased to the minimally effective dose that normalizes IGF-1 levels without side effects.[20,21] Guidelines do not distinguish among the various GH preparations. The various preparations are equally biopotent and have the same natural sequence structure. In addition, daily administration of GH therapy is more effective than three times a week at the same total weekly dose.[1]

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade name)	Medication Class	Generic Availability
Somatropin (Genotropin®)	Human growth hormone	-
Somatropin (Humatrope®)	Human growth hormone	-
Somatropin (Norditropin®)	Human growth hormone	-
Somatropin (Nutropin®)	Human growth hormone	-
Somatropin (Omnitrope®)	Human growth hormone	-
Somatropin (Saizen®)	Human growth hormone	-
Somatropin (Serostim®)	Human growth hormone	-
Somatropin (Tev-Tropin®)	Human growth hormone	-

Indications

Table 2. Food and Drug Administration Approved Indications[3-11]

Indications	Somatropin (Genotropin®)	Somatropin (Humatrope®)	Somatropin (Norditropin®)	Somatropin (Nutropin®)	Somatropin (Omnitrope®)	Somatropin (Saizen®)	Somatropin (Serostim®)	Somatropin (Tev-Tropin®)
Pediatric Indications								
Growth failure associated with chronic renal insufficiency before renal transplant				✔				
Growth failure associated with Noonan syndrome			✔					
Growth failure associated with Prader-Willi syndrome	✔				✔			
Growth failure associated with short-stature homeobox-containing gene deficiency		✔						
Growth failure associated with Turner syndrome	✔	✔	✔	✔ *	✔			
Growth failure in children born small for gestational age	✔	✔	✔		✔			
Growth hormone deficiency	✔	✔	✔	✔ *	✔	✔		✔
Idiopathic short stature	✔	✔		✔ *	✔			
Adult Indications								
Growth hormone deficiency	✔	✔	✔	✔	✔	✔		
Human immunodeficiency virus-associated wasting or cachexia							✔	

*Indicated for long-term treatment.

Pharmacokinetics

Table 3. Pharmacokinetics[3-11]

Generic Name	Bioavailability (%)	Volume of distribution	Serum Half-Life (hours)
Somatropin (Genotropin®)	80	1.3±0.8 L/kg	3
Somatropin (Humatrope®)	75	0.07 L/kg	3.8
Somatropin (Norditropin®)	Unknown	Not reported	7 to 10
Somatropin (Nutropin®)	81±20	0.05 L/kg	2.10±0.43
Somatropin (Omnitrope®)	Not reported	Not reported	2.5 to 2.8
Somatropin (Saizen®)	70 to 90	12.00±1.08 L	1.75
Somatropin (Serostim®)	70 to 90	12.00±1.08 L	4.28±2.15
Somatropin (Tev-Tropin®)	70	Not reported	2.7

Clinical Trials

The clinical trials demonstrating the safety and efficacy of growth hormone (GH) (i.e., somatropin or recombinant human growth hormone), in their Food and Drug Administration approved indications are outline in Table 4. There are limited head-to-head clinical trials comparing different GH preparations to one another.[22-142]

Clinical trials to support the use of GH for the treatment of growth failure associated with chronic renal insufficiency before renal transplant and Noonan syndrome in pediatric patients are limited.[22-25] For the treatment of growth failure associated with chronic renal insufficiency, a Cochrane Review of 15 randomized controlled trials demonstrated that after one year of treatment with GH (28 international unit/m^2/week), height velocity increased 3.8 cm/year more than no treatment. The duration of trials were not long enough to determine if continuing treatment with GH resulted in an increase in final adult height.[24] In addition, a randomized controlled trial evaluating GH in patients with Noonan syndrome, found a positive effect of GH on linear growth. Specifically there was a significantly greater change in height standard deviation score and bone maturation was accelerated with GH compared to no treatment. In this trial, data also suggests that once treatment with GH is discontinued, “catch-down” growth can occur.[25] Meaning, artificially stimulated growth declines once GH is discontinued.

Clinical trials consistently demonstrate the significant benefits of GH in pediatric patients with Prader-Willi syndrome in accelerating growth and in improving body composition. Benefits were also observed in improving bone mineral density, lipid profiles, energy expenditure, strength and agility and pulmonary function.[26-35] Data from Lindgren et al suggests that growth velocity declines dramatically once treatment is discontinued.[34]

GH (Humatrope®) demonstrated efficacy in increasing first year height velocity in patients with Short Stature Homeobox-containing gene deficiency when compared to no treatment (P<0.0001).[36]

Several clinical trials consistently demonstrate that GH significantly increases the growth rate of pediatric patients with Turner syndrome. Overall, various dose ranging trials did not consistently demonstrate a “superior” weight based GH dosing regimen over another; all doses of GH were beneficial. In addition, data suggest that increases in height are greatest during the first year of therapy.[38-49] A Cochrane Review of four randomized controlled trials demonstrated that GH (0.3 to 0.375 mg/kg/week) increased short term growth in patients with Turner syndrome by approximately three centimeters during the first year of treatment. Despite the increase, the final height achieved was still below the normal range.[49]

For the treatment of growth failure in pediatric patients born small for gestational age, clinical trials again consistently demonstrate the significant benefits of GH on increasing growth rates.[50-62] Data from individual clinical trials and three meta analyses demonstrate that response to GH therapy is dose-dependent, and higher doses of GH result in additional gain.[60-62]

Treatment with GH has been shown to increase height velocity in both prepubertal and pubertal pediatric patients with growth hormone deficiency (GHD).[63-72] Two head-to-head trials have demonstrated no differences in safety and efficacy with different GH preparations for the treatment of pediatric GHD. One of the trials compared three GH preparations (Genotropin®, Humatrope® and Saizen®), while the second evaluated two preparations (Genotropin® and Omnitrope®).[66,72]

In pediatric patients with idiopathic short stature, somatropin has been shown to increase first year growth velocity and final height.[73-80] Additionally, once daily compared to three times weekly dosing and higher compared to lower dosing demonstrated a greater increase in growth velocity.[78,79]

Several placebo-controlled, randomized trials have demonstrated the efficacy of GH in improving body composition and lipid profile in adult patients with GHD.[80-135] Furthermore, results from meta-analyses and randomized controlled trials have demonstrated that treatment with GH was associated with improved cardiac function and bone mineral density.[134,135,141,142] However, there are currently conflicting data with regard to the effect of GH on cognitive function, quality of life and exercise capacity.[131-133,137]

In patients with human immunodeficiency virus-associated wasting, GH (Serostim®) has been shown to increase body weight, lean body mass and work output. However, effects on quality of life were variable.[138,139]

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Growth Failure Associated With Chronic Renal Insufficiency Before Renal Transplant				
Fine et al[22] GH (Nutropin®) 0.05 mg/kg/day SC vs placebo The dose of GH was adjusted for change in weight at each 3 month visit. The following drugs were permitted to be administered routinely to all patients: multivitamins, vitamin D analog, calcium carbonate or aluminum hydroxide, sodium bicarbonate, prophylactic antibiotic therapy with sulfamethoxazole/ trimethoprim or nitrofurantoin and antihypertensive medications other than clonidine. At the discretion of the investigator, treatment with recombinant human erythropoietin was also permitted.	MC, PC, RCT Pediatric patients with irreversible renal insufficiency, creatinine clearance >5 and <75 mL/min/1.73m^2, short stature with height <3rd percentile for chronological age, bone age <10 years for girls and <11 years for boys and prepubertal status	N=30 2 years (treatment was discontinued at the time of renal trans-plantation or if significant adverse events occurred)	Primary: Growth, laboratory evaluations, renal function, adverse events Secondary: Not reported	Primary: The mean first year growth rate with GH was 14.1±2.6 cm/year compared to 9.3±1.5 cm/year with placebo (*P*<0.00005). The mean second year growth rates were 8.6±2.1 vs 6.9±1.0 cm/year (*P*=0.025). There was significant improvement in the mean height SDS with GH during the two years (-3.0 to -1.1; *P*<0.00005), whereas there was no change with placebo (-2.5 to -2.7; *P* value not reported). After two years, mean bone age increased by 2.1±0.6 and 1.4±0.2 years with GH and placebo (*P*<0.01). There was a significantly greater mean weight gain with GH compared to placebo (5.6±1.2 vs 4.0±0.9 kg; *P*=0.003). This was accompanied by a decrease in mean triceps skin-fold thickness with GH (-2.3±1.5 mm vs 0.2±3.3 cm; *P*=0.04). There was a significant difference between baseline and two year values for HbA1c (*P*=0.02) and creatinine (*P*=0.005) with placebo, and in IGF-1 (*P*=0.004), alkaline phosphatase (*P*=0.008), post-prandial insulin (*P*=0.007), post prandial glucose (*P*=0.02), HbA1c (*P*=0.03) and creatinine (*P*=0.017) with GH. Despite the increase in mean post-prandial insulin values with GH, there was no clinical evidence of glucose intolerance. Only IGF-1 (*P*=0.04) and post-prandial insulin (*P*=0.02) values were significantly different between placebo and GH for the change between baseline and two years. The mean increment in serum creatinine level from baseline to two years was 0.9 mg/dL (2.0±1.3 to 2.9±1.9; *P*=0.005) with placebo and 0.5 mg/dL (1.5±0.7 to 2.0±0.9; *P*=0.02) with GH. The mean estimated creatinine clearance with placebo declined from 21.9±9.7 to 18.8±9.2 mL/min/1.73 m^2 (*P*=0.12). The mean estimated creatinine clearance with GH declined from 30.9±10.9 to 30.6±13.1 mL/min/1.73 m^2 (*P*=0.92). During the two years the incidence of adverse events was similar with the two treatments. Due to the small sample size and low incidence of adverse events, statistical tests could not be applied. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Santos et al[23] GH (Norditropin®) 0.33 mg/kg/week daily SC vs no GH	MC, OL, PG, PRO, RCT Pediatric patients with a GFR ≤60 mL/min/1.73 m^2, length below -2 SDS for the same chronological age and growth velocity <50th percentile, conservative treatment or long term peritoneal dialysis, euthyroid status and nutritional intake providing a daily amount ≥80% of recommended daily allowances for calories and 10% of calories from high biologic value proteins	N=16 1 year	Primary: Growth, bone mass, hormonal determinations, safety Secondary: Not reported	Primary: Body length SDS increased throughout treatment with GH only. After one year, patients receiving GH gained 14.5±1.2 cm and 1.4±0.3 SDS compared to 9.5±1.1 cm and -0.1±0.3 SDS with patients not receiving GH (*P*=0.024 and *P*=0.031, respectively). Similar results were observed for weight SDS; however, results were not significant between the two treatments (*P* value not reported and *P*=0.18). Head circumference increased with both treatments, from 44.9±0.8 to 47.8±0.6 cm (*P*<0.001) with GH and from 45.3±0.8 to 47.5±0.6 cm (*P*<0.001) with no GH, without a difference between the two treatments (*P* value not reported). There was also no difference between the two treatments with regards to brachial circumference and forearm length (*P* values not reported). Bone area, BMC and BMI increased from the six month visit onward with GH. In patients receiving no GH, BMC and BMI became higher than baseline after six months, but the difference did not persist after one year. There were no differences between the two treatments at any time point. Total IGF-1 SDS increased significantly after three months of GH (from -0.85±0.13 to -0.22±0.12; *P*<0.05) and remained so throughout the trial (-0.08±0.16, 0.20±0.24 and 0.14±0.38 at months six, nine and 12, respectively). Total IGF-1 SDS did not change with no GH (-0.75±0.13 to -0.75±0.12, -0.86±0.16, -0.79±0.241 and -0.75±0.38 at baseline and months three, six, nine and 12). Free IGF-1 SDS increased significantly after nine and 12 months of GH treatment compared to baseline (0.64±0.52, 4.65±1.07, 3.50±0.93, 3.47±0.81 and 3.25±0.72 at baseline and months three, six, nine and 12). IGFBP-3 SDS increased significantly until month nine (*P*<0.05) with GH from -0.22±0.40 to 1.26±0.38, 1.26±0.46, 1.18±0.47 and 0.77±0.51 at months three, six, nine and 12, respectively, whereas it did not change with no GH (0.04±0.40, 0.27±0.38, 0.19±0.46, 0.44±0.47 and 0.18±0.51, respectively). There were no differences in SDS IGFBP-I between the two treatments in basal and final visits; however, at months three, six and nine, levels were significantly higher with no GH (*P* values not reported). No consistent variations or differences between the two treatments were observed for IGF-2, IGFBP-2, GHBP, ghrelin or leptin (data not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Bone age advanced similarly with both treatments throughout the trial (0.98±0.10 and 0.98±0.12 years with GH and no GH, respectively). Basal and final bone age and bone age-chronological age ratios were not different between the two treatments. Blood pressure, hemoglobin, leukocyte and platelet counts, serum concentrations of sodium, bicarbonate, total proteins, albumin, transaminases, fasting glucose, HbA1c, insulin, T_4, TSH, ferritin, cholesterol and TG remained within the normal range throughout the trial with no differences between the two treatments. Serum concentrations of calcium phosphate, 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D and PTH were similar between the two treatments and did not change throughout the trial. There were 29 adverse events; nine with GH and 20 with no GH (*P*=0.065). None of the adverse events were considered to be treatment-related. Mild to moderate adverse events included acute respiratory infection, acute otitis media, chickenpox, abdominal pain and acute gastroenteritis. Serious adverse events occurring with both treatments included urinary tract infections and surgical procedures. Secondary: Not reported
Vimalachandra et al[24] GH vs placebo or no GH (control) OR RCTs that compared two doses of GH (28 IU/m^2/week vs 14 IU/m^2/week or 28 IU/m^2/week vs 58 IU/m^2/week)	SR (15 RCTs) Patients 0 to 18 years of age diagnosed with chronic kidney disease who are predialysis, on dialysis or post transplant	N=629 Duration varied	Primary: Difference in mean change in height SDS between the treatment and control groups Secondary: Change in height SDS from treatment onset to completion, change in height velocity, change in height velocity SDS, change in	Primary: *GH vs control:* The effect of GH compared to control on height SDS was reported in six trials. After one year, treatment with GH increased height (MD, 0.78; 95% CI, 0.52 to 1.04). In one trial, data were available for two years of treatment and most of the growth acceleration occurred during the first year of treatment, while treatment in the second year resulted in a small and nonsignificant increase in height SDS (MD, 0.37; 95% CI, -0.10 to 0.84). However GH treatment for two years resulted in a persisting significant difference in height SDS between GH and control (MD, 1.36; 95% CI, 0.86 to 1.86). Secondary: *GH 28 IU/m^2/week vs GH 14 IU/m^2/week:* Two trials reported no difference in the change in height SDS between the two doses after one year (MD, 0.17; 95% CI, -0.14 to 0.49). One of the trials observed no differences between the two doses after six months (MD, 0.20; 95% CI, -0.33 to 0.73) and between six months and one year of treatment

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			bone age, other outcomes, adverse events	(MD, 0.12; 95% CI, -0.43 to 0.68). *GH 28 IU/m^2/week vs GH 56 IU/m^2/week:* One trial reported no difference in the change in height SDS between the two doses after one year (MD, 0.30; 95% CI, -1.00 to 1.06). *GH vs control:* The effect of GH compared to control on height velocity was reported in nine trials. Two trials reported an increase of 2.85 cm over six months (MD, 2.85 cm/six months; 95% CI, 2.22 to 3.48). Six trials reported an increase over one year of 3.80 cm/year (MD, 3.80 cm/year; 95% CI, 3.20 to 4.39). One trial reported results for the second year in which there was a greater decrease in height velocity with GH compared to control (MD, -1.90 cm/year; 95% CI, -3.04 to -0.76); however, height velocity with GH remained significantly higher compared to control during the second year of treatment (MD, 2.30 cm/year; 95% CI, 1.39 to 3.21). *GH 28 IU/m^2/week vs GH 14 IU/m^2/week:* Three trials combined in a MA showed a significant increase in height velocity with 28 IU/m^2/week (MD, 1.34 cm/year; 95% CI, 0.55 to 2.13). One trial reported an increase in height velocity to six months with 28 IU/m^2/week (MD, 1.96 cm/six months; 95% CI, 0.86 to 3.05), which waned during the second six months of treatment (MD, -0.53 cm/six months; 95% CI, -1.65 to 0.59). Another trial reported a 2.7 cm/year (14 IU/m^2/week) and a 2.6 cm/year (28 IU/m^2/week) increase in height velocity (P<0.05). *GH 56 IU/m^2/week vs GH 28 IU/m^2/week:* One trial reported no difference in mean height velocity after one year (MD, 1.10 cm/year; 95% CI, -1.30 to 3.50). *GH vs control:* The effect of GH compared to control on height velocity SDS was reported in three trials. Two reported an increase in height velocity SDS over six month (MD, 7.80; 95% CI, 6.09 to 9.51) and one reported an increase over one year (MD, 6.14; 95% CI, 3.41 to 8.86).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				GH 28 IU/m^2/week vs GH 14 IU/m^2/week: Among three trials, height velocity SDS at one year was significantly higher with GH 28 IU/m^2/week (MD, 1.48; 95% CI, 0.03 to 2.93). Height velocity SDS was significantly increased with GH 28 IU/m^2/week at six months (MD, 2.05; 95% CI, 0.82 to 3.28) but no between six months and one year (MD, -0.65; 95% CI, -2.09 to 0.80). *GH vs control:* The effect of GH compared to control on bone age was reported in six trials. There was no difference in the change in bone age between the two treatments over six months (MD, -0.15; 95% CI, -1.77 to 1.48), one year (MD, 0.16; 95% CI, -0.72 to 1.03) or between one and two years of treatment (MD, 0.40; 95% CI, -0.99 to 1.79). *GH vs control:* The effect of GH compared to control on kidney function was reported in nine trials and all reported that kidney function did not differ between the two treatments. Two trials reported data on lipids and found no difference in cholesterol, TGs, apo; however, Lp(a) levels were significantly higher with GH. Three trials reported data on glucose tolerance and no significant differences were observed between GH and control. Reported side effects included asthma/wheezing, acute rejection in transplantation, deterioration in kidney function, raised fasting glucose, papilledema, glucose intolerance, granuloma formation, lymph node swelling, claudication, hypertension and worsening of pre-existing idiopathic scoliosis. Only one trial demonstrated a significant increase in adverse events with GH compared to control.
Growth Failure Associated With Noonan Syndrome				
Noordam et al[25] GH 0.15 IU/kg/day SC	MC, RCT Pediatric patients with	N=37 3 years	Primary: Height SDS, mean bone maturation,	Primary: Gain in height SDS over the first year was significantly higher with GH (Groups A+C) compared to no GH (Group B) (0.5±0.14 vs 0.0±0.2; *P*<0.05). Over the second year the gain in height SDS in Group B was comparable with the first

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Eight patients immediately started GH and after 2 years, discontinued treatment for 1 year (Group A). Fifteen patients served as a control group during the first year and started GH after 1 year and received GH for 2 years (Group B). An additional 14 patients were treated with GH for 3 years (Group C).	Noonan syndrome with height SDS below -2 and eligible to receive GH		effect of discontinuing and restarting GH in Group A Secondary: Not reported	year response in Groups A+C (0.5±0.5 vs 0.5±0.4; *P* value not reported). At the two year follow up, the mean changes in height SDS were no different between Groups A+C and B (0.8 vs 0.5; *P* value not reported). Over the first year, the gain in height SDS for bone age was not different between Groups A+C and B. This finding was caused by the significantly lower rate of bone maturation in the first year of the trial in Group B. The effect of the first year of GH treatment on bone maturation was similar in Groups A+C and B (1.2±0.5 vs 1.2±0.9; *P* value not reported). Gain in height SDS over three years was not different between Groups A and B (0.8±0.7 vs 0.8±0.5; *P* value not reported). The change in height SDS for bone age over three years was significantly different; a decrease was observed with Group A (-0.7 vs 0.3; *P* value not reported). Over three years, bone maturation was accelerated with Group A compared to Group B (1.3 vs 0.9; *P*<0.05). Over the third year of the trial alone, "catch-down" growth was seen in Group A, which was reflected by the significantly lower mean change in height SDS compared to Group B (-0.2 vs 0.2; *P*<0.05). Secondary: Not reported
Growth Failure Associated With Prader-Willi Syndrome				
Carrel et al[26] GH 1 mg/m^2/day SC vs no GH (control)	RCT Pediatric patients with PWS	N=54 1 year	Primary: Growth and GH axis, body composition, BMD, energy expenditure, strength and agility, pulmonary function, lipids, carbohydrate metabolism, scoliosis, other adverse events	Primary: After one year, height increased by 10.1±2.5 cm with GH and was accompanied by an increase in growth velocity SDS from -1.1±2.5 to 4.6±2.9 (*P*<0.001). Height increased by 5.0±1.8 cm with control and was accompanied by an increase in growth velocity SDS from -0.9±1.7 to -0.7±1.9 (*P* value not significant). Mean IGF-1, osteocalcin and type 1 procollagen levels increased significantly with GH (*P*<0.01 vs baseline and control). Mean bone age progressed with control; 1.4 years compared to 1.5 years with GH (*P* value not significant). After one year, body fat decreased by eight percent overall (46.3±5.8 to 38.4±10.7%; *P*<0.01) with GH compared to no change with control. LBM increased with GH (to mean of 25.6±4.3 kg; *P*<0.01) and remained unchanged with control.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			Secondary: Not reported	After one year, femoral head BMD increased by 0.9±0.2 g/cm^2 with GH (*P*<0.05 vs baseline and control). GH was also associated with nonsignificant increases in lumbar spine and total body BMD. After one year, resting energy expenditure was not significantly increased with GH; however, respiratory quotient values decreased (0.81±0.07 to 0.77±0.05; *P*<0.0001). Values remained unchanged with control. After one year, GH improved the agility run (faster by 2.3±0.5 seconds), broad jump (farther by 3.3±1.9 inches), abdominal strength (an improvement of 3.0±2.1 sit ups/20 seconds) and upper extremity strength (increase of 2.5±1.8 weight-lift repetitions/30 seconds) (*P*<0.01 vs baseline and control). Increases in both inspiratory (45.8±4.1 to 55.7±13.7 cm/H_20; *P*<0.001) and expiratory (54.6±7.1 to 69.3±20.8 cm/H_20; *P* value not reported) muscle forces occurred only with GH. After one year, mean TC decreased from 184 to 166 mg/dL, mean HDL-C increased from 42 to 50 mg/dL and mean LDL-C decreased from 125 to 106 mg/dL with GH (*P*<0.01 for all). No changes were seen with control. After one year, both fasting and two hour mean insulin levels increased slightly, but not significantly with GH (*P*=0.09). After one year, mean curvature was 16 and 12 degrees with control and GH (*P* value not significant). Headaches occurred in two patients within the first three weeks of GH treatment. In both cases symptoms resolved with temporary cessation and gradual reinstitution of GH. Ophthalmologic examination of one child failed to reveal evidence of pseudotumor cerebri. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Myers et al[27] GH (Nutropin®) 1 mg/m^2/day SC vs no GH (control) All patients were observed for 6 months prior to randomization.	RCT Patients 4 to 16 years of age with genetically confirmed PWS	N=44 1 year	Primary: Height, IGF-1, bone age, body composition, energy expenditure, physical performance, adverse events Secondary: Not reported	Primary: After one year, the mean height increased by 10.0±2.5 cm, with a height velocity SDS of 4.6±2.9 (*P*<0.001) with GH. After one year, mean IGF-1 levels increased to 522±127 ng/mL with GH (*P*<0.01). There was no difference in bone age progression between the two treatments (*P* value not reported). After one year, percentage body fat decreased significantly by 16% to 38.4±10.7% (*P*<0.0001) and LBM increased significantly (*P*<0.0001) with GH. Femoral neck BMD increased significantly (*P*<0.05) with GH, and there were nonsignificant increases in total body and lumbar spine BMDs. Although resting energy expenditure did not change significantly after one year of GH, respiratory quotient decreased from 0.81±0.07 to 0.77±0.05 (*P*<0.0001). Physical performance improved significantly with GH in the timed run, standing broad jump, sit up and arm curl exercises compared to baseline and control (data not reported). Significant increases in respiratory muscle forces, both inspiratory (from 45.8±4.1 to 55.7±13.7 cm/H_20; *P*<0.001) and expiratory (from 54.6±7.1 to 69.3±20.8 cm/H_20; *P* value not reported) occurred after a year of GH. Adverse events with GH were rare. There were no differences in the progression of scoliosis between the two treatments. Headaches occurred in two patients within three weeks of initiating GH but resolved after the temporary cessation and gradual reinstitution of GH. Both fasting and two hour insulin levels increased with GH; however, the changes were not significant. Mean free T_4 levels did not change significantly with GH. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Lindgren et al[28] GH (Genotropin®) 0.1 IU/kg/day SC vs no GH (control)	MC, RCT Patients 3 to 12 years of age with PWS	N=29 1 year	Primary: Growth and GH axis, body composition, bone age, laboratory parameters, BMD, progression to puberty Secondary: Not reported	Primary: Significant changes were observed in height, height velocity, BMI and IGF-1 levels with GH (*P*<0.001 for all). Body composition revealed an average of a 25% reduction in fat mass and a 30% increase in fat-free mass with GH (*P*<0.001 for both). Muscle and fat area of the thigh showed similar results. There were no differences between the two treatments with regards to the progression of bone age during the trial (*P* value not reported). After one year, IV glucose tolerance tests were normal and unchanged with GH; however, basal fasting insulin levels were significantly increased (from 10.4±2.7 to 19.2 mU/L±10.5 SD; *P*<0.001). There were no significant changes in HbA1c with either treatment (*P* value not reported). There was no severe progression of scoliosis with either treatment. The BMD did not differ between the two groups either (*P* value not reported). No difference between the two treatments was observed in the progression of puberty. The only sign of puberty observed was pubic hair. Secondary: Not reported
Carrel et al[29] GH (Genotropin®) 1 mg/m^2/day SC vs no GH (control)	RCT Pediatric patients with genetically confirmed PWS	N=29 1 year	Primary: Growth and GH axis, body composition, energy expenditure, mobility and stability, carbohydrate and lipid metabolism, adverse events	Primary: After one year, there was an increase in height of 15.4±2.3 and 9.2±3.2 cm with GH and control (*P*<0.001). GH was accompanied by an increase in growth velocity SD from 1.4±1.8 to 5.0±1.8 (*P*<0.001), whereas with the control group it remained unchanged (1.2±1.4). GH was associated with a significant improvement in IGF-1 compared to control (231±98 vs 51±28 ng/mL; *P*<0.001). There were no differences in mean bone age progression between the two treatment groups. After one year, body fat decreased 4.8±5.7% with GH compared to 4.1±4.6% with control (*P*=0.001). LBM increased significantly more with GH (3.6±0.5 vs 1.8±0.7 kg; *P*<0.001). No significant changes were observed in total body

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			Secondary: Not reported	BMD, which increased 14.1±10.4 and 9.0±6.9% with GH and control (*P* value not significant). After one year, total energy expenditure significantly increased with GH from 663±149 to 1,025±174 kcal/day compared to 697±124 to 945±341 kcal/day with control (*P*<0.05 vs baseline and control). When the entire cohort is examined, no effect of GH on mobility or stability skill acquisition was observed. After one year, no difference in fasting insulin was observed between the two treatments (5.6±7.1 vs 5.7±7.1 IU/mL; *P* value not significant). TC decreased from 163±34 to 159±40 mg/dL with GH and increased from 170±30 to 183±43 mg/dL (*P* value not significant). No differences were observed after one year of GH with regards to HDL-C, LDL-C and TGs (*P* values not reported). No changes in the prevalence of scoliosis were seen between the two treatments. No other adverse events were noted during the trial. Secondary: Not reported
Hauffa BP (abstract)[30] GH 0.15 IU/kg/day SC vs no GH (control)	RCT Pediatric patients with PWS with a short projected final height	N=17 1 year	Primary: Height, IGF-1 and IGFBP-3, body composition Secondary: Not reported	Primary: After one year, height velocity was significantly increased with GH (5.50 SD) compared to reference values for normal healthy pediatric patients, and decreased with control (-2.30 SD). The difference in height velocity between the two treatments was significant (*P*=0.0012). A gain in height was noted for chronological age (1.07 SD) after one year of GH and height gain remained unchanged (1.02 SD) when analyzed in relation to bone age. IGF-1 and IGFBP-3 increased significantly with GH (*P*<0.008). No differences between the two treatments were noted for parameters of weight and body composition. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Festen et al[31] GH (Genotropin®) 1 mg/m^2/day SC vs no GH (control) After stratification for age, infants were randomized to GH treatment or no GH treatment for 1 year; in the second year, all infants received GH. After stratification for BMI, patients >3 years of age were randomized to GH treatment or no treatment for 2 years.	RCT Patients 6 months to 14 years of age with genetically confirmed PWS, bone age <14 years for girls and <16 years for boys and prepubertal at the start of the trial	N=91 1 (infants) or 2 years (children >3 years of age)	Primary: Anthropometry, body composition (only children >4 years of age), IGF-1, IGFBP-3 Secondary: Not reported	Primary: For infants, median height SDS increased significantly after one (*P*<0.001) and two years (*P*<0.005) with GH. After two years of GH, all infants had a height SDS above -2. With the control group, median height SDS remained low in the first year, but increased significantly when GH was started in the second year (*P*<0.01). Median head circumference SDS increased accordingly (GH, one year; *P*<0.005 and two years; *P*<0.005 and control, one year; *P*<0.05 and two years; *P*<0.01). BMI SDS increased progressively with GH and control, but remained within the normal range for most patients (GH, two years; *P*<0.05 and control, one year; *P*<0.01 and two years; *P*<0.05). For patients greater than three years of age, median height SDS increased significantly compared to baseline after one (*P*<0.001) and two years (*P*<0.001) of GH treatment. With the control group, height SDS remained low. BMI SDS decreased significantly during the first year (*P*<0.001) of GH treatment and then stabilized at a level that was not significantly higher than 0 SDS (*P*=0.08 and *P*=0.12 after one and two years). With the control group, BMI remained significantly higher than 0 SDS. Head circumference increased significantly to normal values during GH treatment (two years; *P*<0.005), with tibia length (*P*<0.05), foot length (*P*<0.005), arm span (*P*<0.05) and sitting height (*P*<0.001) significantly improving, but remaining significantly lower than 0 SDS. For patients greater than three years of age, median LBM corrected for age SDS increased significantly with GH from -1.7 to -0.5 after one year (*P*<0.005), and to -0.1 (*P* value not reported) after two years, resulting in a LBM corrected for age not significantly below 0 SDS after one and two years of GH treatment. With the control group, LBM corrected for age SDS significantly decreased over time from -1.9 to -2.5 after two years (*P*<0.005) and body fat percentage remained high. LBM corrected for height and sex SDS did not significantly increase with GH (from -1.7 to -1.5 to -1.9 after two years; *P* value not reported). With the control group there was a progressive and significant decrease in LBM corrected for height and sex SDS (from -1.4 to -1.9 to -2.3), resulting in a significantly different change in LBM corrected for height and sex between GH and control after one (*P*<0.05) and two years (*P*<0.005). Median body fat percentage SDS decreased significantly from 2.1 to 1.5 to 1.9 at two

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				years (*P*<0.005) but body fat percentage was still significantly higher than 0 SDS after one and two years of GH. Trunk fat decreased significantly in the first year (*P*<0.001) of GH and increased in the second year to a level still significantly below baseline (*P*<0.005). With the control group, trunk fat increased gradually, resulting in significantly higher levels after two years (*P*<0.05). For infants, IGF-1 increased with GH to a median above 2 SDS. After one year of GH, eight of 12 infants (67%) had an IGF-1 level >2 SDS, and after two years, it was five of seven infants (71%). With the control group, IGF-1 increased only during the second year. IGFBP-3 levels increased during GH treatment, but remained low during the first year with the control group. The IGF-1:IGFBP-3 ratio increased from -0.9 to 2.4 after two years of GH treatment (*P*=0.056) and from -0.3 to -1.1 after one year with no GH treatment to 2.5 after one year of GH treatment (*P*=0.056) in the control group. For patients greater than three years of age, after one year of GH, IGF-1 SDS had significantly increased (*P*<0.001) and remained high. After two years, 17 of 19 patients (89%) had IGF-1 SDS levels above 2. IGF-1 SDS remained low with the control group, with levels below 0 SDS during two years. Treatment with GH increased IGFBP-3 (one year; *P*<0.001 and two years; *P*<0.001), but not to the same SDS as IGF-1. Secondary: Not reported
Myers et al[32] GH (Genotropin®) 1 mg/m^2/day SC vs no GH (control) Patients randomized to no GH received no treatment for the	RCT Pediatric patients with genetically confirmed PWS	N=25 2 years	Primary: Growth and GH axis, body composition, motor development, language and cognitive skills, adverse events Secondary:	Primary: Mean length/height SDS normalized after one year of GH (-1.6±1.2 to -0.2±1.5; *P*<0.005) compared to a mean value of -1.5±0.7 (from -1.3±1.1) with control. GH also resulted in significantly greater growth in head circumference over the first year (-0.9 to -0.1 vs -0.5 to -0.2 SDS; *P*<0.01 vs control). IGF-1 increased significantly from 34±21 ng/mL at baseline to 231±98 and 319±106 ng/mL after one and two years of GH (*P* values not reported). The percent increase in LBM after one and two years of GH was 69 (*P*<0.005) and 30% (*P* value not reported), respectively, compared to 23% with control after one year (*P* value not reported). GH resulted in a significant decrease in

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
first year and then were initiated on GH (Genotropin®) 1.5 mg/m^2/day SC. Data collected for these patients at 2 years are not presented within the article.			Not reported	percent body fat during the first year (P<0.005), followed by an increase during the second year (P value not reported). A trend towards improved mobility and stability percentile rankings were noted with GH (P values not reported). Patients receiving GH progressed significantly more during the first year of treatment in both language (P=0.05) and cognitive development (P=0.02) compared to those receiving no treatment. The only potential adverse event noted was scoliosis progression from 28 to 57 degrees despite bracing in one patient receiving GH, resulting in spinal rod placement. No patient required thyroid hormone replacement therapy. Secondary: Not reported
Carrel et al (abstract)[33] GH 0.3 to 1.5 mg/m^2/day SC All patients previously received GH 1 mg/m^2/day for 2 years.	RCT Pediatric patients with PWS	N=46 1 year (3 years total)	Primary: Height, body composition, energy expenditure, BMD, strength and agility Secondary: Not reported	Primary: Further changes in body composition, including decrease in fat mass and increase in LBM, growth velocity and resting energy expenditure were occurred with standard (1.0 mg/m^2/day) and higher doses (1.5 mg/m^2/day), but not with lower doses (0.3 mg/m^2/day). Prior improvements in BMD and strength and agility were sustained during the additional year of GH, regardless of dose. Secondary: Not reported
Lindgren et al (abstract)[34] GH 0.1 IU/kg/day SC for 2 years (Group A) vs GH 0.2 IU/kg/day SC for 1 year (Group B)	RCT Pediatric patients with PWS	N=27 2 years	Primary: Height, body composition Secondary: Not reported	Primary: Height velocity SDS increased from -1.9±2.0 to 6.0±3.2 during the first year of treatment in Group A and from -1.4±1.2 to 10.1±3.9 during the year of treatment in Group B. When GH was stopped, height velocity declined dramatically. Height SDS followed a similar pattern. GH reduced the percentage body fat and increased the muscle area of the thigh. Isometric muscle strength was also increased.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Patients in Group B received no GH treatment for the first year of the trial.				GH appeared to have psychological and behavioral benefits, which were reversed after treatment was discontinued. Secondary: Not reported
Lindgren et al[35] GH 0.1 IU/kg/day SC Patients were originally enrolled in Lindgren et al (abstract). At the end of two years, all patients were observed for a period of 6 months and then restarted on GH 0.1 IU/kg/day SC for up to 5 years of total treatment.	ES of Lindgren et al[33] Pediatric patients with PWS	N=18 5 years	Primary: Height, body composition, laboratory parameters Secondary: Not reported	Primary: After five years, mean height SDS exceeded ±0 SDS in all patients. Four of the patients reached their final heights (range, -1.1 to 0.9 SDS), which were within ±2 SD of their target heights. During the six months of observation only, BMI SDS increased significantly in patients who had only received GH for one year and remained unchanged in those who received GH for two years. During the following years of GH treatment, mean BMI SDS has remained unchanged for all patients. After re-initiation of GH, patients who received GH for two years had fasting insulin levels within the normal range, while three patients who received GH for only one year developed hyperinsulinemia. Two of these patients developed non-insulin-dependent diabetes after a rapid weight gain, probably due to poor dietary compliance. BMI increased from 2.0 to 3.7 SDS and from 5.9 to 7.1 SDS in these two patients. Since discontinuation of GH, their fasting glucose, insulin and HbA1c levels have normalized. Secondary: Not reported
Growth Failure Associated With Short-Stature Homeobox-Containing Gene Deficiency				
Blum et al[36] Somatropin (Humatrope®) 50 µg/kg/day vs no treatment vs	MC, OL, RCT Patients ≥3 years of age with SHOX-D and prepubertal with height <3rd percentile of the local reference range or <10th	N=52 (SHOX-D N=26 (TS) 2 years	Primary: Effect of somatropin on first year height velocity Secondary: Treatment effect in SHOX-D patients	Primary: Somatropin-treated SHOX-D patients had a significantly greater first year height velocity compared to untreated SHOX-D patients (*P*<0.0001). Secondary: There was no significant difference in first year height velocity in the somatropin-treated SHOX-D patients compared to somatropin-treated TS patients (*P*=0.592). There were no patients that discontinued the study due to adverse events.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
somatropin (Humatrope®) 50 µg/kg/day in patients with TS	percentile with height velocity <25th percentile, bone age <10 years for boys and <8 years for girls, no GHD, chronic disease and no known growth-influencing medications		compared to TS patients	
Massart et al[37] GH vs placebo	MA Patients with SHOX-D treated with GH	N=66 24 months	Primary: Final linear height and bone age Secondary: Not reported	Primary: In patients affected by SHOX-D, the mean midparental height was in the normal range following treatment with GH (SDS, -1.594; 95% CI, -2.486 to -0.703), compared to the subnormal mean height at baseline (SDS, -3.083; 95% CI, -3.243 to -2.923). Height outcomes progressively tended to normalize during GH treatment, although the major catch-up growth was detected after 12 months (SDS, -2.731; 95% CI, -2.998 to -2.463). GH-induced growth was constant until final height was achieved, which was in the normal range (SDS, -2.263; 95% CI, -3.214 to -1.312). The bone age chronologically progressed during GH treatment in both SHOX-D patients. Secondary: Not reported
Growth Failure Associated With Turner Syndrome				
Takano et al (abstract)[38] GH 0.5 IU/kg/week SC daily vs	MC, RCT Patients with TS	N=203 1 year	Primary: Not reported Secondary: Not reported	Primary: Not reported Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
GH 1 IU/kg/week SC daily vs GH 0.5 IU/kg/week SC daily plus anabolic steroid				All three treatment groups showed significant growth increases. Fifty percent of patients receiving 0.5 IU/kg/week and 80% of those receiving 1 IU/kg/week showed growth rates more than two cm per year greater than pretreatment values or beyond the second SD of the untreated growth rate. Plasma somatomedin C levels were elevated and no remarkable advances in bone age were observed during treatment. Antibody against GH was observed in 71.4 and 10.8% of the methionyl-humanized GH and methionine-free-humanized GH. However, the antibodies did not suppress the growth promoting effect of methinoyl-humanized GH. No other significant changes in physical or laboratory examinations were observed. No glucose tolerance was observed.
Takano et al[39] GH 0.5 IU/kg/week SC daily vs GH 1 IU/kg/week SC daily	MC, RCT Pediatric patients with TS	N=80 1 year	Primary: Growth rate, bone age, laboratory parameters Secondary: Not reported	Primary: The growth rate significantly increased during treatment in most patients. Growth rates among patients with 45, X karyotype and patients with other chromosomal variants did not differ significantly in both treatment groups (*P* value not significant). During one year of treatment, the mean height increased up to 6.0±1.1 and 7.2±1.3 cm/year (from 3.7±1.0 cm/year) with 0.5 and 1 IU/kg/week, respectively (*P*<0.05 for both). Treatment with 0.5 IU/kg/week resulted in an increase in bone age between 0 and 2.2 with a mean of 0.9±0.6 years. Treatment with 1 IU/kg/week resulted in an increase in bone age between 0 and 1.9 with a mean of 0.8±0.6 years. The increases between the two doses were similar. Antibodies to GH were observed in 10 patients during treatment. The antibodies did not suppress the growth effect of GH. The plasma somatomedin C concentration increased during treatment and was greater with 1 IU/kg/week at two and four months. Neither the basal nor maximal concentration of glucose or insulin glucose relationship changed with 0.5 IU/kg/week. Treatment with 1 IU/kg/week increased basal glucose and basal and maximum concentration insulin significantly after treatment (*P* values not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Secondary: Not reported
Takano et al[40] GH (somatropin) 0.5 IU/kg/week SC daily vs GH (somatropin) 1 IU/kg/week SC daily	MC, RCT Pediatric patients with TS	N=94 2 years	Primary: Growth rate, bone age, development of antibodies, laboratory parameters Secondary: Not reported	Primary: The growth rate of patients with 45, X karyotype and patients with other chromosomal variants did not differ significantly between the two treatments (data not reported). The growth rate significantly increased during treatment in most patients in various age groups. For patients less than eight years, only treatment with 1 IU/kg/week significantly increased the growth rate after one year (from 4.1±0.9 to 6.8±0.6 cm/year; *P*<0.001). For patients eight to 10 years of age, treatment with 0.5 IU/kg/week significantly increased growth rate after one year (from 3.8±0.4 to 5.9±1.1 cm/year; *P*<0.001), while 1 IU/kg/week did after one (from 3.6±0.6 to 6.8±1.7 cm/year; *P*<0.001) and two years (5.1±0.8 cm/year; *P*<0.001). For patients 10 to 12 years of age, treatment with 0.5 and 1 IU/kg/week significantly increased growth rates after one (from 3.9±0.9 to 5.8±1.1 and from 3.7±0.8 to 6.8±0.9 cm/year; *P*<0.001 for both) and two years (4.6±0.9 and 4.7±1.1; *P*<0.05 for both). For patients 12 to 14 years of age, treatment with 0.5 IU/kg/week significantly increased growth rate after one year (from 3.4±0.9 to 4.6±1.1 cm/year; *P*<0.001), while 1 IU/kg/week did after one (3.2±1.1 to 5.9±1.3 cm/year; *P*<0.001) and two years (4.2±0.9; *P*<0.05). For patients 14 years or older, only 0.5 IU/kg/week significantly increased growth rate after one year (from 2.4±0.6 to 3.5±0.6 cm/year; *P*<0.05). Overall, the growth rate increased significantly from 3.7±1.0 to 5.2±1.3 (*P*<0.001) after one year and to 4.1±1.1 (*P*<0.05) after two years with 0.5 IU/kg/week. Corresponding rates with 1 IU/kg/week were 3.5±0.9 to 6.3±1.4 (*P*<0.001) and 4.6±1.1 cm/year (*P*<0.001). The latter two rates were significantly greater compared to 0.5 IU/kg/week (*P*<0.001 and *P*<0.05, respectively). The growth rate was the greatest during the first and second six months of treatment and gradually declined. Bone age increased 1.6±0.9 and 1.9±1.0 years, respectively, with 0.5 and 1 IU/kg/week (*P* value not significant).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Antibodies were observed in 18 patients. The antibodies did not suppress the growth effect of treatment. Somatomedin C concentrations increased during treatment and values were greater at two, six, eight and 12 months with 1 IU/kg/week compared to 0.5 IU/kg/week (*P* values not reported). Neither basal nor the maximum glucose concentration changed with either dose. Basal and maximum insulin increased significantly. HbA1c did not change significantly after one or two years. No patients developed glucose intolerance and there was no significant change in blood count, urinalyses or routine chemistry. Secondary: Not reported
Takano et al[41] GH 0.5 IU/kg/week SC daily vs GH 1 IU/kg/week SC daily	MC, RCT Pediatric patients with TS	N=161 3 years	Primary: Height velocity, height velocity SDS, height SDS, treatment effectiveness, safety Secondary: Not reported	Primary: During the first, second and third year of treatment with 0.5 IU/kg/week, the mean height velocity was 6.0±1.3, 4.6±1.0 and 4.0±1.3 cm/year, respectively. The corresponding values with 1 IU/kg/week were 6.9±1.3, 5.0±1.2 and 4.3±1.1 cm/year, respectively. Values observed during the three years were always greater compared to pretreatment. Only during the first and second years did the 1 IU/kg/week dose significantly increase height velocity to a significant extent (*P*<0.05 for both). Before and during the first, second and third year of treatment with 0.5 IU/kg/week, the mean height velocity SDS was -0.24±0.99, 2.70±1.39, 1.23±1.06 and 0.89±1.34, respectively. The corresponding values with 1 IU/kg/week were -0.24±0.93, 3.57±1.36, 1.72±1.20 and 1.25±1.14, respectively. Values observed during the three years were always greater compared to pretreatment. Again, 1 IU/kg/week increased height velocity SDS by a significant extent during only the first and second year (*P*<0.05 for both). There were no correlations between the increase in height velocity in three years and the chronological age, bone age, height and IGF-1 values before treatment; however, there was a significant reverse correlation with the pretreatment growth rate (*P*<0.001). The mean total increases in height SDS were 1.00±0.61 and 1.32±0.58 with 0.5 and 1 IU/kg/week, respectively (*P*<0.01). During the three years,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				secondary sexual characteristics appeared incompletely in 17 and 11 patients receiving 0.5 and 1 IU/kg/week, respectively. Efficacy, evaluated as the increased height velocity as expressed by the change in SDS for chronological age, was observed in 82.4, 67.6 and 48.6% of patients receiving 0.5 IU/kg/week during the first, second and third year. The corresponding proportions with 1 IU/kg/week were 94.6, 76.2 and 62.4%. The effectiveness of GH was also calculated as the height SDS at six years minus the baseline height SDS, and treatment was tentatively considered as being effective if the change >1. Therefore, treatment was effective in 50.0 and 75.3% of patients receiving 0.5 and 1 IU/kg/week (P<0.01). After three years, some patients already exceeded their projected adult height. Adverse events were uncommon. Glucose intolerance did not occur in any patient, though basal and maximal insulin levels after glucose administration increased slightly. Bone age did not advance beyond the changes in chronological age. At the end of three years, antibody was observed in three of 161 patients. Secondary: Not reported
Takano et al[42] GH 0.5 IU/kg/week SC daily vs GH 1.0 IU/kg/week SC daily	MC, RCT Pediatric patients with TS	N=63 6 years	Primary: Height velocity, degree of overweight, treatment effectiveness Secondary: Not reported	Primary: The height velocity was greatest during the first year of treatment, with height velocity increasing from 4.0±1.0 to 6.0±1.2 cm/year with 0.5 IU/kg/week and from 3.6±1.0 to 7.0±1.4 cm/year with 1 IU/kg/week. Only during the first two years of treatment did 1 IU/kg/week result in a significantly larger height velocity compared to 0.5 IU/kg/week (P value not reported). Patients with GHD did not differ from those without GHD. There was no correlation between the yearly growth rate increases for six years and the chronological age, bone age or height of patients. However, there was a significant negative correlation with the pretreatment growth rate. The mean degree of overweight calculated for 0.5 IU/kg/week increased significantly from 14.0±18.0 to 25.1±18.0% after six years (P<0.05) and for 1 IU/kg/week from 12.7±15.4 to 19.2±13.1% (P<0.05). There was no difference in the increase in overweight between the two treatments (P value not

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				reported). After six years, secondary sex characteristics appeared incompletely in 20 of 63 patients and occurred in similar incidences with the two treatments. The effectiveness of GH was calculated as the height SDS at six years minus the baseline height SDS, and treatment was tentatively considered as being effective if the change was >1. Therefore, treatment was effective in 58 and 87% of patients receiving 0.5 and 1 IU/kg/week. After six years, patients tended to exceed their projected adult height. Secondary: Not reported
Bertrand et al[43] GH 0.45 IU/kg/week SC daily for 1 year, followed by GH 0.90 IU/kg/week SC daily for 2 years (G1) vs GH 0.90 IU/kg/week SC daily for 2 years (G2) Estrogen was permitted in patients with a bone age >12 years.	MC, PG, RCT Female pediatric patients with TS, height 1.5 SD or more below the mean for chronological age, height velocity below the mean age for bone age and weight between -2 and 3 SD of weight for height	N=97 3 years	Primary: Compliance, growth response, adverse events Secondary: Not reported	Primary: Nine patients discontinued GH over the three years due either to poor compliance with study visits, to inefficiency of treatment, to family choice, to adverse events or as required by protocol amendment. Compliance with treatment was usually good. Significant differences in mean height velocity between the two doses were observed only for the first year (5.5 vs 6.7 cm/year; *P*=0.0001). Mean height velocity was markedly accelerated in both treatment groups after six months and during the first year. Doubling the GH dose at month 12, significantly increased height velocity (*P*=0.02). Although progressive attenuation of the effect with time was observed, height velocity remained above the mean for reference untreated TS patients during the three years in both treatment groups. Responders to treatment were 45 vs 70% for G1 and G2 (*P*=0.014). A significant difference between G1 and G2 was observed in mean height gain after one (*P*<0.0001) and two years (*P*=0.0061). After three years, the mean height gain was 1.06±0.06 and 1.17±0.05, but the difference was no longer significant (*P* value not reported). Bone maturation did not differ at any time between the two treatments over the 36 months (33.7 vs 31.9 months; *P* value not reported). Weight was stable

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				within G2 and increased significantly within G1, although there was no difference between the two treatments. Mean IGF-1 increased in both treatment groups for the first three months (from 1.02 to 1.22 within G1 and from 1.00 to 1.55 within G2). Over the first year, the increment was significantly higher within G2 (*P* value not reported). The more frequent adverse events were application site disorders, resistance mechanism disorders, general disorders, gastrointestinal disorders and skin and appendage disorders. Twenty eight hospitalizations for surgery, seemingly unrelated to GH, were classified as severe adverse events. Mean plasma fasting glucose and HbA1c remained stable. Mean free T_4 decreased slightly, but not significantly, over the three years without clinical effects. Secondary: Not reported
van Teunenbroek et al[44] GH (Norditropin®) 4 IU/m^2/day SC for 4 years (Group A) vs GH (Norditropin®) 4 IU/m^2/day SC for 1 year, followed by 6 IU/m^2/day SC for 3 years (Group B) vs GH (Norditropin®) 4 IU/m^2/day SC for 1 year, followed by 6 IU/m^2/day SC for 1 year, followed by 8 IU/m^2/day SC for 2 years (Group C)	MC, RCT Female patients 2 to 11 years of age with TS who are treatment naïve, height below the 50th percentile and normal thyroid function	N=68 4 years	Primary: Growth response, bone maturation, final height prediction, GH measurements, GHBP, IGF-1 and IGFBP-3 Secondary: Not reported	Primary: Compared to baseline, mean height velocity increased significantly with all three treatments from approximately six to 10 cm/year during the first year of GH. Thereafter, a waning of the growth response was observed. In the second year, mean height velocity in Groups B and C were significantly higher compared to Group A. With a dose of 8 IU/m^2/day in Group C, mean height velocity was significantly higher compared to Group B. In the fourth year, only in Group C the mean height velocity remained significantly higher compared to Group A. During the first year of treatment, 29% of all patients managed to double their height velocity. Height velocity SDS for chronological age in Groups B and C were significantly higher compared to Group A in the second through fourth year of treatment. However, in the third and fourth year, Group C was not different than Group B. The change in height SDS for chronological age from the first year was significantly higher for the combined Groups B and C compared to Group A (*P*<0.0001). The second dose-increment in the third year, as well as in the combined third and fourth year, resulted in a significantly higher change from year two in height SDS for chronological age for Group C compared to Group B (*P*=0.04 and *P*=0.02). The increase in mean height SDS for chronological

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				age was highest in the first year of treatment (>1 SDS), without a difference between treatment groups. The change in RUS bone age over the change in chronological age was not different between treatment Groups over the four years, nor during any individual year of treatment. For all groups, the highest advance was found during the third year and the lowest during the fourth year of GH (data not reported). Mean final height prediction increased significantly for all treatment groups after four years (*P* values not reported). Differences between treatment groups for the four year change were not observed, though mean values in Groups B and C were higher than those in Group A. There was a significant dose-dependent increase of the maximum GH level and area under the curve. In contrast, the time to peak concentration, clearance and elimination half-life were not difference between the three doses of GH. GHBP levels after six months of treatment did not differ from baseline. Within treatment groups, each point in time was significantly higher than the previous, except for 30 months (all treatment groups) and 42 months (Group B). At 30 months, IGF-1 levels for Groups B and C became significantly higher compared to Group A ($P<0.004$), but at 48 months only Group C was still significantly higher than Group A ($P=0.008$). Mean IGFBP-3 levels only increased significantly after six months of treatment ($P<0.0001$). At the end of the trial, 31 and 35% of all patients had IGF-1and IGFBP-3 levels higher than the 95th percentile for healthy individuals at the pubertal peak. There were no differences between treatment groups. The IGF-1:IGFBP-3 showed an increase over time, but there were no differences between treatment groups. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Sas et al[45] GH (Norditropin®) 4 IU/m^2/day SC for 4 years (Group A) vs GH (Norditropin®) 4 IU/m^2/day SC for 1 year, followed by 6 IU/m^2/day SC for 3 years (Group B) vs GH (Norditropin®) 4 IU/m^2/day SC for 1 year, followed by 6 IU/m^2/day SC for 1 year, followed by 8 IU/m^2/day SC for 2 years (Group C)	ES of van Teunenbroek et al[42] Female patients 2 to 11 years of age with TS who are treatment naïve, height below the 50th percentile and normal thyroid function	N=68 7 years	Primary: Growth response, bone maturation Secondary: Not reported	Primary: After seven years, 55 of 65 patients (85%) had a height within the normal range for healthy individuals, whereas only 10 patients (15%) had a height just below the 3rd percentile. In all three treatment groups, height SDS increased significantly (*P*<0.001). The mean change in SDS score was significantly higher in Groups B and C compared to Group A (95% CI, 0.08 to 0.95; *P*=0.02 and 95% CI, 0.38 to 1.27; *P*=0.001, respectively). The differences between Groups B and C were not significant (95% CI, -0.19 to 0.81; *P*=0.22). After seven years, the mean height SDS in all three treatment groups had increased to values within the normal range for healthy individuals. Data indicates that treatment with GH was associated with an acceleration of bone maturation compared to healthy individuals. No differences in bone maturation were observed between treatment groups. Secondary: Not reported
van Pareren et al[46] GH (Norditropin®) 4 IU/m^2/day SC for 4 years (Group A) vs GH (Norditropin®) 4 IU/m^2/day SC for 1 year, followed by 6 IU/m^2/day SC for 3 years (Group B) vs GH (Norditropin®) 4 IU/m^2/day SC for 1 year, followed by 6 IU/m^2/day SC for 1 year,	Post hoc analysis of van Teunenbroek et al[42] Female patients 2 to 11 years of age with TSs who are treatment naïve, height below the 50th percentile and normal thyroid function	N=68 7 years	Primary: Final height, estrogen effect Secondary: Not reported	Primary: Final height was 157±6.5, 162.9±6.1 and 163.6±6.0 cm in Groups A, B and C. When translated to SDS, using references for healthy individuals, final height was -1.6±1.0, -0.7±1.0 and -0.6±1.0 cm in Groups A, B and C. The difference in final height, corrected for height SDS and age at the start of treatment, was significant between Groups A and B (regression coefficient, 4.1; 95% CI, 1.4 to 6.9; *P*<0.01) and between Groups A and C (5.0; 95% CI, 2.3 to 7.7; *P*<0.001), but not between Groups B and C (0.9; 95% CI, -1.8 to 3.6; *P* value not reported). Fifty of 60 patients (83%) had reached a normal final height. The mean gain in final height in Group A was 11.9±3.6 cm, being significantly lower compared to 15.7±3.5 cm in Group B (4.2; 95% CI, 1.5 to 6.9; *P*<0.01) and compared to 16.9±5.2 cm in Group C (5.2; 95% CI, 2.6 to 7.8; *P*<0.001), but the height gain in Group B was not different from that in Group C (1.0; 95% CI, -1.6 to 3.6; *P*=0.44). Similarly, the mean increase in SDS from start of treatment until final height in Groups B and C was significantly higher compared to Group A (0.7; 95% CI, 0.31 to 1.11; *P*<0.001), but the increase in Group B was comparable to Group C (0.12; 95% CI, -0.27 to 0.5; *P*=0.5).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
followed by 8 IU/m^2/day SC for 2 years (Group C) In the first 4 years of treatment, no estrogen for pubertal induction was given to patients. After four years, estrogen treatment was started at the yearly visits after the patient had reached the age of 12. In patients who become 12 years old during the first 4 years of treatment, estrogen treatment was started at 4 years of treatment. If puberty had developed spontaneously before the start of estrogen therapy, no exogenous estrogen was given.				Height velocity in the year after initiation of estrogen treatment compared to the height velocity in the previous year showed no difference. The downward trend in height velocity before initiation of estrogen treatment; however, changed significantly to a stable height velocity after initiation (*P*<0.05). Bone maturation in the year before and in the year after initiation of estrogen treatment was no different. GH dosage, GH duration before start of estrogen and height at puberty had no significant effect on the differences of height velocity, in the change in height velocity, or in bone maturation. Secondary: Not reported
Massa et al[47] GH (Humatrope®) 8 IU/m^2 SC TIW in patients <12 years of age vs GH (Humatrope®) 8 IU/m^2 SC TIW in patients >12 years of age	RCT Pediatric patients with TS	N=45 Not reported	Primary: Final height Secondary: Not reported	Primary: Treatment with GH resulted in a significantly greater final height compared to reference treatment naïve patients with TS (152.3±5.3 vs 147.0±6.3 cm; *P*<0.001). No differences were observed between patients <12 years of age and those >12 years of age (151.1±4.3 vs 152±5.6 cm; *P* value not reported) or between three and six times weekly dosing (151.8±5.6 vs 152.8±4.8 cm; *P* value not reported). For all patients, the difference between final height and the initial predicted adult height (147.6±5.4 cm) was 4.7±3.8 cm (*P*<0.0001). Final height was significantly related to height (*P*<0.005) and height SDS (*P*<0.001) at baseline, but not to chronological or bone ages (*P* values not reported). The difference between final height and initial predicted adult height;

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs GH (Humatrope®) 4 IU/m^2 SC 6 times a week in patients <12 years of age vs GH (Humatrope®) 4.0 IU/m^2 SC 6 times a week in patients >12 years of age Estrogen therapy was initiated when patients reached 12 years of age and to patients >12 years of age when they enrolled. After 2 years, GH was changed to 6 IU/m^2 SC 6 times a week in patients >12 years of age.				however, was related to chronological age (*P*<0.005) but not to the other variables. In contrast, the difference between final height and projected adult height from initial height SDS was inversely related to the initial height (*P*<0.05), height SDS (*P*<0.01) and bone age (*P*<0.005) but not to chronological age (*P* value not reported). Secondary: Not reported
Nienhuis et al[48] GH (Humatrope®) 8 IU/m^2 SC TIW in patients <12 years of age (A1) vs GH (Humatrope®) 8 IU/m^2 SC TIW in patients >12 years of age (B1) vs	RCT Pediatric patients with TS	N=29 4 years	Primary: Height velocity, height, bone age, predicted adult height, final height Secondary: Not reported	Primary: There was an increase in height velocity, which was greatest in the first year and still significant in the second year of therapy, and there was also a significant difference between three and six times weekly dosing (*P* values not reported). In groups A1 (*P*=0.15 and *P*=0.20) and A2 (*P*=0.17 and *P*=0.96) in the third and fourth years, height velocity was no longer significantly greater than baseline, nor was there a significant difference between three and six times weekly dosing (*P* value not reported). In patients >12 years of age, Group B, height velocity was only significantly greater than before therapy in the first year. In Group B1, height velocity SDS increased after the dose and frequency were increased. In Group B2, no further decrease in height velocity SDS was observed. In patients <12 and >12 years of age, height increased from 120.8 to 143.4 cm

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
GH (Humatrope®) 4 IU/m^2 SC 6 times a week in patients <12 years of age (A2) vs GH (Humatrope®) 4 IU/m^2 SC 6 times a week in patients >12 years of age (B2) Estrogen therapy was initiated when patients reached 12 years of age and to patients >12 years of age when they enrolled. After 2 years, GH was changed to 6 IU/m^2 SC 6 times a week in patients in Group B1.				and from 136.0 to 152.7 cm. The total increment in height SDS in Groups A1, A2, and B was 1.3, 1.7 and 1.1, respectively, and was significant for all (*P*<0.01). There was no difference between Groups A1 and A2 (*P*=0.12), nor between Groups B and A (*P*=0.07). Chronological and bone ages at baseline correlated negatively with the increment in height SDS (*P*=0.006 and *P*=0.01), respectively. While the increment in height SDS did not differ between Groups A1 and A2, the height SDS after four years was significantly greater with Group A2 (*P*=0.05). For bone age, the observed bone age advancement was compared to the expected bone maturation of reference patients. In Group A1 and B, there was no difference between the observed and expected skeletal maturation (*P* values not reported). In Group A2, the observed bone maturation of 4.0 years was significantly greater than the expected 3.2 years (*P*=0.004). The predicted adult height increased significantly in Groups A2 and B (*P*=0.001), but not in Group A1 (*P*=0.11). The predicted adult height after four years was not significantly different between three and six times a week dosing (*P*=0.63), but the mean increment in Group A2 was significantly higher compared to Group A1 (*P*=0.02). In Group B, the mean attained height after four years was 5.8 cm greater than the initial prediction (*P* value not reported). The increment in height prediction was significantly greater in Group A (*P*=0.03). Final height data is presented for a total of 23 patients. For this group the mean initial age was 15.5 years and duration of therapy 2.9 years. There was a significant increment in height SDS, of 0.5 SDS during treatment (*P*=0.001). At the end of therapy, the mean final height was 150.4 cm and the SDS for age was 1.1. There was no difference in increment of predicted adult heath between three and six times weekly dosing (*P*=0.34). Secondary: Not reported
Baxter et al[49] GH (somatropin) for ≥6	SR (4 RCTs) Pediatric	N=365 1 year	Primary: Final height, height SDS and	Primary: One trial reported final height data. Patients achieved a final height of 148±6 and 141±5 cm with GH and no treatment (95% CI, 6 to 8). These patients also

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
months vs placebo or no treatment	patients with TS		growth velocity Secondary: Bone age, psychological outcomes, adverse events	had a change in height SDS of 1.6±0.6 and 0.3±0.4 (MD, 1.3; 95% CI, 1.1 to 1.5). One trial reported height SDS data. Height SDS was 1.2 (95% CI, 1.0 to 1.5) greater in patients receiving GH compared to patients receiving no treatment. Three trials reported growth velocity data. Two trials reported growth velocity after one year of treatment and patients who received GH grew approximately three cm more in the year than those who did not receive treatment (MD, 3 cm/year; 95% CI, 2 to 4). One of these trials reported growth velocity after two years of treatment that was two cm per year greater with treatment (95% CI, 1.3 to 2.3). The third trial reported growth velocity after 18 months of treatment and patients who received GH grew three cm per year more compared to those who did not receive treatment (95% CI, 2 to 3). Two trials reported that growth velocity SDS for the first year of treatment with GH was approximately three SD greater than no treatment (MD, 3.2; 95% CI, 2.8 to 3.6). One of these trials reported growth velocity SDS after two years and reported it was 1.6 SD greater (95% CI, 1.1 to 2.2) with GH compared to no treatment. Secondary: One trial reported the ratio of changes in bone age to changes in chronological age. After one year of treatment the difference in the ratio was 0.2 (95% CI, -0.03 to 0.40). After two years of treatment the difference in the ratio was -0.1 (95% CI, -0.5 to 0.3). One trial reported on psychological outcomes in relation to GH treatment, but the selective reporting of results leaves in doubt the nature of the unreported results. Bearing in mind possible biases, the presented results suggest the possibility that patients treated with GH do have better psychological adjustment than patients receiving no treatment. Reporting of adverse events was minimal. In one trial, acute otitis media occurred or worsened in 29 and 13% of patients receiving GH and placebo, respectively. In one trial, there were significant differences in treatment emergent adverse effects between treated and control groups.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Growth Failure In Children Born Small For Gestational Age				
De Schepper et al[50] GH (Genotonorm®) 66±3 µg/kg/day SC vs no GH (control)	RCT Patients 3 to 8 years of age SGA with birth weight, length or both below -2 SD for gestational age; current height below -2.5 SD; height velocity below 1 SD	N=25 2 years	Primary: Growth, body composition, safety Secondary: Not reported	Primary: Patients receiving GH gained more height and weight compared to the control group. GH was associated with a marked reduction (*P*<0.001) in limb skinfolds but not truncal skinfolds. GH was accompanied by a gain of lean mass (*P*<0.0001) and by a centripetal redistribution of fat mass (*P*<0.0001), but not by an overall gain or less of fat mass. All patients remained prepubertal, and none had a noteworthy adverse event during the two years. Secondary: Not reported
Arends et al[51] GH (Norditropin®) 33 µg/kg/day SC vs no GH (control) 12 additional patients with GHD were also treated with GH (Norditropin®) 33 µg/kg/day SC. In order to evaluate the GH-induced effect on growth in relation to the severity of growth retardation at start, results of the present trial were compared to those of patients receiving GH 66	MC, OL, RCT Patients with a chronological age 3.00 to 7.99 years with short stature born SGA; non-GHD; birth length SDS below -2 SDS for gestational age; an uncomplicated neonatal period; height SDS for age below -2; height velocity SDS for age below zero; prepubertal and normal liver,	N=104 3 years	Primary: Growth, growth factors, bone age, BMD, safety Secondary: Not reported	Primary: Height SDS increased significantly from -3.0 to -1.3 SDS after three years with GH (*P*<0.001). Patients with GHD demonstrated similar growth, as height increased significantly from -3.4 to -1.2 SDS after three years (*P*<0.001). Control; however, demonstrated a small increase in height SDS from -3.2 to -2.9 SDS (*P*<0.001). IGF-1 and IGFBP-3 increased significantly in all patients receiving GH after three years. In the total group, the three year change in both IGF-1 and IGFBP-3 SDS correlated significantly with the three year change in height SDS (*P*<0.001 for both). For all patients receiving GH, this correlation was weaker but still significant (*P*=0.02). During the three years, the delay in bone maturation of control remained unchanged. In contrast, all patients receiving GH demonstrated a significant increase in bone maturation. The highest ratio between the change in bone age and the change in chronological age with GH was observed during the second year of treatment, and for patients with GHD during the first year of treatment with GH. During the third year, this ratio was comparable for all three treatments. During the entire three year period, the mean ratio was 4.3/3.0 yr/yr with GH and 3.2/3.0 year/year with control (*P*<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
µg/kg/day SC in another trial.	kidney and thyroid functions			No difference was observed in mean total body, lumbar spine and apparent density BMD SDS at baseline and during GH treatment between patients treated with GH and those with GHD (data not reported). Therefore BMD for these two groups were presented together. After two and three years of treatment, all patients had a total body, lumbar spine and apparent density BMD SDS in the normal range. GH was well tolerated and no adverse events were reported during treatment that could be attributed to treatment. Thyroid function and HbA1c levels remained normal during the trial. Secondary: Not reported
Maiorana et al[52] GH 33 or 67 µg/kg/day vs no treatment	MA (4 MC, RCTs) Prepubertal pediatric patients who had a birth weight and/or length of <-2 SDS and who had never received GH treatment	N=391 Mean duration 7.30±0.35 years (treatment was discontinued once adult height was reached)	Primary: Adult height SDS, change in height SDS Secondary: Adult height SDS and change in height SDS corrected for target height	Primary: Mean adult height SDS was -1.5 in the GH group and -2.4 in the untreated group, with a difference of 0.9 SDS or 5.7 cm (*P*<0.0001). There was no difference between the 33 and 67 µg/kg/day regimens. Mean increase in height with GH treatment was 1.5 SDS, or 9.5 cm, compared to 0.25 SDS, or 1.6 cm, with no treatment (*P*<0.0001). Secondary: The difference between the GH and untreated groups with regard to corrected adult height SDS was 0.78 (*P*<0.0001). Corrected gain in height SDS was 1.46 and 0.40 in the GH and untreated groups, respectively (*P*<0.0001).
Boguszewski et al[53] Somatropin (Genotropin®) 0.1 IU/kg/day (low dose) vs somatropin (Genotropin®) 0.2	OL, RCT SGA prepubertal pediatric patients 2 to 8 years of age at start of study, height SDS <-2, height	N=48 3 years	Primary: Growth response, safety Secondary: Not reported	Primary: After one year, the low dose and high dose treatment groups had significantly greater change in height SDS compared to the untreated group (*P*<0.001 for both). After two years, the low dose and high dose treatment groups had significantly greater change in height SDS compared to the untreated group (*P*<0.05 and *P*<0.01). At year three, there were no significant differences in the low dose or high dose treatment group in height SDS compared to baseline.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
IU/kg/day (high dose) vs no treatment After completion of 24 months, patients could continue with treatment and the untreated patients could continue at a dose of 0.2 IU/kg/day	velocity SDS <1, birth weight and/or length SDS <-2 for gestational age, gestational age > 30 weeks, serum GH >20 mU/L during 240 hour profile or after GH stimulation test			After one year, the low dose and high dose treatment groups had significantly smaller attainted height SDS compared to the untreated group (P<0.05 and P<0.01). After two years, the low dose and high dose treatment groups had significantly smaller attainted height SDS compared to the untreated group (P<0.01 and P<0.001). At year thee, the attainted height SDS was significantly less in the low dose and high dose treatment groups compared to baseline (P<0.001 for both). After one year, the low dose and high dose treatment groups had a significantly smaller difference between height SDS and mid-parental height SDS compared to the untreated group (P<0.05 and P<0.001). After two years, the low dose and high dose treatment groups had significantly smaller difference between height SDS and mid-parental height SDS compared to the untreated group (P<0.01 and P<0.001). At year three, the difference between height SDS and mid-parental height SDS was significantly less in the low dose and high dose treatment groups compared to baseline (P<0.001 for both). There were no adverse events detected that were considered drug related. Secondary: Not reported
Chatelain et al[54] GH 0.4 IU/kg/week (low-dose group) vs GH 1.2 IU/kg/week (high-dose group) vs placebo for 6 months followed by GH 0.4 or 1.2 IU/kg/week	DB, MC, OL, PC, RCT Prepubertal pediatric patients between 4 and 11 years of age for boys or 4 and 10 years of age for girls who were diagnosed with IUGR	N=95 2 years (DB, PC for 6 months followed by OL for 18 months)	Primary: Height velocity, change in height SDS Secondary: Bone age, age at onset of puberty, change in serum IGF-1 levels, carbohydrate metabolism, free T_4 and safety	Primary: At six months, height velocity was greater in the high-dose group compared to the low-dose group (9.2±0.4 vs 6.8±0.3 cm/year; P<0.0005). Patients receiving GH had a higher height velocity SDS compared to those receiving placebo (5.0±0.3 cm/year; P<0.0025). At two years, height velocity remained higher in the high-dose group compared to the low-dose group (7.3±0.2 vs 6.2±0.2 cm/year; P=0.0003). At two years, the mean increase in height SDS over chronological age was greater with high-dose GH compared to low-dose GH (1.25±0.07 vs 0.66±0.07; P<0.0001). Secondary: There were no significant differences between the two groups with regard to

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
for 18 months				bone age at two years, age at onset of puberty and serum IGF-1 levels. No significant changes were seen in fasting blood glucose, HbA1c and free T_4 during the study. The incidence of adverse events was similar between the two groups. Most commonly reported adverse events were local pain, erythema and ecchymosis. One patient in the high-dose group was diagnosed with hypothalamic dysgerminoma during the study, and GH was discontinued.
Butenandt et al (abstract)[55] GH 0.1 IU/kg/day vs GH 0.2 IU/kg/day vs no GH (control)	RCT Pediatric prepubertal patients with SGA and nonGHD	N=69 2 years	Primary: Not reported Secondary: Not reported	Primary: Not reported Secondary: Not reported After two years, there was a significant increase in height velocity SDS with GH compared to control. Mean values after the first year were -1.2, 2.8 and 5.5 with control, GH 0.1 IU/kg/day and GH 0.2 IU/kg/day. Corresponding values during the second year of treatment were -0.9, 1.6 and 2.9. A significant difference between 0.1 and 0.2 IU/kg/day was observed during the first year, but there was no difference during the second year of treatment. Catch-up growth was achieved for 86 and 95% of patients receiving 0.1 and 0.2 IU/kg/day during the first year of treatment and was maintained in 65 and 79% of patients during the second year. GH was associated with a distinct acceleration of bone age. Tolerance was good. No clear trends were seen in any of the laboratory parameters.
Bannink et al[56] Somatropin (Norditropin®) 33 µg/kg/day SC (low-dose group) vs	DB, MC, PG, RCT Prepubertal pediatric patients between 3 and 11 years of age	N=38 Mean duration 9.04 years (treatment was discontinued	Primary: Adult height SDS and change in health-related quality of life measured by EQ-5D score	Primary: Adult height SDS was -1.8 in the low-dose group and -1.5 in the high-dose group (*P* value not reported). There was an improvement in adult height SDS by 1.4 and 1.7 SDS in the low- and high-dose groups, respectively (*P*=0.11). Change in EQ-5D score was 0.112 and 0.115 in the low- and high-dose groups, respectively (*P* value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
somatropin (Norditropin®) 67 µg/kg/day SC (high-dose group)	for boys or 3 and 9 years of age for girls who were diagnosed with SGA and who had a height <-2 SDS and height velocity ≤0 SDS	once adult height was reached)	Secondary: Not reported	Secondary: Not reported
Sas et al[57] GH (Norditropin®) 3 IU/m^2/day SC vs GH (Norditropin®) 6 IU/m^2/day SC	MC, RCT Patients 3 to 11 years of age with SGA and short stature, birth length SDs below -1.88 for gestational age, height SDS for chronological age below -1.88, height velocity SDS for chronological age of zero or less, without catch-up growth and an uncomplicated neonatal period	N=79 5 years	Primary: Height, bone age, BMI, IGF-1 and IGFBP-3, safety Secondary: Not reported	Primary: After five years, the mean height SDS for chronological age increased significantly from baseline with both doses (*P*<0.001 for both) and in conformity with the target height SDS. There was no difference between the two doses (2.2±0.6 vs 2.6±0.9; *P*=0.057). The mean ratio of the change in bone age to the change in chronological age per year was significantly higher than 1 for both doses (1.4±0.2 and 1.3±0.2, respectively; *P*<0.001). No differences in bone maturation were observed between the two doses (*P* value not reported). At baseline, mean bone age RUS was 0.6±1.0 year, whereas after five years it advanced to 1.0±1.1 year. After five years, height SDS for bone age increased significantly compared to baseline (*P*≤0.001). The increase was significantly greater with 6 IU/m^2/day (from -2.4±1.0 to 1.2±0.8) compared to 3 IU/m^2/day (from -2.1±1.1 to 1.5±0.8; *P*=0.004). In a subanalysis on prepubertal growth (n=23 and n=16), the increment in height SDS for chronological age was significantly increased with both doses (*P*<0.001). The increase was significantly greater with 6 IU/m^2/day (3.30±0.73 vs 2.35±0.51; *P*<0.001). The mean ratio of the change in bone age to the change in chronological age per year was significantly higher than 1 for both doses (1.39±1.17 and 1.37±0.22; *P*<0.001), without differences between the two (*P* value not reported). Height SDS for bone age increased significantly compared to baseline (*P*<0.05), and the increase was significantly greater with 6.0 IU/m^2/day (from -2.06±1.17 to -0.88±0.93 vs -1.86±1.11 to -1.49±0.89; *P*=0.02). The increase in predicted adult height after five years was 9.1±2.8

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				and 14.0±5.5 cm with 3 and 6 IU/m^2/day, being significantly increased compared to baseline with both doses (*P*<0.005) and significantly higher with 6 IU/m^2/day compared to 3 IU/m^2/day (*P*=0.02). After five years, BMI SDS was significantly increased to -0.3±1.2 and -0.2±0.8 with 3 and 6 IU/m^2/day (*P*<0.001 vs baseline), with no differences between the two doses. IGF-1 SDS was significantly higher than baseline at each visit for both doses. The IGF-1 SDS was significantly higher with 6 IU/m^2/day compared to 3 IU/m^2/day during the first three years. Thereafter, the difference was no longer significant. Results for IGFBP-3 were similar. The five year increase in height SDS for chronological age correlated negatively with baseline chronological age (*P*<0.001) and baseline bone age RUS (*P*<0.001). The change was not related to the target height SDS, baseline bone age delay, pretreatment height velocity SDS, baseline IGF-1 SDS, mean maximal plasma GH response during arginine tolerance test or characteristics of the 24 hour GH profiles established at baseline. No difference was also found between the patients with GHD and those with normal levels. Treatment was well tolerated and no adverse events were detected that were considered to be drug-related. With both doses, the mean fasting glucose level and area under the curve for glucose during oral glucose tolerance test did not significantly change during the first year of treatment compared to baseline. However, mean fasting insulin levels increased significantly with both doses after one year (*P*<0.001). In addition, the area under the curve for insulin during oral glucose tolerance test was significantly higher after one year of treatment (*P*<0.001). HbA1c remained in the normal range and no patent develop diabetes. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Jung et al[58] Somatropin (Humatrope®) 0.067 mg/kg/day (fixed dose) vs somatropin (Humatrope®) 0.035 mg/kg/day for 3 months then either increase to 0.067 mg/kg/day if predicted 1 year change in height SDS was <0.75 or continue at 0.035 mg/kg/day if predicted 1 year change in height SDS was ≥0.75 (individualized dose)	MC, NI, OL, Randomized SGA prepubertal pediatric patients with a bone age ≤9 years for girls and ≤10 years for boys and height SDS ≤-3	N=194 1 year	Primary: Change from baseline in height SDS at one year Secondary: Safety	Primary: There were significant gains in mean height SDS after one year of treatment in both the fixed dose and individualized dose groups (1.13 and 0.89 SDS; *P*<0.001 for both). The fixed dose group had a significantly greater change in height SDS compared to the individualized dose group (least mean square difference, -0.24; 95% CI, -0.35 to -0.12; *P*<0.001). There was no significant between group difference in change of height SDS in the low-dose individualized dose and high-dose individualized dose groups (least mean square difference, 0.03; 95% CI, -0.13 to 0.18). Secondary: There were no differences in adverse events reported in the treatment groups. The most common adverse events were nasopharyngitis, pyrexia, vomiting and headache.
Bozzola et al[59] Somatropin (Genotropin®) 0.23 mg/kg/week for 2 years (Group A) vs somatropin (Genotropin®) 0.23 mg/kg/week for 1 year, followed by somatropin 0.46 mg/kg/week (Group B)	OL SGA pediatric patients 2 to 7 years of age	N=26 2 years	Primary: Growth response Secondary: Not reported	Primary: During year one, growth velocity significantly increased in both groups (*P*<0.0001). There was a significant decrease in growth velocity during year two in Group A (*P*<0.015), but Group B maintained their growth rate. In Group A, height SDS significantly increased compared to baseline during years one and two (*P*<0.000002 and *P*<0.000001). In Group B, height SDS also increased significantly compared to baseline during years one and two (*P*<0.000001 and *P*<0.000001). There was a greater increase in height gain with the patients in Group B compare to the patients in Group A (*P*<0.02). Secondary: Not reported
de Zegher et al[60] Somatropin 33 µg/kg/day (low-dose group) vs	MA (4 OL, RCTs) Prepubertal pediatric patients who were diagnosed with	N=82 Mean duration of 10 years	Primary: Change in height SDS Secondary: Not reported	Primary: In patients who received at least seven years of treatment with somatropin, those who received high-dose somatropin had an additional height gain by 0.38 SDS compared to those who received low-dose somatropin (95% CI, 0.06 to 0.69; *P*=0.019). Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
somatropin 67 µg/kg/day (high-dose group) vs placebo or no treatment	SGA and failed to have catch-up growth during infancy			Not reported
Crabbe et al (abstract)[61] GH 33 µg/kg/day (low-dose group) vs GH 67 µg/kg/day (high-dose group) vs placebo or no treatment	MA Pediatric patients diagnosed with SGA or IUGR	N=not reported 2 years	Primary: Change in height SDS Secondary: Not reported	Primary: At two years, the high-dose group had a greater gain in height SDS by 0.48±0.35 compared to the low-dose group (*P* value not reported). Secondary: Not reported.
de Zegher et al[62] Somatropin 0.033 mg/kg/day vs somatropin 0.067 mg/kg/day vs somatropin 0.1 mg/kg/day vs placebo or no treatment	MA (4 OL, RCTs) Prepubertal pediatric patients between 2 and 8 years of age who had a birth weight or length <-2 SDS for gestational age or height for age <-0.2 SDS and who had never received GH treatment	N=244 2 years	Primary: Height velocity, change in height SDS Secondary: Change in weight, change in bone age	Primary: Due to differences in baseline characteristics, data from one study conducted in France was analyzed separately from the other three studies. In three of the trials, there was a dose-dependent response in height velocity and an increase in height SDS at two years. Height velocity at two years was 5.59±0.14, 8.26±0.20, 9.88±0.18 and 11.38±0.30 cm/year in the untreated, 0.033 mg/kg/day, 0.067 mg/kg/day and 0.1 mg/kg/day groups, respectively (*P*<0.005). The increase in height SDS was 0.12±0.07, 1.13±0.09, 2.11±0.10 and 2.64±0.16 in the untreated, 0.033 mg/kg/day, 0.067 mg/kg/day and 0.1 mg/kg/day groups, respectively (*P*<0.005). Similarly, a dose-dependent response in height velocity and change in height SDS was seen in the French study. The height velocity was 5.54±0.27, 7.46±0.11 and 8.15±0.17 cm/year in the untreated, 0.033 mg/kg/day and 0.067 mg/kg/day groups, respectively (*P*<0.05). The increase in height SDS was 1.33±0.07, 1.04±0.05 and 0.17±0.10 in the untreated, 0.033 mg/kg/day and

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				0.067 mg/kg/day groups, respectively (*P*<0.005). No one in the French study received somatropin at 0.1 mg/kg/day. Secondary: There was a dose-dependent increase in weight in all four studies (*P*<0.05). Annual bone age increment did not differ significantly across all three groups in the French study. In the other three studies, however, there was a dose-dependent response with the bone age increment, which was 0.85±0.06, 1.00±0.06, 1.20±0.06 and 1.41±0.13 years for the untreated, 0.033 mg/kg/day, 0.067 mg/kg/day and 0.1 mg/kg/day groups, respectively (*P*<0.005).
Growth Hormone Deficiency In Children				
Kristrom et al[63] GH 17 to 100 µg/kg/day based on predicted growth response (individualized-dose group) vs GH 43 µg/kg/day (standard-dose group)	MC, OL, RCT Pediatric patients between 3 and 11 years of age for boys or between 3 and 10 years of age for girls who had isolated GHD or ISS with a height SDS ≤-2 or growth velocity SDS ≤-1 and whose current height SDS was ≥1 SDS below target height SDS	N=153 2 years	Primary: Difference between current height SDS and target height SDS Secondary: Changes in mean height SDS, changes in bone age, safety	Primary: At two years, the mean difference between current height SDS and target height SDS was -0.42±0.46 in the individualized-dose group and -0.48±0.67 in the standard-dose group (*P*=0.003). The range in distribution of this difference was 32% narrower in the individualized-dose group compared to the standard-dose group, demonstrating a more consistent treatment response to GH with an individualized-dose regimen. Secondary: The mean gain in height SDS was 1.32 in both treatment groups (*P*>0.05). There was no difference between patients with GHD and those with ISS with regard to change in height SDS. Change in bone age delay was similar between the individualized- and standard-dose groups (0.52 and 0.41 years, respectively; *P*>0.05). Incidence of adverse events was similar between the two groups. No serious adverse events related to GH were reported. There were no significant changes in fasting blood glucose and HbA1c. Fasting serum insulin levels increased significantly from baseline in both groups. Increase in serum IGF-1 levels was comparable between the two groups. Nine children in the individualized-dose group and five children in the fixed-dose group had serum IGF-1 levels above 3 SDS.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Wilson et al[64] GH IM TIW vs GH SC TIW	OL, RCT Pubertal and prepubertal pediatric patients between 5.7 and 18.3 years of age with GHD and who had not received GH in the previous 2 weeks	N=20 6 months	Primary: Growth velocity and presence of anti-GH antibodies Secondary: Changes in serum IGF-1 and IGF-2 levels	Primary: There was no significant difference in growth velocity at six months in the IM (6.1±2.8 cm/year) and SC (4.9±2.0 cm/year) groups. Anti-GH antibodies were positive in one patient in the SC group prior to study; the titer decreased from log 1.5 to 1.0 during the study. One patient from each group developed anti-GH antibodies during the study. The presence of anti-GH antibodies had no major effect on growth. Secondary: Changes in serum IGF-1 and IGF-2 levels were not significantly different between the two groups.
Coelho et al[65] Somatropin (Genotropin®) 15 IU/m^2/week SC daily (standard-dose group) vs somatropin (Genotropin®) 30 IU/m^2/week SC daily (high-dose group)	OL, RCT Prepubertal pediatric patients with GHD who had been receiving GH 15 IU/m^2/week SC daily for at least 1 year	N=49 Mean duration 5.86±1.62 years (treatment was discontinued once final height was reached)	Primary: Change in height SDS Secondary: Age at end of treatment and at mid-puberty	Primary: Change in height SDS at the end of treatment was similar between the high- and standard-dose groups (1.2±1.2 and 1.1±1.7, respectively; *P*=0.81). The final height SDS was also similar between the two groups (-0.71±1.3 and -0.87±1.1; *P*=0.3). Secondary: Patients receiving the standard-dose regimen were older at the end of treatment compared to those receiving the high-dose regimen (17.2±1.7 vs 16.1±1.5 years; *P*=0.026), but the mean age at mid-puberty was similar between the two groups (*P*=0.3).
Shih et al (abstract)[66] Somatropin (Genotropin®) 0.1 IU/kg/day SC daily vs somatropin (Humatrope®) 0.1 IU/kg/day SC daily vs somatropin (Saizen®) 0.2	RCT Prepubertal pediatric patients with GHD	N=15 12 months	Primary: Change in bone age, height velocity, height SDS and anti-GH antibody titers; safety Secondary: Not reported	Primary: The average bone age increased by 0.8±0.2 years in the Genotropin® group, 0.8±0.7 years in the Humatrope® group and 2.1±1.3 years in the Saizen® group. The mean height velocity increased from 3.4±0.7 to 11.3±2.0 cm/year with Genotropin®, from 4.0±1.3 to 9.4±1.9 cm/year with Humatrope® and from 3.7±1.2 to 11.1±3.3 cm/year with Saizen®. Similarly, the height SDS increased from -4.0±0.5 to -2.7±0.7 in the Genotropin® group, from -2.9±0.7 to -2.2±1.0 in the Humatrope® group and -4.2±3.1 to -3.1±2.9 in the Saizen® group.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
IU/kg/day SC TIW				There were no differences among the three treatment groups with regard to change in bone age, height velocity and height SDS (*P* values not reported). Anti-GH antibody titers were detected in one patient in the Saizen® group and one patient in the Genotropin® group. The presence of anti-GH antibodies did not affect height velocity. One patient developed subclinical hypothyroidism. No other adverse events were noted in the other patients. Secondary: Not reported
de Muinck Keizer-Schrama et al[67] Somatropin (Norditropin®) 2 IU/m^2/day SC (standard-dose group) vs somatropin (Norditropin®) 4 IU/m^2/day SC (high-dose group)	MC, RCT Prepubertal pediatric patients with GHD of organic or idiopathic origin and a bone age <12 years for boys and <10 years for girls and who were either treatment-naïve or treatment-experienced to GH	N=38 (21 treatment-naïve and 17 treatment-experienced patients) Up to 2 years (treatment was discontinued once adult height was reached)	Primary: Changes in height velocity, height velocity SDS and height SDS Secondary: Change in, serum IGF-1 levels, BP, thyroid function, anti-GH antibodies, lipid profile, HbA1c and other laboratory values	Primary: In treatment-naïve patients, the increase in height velocity at one year was nonsignificantly greater with the high-dose regimen compared to the low-dose regimen (8.0 vs 5.5 cm/year; *P*>0.05). Similar trends were seen in changes in height velocity SDS and height SDS (9.76 vs 7.25; *P*>0.05, 1.56 vs 1.16; *P*>0.05, respectively). In treatment-experienced patients who had been receiving standard-dose somatropin for at least one year prior to the study, there was an increase in height velocity in the high-dose group and a decrease in the standard-dose group after two years of treatment (0.7 vs -1.0 cm/year; *P*<0.005). Similarly, the improvement in height velocity SDS was seen in the high-dose group but not in the standard-dose group (1.39 vs -0.73; *P*<0.01). Increase in height SDS at two years was also greater in the high-dose group compared to the standard-dose group (1.91 vs 0.69; *P*<0.01). Secondary: Serum IGF-1 levels increased significantly from baseline in both groups, with no significant intergroup differences. No clinically significant changes were seen in BP in both groups. Two patients from the high-dose group had subnormal T_4 and low TSH levels but had no clinical signs of hypothyroidism. One treatment-naïve patient in the high-dose group developed anti-GH antibodies, which became undetectable after 12 months of treatment.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				A nonsignificant decrease in cholesterol, LDL and apo-B was seen in both groups. No significant changes were seen in HbA1c, hemoglobin, hematocrit, platelet count, urea nitrogen, creatinine and alkaline phosphatase.
Sas et al[68] Somatropin (Norditropin®) 2 IU/m^2/day SC (standard-dose group) vs somatropin (Norditropin®) 4 IU/m^2/day SC (high-dose group)	MC, RCT Prepubertal pediatric patients with GHD of organic or idiopathic origin and a bone age <12 years for boys and <10 years for girls and who were either treatment-naïve or treatment-experienced to GH	N=35 (20 treatment-naïve and 15 treatment-experienced patients) Study duration not specified (treatment was discontinued once adult height was reached)	Primary: Difference between adult height SDS and target height SDS Secondary: Adult height SDS, change in height SDS, number of patients whose height was at or above the lower limit of the target height range, duration of treatment, onset of puberty, bone maturation, safety	Primary: The difference between adult height SDS and target height SDS was nonsignificantly smaller in the high-dose group compared to the standard-dose group in both treatment-naïve (-0.3±1.0 and -0.7±0.9, respectively; *P*=0.29) and treatment-experienced patients (0.1±1.1 vs -0.6±0.9, respectively; *P*=0.18). Secondary: Adult height SDS with high- and standard-dose groups was -1.4±1.1 and -1.5±0.9, respectively, in treatment-naïve patients (*P*=0.75) and 0.0±1.1 and -0.6±0.6, respectively, in treatment-experienced patients (*P*=0.24). The onset of puberty was 1.1 years earlier in patients receiving high-dose somatropin compared to those receiving standard-dose somatropin (95% CI, 0.1 to 2.1; *P*=0.04). There were no significant differences between the two groups with regard to change in height SDS, the number of patients whose height was at or above the lower limit of the target height range, duration of treatment with somatropin and bone maturation. Treatment was well-tolerated, with no report of diabetes.
Cohen et al[69] Somatropin (Norditropin®) 0.025 mg/kg/day SC (low-dose group) vs somatropin (Norditropin®) 0.05 mg/kg/day SC (medium-dose group)	RCT Prepubertal pediatric patients with GHD and a bone age <9 years for boys and <8 years for girls and who had never received GH	N=111 2 years	Primary: Change in height SDS Secondary: Changes in serum IGF-1 and IGFBP-3 SDS; changes in bone age, fasting blood glucose,	Primary: In all three groups, height SDS increased significantly from baseline at two years. Patients in the low-dose group had significantly smaller gain in height SDS compared to the medium- and high-dose groups (*P*<0.01). When stratified by gender, a dose-dependent response was seen in boys but not in girls. Secondary: There was a dose-dependent increase in serum IGF-1 and IGFBP-3 levels and SDS (*P*<0.05).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs somatropin (Norditropin®) 0.1 mg/kg/day SC (high-dose group)	treatment		HbA1c, fasting plasma insulin, safety	Bone age advancement was higher with the medium- (1.2±1.0 years) and high-dose groups (1.2±0.9 years) compared to the low-dose group (0.7±0.7 year; *P* value not reported). No significant differences were seen in fasting blood glucose and HbA1c across the three groups, while there was a dose-dependent increase in fasting insulin levels at one year (*P*<0.001) but not at two years (*P*=0.08). Rates of adverse events were similar across all three groups. Anti-GH antibodies were detected in significant levels in 12% of the patients with no correlation to dose or growth response.
MacGillivray et al[70] Somatropin (Nutropin®) 0.3 mg/kg/week SC TIW vs somatropin (Nutropin®) 0.3 mg/kg/week SC administered in daily doses	MC, RCT Prepubertal pediatric patients with GHD and a bone age ≤10 years for girls and ≤11 years for boys and who had never received GH treatment	N=65 4 years	Primary: Annual growth velocity, cumulative change in height and height SDS Secondary: Changes in bone age and age at onset of puberty	Primary: Patients were excluded from statistical analyses once they had reached puberty. The number of patients remaining prepubertal at one, two, three and four years was 51, 40, 26 and 23, respectively. The annual growth velocity was significantly greater with daily dosing compared to TIW dosing throughout the study. The growth velocity at four years was 7.5±1.4 and 6.0±1.3 cm/year in the daily and TIW groups, respectively (*P*=0.037). The cumulative change in height was also significantly greater in the daily group (38.4±5.5 cm) compared to the TIW group (28.7±3.2 cm; *P*=0.0002). Patients receiving daily dosing gained an additional 1.7 height SDS than patients receiving TIW dosing at four years (*P*=0.0003). Secondary: Gain in bone age was similar between the two groups (*P*=0.84). The mean chronological age at the onset of puberty was also similar between the two groups (*P*=0.84).
Mauras et al[71] Somatropin (Nutropin®) 0.7 mg/kg/week SC (high-dose group)	MC, RCT Pubertal pediatric patients between 10 and	N=97 Up to 63 months (treatment	Primary: Near-adult height and height SDS	Primary: A total of 75 patients reached near-adult height, with 42 patients in the standard-dose group and 33 patients in the high-dose group. Patients in the high-dose group attained higher near-adult height by 4.6 cm (95% CI, 2.6 to 6.5; *P*<0.001) compared to patients in the standard-dose group.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs somatropin (Nutropin®) 0.3 mg/kg/week SC (standard-dose group)	18 years of age for boys and between 8 and 16 years of age for girls who had GHD with a bone age ≥14 years for boys and ≥12 years for girls and who had been receiving GH for at least 6 months	was discontinued once adult height was reached)	Secondary: Last measured height, height SDS, growth velocity, mean age and bone age at near-adult height, duration of therapy, change in body weight, BMI, bone age, Tanner pubertal stage, lumbar spine BMD, total body BMC, serum IGF-1 levels, HbA1c, fasting blood glucose, fasting insulin and safety	Height SDS at near-adult height was 0.0±1.2 in the high-dose group and -0.7±0.9 in the standard-dose group (*P*=0.002). There was a significantly greater gain in height SDS with the high-dose regimen compared to the standard-dose regimen (1.1±1.0 vs 0.6±0.8; *P*=0.012). Secondary: Patients in the high-dose group were taller at last measured height by 2.8 cm (95% CI, 0.2 to 5.3; *P*=0.036) compared to the standard-dose group. At 36 months, the height SDS was higher in the high-dose group compared to the standard-dose group (1.4±0.8 vs 0.9±0.7; *P*=0.023). Growth velocity was higher with high-dose somatropin compared to standard-dose somatropin during 0 to 12 months (9.8 vs 8.2 cm/year; *P*=0.001) and during 24 to 36 months (difference, 1.7 cm/year; *P*=0.038). There were no differences between the two groups with regard to mean age and bone age at near-adult height, duration of therapy, body weight, BMI, bone age, Tanner pubertal stage, lumbar spine BMD and total body BMC. There was a greater increase in serum IGF-1 levels in the high-dose group compared to the standard-dose group, although this difference did not reach statistical significance. No significant changes were seen in HbA1c and fasting blood glucose in both groups. Fasting insulin increased to a greater extent in the high-dose group than the standard-dose group at 24 months (*P*=0.011). Incidence of adverse events was similar between the two groups. One case of worsening scoliosis requiring surgery was reported in each group. One case of hip pain, which was considered possibly related to the study drug, was reported in the high-dose group.
Romer et al[72] Somatropin lyophilisate	MC, OL, RCT Prepubertal	N=89 7 years	Primary: Height, height SDS, height	Primary: Forty-nine out of 89 patients completed seven years of treatment. In these patients, the mean height at the end of seven years was 155.3±10.86 cm.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
(Omnitrope®) 0.03 mg/kg/day SC for 15 months, followed by somatropin liquid (Omnitrope®) 0.03 mg/kg/day SC (Group A) vs somatropin lyophilisate (Genotropin®) 0.03 mg/kg/day SC for 9 months, followed by somatropin liquid (Omnitrope®) 0.03 mg/kg/day SC (Group B) Dose was readjusted to body weight after 6 months and then at each scheduled study visit. Treatment was continued until satisfactory height was reached or when epiphyseal fusion had occurred.	pediatric patients between 2 and 14 years of age who had growth failure secondary to idiopathic GHD and who had never had GH treatment		velocity, height velocity SDS, IGF-1, IGFBP-3, safety Secondary: Not reported	At seven years, the mean height SDS increased from -3.06±0.80 at baseline in both treatment groups to -0.78 in Group A and -1.01 in Group B. The mean difference in height SDS between the two groups was 0.13 (95% CI, -0.04 to 0.31) at nine months, 0.14 (95% CI, -0.09 to 0.37) at 15 months and 0.25 (95% CI, -0.33 to 0.83) at seven years. In both groups, the mean height velocity increased from 3.84±1.03 cm/year at baseline to 12.01±4.01 cm/year at three months and slowly declined to 5.53 cm/year at seven years. Height velocity at any point in the study was significantly higher compared to baseline. The mean difference in height velocity between Groups A and B was -0.19 cm/year (95% CI, -1.34 to 0.95) at nine months, -0.14 cm/year (95% CI, -0.98 to 0.70) at 15 months and -0.07 cm/year (95% CI, -1.43 to 1.29) at seven years. At seven years, the mean height velocity SDS increased from -2.27±1.09 at baseline to 6.84±4.63 at three months and then decreased to -0.18 in Group A and 0.11 in Group B. Height velocity SDS at any point in the study was significantly higher compared to baseline. The mean difference in height velocity SDS between the two groups was 0.79 (95% CI, -0.56 to 2.15) at nine months, 0.76 (95% CI, -0.37 to 1.90) at 15 months and -0.37 (95% CI, -2.02 to 1.28) at seven years. The mean serum IGF-1 SDS was -1.84±0.57 at baseline, and the values in both treatment groups were higher compared to baseline at any point in the study. The serum IGF-1 levels between the two groups were not significantly different at any time point during the study (values not reported). The mean serum IGFBP-3 levels at any time point were significantly higher than baseline in both groups. The difference between the two groups was not significant at any time point, with the exception of 48 months, in which the difference was -0.46 (95% CI, -0.86 to -0.07). A total of 1,759 adverse events were reported, out of which 323 were study drug-related. There were no clinically relevant differences between the two groups in terms of frequency, distribution, intensity and outcome of these

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				adverse events. The rate of adverse drug events per patient-year was 0.478, 0.576 and 0.849 for Omnitrope® lyophilisate, Omnitrope® liquid and Genotropin® lyophilisate, respectively. Adverse drug events occurring at a rate of least 0.05 events per patient year with any agent were hypothyroidism, decreased TSH, increased HbA1c, increased TG, eosinophilia, headache and injection site hematoma. The rate of glucose-related adverse drug events was 0.078 with Omnitrope® and 0.059 with Genotropin®. One patient experienced worsening of scoliosis. There were no study withdrawals due to adverse events and no relevant changes in vital signs or clinical laboratory data. Secondary: Not reported
Idiopathic Short Stature				
van Gool et al[73] GH 0.5 or 1 mg/m^2/day for 3 months; a 3 month washout period; XO to 0.5 to 1 mg/m^2/day; a 3 month washout; followed by 2 mg/m^2/day for 2 to 5 years until the onset of puberty vs no treatment	RCT Patients with ISS, height <-2 SDS, age 4 to 8 years for girls and 4 to 10 years for boys, peak GH >10 µg/L after provocative stimulation test and normal sitting height	N=40 5 to 12 years	Primary: Adult height Secondary: Not reported	Primary: The mean duration of GH treatment was 3.3 years. At discontinuation of treatment, there was a significant increase in height SDS with GH-treated patients compared to controls (*P*=0.001). There were no significant between groups differences in adult height SDS and adult height minus starting height SDS (*P*=0.6 and *P*=0.8). Secondary: Not reported
Albertsson-Wikland et al[74] Somatropin (Genotropin®) 33 µg/kg/day (prepubertal patients) vs somatropin (Genotropin®) 67	RCT Patients with height <-2 SDS, chronological age 7 to 13 years and bone age ≤11 years in girls and	N=108 ≥1 year	Primary: Final height, gain in height SDS, difference of final height and mid-parental height Secondary: Not reported	Primary: Compared to untreated controls, patients with ISS treated with somatropin 67 µg/kg/day had a significantly greater final height in boys (*P*=0.001) and girls (*P*=0.018). The gain in height SDS was significantly greater than controls in both the 33 and 67 µg/kg/day groups (*P*=0.004 and *P*=0.001). The difference in final height and mid-parental height was greater in the 67 µg/kg/day group compared to controls (*P*=0.001). Only the difference in final height and mid-parental height was significantly different comparing the 33 and 67 µg/kg/day groups (-0.1 vs 0.4; *P*=0.042).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
µg/kg/day (prepubertal and pubertal) vs no treatment (prepubertal and pubertal)	chronological age 10 to 15 years and bone age ≤13 years in boys			Secondary: Not reported
Hopwood et al[75] First 12 months: somatropin 0.1 mg/kg TIW vs no treatment Months 24 to 36 (re-randomization to): somatropin 0.3 mg/kg/day vs somatropin 0.3 mg/kg TIW	RCT Patients <3rd percentile for height (<-1.88 SD), prepubertal, bone age <9 years for girls or <10 years for boys and GH >10 µg/L after provocative stimulation test	N=121 36 months	Primary: Mean growth rate, height SDS Secondary: Not reported	Primary: During the first year, patients treated with somatropin once daily had a significantly higher growth rate than patients treated with somatropin TIW (9.0±1.6 vs 7.8±1.2 cm/year; *P*<0.0005). During years two and three, there were no significant differences between groups in growth rate. The change in height SDS was significantly greater with once daily compared to TIW dosing (1.2±0.5 vs 1.0±0.6; *P*<0.04). Secondary: Not reported
Kriström et al[76] GH 43 µg/kg/day (standard dose) vs GH 17 to 100 µg/kg/day based on prediction model (individualized dose)	OL, RCT Patients with GHD or ISS who were prepubertal, 3 to 10 years of age for girls and 3 to 11 years of age for boys, height <-2 SDS or growth velocity <-1 SDS, ≤- 1	N=153 2 years	Primary: Range of distribution for difference between current height SDS and mid-parental height SDS Secondary: Height SDS	Primary: After two years, the range of distribution for difference between current height SDS and mid-parental height SDS was significantly reduced by 32% in the individualized dose group compared to the standard dose group (*P*=0.003). The mean values for difference between current height SDS and mid-parental height SDS were not significantly different (-0.42±0.46 for individualized and -0.48±0.67 for the standard dose). Secondary: After two years, there was no significant differences in height SDS for each group compared to baseline (*P*=NS).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	SDS below mid-parental height and born at gestational age >30 weeks			
Wit et al[77] GH 0.24 mg/kg/week vs GH 0.24 mg/kg/week for 1 year, followed by GH 0.37 mg/kg/week vs GH 0.37 mg/kg/week	ES, OL, randomized (2 years) Prepubertal patients ≥5 years with ISS with height <-2 SDS, bone age <10 years in girls and <12 years in boys, height velocity <25th percentile, GH >10 µg/L after provocative stimulation test and normal thyroid function or adequate thyroid replacement	N=239 >2 years (until final height)	Primary: Height velocity and final height Secondary: Not reported	Primary: After two years, height velocity was significantly higher with GH 0.37 mg/kg/week compared to 0.24 mg/kg/week and 0.24 to 0.37 mg/kg/week (treatment difference, 0.8 cm/year; *P*=0.003 and treatment difference, 0.9 cm/year; *P*=0.001, respectively). Duration of treatment was not significantly different between treatment groups. The mean between-dose effect on final height SDS was 0.57±0.25 SDS (3.6 cm; *P*=0.025). There were significant differences between final height and baseline with 0.24 mg/kg/week (*P*≤0.001) and 0.37 mg/kg/week (*P*≤0.001). Final heights were within normal ranges for 94% of patients with 0.37 mg/kg/week and 71% with 0.24 mg/kg/week. Secondary: Not reported
Finkelstein et al[78] GH 0.14 to 0.4 mg/kg/week	MA (10 controlled trials; 28 uncontrolled trials) Pediatric patients with absence of GHD, with no	N=434 (controlled trials) >6 months	Primary: Effect of GH on growth velocity and height SDS at one year and on adult height Secondary: Not reported	Primary: *Controlled trials* After one year, growth velocity with GH was significantly greater than controls (mean between group difference, 2.86±0.37 cm/year; 95% CI, 2.13 to 3.59). In the subset of five RCTs, growth velocity after one year was significantly greater with GH compared to controls (between group difference, 2.53 cm/year; 95% CI, 1.72 to 3.35). The change in growth velocity compared to baseline in the GH treated patients was 3.63±0.32 cm/year (95% CI, 3.00 to 4.25). In the control group the change in growth velocity compared to baseline

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	previous GH treatment, without comorbid condition that impair growth and without previous treatment with sex steroids or anabolic agents			was 0.93±0.35 cm/year (95% CI, 0.25 to 1.62). After one year, the childhood height SDS was significantly greater with GH compared to controls (mean between group difference, 0.60±0.37 SD; 95% CI, 0.26 to 0.95). The adult height SDS was significantly greater in the GH group compared to the placebo group (weighted aggregate between group difference, 0.84±0.19 SD (95% CI, 0.46 to 1.22). The pooled estimate for adult height SDS was -1.51 SD (95% CI, -1.70 to -1.32) with GH compared to -2.29 SD (95% CI, -2.63 to -1.96) with controls. *Uncontrolled trials* After one year, the pooled estimate for growth velocity was 7.57±0.30 cm/year (95% CI, 4.00 to 4.59) compared to 4.29±0.15 cm/year (95% CI, 6.99 to 8.19) at baseline. The childhood height SDS was -2.62±0.09 SD (95% CI, -2.79 to -2.44) at baseline and -2.19±0.10 SD (95% CI, -2.39 to -1.99) after one year of treatment. The mean predicted adult height was -2.18±0.17 SD (95% CI, -2.52 to -1.85) compared to an achieved height of -1.62±0.07 SD (95% CI, -1.77 to -1.47) with GH. Secondary: Not reported
Bryant et al[79] Somatropin vs placebo vs	MA (10 RCT) Pediatric patients with ISS and normal GH secretion	N=741 >6 months	Primary: Final height Secondary: Short term growth, quality of life, adverse effects and cost	Primary: In the one trial that reported near final height, patients treated with somatropin were significantly taller than controls with no treatment or controls that did not consent to randomization (155.3±6.4 vs 147.8±2.6 and 149.3±3.3 cm; *P*=0.003). Near final height SDS was significantly higher in the somatropin group compared to controls and non-consent groups (-1.14±1.06 SDS vs -2.37±0.46 and -2.13±0.55; *P*=0.004). In one trial that reported adult height SDS, patients treated with somatropin

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
no treatment				had a significantly greater adult height by 0.57 SDS compared to patients treated with placebo (3.7 cm; 95% CI, 0.03 to 1.10; *P*<0.04). Secondary: One trial demonstrated a significantly greater change in height SDS at one year with somatropin-treated patients compared to untreated controls (WMD, 0.90 SDS; 95% CI, 0.33 to 1.47; *P*<0.05). Another trial demonstrated a significant change from baseline at one year with somatropin (*P*<0.05) compared to no change with placebo. In two trials no significant differences between treated and untreated groups. One trial showed a significant increase at two years in height SDS with somatropin compared to controls (*P*<0.001). Finally, another trial demonstrated a significant change in height SDS compared to no change in untreated controls (*P*<0.0.001). In the MA of three trials reporting growth velocity at one year, somatropin-treated patients had a significantly greater growth velocity compared to untreated controls (WMD, 2.48; 95% CI, 2.06 to 2.90; *P*<0.00001). In another study, growth velocity at three years was significantly higher with somatropin compared to untreated controls (6.4 vs 5.2 cm/year; *P*<0.003). One study did not find a significant difference between treated and untreated patients (*P*=0.21). Growth velocity SDS was significantly greater at one year with somatropin-treated prepubertal patients (*P*<0.0.001) and pubertal patients (*P*<0.05) compared to untreated controls, and at six months in somatropin pubertal patients compared to placebo (*P*<0.0001). There were no significant differences in quality of life between somatropin-treated patients and controls. There were no serious adverse effects reported.
Growth Hormone Deficiency In Adults				
Chihara et al[80] Somatropin (Genotropin®) 0.003 mg/kg/day SC for 8	ES, OL Adult patients with GHD who	N=71 48 weeks	Primary: Changes in body composition, lipid profile,	Primary: In patients who previously received placebo in the DB phase, LBM increased significantly from 40.4±11.0 kg at baseline to 42.1±11.0 at 48 weeks (*P*=<0.0001) while fat mass was reduced significantly from 19.9±7.3 to

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
weeks, then adjust by increment of up to 0.003 mg/kg/day according to serum IGF-1 levels	previously participated in the 24 week DB, PC, RCT		symptom scores, SF-36 score, QoL-AGHDA score, safety Secondary: Not reported	18.6±7.3 kg (*P*=0.0019). Moreover, there was a significant reduction in TC from 5.66±1.16 mmol/L at baseline to 5.39±1.05 mmol/L at 48 weeks (*P*=0.0181) as well as in LDL from 3.53±1.02 to 3.16±0.83 mmol/L (*P*=0.0018). HDL increased from 1.30±0.36 to 1.38±0.39 (*P* value not reported). In patients who previously received somatropin in the DB phase, LBM continued to increase during the OL phase from 43.9±10.3 kg at the end of DB phase to 44.4±10.4 kg at 48 weeks. Body fat mass increased slightly from 19.7±7.3 to 20.2±7.5 kg but still remained lower compared to the beginning of the PC phase (21.9±7.2 kg). Similarly, following a decrease in TC and LDL during the DB phase, there was an increase in both parameters during the ES phase, from 4.98±0.94 to 5.22±1.02 mmol/L for TC and from 2.94±0.84 to 2.97±0.74 mmol/L for LDL, although the values remained lower compared to the beginning of the DB phase. HDL continued to increase throughout the ES phase, from 1.38±0.40 to 1.44±0.43 mmol/L (*P* values not reported). Symptoms scores, SF-36 and QoL-AGHDA scores improved or remained unchanged in patients who previously received somatropin. The symptoms scores for decreased motor ability and/or muscle strength as well as SF-36 and QoL-AGHDA scores improved in patients who previously received placebo (*P* values not reported). There were a total of 481 adverse events reported in 91.5% of patients. The most commonly reported adverse events were upper respiratory tract infection, emotion lability, abnormal thinking and psychotic depression. Five serious adverse events were reported, including influenza-like symptoms, convulsions, recurrent craniopharyngioma, recurrent cervical cord tumor and colonic diverticulitis, of which recurrent craniopharyngioma and cervical cord tumor were considered to be related to study treatment. No death occurred during the study. Secondary: Not reported
Gilchrist et al[81] GH 0.25 IU/kg/week	OL Patients with	N=61 9 years	Primary: NHP and PGWB scores	Primary: Patients were stratified by continuous treatment during the nine years or discontinuation of treatment after the RCT. At nine years, there was a

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	GHD that completed the NHP and PGWB during a 12 month DB, RCT		Secondary: Not reported	significant increase in energy and mobility scores of the NHP in the patients that received continuous GH replacement compared to baseline (*P*=0.04 for both). There were no significant differences compared to baseline in other subsections of the NHP. In patients that discontinued treatment, there were no significant differences compared to baseline in any of the NHP scores. At nine years, there was a significant differences in the change of energy score between the continuous treatment group and discontinuation of treatment group (*P*=0.008). There were no other significant differences between groups in other NHP scores. At nine years, there was a significant decrease in the general health score of PGWB compared to baseline in patients that discontinued treatment (*P*=0.03). In patients on continuous treatment, there was a significant increase in vitality score (*P*=0.003). There were no other significant differences in other scores in either group. When comparing the continuous treatment and discontinued treatment groups, there was a significant difference in change of vitality score (*P*=0.0004). There were no other significant differences between groups in other scores. Secondary: Not reported
Jørgensen et al (abstract)[82] GH	OL, ES Patients with GHD on uninterrupted GH therapy for 3 years that completed a previous DB, PC, RCT and 16 month OL trial	N=10 3 years	Primary: Body composition, physical performance Secondary; Not reported	Primary: An increase in thigh muscle was maintained after three years of GH therapy. There was an increase in body weight and thigh fat volume. Exercise capacity and isometric muscle strength increased significantly compared to the initial placebo period. Secondary: Not reported
Sneppen et al[83] Somatropin (Genotropin®) 0.02 IU/kg/day for 4 weeks,	DB, PC, RCT Patients 23 to 57 years of age with	N=40 18 months	Primary: Change from baseline in BMD and bone	Primary: There was no significant treatment effect comparing the somatropin and placebo groups after 18 months. The variance of changes was significantly greater in the somatropin treated patients compared to the placebo treated

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
followed by somatropin (Genotropin®) 0.03 IU/kg/day vs placebo	GHD for a minimum of 2 years with a maximal peak GH response of 3 µg/L with the insulin tolerance test and on stable replacement therapy for other deficient hormones for ≥6 months before trial		mineral content at 18 months Secondary: Not reported	patients for total body BMD (*P*=0.03), lumbar spine BMD (*P*=0.001), femoral neck BMD (*P*=0.01) and femoral trochanter BMD (*P*=0.04). Secondary: Not reported
Beauregard et al[84] Somatropin (Genotropin®) 3 µg/kg/day for patients >50 years of age not receiving oral estrogen; 5 µg/kg/day for patients <50 years of age not receiving oral estrogen; 6 µg/kg/day for patients <50 years of age no receiving oral estrogen or had childhood onset GHD regardless of estrogen; doses were increased in all patients depending on IGF-1 levels vs placebo	DB, PC, RCT Female patients with a history of pituitary and/or hypothalamic disease and GHD	N=43 6 months	Primary: Change from baseline in high-sensitivity CRP, serum lipids, tissue plasminogen activator, soluble E-selectin, insulin resistance and visceral fat mass Secondary: Not reported	Primary: At six months, there was a significantly greater decrease in mean high-sensitivity CRP in the somatropin group compared to the placebo group (38.2±9.6 vs 18.2±6.0%; *P*=0.03). Patients treated with somatropin had a mean decrease in tissue plasminogen activator of 13.0±4.6% compared to a mean increase of 1.1±5.2% for patients treated with placebo (*P*=0.02). There was no significant change in soluble E-selectin. Mean TC decreased by 3.1±1.7% with somatropin compared to an increase of 3.8±2.5% with placebo (*P*=0.04). Mean HDL-C increase by 0.4±2.7% with somatropin compared to a decrease of 10.1±2.1% with placebo (*P*=0.004). There were no significant differences in the mean change of TG and LDL-C between the groups. At six months, there were no significant changes in fasting glucose, fasting insulin, HOMA, HOMA-β or HbA1c compared to placebo. There was a mean decrease of visceral fat mass of 9.0±5.9% with somatropin compared to an increase of 4.3±2.7% with placebo (*P*=0.03). Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Not reported
Chihara et al[85] Somatropin (Genotropin®) 0.021 mg/kg/week (as 0.003 mg/kg/day) for 4 weeks, followed by 0.042 mg/kg/week for 4 weeks, followed by 0.084 mg/kg/week for remaining 16 weeks vs placebo	DB, PC, RCT Patients 18 to 65 years of age with organic or idiopathic, isolated or multiple, childhood- or adult-onset GHD of ≥2 years	N=75 24 weeks	Primary: Change from baseline in LBM Secondary: Change from baseline in body fat mass, serum lipid profiles, serum IGF-1 and IGFBP-3; symptoms; quality of life; safety	Primary: At 24 weeks, there was a significant increase in LBM in the somatropin-treated patients compared to baseline (4.7%; *P*<0.05). The increase in LBM with placebo treated patients was not significant (1.0%; *P* value not reported). When compared to placebo, the increase in LBM was significantly greater with somatropin (*P*<0.0003). Secondary: At 24 weeks, the body fat mass was significantly decreased in the somatropin group compared to baseline (*P*<0.05); however, there was a nonsignificant increase with the placebo group. When compared to placebo treated patients the change was significantly different with somatropin-treated patients (-9.3 vs 0.2%; *P*=0.0004). In the somatropin group, there were significant changes at 24 weeks compared to baseline in TC (-0.3 mmol/L; *P*<0.05), LDL-C (-0.36 mmol/L; *P*<0.05), and non-esterified fatty acids (0.1 mEq/L; *P*<0.05). There were no significant changes in HDL-C, TG or phospholipids. In the placebo group, there were no significant changes in any of the serum lipid profiles. When compared to placebo, only the change in TC was significantly different (*P*=0.039). At week 24, there was a significant increase in mean serum IGF-1 levels with somatropin-treated patients compared to baseline (*P*<0.05). The increase in IGF-1 with placebo-treated patients was not significant. The mean change in IGF-1 in the somatropin group was significantly greater than the placebo group (161.9 vs 4.2 µg/L; *P*<0.0001). The mean change from baseline in IGFBP-3 for the somatropin-treated patients was significantly greater than placebo treated patients (1.0 vs 0.1 mg/mL; *P*<0.0001). At 24 weeks, all symptoms were reduced from baseline in both treatment groups; however, no statistical analysis was performed. Compared to baseline, quality of life parameters were improved at 24 weeks; though, there were no significant differences between the somatropin and

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				placebo groups. The change in QoL-AGHDA was not significantly different between the groups (*P*=0.5588). The proportion of patients experiencing adverse events was similar between groups. The most common adverse events associated with somatropin were edema (21.6%), arthralgia (10.8%) and muscle weakness (10.8%). The most common adverse events associated with treatment with placebo were emotional liability (8.3%) and hypertonia (5.6%).
Mauras et al[86] Somatropin (Genotropin®) 0.14 mg/kg/week divided in 6 or 7 weekly doses vs placebo	DB, MC, PC, RCT Patients with a diagnosis of childhood-onset GHD treated with GH with an average dose of 0.3 mg/kg/week or 42 µg/kg/day for 3 years prior to study, persistent GHD (defined as peak GH response to insulin tolerance test <5 µg/L), achieved final height and fully pubertal	N=58 24 months	Primary: Effect of somatropin on body composition, BMD, safety Secondary: Effect of somatropin on plasma lipids, IGF-1, carbohydrate metabolism, cardiac function, exercise tolerance and quality of life	Primary: At 24 months, there were no statistically significant differences between somatropin and placebo in change in weight and BMI (*P* values not reported). At 24 months, there were no significant differences in changes in percent body fat and percent LBM (*P*=0.448 and *P*=0.437). There were no significant differences between the groups in spine and whole body BMD at 24 months (-0.29 vs -1.08; *P*=0.086 and (0.59 vs 0.13; *P*=0.267, respectively). The rates of reported adverse events were similar between the groups (92% for somatropin and 87% for placebo). Secondary: At 24 months, there were no significant differences in fasting glucose, insulin resistance and insulin sensitivity between the groups (data not reported). Also, there were no significant differences in lipid endpoints between the groups (data not reported). The median IGF-1 was significantly higher in the somatropin-treated patients compared to the placebo treated patients (326 vs 141 ng/mL; *P*<0.03). At 24 months, the change in left ventricular systolic function as measured by the shortening fraction was not significantly different between the somatropin and placebo groups (*P*=0.345). There were no significant differences in LVM at 24 months across the groups. There was no significant difference in IRT at month 24 (*P*=0.318).The E/A ratio was not significantly different between the groups (*P*=0.749).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				At 24 months, the change in mean treadmill exercise tolerance was not significantly different between the groups. The proportion of patients that decreased exercise tolerance was similar between the groups (47% with somatropin vs 38% with placebo). There was no significant difference in the change of quality of life scores between the somatropin and placebo groups at 24 months.
McGauley et al[87] Somatropin (Genotropin®) 0.07 IU/kg/day SC vs placebo	DB, PC, RCT Patients 18 to 55 years of age with GHD for at least 12 months	N=24 6 months	Primary: Changes in NHP, PGWB and GHQ scores Secondary: Not reported	Primary: At baseline and one month of study, there was no significant difference in the NHP scores between the somatropin and placebo groups. At six months, patients in the somatropin group had a significantly lower NHP score, indicating a greater improvement in perceived quality of life, compared to those in the placebo group (2.5±1.2 vs 8.2±1.5; *P*<0.01). Subgroup analysis showed that patients in the somatropin group also had significantly higher perceived energy level compared to patients in the placebo group (2.18±2.2 vs 21.8 ±6.7; *P*=0.015). With regard to PGWB scores, which assessed self-perceived emotional states, there were no differences between the two groups at baseline, one or six months. Subgroup analysis showed greater improvement in mood with somatropin compared to placebo at six months (14.4±0.4 vs 12.3±0.5; *P*=0.015). Patients in the somatropin group had a greater reduction in psychological distress, measured by GHQ scores, compared to those in the placebo group at six months (data and *P* value not reported). Secondary: Not reported
Cuneo et al[88] Somatropin (Genotropin®) 0.07 IU/kg/day SC vs	DB, PC, RCT Patients between 18 and 52 years of age with GHD for at	N=24 6 months	Primary: Changes in TC, TG, HDL-C, LDL-C, apo A-1 and apo B	Primary: Treatment with somatropin was associated with a significant decrease in TC, LDL-C and apo B compared to treatment with placebo. TC decreased 12% from 5.8±0.3 mmol/L at baseline to 5.1±0.3 mmol/L at six months with somatropin and remained at 5.3±0.3 mmol/L throughout the study

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo	least 12 months		Secondary: Not reported	with placebo (*P*=0.01). TG increased in the somatropin group from baseline at six months (1.74±0.42 to 1.91±0.41 mmol/L), compared to a decrease from 2.34±0.55 to 1.93±0.47 mmol/L in the placebo group (*P*>0.05). The changes were not statistically significant when compared to baseline. There was no significant difference between the two groups with regard to changes in HDL. Treatment with somatropin led to a 32% decrease in LDL from 4.22±0.25 to 3.19±0.23 mmol/L at six months, compared to an increase from 3.98±0.33 to 4.25±0.28 mmol/L (*P*=0.0003). Serum apo B levels decreased by 37% from 1.07±0.06 to 0.84±0.07 g/L with somatropin and increased from 0.96±0.07 to 1.11±0.07 with placebo (*P*=0.003) Secondary: Not reported
Drake et al[89] Somatropin (Genotropin®) 0.35 IU/kg/week or no treatment	MC, RCT Adolescent patients with a mean age of 17.0±1.4 years who had childhood-onset GHD and had been receiving GH treatment with a height velocity of <2 cm/year	N=24 12 months	Primary: Total BMC, lumbar spine BMD, serum bone-specific alkaline phosphatase, IGF-1 Secondary: Not reported	Primary: The median percentage increase in total BMC was 3.8% with somatropin and 1.9% with no treatment at six months (*P*=0.085) and 6.1 and 2.4% with somatropin and no treatment, respectively, at 12 months (*P*=0.074). When excluding an outlier in the untreated group whose total BMC declined by 25%, the difference in the mean increase in total BMC with somatropin compared to no treatment was 1.7% at six months (95% CI, -0.5 to 4.0; *P*=0.14) and 2.9% at 12 months (95% CI, 0.1 to 5.7; *P*=0.043). When compared to baseline, there were no significant changes in the untreated group at six and 12 months (*P*=0.63 and 0.85; respectively), whereas BMC increased significantly at both six and 12 months compared to baseline (*P*<0.001 for both). There was no significant difference between the somatropin and untreated groups in the percentage change in lumbar spine BMD at six months (2.3 ad 1.7%; *P*=0.84) or at 12 months (4.7 and 2.3%; *P*=0.45). When compared to baseline, patients in the somatropin group led to significant increase in lumbar

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				spine BMD at 12 months (*P*=0.012) while the increase in the untreated group was nonsignificant (*P*=0.15). Serum bone-specific alkaline phosphatase was significantly higher in the somatropin group compared to the untreated group at six months (71.0 vs 44.5 IU/L; *P*=0.019) but not at 12 months (51 vs 44 IU/L; *P*=0.56). In the somatropin group, there were no significant changes in serum IGF-1 levels throughout the study. In the untreated group, however, serum IGF-1 levels decreased significantly from baseline at six months (*P*<0.001) with no further significant changes afterwards (data not reported). Secondary: Not reported
Weaver et al[90] Somatropin (Genotropin®) 0.125 IU/kg/day for 1 month, followed by somatropin (Genotropin®) 0.25 IU/kg/day vs placebo	DB, PC, RCT (6 months) followed by OL (6 months Patients with GHD for ≥2 years	N=22 12 months	Primary: Regional fat distribution, metabolic and cardiac risk factors Secondary: Not reported	Primary: Somatropin-treated patients had a significant reduction to total body fat (*P*<0.01) and percent body fat (*P*=0.03). There were significant increases in BMI (*P*<0.01) and body weight (*P*<0.01) in the somatropin group. There were no significant changes in wait-to-hip ratio and central fat. In the somatropin group, there was a significant reduction in insulin sensitivity (*P*=0.004) and a significant rises in fasting plasma insulin (*P*=0.005) and fasting plasma glucose concentrations (*P*=0.014). There was no change in HbA1c. In the placebo group, plasma glucose had a significant increase (*P*=0.005), but no other parameters has significant changes. After six months of somatropin treatment for all patients, there were significant reductions in total fat (*P*=0.01), percent fat (*P*=0.002), waist-to-hip ratio (*P*=0.05), central fat (*P*=0.01), cholesterol (*P*=0.03) and insulin sensitivity (*P*=0.0002). There were significant increases in fasting total insulin (*P*=0.016), specific insulin (*P*=0.002) and fasting plasma glucose (*P*=0.001). There were no significant changes in body weight, BMI, HbA1c and TG. Secondary: Not reported

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Newman et al[91] Somatropin (Humatrope®) 6.25 µg/kg/day for 1 month, followed by somatropin (Humatrope®) 12.5 µg/kg/day vs placebo	DB, RCT (6 months) OL (12 months) Patients 21 to 71 years of age with documented GHD on stable hormonal replacement regimen and able to walk 3 minutes at low speed on a horizontal treadmill	N=30 18 months	Primary: Change from baseline in exercise duration, VO_2max and LVEF at rest and after exercise Secondary: Peak work double product, left ventricular fractional shortening, LVM and wall thickness parameters and echocardio-graphic indices of diastolic function	Primary: At six months, there were no statistically significant differences between somatropin- and placebo-treated patients in exercise duration (*P*=0.25), VO_2max (*P*=0.12) and LVEF at rest (*P*=0.62) and after exercise (*P*=0.86). There were no significant differences at 18 months in primary cardiac endpoints (*P* values not reported). Secondary: At six months, there were no statistically significant differences in secondary endpoints between treatment groups (*P*>0.5). There were no significant differences at 18 months in secondary cardiac endpoints (*P* values not reported).
Snyder et al[92] Somatropin (Humatrope®) 2 µg/kg/day, increased to a maximum of 12 µg/kg/day vs placebo	DB, MC, PC, RCT Patients ≥21 years of age with GHD caused by hypopituitarism, from known pituitary or hypothalamic disease, acquired in adulthood for at least 2 years	N=67 24 months	Primary: Change from baseline in BMD of lumbar spine at six, 12, 18 and 24 months Secondary: Change from baseline in BMD of hip and total body composition at six, 12, 18 and	Primary: Compared to baseline, there were significant increases in BMD of the spine with the somatropin-treated patients at months 12 (*P*=0.031), 18 (*P*=0.014) and 24 (*P*<0.001). Month 24 was the only time point at which the increase from baseline in BMD of the spine was significantly greater with somatropin compared to placebo (*P*=0.037). Secondary: At month 24, there was a significant increase from baseline in total hip BMD with somatropin (*P*<0.05). There were no significant differences in total hip BMD between patients treated with somatropin and placebo at any time points. There was a significant decrease in trunk fat mass with somatropin compared

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			24 months	to placebo at months 12 (P<0.03) and 24 (P<0.03).There were no significant differences between the groups in increase of trunk lean mass.
Chihara et al[93] Somatropin (Humatrope®) 0.021 mg/kg/day for 4 weeks, increased stepwise to 0.042 mg/kg/day for 8 weeks then increased to 0.084 mg/kg/day for 12 weeks vs placebo	DB, MC, PC, RCT Patients 18 to 64 years of age with organic or idiopathic, isolated or multiple, childhood- or adult-onset GHD of ≥2 years	N=64 24 weeks	Primary: Change from baseline in body composition, IGF-1, IGFBP-3 and lipid levels; safety Secondary: Not reported	Primary: At 24 weeks, there was a significant increase in LBM with somatropin-treated patients (P<0.001), but a nonsignificant decrease with placebo treated patients. The change in LBM was significantly different comparing somatropin- and placebo-treated patients (4.7±3.9 vs -0.5±4.1%; P<0.001). There was a significant decrease in fat mass compared to a nonsignificant increase with placebo (-9.2±11.8 vs 1.1±6.9%; P<0.001). Serum IGF-1 significantly increased in the somatropin group (P<0.001), while there was a nonsignificant decrease in the placebo group. At 24 weeks, TC significantly decreased with somatropin (P=0.025) and did not significantly change with placebo. The difference between somatropin-treated and placebo-treated patients in change from baseline was significant (-14±34 vs 7±39 mg/dL; P=0.036). The change from baseline in LDL-C was not significant in either group; however, the difference between groups was significant (-7±27 vs 9±27 mg/dL; P=0.04). There were no significant differences in HDL-C and TG. Treatment emergent adverse events of musculoskeletal and connective tissue disorders were reported at a significantly higher rate in the somatropin group compared to the placebo group (P=0.016).There was a nonsignificant higher rate of edema with somatropin compared to placebo. Secondary: Not reported
Chipman et al[94] Somatropin (Humatrope®) 6.25 µg/kg/day for 1 month, followed by somatropin (Humatrope®) 12.5 µg/kg/day vs	DB, PC, RCT (6 months) OL (12 months) Patients diagnosed with adult or	N=165 18 months	Primary: Safety Secondary: Not reported	Primary: There were no significant differences in discontinuation rates between somatropin and placebo-treat patients with either adult-onset or childhood-onset GHD. During the DB phase, there were statistically higher incidences of edema and peripheral edema in the adult-onset GHD group treated with somatropin compared to the placebo group (P=0.043 and P=0.017). Somatropin-related

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo	childhood GHD based on pharmacological stimulation test and on stable treatment with other pituitary controlled hormones			adverse events were reported more often in adult-onset patients compared to childhood-set patients. Compared to placebo, adult-onset and childhood-onset patients had significant increases in fasting glucose (*P*=0.002 and *P*=0.048). During the 18 months of the trial, 14 serious adverse events were reported with adult-onset patients and three were possibly related to somatropin therapy (carpal tunnel syndrome and lymphoedema). When compared to the DB phase, there was an increase in the incidence of arthralgia, myalgia and paresthesia in the adult-onset patients (statistically analysis not completed). Hypertension was reported in 7.7% of adult-onset patients. There was no hypertension reported in the childhood-onset patients. At six months, there was a significant decrease in mean SBP in childhood-onset patients compared to baseline (*P*=0.006). There were no significant differences from baseline in SBP at other time points or in other treatment groups. There were no significant changes from baseline in fasting glucose and HbA1c at 18 months in either the adult-onset or childhood onset patients. Secondary: Not reported
Conway et al[95] Somatropin (Norditropin®) 0.2 mg/day, increased to 0.6 mg/day at 1 month, increased to 1.0 mg/day at 3 months until end of trial (males) and 0.4 mg/day, increased to 0.9 mg/day at 1 month, increased to 1.4 mg/day at 3 months until end of trial (females) vs no treatment	MC, OL, RCT Patients 18 to 25 years of age with BMI 10 to 30 kg/m^2 diagnosed with GHD during childhood and 3 or more pituitary hormone deficiencies or a provocative GH test after their 16th birthday	N=160 24 months	Primary: Change from baseline in BMD at 24 months Secondary: Effect of GH treatment on markers of bone metabolism, IGF-1 and IGFBP-3; safety	Primary: At 24 months, there was a significantly greater increase in lumbar spine BMD with somatropin compared to control (estimated treatment difference, 3.5%; 95% CI, 1.5 to 5.5; *P*<0.001). The increase in total hip BMD was significantly greater with somatropin compared to control (*P*=0.05). The change from baseline was not significantly different between the groups for total body BMD (*P*=0.315). Secondary: At 24 months, the difference in mean alkaline phosphatase levels between somatropin-treated patients and control was statistically significant (estimated treatment difference, 12 IU/L; 95% CI, 2.65 to 21.35; *P*=0.012). At 24 months, serum IGF-1 levels were significantly higher in the somatropin group compared to the controls (*P*<0.0001). Mean IGFBP-3 at 24 months was significantly higher in the somatropin treated patients (*P*<0.0001). Adverse effects were similar between somatropin and the controls.

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Rosenfalck et al[96] Somatropin (Norditropin®), dose gradually increased to target of 2 IU/m^2/day vs placebo	DB, PC, RCT Patients with known pituitary pathology and either childhood or adult onset GHD for ≥1 year on adequate substitution of hormonal deficiencies for ≥1 year	N=24 4 months	Primary: Effect of somatropin on body composition, insulin action, non-insulin-mediated glucose uptake and pancreatic β-cell function Secondary: Not reported	Primary: At baseline, patients in the somatropin group had significantly higher body weights compared to patients in the placebo group (P<0.05). At four months, the somatropin-treated patients had significant decreases in body weight (1.6 kg; P<0.05) and fat mass (4.3 kg; P<0.001) and increase in LBM (2.7; P<0.01). There were no significant changes in body composition with placebo treated patients. In placebo-treated patients, there were no significant changes in blood glucose area under the curve after four months. In the somatropin group, fasting blood glucose, insulin, proinsulin and C-peptide significantly increased (P=0.05; P=0.02; P=0.03; P value not reported, respectively). Insulin sensitivity deteriorated significantly in the somatropin-treated patients (P<0.003). The first phase insulin response increased significantly with somatropin-treated patients (P<0.04). There were no significant changes in the placebo-treated patients in insulin sensitivity and first phase insulin response. When compared to placebo, the changes in blood glucose, insulin and insulin sensitivity were significantly different with somatropin (P values not reported). Secondary: Not reported
Burman et al[97] Somatropin (Norditropin®) 0.5 U/m^2/day for 2 weeks, followed by somatropin (Norditropin®) 1.0 U/m^2/day for 4 weeks, followed by somatropin (Norditropin®) then 2.0 U/m^2/day for 9 months vs placebo There was a 3 month washout	DB, PC, XO Men and women with GHD and adequate replacement of other hormone deficiencies	N=36 21 months	Primary: Differences by gender in effects of somatropin on IGF-1, body composition, cardiovascular, morbidity and bone metabolism Secondary: Not reported	Primary: There were significant increases in IGF-1 levels from baseline in both men and women (P=0.0001 and P=0.0007). The increase was significantly greater in men compared to women (P=0.02). There were significant decreases in percent total body fat in men and women (P=0.0001 and P=0.002). The decrease was significantly greater with men compared to women (7.4±4.1 vs 3.3±3.8%; P=0.002). There were significantly greater decreases in abdominal fat mass and fat mass of the upper extremities in men compared to women (P=0.003 for both). The difference in reduction of fat mass between men and women was not significant (P=0.09). The increase in LBM was significant for each group compared to baseline (P<0.001 for both), but the between group difference was not significant (P value not reported). There was no significant difference in total body weight compared to baseline in either group (P value not significant).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
between treatment periods.				There were significant decreases in total serum cholesterol, LDL-C and apo B in men (*P*=0.008; *P*=0.03; *P*=0.0009, respectively). There were no significant changes in these variables in women. Both men and women did not have significant differences in HDL-C and apo A1. There was a significant decrease in LDL/HDL ratio in men (*P*<0.05), but not women. Men and women had significant increases in Lp(a) compared to baseline (*P*<0.01 for both). TG was not significantly different from baseline in men or women. The serum activity of plasminogen activator inhibitor 1 decreased significantly compared to baseline in men (*P*=0.01), but not in women. Serum concentrations of fibrinogen, factor VII and β-thromboglobulin did not differ significantly from baseline in men or women. The serum concentration of osteocalcin, carboxyl-terminal propeptide of type I procollagen level in serum, serum activity of bone-specific alkaline phosphatase, serum level of carboxyl-terminal cross-linked telopeptide of type I collagen in men (*P*=0.0001; *P*=0.0001; *P*=0.0001; *P*=0.0001, respectively). These variables also increased significantly in women (*P*=0.001; *P*=0.0007; *P*=0.0015; *P*=0.0007, respectively). There were no significant differences between the groups. Secondary: Not reported
Chihara et al[98] Somatropin (Norditropin®) 0.003 mg/kg/day for 4 weeks, 0.006 mg/kg/day for 4 weeks, 0.012 mg/kg/day for 16 weeks vs placebo After 24 weeks patients	DB, PC, PG, RCT (24 weeks) OL (48 weeks Patients with GHD with appropriate replacement for other hormones for ≥6 months	N=121 (RCT) N=118 (OL) 72 weeks	Primary: Change from baseline in mean percent trunk fat Secondary: Not reported	Primary: After the 24 week, DB phase, there was a reduction in trunk fat with somatropin and an increase with placebo compared to baseline. The difference between somatropin and placebo was statistically significant (difference in mean percent change, -17.82%; 95% CI, -22.90 to -12.74; *P*<0.0001). The differences in percent total fat mass and percent LBM was significantly greater with somatropin compared to placebo (*P*<0.0001). After 24 weeks, there were reductions in TC and LDL-C with somatropin, but not placebo. The difference in change from baseline in TC was statistically significant comparing somatropin and placebo (difference in mean change, -16.6 mg/dL; 95% CI, -27.9 to -5.3; *P*<0.004). The change from baseline in

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
entered 48-week, OL trial and received either a fixed dose of 0.003 mg/kg/day for 4 weeks, 0.006 mg/kg/day for 8 weeks, then 0.012 mg/kg/day or an individualized dose based on IGF-1 serum levels and adverse effects with a range of 0.1 mg/kg/day to 1 mg/kg/day.				LDL-C was significantly greater with somatropin compared to placebo (*P*=0.009). There were no significant differences in HDL-C and TG. In the 48-week OL study, the reduction in percent trunk fat compared to baseline was not significantly different with the fixed dose or individualized dose (difference in mean percent change, 1.23%; 95% CI, -7.03 to 9.48; *P*=0.768). The changes in percent total fat mass and percent LBM were not significantly different comparing the fixed dose and individualized dose groups (*P*=0.577 and *P*=0.577). After the 48 week trial, there were no significant between group differences in TC, LDL-C and TG. There was a decrease in HDL-C in the individualized dose group and an increase in the fixed dose group; the between group difference was statistically significant (*P*=0.002). Secondary: Not reported
Sesmilo et al[99] Somatropin (Nutropin®) 10 µg/kg/day vs placebo	PC, RCT Men 24 to 64 years of age with normal growth and development; benign sellar neoplasm, pituitary apoplexy or idiopathic hypopituitarism diagnosed after 18 years of age; peak GH level <5 µg/L after two pharmacologic stimuli	N=49 18 months	Primary: Changes in IL-6, CRP, amyloid polypeptide A measurements; anthro-pomorphic, nutritional and fat distribution evaluations; IGF-1, glucose, insulin, lipids and HbA1c values Secondary: Not reported	Primary: Compared to placebo, CRP decreased significantly with long-term (months six to 18) somatropin (net difference, -1.9; 95% CI, -3.1 to -0.7; *P*=0.0027). IL-6 levels also decreased significantly with somatropin compared to placebo (net difference, -1.32; 95% CI, -2.33 to -0.3; *P*=0.013). There was no significant differences between groups in changes of serum amyloid polypeptide A (net difference, -2.4; 95% CI, -4.8 to 0.06; *P*=0.056). Changes in weight, BMI, percentage of IBW, waist-to-hip ratio, and nutrient intake did not differ between the somatropin and placebo groups at any time point. With long-term treatment (months six to 18), there was a significant decrease in truncal-to-total fat ratio with somatropin compared to placebo (-0.014±0.004 vs 0.004±0.005; *P*=0.0087). There was no significant difference in truncal fat-to-extremity ratio between the groups (*P*=0.052). There was a significant short-term effect (months one and three) with somatropin compared to placebo on lipids. Compared to placebo, there were significant decreases in TC (net difference, -0.86; 95% CI, -1.2 to -0.5; *P*<0.001), LDL-C (net difference, -0.63; 95% CI, -0.94 to -0.33; *P*<0.001) and

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				TC-to-HDL-C ratio (net difference, -0.56; 95% CI, -1.1 to -0.03; *P*<0.040). There were no between group differences in HDL-C or TG. Also, there were no significant differences between groups in long-term effect on lipids. Lp(a) levels increased significantly with long-term somatropin compared to placebo (net difference, 22.0; 95% CI, 5.7 to 38.2; *P*<0.001). There was a significant increase in glucose, insulin levels and insulin-to-glucose ratios with short-term somatropin compared to placebo (net difference, 0.54; 95% CI, 0.21 to 0.86; *P*=0.0018, net difference, 37.9; 95% CI, 18.5 to 57.3; *P*<0.001, net difference, 6.01; 95% CI, 2.28 to 9.74; *P*=0.0025, respectively). The significant difference was maintained with long-term somatropin compared to placebo for glucose levels (net difference, 0.56; 95% CI, 0.21 to 0.90; *P*=0.0026), but not insulin levels or insulin-to-glucose ratios. There were no significant differences between groups in HbA1c. Secondary: Not reported
Hoffman et al[100] Somatropin 0.0125 mg/kg/day for 1 month, followed by somatropin 0.025 mg/kg/day as tolerated vs placebo	DB, MC, PC, RCT Patients 18 to 70 years of age with adult GHD as a result of hypothalamic-pituitary disease acquired ≥18 years of age, no previous therapy with GH and no change in glucocorticoid, thyroid hormone or gonadal hormone replacement	N=171 12 months	Primary: Reduction in the proportion of body fat, increase in muscle strength, improved quality of life Secondary: IGF-1 SDS, anthropomorphic measurements, BMD, laboratory evaluations	Primary: At 12 months, mean body weight and BMI did not significantly change from baseline. In the somatropin group, there were significant decreases in total body and trunk fat and significant increase in total LBM compared to baseline and the placebo group (*P*<0.0001). Men experienced a significantly greater reduction of in trunk fat compared to woman (*P*<0.04). At 12 months, there was no significant change in strength and endurance with somatropin-treated patients. Additionally, there was no significant change in quality of life measurements. Secondary: At 12 months, the mean IGF-1 SDS increased significantly with somatropin-treated patients compared to baseline (*P*<0.0001). At month 12, there were no significant changes from baseline or between the groups in anthropomorphic measurements. There were no significant changes in BMD for the somatropin-treated or

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	therapy within 2 months before study			placebo-treated patients. In somatropin-treated patients, there was a significant decrease in LDL-C compared to baseline and placebo-treated patients (*P* value not reported). LDL-C/HDL-C ratio decreased significantly in somatropin-treated patients (*P*<0.05).
Thoren et al (abstract)[101] GH 0.125 IU/kg/week for 1 month, followed by GH 0.25 IU/kg/week vs placebo	RCT Patients 22 to 65 years of age with pituitary insufficiency	N=20 6 months	Primary: BMD Secondary: Not reported	Primary: At six months, there was no change in the lumbar spine BMD in the GH-treated patients, but there was a significant decrease in the femoral neck BMD (*P*<0.05). Secondary; Not reported
Chihara et al (abstract)[102] GH 0.012 mg/kg/day vs placebo	DB, PC, RCT Patients (mean age 37 years) with GHD	N=61 24 weeks	Primary: Change from baseline in trunk fat Secondary: Not reported	Primary: At 24 weeks, there was a -3.4±0.6% change in trunk fat in the GH-treated patients compared to 0.4±0.6% in the placebo treated patients (*P*<0.001). Secondary: Not reported
Salomon et al (abstract)[103] GH 0.07 U/kg/day vs placebo	DB, PC, RCT Patients with GHD receiving appropriate thyroid, adrenal and gonadal hormone replacement	N=24 6 months	Primary: Effect of GH on IGF-1, body composition, metabolic rate, cholesterol and TG Secondary: Not reported	Primary: At six months, there was a mean increase of IGF-1 from 0.41±0.05 to 1.53±0.16 in patients treated with GH. There was no effect of GH on body weight. In GH-treated patients, LBM significantly increased (5.5±1.1 kg; *P*<0.0001) and fat mass significantly decreased (5.7±0.9 kg; *P*<0.0001), but there were no significant changes in placebo-treated patients after six months. Basal metabolic rate increased significantly at six months compared to baseline in the GH-treated patients (34.4±1.6 kcal/kg of LBM; *P*<0.001). Fasting plasma cholesterol levels were lower in the GH-treated patients compared to placebo treated patients (*P*<0.05). TG levels were similar

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				between the groups. Secondary: Not reported
Arwert et al[104] GH SC daily at doses adjusted to serum IGF-1 levels normal for age ±5 SD vs placebo	DB, PC, RCT Adults with a mean age of 27.3±6.9 years who had childhood-onset GHD	N=13 6 months	Primary: Changes in scores of the following neuro-psychological tests: POMS depression, anger, fatigue, vigor and tension, digit span forward, digit span backward, associated learning task, associated learning recognition task, number of mistakes on DNMTS task and reaction time on DNMTS task; changes in functional MRI images; IGF-1; IGFBP-3 Secondary: Not reported	Primary: At six months, an improvement in POMS vigor score was seen in patients treated with placebo but not in patients treated with GH (*P*>0.05). Scores of POMS depression, anger, fatigue and tension improved in both the GH and placebo groups; however, improvement in these scores was not significantly different when comparing GH to placebo. There was no significant difference between the two groups with regard to changes in short-term memory measured by digit span forward, digit span backward and associated learning task scores. In the GH group, the digit span forward score improved slightly from 7.2±1.1 at baseline to 7.8±1.3 at six months and from 6.0±1.0 to 7.1±1.1 in the placebo group (*P*>0.05). The digit span backward score also improved slightly from 6.4±0.9 at baseline to 6.6±1.4 at six months with GH and from 4.9±1.7 to 5.7±1.6 with placebo (*P*>0.05). The score of associated learning task improved from 22.4±3.4 at baseline to 23.2±3.9 at six months in the GH group but decreased from 19.0±2.9 to 17.6±5.8 in the placebo group (*P*>0.05). Long term memory, measured by associated learning recognition task, significantly improved with GH compared to placebo. The score of associated learning recognition task improved from 8.4±0.9 at baseline to 9.0±0.0 at six months with GH but decreased from 6.9±2.2 to 5.3±2.2 with placebo (*P*=0.004). Improvement in verbal recognition memory, measured by DNMTS task, was seen with GH but not with placebo. In the GH group, the number of mistakes on DNMTS task was reduced from 1.2±1.6 at baseline to zero to six months, compared to the placebo group in which the number increased from 1.0+1.3 to 1.1±1.4 (*P*=0.045). The reaction time on DNMTS task also decreased from 1.5±0.3 to 1.2±0.1 seconds with GH and changed from 1.5±0.4 to 1.5±0.4 seconds with placebo (*P*=0.055).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				On functional MRI, decreased activation in the ventrolateral prefrontal cortex was seen in patients receiving GH at six months compared to patients receiving placebo, indicating decreased effort and more efficient recruitment of the neural system. Serum IGF-1 and IGFBP-3 levels both significantly increased at six months in patients receiving GH compared to patients receiving placebo. Serum IGF-1 levels increased from 9.8±4.4 to 30.0±6.6 nmol/L with GH and from 7.6±2.8 to 6.5±2.2 with placebo (*P*<0.005). Serum IGFBP-3 levels increased from 2.9±0.6 to 4.3±0.7 mg/L with GH and from 2.6±0.5 to 2.7±0.6 mg/L with placebo (*P*<0.005). Secondary: Not reported
Russell-Jones et al[105] GH 0.018 IU/kg/day SC for 1 month, followed by GH 0.036 IU/kg/day SC for 1 month vs placebo	DB, PC, RCT Adult patients with severe GHD	N=18 2 months	Primary: Changes in TC, TG, HDL-C, LDL-C, apo A1, apo B, Lp(a), mevalonic acid, lathosterol, fasting serum insulin and IGF-1 levels Secondary: Not reported	Primary: Compared to placebo, somatropin was associated with significant decrease in TC (*P*<0.01), LDL-C (*P*<0.03) and apo B (*P*<0.01). In the somatropin group, TC decreased from 6.44±0.49 mmol/L at baseline to 5.71±0.48 mmol/L at two months, compared to the slight decrease from 5.76±0.35 to 5.57±0.44 mmol/L in the placebo group (*P*<0.01). A significant reduction in LDL-C from 4.259±0.49 to 3.62±0.44 mmol/L was seen in the somatropin group, compared to a change from 3.62±0.33 to 3.58±0.41 mmol/L in the placebo group (*P*<0.03). Apo B significantly decreased from 1.30±0.11 to 1.15±0.11 g/L with somatropin compared to a slight decrease from 1.12±0.05 to 1.09±0.06 g/L with placebo (*P*<0.01). There was a significant reduction in mevalonic acid in the somatropin group compared to the placebo group (*P*<0.03). Fasting serum insulin and IGF-1 levels increased significantly in the somatropin group compared to the placebo group (*P*<0.02 and <0.01, respectively). No significant differences were seen in TG, HDL-C, apo A1, Lp(a) and lathosterol between the two groups.

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				Secondary: Not reported
Verhelst et al[106] Somatropin (Genotropin®) 0.125 IU/kg/week SC daily for 1 month, followed by somatropin (Genotropin®) 0.25 IU/kg/week; maximum 4 IU/day vs placebo for 6 months followed by somatropin (Genotropin®) 0.125 IU/kg/week SC daily for 1 month, followed by somatropin (Genotropin®) 0.25 IU/kg/week; maximum 4 IU/day	DB, ES, MC, OL, PC, RCT Adults patients between 20 and 60 years of age with GHD for at least 24 months and who had not received GH in the previous 12 months	N=148 24 months (DB, PC for 6 months followed by OL for 18 months)	Primary: Changes in body composition, body weight, waist-to-hip ratio, NHP scores, number of sick days, hospitalization rate, IGF-1 levels, safety Secondary: Not reported	Primary: Body composition did not change significantly in the placebo group during the DB phase. After three months of treatment with somatropin, there was significant improvement in body position parameters compared to baseline (P<0.001 for all parameters). The beneficial effects maintained during the first 12 months and declined slightly after 24 months but still remained significantly different compared to baseline. LBM increased from baseline by 2.85±4.63 kg at three months and 2.19±5.14 kg at 24 months. Total body water increased by 1.88±3.53 kg at three months and 1.33±3.84 kg at 24 months. Body fat decreased by 2.51±4.56 kg at three months and 1.48±5.44 kg at 24 months (P<0.001 for all parameters). Total body weight did not change significantly during placebo and somatropin treatment. Waist-to-hip ratio decreased from by 0.01±0.06 at six months (P=0.004) and by 0.02±0.04 at 24 months (P=0.009) compared to baseline. During the DB phase, patients in the somatropin group reported nonsignificantly greater improvement compared to the placebo group in NHP scores in the following categories: emotions, energy, sleep and social isolation. There was a significantly greater improvement in pain with placebo compared to somatropin (P=0.02). The number of sick days during somatropin treatment decreased from 12.17±3.90 days at baseline to 3.30±2.51 days at 24 months, compared to no change with placebo (P=0.026). The hospitalization rate decreased from 14.9 to 7.7% at 24 months (P=0.12) during somatropin treatment and remained unchanged during the placebo phase. Improvement in physical activity, measured by the percentage of patients sitting most of the time, was also seen with somatropin but not during the placebo phase. There were no changes in the number of physician office visits, civil status and social life activities. No change in serum IGF-1 levels was seen in the placebo group during the DB phase. Serum IGF-1 levels increased significantly after 24 months of treatment with somatropin compared to baseline, from -2.0±2.6 to 1.98±2.40

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				SDS (*P*<0.001). More fluid retention-related adverse events were reported in the somatropin group compared to the placebo group during the DB, PC phase (*P*<0.001). Most commonly reported fluid retention-related adverse events were arthralgia, edema and myalgia. After 24 months of treatment with somatropin, a significant reduction from baseline was seen with SBP (-5.33±15.03 mmHg; *P*=0.028) but not with DBP. Fasting plasma glucose rose significantly at 24 months by 0.365±0.855 mmol/L compared to baseline (*P*=0.004). HbA1c was significantly higher compared to baseline at six and 12 months (*P*=0.002 and 0.02, respectively) but was not significantly from baseline at 24 months. Serum free T_4 decreased significantly compared to baseline after six months of somatropin treatment (*P*=0.001) and returned to baseline at 24 months. No significant changes were seen with serum free T_3 with somatropin treatment. Secondary: Not reported
Hwu et al[107] Somatropin (Genotropin®) 0.125 IU/kg/week SC daily for 1 month, followed by somatropin (Genotropin®) 0.25 IU/kg/week for 11 months vs placebo for 6 months followed by somatropin (Genotropin®) 0.125 IU/kg/week SC daily for 1 month, followed by somatropin (Genotropin®) 0.25 IU/kg/week for 5 months	DB, OL, PC, RCT Patients between 20 and 60 years of age with GHD for at least 2 years and due to pituitary tumor, cranio-pharyngioma, Sheehan's syndrome or idiopathic origins and who had not received GH in the previous 12	N=21 12 months (DB, PC for 6 months followed by OL for 6 months)	Primary: Changes in body composition, lipid profile, IGF-1 levels and insulin sensitivity measured by MIST Secondary: Not reported	Primary: At the end of the DB phase, there was a significant reduction in percent fat (-2.9±2.2%) and fat mass (-1.2±1.0 kg) with somatropin compared to placebo (0.1±1.6 and -0.1±0.8, respectively; *P*<0.05 for both). Waist-to-hip ratio decreased nonsignificantly by 0.05±0.05 with somatropin compared to placebo (-0.01±0.03). At the end of the OL phase in which both groups received somatropin, there were no differences in body composition between the two groups. There were no differences in lipid profile between the two groups during the PC phase. At the end of the OL phase, HDL in the somatropin group was significantly higher compared to baseline (28±8 vs 38±9 mg/dL; *P*<0.05). There was a decrease in TC in the placebo group during the PC phase from 215±54 to 179±28 mg/dL and a further decrease to 173±34 mg/dL during the OL phase (*P* values not reported). In the somatropin group, TC decreased slightly from 195±57 to 192±32 mg/dL in the PC phase and increased to 197±48 mg/dL in the OL phase (*P* values not reported). TG decreased by

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	months			15±61 mg/dL at 12 months in the somatropin group and by 1±58 mg/dL in the placebo group (*P* values not reported). LDL decreased by 41±59 mg/dL at 12 months in the placebo group and by 5±53 mg/dL in the somatropin group. Compared to baseline, serum IGF-1 levels increased significantly from baseline at 12 months in both the somatropin (58.7±58.8 vs 188.4±115.8 ng/mL; *P*<0.05) and placebo groups (46.3±29.7 vs 208.1±80.8 ng/mL; *P*<0.05). Normalization of insulin sensitivity was observed after 12 months of treatment with somatropin. Secondary: Not reported
Webster et al[108] Somatropin (Genotropin®) 0.125 IU/kg/week SC daily for 1 month, followed by somatropin (Genotropin®) 0.25 IU/kg/week for 5 months, followed by reinitiating at 0.125 IU/kg/week for 1 month, then 0.25 IU/kg/week for 5 months; maximum 4 IU/day vs placebo for 6 months followed by somatropin (Genotropin®) 0.125 IU/kg/week SC daily for 1 month, followed by somatropin (Genotropin®) 0.25 IU/kg/week for 5 months; maximum 4 IU/day	DB, ES, OL, PC, RCT Patients between 18 and 60 years of age with isolated GHD or hypopituitarism for >24 months and who had not received GH in the previous 12 months	N=18 12 months (DB, PC for 6 months followed by ES, OL for 6 months)	Primary: Changes in lipid profile, Lp(a) and lipoprotein composition Secondary: Changes in BMI, fasting blood glucose, fasting insulin, HbA1c, apo A1 and apo B	Primary: During the DB phase, TC decreased from 6.0±0.4 mmol/L at baseline to 5.2±0.4 mmol/L at six months with somatropin; this change did not reach statistical significance when compared to placebo. Changes in all other primary endpoints were not significantly different between the two groups at six months. In patients who received somatropin for 12 months, TC returned to 5.8±0.3 mmol/L at 12 months, which was not significantly different from baseline. Lp(a) decreased from 103 to 52 mg/L at 12 months, but the change did not reach statistical significance. No significant changes were seen in TG. With regard to Lp composition in the somatropin group, there was a transient decrease in the following LDL compositions: TC, free cholesterol, cholesteryl ester, LDL phospholipids and LDL protein at six months compared to baseline (*P*<0.05); however, these parameters returned to baseline values at 12 months. The composition of HDL, IDL and VLDL did not change significantly throughout the study. Secondary: During the DB phase, fasting plasma glucose increased from 5.0±0.2 mmol/L at baseline to 5.8±0.3 mmol/L at six months in the somatropin group,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				compared an increase from 4.6±0.2 to 4.9±0.2 mmol/L in the placebo group (*P*=0.02). Changes in other secondary endpoints were not significantly different between the two groups. In patients who received somatropin for 12 months, fasting blood glucose continued to be elevated compared to baseline at 12 months (5.70±0.18 mmol/L; *P*=0.036). Fasting insulin was also significantly increased at 12 months compared to baseline (7.8 vs 17.4 mU/L; *P*=0.044). HbA1c transiently increased at six months from 3.7±0.1% at baseline to 4.0±0.1% (*P*=0.014) but returned to 3.40±0.13% at 12 months (*P*>0.05). There were no significant changes in apo A1 and apo B.
Leese et al[109] Somatropin (Genotropin®) 0.125 IU/kg/week SC daily for 1 month, followed by somatropin (Genotropin®) 0.25 IU/kg/week for 5 months, followed by reinitiating at 0.125 IU/kg/week for 1 month, then 0.25 IU/kg/week for 5 months; maximum 4 IU/day vs placebo for 6 months followed by somatropin (Genotropin®) 0.125 IU/kg/week SC daily for 1 month, followed by somatropin (Genotropin®) 0.25 IU/kg/week for 5 months; maximum 4 IU/day	DB, OL, PC, RCT Patients with a mean age of 35.1±2.0 years with GHD for at least 24 months and who had not received GH in the previous 12 months	N=32 12 months (DB, PC for 6 months followed by OL for 6 months)	Primary: Changes in lipid profile and Lp(a) Secondary: Change in IGF-1 levels	Primary: During the six month DB phase, no significant differences were seen between the two groups with regard to lipid profile and Lp(a). Patients in the somatropin group had significantly lower HDL-C compared to baseline (0.97±0.08 mmol/L) at six months (0.76±0.10 mmol/L; *P*<0.01) and 12 months (0.75±0.08; *P*<0.01). In the placebo group, HDL was also lower after somatropin treatment at 12 months (0.59±0.06 mmol/L) compared to baseline (0.92±0.07 mmol/L; *P*<0.01). TC decreased nonsignificantly from baseline in both groups throughout the study. There were no other notable changes in lipid profile and Lp(a) at 12 months. Secondary: During the six month DB phase, IGF-1 levels increased significantly in the somatropin group compared to the placebo group (37.6±4.1 vs 14.0±2.2 mmol/L; *P*<0.01). IGF-1 levels in the placebo group also increased at 12 months after somatropin treatment.
Gomez et al[110] Somatropin (Genotropin®) 0.125 IU/kg/week SC daily for	DB, ES, OL, RCT Patients with a	N=20 24 months (DB, PC for 6	Primary: Changes in lumbar spine and femoral	Primary: There was a significant increase in both lumbar spine and femoral neck BMD Z-score at 24 months compared to baseline. Lumbar spine BMD Z-score increased from -0.3±1.2 at baseline to 0.41±1.33 at 24 months (*P*<0.01).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
1 month, followed by somatropin (Genotropin®) 0.25 IU/kg/week for 23 months vs placebo for 6 months followed by somatropin (Genotropin®) 0.125 IU/kg/week SC daily for 1 month, followed by somatropin (Genotropin®) 0.25 IU/kg/week for 17 months	mean age of 40.3 years with adult-onset GHD for a mean duration of 10.6 years	months followed by OL, ES for 18 months)	neck BMD Secondary: Changes in body composition, IGF-1, IGFBP-3, calcium, phosphate, creatinin, alkaline phosphatase, PTH and osteocalcin	Similarly, femoral neck BMD Z-score increased from -0.56±1.44 to 0.1±1.33 at 24 months (*P*<0.01). Analysis comparing somatropin and placebo was not reported. Twelve months after discontinuation of somatropin, the beneficial effect on lumbar spine and femoral neck BMD was sustained (0.3±1.11 and 0.1±1.1, respectively; *P*<0.01 for both compared to baseline). Secondary: Compared to baseline, there was a significant increase at 24 months in LBM (44.9±8.9 vs 56.1±9.2 kg; *P*<0.01) and total body water (32.7±6.5 vs 39.8±6.2 L; *P*<0.01) as well as a significant decrease in percent body fat (36.2±17.2 vs 20.8±7.9%; *P*<0.01). A significant increase in serum IGF-1 and IGFBP-3 was seen at 24 months. Osteocalcin transiently increased from 20.1±11.6 to 70.9±96.9 ng/mL at 12 months (*P*<0.01) and decreased to 38.9±19.3 ng/mL at 24 months (*P*<0.01). Similarly, serum alkaline phosphatase increased from 1.07±0.32 to 1.46±0.52 µKat/L at 12 months (*P*<0.01) and declined to close to baseline at 24 months (1.1±0.4 µKat/L; *P*<0.01). Serum phosphate was also significantly higher at 24 months compared to baseline (1.09±0.14 vs 1.27±0.16 mmol/L; *P*<0.01). No significant changes were seen in serum calcium, creatinine and PTH.
Holmes et al[111] Somatropin (Genotropin®) 0.125 IU/kg/week SC daily for 1 month, followed by somatropin (Genotropin®) 0.25 IU/kg/week for 11 months vs placebo for 6 months followed by somatropin (Genotropin®) 0.125 IU/kg/week SC daily for 1 month, followed by	DB, OL, PC, RCT Patients with a mean age of 41.5±2.1 years with adult-onset GHD for at least 2 years and who had never received GH treatment	N=22 12 months (DB, PC for 6 months followed by OL for 6 months)	Primary: Changes in vertebral trabecular BMD, forearm cortical and integral BMC and BMD and lumbar spine, femoral neck, trochanteric and Ward's triangle integral BMD	Primary: At six months, patients receiving somatropin had a significant reduction in forearm cortical BMC (-0.015; *P*=0.009), forearm cortical BMD (-0.02 g/cm; *P*=0.005), forearm integral BMD (-0.02 g/cm; *P*=0.009) and femoral neck BMD (-0.034 g/cm; *P*=0.048) compared to patients receiving placebo (0.019, 0.003, -0.005 and -0.008 g/cm^2, respectively). In 21 patients who received at least six months of treatment with somatropin in DB and OL phases, there was a significant reduction from baseline by 0.009 g/cm^2 in forearm cortical BMD (*P*=0.01), by 0.016 g/cm^2 in forearm integral BMD (*P*=0.03*)*, by 0.022 g/cm^2 in lumbar spine BMD (*P*=0.003) and by 0.029 in femoral neck BMD (*P*=0.006). There were no significant changes in other parameters.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
somatropin (Genotropin®) 0.25 IU/kg/week for 5 months			Secondary: Changes in IGF-1, IGFBP-3, alkaline phosphatase and osteocalcin levels	In 13 patients who received 12 months of treatment with somatropin, lumbar spine BMD decreased from 1.176 g/cm^2 at baseline to 1.143 g/cm^2 at 12 months (*P*=0.004) while femoral neck BMD increased from 1.000 to 1.015 g/cm^2 (*P*=0.049). No significant changes were seen in other parameters. Secondary: After six months of treatment with somatropin, there was a significant increase from baseline in serum IGF-1 (135 vs 360 µg/L; *P*=0.0001), IGFBP-3 (4.36 vs 4.65 mg/L; *P*=0.04), alkaline phosphatase levels (67 vs 78 IU/L; *P*=0.003) and osteocalcin (2.5 vs 4.7 µg/L; *P*=0.0003).
Chihara et al[112] Somatropin (Humatrope®) up to 0.084 mg/kg/week SC daily for 24 weeks (fixed-dose regimen), followed by somatropin (Humatrope®) 0.021 mg/kg/week for 8 weeks, then between 0.021 and 0.084 mg/kg/week for 40 weeks; dose adjusted according to serum IGF-1 levels (individualized-dose regimen) (Group A) vs placebo for 24 weeks followed by somatropin (Humatrope®) 0.021 mg/kg/week SC daily for 8 weeks, then between 0.021 and 0.084 mg/kg/week for 40 weeks; dose adjusted according to serum IGF-1 levels (individualized-dose regimen) (Group B)	DB, ES, OL, PC, RCT Patients ≥18 years of age with adult-onset or childhood-onset GHD	N=61 (DB, PC) N=59 (ES, OL) 72 weeks (DB, PC for 24 weeks followed by ES, OL for 48 weeks)	Primary: Changes in LBM, fat mass, TC and LDL; safety Secondary: Dose of somatropin and change in serum IGF-1 SDS	Primary: LBM increased by 4.5±5.3 kg after 48 weeks of individualized-dose regimen in Group B (*P*<0.001 compared to the end of DB phase), which was comparable to the change after 24 weeks of fixed-dose regimen in Group A (4.7±3.9 kg; *P* value not reported). In Group A, a further increase in LBM by 1.2±4.9 kg was seen when transitioning from fixed-dose to individualized-dose regimens (*P* value not reported). In Group B, change in fat mass (-10.5±11.6 kg; *P*<0.001 compared to the end of DB phase) with the 48 week individualized-dose regimen was similar to the change seen with the 24 week fixed-dose regimen in Group A (-9.2±11.8 kg; *P* value not reported). There was a slight increase in fat mass by 0.3±9.7 kg in Group A after converting from fixed-dose to individualized-dose regimens at 72 weeks (*P* value not reported). During the individualized-dose regimen in Group B, TC decreased nonsignificantly from 210±42 mg/dL at 24 weeks to 199±38 mg/dL at 72 weeks (*P*=0.103), whereas LDL-C significantly reduced from 127±34 to 116±38 mg/dL (*P*=0.032). Data from Group A was not reported. The incidence of edema occurred less frequently with the individualized-dose regimen compared to the fixed-dose regimen in Group A (4 vs 0; *P* value not reported). The incidence of other adverse events was comparable between the two regimens. In Group B, no significant changes were seen in SBP and DBP, and there was an increase in HbA1c from 4.5±0.6 to 4.7±0.6%.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Secondary: The mean somatropin doses in both Group A and B with individualized-dose regimen (0.050±0.024 and 0.049±0.026 mg/kg/week, respectively) were lower than that with the fixed-dose regimen in Group A (0.078±0.015 mg/kg/week; *P* value not reported). In Group A, the mean serum IGF-1 SDS at the end of the 24 week fixed-dose regimen was similar to that at the end of 48 week individualized-dose regimen. The number of patients with IGF-1 SDS above normal decreased from six after the fixed-dose regimen to three after the individualized-dose regimen. In Group B, three patients had IGF-1 SDS above normal.
Eden et al[113] Somatropin (Humatrope®) 0.5 IU/kg/week SC daily doses for 6 months, followed by placebo for 6 months vs placebo for 6 months followed by somatropin (Humatrope®) 0.5 IU/kg/week SC daily doses for 6 months	DB, RCT, XO Adult patients with adult-onset GHD who had complete pituitary insufficiency for at least 1 year and had never received GH treatment	N=10 12 months	Primary: Changes in TC, TG, HDL-C, LDL-C, apo A1, apo B, apo E and Lp(a) Secondary: Not reported	Primary: At six weeks of treatment with somatropin, TC significantly decreased from 5.16±1.34 mmol/L at baseline to 4.45±0.75 mmol/L (*P*<0.05) but increased back to 4.97±1.06 mmol/L at six months of treatment, which was not significantly different from baseline. Similarly, LDL-C was reduced significantly with somatropin at six weeks (2.86±0.61 mmol/L) compared to baseline (3.43±1.09 mmol/L; *P*<0.05) and increased to 3.26±0.82 mmol/L at six months, which was not significantly different from baseline. TG nonsignificantly decreased from 1.92±1.14 to 1.59±0.48 mmol/L at six months of treatment with somatropin. At six months, HDL-C increased significantly to 0.99±0.34 mmol/L compared to baseline (0.86±0.33 mmol/L; *P*<0.05). Somatropin was associated with a significant increase in Lp(a) at six weeks (252±152 mg/L; *P*<0.01) and six months (243±152 mg/L; *P*<0.01) compared to baseline (137±113 mg/L). There were no significant changes in apo A1, apo B or apo E during the treatment with somatropin. Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Not reported
Elgzyri et al[114] Somatropin (Humatrope®) 0.017 mg/kg/week SC daily for 1 month, followed by somatropin (Humatrope®) 0.033 mg/kg/week for 5 months, followed by somatropin (Humatrope®) 0.017 mg/kg/week for 1 month, followed by somatropin (Humatrope®) 0.033 mg/kg/week for 11 months vs placebo followed by somatropin (Humatrope®) 0.017 mg/kg/week for 1 month, followed by somatropin (Humatrope®) 0.033 mg/kg/week for 11 months	DB, MC, OL, PC, PG, RCT Patients between 60 and 79 years of age with adult-onset GHD for 0.5 to 40 years and who had never received GH treatment	N=31 18 months (DB, PC for 6 months followed by OL for 12 months)	Primary: Cardiac function measured by echo-cardiography, exercise capacity measured by heart rate, BP and maximum work capacity, IGF-1 levels, TC, TG, HDL-C, LDL-C and HDL-C/LDL-C ratio Secondary: Not reported	Primary: No differences between somatropin and placebo were seen in cardiac function during the DB phase. During the OL phase, with regard to the systolic function, the aortic outflow tract integral decreased from 21.8±0.7 cm at baseline to 20.7±0.8 cm at 12 months (*P*=0.0314) but returned to baseline at 18 months. Similarly, there was a decrease in E-wave from 69±3 to 62±2 cm/second at 12 months (*P*=0.04) and an increase back to baseline at 18 months. No significant changes were seen in the diastolic function or other parameters on echocardiography. At six months, treatment with somatropin led to a significant increase compared to baseline in heart rate at rest (58 vs 67 bpm; *P*=0.029), heart rate at maximum work capacity (142 vs 148 bpm; *P*=0.05) and maximum work capacity (150 vs 160 W; *P*=0.012). During the OL phase, there was a significant increase in heart rate at rest, heart rate at maximum work capacity and maximum work capacity at 12 months (*P*=0.017, 0.005 and 0.014, respectively); however, all three parameters returned to baseline at 18 months. No significant changes were seen in SBP and DBP. Serum IGF-1 levels increased significantly in the somatropin group at six months from 6.9 to 18.5 nmol/L (*P*<0.001). No change was seen in the placebo group during the DB phase but increased from 8.7±0.7 to 18.8±1.6 nmol/L at 18 months (*P*<0.001). TC was significantly reduced from baseline at six months in both the somatropin (5.7 to 5.2 mmol/L; *P*=0.013) and placebo groups (5.8 vs 5.5 mmol/L; *P*=0.02). Similarly, LDL-C decreased significantly from baseline at six months with both somatropin (3.9 to 3.3 mmol/L; *P*=0.013) and placebo (4.0 to 3.6 mml/L; *P*=0.014). There were no significant differences in lipid profiles between the two treatment groups at six months. At 18 months, there was a significant reduction in TC from 5.6 to 5.4 mmol/L (*P*=0.049) and in LDL-C from 3.7 to 3.3 mmol/L (*P*=0.0008). HDL-C significantly increased from 1.2 to 1.4 mmol/L (*P*=0.007) whereas there were no significant changes in TG. Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Not reported
Vahl et al[115] Somatropin (Norditropin®) 2 to 5 IU daily for 12 months (DB), followed by somatropin (Norditropin®) 2 IU daily for 12 months (OL) vs placebo for 12 months (DB), followed by somatropin (Norditropin®) 2 IU daily for 12 months (OL)	DB, OL, PC, PG, RCT Adult patients with a mean age of 20.20±0.65 years who had childhood-onset GHD and had been receiving GH treatment for at least 3 years	N=19 24 months (DB, PC for 12 months followed by OL for 12 months)	Primary: Changes in total body fat, subcutaneous abdominal fat, intra-abdominal fat, muscle and fat of the thigh, LBM, waist-to-hip ratio, isometric quadriceps muscle strength, exercise capacity, GHQ score, IGF-1, IGFBP-1 and IGFBP-3 levels; lipid profile; fasting glucose; serum insulin levels; HbA1c; total T_4 and T_3 and free T_4 and T_3 levels Secondary: Not reported	Primary: Total body fat increased at 12 months (22.68±2.67 kg) compared to baseline in the placebo group (26.49±2.51 kg; *P*=0.01) and subsequently decreased after somatropin treatment at 24 months (21.02±2.57 kg; *P*=0.065 compared to 12 months). The increase in total body fat at 12 months in the placebo group was significantly greater compared to the somatropin group (*P*=0.04). No significant changes were seen in the somatropin group throughout the study (data not reported). Subcutaneous abdominal fat mass increased from 253.71±31.46 cm^2/10 mm at baseline to 318.05±22.69 cm^2/10 mm at 12 months (*P*=0.04) and decreased at 24 months in the placebo group (299.59±34.92 cm^2/10 mm; *P*=0.4). Similarly, compared to baseline, intra-abdominal fat mass slightly increased after 12 months (84.41±20.86 vs 95.66±11.74 cm^2/10 mm; *P*=0.13) and decreased at 24 months in the placebo group (82.27±15.60 cm^2/10 mm; *P*=0.13). No significant changes were seen in the somatropin group with regard to subcutaneous abdominal fat and intra-abdominal fat. Muscle mass of the thigh in patients receiving placebo decreased from 121.3±11.2 cm^2/10 mm at baseline to 118.2±11.7 cm^2/10 mm at 12 months (*P*=0.12) and increased to 130.0±10.9 cm^2/10 mm at 24 months (*P*=0.002). An opposite trend in fat mass of the thigh was observed with the endpoint being 84.1±9.7, 104.9±13.6 and 98.9±16.1 cm^2/10 mm at baseline, 12 months (*P*=0.007) and 24 months (*P*=0.3), respectively. No significant changes were seen in the somatropin group. In the placebo group, LBM remained unchanged at 12 months (50.85±5.88 kg) compared to baseline (52.36±4.86 kg; *P*=0.12) but increased with somatropin treatment at 24 months (60.70±5.59 kg; *P*=0.006). No significant changes were seen in the somatropin group. The waist-to-hip ratio in the placebo group decreased slightly from 0.931±0.06 at baseline to 0.877±0.03 at 12 months (*P*=0.6) and decreased slightly further with somatropin treatment at 24 months (0.837±0.03; *P*=0.12). No significant changes were seen in the somatropin group.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Isometric quadriceps muscle strength and exercise capacity, measured bicycle ergometer, did not change significantly throughout the study with both somatropin and placebo. With regard to the GHQ scores, there was a slight increase from baseline at 12 months in the placebo group (45.1±4.7 vs 50.5±6.9; *P*=0.5) and a decrease at 24 months (38.3±3.5; *P*=0.07), indicating improvement in perceived quality of life after resuming somatropin treatment. There were no significant changes in the somatropin group. In the placebo group, IGF-1 and IGFBP-3 levels decreased significantly from baseline at 12 months (*P*<0.002) and increased significantly at 24 months with somatropin (*P*<0.02). IGFBP-1 decreased significantly from 12 months to 24 months (*P*=0.04). The change in IGF-1 levels at 12 months was significantly different between somatropin and placebo (*P*=0.003). No significant changes were seen with regard to TC in both the somatropin and placebo groups. In the somatropin group, HDL-C remained unchanged from baseline to 12 months (1.27±0.14 vs 1.29±0.30 mmol/L; *P* value not reported) but increased significantly at 24 months compared to 12 months (1.39±0.27 mmol/L; *P*<0.05). HDL-C in the placebo group did not change significantly during the study. In patients receiving somatropin, there was a gradual but nonsignificant decrease of LDL-C throughout the study while TG remained unchanged. In the placebo group, there was a slight but nonsignificant increase from 12 months at 24 months with LDL-C and TG. In the placebo group, fasting glucose decreased from baseline at 12 months (5.1±0.2 vs 4.9±0.2 mmol/L; *P*=0.05) and increased again at 24 months after treatment with somatropin (5.3±0.2 mmol/L; *P*=0.03). No significant changes were seen in the somatropin group.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Similarly, serum insulin levels decreased from baseline at 12 months in the placebo group (100.3±19.9 vs 64.9±8.6 pmol/L; *P*=0.08) and increased at 24 months (131.6±46.0 pmol/L; *P*=0.16). In the somatropin group, serum insulin levels increased gradually throughout 24 months (46.4±6.2, 57.1±14.1 and 66.4±14.2 pmol/L at baseline, 12 months and 24 months; *P*>0.05 for both). The change at 12 months was significantly different between placebo and somatropin (*P*=0.04). HbA1c remained unchanged after 12 months of treatment with placebo (*P*=0.6) but increased at 24 months after resuming somatropin (*P*=0.07). No significant changes were seen in the somatropin group. Total T_3 did not change significantly with either somatropin or placebo. Total T_4 increased significantly in the placebo group at 12 months (166.0±11.3 nmol/L) compared to baseline (149.0±10.5 nmol/L; *P*=0.03) and decreased at 24 months after somatropin treatment (150.0±11.7 nmol/L; *P*=0.09). No significant changes were seen with somatropin. Free T_3 decreased from baseline at 12 months in the placebo group (5.6±0.4 vs 5.0±0.4 pmol/L; *P*=0.02) and increased slightly at 24 months (5.2±0.6 pmol/L; *P*=0.8). No significant changes were seen in the somatropin group. Free T_4 remained unchanged at 12 months compared to baseline and decreased from 23.8±2.6 pmol/L to 19.3±1.6 pmol/L in the placebo group (*P* value not reported). In the somatropin group, free T_4 decreased from 17.1±3.1 pmol/L at 12 months to 14.9±2.7 pmol/L at 24 months (*P* value not reported). Secondary: Not reported
Nolte et al[116] Somatropin (Norditropin®) with a target dose of 2 IU/m^2/day for 24 months	DB, MC, PC, RCT Patients between 18 and 60 years of age	N=38 24 months (DB, PC for 12 months followed by	Primary: Changes in lipid profile and Lp(a) Secondary: Changes in BMI	Primary: Compared to baseline, there was a significant reduction in LDL-C (191 vs 151 mg/dL; *P*<0.001), TC (269 vs 226 mg/dL; *P*<0.001) and TG (214 vs 144 mg/dL; *P*<0.05) at 24 months in the somatropin group. There were no significant changes in these three parameters in the placebo group during both DB and OL phases. No significant changes were seen in HDL-C throughout

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo for 12 months followed by somatropin (Norditropin®) with a target dose of 2 IU/m^2/day for 24 months	with adult-onset GHD due to a known cause and who had never received GH treatment	OL for 12 months)	and waist-to-hip ratio	the study in both treatment groups. Changes in lipid profile were not compared between the two treatment groups. Lp(a) increased significantly at 24 months compared to baseline in both the somatropin (6.7 vs 10.6 mg/dL; *P*<0.001) and placebo groups (9.5 vs 11.8 mg/dL; *P*<0.05). Secondary: The BMI and waist-to-hip ratio did not change significantly throughout the study in both treatment groups.
Bell et al[117] GH 0.125 IU/kg/week daily for 4 weeks, followed by GH 0.25 IU/kg/week daily vs placebo for 6 months, followed by GH 0.125 IU/kg/week daily for 4 weeks, followed by 0.25 IU/kg/week daily	DB, OL, PC, PG, RCT Patients between 21 and 60 years of age with GHD and who had not received GH in the previous 2 years	N=51 12 months (DB, PC for 6 months followed by OL for 6 months)	Primary: Changes in waist and hip circumference, waist-to-hip ratio, BMI, conicity index, absolute trunk fat, somatotype, TC, TG, HDL-C, LDL-C, HDL-C/LDL-C ratio, SBP, DBP and pulse pressure Secondary: Not reported	Primary: In both male and female patients, treatment with placebo during the first six months led to a slight increase in waist and hip circumference, absolute trunk fat and conicity index, whereas an increase in these parameters was observed after initiation of GH both in the GH group throughout the study and in the placebo group during six to 12 months. No notable or consistent trends were seen with other body composition parameters, lipid profile, BP and pulse pressure. In the 27 male patients, significant differences were observed between the GH and placebo groups at six months with regard to changes in waist circumference (-2.4 vs 1.08 cm; *P*=0.0001), absolute trunk fat (-2.4 vs 0.26 kg; *P*=0.0001), conicity index (-0.02 vs 0.01 units; *P*=0.0001) and somatotypes (*P*=0.001). The significance of differences in other parameters was not reported. In the 24 female patients, reduction in absolute trunk fat was significantly different between the GH and placebo groups at six months (-2.3 vs -0.1 kg; *P*=0.033). The significance of differences in other parameters was not reported. Secondary: Not reported
Colao et al[118] GH 3 to 4 µg/kg/day adjusted	RCT, XO Patients 25 to 50	N=34 12 months	Primary: Change from baseline in	Primary: After the first six months in the patients in Group A, there were significant increases in IGF-1 (*P*<0.01) and HDL-C (*P*<0.01) and decreases in DBP

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
up to 50 percentile of normal IGF-1 for age and sex for 6 months then no treatment for 6 months (Group A) vs no treatment for 6 months then GH 3 to 4 µg/kg/day adjusted up to 50 percentile of normal IGF-1 for age and sex for 6 months (Group B)	years of age diagnosed with GHD and partial or complete hypopituitarism		cardiovascular risk factors and IMT Secondary; Not reported	(*P*<0.01), TC/HDL-C ratio (*P*<0.01) and CRP (*P*<0.01). At 12 months, the patients in Group A had a significant decrease in IGF-1 level (*P*<0.05) and significant increases in TC/HDL-C ratio (*P*<0.05) and CRP (*P*<0.01). At 12 months, the mean IMT was significantly lower compared to baseline (*P*=0.0003). After the first six months, there were no significant differences in any of the parameters in the patients of Group B. At 12 months, the patients of Group B had significant increases in IGF-1 level (*P*<0.01) and HDL-C (*P*<0.05) and significant decreases in DBP (*P*<0.01), TC (*P*<0.05), TC/HDL-C ratio (*P*<0.01) and CRP (*P*<0.01). At 12 months, the mean IMT was significantly lower compared to baseline (*P*=0.003). Secondary: Not reported
Underwood et al[119] Somatropin (Nutropin®) 25 µg/kg/day (0.175 mg/kg/week) SC daily (high-dose group) vs somatropin (Nutropin®) 12.5 µg/kg/day (0.085 mg/kg/week) SC daily (low-dose group) vs placebo	DB, MC, PC, RTC Patients <35 years of age with childhood-onset GHD who had completed pediatric GH treatment, had reached adult height and had not received GH in the previous 12 months	N=64 24 months	Primary: Changes in total body fat, trunk fat mass, LBM, lumbar spine BMD, total body BMD, sum of skinfold thickness, lipid profile, cardiac function and quality of life Secondary: Changes in IGF-1 SDS, alkaline phosphatase, glucose metabolism, and other laboratory parameters;	Primary: At 24 months, there was an increase in total body fat in the placebo group (2.3±3.4 kg) and a dose-dependent decrease in the two somatropin groups (-0.7±4.8 and -3.7±3.6 kg in low- and high-dose groups, respectively; *P* value not reported). Similarly, the mean change in trunk fat was 2.6±5.1, -3.8±6.6 and -7.7±5.6 kg in the placebo, low- and high-dose groups, respectively (*P*<0.0001). Only high-dose somatropin led to a significant decrease in trunk fat compared to baseline (*P*=0.0011). LBM increased from baseline by 3.1±5.7% with placebo, 13.4±8.4% with low-dose somatropin and 13.4±10.2% with high-dose somatropin (*P* value not reported). At 24 months, the mean change from baseline in lumbar spine BMD Z-score was 0.09±0.27 with placebo (*P*=0.28 compared to baseline), 0.29±0.28 with low-dose somatropin (*P*=0.013) and 0.41±0.42 with high-dose somatropin (*P*=0.0034), showing a dose-dependent effect (*P*=0.032). A dose-dependent increase in total body BMD was also seen; however, the change was not statistically significant in the active treatment groups when compared to baseline.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			safety	The sum of skinfold thickness decreased from 99.5 mm at baseline to 87.1 mm at 24 months with high-dose somatropin (*P*<0.05) and from 97.3 to 91.2 mm with low-dose somatropin (*P*<0.05) while there was no significant change with placebo. At 12 months high-dose somatropin led to a significant reduction from baseline in LDL-C and LDL-C/HDL-C ratio (*P*<0.04 for both). No significant changes were seen in the other groups. There was a dose-dependent response for LDL-C/HDL-C ratio across the three groups at six and 12 months (*P*=0.006) but not at 24 months. Echocardiography showed no significant change in IVS, LVPW, LVEDD, LVESD and fractional shortening. There was a significant increase in mean LVM at 24 months with high-dose somatropin (*P*=0.01) but not with low-dose somatropin or placebo. There were no significant differences across the three treatment groups with regard to quality of life measured by the Index of General Well-Being, Beck Depression Index, STAI and Rathus Assertiveness Test. Secondary: There was a dose-dependent increase in serum IGF-1 SDS (*P*=0.0001) and serum alkaline phosphatase (*P*≤0.0006) at 24 months. An increase in fasting serum glucose from 79±8 mg/dL at baseline to 90±13 mg/dL at 24 months was seen in the low-dose somatropin group (*P*<0.03) and an increase from 85±7 to 90±11 mg/dL was seen in the high-dose somatropin group (*P*<0.03). Fasting serum insulin also increased from 9 to 10 mU/L with low-dose somatropin and from 10 to 14 mU/L with high-dose somatropin (*P*<0.03 for both). No significant changes were seen in postprandial glucose and insulin or in HbA1c. No significant changes were seen in electrolytes, renal, liver or thyroid functions. Similar numbers of adverse events were reported in the three groups, including edema and arthralgia.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Yuen et al[120] Somatropin (Genotropin®) 0.1 mg/day SC (low-dose group) vs somatropin (Genotropin®) 0.2 mg/day SC, titrated to serum IGF-1 SDS of 0 (standard-dose group) vs no treatment	OL, RCT Adult patients with severe adult-onset or childhood-onset GHD and who had not received GH in the previous 12 months	N=33 12 months	Primary: Change in whole-body insulin sensitivity index (M-value) and fasting blood glucose Secondary: Change in truncal fat, truncal LBM, lipid profile, nonesterified fatty acid, CRP, IL-6, TNF-α and adiponectin	Primary: At 12 months, insulin sensitivity improved with the low-dose regimen (1.3±0.4 mg/kg/minute) compared to the standard-dose regimen (-0.3±0.7 mg/kg/minute; *P*<0.05) and to no treatment (-0.3±0.4 mg/kg/minute; *P*<0.02). There was a decrease in fasting blood glucose in the low dose group (-0.4±0.1 mmol/L) compared to a slight increase in the standard-dose and untreated groups (0.1±0.1 mmol/L for both; *P*<0.01 for both). Secondary: Treatment with both low- and standard -dose regimens led to similar reduction in truncal fat mass (-1.57±0.43 and -0.70±0.58 kg; *P*>0.05). There were no significant differences across all three groups with regard to changes in truncal LBM (-0.30±0.29, 0.23±0.32 and 0.00±0.38 kg for low-dose, standard-dose and no treatment, respectively). No significant differences were seen in TC, TG, HDL-C and LDL-C across the three groups. Compared to the low-dose regimen, the standard-dose regimen led to greater increase in fasting nonesterified fatty acid (455±167 vs 34±113 µmol/L; *P*<0.05) and greater reduction in IL-6 (-2.5±0.8 vs -1.2±1.1 ng/L; *P*<0.05). No significant changes were seen between the two somatropin groups in CRP, TNF-α and adiponectin.
Chihara et al[121] GH (Growject®*) 0.003 mg/kg/day for 4 weeks, followed by GH 0.006 mg/kg/day for 8 weeks, followed by GH 0.0012 mg/kg/day for the last 12 weeks (high dose) vs	DB, PC, RCT (24 weeks) OL (48 weeks) Patients 18 to 64 years of age with idiopathic or organic, isolated or combined with other deficiencies, sever adult GHD	N=96 72 weeks	Primary: Dose relationship of GH replacement on body composition, IGF-1 and serum lipids Secondary: Not reported	Primary: After 24 weeks, there were significant increases in IGF-1 SDS for the high dose and low dose groups compared to baseline (*P*<0.001 for both), but no significant change with the placebo group. Compared to placebo, there were significant changes in IGF-1 SDS (*P*<0.001). The changes in IGF-1 SDS were significant greater with the high dose group compared to the low dose group (*P* value not reported). After 24 weeks, there were significant decreases in percent trunk mass and percent total fat mass in the high dose and low dose groups (*P*<0.001 for all), but not the placebo group. There was a significant increase in percent LBM for the high dose and low dose group (*P*<0.001), but not the placebo group. The

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
GH (Growject®*) 0.003 mg/kg/day for 4 weeks, followed by GH 0.006 mg/kg/day for 8 weeks, followed by GH 0.006 mg/kg/day for the last 12 weeks (low dose) vs placebo In the OL phase doses were adjusted to a range of 0.003 mg/kg/day to 0.012 mg/kg/day according to IGF-1 level.	and stable replacement of other hormone deficiencies for ≥3 months			changes in body composition for the high dose and low dose groups were significant compared to the placebo group (*P*<0.001). The changes in body composition were significantly greater in the high dose group compared to the low dose group (*P* values not reported). At 24 weeks, TC decreased significantly compared to baseline in the high dose and low dose groups (*P*<0.001 and *P*<0.05), but not the placebo group. LDL-C decreased significantly in the high dose group (*P*<0.001). There was a nonsignificant decrease in LDL-C with the low dose group and a nonsignificant increase in the placebo group. The changes in TC and LDL-C were not significant differences between the high dose and low dose groups. There were no significant changes in TG with any of the groups. There was a significant dose-responsiveness in the three groups (*P*<0.001). In the OL phase, there were significant changes at 72 weeks compared to baseline in percent trunk fat mass, percent LBM, percent total fat mass, IGF-1 SDS, TC and LDL-C (*P*<0.001). There were no significant differences in adverse events between the three groups during the 24 week DB phase. There were no clinically relevant adverse reactions during the 48 week OL phase. Secondary: Not reported
Attanasio et al[122] Somatropin (Humatrope®) 25 µg/kg/day (0.18 mg/kg/week) (pediatric dose group) vs somatropin (Humatrope®) 12.5 µg/kg/day (0.09 mg/kg/week) (adult dose group)	MC, OL, RCT Postpubertal patients with childhood-onset GHD who had completed at least 1 year of pediatric GH treatment, had not received GH	N=149 2 years	Primary: Changes in LBM, fat mass and lipid profile Secondary: Not reported	Primary: LBM increased significantly from baseline at two years in both the pediatric and adult dose groups compared to the untreated group (5.2±4.4 and 5.1±3.9 vs 1.0±3.0 kg; *P*<0.001 for both dose regimens combined compared to no treatment). There was no significant difference between the two dose groups. At two years, there was a decrease from baseline in fat mass in both the pediatric and adult dose groups compared to an increase in the untreated group (1.1±4.0 and -1.6±5.8 vs 1.5±5.3 kg; *P*=0.029). There was no significant difference between the two dose groups.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs no treatment	in the previous 6 weeks and had a height velocity <1 cm/year			There were no significant differences at two years with regard to changes in TC among the three treatment groups (-1.2±38.7, 5.2±38.3 and 15.0±29.2 mg/dL with pediatric dose, adult dose and untreated groups, respectively; *P*=0.172). The LDL-C/HDL-C ratio was significantly decreased in the pediatric dose group and remained unchanged in the adult dose group, compared to an increase in the untreated group (-0.09±0.80 and 0.00±0.90 vs 0.39±0.90; *P*=0.05). There was no significant difference between the two dose groups. Secondary: Not reported
Shalet et al[123] Somatropin (Humatrope®) 25 µg/kg/day (0.18 mg/kg/week) (pediatric dose group) vs somatropin (Humatrope®) 12.5 µg/kg/day (0.09 mg/kg/week) (adult dose group) vs no treatment	MC, OL, RCT Postpubertal patients with childhood-onset GHD who had completed at least 1 year of pediatric GH treatment, had not received GH in the previous 6 weeks and had a height velocity <1 cm/year	N=149 2 years	Primary: Changes in total BMC, total BMD, lumbar spine BMD and hip BMC Secondary: Changes in serum bone-specific alkaline phosphatase levels and urinary ICTP-to-creatinine ratio; safety	Primary: At two years, a significant percentage increase was seen with regard to total BMC (5.6±8.3%; *P*<0.001) and total BMD (2.9±5.8; *P*=0.003) in the untreated group when compared to baseline. In the pediatric and adult dose groups, the increase in total BMC (8.1±7.6 and 9.5±8.4%, respectively; *P*=0.008 for both dose groups combined compared to the untreated group) and total BMD (3.2±4.5 and 4.7±4.5%, respectively; *P*=0.019) was significant greater compared to the untreated group. There was no significant difference between the two dose groups. Compared to no treatment, pediatric and adult dose regimens at two years was associated with greater increase in lumbar spine BMC (7.6±8.7 and 10.0±11.2 vs 4.1±6.7%; *P*=0.013) and BMD (5.1±7.1 and 6.1±7.4 vs 3.1±4.4%; *P*=0.027). There were no significant changes at the hip and femoral neck BMD, and there was no difference between the two dose groups. Secondary: At two years, serum bone-specific alkaline phosphatase increased significantly from baseline in both the pediatric and adult dose groups compared to a decrease in the untreated group (5.12±16.55 and 7.86±13.27 vs -0.29±9.74 IU/L; *P*=0.013). Similarly, urinary ICTP-to-creatinine ratio increased in the pediatric and adult dose groups compared to the untreated group (327±1019 and 24±684 vs -265±609; *P*=0.004). There was no significant difference between the two dose groups.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Three clinically relevant serious adverse events were reported, including one case of obstructive sleep apnea in the untreated group, one recurrence of optic glioma in the adult dose group and one osteolytic lesion in a patient with Langerhans cell histiocytosis in the adult dose group.
Attanasio et al[124] Somatropin (Humatrope®) 25 µg/kg/day (0.18 mg/kg/week) (pediatric dose group) vs somatropin (Humatrope®) 12.5 µg/kg/day (0.09 mg/kg/week) (adult dose group) vs no treatment	MC, OL, RCT Postpubertal patients with childhood-onset GHD who had completed at least 1 year of pediatric GH treatment, had not received GH in the previous 6 weeks and had a height velocity <1 cm/year	N=66 2 years	Primary: Change in quality of life measured by QLS-H score Secondary: Not reported	Primary: There were no significant differences between the pediatric and adult dose groups with regard to the change in total QLS-H score at two years. When data from the two somatropin groups were combined, there was no significant change in total QLS-H score (0.12±0.89) compared to the no treatment group (0.0±0.8; *P*=0.385). When looking at individual components of QLS-H, treatment with somatropin was associated with a significant improvement from baseline in body shape (0.46±1.26; *P*=0.035) and the ability to become sexually aroused (0.23±0.78; *P*=0.038); however, the improvement was not significant when compared to no treatment (-0.12±0.78; *P*=0.106, 0.06±0.72; *P*=0.368, respectively). There were no significant changes between somatropin and no treatment with regard to the ability to tolerate noise, ability to tolerate stress, concentration, ability to cope with own anger, initiative, physical endurance and self confidence. Secondary: Not reported
Abrahamsen et al[125] Somatropin (Norditropin®) 2 IU/m^2/day (14 µg/kg/day) SC (high-dose group) vs somatropin (Norditropin®) 1.5 IU/m^2/day (9 µg/kg/day) SC (medium-dose group) vs	DB, PC, RCT Patients ≥18 years of age with adult-onset GHD for at least 1 year and who had never received GH treatment	N=58 12 months	Primary: Changes in body composition and lipid profile Secondary: Change in IGF-1 levels	Primary: At 12 months, the median reduction in fat mass was 0.5 kg with placebo, 1.5 kg with low-dose somatropin, 1.8 kg with medium-dose somatropin and 4.7 kg with high-dose somatropin, demonstrating dose-dependent effect with multiple regression analysis (*P*<0.001). Subanalysis further showed that the reductions in fat mass of the trunk and the extremities were also dose-dependent (*P*<0.001 and <0.05, respectively). There was a median increase in LBM by 0.7 kg with placebo, 3.2 kg with low-dose somatropin, 2.5 kg with median-dose somatropin and 2.4 kg with high-dose somatropin. Multiple regression analysis showed no dose-dependent correlation (*P*=0.97). Subanalysis showed that the increase in LBM was sex-dependent, with a median increase by 4.1 kg in men and 0.6 kg in women

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
somatropin (Norditropin®) 0.5 IU/m^2/day (4 µg/kg/day) SC (low-dose group) vs placebo				(*P*<0.001). When data from all three active treatment groups were combined, there was a significant change from baseline at 12 months in TC (6.3%; *P*<0.01) and LDL-C (10.8%; *P*<0.001) but not in TG or HDL-C. A somatropin dose-dependent effect was seen in the reduction of TC (*P*<0.01*)* and LDL-C (*P*<0.001). In the low dose group, no significant changes were seen in lipid profile. Medium-dose somatropin was associated with a significantly lower LDL-C, whereas high-dose somatropin led to a significant decrease in both LDL-C and TC. Secondary: A dose-dependent increase in serum IGF-1 levels was seen, with the mean change being 8, 161, 239 and 412% in the placebo, low-, medium- and high-dose groups, respectively (*P*<0.001).
Abrahamsen et al[126] Somatropin (Norditropin®) 2 IU/m^2/day (14 µg/kg/day) SC (high-dose group) vs somatropin (Norditropin®) 1.5 IU/m^2/day (9 µg/kg/day) SC (medium-dose group) vs somatropin (Norditropin®) 0.5 IU/m^2/day (4 µg/kg/day) SC (low-dose group) vs placebo	DB, PC, RCT Patients ≥18 years of age with adult-onset GHD for at least 1 year and who had never received GH replacement	N=58 12 months	Primary: Changes in lumbar spine, femur, forearm and whole body BMD Secondary: Changes in serum alkaline phosphatase, ICTP, PICP and PIIINP levels	Primary: Lumbar spine BMD decreased by 2.48±1.09 with placebo and increased by 2.43±1.94 and 3.10±1.45% with low- and medium-dose somatropin, respectively, compared to a decrease of 0.24±1.54 with high-dose somatropin (*P*<0.05 for intergroup differences). Similarly, there was a decrease in proximal forearm and whole body BMD with high-dose somatropin (-1.90±0.99 and -2.29±0.60%, respectively) when there was an increase at these sites with both low- and medium-dose somatropin (*P*<0.05 for both). Similar trend was seen in femoral shaft and total femur BMD, though the intergroup differences were not significant. With regard to ultradistal forearm BMD, there was a decrease with both medium- and high-dose somatropin (-1.09±0.83 and -4.92±1.43%, respectively) compared to an increase with low-dose somatropin and placebo (0.92±1.36 and 0.52±0.59, respectively; *P*<0.01). Secondary: There were no significant changes in bone turnover markers with placebo throughout the study. Serum alkaline phosphatase increased significantly in all three somatropin groups and returned to baseline at 12 months in the low dose group only. ICTP, PICP and PIIINP levels also increased significantly

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				and remained elevated throughout the study in all three somatropin groups.
Kehely et al[127] Somatropin (Humatrope®) 3 µg/kg/day for 3 months, followed by somatropin (Humatrope®) 6 µg/kg/day for 3 months (low-dose group) vs somatropin (Humatrope®) 6 µg/kg/day for 3 months, followed by somatropin (Humatrope®) 12 µg/kg/day for 3 months (standard-dose group)	MC Adult patients with childhood- or adult-onset GHD who had not received GH in the previous 6 months	N=595 6 months	Primary: Changes in LBM and fat mass Secondary: Changes in serum IGF-1 and IGFBP-3 SDS; safety	Primary: At six months, patients in the low-dose group gained 1.81 kg of LBM, compared to 2.33 kg for patients in the standard-dose group (*P*=0.141). The changes in both groups were significant compared to baseline. Patients in the standard-dose group had greater reduction in fat mass compared to those in the low-dose group after six months of treatment (-2.14 vs -1.54 kg; *P*=0.006). The changes in both groups were significant compared to baseline. Secondary: Serum IGF-1 and IGFBP-3 SDS increased significantly from baseline at six months in both treatment groups. The increase in IGF-1 SDS with the standard-dose group was greater than the low-dose group (*P*=0.024). There were no significant differences between the two groups with regard to IGFBP-3 SDS (*P*=0.454). Overall, fewer patients in the low-dose group reported at least one adverse event compared to the standard-dose group (56.0 vs 66.2%; *P*=0.01). The dose-dependent difference was significant in patients with adult-onset GHD (*P*=0.008) but not in patients with childhood-onset GHD (*P*=0.423). The most commonly reported adverse events were arthralgia, headache and peripheral edema.
Rahim et al[128] GH 0.125 IU/kg/week for 4 weeks, followed by GH 0.25 IU/kg/week; up to a maximum of 4 IU/day for 3 years (Group A) vs GH 0.125 IU/kg/week for 4 weeks, followed by GH 0.25	OL Patients with adult onset GHD for at least 2 years that completed a previous RCT and had not received GH prior to the study	N=15 3 years	Primary: Change from baseline in BMD at three years for Group A and two years after completion of GH treatment for Group B Secondary: Not reported	Primary: In Group A at three years, the lumbar spine BMD and trochanter BMD increased significantly from baseline (3.7%; *P*=0.028 and 4.0%; *P*=0.046, respectively). There was a nonsignificant decrease in femoral neck BMD (1.9%; *P*=0.39). Ward's area BMD decreased by 6.5% at three years (*P*=0.09). Forearm cortical BMD decreased by 2.6% (*P*=0.18). Two years after completion of GH therapy in Group B, trochanter BMD significantly increased by 5.9% (*P*=0.049). There were no significant differences from baseline in lumbar spine BMD (*P*=0.67), Ward's area BMD (*P*=0.57), femoral neck BMD (*P*=0.86) and forearm cortical BMD (*P*=0.31).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
IU/kg/week; up to a maximum of 4 IU/day for 6 to 12 months (Group B)				Secondary: Not reported
Hoffman et al[129] Somatropin (Humatrope®) 4 µg/kg/day for 4 months, followed by somatropin (Humatrope®) 8 µg/kg/day for 2 months, followed by somatropin (Humatrope®) 12 µg/kg/day for 2 months (fixed-dose group) vs somatropin (Humatrope®) 200 µg/day for 2 months; titrated every 2 months as needed based on serum IGF-1 levels adjusted for age and sex and perceived clinical benefit of GH treatment (individualized-dose group)	MC, OL, PG, RCT Patients ≥20 years of age with adult- or childhood-onset GHD and who had not received GH in the previous 12 months	N=387 32 weeks	Primary: Change in fat mass Secondary: Somatropin dose requirement, change in LBM, abdominal fat mass, total BMD, waist and hip circumferences, sum of skinfold thickness, hand grip strength, lipid profile, fasting blood glucose, serum acid labile subunit, GHBP, IGF-1, health-related quality of life and safety	Primary: The percentage reduction in body fat mass was significantly smaller with the individualized-dose regimen compared to the fixed-dose regimen (-7.9±11.9 vs -10.9±11.5%; *P*=0.67). Secondary: At 32 weeks, the somatropin dose requirement in the individualized-dose group was significantly lower than the fixed-dose group (0.54±0.22 vs 0.70±0.32 mg/day; *P*<0.001). At 32 weeks, treatment with both regimens led to a significant increase in LBM and a significant decrease in abdominal fat, hip circumference, sum of skinfold thickness, TC and LDL-C compared to baseline; however, there were no significant differences in these parameters between the two groups. Changes in total BMD, waist circumferences, HDL-C and hand grip strength were not significant from baseline and were comparable between the two groups. There was an increase in fasting blood glucose by 4.8±18.1 and 5.4±12.7 mg/dL with fixed- and individualized-dose regimens, respectively (*P*>0.05). In both fixed- and individualized-dose groups, serum acid labile subunit, GHBP and IGF-1 levels increased significantly from baseline at 32 weeks, with no significant differences between the two groups. At 32 weeks, there was a significant improvement from baseline in quality of life, measured by QLS-H and NHP scores, in both treatment groups, with no significant differences between the two groups. Treatment-emergent adverse events were reported in 68.0 and 62.6% of patients in the fixed-dose and individualized-dose groups, respectively (*P*=0.29). Incidence of peripheral edema was lower with the individualized-dose regimen compared to the fixed-dose regimen (9.1 vs 16.5%; *P*=0.03). Rash was also less common in the individualized-dose group than the fixed-

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				dose group (1.1 vs 5.5%; *P*=0.02). Three serious adverse events were considered related to study drug. There was one case of hyperglycemia and one case of re-growth of preexisting residual pituitary tumor in the fixed-dose group and one possible growth of a preexisting pituitary tumor in the individualized-dose group. Two deaths occurred during the study due to cerebrovascular accident and accidental opiate intoxication. Neither was considered related to somatropin.
Janssen et al[130] Somatropin (Genotropin®) 0.6 IU/day for 24 weeks; doses were adjusted individually based on IGF-1 serum levels to a range of 0.6 to 1.8 IU/day between weeks 24 and 52, after 52 weeks doses could be greater than 1.8 IU/day if IGF-1 levels were below the normal range vs somatropin (Genotropin®) 0.6 IU/day for 4 weeks, followed by somatropin (Genotropin®) 1.2 IU/day for 20 weeks; doses were adjusted individually based on IGF-1 serum levels to a range of 0.6 to 1.8 IU/day between weeks 24 and 52, after 52 weeks doses could be greater than 1.8 IU/day if IGF-1 levels were below the normal range vs	RCT Patients with GHD receiving replacement of other hormones	N=47 2 years	Primary: Change in IGF-1, bone turnover and BMD from baseline at 24 weeks, 52 weeks and two years Secondary: Not reported	Primary: There was a significant increase in mean IGF-1 SDS at 24 weeks, 52 weeks and two years (*P*<0.0005 for all). At 24 weeks there were significant increases in the bone formation parameters of serum alkaline phosphatase activity and osteocalcin (*P*=0.0008 and *P*<0.0005). There were significant increases in bone resorption parameters of urinary hydroxyproline/creatine and urinary N-telopeptide/creatinine excretion (*P*<0.0005 for both). Between 24 and 52 weeks there was a significant increase in alkaline phosphatase activity and osteocalcin (*P*=0.021 and *P*=0.006). There were no significant changes in urinary hydroxyproline/creatine and urinary N-telopeptide/creatinine excretion between 24 and 52 weeks. There was no significant change in urinary N-telopeptide/creatinine excretion and osteocalcin from 52 weeks to two years. There were significant decrease in alkaline phosphatase and urinary hydroxyproline/creatine from 52 weeks to two years (*P*=0.003 and *P*=0.018); however, they were significantly increased compared to baseline. Serum calcium significantly increased after 24 weeks and 52 weeks with somatropin, but returned to baseline levels after two years of treatment. Serum phosphate levels significantly increase after 24 weeks, 52 weeks and two years of treatment (*P*<0.001 for all). The urinary calcium/creatinine excretion significantly increased after 24 weeks (*P*=0.002), but was not significantly different at any other time point. There was a significant increase in *Z*-scores after 52 weeks and two years (*P*<0.05 and *P*<0.005). There was a significant increase in BMD after two years (*P*=0.001). There was no significant difference between the three treatment groups.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
somatropin (Genotropin®) 0.6 IU/day for 4 weeks, followed by somatropin (Genotropin®) 1.2 IU/day for 4 weeks, followed by somatropin (Genotropin®) 1.8 IU/day for 16 weeks; doses were adjusted individually based on IGF-1 serum levels to a range of 0.6 to 1.8 IU/day between weeks 24 and 52, after 52 weeks doses could be greater than 1.8 IU/day if IGF-1 levels were below the normal range				Secondary: Not reported
Elbornsson et al[140] The first 64 patients received 11.9 µg/kg per day and the following 62 patients received individualized dosing to normalize serum IGF1 concentration and body composition	OL, PRO Patients with adult onset pituitary disease and all had known pituitary disease or other anterior pituitary hormonal deficiencies	N=126 Up to 15 years	Primary: Physical and laboratory measurements Secondary: Not reported	Primary: The mean initial GH dose of 0.63 mg/day (SEM 0.03) was gradually lowered to 0.41 mg/day after 15 years of treatment. The mean serum IGF1 SDS increased from -1.69 (0.11) at baseline to 0.63 (0.16) after 15 years (*P*<0.001 compared to baseline). The 15 years of GH replacement induced a sustained increase in total body BMC (+5%, *P*<0.001) and BMD (+2%, *P*<0.001). Lumbar (L2 to L4) spine BMC increased by 9% (*P*<0.001) and BMD by 5% (*P*<0.001). In the femur neck, a peak increase in BMC and BMD of 7 and 3%, respectively, occurred after seven years of GH therapy. (*P*<0.001 for both). After 15 years, femur neck BMC was 5% above the baseline value (*P*<0.01), whereas femur neck BMD had returned to the baseline level. In most variables, men had a more marked response to GH replacement compared to women.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Filipsson et al[141] GH vs placebo Three months before randomization (visit 1), other pituitary hormone replacement therapies were optimized if needed, and patients changed from their ordinary GH preparation to somatropin (Norditropin®)	DB, PC, RCT, XO Patients 25 to 75 years of age with pituitary disease, GHD and >3 years of continuous GH replacement therapy	N=60 9 months (XO at 4 months)	Primary: QOL-AGHDA, height, body composition, biochemical markers and adverse events Secondary: Not reported	Primary: The median QOL-AGHDA scores were unchanged between the GH and placebo treatment periods (*P*=0.38). Placebo treatment resulted in a significantly higher QOL-AGHDA score (deterioration) from baseline (*P*=0.014). Two subscores, emotional reaction and positive wellbeing, in the NHP (*P*=0.04) and PGWB (*P*=0.04) questionnaires deteriorated during placebo compared to the GH treatment period. After study completion, patients were asked to identify the period with GH. The GH period was correctly identified by 38% of patients, while 34% of patients identified the placebo period as GH, (*P*=0.746) and 28% reported no difference between treatment periods. Subcutaneous adipose tissue in the thigh and abdomen and visceral adipose tissue increased during placebo treatment compared to GH treatment. Thigh muscle area decreased more during the placebo period compared to the GH treatment period. Thigh muscle attenuation and liver attenuation remained unchanged. Body cell mass (*P*<0.001) and extracellular water (*P*<0.001) decreased and body fat and bone mineral content increased (*P*=0.047) during placebo treatment compared GH treatment. IGF-I decreased by -97.7±46.9 µg/L during placebo treatment to 70.4±27.3 µg/L (*P*<0.001). CRP increased during placebo treatment compared to GH treatment (*P*<0.05). Total cholesterol (*P*<0.05), LDL-C (*P*<0.01), and HDL-C (*P*<0.05) increased, and triglyceride levels decreased (*P*<0.05) during the placebo period compared to the GH treatment period. Glycosylated hemoglobin decreased more with placebo treatment than GH treatment (*P*=0.002). Fasting glucose and insulin did not differ between treatment periods (*P*=0.32). Ten serious adverse events were reported (four during the GH treatment period [tibia fracture, cholecystectomy, severe hip pain, atrial fibrillation], and six during the placebo period [reoccurring hypoglycemia, multiple fractures due to trauma, diarrhea, incidentally discovered abdominal aorta aneurysm, and two episodes of atrial fibrillation in one patient]. There were a total of 105 adverse events reported, most occurring during the first treatment period. The

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				most frequent complaint was psychological deterioration and joint and muscle pain. Secondary: Not reported
Hyldstrup et al (abstract)[142] GH vs placebo	RCT Young adults with childhood-onset GHD	N=160 24 months	Primary: Cortical thickness, Metacarpal index, endosteal diameter and total bone width Secondary: Not reported	Primary: After 24 months, cortical thickness was increased (6.43%; 95% CI, 3.34 to 9.61; *P*=0.0001) as did the metacarpal index (6.14%; 95% CI, 3.95 to 8.38%; *P*<0.0001) and endosteal diameter decreased (-4.64%; 95% CI, -7.15 to -2.05; *P*<0.001) with GH treatment compared to placebo. The total bone width did not change significantly between patients treated with GH and placebo (0.68%; 95% CI, -1.17 to 2.57; *P*=NS). A gender effect was seen on bone width (*P*<0.0001), endosteal diameter (*P*<0.01) and cortical thickness (*P*<0.01) but not with metacarpal index (*P*=NS). Secondary: Not reported
Arwert et al[132] GH only or GH vs placebo	MA (15 OL or PC trials) Adult patients with GHD	N=830 3 to 50 months	Primary: Change in cognitive functions measured by neuro-psychological tests and change in patient-reported outcomes based on one or more of the following questionnaires: NHP, PGWB, HSCL, POMS, STAI or QoL-AGHDA	Primary: Four of the 15 studies (N=85) included results on changes in cognitive functions with treatment duration ranging from six to 24 months. After six months of treatment with GH, there was no significant increase in cognitive functions (effect size, 0.29; 95% CI, -0.18 to 0.77; *P*=0.23). When data from all treatment duration was combined, the effect size remained nonsignificant at 0.35 (95% CI, -0.07 to 0.76; *P*=0.10). Results from five studies showed that after three months of GH treatment, patient-reported outcomes significantly improved from baseline by an effect size of 0.81 (95% CI, 0.32 to 1.30; *P*=0.001). In 10 studies, six months of treatment was associated with a smaller improvement by an effect size of 0.55 (95% CI, 0.31 to 0.79; *P*<0.001). Finally, seven studies showed that 12 months of treatment led to an even smaller improvement in patient-reported outcomes by an effect size of 0.29 (95% CI, 0.11 to 0.47; *P*=0.002). When compared to placebo, six months of GH replacement was not associated with significant improvement in patient-reported outcomes in five

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			Secondary: Not reported	PC studies, with an effect size of -0.075 (95% CI, -0.32 to 0.17; *P*=0.055). When combining results from eight PC studies with varying treatment duration ranging from one to 24 months, there was no significant difference in patient-reported outcomes between GH and placebo, with an effect size of -0.03 (95% CI, -0.30 to 0.24; *P*=0.85). Secondary: Not reported
Falleti et al[133] GH only or GH vs placebo	MA (14 PRO or RCTs) Adult patients with GHD	N=219 Up to 16 years	Primary: Changes in cognitive functions measured by neuro-psychological tests Secondary: Not reported	Primary: Results on cognitive functions from seven RCTs were divided into four cognitive domains: attention, memory, language and executive function. In all four domains, patients in the GH group performed worse compared to patients in the placebo group. The effect size comparing GH to placebo was -0.79, -0.36, -0.90 and -0.23 in the attention, memory, language and executive function domains, respectively (*P* values not reported). When comparing the changes in cognitive functions from baseline, patients receiving GH had an improvement from baseline in the attention domain by an effect size of 0.53 at three to six months and by 0.77 at nine to 12 months of treatment. Spatial ability decreased by an effect size of 0.06 at one month but improved by 0.28 at six months. Memory function increased from baseline by 0.25 at one month, 0.35 at three to six months, 0.64 at nine to 12 months, 0.33 at 24 months, 0.57 at five years and 0.35 at 10 years of GH replacement, showing a sustained improvement. Finally, patients also experienced improvement with regard to executive function by 0.41 at three to six months; the improvement was smaller at nine to 12 months, with an effect size of 0.06 (*P* values not reported). Secondary: Not reported
Davidson et al[134] GH vs	MA (10 PC, RCTs) Adult patients with GHD	N=458 6 to 24 months	Primary: Change in lumbar spine BMD	Primary: There was a small but significant WMD in lumbar spine BMD between GH and placebo throughout 24 months of treatment. The WMD was 0.01 at both six months (95% CI, 0.00 to 0.02; *P*=0.046) and 12 months (95% CI, 0.00 to 0.03; *P*=0.04), 0.02 at 18 months (95% CI, 0.01 to 0.04; *P*<0.001) and 0.03 at 24

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo			Secondary: Changes in femoral neck and total body BMD	months (95% CI, 0.02 to 0.05; *P*=0.046). Secondary: GH replacement was not associated with significant improvement in femoral neck BMD compared to placebo after six months (WMD, 0.01; 95% CI, 0.00 to 0.02; *P*=0.189), 12 months (WMD, 0.02; 95% CI, 0.00 to 0.04; *P*=0.11), 18 months (WMD, 0.00; 95% CI, -0.02 to 0.02; *P*=0.904) and 24 months of treatment (WMD, 0.02; 95% CI, 0.00 to 0.04; *P*=0.116). Five studies showed that the total body BMD was lower with GH compared to placebo after six months of treatment (WMD, -0.02; 95% CI, -0.04 to -0.01; *P*=0.009), while two studies demonstrated no difference between GH and placebo at 24 months (WMD, 0.00; 95% CI, -0.04 to 0.04; *P*=0.879).
Maison et al[135] GH vs placebo	MA (16 RCT or OL trials) Adult patients with GHD	N=468 6 to 36 months	Primary: Changes in LVM, IVS, LVPW, LVESD, LVEDD, stroke volume, E/A ratio, IRT and fractional shortening Secondary: Not reported	Primary: Results from 11 studies showed that treatment with GH was associated with an increase from baseline in LVM by a WMD of 10.8±9.3 g (effect size, 0.23; 95% CI, 0.06 to 0.41; *P*=0.02). In 15 studies, IVS was increased with GH by 0.28±0.38 mm (effect size, 0.18; 95% CI, 0.05 to 0.32; *P*<0.001). LVPW was also increased by 0.98±0.22 mm with GH in 14 studies (effect size, 0.15; 95% CI, 0.01 to 0.29; *P*=0.05). GH replacement led to a significant increase in LVEDD but not LVESD. LVEDD increased by 1.34±1.13 mm (effect size, 0.31; 95% CI, 0.15 to 0.47; *P*<0.001), while LVESD slightly increased by 0.32±1.06 mm (effect size and *P* value not reported). Based on the results from five studies, GH also significantly increased stroke volume by 10.3±8.7 mL (effect size, 0.48; 95% CI, 0.22 to 0.74; *P*<0.001). GH replacement was not associated with significant changes in the following parameters: E/A ratio (WMD, 0.05±0.13; effect size and *P* value not reported), IRT (WMD, -1.60±7.36 ms; effect size and *P* value not reported) and fractional shortening (WMD, 1.06±1.06%; effect size, 0.15; 95% CI, -0.02 to 0.32;

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				P=0.06). In a subgroup analysis including only RCT, GH was associated with a significant increase only in LVPW (effect size, 0.23; 95% CI, 0.02 to 0.45) and stroke volume (effect size, 0.46; 95% CI, 0.05 to 0.87). A subgroup analysis of high GH doses (0.35 to 0.50 IU/kg/week) and low GH doses (0.10 to 0.35 IU/kg/week) showed that high GH doses led to a significant increase in LVM (effect size, 0.26; 95% CI, 0.00 to 0.52), IVS (effect size, 0.38; 95% CI, 0.16 to 0.60) and LVEDD (effect size, 0.41; 95% CI, 0.19 to 0.63), while low GH doses led to a significant increase only in LVM (effect size, 0.23; 95% CI, 0.09 to 0.38). Secondary: Not reported
Rubeck et al[136] GH 5 to 16 µg/kg/day vs placebo	MA (15 DB, RCTs) Patients ≥19 years of age with GHD	N=306 3 to 12 months	Primary: Aerobic exercise capacity measured as either VO_2max, total work performed or exercise time, muscle strength measured by a dynamometer and muscle mass measured by CT Secondary: Not reported	Primary: Compared to control there was a significant increase in exercise capacity with GH (WMD, 8.94; 95% CI, 7.42 to 10.46; *P*<0.001). There was an increase in muscle strength with GH compared to control; however, it was not significant (WMD, 3.24; 95% CI, -1.12 to 7.60; *P*=0.15). There was a significant increase in muscle volume with GH compared to control (WMD, 7.1; *P*<0.001). Secondary: Not reported
Widdowson et al[137] GH	MA (8 PC, RCTs) Adult patients	N=231 Mean duration 6.8 months	Primary: Quadriceps strength in isometric or	Primary: In six studies, GH replacement was associated with improvement in muscle strength ranging from one to 15% compared to placebo, while the other two studies showed a reduction in muscle strength by three to five percent

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo	with GHD		isokinetic measurement Secondary: Not reported	compared to placebo. The data analysis failed to show any significant improvement in muscle strength from baseline when comparing GH to placebo. The effect size for changes in isometric and isokinetic quadriceps strength was 0.02 (95% CI, -0.30 to 0.33) and 0.00 (95% CI, -0.45 to 0.45), respectively. The effect size combining both isometric and isokinetic measurements was 0.01 (95% CI, -0.25 to 0.27). When data from the two negative studies were removed, the effect size was 0.09 (95% CI, -0.22 to 0.41), remaining nonsignificant. Secondary: Not reported
Human Immunodeficiency Virus-Associated Wasting Or Cachexia				
Schambelan et al[138] Somatropin (Serostim®) 0.1 mg/kg/day vs placebo	DB, MC, PC, RCT Patients ≥18 years of age with antibodies to HIV type I, documented unintentional weight loss ≥10% or weight <90% lower limit of IBW, a Karnofsky score ≥50 and life expectancy ≥4 months	N=178 12 weeks	Primary: Effect of somatropin on weight, body composition, functional performance and quality of life Secondary: Not reported	Primary: At week 12, there was a significant increase in weight in the somatropin group compared to the placebo group (*P*=0.011). There was a significant increase in LBM with somatropin compared to placebo (*P*<0.001). Body fat decreased significantly in the somatropin-treated patients compared to the placebo group (*P*<0.001). There were no significant changes in BMC (*P* value not reported). There were significant increases in total body water (*P*<0.001), intracellular water (*P*<0.001) and extracellular water (*P*=0.003). There was a significant increase in work output with somatropin compared to placebo (*P*=0.039). There were no significant differences between groups in quality of life at 12 weeks. Swelling or puffiness (*P*<0.001), arthralgia or myalgia (*P*=0.05) and diarrhea (*P*=0.041) were the only common adverse effects that differed significantly between groups. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Moyle et al[139] Somatropin (Serostim®) 0.1 mg/kg/day vs Somatropin (Serostim®) 0.1 mg/kg every other day vs placebo	MC, PC, RCT (12 weeks) ES, OL (36 weeks) Patients with documented HIV infection and 10% body weight loss or BMI <20 kg/m^2 or body weight <90% of ideal, consuming ≥90% of estimated caloric requirements and on antiretroviral medications	N=757 48 weeks	Primary: Change from baseline at 12 weeks in total work output to exhaustion, LBM, body composition and quality of life Secondary: Not reported	Primary: At 12 weeks, there was an increase in median maximum work output of 2.35 kJ in the alternate day dosing group and 2.60 kJ in the once daily dosing group. The median treatment difference between once daily dosing somatropin and placebo was statistically significant (*P*<0.0001). At 12 weeks, there was a median increase in LBM of 3.3 kg with alternate day dosing and 5.2 kg with once daily. The change was significantly greater than placebo for both groups (*P*<0.0001) and significantly greater with once daily dosing compared to alternate day dosing (*P*=0.0173). At 12 weeks, body cell mass and intracellular water content significantly increase in both treatment groups compared to placebo (*P*<0.0001). Median increase in body weight from baseline was significantly greater in the alternate day dosing and once daily dosing compared to placebo (*P*<0.0001). At 12 weeks, there were significant increases in quality of life in the alternate day dosing and once daily dosing groups compared to placebo (*P*=0.002 and *P*=0.0004). In the OL phase, alternate day dosing was associated with an increase in median maximum work output of 4.7 kJ, and once daily dosing was associated an increase in median maximum work output of 7.6 kJ at 48 weeks. There was an increase in LBM of 4.7 and 3.7 kg in the alternate day dosing at 24 and 48 weeks, respectively. There was an increase in LBM of 5.2 and 7.8 kg in the once daily dosing at 24 and 48 weeks, respectively. Secondary: Not reported

*Agent not currently available in the United States.
Drug regimen abbreviations: IM=intramuscular, IV=intravenous, IU=international units, SC=subcutaneous, TIW=three times weekly
Study abbreviations: CI=confidence interval, DB=double-blind, ES=extension study, MA=meta-analysis, MC=multicenter, MD=mean difference, NI=noninferiority, NS=not significant, OL=open-label, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, SR=systematic review, WMD=weighted mean difference, XO=crossover
Miscellaneous abbreviations: apo=apolipoprotein, BMC=bone mineral content, BMD=bone mineral density, BMI=body mass index, BP=blood pressure, bpm=beats per minute, CRP=C-reactive protein, CT=computed tomography, DNMTS=delayed-non-match to sample, DBP=diastolic blood pressure, E/A=E-wave and A-wave peak velocities of the mitral flow profile, EQ-5D=European Quality of Life-5 Dimensions, GFR=glomerular filtration rate, GH=growth hormone, GHBP=growth hormone binding protein, GHD=growth hormone deficiency, GHQ=General Health Questionnaire, HbA1c=glycosylated hemoglobin, HDL-C=high-density lipoprotein cholesterol, HIV=human immunodeficiency virus, HOMA=homeostasis model assessment, HOMA-β= homeostasis model assessment-β, HSCL=Hopkins Symptom Checklist, IBW=ideal body weight, ICTP=type I collagen C-terminal telopeptide, IDL=intermediate-density lipoprotein, IGF=insulin-like growth factor,

IGFBP=insulin-like growth factor binding protein, IL=interleukin, IMT=intima-media thickness, IRT=isovolumic relaxation time, ISS=idiopathic short stature, IUGR=intrauterine growth restriction, IVS=interventricular septum thickness, LBM=lean body mass, LDL-C=low-density lipoprotein cholesterol, Lp(a)=lipoprotein (a), LVEDD=left ventricular end-diastolic diameters, LVEF=left ventricular ejection fraction, LVESD=left ventricular end-systolic diameters, LVM=left ventricular mass, LVPW=left ventricular posterior wall, MIST=modified insulin suppression test, MRI=magnetic resonance imaging, NHP=Nottingham Health Profile, PGWB=Psychological General Well Being Schedule, PICP= procollagen type I C-terminal propeptide, PIIINP=procollagen type III N-terminal propeptide, POMS=Profile of Mood States, PTH=parathyroid hormone, PWS=Prader-Willi syndrome, QLS-H=Questions on Life Satisfaction-Hypopituitarism, QoL-AGHDA=Quality of Life Assessment of Growth Hormone Deficiency in Adults, RUS= Radius, ulna, short-bones score, SBP=systolic blood pressure, SD=standard deviation, SDS=standard deviation score, SF-36=Short Form 36, SGA=small for gestational age, SHOX-D=short stature homeobox-containing gene deficiency, STAI=State-Trait Anxiety Inventory, T_3=triiodothyronine, T_4=thyroxine, TC=total cholesterol, TG=triglyceride, TNF=tumor necrosis factor, TS=Turner syndrome, TSH=thyroid-stimulating hormone, VLDL=very low-density lipoprotein, VO_2max=maximal oxygen consumption

Special Populations

Table 5. Special Populations[3-11]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Somatropin (Genotropin®)	Safety and efficacy in elderly patients have not been established. FDA approved for use in children.	Not studied in renal dysfunction.	Not studied in hepatic dysfunction.	B	Unknown
Somatropin (Humatrope®)	Safety and efficacy in elderly patients have not been established. FDA approved for use in children.	Not studied in renal dysfunction.	Not studied in hepatic dysfunction.	C	Unknown
Somatropin (Norditropin®)	Safety and efficacy in elderly patients have not been established. FDA approved for use in children.	Not studied in renal dysfunction.	Not studied in hepatic dysfunction.	C	Unknown
Somatropin (Nutropin®)	Safety and efficacy in elderly patients have not been established. FDA approved for use in children.	Clearance may be decreased in patients with chronic kidney disease or renal failure; clinical significance is unknown.	Clearance may be decreased in patients with severe liver dysfunction; clinical significance is unknown.	C	Unknown
Somatropin (Omnitrope®)	Safety and efficacy in elderly patients have not been established. FDA approved for use in children.	Not studied in renal dysfunction.	Not studied in hepatic dysfunction.	B	Unknown
Somatropin (Saizen®)	Safety and efficacy in elderly patients have not been established. FDA approved for use in children.	Clearance may be decreased in patients with chronic kidney disease or renal failure; clinical significance is unknown.	Clearance may be decreased in patients with severe liver dysfunction; clinical significance is unknown.	B	Unknown
Somatropin (Serostim®)	Safety and efficacy in elderly patients have not been established. Safety and efficacy in children have not been	Clearance may be decreased in patients with chronic kidney disease or renal failure;	Clearance may be decreased in patients with severe liver dysfunction;	B	Unknown

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
	established.	clinical significance is unknown.	clinical significance is unknown.		
Somatropin (Tev-Tropin®)	Safety and efficacy in elderly patients have not been established. Safety and efficacy in adults have not been established. FDA approved for use in children.	Not studied in renal dysfunction.	Not studied in hepatic dysfunction.	C	Unknown

FDA=Food and Drug Administration

Adverse Drug Events

Table 6. Adverse Drug Events (%)[3-11]

Adverse Event	Somatropin (Genotropin®)	Somatropin (Humatrope®)	Somatropin (Norditropin®)	Somatropin (Nutropin®)	Somatropin (Omnitrope®)	Somatropin (Saizen®)	Somatropin (Serostim®)	Somatropin (Tev-Tropin®)
Abdominal pain	-	-	✔	-	-	-	-	-
Abnormal bone or other growth	-	-	-	✔	-	-	-	-
Acne	-	0 to 5.8	-	-	-	-	-	-
Aggressiveness	✔	-	-	-	✔	-	-	-
ALT increased	-	5.7 to 6.3	-	-	-	-	-	-
Altered mood	✔	-	-	-	✔	-	-	-
Arthralgia	3.0 to 17.3	3 to 17.3	19	0.1	3.0 to 17.3	23.3	24.5 to 37.1	-
Arthrosis	-	4	-	-	-	-	7.8 to 10.7	-
AST increased	-	5.7 to 12.5	-	-	-	-	-	-
Asthenia	-	2.9 to 6.3	-	-	-	-	-	-
Back pain	2.8 to 5.0	9.6 to 10.9	-	-	2.8 to 5.0	10	-	-
Benign intracranial hypertension	✔	-	-	-	✔	-	-	-
Benign new or recurring tumor	-	-	-	0.1	-	-	-	-
Bronchitis	-	-	9	-	-	-	2.3 to 4.7	-
Carpal tunnel syndrome	2	✔	✔	-	2	5	✔	-
Chest pain	-	-	-	-	-	5	-	-
Cough increased	-	0 to 6.3	-	-	-	-	-	-
Depression	-	-	-	-	-	5	-	-
Diabetes mellitus	-	-	-	0.1	-	-	-	-
Diarrhea	-	-	-	-	-	-	5.5 to 10.1	-
Dizziness	-	-	-	-	-	6.7	-	-
Ear disorders	-	13	-	-	-	-	-	-
Ear infection	-	-	✔	-	-	-	-	-
Eczema	-	-	✔	-	-	-	-	-
Edema	✔	2.5 to 21.2	25	0.1	✔	5	1.2 to 5.9	-
Elevated hemoglobin A1c	-	-	-	-	9 to 14	-	-	-
Eosinophilia	-	-	-	-	11 to 12	-	-	-
Exacerbation of psoriasis	-	-	-	-	-	✔	-	-
Excessive number of cutaneous nevi	✔	2	-	-	✔	-	-	-
Fatigue	1.7 to 6.3	-	-	-	1.7 to 6.3	-	3.5 to 8.9	-

Adverse Event	Somatropin (Genotropin®)	Somatropin (Humatrope®)	Somatropin (Norditropin®)	Somatropin (Nutropin®)	Somatropin (Omnitrope®)	Somatropin (Saizen®)	Somatropin (Serostim®)	Somatropin (Tev-Tropin®)
Fluid balance disturbance	-	-	-	-	-	✔	-	-
Fluid retention	-	-	-	-	-	-	2.5 to 5.2	-
Fracture	✔	-	-	✔	-	-	-	-
Gastritis	-	0 to 5.7	-	-	-	-	-	-
Gastroenteritis	✔	-	8	-	✔	-	-	-
Gynecomastia	-	1 to 2	✔	0.1	-	-	3.5 to 5.5	-
Hair loss	✔	-	-	-	✔	-	-	-
Headache	0 to 9.9	7.7 to 11.4	9	-	0 to 9.9	18.3	3.8 to 14.1	✔
Hematoma	-	-	-	-	9	-	-	-
Hematuria	✔	-	-	-	✔	-	-	-
Hip pain	-	1	-	-	-	-	-	-
Hyperglycemia	✔	-	-	-	✔	✔	7.1 to 8.8	-
Hyperlipidemia	-	3	-	-	-	-	-	-
Hypertension	-	1.0 to 7.7	8	-	-	-	-	-
Hypertriglyceridemia	-	-	-	-	5	-	✔	-
Hypesthesia	-	0 to 6.3	-	-	-	6.7	1.6 to 15.0	-
Hypothyroidism	✔	-	-	-	16	5	-	-
Impaired glucose tolerance	-	-	6	-	-	-	-	-
Increased appetite	✔	-	-	-	✔	-	-	-
Increased sweating	-	-	8	-	-	-	-	-
Infection	-	-	13	-	-	-	-	-
Influenza-like syndrome	-	3.9 to 22.9	8	-	-	15	-	-
Injection site reaction	✔	✔	-	0.3	✔	✔	-	✔
Insomnia	-	-	-	-	-	5	3.9 to 8.3	-
Joint disorder	-	2.2 to 5.8	-	✔	-	-	-	-
Joint pain	✔	-	-	-	✔	-	-	-
Joint stiffness	-	-	-	-	-	-	3.8 to 7.7	-
Joint swelling	-	-	-	-	-	-	5.0 to 6.1	-
Laryngitis	-	-	6	-	-	-	-	-
Leg edema	-	-	15	-	-	-	-	-
Lipoatrophy	✔	-	-	-	✔	-	-	-
Musculoskeletal stiffness	-	-	-	-	-	-	3.8 to 8.0	-
Myalgia	2.0 to 6.7	5.7 to 13.5	15	-	2.0 to 6.7	8.3	2.5 to 30.4	-
Nausea	-	-	-	-	-	5	1.3 to 9.1	-
Otitis externa	-	-	-	-	-	-	-	-

Adverse Event	Somatropin (Genotropin®)	Somatropin (Humatrope®)	Somatropin (Norditropin®)	Somatropin (Nutropin®)	Somatropin (Omnitrope®)	Somatropin (Saizen®)	Somatropin (Serostim®)	Somatropin (Tev-Tropin®)
Otitis media	✔	6 to 32	✔	-	✔	-	-	-
Pain	-	6.3 to 13.5	-	-	-	-	-	-
Pain, extremities	1.6 to 14.7	-	-	-	1.6 to 14.7	-	5.0 to 19.3	-
Paresthesia	0 to 9.6	13.0 to 17.3	11	-	0 to 9.6	6.7	7.4 to 12.5	-
Peripheral edema	0 to 10.8	11.5 to 17.4	42	✔	0 to 10.8	15	11.3 to 45.4	-
Peripheral swelling	0 to 17.5	-	-	-	0 to 17.5	-	-	-
Pharyngitis	✔	3.1 to 14.3	✔	-	✔	-	-	-
Pyrexia	✔	-	-	-	✔	-	-	-
Respiratory disorder	-	3.1 to 5.7	-	-	-	-	-	-
Respiratory illness	✔	-	-	-	✔	-	-	-
Rhinitis	✔	5.7 to 13.5	-	-	✔	8.3	4.0 to 5.1	-
Scoliosis	✔	1 to 7	✔	0.2	✔	-	-	-
Seizures	-	-	-	-	-	✔	-	-
Skeletal pain	-	-	11	-	-	5	-	-
Stiffness of extremities	0 to 7.9	-	-	-	0 to 7.9	-	-	-
Surgical procedure	33	-	-	-	33	-	-	-
Upper respiratory infection	-	-	✔	-	-	6.7	3.6 to 10.0	-
Urinary tract infection	13.1 to 15.9	-	-	-	13.1 to 15.9	-	-	-

-Incidence not reported or <0.1%.
✔ Percent not specified.
ALT=alanine aminotransferase, AST=aspartate aminotransferase

Contraindications

Table 7. Contraindications[3-11]

Contraindication	Somatropin (Genotropin®)	Somatropin (Humatrope®)	Somatropin (Norditropin®)	Somatropin (Nutropin®)	Somatropin (Omnitrope®)	Somatropin (Saizen®)	Somatropin (Serostim®)	Somatropin (Tev-Tropin®)
Active malignancy; preexisting malignancy should be inactive and treatment complete prior to initiating somatropin	✔	✔	✔	✔	✔	✔	✔	✔
Acute critical illness; complications have been reported following surgery, trauma, or in patients with acute respiratory failure	✔	✔	✔	✔	✔	✔	✔	✔
Diabetic retinopathy; patients with active proliferative or severe non-proliferative diabetic retinopathy	✔	✔	✔	✔	✔	✔	✔	✔
Hypersensitivity; patients with a known hypersensitivity to somatropin or any excipients of the product	✔	✔	✔	✔	✔	✔	✔	✔
Hypersensitivity to benzyl alcohol	-	-	-	-	-	-	-	✔
Pediatric patients with closed epiphyses	✔	✔	✔	✔	✔	✔	-	✔
Prader-Willi Syndrome in children; reports of death in patients who are obese, have a history of upper airway obstruction or sleep apnea, or have severe respiratory impairment	✔	✔	✔	✔	✔	✔	-	✔

Warnings/Precautions

Table 8. Warnings and Precautions[3-11]

Warning/Precaution	Somatropin (Genotropin®)	Somatropin (Humatrope®)	Somatropin (Norditropin®)	Somatropin (Nutropin®)	Somatropin (Omnitrope®)	Somatropin (Saizen®)	Somatropin (Serostim®)	Somatropin (Tev-Tropin®)
Acute critical illness; benefit of treatment continuation with somatropin in patients having acute critical illnesses should be weighed against the risk	✔	✔	✔	✔	✔	✔	-	✔
Benzyl alcohol; serious adverse events have been reported in pediatric patients	-	-	-	-	✔	✔	-	✔
Cardiovascular disorders; patients with Turner syndrome should be monitored closely for cardiovascular disorders	✔	✔	✔	✔	✔	-	-	-
Childhood onset adult GHD; patients with epiphyseal closure treated with somatropin in childhood should be reevaluated before continuation of somatropin therapy at the reduced dose level recommended for GH deficient adults	-	-	-	-	✔	✔	-	-
Chronic kidney disease; pediatric patients should be examined periodically for evidence of progression of renal osteodystrophy	-	-	-	✔	✔	-	-	-
Concomitant antiretrovirals; patients should receive antiretroviral therapy for the duration of treatment.	-	-	-	-	-	-	✔	-
Fluid retention; symptoms are usually transient and dose-dependant	✔	✔	✔	✔	✔	✔	✔	-
Hypopituitarism; other	✔	✔	✔	✔	✔	✔	-	✔

Warning/Precaution	Somatropin (Genotropin®)	Somatropin (Humatrope®)	Somatropin (Norditropin®)	Somatropin (Nutropin®)	Somatropin (Omnitrope®)	Somatropin (Saizen®)	Somatropin (Serostim®)	Somatropin (Tev-Tropin®)
hormone deficiencies should be treated and monitored during somatropin treatment								
Hypothyroidism; undiagnosed/untreated hypothyroidism may prevent an optimal response to somatropin	✔	✔	✔	✔	✔	✔	-	✔
Impaired glucose tolerance/diabetes mellitus; monitor blood glucose periodically as somatropin may decrease insulin sensitivity, particularly at higher doses in susceptible patients	✔	✔	✔	✔	✔	✔	✔	✔
Intracranial hypertension; patients with Turner syndrome and Prader-Willi syndrome may be at increased risk	✔	✔	✔	✔	✔	✔	✔	✔
Laboratory tests; levels of inorganic phosphorus, alkaline phosphatase, parathyroid hormone and IGF-I may increase during therapy	✔	✔	✔	✔	✔	✔	-	✔
Local and systemic reactions have been reported	✔	✔	✔	✔	✔	✔	✔	✔
Neoplasm; patients with preexisting tumors should be monitored for progression or recurrence	✔	✔	✔	✔	✔	✔	-	✔
Otitis media; treatment may increase incidence in patients with Turner syndrome	✔	✔	✔	✔	✔	-	-	-
Pancreatitis; consider in patients who develop persistent severe abdominal pain	✔	✔	✔	✔	✔	✔	✔	✔

Warning/Precaution	Somatropin (Genotropin®)	Somatropin (Humatrope®)	Somatropin (Norditropin®)	Somatropin (Nutropin®)	Somatropin (Omnitrope®)	Somatropin (Saizen®)	Somatropin (Serostim®)	Somatropin (Tev-Tropin®)
Prader-Willi Syndrome in children; patients treated with somatropin should have effective weight control and be monitored for respiratory infection	✔	✔	✔	✔	✔	✔	-	✔
Progression of preexisting scoliosis; monitor pediatric patients who experience rapid growth	✔	✔	✔	✔	✔	✔	-	✔
Slipped capital femoral epiphyses in children; onset of a limp or complaints of hip or knee pain during somatropin therapy should be carefully evaluated	✔	✔	✔	✔	✔	✔	-	✔

Drug Interactions

The drug interactions for somatropin are common for all formulations and are listed in Table 9.

Table 9. Drug Interactions[3-11]

Generic Name	Interacting Medication or Disease	Potential Result
Somatropin	11 β-hydroxysteroid dehydrogenase type 1 enzyme	Somatropin inhibits the microsomal enzyme 11 β-hydroxysteroid dehydrogenase type 1 which is required for the conversion of cortisone to cortisol. Patients with growth hormone deficiency have relative increases in 11 β-hydroxysteroid dehydrogenase type 1 and cortisol. Therefore, undiagnosed hypoadrenalism may be unmasked. In addition, patients already receiving glucocorticoid replacement may need an increase in their dose.
Somatropin	Estrogen	Estrogens may reduce the serum insulin-like growth factor-1 and greater doses of somatropin may be required.
Somatropin	Glucocorticoid therapy	Glucocorticoid therapy may attenuate growth promoting affects of somatropin; therefore glucocorticoid doses should be carefully adjusted to avoid hypoadrenalism and inhibitory effect on growth.
Somatropin	Insulin and hypoglycemic agents	Dose adjustment of insulin and hypoglycemic agents may be required with concomitant somatropin.

Dosage and Administration

Dosage and administration schedule of somatropin should be individualized based on the growth response of each patient. Serum insulin-like growth factor 1 levels may be useful during dose titration. Response to somatropin therapy in pediatric patients tends to decrease with time. However, in pediatric patients, the failure to increase growth rate, particularly during the first year of therapy, indicates the need for close assessment of compliance and evaluation for other causes of growth failure. Treatment with somatropin for short stature should be discontinued when the epiphyses are fused. A lower starting dose and smaller dose increments should be considered for older patients, who are more prone to the adverse effects of somatropin than younger individuals. In addition, obese individuals are more likely to manifest adverse effects when treated with a weight-based regimen. In order to reach the defined treatment goal, estrogen-replete women may need higher doses than men. Oral estrogen administration may increase the dose requirements in women. Recent literature has recommended initial treatment with larger doses of somatropin (e.g., 0.48 mg/kg/week), especially in very short children (i.e., height standard deviation score [SDS] <–3), and/or older/pubertal children, and that a reduction in dosage (e.g., gradually towards 0.24 mg/kg/week) should be considered if substantial catch-up growth is observed during the first few years of therapy. On the other hand, in younger short for gestational age children (e.g., approximately <4 years) (who respond the best in general) with less severe short stature (i.e., baseline height SDS values between -2 and -3), consideration should be given to initiating treatment at a lower dose (e.g., 0.24 mg/kg/week), and titrating the dose as needed over time. In all children, clinicians should carefully monitor the growth response, and adjust the somatropin dose as necessary. All somatropin products can be self-administered.

Table 10. Dosing and Administration[3-11]

Generic Name	Adult Dose	Pediatric Dose	Availability
Somatropin (Genotropin®)	Grown hormone deficiency: Cartridge, powder for reconstitution: initial (non-weight based), 0.15 to 0.30 mg SC daily, then increase every one to two months by increments of 0.1 to 0.2	Growth failure associated with Prader-Willi syndrome: Cartridge, powder for reconstitution: 0.24 mg/kg/week SC divided into six or seven doses	Cartridge, powder for reconstitution: 5 mg 12 mg Cartridge, powder for reconstitution

Generic Name	Adult Dose	Pediatric Dose	Availability
	mg/day, based on the clinical response and serum IGF-1 concentrations; initial (weight-based), 0.04 mg/kg/week SC divided into six or seven doses, then increase every four to eight weeks by no more than 0.08 mg/kg/week based on the clinical response, adverse effects and serum IGF-I concentrations	Growth failure associated with Turner syndrome: Cartridge, powder for reconstitution: 0.33 mg/kg/week SC divided into six or seven doses Growth failure in children born small for gestational age: Cartridge, powder for reconstitution: 0.48 mg/kg/week SC divided into six or seven doses Grown hormone deficiency: Cartridge, powder for reconstitution: 0.16 to 0.24 mg/kg/week SC divided into six or seven doses Idiopathic short stature: Cartridge, powder for reconstitution: 0.47 mg/kg/week SC divided into six or seven doses	(preservative-free): 0.2 mg 0.4 mg 0.6 mg 0.8 mg 1.0 mg 1.2 mg 1.4 mg 1.6 mg 1.8 mg 2.0 mg
Somatropin (Humatrope®)	Grown hormone deficiency: Cartridge, powder for reconstitution, vial, powder for reconstitution: initial (non-weight based), 0.15 to 0.30 mg SC daily, then adjust every one to two months by increments of 0.1 to 0.2 mg/day, based on the clinical response and serum IGF-1 concentrations; initial (weight-based), 0.006 mg/kg SC daily, then adjust based on the clinical response, adverse effects and serum IGF-I concentrations; maximum, 0.0125 mg/kg/day	Growth failure associated with short-stature homeobox-containing gene deficiency: Cartridge, powder for reconstitution, vial, powder for reconstitution: 0.05 mg/kg SC daily (0.35 mg/kg/week) Growth failure associated with Turner syndrome: Cartridge, powder for reconstitution, vial, powder for reconstitution: 0.054 mg/kg SC daily (0.375 mg/kg/week) Growth failure in children born small for gestational age: Cartridge, powder for reconstitution, vial, powder for reconstitution: 0.067 mg/kg SC daily (0.47 mg/kg/week) Grown hormone deficiency: Cartridge, powder for reconstitution, vial, powder for reconstitution: 0.026 to 0.043 mg/kg SC daily (0.18 to 0.30 mg/kg/week)	Cartridge, powder for reconstitution: 6 mg 12 mg 24 mg Vial, powder for reconstitution: 5 mg

Generic Name	Adult Dose	Pediatric Dose	Availability
		Idiopathic short stature: Cartridge, powder for reconstitution, vial, powder for reconstitution: 0.053 mg/kg SC daily (0.37 mg/kg/week)	
Somatropin (Norditropin®)	Grown hormone deficiency: Prefilled cartridge, prefilled pen: initial (non-weight based), 0.15 to 0.30 mg SC daily, then adjust every one to two months by increments of 0.1 to 0.2 mg/day, based on the clinical response and serum IGF-1 concentrations; initial (weight-based), 0.004 mg/kg SC daily, then adjust after six weeks based on the clinical response, adverse effects and serum IGF-I concentrations; maximum, 0.016 mg/kg/day	Growth failure associated with Noonan syndrome: Prefilled cartridge, prefilled pen: 0.066 mg/kg SC daily Growth failure associated with Turner syndrome: Prefilled cartridge, prefilled pen: 0.067 mg/kg SC daily Growth failure in children born small for gestational age: Prefilled cartridge, prefilled pen: 0.067 mg/kg SC daily Grown hormone deficiency: Prefilled cartridge, prefilled pen: 0.024 to 0.034 mg/kg SC daily, six to seven times a week	Prefilled cartridge: 5 mg/1.5 mL Prefilled pen (Norditropin® FlexPro®): 5 mg/1.5 mL 10 mg/1.5 mL 15 mg/1.5 mL Prefilled pen (Norditropin NordiFlex®): 30 mg/3 mL
Somatropin (Nutropin®)	Grown hormone deficiency: Vial, powder for reconstitution, vial, liquid, prefilled cartridge, prefilled pen cartridge: initial (non-weight based), 0.15 to 0.30 mg SC daily, then adjust every one to two months by increments of 0.1 to 0.2 mg/day, based on the clinical response and serum IGF-1 concentrations; initial (weight-based), 0.006 mg/kg SC daily, then adjust based on the clinical response, adverse effects and serum IGF-I concentrations; maximum, 0.025 mg/kg/day in patients <35 years old and 0.0125 mg/kg/day in patients >35 years old	Growth failure associated with chronic renal insufficiency before renal transplant: Vial, powder for reconstitution, vial, liquid, prefilled cartridge, prefilled pen cartridge: 0.35 mg/kg/week SC divided into daily doses, continue up to the time of renal transplantation Growth failure associated with Turner syndrome: Vial, powder for reconstitution, vial, liquid, prefilled cartridge, prefilled pen cartridge: 0.375 mg/kg/week SC divided into three to seven doses Grown hormone deficiency: Vial, powder for reconstitution, vial, liquid, prefilled cartridge, prefilled pen cartridge: 0.3 mg/kg/week SC divided into daily doses; 0.7 mg/kg/week may be used in pubertal patients Idiopathic short stature:	Vial, powder for reconstitution: 5 mg 10 mg Vial, liquid: 10 mg/2 mL Prefilled cartridge: 5 mg/2 mL 10 mg/2 mL 20 mg/2 mL Prefilled pen cartridge: 10 mg/2 mL 20 mg/2 mL

Generic Name	Adult Dose	Pediatric Dose	Availability
		Vial, powder for reconstitution, vial, liquid, prefilled cartridge, prefilled pen cartridge: 0.3 mg/kg/week SC divided into daily doses	
Somatropin (Omnitrope®)	Grown hormone deficiency: Prefilled cartridge, vial, powder for reconstitution: initial (non-weight based), 0.15 to 0.30 mg SC daily, then adjust every one to two months by increments of 0.1 to 0.2 mg/day, based on the clinical response and serum IGF-1 concentrations; initial (weight-based), 0.04 mg/kg/week SC divided into daily doses, then adjust every four to eight weeks based on the clinical response, adverse effects and serum IGF-I concentrations; maximum, 0.008 mg/kg/week	Growth failure associated with Prader-Willi syndrome: Prefilled cartridge, vial, powder for reconstitution: 0.24 mg/kg/week SC divided into six or seven doses Growth failure associated with Turner syndrome: Prefilled cartridge, vial, powder for reconstitution: 0.33 mg/kg/week SC divided into six to seven doses Growth failure in children born small for gestational age: Prefilled cartridge, vial, powder for reconstitution: 0.48 mg/kg/week SC divided six or seven doses Grown hormone deficiency: Prefilled cartridge, vial, powder for reconstitution: 0.16 to 0.24 mg/kg/week SC divided into six or seven doses Idiopathic short stature: Prefilled cartridge, vial, powder for reconstitution: 0.47 mg/kg/week SC divided into six or seven doses	Prefilled cartridge: 5 mg/1.5 mL 10 mg/1.5 mL Vial, powder for reconstitution: 5.8 mg
Somatropin (Saizen®)	Grown hormone deficiency: Cartridge, powder for reconstitution, vial, powder for reconstitution: initial (non-weight based), 0.15 to 0.30 mg SC daily, then adjust every one to two months by increments of 0.1 to 0.2 mg/day, based on the clinical response and serum IGF-1 concentrations; initial (weight-based), 0.005 mg/kg SC daily, then adjust after four weeks based on the clinical response,	Grown hormone deficiency: Cartridge, powder for reconstitution, vial, powder for reconstitution: 0.18 mg/kg/week SC or IM divided into three, six or seven doses	Cartridge, powder for reconstitution: 8.8 mg Vial, powder for reconstitution: 5 mg (15 IU) 8.8 mg (26.4 IU)

Generic Name	Adult Dose	Pediatric Dose	Availability
	adverse effects and serum IGF-I concentrations; maximum, 0.01 mg/kg/week		
Somatropin (Serostim®)	Human immunodeficiency virus-associated wasting or cachexia: Vial, powder for reconstitution: SC at bedtime with the following weight-based dosage: body weight <35 kg, 0.1 mg/kg/day; 35 to 45 kg, 4 mg/day; 45 to 55 kg, 5 mg/day; >55 kg, 6 mg/day; maximum, 6 mg/day	Safety and efficacy in children have not been established.	Vial, powder for reconstitution: 4 mg (12 IU) Vial, powder for reconstitution (preservative-free): 5 mg (15 IU) 6 mg (18 IU)
Somatropin (Tev-Tropin®)	Safety and efficacy in adults have not been established.	Grown hormone deficiency: Vial, powder for reconstitution: 0.1 mg/kg SC three times a week	Vial, powder for reconstitution: 5 mg (15 IU)

Drug regimen abbreviations: IM=intramuscular, IU=international unit, SC=subcutaneous
Other abbreviations: IGF-1=insulin-like growth factor 1

Clinical Guidelines

Current guidelines are summarized in Table 11. Due to the complexity of the diseases for which growth hormone is indicated, the guidelines summaries focus on the role of growth hormone in disease management. In addition, because of the rarity of these diseases, national consensus guidelines have not been developed for all indications. In such cases, guideline summaries from national groups or conference, when available, are summarized below.

Table 11. Clinical Guidelines

Clinical Guideline	Recommendations
Endocrine Society: **Evaluation and Treatment of Adult Growth Hormone Deficiency (2011)**[21]	Definition of growth hormone deficiency (GHD) in adults • Patients with childhood-onset GHD who are candidates for growth hormone (GH) therapy after adult height is achieved are recommended to be retested for GHD unless they have known mutations, embryopathic lesions causing multiple hormone deficits or irreversible structural lesions/damage. • In adult patients with structural hypothalamic/pituitary disease, surgery or irradiation in these areas, head trauma, or evidence of other pituitary hormone deficiencies, consideration for evaluation for acquired GHD is recommended. • Because in the absence of suggestive clinical circumstances there is a significant false-positive error rate in the response to a single GH stimulation test, the use of two tests before making a diagnosis of idiopathic GHD is suggested. The presence of a low insulin-like growth factor (IGF-I) also increases the likelihood of this diagnosis. Diagnosis of GHD • The insulin tolerance test (ITT) and the growth hormone releasing hormone (GHRH)-arginine (ARG) test are recommended to have sufficient sensitivity and specificity to establish the diagnosis of GHD. However, in those with clearly established, recent (within 10 years)

Clinical Guideline	Recommendations
	hypothalamic causes of suspected GHD (e.g., irradiation) testing with GHRH-ARG may be misleading. • When GHRH is not available and ITT is either contraindicated or not practical in a given patient, the glucagon test can be used. • Because of the irreversible nature of the cause of the GHD in children with structural lesions with multiple hormone deficiencies and those with proven genetic causes, a low IGF-I level at least one month off GH therapy is recommended as sufficient documentation of persistent GHD without additional provocative testing. • A normal IGF-I level does not exclude the diagnosis of GHD, but provocative testing is recommended as mandatory to make the diagnosis of GHD. However, a low IGF-I level, in the absence of catabolic conditions such as poorly controlled diabetes, liver disease, and oral estrogen therapy, may be useful in identifying patients who may benefit from treatment and therefore require GH stimulation testing. • Provocative testing is optional in patients with deficiencies in three or more pituitary axes as GHD is strongly suggested. Side effects and risks associated with GH therapy • Treatment is contraindicated in the presence of active malignancy. • It is recommended that GH treatment in patients with diabetes may require adjustments in antidiabetic medications. • Monitoring of thyroid and adrenal function during therapy with GH is suggested. Treatment regimens • GH dosing regimens should be individualized rather than weight based, and start with low doses and titrate according to clinical response, side effects and IGF-1 levels. • GH dosing taking gender, estrogen status and age into consideration is recommended. • Monitoring patients at one- to two-month intervals during dose titration and semiannually thereafter with clinical assessment and an evaluation for adverse effects, IGF-1 levels and other parameters of GH response are suggested.
American Association of Clinical Endocrinologists: **American Associated of Clinical Endocrinologists Medical Guidelines for Clinical Practice for Growth Hormone Use in Growth Hormone-Deficient Adults and Transition Patients – 2009 Update (2009)**[20]	• GH is recommended for the approved uses of the drug in patients with clinical features suggestive of adult GHD and biochemically proven evidence of adult GHD. Recommendations for transition patients • Patients with childhood-onset GHD previously treated with GH in childhood should be retested after final height is achieved and GH therapy should be discontinued at least one month to determine GH status before considering restarting therapy. Exceptions to this include patients with known mutations, patients with embryonic/congenital defects, patients with irreversible hypothalamic-pituitary structural lesions and patients with evidence of panhypopituitarism (at least three pituitary hormone deficiencies) and serum IGF-1 levels below the age and sex appropriate reference range off GH therapy. For patients that received childhood GH therapy for conditions other than GHD (e.g., Turner's syndrome, idiopathic short stature), retesting and GH therapy is not recommended after final height has been achieved. • The preferred GH stimulation test to establish the diagnosis of GHD is

Clinical Guideline	Recommendations
	the ITT. Alternative tests include GHRH-ARG test, glucagon test and rarely the ARG test alone. An ITT or glucagon test should be used for patients with hypothalamic GHD (e.g., idiopathic isolated GHD of childhood). • Upon restarting GH therapy, the dose should be approximately 50% of the dose between the pediatric dose required and the adult dose. <u>Recommendations for diagnosis of adult GHD</u> • Patients with irreversible hypothalamic-pituitary structural lesions and patients with evidence of panhypopituitarism (at least three pituitary hormone deficiencies) and serum IGF-1 levels below the age and sex appropriate reference range off GH therapy do not require further testing. • The preferred GH stimulation test to establish the diagnosis of adult GHD is the ITT. Alternative tests include GHRH-ARG test, glucagon test and rarely the ARG test alone. • In patients where the ITT is not desirable and when GHRH is not available, the glucagon test is an alternative, but not the levodopa and clonidine tests. • Because of the potential for false-negative results with the GHRH-ARG test in patients with hypothalamic GHD, patients should be retested with ITT, glucagon test or rarely the ARG test alone if the GH is above the cut point. • In patients with traumatic brain injury and aneurysmal subarachnoid hemorrhage, GHD may be transient and GH stimulation tests should be 12 months after the event. <u>Recommendations for GH dosing regimens</u> • GH dosing regimens should be individualized independent of body weight, starting with a low dose and gradually increasing to the minimal dose that normalizes serum IGF-1 levels without causing unacceptable side effects. • GH deficient women with an intact hypothalamic-pituitary-gonadal axis and woman on oral estrogens are more GH resistant than men and will require higher initial and maintenance doses of GH compared to their male counterparts to achieve the same clinical and biochemical response. • The starting dose, size of dose adjustments and target serum IGF-1 levels should be reduced in the elderly due to a greater sensitivity to side effects of exogenous GH. • For patients with compliance issues, administration of GH on alternate days or three times per week using the same total weekly dosage may be considered. • There is no evidence that one GH product is more advantageous over the other, apart from differences in pen devices, dose increments and decrements and whether or not the product requires refrigeration; therefore, the use of one commercial GH preparation over another is not recommended. • Initiating and maintaining GH therapy using low GH dosages (0.1 to 0.2 mg/day) may be more appropriate in patients with concurrent diabetes, obesity and in those with previous gestational and family history of diabetes so as not to aggravate blood glucose levels. • After initiation of GH therapy, patients should be followed-up at one to

Clinical Guideline	Recommendations
	two month intervals, and the dosage should be increased in steps of 0.1 to 0.2 mg/day based on clinical response, serum IGF-1 levels, side effects and individual considerations. Longer time intervals and smaller dose increments may be needed for older patients. Recommendation for monitoring efficacy • When maintenance doses are achieved, serum IGF-1, fasting glucose, hemoglobin A1c, body mass index, waist circumference, waist-to-hip ratio, serum-free T_4 and assessment of hypothalamic-pituitary-adrenal axis clinically or via early morning cortisol or cosyntropin stimulation (in patients not on glucocorticoid replacement), testosterone and fasting lipid panel and overall clinical status should be performed at six to 12 month intervals. Monitoring of fasting lipid profile, systolic and diastolic blood pressure, heart rate and electrocardiogram results should be considered at follow-up. Echocardiogram and echo-Doppler examinations should be performed only if clinically indicated. • Measurement of bone mineral content and bone mineral density should be measured before starting GH therapy. If the dual-energy X-ray absorptiometry scan is abnormal, repeat scans are recommended at two- to three-year intervals. • In patients with pituitary microadenomas or postsurgery residual pituitary tumor, periodic magnetic resonance imaging should be undertaken to assess the size of the tumor. • Patients should be administered a specific quality of life questionnaire before they begin GH therapy, and annual evaluation is recommended to determine whether there is a change or sustained impact of GH therapy on quality of life. • Depending on individual circumstances, targeting the serum IGF-1 to the middle of the age and sex appropriate reference range is recommended for titrating the dose of GH. • Dose adjustments of other hormones may be required. • Indefinite continuation of GH is recommended if patients report significant quality of life benefits and objective improvements of biochemistry and body composition. However, if the patient reports neither subjective nor objective benefits, then it is reasonable to consider discontinuing GH treatment altogether. Recommendations for safety of GH replacement • If diabetes is diagnosed during GH therapy, or if GH is considered for patients with diabetes, adjustments in anti-diabetic medications and treatment with low-dose GH may be necessary. Alternatively, it is reasonable to withhold or discontinue GH therapy and to optimize the treatment of the diabetes before reconsidering later resumption of low-dose GH replacement. • GH treatment is contraindicated in patients with a previous history of malignancy or in the presence of active malignancy. • Continued long-term surveillance of patients with pituitary-region tumors regardless of whether or not these patients are treated with GH therapy is recommended.
National Institute for Health and Clinical Excellence: **Human Growth**	• Somatropin is recommended as a treatment option for children with growth failure associated with any of the following: GHD, Turner syndrome, Prader-Willi syndrome, chronic renal insufficiency, born small for gestational age with subsequent growth failure at four years of age or

Clinical Guideline	Recommendations

Hormone (Somatropin) for the Treatment of Growth Failure in Children (2010)[12]	later and short stature homeobox-containing gene deficiency.
	• Treatment with somatropin should always be initiated and monitored by a pediatrician with specialist expertise in managing GH disorders in children. The choice of product should be individualized after informed discussion between the responsible clinician and the patient and/or caretaker about the advantages or disadvantages of available products, taking into consideration therapeutic need and likelihood of adherence to treatment. If more than one product is suitable, the least costly product should be chosen.
	• Treatment with somatropin should be discontinued if any of the following apply:
	  ◦ Growth velocity increase less than 50% from baseline in the first year of treatment.
	  ◦ Final height is approached and growth velocity is less than 2 cm in one year.
	  ◦ There are insurmountable problems with adherence.
	  ◦ Final height is attained.
	• In Prader-Willi syndrome, evaluation of response to therapy should also consider body composition.
	• Treatment should not be discontinued by default. The decision to stop treatment should be made in consultation with the patient and/or caretakers either by a pediatrician with specialist expertise in managing GH disorders in children or an adult endocrinologist, if the care has been transferred from pediatric to adult services.

National Kidney Foundation: **Kidney Disease Outcomes Quality Initiative Clinical Practice Guideline for Nutrition in Children with Chronic Kidney Disease: 2008 Update (2008)**[13]	• Identification and treatment of existing nutritional deficiencies and metabolic abnormalities should be aggressively pursued in children with chronic kidney disease stages 2 to 5 and 5D, short stature (height standard deviation score <-1.88 or height-for-age <3rd percentile) and potential for linear growth. • Serum bicarbonate should be corrected to at least the lower limit of normal (22 mmol/L) in children with chronic kidney disease stages 2 to 5 and 5d. • Recombinant human growth hormone therapy should be considered in children with chronic kidney disease stages 2 to 5 and 5d, short stature (height standard deviation score <-1.88 or height-for-age <3rd percentile) and potential for linear growth if growth failure (height velocity-for-age standard deviation score <-1.88 or height velocity-for-age <3rd percentile) persists beyond three months despite treatment of nutritional deficiencies and metabolic abnormalities.
Dyscerne: **Management of Noonan Syndrome: a Clinical Guideline (2010)**[14]	Patients one to 11 years of age • Plotting growth on a Noonan syndrome growth chart is recommended as many patients will reach a height within the normal range without GH therapy. • All children with a height below the mean for Noonan syndrome should be referred to a pediatric endocrinologist for assessment. If height is below 2.5 standard deviations from the mean on standard childhood charts, GH therapy may be considered without evaluation for the GH axis. If IGF-1 levels are low, testing of the GH axis should be considered to show GHD.
Noonan Syndrome Support Group: **Noonan Syndrome: Clinical Features,**	• Children should be weighed and measured regularly by the primary care provider, and the data should be plotted on appropriate growth charts. • Children with evidence of growth failure (growth deceleration, height less than -2 standard deviations, or height inappropriate for genetic

Clinical Guideline	Recommendations
Diagnosis, and Management Guidelines (2010)[15]	background) that cannot be explained by a comorbidity should be monitored more often, have nutrition optimized, have baseline laboratory tests run and/or be referred to a pediatric endocrinologist. • Therapeutic interventions as indicated are recommended (e.g., GH for growth failure).
Growth Hormone Research Society: **Workshop Summary: Consensus Guidelines for Recombinant Human Growth Hormone Therapy in Prader-Willi Syndrome (2013)**[17]	• After genetic confirmation of Prader-Willi syndrome, GH therapy should be considered and, if initiated, continued for as long as demonstrated benefits outweigh the risks. • GH stimulation testing should not be required as part of the decision-making process in infants and children with Prader-Willi syndrome. • Adults with Prader-Willi syndrome should have an evaluation of the GH/IGF axis prior to GH treatment. • Prior to initiation of GH treatment, patients with Prader-Willi syndrome should have a genetically confirmed diagnosis and expert multidisciplinary evaluation. • Exclusion criteria for starting GH in patients with Prader-Willi syndrome include severe obesity, uncontrolled diabetes, untreated severe obstructive sleep apnea, active cancer and active psychosis. • Scoliosis is not a contraindication to GH treatment in patients with Prader-Willi syndrome. • Infants and children with Prader-Willi syndrome should start with a daily dose of 0.5 mg/m^2/day subcutaneously with subsequent adjustments toward 1.0 mg/m^2/day every three to six months according to clinical response and guided by maintenance of physiologic levels of IGF-I. • Adults with Prader-Willi syndrome should receive a starting dose of 0.1 to 0.2 mg/day based on age, presence of edema, prior GH treatment, sensitivity and concomitant oral estrogen use. Subsequent dosage titration should be based on clinical response, age, and sex appropriate IGF-I levels in the zero to two standard deviation range. • IGF-I levels in patients with Prader-Willi syndrome on GH treatment should be maintained within the upper part of normal range (one to two standard deviations) for healthy, age-matched normal individuals. • Clinical outcome priorities should vary depending on the age, and on the presence of physical, mental and social disability. • Monitoring of GH treatment in patients with Prader-Willi syndrome should address specific benefits and risks of treatment in this population and the potential impact of other hormonal deficiencies. • Patients with Prader-Willi syndrome receiving GH treatment must be followed carefully for potential adverse effects during GH treatment. • Treatment with GH must be in the context of appropriate dietary, environmental, and lifestyle interventions necessary for care of all patients with Prader-Willi syndrome. • Cognitive impairment should not be a barrier to treatment with GH for patients with Prader-Willi syndrome.
Expert Meeting of the Comprehensive Care of Patients with Prader-Willi Syndrome: **Recommendations for the Diagnosis and Management of Prader-Willi Syndrome (2008)**[16]	• GH therapy should be started early in childhood, taking into account cautions and relative contraindications. • Appropriate monitoring of GH replacement is essential. • Before starting GH therapy, there should be genetic confirmation of Prader-Willi syndrome, nutritional evaluation and evaluation of IGF-1 status and, if possible, GH status. Additionally, an oral glucose tolerance test, scoliosis evaluation, sleep and breathing evaluation and evaluation of hypothyroidism are recommended.

Clinical Guideline	Recommendations
	• During GH treatment, regular clinical assessment of height, weight, body mass index, body composition, pubertal status, scoliosis, IGF-1 and side effects are recommended every three to six months. Regular bone age and monitoring for hypothyroidism are also recommended. • Cessation of GH treatment should be considered if there is uncontrolled progression of obesity, continued worsening of glycemic control, continued worsening of sleep-disordered breathing or attainment of final height.
Turner Syndrome Study Group: **Care of Girls and Women with Turner Syndrome (2007)**[18]	• Provocative GH testing should only be performed in patients with abnormal growth relative to expected for Turner syndrome on a Turner syndrome specific growth curve. • Treatment with GH should be considered as soon as growth failure has been demonstrated. • GH doses can be changed based on growth response and IGF-1 levels. • Therapy may be continued until final height has been attained or little growth potential remains. • Therapy should be directed by a pediatric endocrinologist and the patient monitored every three to six months. Evaluation should include monitoring for orthopedic problems and growth velocity.
Growth Hormone Research Society/Lawson Wilkins Pediatric Endocrine Society/European Society for Pediatric Endocrinology: **Consensus Statement on the Diagnosis and Treatment of Children with Idiopathic Short Stature (2008)**[19]	• Other causes of short stature (e.g., GHD) must be ruled out in order to make a diagnosis of idiopathic short stature. • The height below which GH treatment could be considered is -2 to 3-standard deviation score. • Age should be taken into consideration when initiating GH therapy. • There are no biochemical criteria for initiating GH treatment in idiopathic short stature. • Predicted adult height can be used with other criteria to decide to treat with GH therapy. • A successful first year response can be defined as a change in height standard deviation score more than 0.3 to 0.5, a first year height velocity increment of more than 3 cm/year or a height velocity of standard deviation score more than 1. • Therapy can be stopped when near adult height is achieved (height velocity of <2 cm/year and/or bone age >16 years in boys and >14 years in girls) or when height is in the normal adult range (above -2 standard deviation score).

Conclusions

The safety and efficacy of growth hormone (GH) therapy in pediatric patients with failure to grow is well established.[22-79] Once a diagnosis of growth hormone deficiency (GHD) is confirmed, GH therapy should be initiated immediately and continued at least until linear growth is nearly complete (e.g., decreased to less than 2.5 cm/year). Available GH preparations are indicated for use in a variety of pediatric conditions associated with a failure in growth, including growth failure associated with chronic kidney disease, Turner syndrome, being born small for gestational age, Prader-Willi syndrome, mutations in the Short Stature Homeobox gene and Noonan syndrome, as well as for idiopathic short stature.[1,3-9,11]

The role of GH therapy in adult patients with GHD is less clear. There is evidence to demonstrate that when used in adult patients with GHD, GH therapy increases muscle mass and decreases body fat. Evidence of other potential beneficial effects of GH therapy in adults are not as established, including improvement in bone mineral density, sense of well-being, muscle strength and lipid profile.[2]

There are several GH preparations currently available, which all contain somatropin or recombinant human growth hormone.[3-11] The various preparations are equally biopotent and have the same natural

sequence structure.[1] All of the available GH preparations are available for subcutaneous injection and there are currently no generics available within the class.[3-11]

For pediatric patients, treatment guidelines recommend the use of GH therapy with somatropin as a treatment option for children with growth failure associated with any of the following: GHD, Turner syndrome, Prader-Willi syndrome, chronic renal insufficiency, born small for gestational age with subsequent growth failure at four years of age or later and short stature homeobox-containing gene deficiency.[12-19] Choice of preparation should be individualized based on potential advantages and disadvantages of therapy, therapeutic need and the likelihood of adherence. If more than one preparation is suitable for a particular patient, the least costly one should be utlized.[12] For adult patients, treatment guidelines recommend the use of GH therapy for the approved indications of the preparations in patients with clinical features suggestive of adult GHD and biochemically proven evidence of adult GHD.[20] Therapy should be individualized independent of body weight. The dose of GH should be low initially and gradually increased to the minimally effective dose that normalizes insulin growth factor 1 levels without side effects.[20,21] Guidelines do not distinguish among the various GH preparations.

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