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Clinical Research Article

Efficacy and Safety of Weekly Somatrogon vs Daily Somatropin in Children With Growth Hormone Deficiency: A Phase 3 Study

Cheri L. Deal,[1] Joel Steelman,[2] Elpis Vlachopapadopoulou,[3] Renata Stawerska,[4] Lawrence A. Silverman,[5] Moshe Phillip,[6] Ho-Seong Kim,[7] CheolWoo Ko,[8] Oleg Malievskiy,[9] Jose F. Cara,[10] Carl L. Roland,[11] Carrie Turich Taylor,[10] Srinivas Rao Valluri,[10] Michael P. Wajnrajch,[10,12] Aleksandra Pastrak,[13] and Bradley S. Miller[14]

[1]Centre de recherche CHU Ste-Justine, Université de Montréal, Montréal, Canada
[2]Cook Children's Medical Center, Fort Worth, TX, USA
[3]Children's Hospital P. & A. Kyriakou, Athens, Greece
[4]Polish Mother's Memorial Hospital-Research Institute, Lodz, and Medical University of Lodz, Lodz, Poland
[5]Goryeb Children's Hospital, Atlantic Health System, Morristown, NJ, USA
[6]Schneider Children's Medical Center of Israel, Petah Tikva, and Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel
[7]Yonsei University College of Medicine, Seoul, South Korea
[8]Kyungpook National University Children's Hospital, Daegu, South Korea
[9]Bashkir State Medical University, Ufa, Russia
[10]Pfizer Inc, New York, NY, USA
[11]Pfizer Inc, Sanford, NC, USA
[12]New York University Langone Medical Center, New York, NY, USA
[13]OPKO Health, Miami, FL, USA
[14]University of Minnesota Masonic Children's Hospital, Minneapolis, MN, USA

Correspondence: Bradley S. Miller, MD, PhD, Division of Endocrinology, Department of Pediatrics, University of Minnesota Masonic Children's Hospital, Academic Office Building 201, 2450 Riverside Avenue, Minneapolis, MN 55454, USA. Email: mille685@umn.edu.

Abstract

Context: Somatrogon is a long-acting recombinant human growth hormone (rhGH) in development for once-weekly treatment of children with growth hormone deficiency (GHD).

Objective: We aimed to compare the efficacy and safety of once-weekly somatrogon with once-daily somatropin in prepubertal children with GHD.

Methods: In this 12-month, open-label, randomized, active-controlled, parallel-group, phase 3 study, participants were randomized 1:1 to receive once-weekly somatrogon (0.66 mg/kg/week) or once-daily somatropin (0.24 mg/kg/week) for 12 months. A total of 228 prepubertal children (boys aged 3-11 years, girls aged 3-10 years) with GHD, impaired height and height velocity (HV), and no prior rhGH treatment were randomized and 224 received ≥1 dose of study treatment (somatrogon: 109; somatropin: 115). The primary endpoint was annualized HV at month 12.

Results: HV at month 12 was 10.10 cm/year for somatrogon-treated subjects and 9.78 cm/year for somatropin-treated subjects, with a treatment difference (somatrogon-somatropin) of 0.33 (95% CI: −0.24, 0.89). The lower bound of the 2-sided 95% CI was higher than the prespecified noninferiority margin (−1.8 cm/year), demonstrating noninferiority of once-weekly somatrogon vs daily somatropin. HV at month 6 and change in height standard deviation score at months 6 and 12 were similar between both treatment groups. Both treatments were well tolerated, with a similar percentage of subjects experiencing mild to moderate treatment-emergent adverse events in both groups (somatrogon: 78.9%, somatropin: 79.1%).

Conclusion: The efficacy of once-weekly somatrogon was noninferior to once-daily somatropin, with similar safety and tolerability profiles. (ClinicalTrials.gov no. NCT02968004).

Key Words: growth hormone, growth hormone deficiency, long-acting growth hormone, somatrogon, somatropin, pediatric

Abbreviations: ADA, anti-drug antibody; AE, adverse event; ANCOVA, analysis of covariance; BMI, body mass index; CTP, C-terminal peptide; GH, growth hormone; GHD, growth hormone deficiency; HbA1c, glycated hemoglobin A1c; hGH, human growth hormone; HV, height velocity; IGF-1, insulin-like growth factor 1; LS, least squares; MedDRA, Medical Dictionary for Regulatory Activities v22.0; OLE, open-label extension; PK/PD, pharmacokinetic/pharmacodynamic; rhGH, recombinant human growth hormone; SAE, serious adverse event; SDS, standard deviation score; TEAE, treatment-emergent adverse event.

Growth hormone deficiency (GHD) in children results in growth attenuation and ultimately, adult short stature. Treatment of GHD requires administration of growth hormone in the form of daily subcutaneous injections, which constitute a substantial burden for both pediatric patients (1) and their caregivers (2). Recombinant human growth

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hormone (rhGH) has been used to treat children with GHD for more than 30 years, and it has a well-established efficacy and safety profile (3). Treatment with rhGH has been demonstrated to promote linear growth, optimize adult height, increase bone mineral density, manage known risk factors (ie, increased body fat and insulin resistance, and cardiovascular risks), and improve body composition in children with GHD.

Most formulations of rhGH are currently administered via daily subcutaneous (SC) injections, with studies showing high rates of treatment cessation (4, 5). Poor adherence is associated with suboptimal response to treatment, with reduced linear growth and nonattainment of genetic height potential (4, 6). Noncompliance has been shown to increase over time and is a significant issue for long-term treatment (7, 8). Given the patient complaints surrounding the burden of daily growth hormone (GH) treatment, such as unhappiness with frequent injections, disruption of overnight travel plans, and nightly interruption of activities to administer medication (1), it is thought that these complaints will be mitigated by less-frequent injections (9, 10). A recently conducted discrete choice experiment demonstrated that patients prefer a less-frequent injection regimen for treating GHD (11). Furthermore, data from other indications demonstrate patient preference for long-acting treatments, as seen for preparations of recombinant follicle-stimulating hormone for fertility induction (12) and long-acting treatments for hemophilia (13, 14).

Somatrogon (MOD-4023) is a long-acting rhGH that is currently in development for the treatment of pediatric patients who have growth failure due to an inadequate secretion of endogenous GH. Somatrogon contains the amino acid sequence of hGH and 3 copies of the C-terminal peptide (CTP) of human chorionic gonadotropin. It was previously shown that the inclusion of CTP in proteins such as follicle-stimulating hormone (15, 16) and erythropoietin (17) led to increased half-life. In vitro data demonstrated that somatrogon binds to the GH receptor (18), and animal studies showed that the addition of CTP to rhGH extends the half-life of rhGH and that somatrogon effectively raises circulating levels of insulin-like growth factor 1 (IGF-1). A clinical study in adults with GHD revealed that most patients who received once-weekly somatrogon maintained IGF-1 standard deviation score (SDS) levels within the normal range (19).

A multicenter, open-label, randomized phase 2 study was conducted in children with GHD to compare the safety, tolerability, and efficacy of 3 different doses of somatrogon (0.25, 0.48, and 0.66 mg/kg/week) administered once weekly vs rhGH (Genotropin® [somatropin]; 0.24 mg/kg/week) administered once daily (20). The estimated half-life of somatrogon administered once weekly was 18 to 36 hours, which was ~5- to 10-fold longer than that of somatropin (20). Subjects in all 3 somatrogon dose cohorts showed acceleration of growth velocity following 12 months of somatrogon treatment. The somatrogon cohort who received 0.66 mg/kg/week had the highest mean annualized height velocity (HV; 11.9 cm/year), which was closest to that of the daily somatropin cohort (12.5 cm/year) (20). Somatrogon demonstrated an acceptable safety profile during treatment up to 12 months; no serious adverse events (SAEs) were reported, and there were no discontinuations due to adverse events (AEs) associated with somatrogon or somatropin. The tolerability of treatment with once-weekly somatrogon was similar to that of somatropin. Data collection is ongoing for the open-label extension (OLE) of this phase 2 study (21).

The results of the phase 2, dose-finding study by Zelinska and coauthors (20) demonstrated a dose-dependent trend of HV outcome and progressive increase in IGF-1 levels between the 3 doses of somatrogon, with no IGF-1 accumulation. The phase 2 data indicated that the somatrogon dose of 0.66 mg/kg/week elicited a comparable response outcome (HV SDS and height SDS at 12 months) to daily somatropin administration. Based on these findings, a 12-month, open-label, multicenter, randomized, active-controlled, parallel-group, phase 3 study was initiated to evaluate whether somatrogon administered once weekly (0.66 mg/kg/week) was noninferior to somatropin administered once daily (0.034 mg/kg/day) in prepubertal children with GHD.

Methods

Study Design and Treatment

This study was a 12-month, open-label, multicenter, randomized, active-controlled, parallel-group, phase 3 study comparing the safety and efficacy of somatrogon administered once weekly to somatropin administered once daily in prepubertal children with GHD who were GH-treatment naïve. This study was sponsored by OPKO Health (NCT02968004) and was conducted from April 2017 to August 2019 at 83 sites in 21 countries (Argentina, Australia, Belarus, Bulgaria, Canada, Colombia, Georgia, Greece, India, Israel, Mexico, New Zealand, Poland, Russian Federation, Spain, Republic of Korea, Taiwan, Turkey, Ukraine, the United Kingdom, and United States).

Following a 12-week screening period, subjects were randomized 1:1 (stratified according to region, GH peak levels, and chronological age) using the Interactive Web Response Technology system to receive SC doses of somatrogon administered once weekly (0.66 mg/kg/week) or SC doses of somatropin (Genotropin®) administered once daily (0.24 mg/kg/week) for 12 months (Fig. 1A). The daily somatropin dose was selected as per recommendations from the current product label. Both treatments were administered using a single-patient-use, multi-dose, disposable, pre-filled pen device utilizing 31-gauge, 5-mm-long BD Micro-Fine pen needles. During the study, doses of somatrogon and somatropin were adjusted every 3 months based on the subject's body weight. Furthermore, a predefined dose-adjustment algorithm was followed to guide decreases in dose when repeated elevated IGF-1 levels were observed (> +2 SD score [SDS]). Subjects who completed the 12-month main study were eligible to participate in a single-arm, long-term OLE. During the OLE period, subjects who received somatrogon in the main study continued the same treatment and subjects who received somatropin in the main study were switched to somatrogon (0.66 mg/kg/week).

The primary objective of the study was to demonstrate that 12-month HV following once-weekly somatrogon administration was noninferior to daily somatropin administration in children with GHD. The secondary objectives included additional efficacy endpoints (change in 6-month HV, change in height SDS at 6 and 12 months, change in bone maturation at 12 months, IGF-1 levels, and IGFBP-3 levels) as well as an evaluation of the safety and tolerability of somatrogon (incidence of AEs and SAEs, and clinical, biochemical, and hormonal

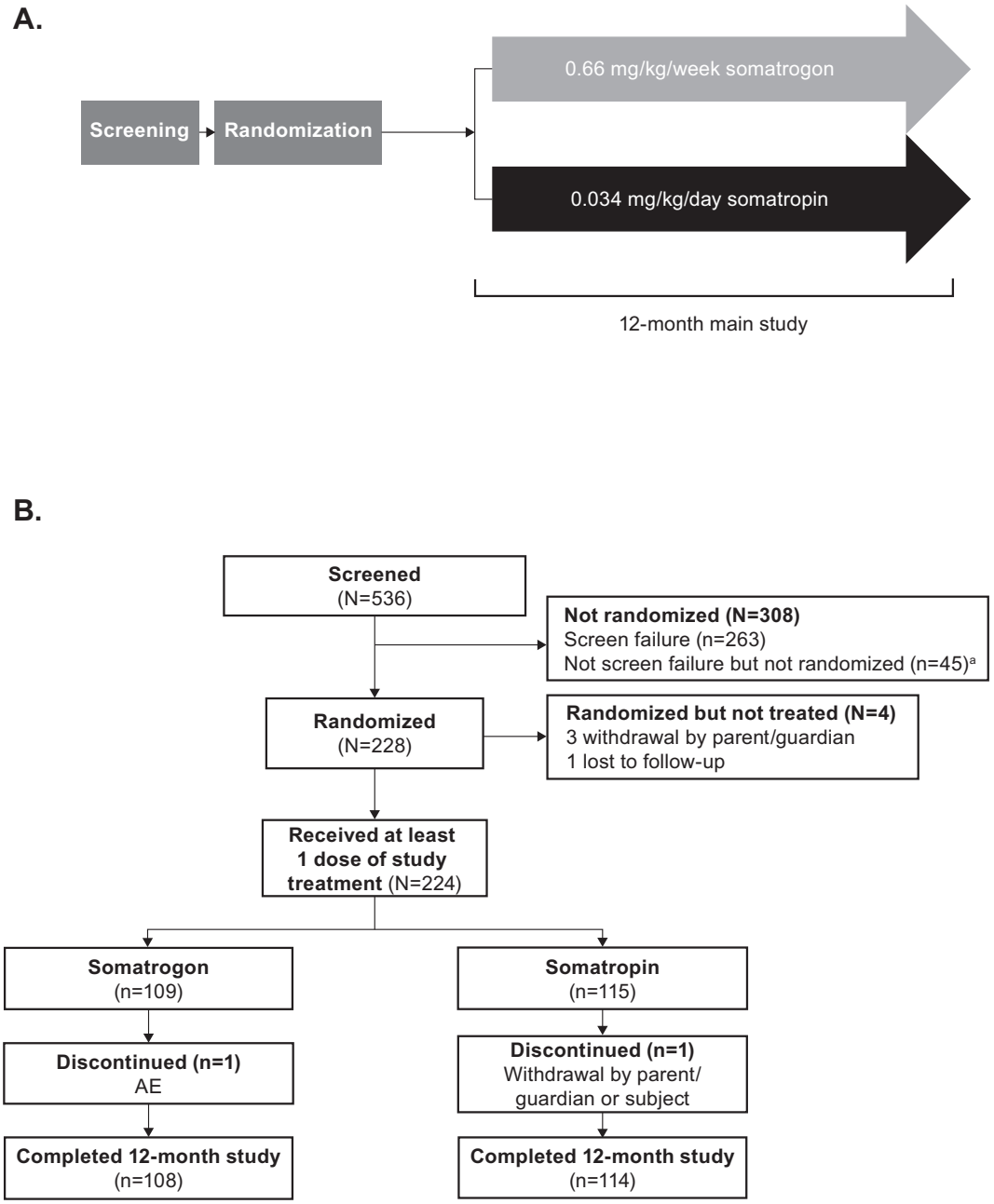

Figure 1. (A) Study design and (B) subject disposition. [a]Subjects who were in screening when enrollment target was met, and therefore not randomized to study treatment.

assessments described below). This study was approved by the institutional review board or independent ethics committee of the participating institutions and followed the Declaration of Helsinki and International Conference on Harmonization Good Clinical Practice guidelines. An independent, external Data and Safety Monitoring Board reviewed the key safety data approximately every 4 months or on an ad hoc basis as required. Prior to commencement of the study, written informed consent from each subject's parents/guardians and written assent from the pediatric subjects (where applicable based on age and country-specific regulations) were obtained.

Subjects

Prepubertal children (boys age range, 3-11 years; girls age range, 3-10 years) diagnosed with GHD were eligible for enrollment in this study if they had impaired height and HV (annualized HV below the 25th percentile for chronological age [HV < −0.7 SDS]), baseline IGF-1 level ≥ 1 SD below the age- and sex-standardized mean IGF-1 level (SDS ≤ −1), and had not received prior rhGH therapy. Subject height was not required to be < −2 SDS for inclusion in this study. IGF-1 levels were quantified using the same validated assay across all testing laboratories to ensure test alignment, irrespective of physical location. Diagnosis of GHD had to be confirmed using 2 different GH provocation tests (peak plasma GH level ≤ 10 ng/mL), determined at a local or central laboratory using a validated assay (insulin tolerance test, with serum cortisol response to hypoglycemia if insulin stimulation test was chosen; Arginine test; Clonidine test; Glucagon test; or L-dopa test). Subjects with congenital

causes of multiple pituitary hormone deficits were eligible but hydrocortisone and/or L-thyroxin replacement doses had to be stable for a minimum of 3 months prior to enrollment. Children in treatment for attention-deficit hyperactivity disorder were also eligible if their medication was stable for at least 3 months.

Subjects were excluded if they had any prior history of cancer or had received radiation therapy or chemotherapy. Subjects who had a body mass index (BMI) < −2 SDS (age- and sex-standardized), anti-rhGH antibodies at screening, psychosocial dwarfism, chromosomal abnormalities (including Turner's syndrome, Laron syndrome, Noonan syndrome, Prader-Willi syndrome, Silver-Russell syndrome, SHOX mutations/deletions, or skeletal dysplasia), or who were born small for their gestational age (birth weight and/or birth length < −2 SDS for gestational age) were also excluded from the study. Children with type 1 or type 2 diabetes mellitus were also excluded from the study if they were deemed by the investigator as not receiving standard of care, were noncompliant with their prescribed treatment, or were in poor metabolic control. Additional inclusion/exclusion criteria are listed in the Supplemental Methods (22).

Study Assessments

Efficacy

Height measurements were performed at screening, baseline, and months 3, 6, 9, and 12 using a calibrated, wall-mounted stadiometer; 3 independent readings were recorded for each visit. Height SDS was derived from the age and sex standards from the 2000 Centers for Disease Control Growth Charts (23). Annualized HV was calculated as the change in height from visit 2 (baseline) to visit 6 (month 6) and visit 8 (month 12). Bone age was determined via x-ray according to the Greulich-Pyle method (24) using a central bone age reader at screening, baseline, and month 12. A single radiologist, at a centralized Core Imaging Laboratory (Calyx) across all centers, reviewed all of the images, utilizing analysis software that provides magnification and panning tools. IGF-1 measurements were obtained at the same visits as the height measurements, as well as at month 1; IGF-1 was measured in a central laboratory using a chemiluminescence IGF-1 immunoassay (25). IGF-1 SDS was calculated using the modified least squares (LS) mean model as described by Bidlingmaier and coauthors (25). A previously developed indirect response pharmacokinetic/pharmacodynamic (PK/PD) model was applied to IGF-1 observations to estimate IGF-1 SDS profiles over the dosing interval (26).

Safety and tolerability

Safety evaluations included all AEs, concomitant medication use, treatment compliance (monitored via patient diaries), vital signs, electrocardiogram, physical examination, and laboratory assessments that consisted of: hematology, blood chemistry, glucose metabolism (fasting blood glucose, fasting insulin level, and glycated hemoglobin A1c [HbA1c]), endocrinology (free T4 and thyrotropin [TSH] levels), IGF-1 level, immunogenicity (anti-hGH antibodies in both groups and anti-somatrogon antibodies [with full length somatrogon used as the antigen] in the somatrogon group), and urinalysis. An AE was defined as any adverse change from the baseline condition of the subject, regardless of whether it was considered related to the investigational product. All AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA v22.0) and were classified according to the MedDRA preferred term and system organ class. The intensity or severity of an AE was characterized as mild, moderate, or severe. AEs of special interest (Supplemental Methods (22)) were selected from the class-based important potential identified risks relating to somatropin-containing products.

The tolerability of injection site pain was closely monitored and carefully documented in this study. Per protocol, the intensity of injection site pain was monitored with a Pain Assessment Scale from 0 ("no hurt") to 5 ("hurts worse"); the pain intensity scores were recorded in the patient diary. Pain was to be reported as an AE if the subject recorded a pain severity score ≥ 4 in the patient diary. In the somatrogon group, the severity of injection site pain after each weekly injection was recorded, whereas, in the somatropin group, the most-severe pain for the week was recorded (ie, once a week) rather than after each daily injection. Furthermore, if a somatropin-treated subject experienced multiple instances of pain with severity ≥ 4 during a week, only 1 occurrence would be recorded in the diary, and therefore only 1 AE would be recorded. As mandated by the study protocol, all episodes of injection site pain with pain assessment scale scores of 4 or 5 were then assigned severity scores (mild, moderate, severe) by investigators.

Serial serum samples were collected to test for antibodies against somatrogon using qualitative, validated methods as described by Zelinska et al (20).

Adherence

Adherence to somatrogon and somatropin treatment was assessed according to the following method: adherence rate (number of doses administered/number of doses expected) × 100, where number of doses administered was the difference between the number of expected doses and the number of missed doses. Patients reported missed or delayed doses in a patient diary. All used and unused injection devices were returned at various study visits and the amount of used and unused study drug was recorded.

Statistical Analyses

The safety analysis set consisted of all enrolled subjects who received at least 1 dose of the study treatment. The full analysis set included all randomized subjects who received at least 1 dose of the study drug, and this constituted the primary efficacy analysis set. The primary study endpoint was annual HV (cm/year) following 12 months of treatment. The noninferiority of somatrogon compared with somatropin was concluded if the lower bound of the 2-sided 95% CI for the mean treatment difference (somatrogon – somatropin) in the primary efficacy endpoint was ≥ −1.8 cm/year.

The CI for the difference in means between the 2 treatments was derived using analysis of covariance (ANCOVA). The ANCOVA model included terms for treatment, age group, sex, peak GH level, geographic region, and baseline height SDS as covariates. Delta-adjusted pattern imputation was applied and the imputed values were reduced by 1.8 cm/year, ie, the noninferiority margin. The secondary endpoints were annualized HV following 6 months of treatment, change in height SDS at 6 and 12 months (compared with baseline), change in bone maturation after 12 months (compared with bone age at screening), and IGF-1 SDS at baseline and 12 months. These endpoints were characterized using descriptive statistics. To

support the interpretation of the ANCOVA-based primary analysis, additional sensitivity analyses were also conducted using observed data, last height carried forward, and subgroup analyses.

Results

Patients and Treatment

A total of 536 subjects were screened, 228 were randomized, and 224 received at least 1 dose of study treatment (Fig. 1B). Screening failures were mainly due to subject IGF-1 levels being > −1.0 SD (~50% of screen failures) or subjects achieving a GH peak >10 ng/mL (~25% of screen failures). One subject from the somatrogon group discontinued from the study due to injection site erythema and injection site induration, and one subject in the somatropin group was withdrawn from the study (Fig. 1B). In all, 99% of subjects completed the study. Most subjects in the study were male (71.9%) and White (74.6%). Demographic and baseline characteristics were similar between the 2 treatment groups (Table 1).

Efficacy

At month 12, the LS mean estimate of annual HV using the ANCOVA model was 10.10 cm/year for somatrogon and 9.78 cm/year for somatropin. The treatment mean difference (somatrogon – somatropin) was 0.33 cm (95% CI: −0.24, 0.89). As the lower bound of the 2-sided 95% CI was greater

Table 1. Patient demographics and baseline characteristics (safety analysis set)

	Somatrogon (n = 109)	Somatropin (n = 115)	Total (N = 224)
Age, mean (range), y	7.83 (3.01-11.96)	7.61 (3.05-11.85)	7.72 (3.01-11.96)
Sex, n (%)			
Male	82 (75.2)	79 (68.7)	161 (71.9)
Female	27 (24.8)	36 (31.3)	63 (28.1)
Race, n (%)			
White	81 (74.3)	86 (74.8)	167 (74.6)
Black or African American	0	2 (1.7)	2 (0.9)
Asian	24 (22.0)	21 (18.3)	45 (20.1)
American Indian or Alaska Native	1 (0.9)	0	1 (0.4)
Native Hawaiian or Other Pacific Islander	0	1 (0.9)	1 (0.4)
Other	3 (2.8)	5 (4.3)	8 (3.6)
Height SDS			
Mean (SD)	−2.94 (1.29)	−2.78 (1.27)	−2.86 (1.28)
Weight SDS			
Mean (SD)	−2.66 (2.00)	−2.41 (1.50)	−2.53 (1.76)
BMI, SDS			
Mean (SD)	−0.28 (1.04)	−0.20 (1.01)	−0.24 (1.02)
Peak GH level group, n (%)			
≤3 ng/mL	22 (20.18)	21 (18.26)	43 (19.20)
>3 ng/mL to ≤7 ng/mL	53 (48.62)	56 (48.70)	109 (48.66)
>7 ng/mL	34 (31.19)	38 (33.04)	72 (32.14)
Peak GH (ng/dL)			
n	109	115	224
Mean (SD)	5.45 (2.81)	5.76 (2.59)	5.61 (2.70)
Range (min, max)	(0.10, 9.93)	(0.10, 9.90)	(0.10, 9.93)
Target height, males (cm)			
n	82	78	160
Mean (SD)	169.4 (7.04)	172.7 (5.56)	171.0 (6.56)
Range (min, max)	(152.0, 184.9)	(159.5, 184.5)	(152.0, 184.9)
Target height, females (cm)			
n	25	35	60
Mean (SD)	159.5 (6.26)	156.7 (8.82)	157.8 (7.92)
Range (min, max)	(149.8, 175.0)	(140.4, 171.3)	(140.4, 175.0)
Bone age, years			
n	107	107	214
Mean (SD)	5.46 (2.72)	5.19 (2.45)	5.33 (2.59)
Range (min, max)	(1.00, 11.00)	(1.25, 11.00)	(1.00, 11.00)

Abbreviations: BMI, body mass index; GH, growth hormone; min max, minimum maximum.

than the prespecified noninferiority margin (–1.8 cm/year), the study was considered to have met its primary objective of demonstrating that somatrogon administered once weekly was noninferior to somatropin administered once daily with respect to annual HV at 12 months in children with GHD. Results obtained using various sensitivity analyses were consistent with and supportive of the primary endpoint. The prespecified subgroup analyses comparing somatrogon and somatropin treatment based on age, sex, or peak GH levels showed that similar HVs were achieved in response to both treatments (Fig. 2).

The mean annualized HV at 6 months in the somatrogon group was similar to the somatropin group, with LS mean estimates of 10.59 and 10.04 cm/year, respectively (LS mean treatment difference 0.55 cm [95% CI, –0.13, 1.23]). At all post-baseline visits, both treatment groups had similar HV (Fig. 3A). Subjects in both the somatrogon and somatropin groups showed similar increases in mean change in height SDS from baseline to 6 months (LS mean treatment difference: 0.06 [95% CI, –0.01, 0.13]) (Fig. 3B). Similar improvements were also observed for both treatment groups from baseline to 12 months (LS mean treatment difference: 0.05 [95% CI, –0.06, 0.16]).

Plotting the individual growth responses of patients receiving somatrogon and somatropin (Supplemental Figure S1) (22) demonstrates similar growth trends and variability in both groups; peak height velocity was seen at 3 months. The large variability of height velocity in both groups at 3 months is expected due to the known impact of height measurement errors in this short interval.

The secondary endpoint of change in bone maturation was assessed as mean change in bone age relative to change in chronological age from baseline to 12 months; change in bone maturation was similar between treatment groups (somatrogon: 1.07; somatropin: 1.12). In the somatrogon group, the mean value for IGF-1 SDS was –1.95 at baseline, approached 0 at 1 month post-baseline, and was 0.65 SDS (range: –3.64 to 3.22) at 12 months post-baseline (Fig. 4). The mean IGF-1 SDS value in the somatropin group was –1.72 at baseline and remained near 0 at all post-baseline visits, ranging from –0.69 (12 months) to –0.16 SDS (Fig. 4).

Safety and Tolerability

The 2 treatment groups had a similar mean (SD) duration of treatment: somatrogon: 363 (32) days; somatropin: 355 (28) days. In all, 192 of 224 patients (85.7%) experienced a treatment-emergent AE (TEAE). The incidence of TEAEs was similar between the somatrogon (87.2%) and somatropin groups (84.3%) (Table 2). Most of the all-causality TEAEs experienced with somatrogon vs somatropin were mild (54.1% vs 60.0%) or moderate (24.8% vs 19.1%) in intensity (Supplemental Table S1 (22)). The incidence of severe TEAEs was 8.3% and 5.2% in the respective groups.

The most frequently reported all-causality TEAEs by MedDRA preferred term that occurred in ≥ 5% of subjects in any treatment group were injection site pain, nasopharyngitis, headache, pyrexia, cough, vomiting, anemia, arthralgia, bronchitis, pharyngitis, otitis media, tonsillitis, blood creatinine phosphokinase increased, oropharyngeal pain, hypothyroidism, ear pain, injection site erythema, abdominal pain

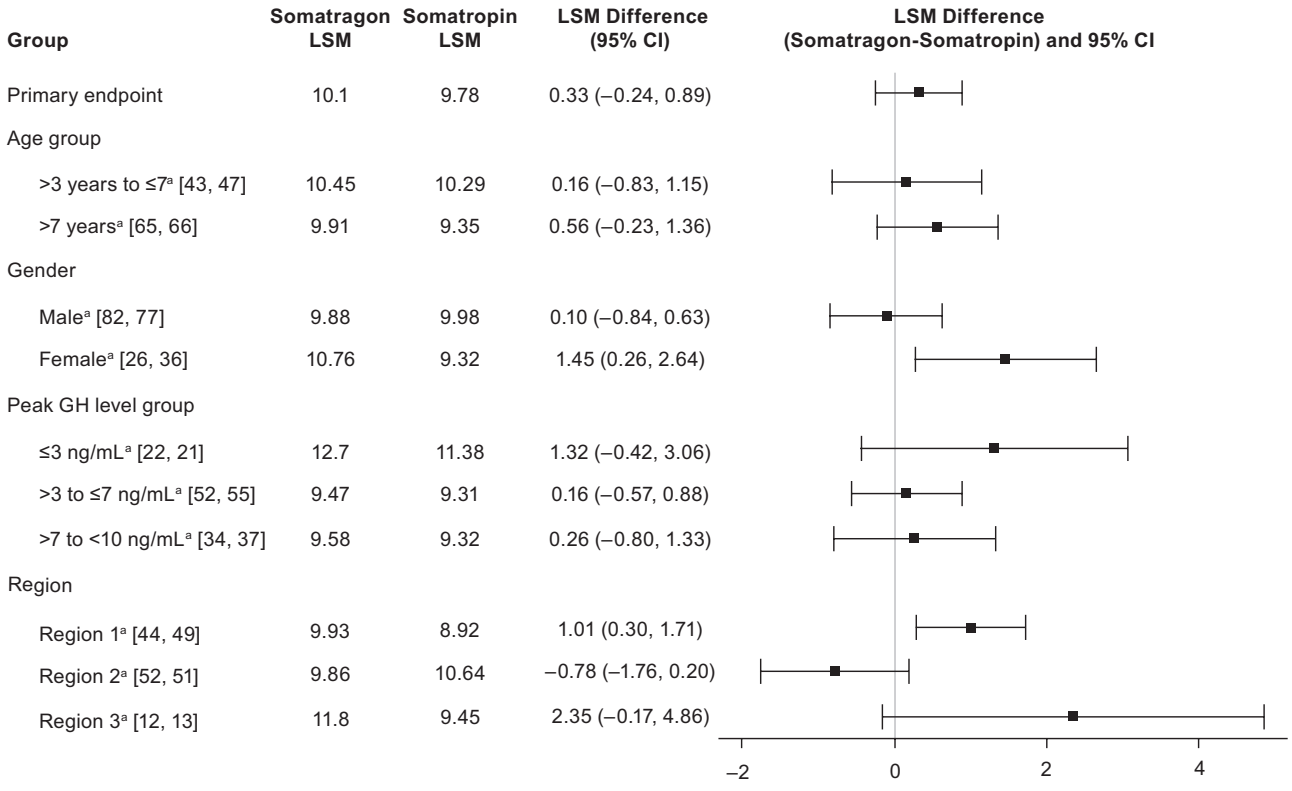

Figure 2. Subgroup analyses for the primary endpoint of height velocity at month 12. [a][n1, n2] represents the sample sizes for somatrogon and somatropin, respectively, within each subgroup. *Region 1*: Western Europe, Israel, Greece, Australia, New Zealand, Canada, and USA. *Region 2:* Central and Eastern Europe, Turkey, Latin America, and Asia, except for India and Vietnam. *Region 3*: India and Vietnam. Abbreviations: GH, growth hormone; LSM, least squares mean.

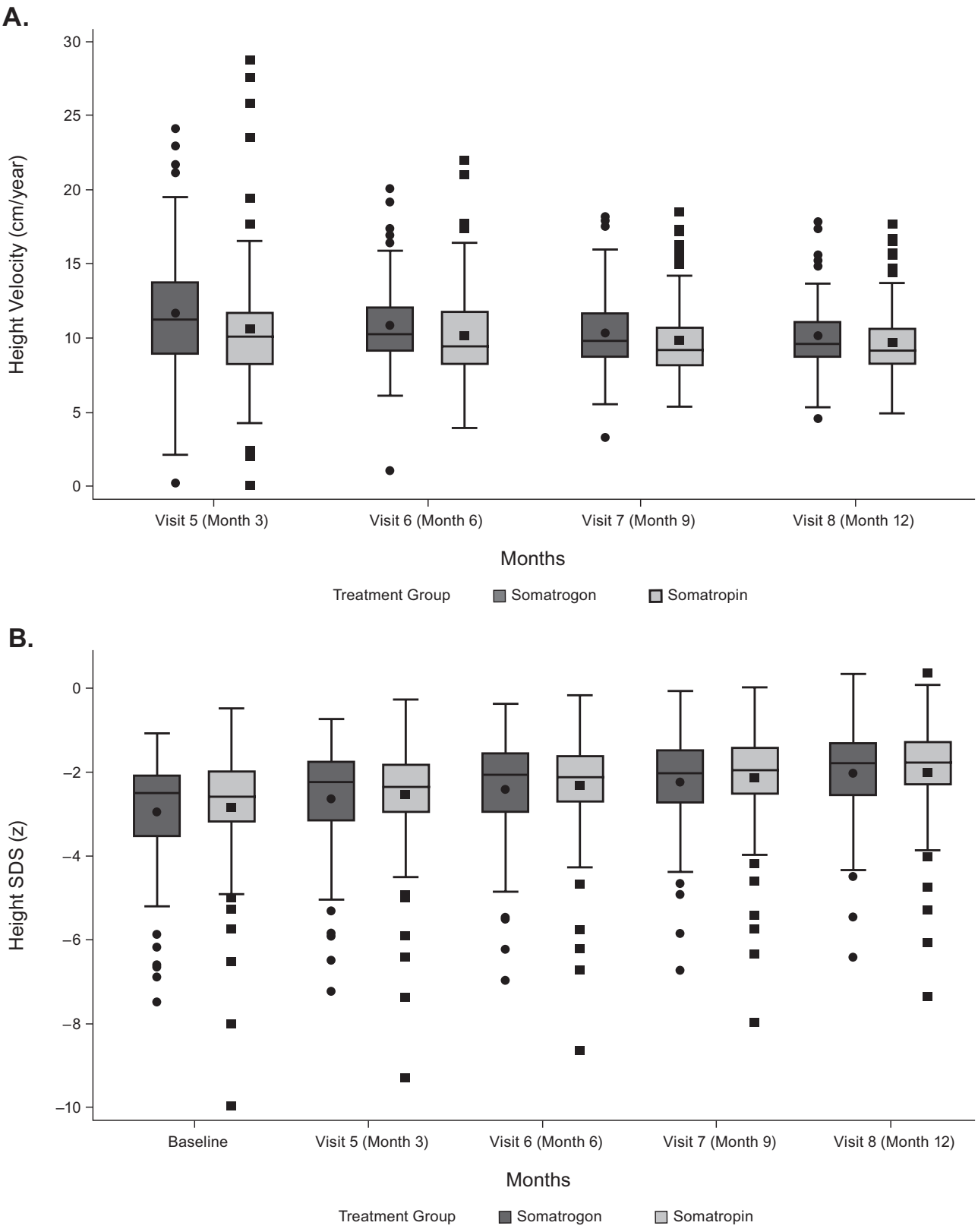

Figure 3. Summary of (A) height velocity and (B) height SDS over time. Baseline is defined as the last non-missing measurement prior to the start of study drug. Abbreviation: SDS, standard deviation score.

upper, rhinitis, arthropod bite, and injection site pruritus (Table 3). All-causality TEAEs with ≥ 5% higher incidence in the somatrogon group than in the somatropin group were injection site erythema, injection site pain, and injection site pruritus (Table 3).

Most TEAEs of injection site pain were mild or moderate in severity for subjects in both treatment groups. Eight subjects reported severe injection site pain (somatrogon: n = 5 [4.6%]; somatropin: n = 3 [2.6%]). The severity of injection site pain TEAEs over time in both treatment groups are shown as heat

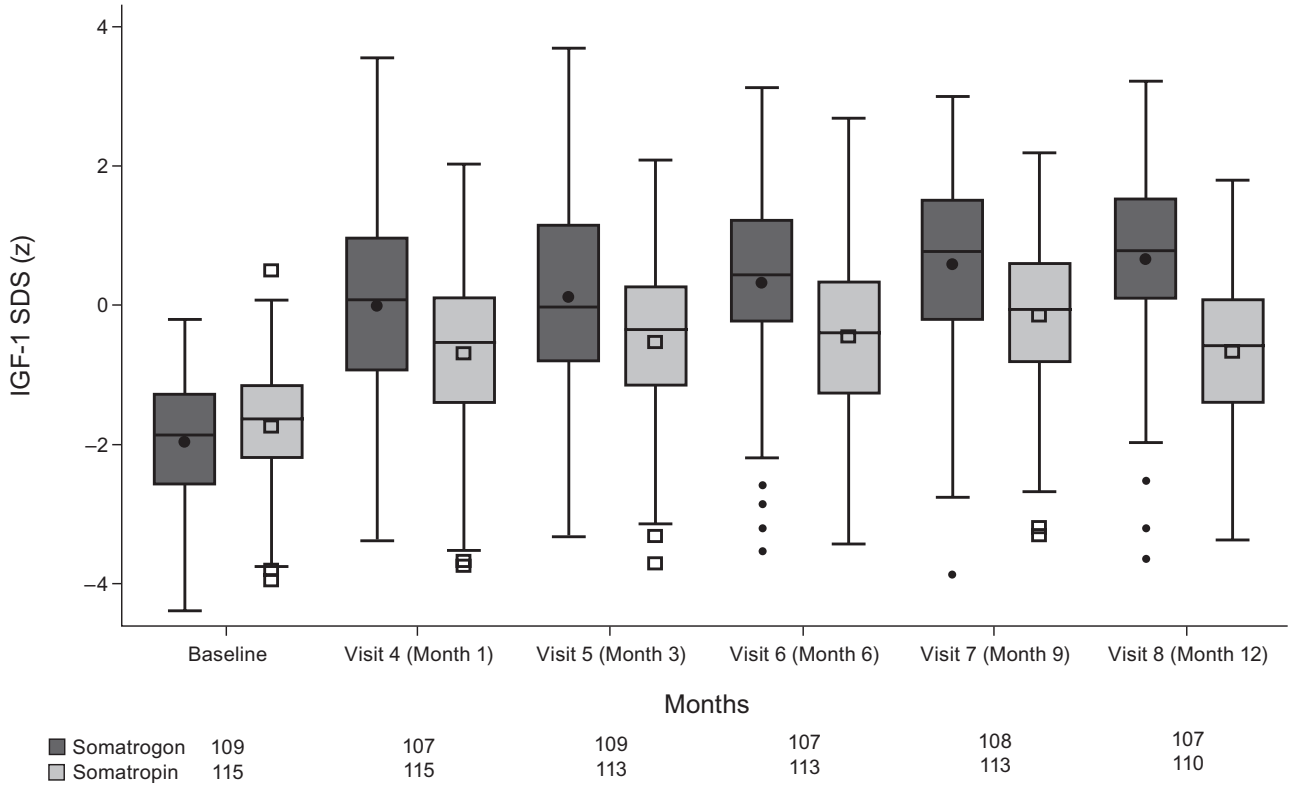

Figure 4. IGF-1 SDS over time. Abbreviation: SDS, standard deviation score.

Table 2. Treatment-emergent adverse events (all-causality)

Number (%) of subjects	Somatrogon (n = 109)	Somatropin (n = 115)	Total (N = 224)
Number of AEs	868	570	1438
Subjects with AEs	95 (87.2%)	97 (84.3%)	192 (85.7%)
Subjects with serious AEs	3 (2.8%)	2 (1.7%)	5 (2.2%)
Subjects with severe AEs	9 (8.3%)	6 (5.2%)	15 (6.7%)
Subjects discontinued from study due to AEs[a]	1 (0.9%)	0	1 (0.4%)
Subjects discontinued study drug due to AE and continued study[b]	0	0	0
Subjects with dose reduced or temporary discontinuation due to AEs	3 (2.8%)	2 (1.7%)	5 (2.2%)

Serious AEs are based on the investigator's assessment. Abbreviation: AE, adverse event.
[a]Subjects who have an AE record that indicates that the AE caused the subject to be discontinued from the study.
[b]Subjects who have an AE record that indicates that action taken with study treatment was drug withdrawn but AE did not cause the subject to be discontinued.

maps in Supplemental Figure S2 (22). The heat maps demonstrate that most TEAEs of injection site pain occurred during the first 6 months of treatment. For some subjects, however, TEAEs of injection site pain were reported throughout the study, usually with mild or decreasing severity.

Both treatment groups had a similarly low incidence of SAEs (somatrogon: 2.8%; somatropin: 1.7%) (Table 2) and none were considered related to the study treatment. No deaths occurred during the study and only 1 subject (somatrogon group) discontinued from the study due to an AE (injection site erythema and injection site induration) (Table 2). The incidence of dose reductions or temporary study drug discontinuations due to an AE was low overall (2.2% [n = 5]) and similar between somatrogon (2.8% [n = 3]) and somatropin (1.7% [n = 2]). No TEAEs led to a dose reduction of the study drug.

Overall, 29 subjects experienced IGF-1 levels > 2 SDS sometime during the study (somatrogon: n = 26; somatropin; n = 3). There was a total of 26 subjects in the somatrogon group with initially high IGF-1, but 14 of them were not high on the mandatory retest. Closer scrutiny of these 26 samples showed that 23 of them were obtained on day 2 or 3 after administration, which represents peak IGF-1 levels, not the mean, explaining the high IGF-1 levels. A total of 12 patients did require a dose reduction, as per protocol (due to 2 consecutive measurements with SDS > 2).

Using the data collected, a PK/PD analysis was performed to simulate IGF-1 profiles for each of the study subjects and to estimate the mean IGF-1 SDS over the dosing interval, regardless of when the sample had been collected. Among somatrogon-treated subjects, 10 of 535 (1.9%) samples that corresponded to mean IGF-1 SDS over the dosing interval

Table 3. All-causality treatment-emergent adverse events reported in ≥5% of subjects in either treatment group (safety analysis set)

Number (%) of subjects	Somatrogon (n = 109)	Somatropin (n = 115)	Total (N = 224)
With any AE	92 (84.4%)	90 (78.3%)	182 (81.3%)
Injection site pain	43 (39.4%)	29 (25.2%)	72 (32.1%)
Nasopharyngitis	25 (22.9%)	29 (25.2%)	54 (24.1%)
Headache	18 (16.5%)	25 (21.7%)	43 (19.2%)
Pyrexia	18 (16.5%)	16 (13.9%)	34 (15.2%)
Cough	9 (8.3%)	9 (7.8%)	18 (8.0%)
Vomiting	8 (7.3%)	9 (7.8%)	17 (7.6%)
Anemia	7 (6.4%)	7 (6.1%)	14 (6.3%)
Arthralgia	5 (4.6%)	8 (7.0%)	13 (5.8%)
Bronchitis	3 (2.8%)	9 (7.8%)	12 (5.4%)
Pharyngitis	7 (6.4%)	5 (4.3%)	12 (5.4%)
Otitis media	4 (3.7%)	7 (6.1%)	11 (4.9%)
Tonsillitis	5 (4.6%)	6 (5.2%)	11 (4.9%)
Blood creatine phosphokinase increased	2 (1.8%)	8 (7.0%)	10 (4.5%)
Oropharyngeal pain	6 (5.5%)	4 (3.5%)	10 (4.5%)
Hypothyroidism	7 (6.4%)	3 (2.6%)	10 (4.5%)
Ear pain	2 (1.8%)	7 (6.1%)	9 (4.0%)
Injection site erythema	9 (8.3%)	0	9 (4.0%)
Abdominal pain upper	2 (1.8%)	6 (5.2%)	8 (3.6%)
Rhinitis	6 (5.5%)	1 (0.9%)	7 (3.1%)
Arthropod bite	6 (5.5%)	1 (0.9%)	7 (3.1%)
Injection site pruritus	6 (5.5%)	0	6 (2.7%)

Abbreviation: AE, adverse event.

were > 2. These 10 instances of mean IGF-1 SDS >2 occurred in 3 subjects and no subject had a mean IGF-1 SDS ≥ 3. The use of PK/PD modeling as a tool to estimate IGF-1 SDS profiles in patients receiving somatrogon over the dosing interval confirmed that samples collected close to 96 hours after dose administration represent the mean IGF-1 SDS over the week between doses. The PK/PD modeling also confirmed that samples collected 48 to 72 hours after dose administration represent peak IGF-1 SDS over the week between doses.

Glucose, HbA1c, and insulin levels rose modestly during the 12-month period in both the somatrogon and somatropin groups (Supplemental Table S3 (22)); values remained within the normal range. No clinically meaningful differences in thyroid function, TSH, insulin, lipids, vital assessments, or physical examinations were observed between subjects treated with somatrogon vs somatropin. There were no cases of drug-induced liver function abnormalities in any subjects.

Immunogenicity

Among 109 somatrogon-treated subjects, 84 subjects (77.1%) tested positive for anti-drug antibodies (ADAs) at any time during the 12-month study period. Among 115 somatropin-treated subjects, 18 (15.6%) tested positive for ADAs. Post hoc analyses comparing clinical endpoint results to ADA status indicate that the presence of ADAs did not have an effect on overall safety (eg, adverse events) or efficacy (eg, growth rate) during the main study. Further, no ADAs had evidence of neutralizing activity on safety or efficacy. Analyses of immunogenicity are ongoing since the conduct of the OLE portion of the study is actively in progress and monitoring subjects for safety and efficacy continues accordingly.

Adherence

The overall adherence rate for this study was 99.6%, with very high adherence observed in both the somatrogon (99.4%) and somatropin (99.7%) groups. The lowest adherence rate observed for an individual patient was 87.5% in the somatrogon group and 91.5% in the somatropin group.

Discussion

The objective of this clinical study was to evaluate the safety and efficacy of somatrogon administered once weekly compared with somatropin administered once daily in prepubertal children with GHD. Conducted in 21 countries, this study met its primary objective, demonstrating that once-weekly treatment with somatrogon was noninferior to daily treatment with somatropin. The LS mean estimate of annual HV at 12 months was 10.10 cm/year for somatrogon and 9.78 cm/year for somatropin. The efficacy of somatrogon administered once weekly in this study was consistent with what was observed for the highest dose group (somatrogon 0.66 mg/kg/week) in the previous phase 2 study, as reported by Zelinska et al, with the mean annualized HV in the somatrogon group similar to that for the somatropin group (11.9 cm/year and 12.5 cm/year, respectively) and a similar improvement observed in height SDS (20).

The safety and tolerability of somatrogon administered once weekly was similar to that of somatropin administered once daily in prepubertal children with GHD. The most commonly reported all-causality TEAE in this study was injection site pain, which was reported by 39.4% and 25.2% of subjects in the somatrogon and somatropin groups,

respectively. This likely reflects the thoroughness of the study protocol for tracking patient and family perceptions of injection pain. The between-group difference in the number of reports of injection site pain did not appear to be due to a difference in age or injection site location and may have been a result of differences in the way that injection site pain was recorded in the 2 treatment groups, as outlined in the Methods above. The modest increases in glucose and HbA1c levels observed have also been described in previous studies (27, 28); however, the resulting values in this study were still within the normal range. The tolerability of once-weekly somatrogon and once-daily somatropin was underscored by the fact that, of the 224 subjects who enrolled in the study, 222 (99%) completed the main study. Furthermore, of these 222 subjects, 212 (somatrogon: n = 104 [95%]; somatropin: n = 108 [94%]) chose to enroll into the optional OLE. The safety findings from this study were similar to those reported in the previous phase 2 study (20).

The safety profile of the subjects with 2 consecutive IGF-1 values > 2 SDS was similar to that of subjects without elevated IGF-1 values. There is currently little clinical evidence to suggest that high IGF-1 levels (in the short term) increase the risk of adverse events (29); however, prolonged and sustained increases in IGF-1 may be deleterious. With daily administered rhGH products, the time of sample collection for IGF-1 measurement is not a concern, as fluctuations over the 24-hour dosing interval are modest and as such, all sampling times provide reasonable estimates of the average IGF-1 SDS. However, as noted previously (26) and highlighted by Bidlingmaier (30), interpretation of IGF-1 SDS for somatrogon needs to consider the timing of sample collection due to the significant peak trough fluctuation over the dosing interval. With weekly dosing of long-acting somatrogon, samples collected 2 or 3 days after the dose provide good estimates of peak IGF-1. Although collecting samples approximately 96 hours (4 days) post somatrogon dose will provide an accurate estimate of the mean IGF-1 SDS over the dosing interval, in real-world practice, IGF-1 SDS monitoring at any day after dosing will require the use of PK/PD-generated models for all long-acting GH products (30).

Clinical studies of a number of other long-acting GH products were recently described in a review by Yuen and coauthors (31). Thornton and coauthors (10) recently published a study describing the efficacy and safety of another long-acting GH molecule, lonapegsomatropin, showing similar findings to those reported in the current study. Lonapegsomatropin employs a different mechanism to prolong half-life than does somatrogon; lonapegsomatropin consists of somatropin bound to a methoxy polyethylene glycol carrier via a cleavable linker. In a study of 161 treatment-naïve, prepubertal children with GHD, once-weekly lonapegsomatropin demonstrated noninferiority over once-daily somatropin in terms of efficacy based on LS mean annualized HV. Lonapegsomatropin had a similar safety and tolerability profile to once-daily somatropin. However, it is impossible to directly compare the phase 3 results of different long-acting GH molecules with regard to growth response because of the differences in inclusion and exclusion criteria, sample sizes, subject demographics, and molecular characteristics including PK/PD. Moving forward, it will be important to continue monitoring the safety and long-term efficacy of all long-acting GH products.

The use of long-acting GH products such as somatrogon for the treatment of pediatric GHD may address some of the issues with adherence and persistence currently associated with daily rhGH treatment, without compromising patient health and development, although this remains to be proven for all the long-acting GH products (32, 33). Poor adherence to treatment and early cessation have been identified as key issues associated with daily rhGH treatment (4, 5, 34). In addition to reduced efficacy, poor adherence can also result in substantial costs being borne for unused treatment (4). A recent study of pediatric patients, caregivers, and adult patients showed a strong preference for a less-frequent injection schedule for the treatment of GHD (35).

One of the key strengths of this study is that it provides a direct comparison of somatrogon administered once weekly vs somatropin administered once daily, which helps address patient preference for a treatment regimen with less-frequent injections. Other strengths of this study include the diversity of subjects (21 countries), the examination of adherence, and the fact that the range of peak GH values in this study reflect those seen in a clinical setting. The potential weaknesses of the study include the difficulty of knowing what constitutes a safe and optimal level of IGF-1 and the lack of long-term safety and efficacy data on long-acting GH preparations (30, 31). However, the latter is currently being addressed in the OLE period of this study as well as the OLE of the phase 2 study (20) of somatrogon mentioned previously.

In conclusion, the efficacy of somatrogon administered once weekly was noninferior to somatropin administered once daily for the treatment of prepubertal children with GHD. Once-weekly somatrogon resulted in an increase in HV comparable to that achieved with daily GH treatment, while maintaining IGF-1 and bone age advancement within the normal range. Long-acting somatrogon and daily GH had similar safety and tolerability profiles. Compared with somatropin administered once daily, the less-frequent injection schedule afforded by somatrogon administered once weekly has the potential to improve poor adherence and increase quality of life (1), which are key unmet needs in this pediatric population.

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Clinical Trial Information

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Disclosure Statements

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Data Availability

Upon request, and subject to certain criteria, conditions and exceptions (see https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information), Pfizer will provide access to individual de-identified participant data from Pfizer-sponsored global interventional clinical studies conducted for medicines, vaccines and medical devices (1) for indications that have been approved in the US and/or EU or (2) in programs that have been terminated (ie, development for all indications has been discontinued). Pfizer will also consider requests for the protocol, data dictionary, and statistical analysis plan. Data may be requested from Pfizer trials 24 months after study completion. The de-identified participant data will be made available to researchers whose proposals meet the research criteria and other conditions, and for which an exception does not apply, via a secure portal. To gain access, data requestors must enter into a data access agreement with Pfizer.

Restrictions apply to the availability of some or all data generated or analyzed during this study to preserve patient confidentiality or because they were used under license. The corresponding author will on request detail the restrictions and any conditions under which access to some data may be provided.

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